Stochastic modelling of diversity and ageing in the naïve T cell repertoire

Emily Ruth Stirk

Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
Department of Applied Mathematics

March 2010

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated overleaf. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.
Jointly-authored publications

Work from the following jointly-authored publications is included in this thesis:

• Paper 1

• Paper 2

• Paper 3

Copies of these papers, as published or submitted, are provided in Appendix E. The contribution of authors to the above mentioned papers consists of:
• Paper 1

The derivation of the birth and death rates in Section 2 of the paper is the work of Carmen Molina-París and Hugo van den Berg. The derivation of the bound on $\langle \nu \rangle$ stated in Eq. (33) is the work of Hugo van den Berg. The derivation of expressions for $\langle p_i \rangle$ in Section 4 and $\nu_i$ in Appendix C is also the work of Hugo van den Berg.

• Paper 2

The work presented in Section 6 of the paper, where continuous migration from the thymus is included in the model, is the work of Gareth A. D. Hurst. The proof described in Appendix C of this paper is the work of Harry Kesten.

• Paper 3

The derivation of the birth rates of the competition process is the work of Hugo van den Berg and Carmen Molina-París. The first version of the code used to carry out the simulation described in Section 4.3 of the paper is the work of Grant Lythe.

The contribution of Ms Emily Stirk consists of the remainder of the papers listed above.

Chapter 3 of this thesis is based on Paper 1, Chapter 4 is based on Paper 2 and Sections 5.1–5.2 of Chapter 5 and Sections 6.2–6.3 of Chapter 6 are based on Paper 3.
Acknowledgements

This research was funded by the Engineering and Physical Sciences Research Council and the University of Leeds.

First and foremost, I am gratefully indebted to my supervisors, Dr. Carmen Molina-París and Dr. Grant Lythe, for their guidance, support and enthusiasm over the last three years of research. It has been a privilege to work with them and other members of the mathematical immunology group.

In addition, various members of staff within the School of Mathematics and other university departments have provided me with helpful advice and feedback. These include Steve Tobias, Mark Kelmanson, Alexander Veretennikov, Mikhail Ivanchenko, Hugo van den Berg, Damian Clancy, Harry Kesten, Phil Pollett and Erik van Doorn.

I would also like to thank my family and friends (especially Paul) for all their help, patience and understanding.

Finally, special thanks must go to my fiancé, James Jackson, who has provided unfailing love, support and encouragement whilst also carrying out his own PhD.
A characteristic feature of the adaptive immune response is the large diversity of T cell variants, called clonotypes, that it contains. The size and diversity of the T cell repertoire is crucial to the reliability of the immune response because the organism is unable to predict precisely which pathogens it will be exposed to throughout life. The number and diversity of T cells in a healthy adult human are both subject to homeostatic control, remaining approximately constant throughout life until old age, at which point T cell diversity rapidly declines. Hence it is of importance to study, for different T cell clonotypes, the probability of population extinction and the mean time until extinction occurs. These problems cannot be addressed with deterministic models and instead a stochastic framework is necessary. In this thesis, T cell repertoire maintenance is modelled by means of a continuous-time Markov process using a mean field assumption concerning competition for survival signals between different clonotypes. In particular, it is assumed that although a given T cell clonotype may compete with many other clonotypes for access to survival signals, individual competitive interactions between pairs of clonotypes are small. It is shown that ultimate clonotype extinction is certain for all parameter values of the model and mean extinction times are calculated. It is proved that a unique limiting conditional probability distribution exists, which is used to describe the homeostatic number of T cells, and analytical approximations to this distribution are studied. The model is then extended to the case of a pair of clonotypes for which the mean
field assumption does not hold, by means of a bivariate competition process. As the
two clonotypes become more similar in terms of the resources that they share, one
clonotype quickly becomes extinct in a process resembling the ecological principle
of classical competitive exclusion. The limiting conditional probability distribution
of this bivariate model is introduced and its existence is studied. The model is
then extended further to include \( k \in \mathbb{Z}^+ \) competing clonotypes using a multivariate
competition process. It is proved that eventual extinction of all clonotypes occurs
with certainty within a finite time. The limiting conditional distribution for this
multivariate process is defined and existence is studied. A Gillespie algorithm is
used to simulate the dynamics of the full repertoire in cases when analytic results
cannot be obtained.
## Contents

1 Biological background and overview of the thesis .......................... 1

1.1 The mammalian immune system ........................................... 1

1.2 The role of T lymphocytes in the adaptive immune response ........... 2

1.2.1 T cell maturation in the thymus ........................................ 4

1.2.2 Antigen presentation .................................................... 6

1.2.3 T cell activation ......................................................... 7

1.3 Peripheral maintenance of T cell diversity ................................. 8

1.3.1 Homeostatic proliferation of T cells and competition for survival signals from self-pMHC complexes .................. 10

1.3.2 Repertoire maintenance and ageing ................................... 11

1.4 Outline of the thesis ....................................................... 12

2 Mathematical background ....................................................... 15

2.1 Basic review of probability ................................................ 16

2.2 Stochastic processes ....................................................... 20

2.2.1 Continuous-time Markov processes ................................ 21

vi
2.2.2 The general birth and death process .......................... 22
2.2.3 Stationary and limiting probability distributions of the birth
and death process .................................................. 24
2.2.4 Finite-state birth and death processes ......................... 27
2.2.5 Sojourn times and the Gillespie algorithm .................. 28
2.2.6 Birth and death processes with an absorbing state at $n = 0$ . 30

3 A stochastic model of T cell repertoire maintenance 32

3.1 A birth and death process modelling the number of T cells belonging
to a given clonotype ............................................. 33
3.1.1 Derivation of the birth and death rates ....................... 34
3.1.2 Summary of the model ...................................... 38
3.1.3 Two special cases ........................................... 40
3.2 Analysis and results ............................................. 42
3.2.1 The ultimate fate of all clonotypes is extinction .......... 42
3.2.2 Mean extinction times ....................................... 44
3.2.3 The limiting conditional probability distribution represents
homeostatic numbers of T cells prior to extinction occurring . 50
3.2.4 The selection mechanism maximises T cell repertoire diversity 55
3.3 Discussion ....................................................... 59

4 Approximations to the limiting conditional probability distribution 62

4.1 Existence of a unique limiting conditional probability distribution . 63
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.1</td>
<td>Existence of a quasi-stationary probability distribution</td>
<td>64</td>
</tr>
<tr>
<td>4.1.2</td>
<td>The quasi-stationary probability distribution is not unique</td>
<td>69</td>
</tr>
<tr>
<td>4.1.3</td>
<td>The limiting conditional probability distribution exists and is unique</td>
<td>70</td>
</tr>
<tr>
<td>4.2</td>
<td>Two approximating processes</td>
<td>71</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Approximating process ( \mathcal{X}^{(1)}(t) : t \geq \tilde{t}_i )</td>
<td>72</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Approximating process ( \mathcal{X}^{(2)}(t) : t \geq \tilde{t}_i )</td>
<td>74</td>
</tr>
<tr>
<td>4.3</td>
<td>Approximations in the special cases ( \nu \ll 1 ) and ( \nu \gg 1 )</td>
<td>77</td>
</tr>
<tr>
<td>4.3.1</td>
<td>The case ( \nu \ll 1 )</td>
<td>77</td>
</tr>
<tr>
<td>4.3.2</td>
<td>The case ( \nu \gg 1 )</td>
<td>79</td>
</tr>
<tr>
<td>4.4</td>
<td>A normal approximation to the LCD</td>
<td>82</td>
</tr>
<tr>
<td>4.4.1</td>
<td>Normal approximation in the special case ( \nu \ll 1 )</td>
<td>84</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Normal approximation in the special case ( \nu \gg 1 )</td>
<td>88</td>
</tr>
<tr>
<td>4.5</td>
<td>The diffusion approximation</td>
<td>90</td>
</tr>
<tr>
<td>4.5.1</td>
<td>The diffusion approximation for a general birth and death process</td>
<td>91</td>
</tr>
<tr>
<td>4.5.2</td>
<td>The diffusion approximation in the special case ( \nu \ll 1 )</td>
<td>94</td>
</tr>
<tr>
<td>4.5.3</td>
<td>The diffusion approximation in the special case ( \nu \gg 1 )</td>
<td>96</td>
</tr>
<tr>
<td>4.6</td>
<td>A Poisson approximation</td>
<td>98</td>
</tr>
<tr>
<td>4.7</td>
<td>Accuracy of the three approximations</td>
<td>102</td>
</tr>
<tr>
<td>4.8</td>
<td>Discussion</td>
<td>104</td>
</tr>
</tbody>
</table>
5 A stochastic model for a pair of competing clonotypes

5.1 A competition process modelling the number of T cells belonging to a pair of clonotypes .................................................. 110

5.1.1 Derivation of the birth and death rates .................................. 112

5.1.2 Summary of the model .......................................................... 118

5.1.3 The limits \( p_1 = p_2 = 0 \) and \( p_1 = p_2 = 1 \) ......................... 121

5.2 Guaranteed extinction and finite mean extinction times ............... 122

5.2.1 The ultimate fate of both clonotypes is extinction ...................... 123

5.2.2 A bound on the mean time until extinction .............................. 126

5.3 The quasi-stationary probability distribution of the bivariate compet-
tition process ........................................................................ 127

5.3.1 The stationary probability distribution of the process conditional on the event that at least one of the pair of clonotypes is present in the repertoire .......................................................... 128

5.3.2 Existence of the stationary probability distribution conditional on the event that at least one of the pair of clonotypes is present in the repertoire .......................................................... 130

5.3.3 The stationary probability distribution of the process conditional on the event that both clonotypes are present in the repertoire .......................................................... 136

5.3.4 Existence of the stationary probability distribution conditional on the event that both clonotypes are present in the repertoire 140

5.4 Discussion ............................................................................. 145
6 Special cases of the bivariate competition process

6.1 The six special cases .......................................... 149
6.2 Mean extinction times in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ ..................... 152
6.3 A normal approximation to the LCD in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ ...... 160
   6.3.1 A deterministic approximation .......................... 162
   6.3.2 Fluctuations about the stable steady state and an approxima-
   tion to the limiting conditional probability distribution ...... 164
6.4 The diffusion approximation in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ ........... 170
6.5 Other special cases ............................................. 175
   6.5.1 The case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ ............................ 176
   6.5.2 The case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ ............................ 179
   6.5.3 The case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ ............................ 184
   6.5.4 The case $\nu_{12} \ll 1$, $\nu_1 \gg 1$, $\nu_2 \gg 1$ ............................ 187
   6.5.5 The case $\nu_{12} \gg 1$, $\nu_1 \gg 1$, $\nu_2 \gg 1$ ............................ 189
6.6 Arbitrary values of $\nu_{12}$, $\nu_1$ and $\nu_2$ ............................................. 193
6.7 Discussion ...................................................... 200

7 Many competing clonotypes ................................. 202

7.1 A competition process modelling the number of T cells belonging to
   $k$ clonotypes ..................................................... 203
7.2 Guaranteed extinction and finite mean extinction times .................. 206
7.3 The quasi-stationary probability distribution of the multivariate competition process ........................................ 210

7.3.1 The stationary probability distribution of the process conditional on the event that at least one of the \( k \) clonotypes is present in the repertoire ........................................ 210

7.3.2 Existence of the stationary probability distribution conditional on the event that at least one of the \( k \) clonotypes is present in the repertoire ........................................ 212

7.3.3 The stationary probability distribution of the process conditional on the event that all \( k \) clonotypes are present in the repertoire ........................................ 217

7.3.4 Existence of the stationary probability distribution conditional on the event that all \( k \) clonotypes are present in the repertoire 219

7.4 An exact numerical simulation for \( N_C \) clonotypes ....................... 224

7.4.1 Simulations of a repertoire where the mean field assumption holds for all pairs of clonotypes and a repertoire where it does not .......................... 225

7.4.2 Simulations of a randomly generated T cell repertoire ........... 228

7.5 Discussion ................................................................. 237

8 Concluding Remarks ....................................................... 241

References ................................................................. 249

Appendices ................................................................. 266

A Proof that Eq. (5.59) defines a bijective mapping from \( S \) to \( \tilde{S} \) .... 266
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Proof that there is a unique stable steady state in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1, \nu_2 \ll 1$</td>
<td>268</td>
</tr>
<tr>
<td>C</td>
<td>Proof that there is a unique stable steady state in the case $\nu_{12} \gg 1$, $\nu_1 \ll 1, \nu_2 \ll 1$</td>
<td>273</td>
</tr>
<tr>
<td>D</td>
<td>A stable steady state does not exist in the region $R$ in the case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \gg 1$ when the steady state at $(1, 0)$ is stable</td>
<td>275</td>
</tr>
<tr>
<td>E</td>
<td>Copies of jointly-authored publications</td>
<td>277</td>
</tr>
</tbody>
</table>
List of figures

1.1 Schematic representation of T cell and APC surfaces ....................... 4
1.2 Positive and negative selection in the thymus ................................ 6
1.3 T cell activation followed by clonal expansion ............................... 8
3.1 Schematic diagram of the sets of APPs and T cell clonotypes and the interactions between them .............................................. 35
3.2 Four realisations of the birth and death process ............................... 43
3.3 $\tau_1$ as a function of $\nu$ for varying $\varphi$ ................................. 46
3.4 $\tau_1$ as a function of $\nu$ for varying $\langle n \rangle$ ............................. 46
3.5 $\tau_{\tilde{n}}$ as a function of $\tilde{n}$ for varying $\nu$ where $\tilde{n} = 1, 2, \ldots, 10$ ........ 47
3.6 $\tau_{\tilde{n}}$ as a function of $\tilde{n}$ for varying $\nu$ where $\tilde{n} = 1, 2, \ldots, 100$ .......... 47
3.7 The LCD, $q_n$, for varying $\nu$ ................................................. 54
3.8 Expected number of T cells at the LCD as a function of $\nu$ for varying $\varphi$ 54
3.9 Expected number of T cells at the LCD as a function of $\nu$ for varying $\langle n \rangle$ ................................................................. 55
3.10 Coefficient of variation of the LCD as a function of $\nu$ .................... 57
LIST OF FIGURES

3.11 Simpson’s diversity index as a function of $\nu$ ............... 59

4.1 The LCD and the approximations $\bar{p}^{(1)}$ and $\bar{p}^{(2)}$ in the case $\nu \ll 1$. .. 80
4.2 The LCD and the approximations $\bar{p}^{(1)}$ and $\bar{p}^{(2)}$ in the case $\nu \gg 1$. .. 82
4.3 The LCD and the normal approximation in the case $\nu \ll 1$. ........ 87
4.4 The LCD and the normal approximation in the case $\nu \gg 1$. ........ 90
4.5 The LCD and the Poisson approximation in the case $\nu \ll 1$. ....... 103
4.6 The Jenson-Shannon divergence between the LCD and the various approximations as a function of $\varphi/\mu$ in the case $\nu \ll 1$. ........ 105
4.7 The Jenson-Shannon divergence between the LCD and the various approximations as a function of $\varphi/\mu - \nu \langle n \rangle$ in the case $\nu \gg 1$. ... 105

5.1 The sets $Q_i$ and $Q_j$ in the case when $|Q_i \cap Q_j| \sim |Q_i|$ ............ 109
5.2 A schematic representation of the bivariate competition process. ... 113
5.3 Schematic representation of the sets $S_j'$ for $j \geq 0$. ............. 123
5.4 The limiting probability distribution of the process conditional on the event that at least one of the pair of clonotypes is present in the repertoire in the case $\varphi_1 = \varphi_2$. ...................... 136
5.5 The limiting probability distribution of the process conditional on the event that at least one of the pair of clonotypes is present in the repertoire in the case $\varphi_1 \neq \varphi_2$. ...................... 137
5.6 Schematic representation of the sets $S_j$ for $j \geq 0$. ............... 141
5.7 The limiting probability distribution of the process conditional on the event that both of the pair of clonotypes are present in the repertoire in the case $\varphi_1 = \varphi_2$. ...................... 145
5.8 The limiting probability distribution of the process conditional on the event that both of the pair of clonotypes are present in the repertoire in the case $\varphi_1 \neq \varphi_2$. ......................................................... 146

6.1 $\hat{t}_{n_1,n_2}$ as a function of $p_1$ for various initial conditions where $n_1+n_2 = 10$. 156
6.2 $\hat{t}_{n_1,n_2}$ as a function of $p_1$ for various initial conditions where $n_1 = n_2$. 156
6.3 $\hat{t}_{n_1,n_2}$ as a function of $p_1$ for different values of $\varphi_1$. ......................... 157
6.4 $\hat{t}_{n_1,n_2}/\tau_{n_1,n_2}$ as a function of $p_1$ for different values of $\varphi_1$ with $n_1 = n_2$. 157
6.5 $\hat{t}_{n_1,n_2}/\tau_{n_1,n_2}$ as a function of $p_1$ for different values of $\varphi_1$ with $n_1 \neq n_2$. 158
6.6 $\varphi_{n_1,n_2}$ as a function of $p_1$ for different values of $\varphi_1$. ......................... 159
6.7 $\varphi_{n_1,n_2}$ as a function of $p_1$ for various initial states. ............................ 159
6.8 The quantities $\langle \eta_1 \rangle$ and $\langle \eta_2 \rangle$ as a function of time. ...................... 167
6.9 The quantities $\langle \eta_1^2 \rangle$, $\langle \eta_2^2 \rangle$ and $\langle \eta_1 \eta_2 \rangle$ as a function of time ........ 168
6.10 Correlation between clonotype 1 and clonotype 2 for the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$. ................................. 169
6.11 The coefficient of variation for the number of T cells belonging to clonotype 1 at the LCD with $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$. ................................. 170
6.12 Phase-plane diagram for the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$. ...................... 178
6.13 The LCD of the process in the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$. ...................... 179
6.14 Phase-plane diagram for the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$. ...................... 181
6.15 The LCD of the process in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ with a set of parameters for which $(1,0)$ is a stable steady state. .......................... 183
LIST OF FIGURES

xvi

6.16 The LCD of the process in the case ν12  1, ν1  1, ν2  1 with a
set of parameters for which (1, 0) is an unstable steady state. . . . . . 184
6.17 Phase-plane diagram for the case ν12  1, ν1  1, ν2  1. . . . . . . 186
6.18 Phase-plane diagram for the case ν12  1, ν1  1, ν2  1. . . . . . . 188
6.19 Phase-plane diagram for the case ν12  1, ν1  1, ν2  1. . . . . . . 191
6.20 τ̂n1 ,n2 as a function of ν12 and ν2 with n1 = n2 . . . . . . . . . . . . . . 194
6.21 τ̂n1 ,n2 as a function of ν12 , ν1 and ν2 with n1 6= n2 . . . . . . . . . . . . 195
6.22 τ̂n1 ,n2 as a function of ν12 , ν1 and ν2 with n1 6= n2 and ϕ 6= ϕ2 . . . . . 195
6.23 τ̂n1 ,n2 as a function of ν12 and ν2 with ν12 = ν2 = 10 when these
parameters are not fixed. . . . . . . . . . . . . . . . . . . . . . . . . . 197
6.24 ℘n1 ,n2 as a function of ν12 , ν1 and ν2 where n1 = n2 . . . . . . . . . . . 197
6.25 ℘n1 ,n2 as a function of ν12 , ν1 and ν2 where n1 6= n2 . . . . . . . . . . . 198
6.26 E(qn1 ,− ) as a function of ν12 , ν1 and ν2 with ϕ1 = ϕ2 . . . . . . . . . . 198
6.27 E(qn1 ,− ) as a function of ν12 , ν1 and ν2 with ϕ1 6= ϕ2 . . . . . . . . . . 199
6.28 E(qn1 ,− ) as a function of ν12 , ν1 and ν2 with ν12 = ν1 = ν2 = 10 when
these parameters are fixed. . . . . . . . . . . . . . . . . . . . . . . . . 199
7.1

The number of T cells belonging to a typical clonotype as a function of
time for a repertoire where |Qi ∩Qj |  |Qi | for all pairs of clonotypes
with µi = 0.1 for all clonotypes. . . . . . . . . . . . . . . . . . . . . . 226

7.2

The number of T cells belonging to a typical clonotype as a function of
time for a repertoire where |Qi ∩Qj |  |Qi | for all pairs of clonotypes
with µi = 1 for all clonotypes. . . . . . . . . . . . . . . . . . . . . . . 227


7.3 The number of T cells belonging to a particular clonotype as a function of time for a repertoire where $|Q_i \cap Q_j| \sim |Q_i|$ but $|Q_i \cap Q_k| \ll |Q_i|$ and $|Q_j \cap Q_k| \ll |Q_j|$ for all other clonotypes $k$ in the repertoire. 228

7.4 $N_C \langle n \rangle$ as a function of time. 230

7.5 $N_C$ as a function of time. 230

7.6 $\langle \nu \rangle$ as a function of time. 232

7.7 The mean niche overlap value of a clonotype at the time it becomes extinct from the repertoire. 232

7.8 $\langle n \rangle$ as a function of time. 234

7.9 $D_S$ as a function of time. 234

7.10 $N_C$ as a function of time for varying $\gamma$. 235

7.11 The distribution of the number of clonotypes that are able to receive survival signals from an APP at different timepoints for $\gamma = 1$. 236

7.12 The distribution of the number of clonotypes that are able to receive survival signals from an APP at different timepoints for $\gamma = 0.1$. 237

7.13 The distribution of $\nu_i$ at different timepoints for $\gamma = 0.1$. 238

7.14 The distribution of $\nu_i$ at different timepoints for $\gamma = 0.01$. 239
List of abbreviations

PAMP  Pathogen associated molecular patterns
APC   Antigen presenting cell
MHC   Major histocompatibility complex
TCR   T cell receptor
pMHC  Peptide-major histocompatibility complex
IL-7  Interleukin-7
cdf   Cumulative distribution function
pmf   Probability mass function
pdf   Probability density function
APP   Antigen presentation profile
LCD   Limiting conditional probability distribution
QSD   Quasi-stationary probability distribution
PDE   Partial differential equation
mgf   Moment generating function
cgf   Cumulant generating function
ODE   Ordinary differential equation
AICD  Activation induced cell death
CMV   Cytomegalovirus
EBV   Epstein-Barr virus
Chapter 1

Biological background and overview of the thesis

1.1 The mammalian immune system

The function of the immune system is to defend the organism against attack from invading pathogens. The mammalian immune system consists of two interacting components which are known as the innate and the adaptive immune systems. The innate immune response is non-specific, as it is essentially the same regardless of the exact nature of the invading pathogen, and involves mechanisms such as epithelial barriers (e.g., the skin and the lining of the gastrointestinal tract) which foreign material has to pass through in order to infect the individual, and also pattern recognition strategies. Phagocytic cells are a class of white blood cells including dendritic cells, macrophages and neutrophils which ingest (phagocytose) foreign material. These cells express pattern recognition receptors on their surface which are specific for pathogen associated molecular patterns (PAMPs) and binding of this receptor to its ligand triggers phagocytosis. PAMPs are common microbial products which are structurally distinct from eukaryotic proteins (eukaryotic cells possess a
nucleus and include plant and animal cells, but not bacteria or viruses) and so are recognised as being foreign to the host.

On the other hand, the adaptive immune response is antigen-specific, meaning that it is tailored to act only against the particular pathogen (an antigen is a protein fragment that triggers an immune response) and, in terms of evolution, is a much more recent acquisition than the less complex innate response \[42, 86\]. This arm of the immune response also differs from the innate component in that it exhibits immunological memory, which results in a swifter secondary response following re-infection with the same pathogen \[1\]. The two main cell types involved in the adaptive immune response are the T and B lymphocytes.

1.2 The role of T lymphocytes in the adaptive immune response

This thesis is concerned with T cells, which are small lymphocytes (having a radius of approximately 5\(\mu\)m \[54\]) comprising the cell-mediated component of the adaptive immune response. These cells mature in the thymus, which is a small organ located close to the heart. Peptides are protein fragments which are presented to T cells on the surface of professional cells called antigen presenting cells (APCs). The peptides are displayed on the major histocompatibility complex (MHC) molecules that are found on the APC cell surface. Usually the APC will present only self-peptides (peptides derived from the body’s own proteins) but in the case of infection, foreign peptides are also displayed.

The number of naïve T cells present in a healthy adult human remains roughly constant throughout life and is approximately \(10^{11}\) \[63\]. This total is composed of around \(10^7 - 10^8\) different T cell specificities (called clonotypes) \[6\], which are deter-
mined by a receptor presented on the cell surface, called the T cell receptor (TCR). Each T cell expresses around 30,000 identical copies of this receptor [72]. Thus, although each individual cell expresses only one specificity of receptor, the T cell repertoire is highly diverse in terms of the different receptors that are displayed. The T cell and the APC interact with each other in the lymph nodes via the TCR and the peptide-MHC (pMHC) complex. Figure 1.1 shows a schematic representation of the T cell and APC surfaces.

Mature T cells may be divided into several distinct classes, the two broadest of which are determined according to whether the T cell expresses the CD4 or CD8 surface protein. CD4+ T cells (also referred to as helper T cells) interact with peptides bound to MHC class II molecules, which are expressed on dendritic cells, macrophages and B lymphocytes. The function of CD4+ T cells is to direct the activity of other immune cells such as B cells and to secrete chemicals called cytokines, which affect the behaviour of other cells. On the other hand, CD8+ T cells interact with peptides bound to MHC class I molecules, which are constitutively expressed on all nucleated cells. Fragments of intracellular proteins are loaded onto the MHC class I molecules so that CD8+ T cells are able to detect virally infected cells. CD8+ T cells are also called cytotoxic T cells as their function is to induce the death of infected cells. They also have an important role in controlling tumour growth.

The lymphoid system is composed of the primary (central) lymphoid organs where lymphocytes are generated and the secondary (peripheral) lymphoid organs where mature lymphocytes are maintained. The primary lymphoid organs are the bone marrow and the thymus, while the secondary lymphoid organs are more numerous and include the spleen, lymph nodes, appendix and Peyer’s patches. Mature T cells continuously recirculate throughout the body between the blood and the lymphoid organs. At any one time, approximately 2% of T cells are found in the blood [9],
while approximately 41% and 15% are found in the lymph nodes and spleen, respectively [55, 127].

Figure 1.1: Schematic representation of T cell and APC surfaces. This interaction occurs in the lymph nodes.

1.2.1 T cell maturation in the thymus

T and B cells are derived from common lymphoid progenitor cells which are produced in the bone marrow and are descendants of haematopoietic stem cells. Some of these common lymphoid progenitor cells migrate from the bone marrow to the thymus and are then committed to the T cell lineage. Once in the thymus, these T cell precursors are referred to as thymocytes.

The thymus has a crucial role in generating the diversity of T cell clonotypes that make up the T cell repertoire. Initially, common lymphoid progenitor cells do not express receptors, such as CD4, CD8 and the TCR, on their surface. During T cell maturation in the thymus, the genes that encode the TCR structure are randomly rearranged in a process known as genetic recombination. This creates a large number of TCR structures and the possible diversity is further increased by the random addition and deletion of nucleotides when the rearranged gene segments are joined [35, 78].
One of the major challenges facing the adaptive immune system is to eliminate pathogens whilst avoiding damage to the host. Inevitably, due to its random nature, the process of genetic recombination produces TCRs which are able to bind to self-peptides and this may lead to autoimmune disease where the immune system acts against the body’s own tissues. In order to ensure that the T cell repertoire is functional and yet avoid autoimmunity, thymocytes undergo two selection processes during their development in the thymus.

Thymocytes that fail to receive a weak signal from an APC presenting self-pMHCs die by neglect in order to ensure that the TCR can bind to MHC molecules [62, 119]. Approximately 90% of all thymocytes are deleted by this process [103]. As shall be seen later, low affinity signals from self-peptides are crucial to T cell survival in the peripheral lymphoid system and so it is important that T cells are able to interact with them [45]. On the other hand, if a thymocyte has a very high affinity for a self-peptide presented in the thymus, it is deleted by negative selection in order to avoid autoimmune disease [119, 138, 139]. This process removes approximately 5% of all thymocytes (see Fig. 1.2). Those cells with a low affinity for self-pMHCs receive a positive selection signal, and whether a thymocyte is positively selected by MHC class I or MHC class II determines if the T cell has a CD4+ or CD8+ phenotype [62].

As few as 5% of all thymocytes survive the positive and negative selection process [103, 135]. Those that do survive then migrate to the periphery where they become part of the naïve T cell compartment, so-called because these T cells have not yet been activated by exposure to their specific antigen. Here they continuously recirculate through the blood, lymph and secondary lymphoid organs such as the spleen, lymph nodes and Peyer’s patches. Since the number of self-peptides that can be presented to T cells in the thymus is limited, some autoreactive T cells escape the negative selection process [16, 95]. For this reason, peripheral tolerance mechanisms such as those involving regulatory T cells [23] are also necessary to prevent
1.2.2 Antigen presentation

Professional antigen presenting cells, such as dendritic cells, internalise cell debris and pathogens through processes known as phagocytosis and receptor-mediated endocytosis. Within the APC, these proteins are degraded into peptide fragments which are then loaded onto MHC class II molecules and displayed on the cell surface. Peptides derived from proteins found in the cytosol of other cell types are loaded onto MHC class I molecules and displayed on the cell surface. This pathway is important for the recognition of virally infected cells. APCs interact with T cells in the lymph nodes where the T cells scan the APC surface for peptides which are specific to their TCR. A single APC expresses around $100,000$ MHC molecules on its surface [103], but only a small proportion (between 0.01 and 0.1%) of the peptides displayed will be specific to any one T cell [103].
1.2.3 T cell activation

Upon infection, only the T cell clonotypes which have a TCR that is specific for the invading pathogen are able to respond. This is known as the clonal selection hypothesis [19] and means that initially there is a low frequency of T cells available to fight the infection. Following exposure to their specific antigen, T cells become activated and differentiate from a naïve to an effector phenotype, after which they undergo many rounds of proliferation. The process of T cell activation is complex and involves a signalling cascade beginning with a high affinity binding between the TCR and the pMHC complex [1], and a second signal via the co-stimulatory surface molecule CD28 is also necessary [108]. The rapid burst of proliferation following T cell differentiation is termed “clonal expansion” and results in the creation of a large population of T cells specific for the invading pathogen (see Figure 1.3).

Naïve T cells migrate continuously around the body through the lymph nodes and blood but cannot enter other non-lymphoid tissues. One of the hallmarks of an effector cell is the presence of homing receptors on their surface, which enable them to enter other tissues, for example the lung to combat a respiratory infection [118]. Effector cells are also larger than naïve T cells due to their greater levels of protein expression. CD4+ effector cells have a wide range of functions, including signalling to B cells and the expression of cytokines (cytokines are signalling molecules which influence the behaviour of other cells). CD8+ effector cells kill infected cells by two mechanisms. The first is to secrete perforin which creates holes in the cell membrane of the target cell, allowing granzymes (also secreted by the cytotoxic T cell) to enter and induce apoptosis (programmed cell death). CD8+ effector cells also express the Fas ligand, which binds with the Fas receptor on the surface of the infected cell, again resulting in apoptosis.

Following clearance of the infection, the reduced level of antigenic stimulus causes
most of these effector T cells to die by apoptosis. However, some cells differentiate into long-lived memory T cells, resulting in an increased frequency of T cells specific for the pathogen to around $1 \times 10^{−100}$ in the memory T cell pool, compared to $1 \times 10^{4} − 10^{5}$ in the naïve T cell pool [14]. This, along with the fact that the memory T cells are already activated, means that should the same pathogen reappear in the future, the response will be much swifter and there may not be any clinical symptoms [14, 118]. This forms the basis of vaccination strategies [149].

Figure 1.3: T cell activation followed by clonal expansion, which results in a large population of T cells specific for the foreign antigen.

1.3 Peripheral maintenance of T cell diversity

A characteristic feature of the naïve T cell repertoire is the large diversity of different T cell clonotypes that it contains. However, this is still small compared to the molecular diversity of all possible pathogens [89]. A one-to-one correspondence
between TCRs and foreign antigens is impossible as this would require far more T cells than can be accommodated in the lymphoid system: for example, a mouse would require a spleen that is several orders of magnitude larger than itself [89]. Hence, in order to provide adequate protection, T cells must be cross-reactive to some extent [5, 89].

The size and diversity of the T cell repertoire is crucial to the reliability of the immune response [34] because the immune system is unable to predict precisely which pathogens the organism will be exposed to throughout life. The diversity of different TCRs is generated by a random process of genetic recombination during T cell maturation in the thymus (see Section 1.2.1). The subject of this thesis is T cell homeostasis and the peripheral maintenance of T cell diversity, which is mediated by survival signals from APCs presenting self-peptides [45, 50, 62].

Naïve T cells can be produced by two mechanisms. They can be generated from precursor haematopoietic stem cells in the thymus, or they may be produced directly from existing T cells in the peripheral lymphoid organs by a process called homeostatic proliferation [63]. The proposed mechanism of this process is discussed in more detail in Section 1.3.1. Novel T cell clonotypes not already present in the naïve repertoire can only be produced by the thymus.

Homeostasis is defined as an ability to maintain an internal steady state. In the peripheral lymphoid system, the number of T cells is subject to homeostatic control [88]: it remains approximately constant throughout the majority of an individual’s lifetime, returning to a steady state after perturbation (following infection or therapeutic lymphocyte depletion, for example). Homeostatic regulation is important in maintaining both the size and the diversity of the T cell repertoire [63] and can markedly alter the T cell repertoire in the periphery [3, 32].

Several early studies concluded that naïve and memory T cell pools are regulated by independent homeostatic mechanisms [124, 125], which makes intuitive sense
as competition between these cell types could result in a loss of T cell repertoire diversity due to replacement of naïve cells by rapidly proliferating memory cells, or conversely may lead to the loss of swift memory responses due to substitution of memory T cells by naïve T cells produced by either the thymus or homeostatic proliferation. However, more recent data suggest that the two pools are not independently regulated [57, 94, 113] and competition between memory and naïve cells may have a role in the observed dominance of the memory pool in old age. This is not crucial to the model that will be presented here, and since the memory T cell pool accounts for only around 1% of total TCR diversity in young adults [6], the naïve repertoire will be the focus of this thesis. It appears that CD4+ and CD8+ T cells also have overlapping mechanisms of homeostatic regulation [48, 62].

1.3.1 Homeostatic proliferation of T cells and competition for survival signals from self-pMHC complexes

It has long been established that self-peptides have an important role during T cell repertoire selection in the thymus [119] and there is now increasing experimental evidence that signals from self-peptides also play an important role in peripheral T cell repertoire maintenance [45, 50, 62]. T cells are able to interact weakly with a large variety of self-peptides presented on the surface of APCs. These low affinity interactions are important in keeping naïve T cells alive in the periphery and in homeostatic proliferation. This process is clonotype specific in that the efficiency of homeostatic proliferation depends on the particular TCR expressed on the T cell surface [48], as this affects which self-peptides the T cell is able to interact with. The signalling pathways involved in this process are only just beginning to be understood [123]. However, it is important to note that the requirements for homeostatic proliferation are distinct from those for T cell activation [71]; in particular co-stimulation may not be required [108].
After receiving a survival signal following such an interaction, the T cell undergoes a single round of cell division [147]. Competition for these signals between T cells belonging to the same clonotype and T cells belonging to different clonotypes is thought to regulate the diversity of the T cell repertoire [87]. In humans, homeostatic proliferation may be a significant mechanism of T cell production [64] and is particularly important in lymphopenic conditions (i.e., when the number of T cells is very low), when it is more pronounced [61, 79] due to decreased competition for access to survival signals.

Experimental results have also suggested an important role for several cytokines in naïve peripheral T cell homeostasis, in particular interleukin-7 (IL-7) [18, 52, 71]. However, the action of cytokines is not TCR specific and so they have a role in controlling total T cell numbers, while TCR specific signals from self-pMHC complexes regulate naïve T cell repertoire diversity [87]. Hence, this thesis will focus on the effect on the T cell repertoire of competition for signals from self-peptides displayed on the surface of APCs and will exclude the effect of cytokines.

1.3.2 Repertoire maintenance and ageing

Experimental evidence suggests a lack of homeostatic feedback mechanisms from the periphery to the thymus, i.e., the rate of export of new T cells from the thymus does not depend on the number of T cells already present in the periphery [12, 53]. On the other hand, it is well established that thymic export decreases over time as the thymus involutes with increasing age [7], although some thymic activity does continue well into old age [116]. T cell production in the thymus is at a maximum in the young and declines during adult life following the reduction in thymic volume at a rate of around 4% per year from puberty onwards [40]. Indeed, mathematical modelling has revealed that for the CD4\(^+\) pool in young adults, only 30% of newly produced naïve T cells come from the thymus [9], which suggests that, even in young
individuals, homeostatic proliferation is an important mechanism of T cell production. The model presented in [9] is particularly robust because it does not include any assumptions regarding the dependence of the rates of homeostatic proliferation and T cell death on the number of T cells already present in the population.

Despite the decrease in thymic output with age, a relatively constant number of T cells is maintained throughout adulthood by the homeostatic proliferation of existing cells [7]. However, in old age, homeostatic mechanisms appear to suddenly break down [96] and so naïve T cell repertoire diversity declines as T cell clonotypes die out, which may lead to “gaps” appearing in the repertoire [146]. A similar loss of diversity has also been observed for the B cell population [58] and this decline is correlated with poor health status. Elderly individuals have increased susceptibility to infectious diseases [39], respond less well to vaccination [13], and it is thought that the majority of immune responses are from expanded cross-reactive memory T cells [144], which are the dominant population. Hence it is of importance to study, for different T cell clonotypes, the probability of population extinction and the mean time until the clonotype becomes extinct from the repertoire. These problems cannot be addressed with deterministic models and instead a stochastic framework is necessary.

1.4 Outline of the thesis

In this thesis, the number of T cells belonging to a particular clonotype will be modelled using a type of stochastic process known as a birth and death process. In Chapter 2 a brief overview of probability theory and a basic introduction to stochastic processes, in particular birth and death processes, are provided. In Chapter 3 a birth and death model for the number of T cells belonging to a particular clonotype is described. It is shown that a parameter measuring the strength of the competition
between the given clonotype and other clonotypes in the repertoire has a critical impact on the length of time that T cells of this specificity remain in the repertoire. The limiting conditional probability distribution is introduced as the appropriate tool to describe the homeostatic number of T cells of the given clonotype before extinction occurs, and the diversity of the repertoire is characterised in terms of the parameters of this distribution. The limiting conditional probability distribution is studied in more detail in Chapter 4. It is proved that the birth and death process has a unique limiting conditional probability distribution for all values of the parameters. Several approximations to this distribution are also introduced and their accuracy is assessed in two special cases of the model. In Chapter 5 a model is developed for a pair of clonotypes which overlap significantly in terms of the survival signals which they are able to receive. In this case, the assumptions used in Chapter 3 break down and a bivariate competition process is required. The limiting conditional probability distribution of this bivariate process is defined and its existence is discussed. In Chapter 6, various special cases of the model for the pair of clonotypes are analysed. In particular, the case when the pair of clonotypes compete little with other T cell clonotypes in the repertoire is focussed on, since this case is an upper bound to all other cases in the sense that this region of parameter space is associated with the longest T cell residence times in the naïve repertoire. It is shown that as the two clonotypes become more similar, in terms of the proportion of the survival signals which are shared between them, one clonotype quickly becomes extinct from the repertoire in a process resembling the ecological principle of classical competitive exclusion. In Chapter 7, the model is extended to include \( k \in \mathbb{Z}^+ \) competing clonotypes. It is shown that extinction of all clonotypes occurs within a finite time with probability one. The limiting conditional probability distribution of this multivariate process is defined and its existence is discussed. A Gillespie algorithm, which can be used to simulate the full T cell repertoire dynamics without the need for any type of approximation, is then presented. In Chapter 8, the main
conclusions of the thesis are stated and areas for future research are outlined.
Chapter 2

Mathematical background

Mathematical modelling has proved to be an immensely powerful tool in the understanding of complex biological systems [92]. Mathematics has long being associated with the physical sciences, but over the past few decades there have been increasing efforts in the field of theoretical biology, leading to the life sciences becoming more quantitative in nature. This has had enormous benefits for both fields [31].

One particular example is in the modelling of immunological processes. The immune system is highly non-linear in that small perturbations may produce large effects, and involves many interactions between different molecules and cell types. As experimental work has greatly increased our understanding of cellular immunology in recent years, the need for quantitative tools and mathematical modelling has also grown. Here, theoretical immunology has been of great value in the interpretation of complex experimental data and in the identification of errors in intuitive ideas [15]. Mathematical modelling also provides testable hypotheses and so suggests new experiments to be performed by immunologists [22]. Hence, mathematical modelling can lead to a greater understanding of a particular biological process. On the other hand, this may lead to the development of innovative mathematical methods [20]. Indeed, in Chapter 5 of this thesis, a new method of proving the existence of a quasi-
stationary probability distribution for a two-dimensional analogue of the birth and death process is introduced.

In this thesis, naïve T cell repertoire maintenance will be studied using a stochastic model for the number of T cells belonging to a particular clonotype. T cell repertoire diversity has been analysed before by means of deterministic models [36, 37]. Such models are a good approximation when the number of cells is large. However, the number of T cells belonging to a particular clonotype may be small, in which case random fluctuations become important. Moreover, as described in Chapter 1, it is of relevance to study the probability of population extinction and the mean time until extinction occurs for a given T cell clonotype. These questions cannot be addressed within a deterministic framework and, hence, a stochastic model is needed. A stochastic model also naturally incorporates the discrete nature of cells, while in a deterministic model the number of cells is considered to be a continuous quantity. In this chapter, the necessary mathematical background material related to probability and stochastic processes is presented.

2.1 Basic review of probability

In this section, a brief review of important concepts and definitions from the theory of probability is provided before stochastic processes are introduced in Section 2.2. The sample space \( \Omega \) is the set of all possible outcomes of an experiment. Let \( \mathcal{G} \) be a \( \sigma \)-field of subsets of \( \Omega \). This means that

1. \( \emptyset \in \mathcal{G} \),
2. if \( A_1, A_2, \ldots \in \mathcal{G} \) then \( \bigcup_{i=1}^{+\infty} A_i \in \mathcal{G} \),
3. if \( A \in \mathcal{G} \) then \( \bar{A} \in \mathcal{G} \),
where $\bar{A}$ denotes the complement of the set $A$ in $\Omega$. Then a function $\mathbb{P}$ on $(\Omega, \mathcal{G})$, where $\mathbb{P} : \mathcal{G} \to [0,1]$, is a probability measure if

1. $0 \leq \mathbb{P}(A)$ for all $A \subset \mathcal{G}$,
2. $\mathbb{P}(\Omega) = 1$,
3. If $A_i \cap A_j = \emptyset$ for $i, j = 1, 2, \ldots, i \neq j$ with $A_i, A_j \in \mathcal{G}$ then

$$\mathbb{P}\left( \bigcup_{i=1}^{+\infty} A_i \right) = \sum_{i=1}^{+\infty} \mathbb{P}(A_i), \quad (2.1)$$

where $\mathbb{P}(A)$ denotes the probability of event $A$.

For two events $A_1$ and $A_2$ which are defined on $\mathcal{G}$, the conditional probability of $A_2$ occurring given that $A_1$ has occurred is defined by

$$\mathbb{P}(A_2|A_1) = \frac{\mathbb{P}(A_1 \cap A_2)}{\mathbb{P}(A_1)}, \quad (2.2)$$

provided that $\mathbb{P}(A_1) > 0$. Events $A_1$ and $A_2$ are said to be independent if and only if

$$\mathbb{P}(A_1 \cap A_2) = \mathbb{P}(A_1)\mathbb{P}(A_2). \quad (2.3)$$

Hence, for two independent events, $A_1$ and $A_2$, $\mathbb{P}(A_2|A_1) = \mathbb{P}(A_2)$ and $\mathbb{P}(A_1|A_2) = \mathbb{P}(A_1)$.

A random variable $\mathcal{X}$ is a real-valued function $\mathcal{X} : \Omega \to \mathbb{R}$ where there is an associated probability measure $\mathbb{P}(\Omega, \mathcal{G})$. The state-space $\mathcal{S}$ of the random variable is the set of all possible values it can take i.e., $\mathcal{S} = \{x \mid \mathcal{X}(\omega) = x, \omega \in \Omega\}$. In this thesis it is assumed that the state-space consists entirely of real values without loss of generality. If $\mathcal{S}$ is a finite or denumerably infinite set then $\mathcal{X}$ is said to be a discrete random variable, while if $\mathcal{S}$ is a non-denumerably infinite set then $\mathcal{X}$ is
known as a *continuous random variable*. It is possible to have state-spaces which are combinations of these two types, in which case the random variable is referred to as a *mixed random variable*.

The *cumulative distribution function* (*cdf*) of a random variable $\mathcal{X}$ is a function $F : \mathbb{R} \rightarrow [0, 1]$ which is given by

$$F(x) = \mathbb{P}(\omega \in \Omega : \mathcal{X}(\omega) \leq x), \quad (2.4)$$

for both discrete and continuous random variables. For simplicity of notation, this is usually denoted by

$$F(x) = \mathbb{P}(\mathcal{X} \leq x), \quad (2.5)$$

where it is understood that $\mathcal{X} \leq x$ means that the image of the function $\mathcal{X}$ takes a value which is less than or equal to $x$. Hence, from the three probability axioms listed above,

$$\lim_{x \to -\infty} F(x) = 0, \quad (2.6)$$

$$\lim_{x \to +\infty} F(x) = 1, \quad (2.7)$$

$$F(x) \leq F(y) \text{ for } x < y. \quad (2.8)$$

For a discrete random variable $\mathcal{X}$ on the state-space $\mathcal{S} = \{x_i : i = 0, 1, \ldots\}$, the *probability mass function* (*pmf*) $f : \mathbb{R} \rightarrow [0, 1]$ is given by

$$f(x_i) = \mathbb{P}(\mathcal{X} = x_i), \quad (2.9)$$

so that

$$F(x) = \sum_{x_i \leq x} f(x_i). \quad (2.10)$$

For a continuous random variable $\mathcal{X}$ the *probability density function* (*pdf*) is an
integrable function $f : \mathbb{R} \to [0, +\infty)$ which satisfies
\[ F(x) = \int_{-\infty}^{x} f(y) dy, \] (2.11)
so that
\[ \frac{dF(x)}{dx} = f(x). \] (2.12)

For a discrete random variable $X$ with pmf $f$ and state-space $S$, the expected value (or expectation) of the random variable is defined as
\[ \mathbb{E}(X) = \sum_{x \in S} xf(x), \] (2.13)
while for a continuous random variable $X$ on the state-space $S$ with pdf $f$, this becomes
\[ \mathbb{E}(X) = \int_{S} xf(x) dx. \] (2.14)

For either a discrete or continuous random variable $X$, the $k$th moment of $X$ is defined to be $\mathbb{E}(X^k)$ and the $k$th central moment is given by $\mathbb{E}[(X - \mathbb{E}(X))^k]$ for $k \in \mathbb{N}$. The second central moment of $X$ is known as the variance of $X$ and is thus given by
\[ \mathbb{V}(X) = \mathbb{E}[(X - \mathbb{E}(X))^2], \] (2.15)
which measures the amount by which $X$ deviates from its mean value $\mathbb{E}(X)$. The standard deviation is the positive square root of the variance, $\sqrt{\mathbb{V}(X)}$. A useful result for the calculation of the variance is
\[ \mathbb{V}(X) = \mathbb{E}(X^2) - [\mathbb{E}(X)]^2. \] (2.16)

The coefficient of variation of a random variable provides a dimensionless measure
of its dispersion and is defined by

\[ CV(\mathcal{X}) = \frac{\sqrt{\text{Var}(\mathcal{X})}}{\text{E}(\mathcal{X})}. \]  

(2.17)

For two random variables, \( \mathcal{X} \) and \( \mathcal{Y} \), the covariance of \( \mathcal{X} \) and \( \mathcal{Y} \) is defined by

\[ \text{Cov}(\mathcal{X}, \mathcal{Y}) = \text{E}[(\mathcal{X} - \text{E}(\mathcal{X}))(\mathcal{Y} - \text{E}(\mathcal{Y}))] = \text{E}(\mathcal{X}\mathcal{Y}) - \text{E}(\mathcal{X})\text{E}(\mathcal{Y}), \]  

(2.18)

and the correlation coefficient is given by

\[ \rho(\mathcal{X}, \mathcal{Y}) = \frac{\text{Cov}(\mathcal{X}, \mathcal{Y})}{\sqrt{\text{Var}(\mathcal{X})\text{Var}(\mathcal{Y})}}, \]  

(2.19)

for \( \forall(\mathcal{X}), \forall(\mathcal{Y}) \neq 0 \). For any pair of random variables, \( \mathcal{X} \) and \( \mathcal{Y} \), \( -1 \leq \rho(\mathcal{X}, \mathcal{Y}) \leq 1 \) by definition. The random variables \( \mathcal{X} \) and \( \mathcal{Y} \) are said to be uncorrelated if \( \rho(\mathcal{X}, \mathcal{Y}) = 0 \) which means that if \( \mathcal{X} \) and \( \mathcal{Y} \) are independent, they are uncorrelated because \( \text{Cov}(\mathcal{X}, \mathcal{Y}) = 0 \). However, the converse of this statement is not always true.

### 2.2 Stochastic processes

A stochastic process \( \{\mathcal{X}(t) : t \in T\} \) is a collection of random variables \( \mathcal{X} \) indexed by a set \( T \), the elements of which usually correspond to time values. The state-space \( S \) of the process is the range of all possible values that the random variables \( \mathcal{X}(t) \) can take. For the stochastic processes studied in this thesis, the values of the random variables will represent the number of \( T \) cells belonging to a particular clonotype and so the state-space will be discrete. Production of a new cell or death of an existing cell may occur at any time and so the set \( T \) will be continuous and consist of non-negative values.
2.2.1 Continuous-time Markov processes

The stochastic processes utilised in this thesis are known as continuous-time Markov processes. These are defined as stochastic processes \( \{X(t) : t \geq t_0\} \) on the state-space \( S = \{0, 1, \ldots, \} \) which satisfy the following property: for \( 0 \leq t_0 < t_1 < \ldots < t_j < t_{j+1} \) and \( n_0, n_1, \ldots, n_{j+1} \in S \)

\[
\mathbb{P}(X(t_{j+1}) = n_{j+1} | X(t_0) = n_0, X(t_1) = n_1, \ldots, X(t_j) = n_j) = \mathbb{P}(X(t_{j+1}) = n_{j+1} | X(t_j) = n_j),
\]

(2.20)

which is known as the Markov property. It says that, given the current state of the process, the probability of future behaviour is not influenced by any additional knowledge of the past history of the process. The transition probabilities are given by

\[
p_{n,m}(t_1, t_2) = \mathbb{P}(X(t_2) = m | X(t_1) = n)
\]

(2.21)

for \( t_1 < t_2 \) and \( n, m \in S \), i.e., \( p_{n,m}(t_1, t_2) \) is the probability that the process is in state \( m \) at time \( t_2 \) given that it was in state \( n \) at time \( t_1 \). Note that some texts, for example [2], use an alternative notation for the transition probabilities where \( p_{m,n}(t_2, t_1) \) is the probability that the process is in state \( m \) at time \( t_2 \) given that it was in state \( n \) at time \( t_1 \). If the transition probabilities do not depend on the times \( t_1 \) and \( t_2 \) but only on the time interval, \( t_2 - t_1 \), then the transition probabilities and the Markov process are said to be stationary. This will always be the case for the Markov processes introduced in this thesis. Then the notation becomes

\[
p_{n,m}(t_2 - t_1) = \mathbb{P}(X(t_2) = m | X(t_1) = n) = \mathbb{P}(X(t_2 - t_1) = m | X(0) = n).
\]

(2.22)
CHAPTER 2. MATHEMATICAL BACKGROUND

The transition probabilities satisfy the equations

\[ p_{n,m}(t+s) = \sum_{k=0}^{+\infty} p_{n,k}(t)p_{k,m}(s), \]

(2.23)

for all \( s, t \in [t_0, +\infty) \) and all \( n, m \in \mathcal{S} \), which are known as the Chapman-Kolmogorov equations. Also, for \( t \in [t_0, +\infty) \) it is clear that \( p_{n,m}(t) \geq 0 \) for \( n, m \in \mathcal{S} \), \( p_{n,m}(t) = 0 \) for \( n \notin \mathcal{S} \) or \( m \notin \mathcal{S} \) and \( \sum_{m \in \mathcal{S}} p_{n,m}(t) = 1 \) for \( n \in \mathcal{S} \).

State \( m \) is accessible from state \( n \) if there exists some \( t \geq t_0 \) such that \( p_{n,m}(t) > 0 \). If state \( m \) is accessible from state \( n \) and state \( n \) is also accessible from state \( m \) then states \( m \) and \( n \) are said to communicate. A communicating class of states is a set of states that communicate with each other. The process is said to be irreducible if the entire state-space forms a communicating class. If \( p_{n,n}(t) = 1 \) for all \( t \geq t_0 \) then \( n \) is said to be an absorbing state. This means that once the process reaches this state, it remains there forever.

2.2.2 The general birth and death process

For a general stationary continuous-time Markov process as defined above, the process begins in some initial state \( \mathcal{X}(t_0) \) where it remains for a random amount of time \( t_1 - t_0 \) until a transition to another state \( \mathcal{X}(t_1) \) occurs. The process then stays in this state for a random amount of time \( t_2 - t_1 \) and then moves to state \( \mathcal{X}(t_2) \) and so on. For the biological situation that is modelled in this thesis, it is assumed that in a very small interval of time the number of T cells belonging to a particular clonotype may either remain the same, increase by one corresponding to the production of a T cell (either by the thymus or from homeostatic proliferation), or decrease by one corresponding to the death of a T cell. Hence, transitions may only occur to adjacent states. The resulting continuous-time Markov process \( \{\mathcal{X}(t) : t \geq t_0\} \) on the state-space \( \mathcal{S} = \{0, 1, 2, \ldots\} \) is known as a birth and death process and has the
following transition probabilities as $\Delta t \to 0^+$:

$$p_{n,m}(\Delta t) = \mathbb{P}(\mathcal{X}(t + \Delta t) = m | \mathcal{X}(t) = n)$$

$$= \begin{cases} 
\lambda_n \Delta t + o(\Delta t) & m = n + 1, \\
\mu_n \Delta t + o(\Delta t) & m = n - 1, \\
1 - (\lambda_n + \mu_n)\Delta t + o(\Delta t) & m = n, \\
o(\Delta t) & \text{otherwise,}
\end{cases}$$

(2.24)

where $f(\Delta t) = o(\Delta t)$ as $\Delta t \to 0^+$ if $\lim_{\Delta t \to 0^+} \frac{f(\Delta t)}{\Delta t} = 0$. The birth rate, $\lambda_n$, is the rate of transition from state $n$ to $n + 1$ while the death rate, $\mu_n$, is the rate of transition from state $n$ to $n - 1$. The birth and death rates satisfy $\lambda_n \geq 0$, $\mu_n \geq 0$ for $n = 0, 1, 2, \ldots$ and $\mu_0 = 0$ so that transitions outside of the state-space cannot occur. The process can be represented as

$$0 \xrightarrow{\lambda_0} \frac{\lambda_1}{\mu_1} 1 \xrightarrow{\mu_2} \frac{\lambda_2}{\mu_2} 2 \cdots n - 1 \xrightarrow{\mu_n} \frac{\lambda_n}{\mu_n} n \xrightarrow{\mu_{n+1}} n + 1 \cdots .$$

The infinitesimal generator matrix of the process, $Q = (q_{i,j})$, is given by

$$Q = \begin{pmatrix} 
-\lambda_0 & \lambda_0 & 0 & 0 & \ldots \\
\mu_1 & -(\lambda_1 + \mu_1) & \lambda_1 & 0 & \ldots \\
0 & \mu_2 & -(\lambda_2 + \mu_2) & \lambda_2 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \ddots
\end{pmatrix},$$

(2.25)

and the entries of this matrix are known as the infinitesimal transition probabilities. The birth and death process $\mathcal{X}(t)$ is said to be conservative if

$$-q_{n,n} = \sum_{m \neq n} q_{n,m},$$

(2.26)
for all \( n \in S \), which means that the total of the entries in each row of \( Q \) is zero. This will always be the case for the processes introduced in this thesis.

### 2.2.3 Stationary and limiting probability distributions of the birth and death process

In the next chapter, the number of T cells belonging to a particular clonotype at time \( t \) is modelled by means of a continuous-time birth and death process \( \{X(t) : t \geq t_0\} \) on the state-space \( S = \{0, 1, 2, \ldots\} \). Let

\[
p_n(t) = \mathbb{P}(X(t) = n|X(t_0) = n_0), \tag{2.27}
\]

which is the probability that the birth and death process is in state \( n \) at time \( t \), given that the initial state of the process is \( n_0 \). Then, from the Chapman-Kolmogorov equations (2.23), this can be written as

\[
p_n(t + \Delta t) = \sum_{k=0}^{\infty} p_{k,n}(\Delta t)p_k(t). \tag{2.28}
\]

Using the transition probabilities for the general birth and death process given by Eq. (2.24) this becomes

\[
p_n(t + \Delta t) = \lambda_{n-1}\Delta tp_{n-1}(t) + \mu_{n+1}\Delta tp_{n+1}(t) + [1 - (\lambda_n + \mu_n)\Delta t]p_n(t) + o(\Delta t) \quad \text{for } n \geq 1, \tag{2.29}
\]

and so

\[
\frac{p_n(t + \Delta t) - p_n(t)}{\Delta t} = \lambda_{n-1}p_{n-1}(t) + \mu_{n+1}p_{n+1}(t) - (\lambda_n + \mu_n)p_n(t) + \frac{o(\Delta t)}{\Delta t}. \tag{2.30}
\]
Taking the limit as $\Delta t \to 0^+$ gives a set of differential equations known as the forward Kolmogorov equations:

$$\frac{dp_n(t)}{dt} = \lambda_{n-1}p_{n-1}(t) + \mu_{n+1}p_{n+1}(t) - (\lambda_n + \mu_n)p_n(t) \quad \text{for } n \geq 1.$$  (2.31)

For the endpoint, $n = 0$, the forward Kolmogorov equation is

$$\frac{dp_0(t)}{dt} = \mu_1p_1(t) - \lambda_0p_0(t).$$  (2.32)

These equations can be written in matrix form as $\mathbf{P}'(t) = \mathbf{Q}^T \mathbf{P}$, where $\mathbf{Q}^T$ denotes the transpose of the matrix $\mathbf{Q}$ and $\mathbf{P}^T = (p_0(t), p_1(t), \ldots)$.

A probability distribution which does not change with time is called a stationary probability distribution. Such a distribution will be denoted by $\bar{p}$ where $\bar{p}_n \geq 0$ for $n \in S$, $\bar{p}_n = 0$ for $n \notin S$ and $\sum_{n=0}^{+\infty} \bar{p}_n = 1$. This distribution satisfies the equations

$$0 = \lambda_{n-1}\bar{p}_{n-1} + \mu_{n+1}\bar{p}_{n+1} - (\lambda_n + \mu_n)\bar{p}_n \quad \text{for } n \geq 1,$$  (2.33)

and

$$0 = \mu_1\bar{p}_1 - \lambda_0\bar{p}_0,$$  (2.34)

which are the forward Kolmogorov equations with the time derivatives set to be equal to zero. Whether or not a unique stationary probability distribution exists can be determined from the form of the birth and death rates [2]. For a birth and death process $\{X(t) : t \geq t_0\}$ on the state-space $S = \{0, 1, 2, \ldots\}$ with transition probabilities given by Eq. (2.24), a unique positive stationary probability distribution exists if and only if

$$\lambda_n > 0 \quad \text{for } n = 0, 1, \ldots \quad \text{and} \quad \mu_n > 0 \quad \text{for } n = 1, 2, \ldots$$  (2.35)
and
\[ \sum_{n=1}^{+\infty} \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} < +\infty . \]  
(2.36)

If these conditions are satisfied, the stationary probability distribution is given by [2]
\[ \tilde{p}_0 = \frac{1}{1 + \sum_{n=1}^{+\infty} \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} } , \]  
(2.37)
\[ \tilde{p}_n = \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} \tilde{p}_0 \text{ for } n = 1, 2, \ldots . \]  
(2.38)

While individual realisations of the process will continue to make transitions between adjacent states (unless an absorbing state is reached), after a period of time it may be expected that the probability distribution of the process being in a particular state, \( p_n(t) \), will settle down to a stationary probability distribution. This is called the limiting probability distribution of the process and is denoted by \( p \) where
\[ p_n = \lim_{t \to +\infty} p_n(t) \text{ for all } n \in S . \]  
(2.39)

Such a limiting probability distribution exists if and only if [74]
\[ \sum_{n=1}^{+\infty} \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} < +\infty \text{ and } \frac{1}{\lambda_0} + \sum_{n=1}^{+\infty} \frac{\mu_1 \mu_2 \ldots \mu_n}{\lambda_0 \lambda_1 \ldots \lambda_n} = +\infty . \]  
(2.40)

If these conditions are satisfied, the process is said to be ergodic and the limiting probability distribution is given by the unique stationary probability distribution defined by Eqs. (2.37)–(2.38) [74]. The speed of convergence to the limiting probability distribution is characterised by the decay parameter of the process, \( \alpha \), which is defined by [132]
\[ \alpha = \sup\{ a \geq 0 | p_{m,n}(t) - p_n = O(e^{-at}) \text{ as } t \to +\infty \text{ for all } m, n \in S \} , \]  
(2.41)
and the relaxation time is given by $\frac{1}{\alpha}$.

### 2.2.4 Finite-state birth and death processes

If the state-space of the process is finite i.e., $S = \{0, 1, \ldots, N\}$ with $\mu_0 = \lambda_N = 0$ so that transitions outside of the state-space cannot occur, the forward Kolmogorov equations become

$$
\frac{dp_0(t)}{dt} = \mu_1 p_1(t) - \lambda_0 p_0(t),
$$

(2.42)

$$
\frac{dp_n(t)}{dt} = \lambda_{n-1} p_{n-1}(t) + \mu_{n+1} p_{n+1}(t) - (\lambda_n + \mu_n) p_n(t) \quad 1 \leq n \leq N - 1,
$$

(2.43)

$$
\frac{dp_N(t)}{dt} = \lambda_{N-1} p_{N-1}(t) - \mu_N p_N(t).
$$

(2.44)

As in the infinite state-space case, these equations can be written in matrix form as

$$
P'(t) = Q^T P
$$

where the infinitesimal generator matrix is

$$
Q =
\begin{pmatrix}
-\lambda_0 & \lambda_0 & 0 & \ldots & 0 & 0 \\
\mu_1 & -(\lambda_1 + \mu_1) & \lambda_1 & \ldots & 0 & 0 \\
0 & \mu_2 & -(\lambda_2 + \mu_2) & \ldots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & \ldots & -(\lambda_{N-1} + \mu_{N-1}) & \lambda_{N-1} \\
0 & 0 & 0 & \ldots & \mu_N & -\mu_N
\end{pmatrix}.
$$

(2.45)

Conditions (2.36) and (2.40) are automatically satisfied for a birth and death process with finite state-space and hence, if condition (2.35) holds, the unique positive stationary probability distribution is equal to the limiting probability distribution of the process which is given by Eqs. (2.37)–(2.38), where the upper limit of summation in Eq. (2.37) is changed from $+\infty$ to $N$. 
The matrix $Q$, and hence also the matrix $Q^T$, has an eigenvalue of zero because

$$Q(1, 1, \ldots, 1)^T = 0(1, 1, \ldots, 1)^T.$$ (2.46)

All other eigenvalues are real, distinct and negative [25, 73] and are denoted by $-\omega_1, -\omega_2, \ldots, -\omega_N$. Thus, there are $N + 1$ linearly independent eigenvectors [73], which are denoted by $v_0, v_1, \ldots, v_N$. Then the solution of the forward Kolmogorov equations $P'(t) = Q^T P$ is given by

$$P = v_0 + v_1 e^{-\omega_1 t} + v_2 e^{-\omega_2 t} + \ldots + v_N e^{-\omega_N t},$$ (2.47)

and so $P \to v_0$ as $t \to +\infty$. Therefore, the unique limiting probability distribution of the process is given by $v_0$, which is the eigenvector corresponding to the zero eigenvalue of the matrix $Q^T$.

### 2.2.5 Sojourn times and the Gillespie algorithm

The *sojourn time* for state $n$ is the time until the process leaves state $n$, given that this is the current state of the process. For a birth and death process, this time follows an exponential distribution with mean $(\lambda_n + \mu_n)^{-1}$ [126]. Thus, if the process is in state $n$ at the current time, it remains there for a random length of time which has an exponential distribution with mean $(\lambda_n + \mu_n)^{-1}$ and then moves to either state $n + 1$ with probability $\frac{\lambda_n}{\lambda_n + \mu_n}$ or state $n - 1$ with probability $\frac{\mu_n}{\lambda_n + \mu_n}$. This characterisation leads to a simple method of simulating an individual realisation of the process which was first described by Daniel Gillespie and is now known as the *Gillespie algorithm* [59, 60]. The procedure is as follows:

1. The initial condition of the process is specified.
2. The time at which the next transition occurs is obtained by generating a random number, $T_n$, from an exponential distribution with mean $(\lambda_n + \mu_n)^{-1}$, where $n$ is the current state of the process.

3. The transition probabilities $\frac{\lambda_n}{\lambda_n + \mu_n}$ and $\frac{\mu_n}{\lambda_n + \mu_n}$ are calculated. A random number is generated from a uniform distribution in the interval $[0,1]$, which is used to determine whether a birth or a death occurs according to the probabilities above. If the random number belongs to the interval $[0, \lambda_n/(\lambda_n + \mu_n)]$ a birth occurs and so the state of the process $n$ is updated to $n + 1$, while if the random number belongs to the interval $(\lambda_n/(\lambda_n + \mu_n), 1]$ a death occurs and $n$ is updated to $n - 1$.

4. The time of the simulation is updated to $t = t + T_n$.

5. Steps 2 – 4 are repeated until an absorbing state is reached, or the time of the simulation exceeds a predetermined maximum value.

Although some computer programming languages e.g., python, have standard inbuilt functions for generating pseudo-random numbers from various distributions, including the exponential distribution, others such as C only generate pseudo-random numbers according to a uniform distribution on the interval $[0,1]$. Therefore, to carry out step 2, it is necessary to transform this uniform random variable, $U$, into an exponentially distributed random variable $T_n$ with mean $(\lambda_n + \mu_n)^{-1}$ according to the formula

$$T_n = -\frac{\log(U)}{\lambda_n + \mu_n},$$

(2.48)

using Theorem 5.5 of [2].

The Gillespie algorithm has become more widely used with the increasing speed of modern computers, as it is possible to quickly obtain several thousand individual realisations of a process and average over them all to estimate quantities of interest.
e.g., the mean time until an absorbing state is reached.

2.2.6 Birth and death processes with an absorbing state at $n = 0$

This chapter is concluded with some definitions for birth and death processes with an absorbing state, as such processes will be extensively utilised in later chapters. If $\lambda_0 = \mu_0 = 0$, then $n = 0$ is an absorbing state, meaning that once the process reaches this state, it remains there forever. Condition (2.35) is not satisfied, so the process does not have a positive stationary probability distribution. Instead, the stationary probability distribution of the process has all its mass at the absorbing state $n = 0$, i.e., $\bar{p} = (1, 0, 0, \ldots)^T$.

Define

$$\pi_1 = 1 \text{ and } \pi_n = \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_2 \mu_3 \cdots \mu_n} \text{ for } n \geq 2,$$

(2.49)
called the potential coefficients. The transition probabilities of the process $p_{n,m}(t)$ can be represented by

$$p_{n,m}(t) = \pi_m \int_0^{+\infty} e^{-xt} Q_n(x) Q_m(x) d\psi(x) \text{ for } m, n \in S \setminus \{0\}. \quad (2.50)$$

The polynomials $Q_n(x)$ are defined by

$$Q_1(x) = 1,$$

$$-xQ_1(x) = - (\lambda_1 + \mu_1)Q_1(x) + \lambda_1 Q_2(x),$$

$$-xQ_n(x) = \mu_n Q_{n-1}(x) - (\lambda_n + \mu_n)Q_n(x) + \lambda_n Q_{n+1}(x) \text{ for } n > 1,$$

(2.51)

where $\psi$ is a positive measure of total mass one on the interval $[0, +\infty)$. The polynomials $Q_n(x)$ are orthogonal with respect to this measure. This definition of
the transition probabilities is called the \textit{Karlin-McGregor representation} \cite{75} and can be used to classify different types of birth and death processes \cite{74}. However, it will not be used extensively in this thesis (it is required only in Section 4.1.1).

The infinitesimal generator matrix of the process is said to be \textit{regular} if

\begin{equation}
\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \sum_{j=1}^{n} \pi_j = +\infty ,
\end{equation}

which means that the infinitesimal generator matrix $Q$ uniquely specifies the process.

Let

$$\rho_0 = 1 \quad \text{and} \quad \rho_n = \frac{\mu_1 \mu_2 \cdots \mu_n}{\lambda_1 \lambda_2 \cdots \lambda_n} \quad \text{for} \quad n \geq 1 .$$

The absorbing state is reached with certainty from any initial state $n \in S$ if the series

$$\sum_{n=1}^{+\infty} \rho_n$$

diverges \cite{74, 126}. On the other hand, if series (2.54) converges the probability of reaching the absorbing state at $n = 0$ when the initial state of the process is $n_0$ is \cite{126}

$$\lim_{t \to +\infty} p_0(t) = \frac{\sum_{n=n_0}^{+\infty} \rho_n}{1 + \sum_{n=1}^{+\infty} \rho_n} .$$

The mean time to reach the absorbing state from the initial state $n_0$ is denoted by $\tau_{n_0}$. If the series

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n}$$

diverges, $\tau_{n_0}$ is infinite \cite{126}. However, if (2.56) converges, $\tau_{n_0}$ is finite for all initial states $n_0 \in S/\{0\}$ and \cite{126}

$$\tau_{n_0} = \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n} + \sum_{k=1}^{n_0-1} \rho_k \sum_{j=k+1}^{+\infty} \frac{1}{\lambda_j \rho_j} .$$
Chapter 3

A stochastic model of T cell repertoire maintenance

In this chapter, the number of naïve T cells belonging to a particular clonotype will be modelled as a continuous-time birth and death process where the birth rate is based on competition for survival signals from self-peptides presented on the surface of APCs. It will be shown that the stochastic disappearance of existing clones from the repertoire is crucial in maximising the diversity of the system. Also, the number of T cells belonging to a given clonotype may be small, in which case stochastic fluctuations are important. Hence, a deterministic analysis is inadequate. A stochastic model also allows the calculation of both the probability of a given clonotype eventually becoming extinct and the mean time it takes for this to happen which, as described in Chapter 1, may have an impact on the functionality of the immune response. It is proved that the ultimate fate of any given clonotype is extinction and the mean extinction times are computed. The limiting conditional probability distribution of the process is introduced to represent homeostatic levels of T cells before extinction occurs and the coefficient of variation of this probability distribution is used to provide a measure of the diversity of the naïve T cell repertoire.
3.1 A birth and death process modelling the number of T cells belonging to a given clonotype

It is assumed that the thymus produces T cells of clonotype $i$ within a very short space of time. The time at which this “burst” of production occurs is denoted by $\tilde{t}_i$ and is the time at which T cells of clonotype $i$ first appear in the peripheral repertoire. Furthermore, it is assumed that, although the thymus may produce T cells of other specificities, no further T cells of clonotype $i$ are produced after this time. This is reasonable if it is assumed that all possible TCR gene rearrangements are equally likely, because then it is improbable that the process of random genetic recombination will result in exactly the same rearrangement twice, due to the large number of possibilities (the total number of possible TCRs that may be generated is estimated to be around $10^{15}$ [35]). However, if this distribution is not uniform and some clonotypes are produced more frequently than others, the model that will be introduced here may be modified to include continuous thymic production of T cells of clonotype $i$ at rate $\phi_i$ [121]. Since T cells are continuously recirculating through the blood and lymphatic system [10, 112], none of the models presented in this thesis will include spatial effects.

The number of naïve T cells belonging to clonotype $i$ at time $t$, which is denoted by $n_i(t)$, is modelled as a stationary birth and death process $\{X(t) : t \geq \tilde{t}_i\}$ on the state-space $S = \{0, 1, 2, \ldots\}$ and so the number of T cells of clonotype $i$ produced by the thymus at $\tilde{t}_i$ gives the initial state of the process, which is denoted by $n_i(\tilde{t}_i) = \tilde{n}_i$. The birth and death rates take the form of those in Eq. (2.24) and the infinitesimal generator matrix of the process is given by Eq. (2.25). The model includes T cell death and also proliferation which occurs when a T cell receives the appropriate survival signal from an APC causing it to undergo a single round of cell division, as described in Section 1.3.1. In the next section, expressions for the birth and death
3.1.1 Derivation of the birth and death rates

The derivation of the birth and death rates of the process is the work of Carmen Molina-París and Hugo van den Berg [122] and is now described. A single APC may present around $10^3$ distinct peptides at a given instant, each occurring in differing quantities with a mean of around 100 copies per peptide [87], and the particular peptides displayed will change continuously over time. The array of peptides presented at a single point in time is referred to as an antigen presentation profile (APP) [128, 129]. Usually the APP will be comprised solely of self-peptides (peptides derived from the body’s own proteins) but in the case of infection, foreign peptides are also displayed. Hence, the stimulatory environment of a T cell consists of a set of APPs rather than APCs.

Whether or not a T cell of clonotype $i$ is able to receive a survival signal from a given APP depends on the specificity of the TCR which is expressed on its surface. This means that T cells compete for signals from APPs not only with other T cells of the same clonotype, but also with T cells belonging to different clonotypes. It is assumed that the survival signals from any particular APP are shared equally among all the T cells that are capable of receiving them. Let $\gamma_q$ be the rate of survival signals emanating from all APCs that present APP $q$. This will be a different set of APCs at different moments; however the associated fluctuations will be ignored and so it is assumed that the collective stimulus remains constant over time [130].

Let $C$ be the set of all T cells in the naïve repertoire. The subset $C_q$ is defined to be the set of all T cells that are capable of receiving a survival signal from APP $q$, and so $n_q = |C_q|$ is the total number of T cells that the survival signals from APP $q$ are shared between. Also, $Q$ is the set of all APPs which may occur in the periphery.
and $Q_i$ is the subset of APPs from which T cells of clonotype $i$ can receive a survival signal. Fig. 3.1 shows a schematic representation of these sets.

Let $\lambda^{(i)}$ be the per cell birth rate for T cells of clonotype $i$, which is proportional to the survival signal received. Then

$$\lambda^{(i)} = \sum_{q \in Q_i} \frac{\gamma}{n_q},$$

(3.1)

where, for the sake of simplicity, it is assumed that $\gamma$ is independent of $q$. The number of T cells receiving a survival signal from an APP $q \in Q_i$ can be divided into T cells which belong to clonotype $i$ and T cells belonging to other clonotypes. Thus,

$$\lambda^{(i)} = \sum_{q \in Q_i} \frac{\gamma}{n_i + n_{iq}},$$

(3.2)

where $n_{iq} = n_q - n_i$. Next, the set $Q_i$ is divided into disjoint subsets. Let $Q_{ir}$ be the set of APPs which provide survival signals to T cells of clonotype $i$ and to $r$ other distinct clonotypes in the repertoire. Then $Q_{ir} \cap Q_{ir'} = \emptyset$ for $r \neq r'$ and
∪_{r=0}^{+∞} Q_{ir} = Q_{i}$. Hence,
\[
\lambda^{(i)} = \gamma \sum_{q \in Q_{i}} \sum_{r=0}^{+∞} \frac{1}{n_{i} + n_{iq}}.
\] (3.3)

In principle, $\lambda^{(i)}$ depends not only on the number of T cells of clonotype $i$ but also on the numbers of T cells belonging to all other clonotypes which compete with clonotype $i$ for access to an APP $q \in Q_{i}$, through the term $n_{iq}$. This means that the birth rates for different clonotypes are coupled. Consequently, the Markov property defined in Eq. (2.20) is satisfied only by the family of random variables which take their values in the full state-space $\hat{N}_{NC}$, where $\hat{N}_{C}$ is the total number of possible clonotypes that may be generated by the thymus. In order to recover a birth and death process for a single clonotype, $i$, mean field approximations concerning competition between this clonotype and others are used. The expectation and variance of $n_{iq}$ over the set of APPs $Q_{ir}$ needed to derive this approximation are defined by
\[
E_{ir}[n_{iq}] = \frac{1}{|Q_{ir}|} \sum_{q \in Q_{ir}} n_{iq},
\] (3.4)
and
\[
V_{ir}[n_{iq}] = \frac{1}{|Q_{ir}|} \sum_{q \in Q_{ir}} (n_{iq} - E_{ir}[n_{iq}])^2,
\] (3.5)
respectively. Then, carrying out a Taylor expansion about $E_{ir}[n_{iq}]$ [8] results in
\[
\sum_{q \in Q_{ir}} \frac{1}{n_{i} + n_{iq}} = |Q_{ir}| \left( \frac{1}{n_{i} + E_{ir}[n_{iq}]} \right)
= |Q_{ir}| \left( \frac{1}{n_{i} + E_{ir}[n_{iq}]} + \frac{V_{ir}[n_{iq}]}{(n_{i} + E_{ir}[n_{iq}])^3} + \ldots \right)
\approx \frac{|Q_{ir}|}{n_{i} + E_{ir}[n_{iq}]}.
\] (3.6)

The mean field approximation consists of two assumptions. The first is that the second and subsequent terms in the Taylor expansion in Eq. (3.6) are small and can
be neglected. Next, note that for a given APP \( q \in \mathcal{Q}_{ir} \) there are precisely \( r \) distinct clonotypes competing with T cells of clonotype \( i \) for access to APP \( q \). The second approximation is that the average number of T cells belonging to a clonotype across the \( r \) competing clonotypes is the same as the average number of T cells belonging to a clonotype across the whole repertoire, which is denoted by \( \langle n \rangle \). This means that

\[
\mathbb{E}_{ir}[n_{iq}] = r \langle n \rangle .
\] (3.7)

The total number of T cell clonotypes in the repertoire is denoted by \( N_C \), so that

\[
\langle n \rangle = \frac{1}{N_C} \sum_{i=1}^{N_C} n_i .
\] (3.8)

Then

\[
\lambda^{(i)} \approx \gamma \sum_{r=0}^{+\infty} \frac{|\mathcal{Q}_{ir}|}{n_i + r \langle n \rangle} ,
\] (3.9)

where competition between T cells of clonotype \( i \) and T cells of other clonotypes in the repertoire is included in the term \( r \langle n \rangle \). This approximation means that it is possible to treat the number of T cells belonging to clonotype \( i \) as an independent univariate birth and death process. The validity of the mean field approximation will be discussed in Section 3.3.

The final stage in the specification of the birth rate is to derive an expression for \( |\mathcal{Q}_{ir}| \) for fixed \( i \) and \( r \). Let \( p_i \) be the probability that an APP chosen at random from the set of all APPs, \( \mathcal{Q} \), provides a survival signal to T cells of clonotype \( i \), \text{i.e.}, \( p_i = \mathbb{P}(q \in \mathcal{Q}_i) \) so that \( |\mathcal{Q}_i| = p_i |\mathcal{Q}| \). Now define \( p_{ij} \) to be the probability that an APP chosen at random from the set \( \mathcal{Q}_i \) is able to provide a survival signal to T cells of another clonotype, \( i' \), chosen at random from the repertoire. Then the number of clonotypes competing with T cells of clonotype \( i \) can be computed using
CHAPTER 3. STOCHASTIC MODEL OF REPERTOIRE MAINTENANCE

the binomial distribution as follows:

\[ |Q_{ir}| = |Q_i| \binom{N_C - 1}{r} (p_{ji})^r (1 - p_{ji})^{N_C - 1 - r} \]

\[ = p_i |Q| \binom{N_C - 1}{r} (p_{ji})^r (1 - p_{ji})^{N_C - 1 - r} . \quad (3.10) \]

Since \( N_C \gg 1 \) and \( p_{ji} \ll 1 \) [87], the Poisson approximation to the binomial distribution may be applied. Thus, the mean niche overlap for T cells of clonotype \( i \) is defined as \( \nu_i = p_{ji} (N_C - 1) \simeq p_{ji} N_C \) and then

\[ |Q_{ir}| = p_i |Q| e^{-\nu_i} \frac{\nu_i^r}{r!} . \quad (3.11) \]

Substituting Eq. (3.11) into Eq. (3.9) results in

\[ \lambda^{(i)} = \gamma p_i |Q| e^{-\nu_i} \sum_{r=0}^{+\infty} \frac{\nu_i^r}{r!} \frac{1}{\langle n \rangle + r n_i} \]

\[ = \varphi_i e^{-\nu_i} \sum_{r=0}^{+\infty} \frac{\nu_i^r}{r!} \frac{1}{n_i + r \langle n \rangle} , \quad (3.12) \]

where \( \varphi_i = \gamma p_i |Q| \). The per cell death rate for a given clonotype is assumed to be constant and for T cells of clonotype \( i \) is denoted by \( \mu^{(i)} \). Thus, the birth and death rates for the process, as defined in Eq. (2.24), are given by \( \lambda_n = \lambda^{(i)} n_i \) and \( \mu_n = \mu^{(i)} n_i \), respectively.

3.1.2 Summary of the model

The number of T cells belonging to a fixed clonotype \( i \) is modelled as a continuous-time birth and death process \( \{X(t) : t \geq \tilde{t}_i \} \) on the state-space \( S = \{0, 1, 2, \ldots \} \).
with the birth and death rates

\[ \lambda_0 = 0 , \]  

\[ \lambda_n = \varphi n e^{-\nu} \sum_{r=0}^{\infty} \frac{\nu^r}{r! n + r \langle n \rangle} , \quad n \geq 1 , \]  

\[ \mu_n = \mu n , \quad n \geq 0 , \]

where the sub/superscript \( i \) has been dropped for notational convenience. The model has four parameters:

(i) \( \varphi \) is a parameter proportional to the number of APPs which can provide survival signals to T cells of the fixed clonotype \( i \). Then \( \varphi^{-1} \) is proportional to the mean time until a T cell of this clonotype receives a survival signal from an APP in the absence of competition with T cells of other clonotypes.

(ii) \( \nu \) is the “mean niche overlap” and encodes competition for survival signals between T cells of the fixed clonotype, \( i \), and T cells of other clonotypes. It is the mean number of clonotypes that compete with T cells of clonotype \( i \) for survival signals from an APP, where the average is taken over all the APPs belonging to the set \( Q_i \).

(iii) \( \langle n \rangle \) is the average clonotype size over the naïve T cell repertoire.

(iv) \( \mu \) is the death rate per T cell of clonotype \( i \).

Note that \( \mu_0 = 0 \) and so transitions outside of the state-space are not possible. Also \( \lambda_0 = 0 \), which implies that \( n = 0 \) is an absorbing state, meaning that once the process reaches this state it remains there forever. Physically this corresponds to extinction of clonotype \( i \) from the repertoire. By definition, \( \varphi, \nu, \langle n \rangle, \mu > 0 \), and so, except for \( \lambda_0 = \mu_0 = 0 \), all other birth and death rates are strictly positive which means that the set of states \( S \setminus \{0\} \) forms a transient communicating class.
The parameters $\varphi$, $\nu$ and $\mu$ are clonotype specific, while the parameter $\langle n \rangle$ denotes a property of the repertoire as a whole. The parameter $\mu$ is a timescale which can be used to non-dimensionalise the model. The birth and death process is represented by the following diagram, where arrows indicate possible transitions between states:

$$
\begin{array}{cccccccc}
0 & \leftarrow & 1 & \overset{\lambda_1}{\underset{\mu_1}{\Rightarrow}} & 2 & \cdot & \cdot & \cdot & n - 1 & \overset{\lambda_{n-1}}{\underset{\mu_n}{\Rightarrow}} & n & \overset{\lambda_n}{\underset{\mu_{n+1}}{\Rightarrow}} & n + 1 & \cdot & \cdot
\end{array}
$$

### 3.1.3 Two special cases

In the following analysis of the model, two special cases will be referred to and these are now defined. In ecological terms, a clonotype with $\nu \ll 1$ occupies a “hard niche” in the repertoire, while clonotypes with $\nu \gg 1$ occupy a very “soft niche”. Biologically, a T cell with $\nu \ll 1$ possesses a TCR that is very different from other TCRs in the repertoire in terms of the APPs that it is able to receive survival signals from, whereas a T cell with $\nu \gg 1$ has a TCR that is very similar to the TCRs of many other clonotypes. In these two cases, the form of the birth rate may be simplified considerably. For $\nu \ll 1$ the first term in the sum in Eq. (3.14) dominates and so the birth and death rates for this case are given by

$$
\begin{align*}
\lambda_0 &= 0 \, , \\
\lambda_n &= \varphi \, , \quad n \geq 1 \, , \\
\mu_n &= \mu n \, , \quad n \geq 0 .
\end{align*}
$$

To find an expression for the birth rate in the case $\nu \gg 1$, Eq. (3.14) is written as

$$
\lambda_n = \varphi n \sum_{r=0}^{+\infty} \frac{e^{-\nu} \nu^r}{r!} \frac{1}{n+r\langle n \rangle} = \varphi n \mathbb{E}_Y \left[ \frac{1}{n+\mathbb{Y}\langle n \rangle} \right] ,
$$

where $\mathbb{Y}$ is a random variable having a Poisson distribution with mean $\nu$. Carrying
out a Taylor expansion of Eq. (3.19) about the point $Y = \nu$ results in

$$\lambda_n = \varphi_n \left( \frac{1}{n + \nu \langle n \rangle} + \frac{(\langle n \rangle)^2 \nu}{(n + \nu \langle n \rangle)^3} + \ldots \right).$$

(3.20)

Thus, in the limit $\nu \gg 1$, the approximation is

$$\lambda_n = \frac{\varphi n}{n + \nu \langle n \rangle},$$

(3.21)

$$\mu_n = \mu n,$$  

(3.22)

when only the first term in the expansion (3.20) is retained. The approximation may be taken to higher orders, but these terms are negligible for $\nu \gg 1$.

The most general form of the birth rate, given by Eq. (3.14), is bounded from above as follows:

$$\lambda_n = \varphi n e^{-\nu} \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{n + r \langle n \rangle}$$

$$\leq \varphi n e^{-\nu} \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{n}$$

$$= \varphi e^{-\nu} e^\nu$$

$$= \varphi,$$  

(3.23)

so that the birth rate in the “hard niche” case provides an upper bound on the birth rate in all other cases. This is biologically realistic since resources are limited and so the birth rate cannot grow without bound.
3.2 Analysis and results

Four individual realisations of the process, produced using a Gillespie algorithm for different values of the parameters are shown in Fig. 3.2. In each realisation, the absorbing state at \( n = 0 \) is reached eventually, and the time taken to reach the absorbing state seems to increase as \( \nu \) decreases. Other simulations (not shown) show that for \( \nu \ll 1 \), although the process reaches \( n = 0 \) eventually, this takes a long time to occur and prior to extinction the process appears to wander stochastically around an equilibrium value (see Section 3.2.3). In this section, it is proved that extinction of any given clonotype occurs with probability one for all values of the parameters and mean extinction times are computed. The behaviour of the process before extinction occurs is analysed by means of the limiting conditional probability distribution, the parameters of which are then used to provide an estimate of the diversity of the naïve T cell repertoire.

3.2.1 The ultimate fate of all clonotypes is extinction

In this section it is proved that the probability of absorption at state \( n = 0 \) occurring is one for all values of the parameters \( \varphi, \nu, \langle n \rangle \) and \( \mu \). From Chapter 2, absorption at the origin is guaranteed from any initial state \( \tilde{n} \in S \) if the series

\[
\sum_{n=1}^{+\infty} \rho_n \quad (3.24)
\]

diverges [74, 126], where \( \rho_n \) is defined by Eq. (2.53). For the birth and death rates given by Eqs. (3.14)–(3.15)

\[
\sum_{n=1}^{+\infty} \rho_n \geq \sum_{n=1}^{+\infty} \frac{\mu^n n!}{\varphi^n}, \quad (3.25)
\]
using the bound stated in Eq. (3.23). Let

\[ b_n = \frac{\mu^n n!}{\varphi^n}. \]  

(3.26)

Then

\[ \frac{b_{n+1}}{b_n} = \frac{\mu(n + 1)}{\varphi} \to +\infty \text{ as } n \to +\infty, \]

(3.27)

and so \( \sum_{n=1}^{+\infty} b_n \) diverges by the ratio test. Hence, \( \sum_{n=1}^{+\infty} \rho_n \) also diverges by comparison and thus absorption at the state \( n = 0 \) is guaranteed for all values of the parameters. This means that the eventual fate of any clonotype is extinction and disappearance from the repertoire. Therefore, it is of importance to determine which clonotypes persist in the repertoire for the longest times and which become extinct.
more quickly. This question is addressed in the next section.

### 3.2.2 Mean extinction times

In Chapter 2 it was stated that the mean time until the absorbing state is reached from an initial state $\tilde{n} \in S \setminus \{0\}$ is finite if

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n}$$

converges. For the birth and death rates given by Eqs. (3.14)–(3.15)

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n} = \sum_{n=1}^{+\infty} \frac{\lambda_1 \lambda_2 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} \leq \sum_{n=1}^{+\infty} \frac{\varphi^{n-1}}{\mu^n n!}.$$  

Let

$$\beta_n = \frac{\varphi^{n-1}}{\mu^n n!}.$$  

Then

$$\frac{\beta_{n+1}}{\beta_n} = \frac{\varphi}{\mu(n+1)} \to 0 \text{ as } n \to +\infty,$$

and so $\sum_{n=1}^{+\infty} \beta_n$ converges by the ratio test. Hence, $\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n}$ converges by comparison and so mean extinction times from any initial state $\tilde{n} \in S \setminus \{0\}$ are finite. This time is denoted by $\tau_{\tilde{n}}$ and can be determined directly from the birth and death rates of the process [126] by

$$\tau_{\tilde{n}} = \begin{cases} \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n} & \tilde{n} = 1 \\ \tau_1 + \sum_{k=1}^{\tilde{n}-1} \rho_k \sum_{j=k+1}^{+\infty} \frac{1}{\lambda_j \rho_j} & \tilde{n} \geq 2. \end{cases}$$

Clearly, $\tau_1 < \tau_2 < \ldots < \tau_{\tilde{n}} < \tau_{\tilde{n}+1} < \ldots$. Alternatively, mean extinction times can be computed by simulating the process a large number of times using the Gillespie algorithm introduced in Chapter 2. For each individual realisation, the time at which
extinction occurs is recorded and the mean extinction time over a large number of realisations is calculated. The results agree closely with those given by Eq. (3.32). However, for $\nu \ll 1$ the mean time until extinction occurs is very large for some parameter values (see Figs. 3.3–3.4), which means that each simulation takes a long time to run and so this method of calculation becomes inefficient. For the birth and death rates of the process studied here, the mean extinction times are bounded as follows:

$$
\tau_1 = \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \rho_n}
\leq \sum_{n=1}^{+\infty} \frac{\lambda_1 \lambda_2 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n}
\leq \sum_{n=1}^{+\infty} \frac{\varphi^{n-1}}{\mu^n n!}
= \frac{1}{\varphi} \left( e^{\frac{\varphi}{\mu}} - 1 \right), \tag{3.33}
$$

and

$$
\tau_{\tilde{n}} = \tau_1 + \sum_{k=1}^{\tilde{n}-1} \sum_{j=k+1}^{+\infty} \rho_k \sum_{j=k+1}^{+\infty} \frac{1}{\lambda_j \rho_j}
\leq \tau_1 + \sum_{k=1}^{\tilde{n}-1} \frac{\mu_1 \mu_2 \ldots \mu_k}{\lambda_1 \lambda_2 \ldots \lambda_k} \sum_{j=k+1}^{+\infty} \frac{\lambda_1 \lambda_2 \ldots \lambda_{j-1}}{\mu_1 \mu_2 \ldots \mu_j}
\leq \tau_1 + \sum_{k=1}^{\tilde{n}-1} \frac{k!}{\varphi j!} \left( \frac{\varphi}{\mu} \right)^{j-k}
\leq \tau_1 + \sum_{k=1}^{\tilde{n}-1} \frac{k!}{\mu} \left( \frac{\mu}{\varphi} \right)^{k+1}
\left[ e^{\frac{\varphi}{\mu}} - \sum_{j=0}^{k} \left( \frac{\varphi}{\mu} \right)^j \frac{1}{j!} \right]
\text{for } \tilde{n} \geq 2. \tag{3.34}
$$
These two bounds become equalities in the case $\nu \ll 1$ and so the hard niche case is associated with the longest mean extinction times. Therefore, clonotypes with $\nu \ll 1$ will tend to persist in the repertoire. This is illustrated in Figs. 3.3–3.4.

![Figure 3.3](image1.png)

Figure 3.3: $\tau_1$ as a function of $\nu$ with $\varphi = 20, 200$ and $\langle n \rangle = 10$.

![Figure 3.4](image2.png)

Figure 3.4: $\tau_1$ as a function of $\nu$ with $\varphi = 200$ and $\langle n \rangle = 10, 100$.

The initial number of T cells of a particular clonotype entering the repertoire from the thymus is given by $n(t = \tilde{t}) = \tilde{n}$ and so $\tau_{\tilde{n}}$ is the time for which a clonotype is present in the peripheral repertoire. However, the results shown in Figs. 3.5–3.6 imply that $\tau_{\tilde{n}}$ behaves qualitatively as $\tau_1$. Hence, in Figs. 3.3 and 3.4 only $\tau_{\tilde{n}}$ with
$\tilde{n} = 1$ has been considered.

Figure 3.5: $\tau_{\tilde{n}}$ as a function of $\tilde{n}$ with $\nu = 0.001, 1, 1000, \varphi = 20$ and $\langle n \rangle = 10$ where $\tilde{n} = 1, 2, \ldots, 10$.

Figure 3.6: $\tau_{\tilde{n}}$ as a function of $\tilde{n}$ with $\nu = 0.001, 1, 1000, \varphi = 20$ and $\langle n \rangle = 10$ where $\tilde{n} = 1, 2, \ldots, 100$.

The expected time to extinction from an initial state $\tilde{n} \in \mathcal{S}\setminus\{0\}$, $\tau_{\tilde{n}}$, depends on the parameters $\nu$, $\varphi$, $\langle n \rangle$, $\mu$ and $\tilde{n}$ and so the timescale of extinction will depend on these parameters as well. For the naïve T cell repertoire, $\langle n \rangle \approx 1000$ cells [64]. Estimates of $\mu^{-1}$ vary from several weeks to years [15, 51, 93, 120, 140], while the
parameters $\varphi$ and $\nu$ have not yet been experimentally measured and so reliable estimates of timescales for extinction cannot yet be given. However, if $\tau_n$ can be measured experimentally, it will be possible to estimate the values of some of the model parameters from this data.

For any set of parameters $\nu$, $\varphi$, $\langle n \rangle$ and $\mu$, the case $\nu \ll 1$ gives an upper bound on the mean time to extinction, as demonstrated by Eqs. (3.33)–(3.34). In this case $\tau_n$ depends only on the parameters $\varphi$ and $\mu$, where $\mu^{-1}$ is the mean lifespan of a T cell of a given clonotype and $\varphi^{-1}$ is a parameter proportional to the mean time until the T cell receives a survival signal from an APP in the absence of competition with T cells of other clonotypes. These parameters will change depending on the particular T cell clonotype at hand. Taking values of $\mu^{-1}$ of 20 weeks and 10 years to allow for varying estimates in the literature [15, 140], and assuming that initially there are 100 cells of the given clonotype [63], the mean time until extinction from this initial state is now calculated. There are three possible parameter regimes:

(i) $\mu^{-1} < \varphi^{-1}$

If $\mu^{-1} = 20$ weeks and $\varphi^{-1} = 100$ weeks then $\tau_{100} = 108$ weeks, while for $\mu^{-1} = 10$ years and $\varphi^{-1} = 50$ years, $\tau_{100} = 54$ years.

(ii) $\mu^{-1} \sim \varphi^{-1}$

For $\mu^{-1} = \varphi^{-1} = 20$ weeks, $\tau_{100} = 130$ weeks and for $\mu^{-1} = \varphi^{-1} = 10$ years, $\tau_{100} = 65$ years.

(iii) $\mu^{-1} > \varphi^{-1}$

For $\mu^{-1} = 20$ weeks and $\varphi^{-1} = 4$ weeks, $\tau_{100} = 862$ weeks, while for $\mu^{-1} = 10$ years and $\varphi^{-1} = 2$ years, $\tau_{100} = 431$ years.

This suggests that clonotypes with $\nu \ll 1$ can be maintained for a long time if $\mu^{-1}$ is of the order of a few years, while thymic output will have a major function in
maintaining naïve T cell repertoire diversity if \( \mu^{-1} \) is of the order of a few weeks. Nevertheless, reliable estimates of \( \varphi \) are needed to make better predictions.

However, the key factor that determines the reliability of the immune response is not the lifespan of a given clonotype, but its ability to persist in the repertoire as a function of the degree to which its TCR overlaps with those of other clonotypes also present in the repertoire. Clonotypes that overlap little with other clonotypes need to have long lifespans to avoid gaps in the repertoire developing. Regardless of the timescale of extinction, there is a very sharp jump in mean extinction time as a function of mean niche overlap at around \( \nu = 1 \), as shown in Figs. 3.3–3.4. This induces a strong selection pressure towards T cell clonotypes whose \( \nu \) parameters are less than one, which correspond to clonotypes that overlap little with other clonotypes in the repertoire in terms of the APPs that their TCR can recognise. Clonotypes with \( \nu \gg 1 \) will become extinct quickly (with a timescale of \( \mu^{-1} \)). The steepness of the jump indicates that most clonotypes fall into one of the two regimes \( \nu \ll 1 \) or \( \nu \gg 1 \), even though exact timescales for extinction are as yet unknown.

Fig. 3.3 shows that increasing \( \varphi \) also increases \( \tau_1 \) as the T cells have access to a higher level of resources, but does not change the location of the steep jump at around \( \nu = 1 \). Fig. 3.4 illustrates that a decrease in \( \langle n \rangle \), the mean clonotype size, shifts the location of this steep jump towards higher values of \( \nu \). This means that in lymphopenic conditions, which are associated with small values of \( \langle n \rangle \), T cells clonotypes will persist for longer in the repertoire.

The mean niche overlap of a T cell clonotype newly exported from the thymus depends on the TCR it expresses and, importantly, also depends on existing APP coverage by other clonotypes in the periphery. Once APP space is covered by the peripheral repertoire, new clonotypes produced from the thymus will have \( \nu \geq 1 \) by definition. Hence, there is likely to be a preponderance of clonotypes with high \( \nu \) values produced by the thymus. This tends to drive the repertoire average of \( \nu \),
which is denoted by $\langle \nu \rangle$, up while the selection process demonstrated in Figs. 3.3–3.4 drives it down.

### 3.2.3 The limiting conditional probability distribution represents homeostatic numbers of T cells prior to extinction occurring

For stochastic processes which eventually reach extinction but remain approximately stationary on an intermediate timescale, the limiting conditional probability distribution (LCD) is important in determining the late-time behaviour of the process before extinction occurs. LCDs have previously been applied to the study of other biological processes such as those in genetics [114] and in particular, epidemiological processes [30, 80, 98, 99]. In this section, the LCD is applied to the immune system in order to model the number of T cells belonging to a given clonotype before extinction occurs. In the next section, it will be shown that the diversity of the repertoire depends critically on the parameters of this probability distribution.

Let $p_n$ be the probability that there are $n$ T cells belonging to clonotype $i$ at time $t$, i.e., $p_n(t) = \mathbb{P}(X(t) = n|X(\hat{t}_i) = \hat{n})$. Then $p_n(t) \geq 0$ for $n \in S$, $p_n(t) = 0$ for $n \notin S$ and $\sum_{n=0}^{+\infty} p_n(t) = 1$ for $t \geq \hat{t}_i$. These probabilities satisfy the following system of differential equations

\[
\begin{align*}
\frac{dp_0(t)}{dt} &= \mu_1 p_1(t) , \\
\frac{dp_1(t)}{dt} &= \mu_2 p_2(t) - (\mu_1 + \lambda_1)p_1(t) , \\
\frac{dp_n(t)}{dt} &= \lambda_{n-1} p_{n-1}(t) + \mu_{n+1} p_{n+1}(t) - (\lambda_n + \mu_n)p_n(t) \quad \text{for } n \geq 2 ,
\end{align*}
\]

which are the forward Kolmogorov equations introduced in Chapter 2. The unique stationary probability distribution (which is also the limiting probability distribution
of the process) is given by \((1, 0, 0, \ldots)^T\) because eventual absorption at the origin is guaranteed. In order to study the stationary behaviour of the process before extinction occurs, these equations are written in terms of a new variable. Let

\[
q_n(t) = \frac{p_n(t)}{1 - p_0(t)} \quad \text{for } n \geq 1 ,
\]

which is the probability that there are \(n\) T cells of clonotype \(i\) at time \(t\), conditional on the event that extinction has not yet occurred. For all \(t \geq \tilde{t}_i\), \(q_n(t) \geq 0\) for \(n \in \mathcal{S}\{0\}\), \(q_n(t) = 0\) for \(n \notin \mathcal{S}\{0\}\) and \(\sum_{n=1}^{+\infty} q_n(t) = 1\). From Eqs. (3.36)–(3.37), these probabilities satisfy

\[
\frac{dq_1(t)}{dt} = \mu_2 q_2(t) - (\lambda_1 + \mu_1) q_1(t) + \mu_1 q_1^2(t) ,
\]

\[
\frac{dq_n(t)}{dt} = \lambda_{n-1} q_{n-1}(t) + \mu_{n+1} q_{n+1}(t) - (\lambda_n + \mu_n) q_n(t) + \mu_1 q_1(t) q_n(t) \quad \text{for } n \geq 2 .
\]

A probability distribution \(\bar{q}\) is called a quasi-stationary probability distribution (QSD) if it satisfies

\[
0 = \mu_2 \bar{q}_2 - (\lambda_1 + \mu_1) \bar{q}_1 + \mu_1 \bar{q}_1^2
\]

\[
0 = \lambda_{n-1} \bar{q}_{n-1} + \mu_{n+1} \bar{q}_{n+1} - (\lambda_n + \mu_n) \bar{q}_n + \mu_1 \bar{q}_1 \bar{q}_n \quad \text{for } n \geq 2 ,
\]

where \(\bar{q}_n \geq 0\) for \(n \in \mathcal{S}\{0\}\), \(\bar{q}_n = 0\) for \(n \notin \mathcal{S}\{0\}\) and \(\sum_{n=1}^{+\infty} \bar{q}_n = 1\). In most cases, it is not possible to obtain an explicit solution to these non-linear equations, but several approximations may be used. These are studied in detail in Chapter 4, where questions concerning the existence and uniqueness of the QSD are also addressed.

The QSD can be calculated numerically by several methods. Eqs. (3.41)–(3.42) have
CHAPTER 3. STOCHASTIC MODEL OF REPERTOIRE MAINTENANCE

the solution [101]

\[ \bar{q}_n = \bar{q}_1 \pi_n \sum_{k=1}^{n} \rho_{k-1} \left( 1 - \sum_{j=1}^{k-1} \bar{q}_j \right), \]  

(3.43)

for \( n \geq 1 \) where \( \rho_{k-1} \) is defined by Eq. (2.53), \( \pi_n \) is defined by Eq. (2.49) and \( \bar{q}_1 \) is determined from the normalisation condition \( \sum_{n=1}^{+\infty} \bar{q}_n = 1 \). This does not provide an explicit solution as all the terms \( \bar{q}_n \) are needed in order to determine \( \bar{q}_1 \), but it may be used as the basis of an iteration method introduced by Nåsell [101], which is now described. Firstly, the state-space of the process is truncated to be finite, with \( N \) the maximum number of T cells that may belong to a particular clonotype. Then \( \mathcal{S} = \{0, 1, \ldots, N\} \) and \( \lambda_N = 0 \) to ensure that transitions outside of the state-space cannot occur, while all other birth and death rates remain unchanged. The first step is to make an initial guess for the QSD which is denoted by \( \bar{q}_n^{(0)} \). This initial distribution is usually taken to be one of the approximating probability distributions which will be introduced in Chapter 4. Then \( \bar{q}_1^{(1)} \) is determined by

\[ \bar{q}_1^{(1)} = \frac{1}{\sum_{n=1}^{N} \pi_n \sum_{k=1}^{n} \rho_{k-1} \left( 1 - \sum_{j=1}^{k-1} \bar{q}_j^{(0)} \right) \}, \]  

(3.44)

and so

\[ \bar{q}_n^{(1)} = \bar{q}_1^{(1)} \pi_n \sum_{k=1}^{n} \rho_{k-1} \left( 1 - \sum_{j=1}^{k-1} \bar{q}_j^{(0)} \right), \quad 2 \leq n \leq N. \]  

(3.45)

For the next iteration, \( \bar{q}_n^{(1)} \) is taken to be the initial guess and so on, until the required precision is reached.

The QSD may also be determined from the infinitesimal generator matrix of the process, \( \mathbf{Q} \). Again, the state-space of the process is truncated so that \( \mathcal{S} = \{0, 1, \ldots, N\} \) and \( \lambda_N = 0 \), in order to allow numerical computation. Then the forward Kolmogorov equations \( \mathbf{P}'(t) = \mathbf{Q}^T \mathbf{P}(t) \), where \( \mathbf{P}^T = (p_0(t), p_1(t), \ldots, p_N(t)) \), have the solution

\[ \mathbf{P}(t) = \mathbf{v}_0 e^{-\omega_0 t} + \mathbf{v}_1 e^{-\omega_1 t} + \ldots + \mathbf{v}_N e^{-\omega_N t}, \]  

(3.46)
where $-\omega_0, \ldots, -\omega_N$ are the eigenvalues of $Q^T$ and $v_0, \ldots, v_N$ are the corresponding eigenvectors. Since absorption at the origin is guaranteed, $v_0 = (1, 0, \ldots, 0)^T$ and $\omega_0 = 0$ (see Eq. (2.46)). All other eigenvalues are real, distinct and negative [25, 73] and the eigenvalue $-\omega_1$ gives the speed of convergence to $v_0$. In order to determine the QSD, the infinitesimal generator matrix is restricted to the communicating class of states $C = \{1, 2, \ldots, N\}$ from which eventual exit to state 0 occurs with probability one. This $N \times N$ matrix is denoted by $Q_C$ and is given by

$$Q_C = \begin{pmatrix} - (\lambda_1 + \mu_1) & \lambda_1 & 0 & \ldots & 0 \\ \mu_2 & - (\lambda_2 + \mu_2) & \lambda_2 & \ldots & 0 \\ 0 & \mu_3 & - (\lambda_3 + \mu_3) & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \ldots & - \mu_N \end{pmatrix}. \quad (3.47)$$

The eigenvalues of $Q_C$ have negative real parts and the eigenvalue with maximal real part is real and has multiplicity one [106]. The QSD is given by the corresponding left eigenvector, normalised so that $\sum_{n=1}^{N} \bar{q}_n = 1$ [33]. Making use of the sparse structure of the matrix $Q_C$, the QSD can be readily evaluated by this method in the matrix algebra package MATLAB [69] for reasonably large values of $N$. For numerical calculations, both of the above described methods were used with $N = 500$, giving almost identical results.

The limiting conditional probability distribution (LCD), if it exists, is denoted by $q$ and is defined as

$$q_n = \lim_{t \to +\infty} q_n(t) \text{ for } n \geq 1, \quad (3.48)$$

where $q_n \geq 0$ for $n \in S \setminus \{0\}$, $q_n = 0$ for $n \notin S \setminus \{0\}$ and $\sum_{n=1}^{+\infty} q_n = 1$. The LCD does not depend on time, and so by definition it is a QSD. However, the converse is not always true. For a process with finite state-space, i.e., $S = \{0, 1, \ldots, N\}$, there exists a unique QSD, which is also the LCD of the process [33]. This will always be
the case when the LCD is calculated numerically by the methods described above. For a process with infinite state-space, i.e., \( \mathcal{S} = \{0, 1, 2, \ldots\} \), a QSD may not exist and, even if a QSD does exist, it may not be unique. The existence and uniqueness of the QSD for the infinite state-space process is studied in Chapter 4.

![Figure 3.7: The LCD, \( q_n \), with \( \nu = 0.001, 1, 1000, \varphi = 20, \langle n \rangle = 10 \) and \( \mu = 1 \).](image)

In Fig 3.7 the LCD is plotted for several values of the mean niche overlap parameter, \( \nu \). For \( \nu \gg 1 \) most of the weight of the distribution is in state \( n = 1 \) because, for

![Figure 3.8: Expected number of T cells at the LCD as a function of \( \nu \) with \( \varphi = 20, 200, \langle n \rangle = 10 \) and \( \mu = 1 \).](image)
Figure 3.9: Expected number of T cells at the LCD as a function of $\nu$ with $\varphi = 200$, $\langle n \rangle = 10$, 100 and $\mu = 1$.

this set of parameter values, mean extinction times are small and so the clonotype is “on the brink of extinction” at the LCD. For $\nu = 1$ and $\nu \ll 1$ the LCD appears to be approximately normally distributed (see Chapter 4). Figs. 3.8–3.9 show that for $\nu \ll 1$, the expected number of T cells at the LCD, denoted by $\bar{n}$, is given by $\frac{\varphi}{\mu}$, which agrees with analytic results based on approximations to the LCD (see Chapter 4). In ecological terms, $\frac{\varphi}{\mu}$ is the carrying capacity of the set of APPs that provide survival signals to T cells of this clonotype. Fig 3.9 shows that for decreasing values of $\langle n \rangle$ the curve shifts towards higher values of $\nu$. This is intuitive, as with all other parameters being equal, there is less competition for a system with lower mean clonotype size and so the results are in agreement with experimental observations of increased levels of T cell proliferation under lymphopenic conditions [61, 79].

### 3.2.4 The selection mechanism maximises T cell repertoire diversity

A diverse naïve T cell repertoire is essential to protect against infection from previously unencountered pathogens. However, it is not just the number of T cell
clonotypes present in the repertoire, $N_C$, that is important, but also the distribution of the T cells among these different clonotypes. The response rate to foreign antigen by T cells of clonotype $i$ is proportional to

$$\frac{n_i}{N_C\langle n \rangle},$$

which is the fraction of T cells belonging to clonotype $i$ in the naïve repertoire. This means that the average repertoire response rate is proportional to

$$\frac{1}{N_C \sum_{i=1}^{N_C} \frac{n_i}{N_C\langle n \rangle}} = \frac{1}{N_C^2 \langle n \rangle} \sum_{i=1}^{N_C} n_i = 1 \frac{1}{N_C \langle n \rangle} = \frac{1}{N_C}.$$  

Hence, the average repertoire response rate is inversely proportional to $N_C$, regardless of the distribution of T cells among the different clonotypes. Therefore, the reason that the naïve repertoire is not composed of single cells of many different clonotypes is that average response times would be too long, potentially allowing the invading pathogen to grow to uncontrollable levels. For a reliable immune response it is important that the probability of the response time exceeding the time at which the pathogen has become uncontrollable, or caused considerable damage, is low. This is related to the evenness of the distribution of T cells amongst the different clonotypes because if some clonotypes are much less common than others in the naïve repertoire, the response rate to foreign antigen for these clonotypes will be slow from Eq. (3.49). It will now be shown that a measure of the evenness of the repertoire can be calculated in terms of the coefficient of variation of the LCD for a typical clonotype.

The coefficient of variation for the LCD is a normalised measure of the dispersion of
the distribution and is given by $\sigma/\bar{n}$, where $\sigma^2$ is the variance of the LCD. Fig. 3.10 shows the coefficient of variation of the LCD as a function of $\nu$. For $\nu \gg 1$ the coefficient of variation is very small because most of the weight of the LCD is concentrated at a single state, $n = 1$ (see Fig. 3.7).

Simpson’s diversity index (also known as the equalitability index) is well-known in ecology, where it characterises the evenness of the number of individuals belonging to different species [11]. With the T cell repertoire viewed as an ecosystem where individual clonotypes correspond to different species, this index is defined by

$$D_S = \left( N_C \sum_{i=1}^{N_C} \left( \frac{n_i}{N_C \langle n \rangle} \right)^2 \right)^{-1} = \left( \frac{1}{N_C \langle n \rangle^2} \sum_{i=1}^{N_C} n_i^2 \right)^{-1}. \quad (3.51)$$

The population variance is given by

$$\frac{1}{N_C} \sum_{i=1}^{N_C} n_i^2 - \langle n \rangle^2 \geq 0, \quad (3.52)$$
and so
\[
\frac{1}{N_C(n)^2} \sum_{i=1}^{N_C} n_i^2 \geq 1 \Rightarrow D_S = \left( \frac{1}{N_C(n)^2} \sum_{i=1}^{N_C} n_i^2 \right)^{-1} \leq 1. \tag{3.53}
\]

Therefore, $D_S$ takes values in the interval $[0, 1]$ so that $D_S = 1$ corresponds to a T cell repertoire with maximal diversity which is associated with the greatest reliability of the immune response to pathogenic challenge [11].

By the ergodic hypothesis [107], the population variance (3.52) is replaced by the variance at the LCD of a single typical clonotype, $\sigma^2$. Also, for a typical clonotype the mean number of cells at the LCD is equal to the mean clonotype size, i.e., $\bar{n} = \langle n \rangle$. This results in
\[
\sum_{i=1}^{N_C} n_i^2 = N_C(\sigma^2 + \bar{n}^2). \tag{3.54}
\]

Substituting this into Eq. (3.51) gives
\[
D_S = \left( \frac{1}{N_C \bar{n}^2} N_C(\sigma^2 + \bar{n}^2) \right)^{-1} = \frac{1}{1 + \left( \frac{\sigma}{\bar{n}} \right)^2}, \tag{3.55}
\]

where $\sigma / \bar{n}$ is the coefficient of variation of the LCD. In the case $\nu \ll 1$, $\sigma^2 = \bar{n} = \varphi / \mu$ and so
\[
D_S = \frac{1}{1 + \frac{\varphi}{\mu}}, \tag{3.56}
\]
as illustrated in Fig. 3.11. Clonotypes for which $\nu \gg 1$ need not be considered as the results imply that they will quickly become extinct before the process relaxes to the LCD. Fig 3.11 shows that diversity, as measured by this index, is maximal for $\nu \ll 1$. Hence, the selection mechanism demonstrated in Section 3.2.1 which results in these clonotypes being associated with the longest survival times, promotes maximal T cell repertoire diversity.
3.3 Discussion

In this chapter it has been shown that, despite the existence of homeostatic mechanisms to maintain T cell numbers in the periphery, eventual extinction of any given clonotype occurs with certainty. The clonotypes that survive in the repertoire for the longest time are those which have the least overlap with other clonotypes in the repertoire in terms of the APPs from which they are able to receive survival signals, which is quantified by the mean niche overlap parameter, $\nu$. Clonotypes with low mean niche overlap persist for a long time in the repertoire, while those with high values of $\nu$ quickly become extinct due to competition from T cells belonging to other clonotypes. This selection mechanism acts to maximise the diversity of the T cell repertoire which leads to a greater reliability of the immune response. This is because the mean lifespan of a clonotype as a function of how well it fills any gaps in the repertoire is more important than the indefinite persistence of any particular clonotype.

If T cells with very small values of $\nu$ (i.e., those that have TCRs which are very different from other T cells in terms of the APPs that they are able to recognise) are
common, then protection against all possible foreign antigens will be reduced when such a clonotype becomes extinct. Hence, in order for the repertoire to be robust, it needs to be insensitive to the loss of individual clonotypes but at the same time avoid unnecessary overlap. Output of new clonotypes from the thymus may play a crucial role here. While the selection mechanism described in Section 3.2.2 reduces the population mean niche overlap $\langle \nu \rangle$ to a value of less than one over time, thymic output may act to increase it. This is reasonable because, once the set of all APPs is covered by the naïve T cell repertoire, any new clonotypes produced by the thymus will have a mean niche overlap that is greater than one by definition. As thymic output declines with age, $\langle \nu \rangle$ will decrease and the repertoire will become more sensitive to the removal of individual T cell clonotypes, leading to a compromised adaptive immune response.

The model is based on T cell death and proliferation after a T cell receives the appropriate survival signal from an APP. Telomeres are DNA structures found at the end of chromosomes which are not fully replicated during cell division. This means that T cells have a finite replicative capacity [44, 104] and it has been observed that the telomeric length of naïve T cells decreases with age [77, 142]. Hence, in elderly individuals an increasing number of cells will begin to approach their replicative limit. This is likely to be one of the reasons behind the abrupt failure of homeostatic mechanisms in advanced age [63], and will reduce effectiveness of the immune response as clonal expansion may be impaired. Chronic stimulation of T cells by persistent infections, such as cytomegalovirus, may also result in the erosion of telomeres and lead to T cell senescence. However, the model presented here does not include the effect of foreign antigens on the repertoire.

The current model is based on the mean field approximation introduced in Section 3.1.1. The validity of this approximation depends on the nature of the connections between the set of all T cell clonotypes $\mathcal{C}$ and the set of all APPs $\mathcal{Q}$. Firstly,
the case when each T cell clonotype $i$ is able to receive survival signals from only one self-peptide is considered. Then the presence of this self-peptide in APP $q$ implies that $q \in \mathcal{Q}_i$. Hence, T cells of clonotype $i$ compete with the same subset of T cells for each APP in $\mathcal{Q}_i$. If this were the case, only the clonotype with the highest affinity for each APP would survive [36] with the remaining clonotypes quickly becoming extinct by the classical competitive exclusion principle of ecology [68]. This means that the repertoire would be susceptible to takeover by rare clonotypes with high avidity for two or more self-peptides and moreover, the mean field approximation would be poor. However, current data suggests that this scenario is unlikely [5, 89]. Alternatively, if each T cell clonotype can recognise a small number of self-peptides then combinatorial arguments mean that the number of connections between the set of all APPs and the set of T cell clonotypes becomes much larger so that each APP provides survival signals to T cells of many clonotypes and for a given T cell clonotype, $i$, the cardinality of the set $\mathcal{Q}_i$ is very large [122]. The key point is that even though a T cell of clonotype $i$ may compete with T cells of many other clonotypes for access to APPs in the set $\mathcal{Q}_i$, competitive interactions between any two T cell clonotypes are typically small, even if $\nu_i$ is large; in mathematical terms, this means that for any pair of clonotypes $i$ and $i'$, $|\mathcal{Q}_i \cap \mathcal{Q}_{i'}| \ll |\mathcal{Q}_i|$. The mean field approximation breaks down for pairs of clonotypes for which this condition does not hold. The current model is extended to include such clonotypes in Chapter 5, where it is shown that one of the pair of clonotypes is quickly deleted from the repertoire by a process that more closely resembles classical competitive exclusion as the size of the set $\mathcal{Q}_i \cap \mathcal{Q}_{i'}$ increases.
Chapter 4

Approximations to the limiting conditional probability distribution

In Chapter 3, the birth and death process \( \{ \mathcal{X}(t) : t > \tilde{t}_i \} \) on the state-space \( \mathcal{S} = \{0, 1, 2, \ldots\} \) was used to model the number of T cells belonging to a particular clonotype, labelled \( i \). It was shown that ultimately the process reaches the state \( n_i = 0 \) corresponding to clonotype extinction and the limiting conditional probability distribution (LCD) was introduced as the appropriate tool to study the late-time behaviour of the process before extinction occurs. In this chapter, the LCD of this process is studied in more detail. It is first proved that a unique LCD exists for all parameter values of the model. As it is difficult to obtain analytic expressions for the LCD of birth and death processes in all but the most simple cases, approximations are needed. In this chapter, the LCD is approximated by the stationary probability distributions of two birth and death processes which lack absorbing states, and these approximations are studied in more detail for the special cases \( \nu \ll 1 \) and \( \nu \gg 1 \). The LCD is also approximated by means of a normal
distribution, derived using van Kampen’s “large $N$ expansion” [134], in these two special cases. This approximation is also derived using the more rigorous diffusion approximation formulated by Kurtz [81, 82]. Finally, a Poisson approximation is derived from a partial differential equation for the cumulants of the process. The accuracy of the various approximation methods is then discussed.

4.1 Existence of a unique limiting conditional probability distribution

Recall that a QSD is a stationary probability distribution of a Markov process, conditioned on non-extinction, while the LCD is the limiting probability distribution of this conditioned process. Since the LCD is independent of time it is, by definition, a QSD but the converse is not always true. For a continuous-time Markov process on a finite state-space $S = \{0, 1, \ldots, N\}$, a unique QSD exists and this is also the unique LCD of the process [33]. However, for a process with infinite state-space $S = \{0, 1, \ldots\}$, such as the birth and death process introduced in Chapter 3, existence of a QSD and an LCD is not guaranteed and, even if a QSD does exist, it may not be unique. In this section it is proved that the process $\{X(t) : t > \tilde{t}\}$ on the state-space $S = \{0, 1, \ldots\}$ with birth and death rates defined by Eqs. (3.13)–(3.15) has a unique limiting conditional probability distribution. The first stage is to prove that a QSD exists for the process, as this is a necessary condition for the existence of an LCD.
4.1.1 Existence of a quasi-stationary probability distribution

For a regular birth and death process on the state-space $S = \{0, 1, \ldots\}$ where the absorbing state at $n = 0$ is reached with certainty and the remaining states form a communicating class, van Doorn [132] showed that there are three possibilities regarding the existence of a QSD:

1. there is no QSD;
2. there exists a unique QSD;
3. there are an infinite number of QSDs forming a one-parameter family of probability distributions.

It will now be shown, using two different methods, that at least one QSD exists for the process under consideration, in order to eliminate the first possibility. The question of uniqueness of the QSD is addressed in the next section. First, it is shown that the process is regular, as both methods used require that this is the case. The terms $\pi_k$, defined by Eq. (2.49) are all strictly positive for $k \geq 1$ meaning that

\[
\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \sum_{k=1}^{n} \pi_k > \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \pi_n = \sum_{n=1}^{+\infty} \frac{1}{\lambda_n} = +\infty,
\]

and so the infinitesimal generator matrix of the process is regular by Eq. (2.52).
CHAPTER 4. APPROXIMATIONS TO THE LCD

Method 1

Recall from Chapter 2 that the transition probabilities \( p_{n,m}(t) \) can be represented by

\[
p_{n,m}(t) = \pi_m \int_{0}^{+\infty} e^{-xt} Q_{n}(x) Q_{m}(x) d\psi(x) \quad \text{for } m, n \in \mathcal{S} \setminus \{0\},
\]

where \( \pi_n, Q_n(x) \) and \( \psi \) are defined in Chapter 2. The polynomials \( Q_n(x) \) have \( n \) positive zeros \( x_{n,1} < x_{n,2} < \ldots < x_{n,n} \) which satisfy

\[
0 < x_{n+1,j} < x_{n,j} < x_{n+1,j+1},
\]

for \( j = 1, 2, \ldots, n \) and \( n = 1, 2, \ldots \) [132]. Then the limit

\[
\xi_j = \lim_{n \to +\infty} x_{n,j},
\]

exists and \( 0 \leq \xi_j \leq \xi_{j+1} \leq +\infty \) [131, 132], where \( j = 1, 2, \ldots, n \). Thus, the limit

\[
\sigma = \lim_{j \to +\infty} \xi_j,
\]

can also be defined and satisfies \( 0 \leq \sigma \leq +\infty \) [131, 132].

For a birth and death process with an absorbing state at the origin, the decay parameter of the process, defined by Eq. (2.41), is given by \( \alpha = \xi_1 \) [131]. Such a process is said to be exponentially ergodic if and only if the decay parameter is positive, \( i.e., \alpha > 0 \) [131]. From Theorem 5.1 of van Doorn [131], an equivalent condition for exponential ergodicity is that

\[
\sigma > 0.
\]

Also, from Theorem 3.2 of van Doorn [132], positivity of the decay parameter (exponential ergodicity) is a necessary and sufficient condition for the existence of a QSD
for a regular birth and death process where absorption at the origin is guaranteed. Hence, if \( \sigma > 0 \) then a QSD exists for the process considered here. Theorem 5.3 of van Doorn [131] states that if \( \lambda_n \to \lambda \leq +\infty \) and \( \mu_n \to \mu \leq +\infty \) as \( n \to +\infty \) then

\[
\sigma = (\sqrt{\lambda} - \sqrt{\mu})^2 \text{ if } \lambda < +\infty \text{ and } \mu < +\infty , \tag{4.7}
\]
\[
\sigma = +\infty \text{ if } \lambda < +\infty, \mu = +\infty \text{ or } \lambda = +\infty, \mu < +\infty . \tag{4.8}
\]

For the birth and death rates (3.13)–(3.15),

\[
\lambda_n \to \varphi \text{ and } \mu_n \to +\infty \text{ as } n \to +\infty , \tag{4.9}
\]
which means that \( \sigma \neq 0 \) and, hence, \( \alpha = \xi_1 > 0 \). Therefore, at least one QSD exists for the process \( \{X(t) : t \geq \tilde{t}_i\} \).

**Method 2**

In this section, existence of a QSD is proved using the method of Ferrari et. al [47]. While this proof is more lengthy than Method 1, the conditions are easier to interpret and, as shall be seen in Chapter 5, the method applies to a wider class of Markov processes, while the previous proof is restricted to the univariate birth and death case.

Let

\[
R = \inf \{t \geq 0 : X(t) = 0\} , \tag{4.10}
\]

which is the time at which absorption occurs. In Section 3.2.2 it was shown that the expected time to absorption from the initial state \( \tilde{n} \in \mathcal{S} \) is finite, as required. The first part of the proof is to show that

\[
\lim_{\tilde{n} \to +\infty} \mathbb{P}(R < t | X(\tilde{t}_i) = \tilde{n}) = 0 \quad \text{for all } t \geq \tilde{t}_i , \tag{4.11}
\]
i.e., the mean time to extinction can be made arbitrarily large by taking the initial state of the process, \( \tilde{n} \), to be sufficiently far away from the origin. Condition (4.11) is referred to as the “asymptotic remoteness” condition. First note that the time until the death of a T cell of a given clonotype is an independent exponential random variable with expected value \( \mu^{-1} \). If the initial state of the process is given by \( X(\tilde{t}_i) = \tilde{n} \) then prior to extinction occurring, all of the \( \tilde{n} \) cells initially present must die. Extinction occurs at the time of death of the last of these \( \tilde{n} \) initial cells if none of them has divided, and will occur strictly later if at least one T cell has divided before the last of the initial cells dies. Hence, for any \( t > \tilde{t}_i \)

\[
\mathbb{P}(R < t | X(\tilde{t}_i) = \tilde{n}) \leq (1 - e^{-\mu t})\tilde{n} \to 0 \text{ as } \tilde{n} \to +\infty ,
\]

and so the “asymptotic remoteness” condition given by Eq. (4.11) holds.

Next, a function \( f \) on \( S \) is defined with the constants \( D_1, D_4, D_5 > 0, D_2, D_3, D_6 < +\infty \), where \( D_6 \) is an integer, which satisfies the following conditions [47]:

\[
f(n) \geq 0 \text{ and } f(n) \to +\infty \text{ as } n \to +\infty ,
\]

\[
\sum_{m \neq n} \frac{q_{n,m}}{-q_{n,n}} f(m) \leq f(n) - D_1 \text{ for } n \geq D_6 ,
\]

\[
|f(n) - f(m)| \leq D_2 \text{ for } n \geq D_6 \text{ and } q_{n,m} > 0 ,
\]

\[
\sum_{m \neq n \atop f(m) \geq x} q_{n,m} \leq D_3 e^{-D_4x} \text{ for } 1 \leq n \leq D_6 - 1 \text{ and } x \geq 1 ,
\]

\[-q_{n,n} \geq D_5 \text{ for } n \geq D_6 ,
\]

where \( q_{n,m} \) are the entries of the infinitesimal generator matrix defined by Eq. (2.25). Ref. [28] corrects an error in Eq. (1.10) of [47], which has been noted in condition (4.14) and so \( q_{n,m} \) has been replaced with \( \frac{q_{n,m}}{-q_{n,n}} \) accordingly. Together, Theorem 1.1 and Lemma 4.3 of Ferrari et al. [47] state that a QSD exists for a regular, con-
servative Markov process if it satisfies Eq. (4.11) and conditions (4.13)–(4.17) hold. For the process \( \mathcal{X}(t) : t > \tilde{t}_i \), the entries of the infinitesimal generator matrix, \( Q \), are given by

\[
q_{n,n+1} = \varphi e^{-\nu} na_n ,
\]

\[
q_{n,n-1} = \mu n ,
\]

\[
q_{n,n} = \varphi e^{-\nu} na_n + \mu n ,
\]

\[
q_{n,m} = 0 \quad \text{for } m \neq n - 1, n, n + 1 ,
\]

where \( a_n = \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{n+r(n)} \). This matrix is conservative and regular, as required. Let \( f(n) = n \).

(i) For \( n \in S \), the function \( f(n) \geq 0 \) and \( f(n) \to +\infty \) as \( n \to +\infty \), satisfying condition (4.13).

(ii)

\[
\sum_{m \neq n} \frac{q_{n,m}}{-q_{n,n}} f(m) - f(n) = \frac{\varphi e^{-\nu} na_n(n + 1) + \mu(n - 1)}{\varphi e^{-\nu} na_n + \mu n} - n
\]

\[
= \frac{\varphi e^{-\nu} a_n - \mu}{\varphi e^{-\nu} a_n + \mu} \to -1 \quad \text{as } n \to +\infty ,
\]

because \( a_n \to 0 \) as \( n \to +\infty \). Then by taking \( D_1 = \frac{1}{2} \), a suitable integer, \( D_6 \), can be found such that

\[
\sum_{m \neq n} \frac{q_{n,m}}{-q_{n,n}} f(m) \leq f(n) - D_1 \quad \text{for } n \geq D_6 ,
\]

and condition (4.14) is thus satisfied.

(iii) For a birth and death process, transitions are only allowed to neighbouring
states and so for all values of \( m \) such that \( q_{n,m} > 0 \)

\[
|f(n) - f(m)| \leq 1 \quad \text{for all } n \in S. \tag{4.24}
\]

Then condition (4.15) is satisfied by taking \( D_2 = 1 \).

(iv) Now \( n \) is fixed. Then for \( 1 \leq n \leq D_6 - 1 \) the following bound is obtained:

\[
\sum_{m \neq n} q_{n,m} = \varphi e^{-\nu} n a_n + \mu n \leq \varphi + \mu n \leq \varphi + \mu (D_6 - 1). \tag{4.25}
\]

Now, \( D_3 \) is chosen such that \( 0 < \frac{1}{D_3} (\varphi + \mu (D_6 - 1)) < 1 \), and then \( D_4 \) is defined for \( x \geq 1 \) by \( D_4 = -\frac{1}{x} \log(\frac{1}{D_3} (\varphi + \mu (D_6 - 1))) > 0 \). Therefore, \( D_3 e^{-D_4 x} = \varphi + \mu (D_6 - 1) \) and hence condition (4.16) is satisfied.

(v) Finally,

\[
-q_{n,n} = \varphi e^{-\nu} n a_n + \mu n \geq \mu \quad \text{for } n \geq 1, \tag{4.26}
\]

and so in order to satisfy condition (4.17), define \( D_5 = \mu > 0 \).

Hence, by Lemma 4.3 and Theorem 1.1 of Ferrari et al. [47] a QSD exists for the process \( \{X(t) : t > \tilde{t}_i\} \).

### 4.1.2 The quasi-stationary probability distribution is not unique

If the series

\[
\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \sum_{k=n+1}^{+\infty} \pi_k \tag{4.27}
\]

converges, then there is a unique QSD (where \( \pi_n \) is defined by Eq. (2.49)). On the other hand, if series (4.27) diverges, there is either no QSD or a one-parameter
family of QSDs [132]. The terms \( \pi_k \) are all strictly positive for \( k \geq 1 \) so that
\[
\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \sum_{k=n+1}^{+\infty} \pi_k > \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \pi_{n+1} = \sum_{n=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_n \lambda_1 \lambda_2 \ldots \lambda_n}{\lambda_1 \lambda_2 \ldots \lambda_n \mu_2 \mu_3 \ldots \mu_{n+1}} = \sum_{n=1}^{+\infty} \frac{1}{\mu_{n+1}} = \frac{1}{\mu} \sum_{n=1}^{+\infty} \frac{1}{n+1} = +\infty ,
\]
by the integral test. Hence, series (4.27) diverges by comparison. In Section 4.1.1 it was proved that at least one QSD exists and so it can be concluded that there exists a one-parameter family of QSDs. This family is indexed by the parameter \( x \) as follows:
\[
\bar{q}_n(x) = \mu_1^{-1} \pi_n x Q_n(x) \text{ for } 0 < x \leq \alpha , \quad n \geq 1 ,
\]
where \( \alpha \) is the decay parameter of the process and with \( \pi_n \) and \( Q_n(x) \) defined by Eq. (2.49) and Eq. (2.51), respectively [132].

### 4.1.3 The limiting conditional probability distribution exists and is unique

Since there are infinitely many QSDs, the LCD of the process depends on the initial probability distribution of the process. For example, if the initial probability distribution of the process is a QSD, this distribution will also be the LCD of the process. In this section it is shown that for biologically realistic initial conditions, the process \( \{X(t) : t > \tilde{t}_i\} \) has a unique LCD.

The speed of convergence to the limiting probability distribution of the uncondi-
CHAPTER 4. APPROXIMATIONS TO THE LCD

The mentioned process (which has all of its mass at the origin, since absorption is guaranteed) is characterised by the decay parameter, $\alpha$. In Section 4.1.1 it was proved that $\alpha > 0$. At time $t = \tilde{t}$, an initial number of cells of clonotype $i$, $\tilde{n}$, is released from the thymus. This means that the initial probability distribution of the process has all its mass at one state, i.e., $X(0) = \tilde{n}$ and so by Theorem 4.1 of [132] an LCD exists and this distribution is given by the QSD which corresponds to the decay parameter $\alpha$, i.e.,

$$q_n = \mu_1^{-1} \pi_n \alpha Q_n(\alpha).$$

Thus, although there are infinitely many QSDs, only one of them corresponds to the LCD of the birth and death process. A useful analogy can be drawn with a deterministic system which may have more than one steady state. Then, the LCD corresponds to the stable steady state of the system that is reached at late times. In general, the parameter values may affect the number of steady states and their stability and the initial conditions may determine which stable steady state is reached. However, for the type of initial conditions described above, the LCD is always given by the QSD corresponding to the decay parameter of the process.

### 4.2 Two approximating processes

In most cases, the LCD of the process cannot be found analytically and instead numerical methods are employed (the exceptions are the process with constant birth and death rates $\lambda_0 = 0, \lambda_n = \lambda$ for $n \geq 1$ and $\mu_n = \mu$ for $n \geq 0$, and the process with linear birth and death rates $\lambda_n = \lambda n$ and $\mu_n = \mu n$ for all $n \geq 0$, where expressions for the LCD can be calculated explicitly [24]). Therefore, to make further analytical progress, approximations are needed. The LCD can be approximated by the limiting probability distributions of two continuous-time birth and death processes which are related to the original process, but lack absorbing states [101]. In this section, the
two approximations are defined and the forms of the approximating probability distributions are calculated for the birth and death process defined in the previous chapter. It is useful to understand how these approximations are related to the LCD of the original process [30, 80] and it is shown that one approximation provides an upper bound to the LCD, while the other provides a lower bound in the sense of likelihood ratio ordering.

4.2.1 Approximating process \( \{X^{(1)}(t) : t \geq \tilde{t}_i\} \)

The first approximating process is denoted by \( \{X^{(1)}(t) : t \geq \tilde{t}_i\} \). It differs from the original process in that \( \mu_1 = 0 \), while all other birth and death rates remain unchanged. Therefore, the state-space of the process is given by \( S^{(1)} = \{1, 2, \ldots\} \) which is a communicating class, and hence the process is irreducible. The process can be represented as follows:

\[
1 \xleftrightarrow{\mu_2} 2 \cdots n - 1 \xleftrightarrow{\mu_n} n \xleftrightarrow{\mu_{n+1}} n + 1 \cdots .
\]

From Eqs. (2.35)–(2.36), this process has a unique positive stationary probability distribution if and only if \( \mu_n > 0 \) and \( \lambda_{n-1} = 0 \) for \( n \geq 2 \) and

\[
\sum_{n=2}^{+\infty} \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_2 \mu_3 \cdots \mu_n} < +\infty. \tag{4.31}
\]

These conditions are satisfied for the birth and death rates given by Eqs. (3.14)–(3.15). Hence, from Eqs. (2.37)–(2.38), the unique stationary probability distribution of approximating process \( \{X^{(1)}(t) : t \geq \tilde{t}_i\} \), which is denoted by \( \bar{p}^{(1)} \), is given
by

$$\hat{p}_n^{(1)} = \frac{1}{1 + \sum_{n=2}^{+\infty} \frac{1}{n} \left( \frac{\varphi}{\mu e^\varphi} \right)^{n-1} \prod_{k=1}^{n-1} a_k} , \quad (4.32)$$

$$\hat{p}_n^{(1)} = \hat{p}_1^{(1)} \frac{1}{n} \left( \frac{\varphi}{\mu e^\varphi} \right)^{n-1} \prod_{k=1}^{n-1} a_k , \quad n \geq 2 , \quad (4.33)$$

where $$a_k = \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{k+r(n)}$$. Also,

$$\frac{1}{\lambda_1} + \sum_{n=2}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_n}{\lambda_1 \lambda_2 \ldots \lambda_n} = +\infty , \quad (4.34)$$

and so the process is ergodic [74] which means that $$\hat{p}^{(1)}$$ is also the unique limiting probability distribution of approximating process \{$$\hat{X}^{(1)}(t) : t \geq \hat{t}_i$$\}.

Two measures of ordering for probability distributions are now introduced so that the relationship between the limiting probability distribution of \{$$\hat{X}^{(1)}(t) : t \geq \hat{t}_i$$\} and the actual LCD of the process may be studied. For two probability distributions $$\zeta^{(1)} = (\zeta_1^{(1)}, \zeta_2^{(1)}, \ldots)$$ and $$\zeta^{(2)} = (\zeta_1^{(2)}, \zeta_2^{(2)}, \ldots)$$ the likelihood ratio ordering $$\prec_{LR}$$ is defined as follows:

$$\zeta^{(1)} \prec_{LR} \zeta^{(2)}$$ if $$\zeta_i^{(1)} \zeta_j^{(2)} \geq \zeta_j^{(1)} \zeta_i^{(2)}$$ for $$1 \leq i \leq j$$ , \quad (4.35)

while the usual stochastic ordering, $$\prec_{ST}$$, is defined by

$$\zeta^{(1)} \prec_{ST} \zeta^{(2)}$$ if $$\sum_{j=1}^{n} \zeta_j^{(2)} \leq \sum_{j=1}^{n} \zeta_j^{(1)}$$ for $$n = 1, 2 \ldots . \quad (4.36)$$

Loosely speaking, Eq. (4.36) means that $$\zeta^{(2)}$$ assumes large values with higher probability than $$\zeta^{(1)}$$. Likelihood ratio ordering implies the usual stochastic ordering [115]. Clancy and Pollett [30] prove that for birth and death processes where the absorbing state at $$n = 0$$ is reached with certainty, the limiting probability distribution of
approximating process \( \{ X^{(1)}(t) : t \geq \tilde{t}_i \} \) is a lower bound to the QSD in the sense that
\[
\bar{p}^{(1)} <_{LR} \bar{q} ,
\]
and, hence,
\[
\bar{p}^{(1)} <_{ST} \bar{q} .
\]
For the birth and death process considered here, the QSD is not unique; in fact it has been shown that there are infinitely many QSDs. However, Eq. (4.38) applies to all QSDs, in particular the LCD of the process.

### 4.2.2 Approximating process \( \{ X^{(2)}(t) : t \geq \tilde{t}_i \} \)

The second approximating process is denoted by \( \{ X^{(2)}(t) : t \geq \tilde{t}_i \} \). This process has the same birth rates as the original process but the death rates are shifted by replacing \( \mu_n \) with \( \mu_{n-1} \), allowing for one immortal individual. The state-space is given by \( S^{(2)} = \{ 1, 2, \ldots \} \), which forms a communicating class and so, as in the previous approximation, the process is irreducible and can be represented by the following diagram:

\[
1 \leftarrow_{\mu_1} 2 \cdots n - 1 \leftarrow_{\mu_{n-1}} n \leftarrow_{\mu_n} n + 1 \cdots .
\]

From Eqs. (2.35)–(2.36), this process has a unique positive stationary probability distribution if and only if \( \mu_n > 0 \) and \( \lambda_n > 0 \) for \( n \geq 1 \) and
\[
\sum_{n=2}^{+\infty} \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_1 \mu_2 \cdots \mu_{n-1}} < +\infty .
\]
These conditions are satisfied for the birth and death rates defined by Eqs. (3.14)–(3.15) and, from Eqs. (2.37)–(2.38), the unique stationary probability distribution
of approximating process \( \{X^{(2)}(t) : t \geq \tilde{t}_i\} \), which is denoted by \( \bar{p}^{(2)} \), is given by

\[
\bar{p}_1^{(2)} = \frac{1}{1 + \sum_{n=2}^{+\infty} \left( \frac{\varphi}{\mu e^\nu} \right)^n \prod_{k=1}^{n-1} a_k},
\]
(4.40)

\[
\bar{p}_n^{(2)} = p_1^{(2)} \left( \frac{\varphi}{\mu e^\nu} \right)^{n-1} \prod_{k=1}^{n-1} a_k, \quad n \geq 2,
\]
(4.41)

where \( a_k = \sum_{r=0}^{+\infty} \frac{\nu^r}{k! r!} \). Since,

\[
\frac{1}{\lambda_1} + \sum_{n=2}^{+\infty} \frac{\mu_1 \mu_2 \cdots \mu_{n-1}}{\lambda_1 \lambda_2 \cdots \lambda_n} = +\infty,
\]
(4.42)

the process is ergodic [74] and \( \bar{p}^{(2)} \) is also the unique limiting probability distribution of \( \{X^{(2)}(t) : t \geq \tilde{t}_i\} \). It is now proved that this approximating probability distribution provides an upper bound on the LCD of the process in the sense of stochastic ordering.

First, a new Markov process is constructed as follows. Let \( \zeta = (\zeta_1, \zeta_2, \ldots) \) be a probability distribution. Whenever the original process reaches the absorbing state at \( n = 0 \), it is restarted immediately in state \( j \in \{1, 2, \ldots\} \) with probability \( \zeta_j \). The state-space of this resurrection process is irreducible and, since the original process has the property of guaranteed absorption, the new process has a unique stationary probability distribution, which is denoted by \( \theta = (\theta_1, \theta_2, \ldots) \) [30]. Next, the map \( \Phi \) is defined by

\[
\Phi(\zeta) = \theta,
\]
(4.43)

and so a QSD, \( \bar{q} \), satisfies

\[
\Phi(\bar{q}) = \bar{q}.
\]
(4.44)

Since there are infinitely many QSDs, this fixed point is not unique. The next step
is to find the probability distribution $\zeta$ such that $\Phi(\zeta) = \tilde{p}^{(2)}$, which satisfies

$$
\lambda_{n-1}\tilde{p}_{n-1}^{(2)} - (\lambda_n + \mu_n)\tilde{p}_n^{(2)} + \mu_{n+1}\tilde{p}_{n+1}^{(2)} = -\mu_1\tilde{p}_1^{(2)} \zeta_n ,
$$

(4.45)

for $n \geq 1$ [30]. Solving this equation for $\zeta_n$ results in

$$
\zeta_n = \left(\frac{\varphi}{\mu e^\nu}\right)^{n-1} \left(1 - \frac{\varphi}{\mu e^\nu} a_n\right) \prod_{k=1}^{n-1} a_k , \quad n \geq 1 .
$$

(4.46)

Then

$$
\tilde{p}_i^{(2)} \zeta_j - \tilde{p}_j^{(2)} \zeta_i = \left(\frac{\varphi}{\mu e^\nu}\right)^{i+j-1} \tilde{p}_1^{(2)} (a_i - a_j) \prod_{k=1}^{i-1} a_k \prod_{k=1}^{j-1} a_k \geq 0 ,
$$

(4.47)

for $1 \leq i \leq j$, because $\{a_n\}_{n=1}^{+\infty}$ is a decreasing sequence. Hence, from definition (4.35), $\tilde{p}^{(2)} <_{LR} \zeta$, i.e., $\Phi(\zeta) <_{LR} \zeta$. Theorem 1 of [30] states that the map $\Phi$ preserves likelihood ratio ordering, and so from repeated application of this map

$$
\Phi^m(\zeta) <_{LR} \Phi^{m-1}(\zeta) <_{LR} \cdots <_{LR} \tilde{p}^{(2)} <_{LR} \zeta .
$$

(4.48)

Now, Theorem 6.1 of [47] states that

$$
\lim_{m \to +\infty} \Phi^m(\zeta) = q .
$$

(4.49)

Hence,

$$
q <_{LR} \tilde{p}^{(2)} ,
$$

(4.50)

which implies that

$$
q <_{ST} \tilde{p}^{(2)} .
$$

(4.51)

Note that the process considered here does not satisfy condition 6.1 of [47] which states that

$$
-q_{n,n} < c \quad \forall \ n \in \mathcal{S} ,
$$

(4.52)
where $c < +\infty$. This condition is not satisfied because $-q_{n,n} = \lambda_n + \mu_n$ and $\mu_n = \mu n \rightarrow +\infty$ as $n \rightarrow +\infty$. However, it can be shown that Eq. (4.49) also holds for the process with birth and death rates given by Eqs. (3.14)–(3.15) [Harry Kesten, personal communication]. Hence, $\widebar{p}^{(2)}$ is an upper bound to all QSDs of the process, in particular the LCD.

### 4.3 Approximations in the special cases $\nu \ll 1$ and $\nu \gg 1$

In this section, the approximations described in Section 4.2 are studied in more detail for the two special cases $\nu \ll 1$ and $\nu \gg 1$, which were introduced in Section 3.1.3.

#### 4.3.1 The case $\nu \ll 1$

In the case $\nu \ll 1$, the birth and death rates for the process are given by

\begin{align*}
\lambda_0 &= 0 , \\
\lambda_n &= \varphi , \quad n \geq 1 , \\
\mu_n &= \mu n , \quad n \geq 0 . 
\end{align*}

(4.53) \hfill (4.54) \hfill (4.55)

This birth and death process is the same as the final example given in [132], where it is claimed that it is not possible to give an explicit expression for the LCD for this special case. The stationary probability distribution of approximating process $\{X^{(1)}(t) : t \geq \tilde{t}_i\}$ is given by

\[ \widebar{p}^{(1)}_n = \left( \frac{\varphi}{\mu} \right)^n \frac{1}{n! \left( e^\varphi - 1 \right)} , \quad n \geq 1 , \]  

(4.56)
which is a Poisson distribution with parameter $\frac{\varphi}{\mu}$, conditioned not to take the value zero. This distribution has mean

$$\mathbb{E}(\bar{p}^{(1)}) = \frac{\varphi}{\mu(1 - e^{-\frac{\varphi}{\mu}})},$$  

and variance

$$\mathbb{V}(\bar{p}^{(1)}) = \frac{1}{(1 - e^{-\frac{\varphi}{\mu}})} \left( \frac{\varphi}{\mu} \right)^2 \left( 1 + \frac{\mu}{\varphi} - \frac{1}{1 - e^{-\frac{\varphi}{\mu}}} \right).$$  

From Eq. (4.56)

$$\bar{p}^{(1)}_{n+1} - \bar{p}^{(1)}_n = \frac{\varphi}{\mu} \left[ \frac{1}{n!} \left( \frac{\varphi}{\mu(n+1)} - 1 \right) \right],$$  

so that $\bar{p}^{(1)}_{n+1} - \bar{p}^{(1)}_n \geq 0$ for $n \leq \frac{\varphi}{\mu} - 1$. Using definition (4.35) and the fact that $\bar{p}^{(1)} <_{LR} q$, it can be shown that

$$1 \leq \frac{\bar{p}^{(1)}_{n+1}}{\bar{p}^{(1)}_n} \leq \frac{q_{n+1}}{q_n} \quad \text{for} \quad n \leq \frac{\varphi}{\mu} - 1,$$

which means that the components of the LCD, $q$, are non-decreasing in $n$ for $n \leq \frac{\varphi}{\mu} - 1$.

For the birth and death rates given by Eqs. (4.54)–(4.55), the stationary probability distribution of the approximating process $\{X^{(2)}(t) : t \geq \tilde{t}\}$ is

$$\bar{p}^{(2)}_n = \frac{1}{(n-1)!} \left( \frac{\varphi}{\mu} \right)^{n-1} e^{-\frac{\varphi}{\mu}}, \quad n \geq 1,$$

which has mean

$$\mathbb{E}(\bar{p}^{(2)}) = \frac{\varphi}{\mu} + 1,$$

and variance

$$\mathbb{V}(\bar{p}^{(2)}) = \frac{\varphi}{\mu}. $$
\[
\bar{p}_{n+1}^{(2)} - \bar{p}_n^{(2)} = \bar{p}_1^{(2)} \left( \frac{\varphi}{\mu} \right)^{n-1} \frac{1}{(n-1)!} \left( \frac{\varphi}{\mu n} - 1 \right),
\]

so that \(\bar{p}_{n+1}^{(2)} - \bar{p}_n^{(2)} \leq 0\) for \(n \geq \frac{\varphi}{\mu}\). Using \(q < \text{LR} \bar{p}^{(2)}\), it follows that

\[
\frac{q_{n+1}}{q_n} \leq \frac{\bar{p}_{n+1}^{(2)}}{\bar{p}_n^{(2)}} \leq 1 \quad \text{for} \quad n \geq \frac{\varphi}{\mu}.
\]

Taking this result together with Eq. (4.60), the regions over which the LCD is increasing and decreasing are completely determined for this special case. This is illustrated in Fig. 4.1, where the LCD and the two approximating probability distributions, \(\bar{p}^{(1)}\) and \(\bar{p}^{(2)}\), are plotted for different values of \(\frac{\varphi}{\mu}\) which corresponds to the maximum of the LCD in each case. It also appears that approximation \(\bar{p}^{(1)}\) becomes closer to the true LCD of the process as \(\frac{\varphi}{\mu}\) increases, while \(\bar{p}^{(2)}\) is the better approximation when \(\frac{\varphi}{\mu}\) is small. The accuracy of these approximations will be investigated further in Section 4.7.

### 4.3.2 The case \(\nu \gg 1\)

In the case where the T cells of the given clonotype compete with T cells of many other clonotypes for access to an APP, \(i.e., \nu \gg 1\), the birth and death rates (3.13)–(3.15) become

\[
\lambda_n = \frac{\varphi n}{n + \nu \langle n \rangle}, \quad (4.66)
\]

\[
\mu_n = \mu n, \quad (4.67)
\]
Figure 4.1: The LCD $q$ and the approximations $\bar{p}^{(1)}$ and $\bar{p}^{(2)}$ in the case $\nu \ll 1$ with $\mu = 1$ and (a) $\varphi = 1$, (b) $\varphi = 5$, (c) $\varphi = 10$, (d) $\varphi = 50$. In plots (c) and (d) the probability distributions $q$ and $\bar{p}^{(1)}$ are almost indistinguishable.

for all $n \geq 0$. The stationary probability distribution of the approximating process $\{X^{(1)}(t) : t \geq \tilde{t}_1\}$ is given by

$$\bar{p}^{(1)}_1 = \frac{1}{1 + \sum_{n=2}^{+\infty} \frac{1}{n} \left( \frac{\varphi}{\mu} \right)^{n-1} \prod_{k=1}^{n-1} \frac{1}{k + \nu(n)} },$$

(4.68)

$$\bar{p}^{(1)}_n = \frac{1}{n} \left( \frac{\varphi}{\mu} \right)^{n-1} \bar{p}^{(1)}_1 \prod_{k=1}^{n-1} \frac{1}{k + \nu(n)} , \quad n \geq 2.$$  

(4.69)

Then

$$\bar{p}^{(1)}_{n+1} - \bar{p}^{(1)}_n = \left( \frac{\varphi}{\mu} \right)^{n-1} \left( \frac{\varphi}{\mu(n+1)(n + \nu(n))} - \frac{1}{n} \right) \bar{p}^{(1)}_1 \prod_{k=1}^{n-1} \frac{1}{k + \nu(n)} ,$$

(4.70)
and it follows that for $\frac{\varphi}{\mu} < \nu\langle n \rangle$, $\tilde{p}^{(1)}_{n+1} \leq \tilde{p}^{(1)}_n$ for all $n$.

The stationary probability distribution of the approximating process $\{X^{(2)}(t) : t \geq \tilde{t}_i\}$ is given by

$$
\tilde{p}^{(2)}_1 = \frac{1}{1 + \sum_{n=2}^{+\infty} \left( \frac{\xi}{\mu} \right)^{n-1} \prod_{k=1}^{n-1} \frac{1}{k + \nu\langle n \rangle}}, 
$$

$$
\tilde{p}^{(2)}_n = \left( \frac{\varphi}{\mu} \right)^{n-1} \tilde{p}^{(2)}_1 \prod_{k=1}^{n-1} \frac{1}{k + \nu\langle n \rangle}, \quad n \geq 2. 
$$

Then

$$
\tilde{p}^{(2)}_{n+1} - \tilde{p}^{(2)}_n = \tilde{p}^{(2)}_1 \left( \frac{\varphi}{\mu} \right)^{n-1} \frac{1}{\mu(n + \nu\langle n \rangle)} \prod_{k=1}^{n-1} \frac{1}{k + \nu\langle n \rangle}, 
$$

and so $\tilde{p}^{(2)}_{n+1} \leq \tilde{p}^{(2)}_n$ for $n \geq \frac{\varphi}{\mu} - \nu\langle n \rangle$. Since $q <_{LR} \tilde{p}^{(2)}$, it follows that

$$
\frac{q_{n+1}}{q_n} \leq \frac{\tilde{p}^{(2)}_{n+1}}{\tilde{p}^{(2)}_n} \leq 1 \quad \text{for} \quad n \geq \frac{\varphi}{\mu} - \nu\langle n \rangle. 
$$

In particular, if $\frac{\varphi}{\mu} < \nu\langle n \rangle$, then $q$ is decreasing for all $n$, i.e., $q_1 > q_2 > \ldots$ and so most of the weight of the LCD is in the state $n = 1$, meaning that the clone is “on the brink of extinction”. This is shown in panels (a) and (b) of Fig. 4.2 where the LCD and the two approximating probability distributions, $\tilde{p}^{(1)}$ and $\tilde{p}^{(2)}$, are plotted for different values of $\varphi/\mu - \nu\langle n \rangle$. For negative values of $\varphi/\mu - \nu\langle n \rangle$, which correspond to short mean extinction times, $\tilde{p}^{(2)}$ is a good approximation to the LCD. Panel (d) of Fig. 4.2 shows that when $\varphi/\mu - \nu\langle n \rangle$ is large, the behaviour resembles that of a “hard niche” clonotype and $\tilde{p}^{(1)}$ becomes the better approximation. In the intermediate case with $\varphi/\mu - \nu\langle n \rangle \sim 0$, as shown in panel (c), neither approximation performs well.
Figure 4.2: The LCD $q$ and the approximations $\bar{p}^{(1)}$ and $\bar{p}^{(2)}$ in the case $\nu \gg 1$ with $\nu = 10$, $\langle n \rangle = 10$, $\mu = 1$ and (a) $\varphi = 10$, (b) $\varphi = 50$, (c) $\varphi = 100$, (d) $\varphi = 200$. In plots (a) and (b) the probability distributions $q$ and $\bar{p}^{(2)}$ are almost indistinguishable, whereas in plot (d) the probability distributions $q$ and $\bar{p}^{(1)}$ are very similar.

4.4 A normal approximation to the LCD

In this section, van Kampen’s “large $N$ expansion” [133, 134] is used in order to find a normal probability distribution which will provide a third approximation to the LCD. In the large $N$ expansion, it is expected that the number of T cells of clonotype $i$ consists of a deterministic component plus fluctuations. Let $\Omega$ be a parameter measuring the volume of the system, such that for large $\Omega$ the fluctuations are relatively small. Therefore, the change of variables

$$n = \Omega x(t) + \Omega^{1/2} \eta(t) ,$$

(4.75)
is defined, so that the fluctuations are of order $\Omega^{\frac{1}{2}}$. The large $N$ approximation provides a systematic method of expanding the forward Kolmogorov equation (3.37) as a power series in the parameter $\Omega$. The first stage is to define the difference operators

$$M_n f(n) = f(n + 1),$$  
(4.76)

$$M_n^{-1} f(n) = f(n - 1).$$  
(4.77)

The forward Kolmogorov equation (3.37) can be written in terms of these operators as

$$\frac{dp_n(t)}{dt} = (M_n^{-1} - 1)[\lambda_n p_n(t)] + (M_n - 1)[\mu_n p_n(t)].$$  
(4.78)

The change of variables given by Eq. (4.75) means that, rather than a probability distribution $p$ of $n$, there is a probability distribution $\Pi$ of $\eta$, i.e.,

$$\Pi(\eta, t) = p_n(t) = p_{\Omega x + \Omega^{\frac{1}{2}} \eta}(t),$$  
(4.79)

and so by the chain rule

$$\frac{dp_n(t)}{dt} = \frac{\partial \Pi(\eta, t)}{\partial t} - \Omega^{\frac{1}{2}} \frac{dx(t)}{dt} \frac{\partial \Pi(\eta, t)}{\partial \eta},$$  
(4.80)

because $n$ is fixed in Eq. (4.78) and

$$\frac{dn}{dt} = 0 \Rightarrow \Omega \frac{dx(t)}{dt} = -\Omega^{\frac{1}{2}} \frac{d\eta(t)}{dt}.$$  
(4.81)

Also,

$$M_n f(n) = M_n f(\Omega x + \Omega^{\frac{1}{2}} \eta) = f(\Omega x + \Omega^{\frac{1}{2}} (\eta + \Omega^{-\frac{1}{2}})),$$  
(4.82)
and so the operator $M_n$ changes $\eta$ to $\eta + \Omega^{-\frac{1}{2}}$. This leads to the Taylor expansion

$$M_n f(\eta) = f(\eta + \Omega^{-\frac{1}{2}}) = f(\eta) + \Omega^{-\frac{1}{2}} \frac{\partial f}{\partial \eta} + \frac{1}{2!} \Omega^{-1} \frac{\partial^2 f}{\partial \eta^2} + \ldots .$$  

(4.83)

Therefore, in terms of the new variables, the operator $M_n$ is given by

$$M_n = 1 + \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2!} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots ,$$  

(4.84)

and similarly

$$M_n^{-1} = 1 - \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2!} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots .$$  

(4.85)

In terms of the new variables, Eq. (4.78) becomes

$$\frac{\partial \Pi}{\partial t} - \Omega^\frac{1}{2} \frac{dx}{dt} \frac{\partial \Pi}{\partial \eta} = \left( - \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left( \lambda_{\omega x + \Omega^\frac{1}{2} \eta} \Pi \right)$$

$$+ \left( \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left( \mu_{\omega x + \Omega^\frac{1}{2} \eta} \Pi \right).$$  

(4.86)

This expansion is now applied to the special cases $\nu \ll 1$ and $\nu \gg 1$, as these are the cases for which analytic results are possible.

### 4.4.1 Normal approximation in the special case $\nu \ll 1$

For the birth and death rates (4.54)–(4.55), Eq. (4.86) becomes

$$\frac{\partial \Pi}{\partial t} - \Omega^\frac{1}{2} \frac{dx}{dt} \frac{\partial \Pi}{\partial \eta} = \left( - \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left( \tilde{\varphi} \Omega \Pi \right)$$

$$+ \left( \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left( \mu (\Omega x + \Omega^\frac{1}{2} \eta) \Pi \right),$$  

(4.87)

where $\varphi = \tilde{\varphi} \Omega$ in order to ensure dimensional consistency. Collecting terms of order $\Omega^\frac{1}{2}$ from Eq. (4.87) yields the deterministic equation for the process, which is an approximation to the stochastic model when the number of cells of clonotype $i$ is
large. The deterministic equation is given by
\[
\frac{dx(t)}{dt} = \tilde{\phi} - \mu x(t) ,
\] (4.88)
which has the solution
\[
x(t) = \frac{\tilde{\phi}}{\mu} + \left( x_0 - \frac{\tilde{\phi}}{\mu} \right) e^{-\mu t} ,
\] (4.89)
where \( x_0 = x(t = 0) \) is the initial density of T cells belonging to the fixed clonotype. Thus, the deterministic model predicts that as \( t \to +\infty \), \( x \to \tilde{\phi}/\mu \), or in terms of the original variable, \( n \to \varphi/\mu \), which is the stable steady state of the system. This is in contrast to the stochastic model, which predicts that the fixed clonotype becomes extinct with probability one. However, if the mean time until extinction is long, the mean of the LCD can be approximated by this stable steady state.

If one carries out the expansion to the next order, it is possible to study the fluctuations about the deterministic stable steady state and obtain a third approximation to the LCD of the process. Collecting terms of order \( \Omega^0 \) from Eq. (4.87) results in
\[
\frac{\partial \Pi}{\partial t} = \frac{1}{2} \left( \tilde{\phi} + \mu x \right) \frac{\partial^2 \Pi}{\partial \eta^2} + \mu \frac{\partial}{\partial \eta} (\eta \Pi) ,
\] (4.90)
which is a linear Fokker-Planck equation for the probability distribution of the fluctuations \( \Pi(\eta, t) \). The solution of this equation is an Ornstein-Uhlenbeck process \([134]\) and is therefore fully determined by its first and second moments. Now,
\[
\langle \eta \rangle = \int_{\mathbb{R}} d\eta \, \eta \Pi(\eta, t) ,
\] (4.91)
and so multiplying Eq. (4.90) by \( \eta \) and integrating over \( \eta \in \mathbb{R} \) results in the differential equation
\[
\frac{d}{dt} \langle \eta \rangle = -\mu \langle \eta \rangle ,
\] (4.92)
so that \( \langle \eta \rangle = \langle \eta_0 \rangle e^{-\mu t} \) where \( \langle \eta(t = 0) \rangle = \langle \eta_0 \rangle \) and so \( \langle \eta \rangle \to \langle \eta \rangle_{s} = 0 \) as \( t \to +\infty \).
Multiplying Eq. (4.90) by $\eta^2$ and integrating over $\eta \in \mathbb{R}$ gives

$$\frac{d}{dt} \langle \eta^2 \rangle = -2\mu \langle \eta^2 \rangle + \tilde{\varphi} + \mu x(t),$$

(4.93)

where $x(t)$ is a solution of Eq. (4.88). In order to study the fluctuations about the stable steady state, $\bar{x} = \tilde{\varphi}/\mu$, this value of $x$ is substituted into the above equation resulting in

$$\frac{d}{dt} \langle \eta^2 \rangle = -2\mu \langle \eta^2 \rangle + 2 \tilde{\varphi},$$

(4.94)

which has the solution

$$\langle \eta^2 \rangle = \frac{\tilde{\varphi}}{\mu} + \left( \langle \eta^2 \rangle_0 - \frac{\tilde{\varphi}}{\mu} \right) e^{-2\mu t},$$

(4.95)

so that $\langle \eta^2 \rangle \rightarrow \langle \eta^2 \rangle_s = \frac{\tilde{\varphi}}{\mu}$ as $t \rightarrow +\infty$. Hence, the LCD of the process may be approximated by a normal distribution with mean $\bar{n} = \varphi/\mu$ and variance $\sigma^2 = \Omega \langle \eta^2 \rangle_s = \varphi/\mu$. For this to be a good approximation it is required that the steady state $\bar{n} = \varphi/\mu$ is stable and that it is large enough to ensure that it is unlikely for the Ornstein-Uhlenbeck process to reach the absorbing boundary at $n = 0$. This is because the normal distribution assigns non-zero probability to negative values and, since the state-space of the process is $S = \{0, 1, \ldots\}$, if a lot of the weight of the distribution is assigned to negative values the approximation will be poor. For a normal distribution, around 99% of the weight of the distribution lies within three standard deviations of the mean [111]. Hence, negligible probabilities are assigned to negative values if $\bar{n} - 3\sigma > 0$, or equivalently

$$\frac{\sigma}{\bar{n}} < \frac{1}{3}.$$  

(4.96)

In the case $\nu \ll 1$, this means that the normal approximation should be reasonable
provided that

\[ 9\mu < \varphi . \]  

(4.97)

The accuracy of this approximation is studied in more detail in Section 4.7. Fig. 4.3 shows the normal approximation and the LCD of the process for several values of the parameter \( \frac{\varphi}{\mu} \) in the case \( \nu \ll 1 \). It is clear that the approximation improves as \( \frac{\varphi}{\mu} \) increases.

Figure 4.3: The LCD \( q \) and the normal approximation in the case \( \nu \ll 1 \) with \( \mu = 1 \) and (a) \( \varphi = 1 \), (b) \( \varphi = 5 \), (c) \( \varphi = 10 \), (d) \( \varphi = 50 \).
4.4.2 Normal approximation in the special case $\nu \gg 1$

For the birth and death rates (4.66)–(4.67), the forward Kolmogorov equation (4.86) becomes

$$\frac{\partial \Pi}{\partial t} - \Omega^\frac{1}{2} \frac{dx}{dt} \frac{\partial \Pi}{\partial \eta} = \left( - \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left[ \hat{\varphi}(\Omega x + \Omega^\frac{1}{2} \eta) \left( \frac{1}{x + \nu \langle \hat{n} \rangle} \right) \Pi \right]$$

$$+ \left( \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta^2} + \ldots \right) \left[ \mu(\Omega x + \Omega^\frac{1}{2} \eta) \Pi \right],$$

(4.98)

where $\varphi = \hat{\varphi} \Omega$ and $\langle n \rangle = \langle \hat{n} \rangle \Omega$ for dimensional consistency. Collecting terms of order $\Omega^\frac{1}{2}$ from Eq. (4.98) gives the deterministic equation

$$\frac{dx}{dt} = \frac{\hat{\varphi} x}{x + \nu \langle \hat{n} \rangle} - \mu x.$$  

(4.99)

In terms of the original variables, if $\varphi/\mu \leq \nu \langle n \rangle$ then 0 is the only steady state of the deterministic system and it is stable. However, if $\varphi/\mu > \nu \langle n \rangle$ the system has two steady states: 0 is an unstable steady state and $\varphi/\mu - \nu \langle n \rangle$ is a stable steady state. For the stochastic model, if $\varphi/\mu \leq \nu \langle n \rangle$ then extinction occurs rapidly (see Chapter 3), while if $\varphi/\mu > \nu \langle n \rangle$ the behaviour of the system is that of a “hard niche” clone and the mean time to extinction may be long, even though $\nu$ is large.

The fluctuations about the stable positive steady state $\hat{n} = \varphi/\mu - \nu \langle n \rangle$, or equivalently $\hat{x} = \hat{\varphi}/\mu - \nu \langle \hat{n} \rangle$, are now studied. Collecting terms of order $\Omega^0$ from Eq. (4.98) results in

$$\frac{\partial \Pi}{\partial t} = \frac{1}{2} \left( \frac{\hat{\varphi} x}{x + \nu \langle \hat{n} \rangle} + \mu x \right) \frac{\partial^2 \Pi}{\partial \eta^2} + \left( \frac{\hat{\varphi} x}{x + \nu \langle \hat{n} \rangle} \right)^2 - \frac{\hat{\varphi}}{x + \nu \langle \hat{n} \rangle} + \mu \frac{\partial}{\partial \eta} (\eta \Pi),$$

(4.100)

which, as in the previous case, is a linear Fokker-Planck equation. Multiplying
Eq. (4.100) by \( \eta \) and integrating over \( \eta \in \mathbb{R} \) gives

\[
\frac{d}{dt} \langle \eta \rangle = \mu \left( \frac{\mu \nu \langle \tilde{n} \rangle}{\tilde{\varphi}} - 1 \right) \langle \eta \rangle ,
\]

(4.101)

where \( x \) has taken its steady state value, \( \bar{x} = \tilde{\varphi}/\mu - \nu \langle \tilde{n} \rangle \). Hence, \( \langle \eta \rangle \to \langle \eta \rangle_s = 0 \) as \( t \to +\infty \). Multiplying Eq. (4.100) by \( \eta^2 \) and integrating over \( \eta \in \mathbb{R} \) results in

\[
\frac{d}{dt} \langle \eta^2 \rangle = \left( -2\mu + \frac{2\mu^2 \nu \langle \tilde{n} \rangle}{\tilde{\varphi}} \right) \langle \eta^2 \rangle + 2\tilde{\varphi} - 2\mu \nu \langle \tilde{n} \rangle ,
\]

(4.102)

where, again, \( x = \bar{x} = \tilde{\varphi}/\mu - \nu \langle \tilde{n} \rangle \). This means that the steady state value of \( \langle \eta^2 \rangle \) is given by

\[
\langle \eta^2 \rangle_s = \frac{\tilde{\varphi}}{\mu} .
\]

(4.103)

Hence, in this case, the LCD can be approximated by a normal distribution with mean \( \bar{n} = \varphi/\mu - \nu \langle n \rangle \) and variance \( \sigma^2 = \Omega \langle \eta^2 \rangle_s = \varphi/\mu \). For this to be a good approximation it is required that the steady state \( \bar{n} = \varphi/\mu - \nu \langle n \rangle \) is stable and that it is large enough to ensure that it is unlikely for the Ornstein-Uhlenbeck process to reach the absorbing boundary at \( n = 0 \). As in the hard niche case, it is expected that this approximation will be reasonable if the coefficient of variation of the approximating normal distribution is less than 1/3 (see Eq. (4.96)), i.e.,

\[
9 < \frac{\mu (\varphi/\mu - \nu \langle n \rangle)^2}{\varphi} .
\]

(4.104)

The normal approximation and the LCD are plotted for several values of \( \varphi/\mu - \nu \langle n \rangle \) in the case \( \nu \gg 1 \) in Fig. 4.4. In panel (a), \( \varphi/\mu - \nu \langle n \rangle = 0 \) and the normal approximation performs poorly. However, as \( \varphi/\mu - \nu \langle n \rangle \) increases, so does the accuracy of the normal approximation.
4.5 The diffusion approximation

In the previous section, van Kampen’s large $N$ expansion was used in order to derive a normal approximation to the LCD. In this section, the approximation is derived in a more rigorous manner, using the theorems of Kurtz which relate to a class of Markov process known as density dependent processes [46, 81, 82]. This method of approximation is referred to as the “diffusion approximation” and is derived here for a general density dependent birth and death process and for the special cases $\nu \ll 1$ and $\nu \gg 1$.

A univariate Markov process is said to be density dependent if the infinitesimal
transition probabilities are of the form
\[ q_{n,n+l} = \Omega \beta_l \left( \frac{n}{\Omega} \right) = \Omega \beta_l(x) , \quad (4.105) \]
where \( l \in \mathbb{Z}, \ x = \frac{n}{\Omega} \) and \( \beta_l(x) \) denotes that \( \beta_l \) is a function of \( x \) only. As in Section 4.4, \( \Omega \) is a parameter which represents the size of the system and, hence, \( x \) represents the density of T cells of a given clonotype. The diffusion approximation is derived by taking the limit \( \Omega \to +\infty \).

### 4.5.1 The diffusion approximation for a general birth and death process

A univariate birth and death process \( \{X(t) : t \geq 0\} \) on the state-space \( S = \{0, 1, 2, \ldots\} \) is density dependent if the birth and death rates are of the form
\[
\lambda_n = \Omega \beta_1(x) , \quad (4.106)
\]
\[
\mu_n = \Omega \beta_{-1}(x) . \quad (4.107)
\]
As transitions can only occur to adjacent states, \( \beta_l = 0 \) for \( l \neq 1, -1 \). First define
\[
F(x) = \beta_1(x) - \beta_{-1}(x) . \quad (4.108)
\]
Now, define \( X_d(t) \) to be the solution of
\[
\frac{dX_d(t)}{dt} = F(x) , \quad (4.109)
\]
so that \( X_d(t) \) is the deterministic process representing the time evolution of the density of cells, \( x \). Let \( x_0 = X_d(t = 0) \) and suppose that \( \lim_{\Omega \to +\infty} \frac{X(t=0)}{\Omega} = x_0 \), so that the initial condition of the deterministic process and the initial state of the
stochastic process are the same in the limit $\Omega \to +\infty$. The state-space of the process $\{X(t)/\Omega : t \geq 0\}$ is denoted by $S_\Omega$ and is given by $\{0, 1/\Omega, 2/\Omega, \ldots\}$. Suppose that for each compact set $K \subset S_\Omega$

$$\sum_{l \in \mathbb{Z}} |l| \sup_{x \in K} \beta_l(x) = \sup_{x \in K} (\beta_1(x)) + \sup_{x \in K} (\beta_{-1}(x)) < +\infty, \quad (4.110)$$

and there exists $M_K > 0$ such that

$$|F(x) - F(y)| \leq M_K |x - y| \text{ for } x, y \in K. \quad (4.111)$$

Then, by Theorem 11.2.1 of [46],

$$\lim_{\Omega \to +\infty} \sup_{s \leq t} \left| \frac{X(s)}{\Omega} - X_d(s) \right| = 0, \quad (4.112)$$

for all $t \geq 0$, which means that $X(t)/\Omega$ converges to the deterministic process $X_d(t)$ in the limit $\Omega \to +\infty$. Next, the fluctuations about the deterministic process are considered. Let

$$V_\Omega(t) = \sqrt{\Omega} \left( \frac{X(t)}{\Omega} - X_d(t) \right), \quad (4.113)$$

where $V_\Omega$ is the distribution of the fluctuations, which is the same change of variables as that employed in Section 4.4. Next, define

$$V(t) = V(0) + \sum_{l \in \mathbb{Z}} l W_l \left( \int_0^t \beta_l(X_d(s)) \, ds \right) + \int_0^t \frac{dF(X_d(s))}{dx} V(s) \, ds, \quad (4.114)$$

where $W_l(x)$ denotes a Wiener process with mean zero and variance $x$. Since, for each compact set $K \subset S_\Omega$

$$\sum_{l \in \mathbb{Z}} |l|^2 \sup_{x \in K} \beta_l(x) = \sup_{x \in K} (\beta_1(x)) + \sup_{x \in K} (\beta_{-1}(x)), \quad (4.115)$$

$$\left| F(x) - F(y) \right| \leq M_K |x - y| \text{ for } x, y \in K. \quad (4.111)$$

Then, by Theorem 11.2.1 of [46],

$$\lim_{\Omega \to +\infty} \sup_{s \leq t} \left| \frac{X(s)}{\Omega} - X_d(s) \right| = 0, \quad (4.112)$$

for all $t \geq 0$, which means that $X(t)/\Omega$ converges to the deterministic process $X_d(t)$ in the limit $\Omega \to +\infty$. Next, the fluctuations about the deterministic process are considered. Let

$$V_\Omega(t) = \sqrt{\Omega} \left( \frac{X(t)}{\Omega} - X_d(t) \right), \quad (4.113)$$

where $V_\Omega$ is the distribution of the fluctuations, which is the same change of variables as that employed in Section 4.4. Next, define

$$V(t) = V(0) + \sum_{l \in \mathbb{Z}} l W_l \left( \int_0^t \beta_l(X_d(s)) \, ds \right) + \int_0^t \frac{dF(X_d(s))}{dx} V(s) \, ds, \quad (4.114)$$

where $W_l(x)$ denotes a Wiener process with mean zero and variance $x$. Since, for each compact set $K \subset S_\Omega$

$$\sum_{l \in \mathbb{Z}} |l|^2 \sup_{x \in K} \beta_l(x) = \sup_{x \in K} (\beta_1(x)) + \sup_{x \in K} (\beta_{-1}(x)), \quad (4.115)$$
The condition
\[ \sum_{l \in \mathbb{Z}} |l|^2 \sup_{x \in K} \beta_l(x) < +\infty, \quad (4.116) \]
is automatically satisfied if condition (4.110) holds. Suppose that \( \beta_1(x), \beta_{-1}(x) \) and \( \frac{dF}{dx} \) are continuous, that \( \lim_{\Omega \to +\infty} V_\Omega(t = 0) = V(t = 0) \) and that condition (4.116) holds. Then, by Theorem 11.2.3 of [46], \( V_\Omega(t) \to V(t) \) in distribution as \( \Omega \to +\infty \), where \( V(t) \) is the solution of Eq. (4.114).

Let \( \bar{x} \) denote the stable steady state of the deterministic process \( X_d(t) \), assuming that it exists. Then, from Eq. (4.109),
\[ \beta_1(\bar{x}) = \beta_{-1}(\bar{x}). \quad (4.117) \]
The fluctuations about this stable steady state are now considered. Let the initial state of the process be given by the stable steady state, assuming that it exists, so that
\[ x_0 = X_d(t = 0) = \frac{\mathcal{X}(t = 0)}{\Omega} = \bar{x}, \quad (4.118) \]
and, hence, \( X_d(t) = \bar{x} \) for all \( t \geq 0 \). Then
\[
\sum_{l \in \mathbb{Z}} lW_l \left( \int_0^t \beta_l(\mathcal{X}_d(s))ds \right) = W_1 \left( \int_0^t \beta_1(\bar{x})ds \right) - W_{-1} \left( \int_0^t \beta_{-1}(\bar{x})ds \right) \\
= W_1(\beta_1(\bar{x})t) - W_{-1}(\beta_{-1}(\bar{x})t) \\
= W_1(\beta_1(\bar{x})t) - W_{-1}(\beta_1(\bar{x})t), \quad (4.119)
\]
using Eq. (4.117), where \( W_1 \) and \( W_{-1} \) denote independent Wiener processes, each with mean zero and variance \( \beta_1(\bar{x})t \). Now,
\[
W_1(\beta_1(\bar{x})t) - W_{-1}(\beta_1(\bar{x})t) = \sqrt{2\beta_1(\bar{x})}W(t), \quad (4.120)
\]
where \( W(t) \) denotes the standard Wiener process which has mean zero and variance.
Also, if \( \bar{x} \) is the stable steady state of the deterministic system, there exists a real constant \( k \) such that

\[
\left. \frac{dF}{dx} \right|_{x=\bar{x}} = -k < 0 .
\] (4.121)

Then

\[
V(t) = V(0) + \sqrt{2\beta_1(\bar{x})} W(t) - k \int_0^t V(s) ds ,
\] (4.122)

or equivalently,

\[
dV = -kV dt + \sqrt{2\beta_1(\bar{x})} dW ,
\] (4.123)

which is an Ornstein-Uhlenbeck process whose stationary probability distribution is normal with mean zero and variance \( \frac{\beta_1(\bar{x})}{k} \). Hence, the LCD of the process may be approximated by a normal distribution with mean \( \Omega \bar{x} \) and variance \( \frac{\Omega\beta_1(\bar{x})}{k} \).

### 4.5.2 The diffusion approximation in the special case \( \nu \ll 1 \)

In the case \( \nu \ll 1 \), the birth and death rates of the process are given by

\[
\lambda_n = \varphi = \tilde{\varphi} \Omega ,
\] (4.124)

\[
\mu_n = \mu n = \mu \Omega x ,
\] (4.125)

where \( \varphi = \tilde{\varphi} \Omega \). Hence, the process is density dependent with \( \beta_1(x) = \tilde{\varphi} \), \( \beta_{-1}(x) = \mu x \) and \( \beta_l(x) = 0 \) for \( l \neq 1, -1 \). Next let

\[
F(x) = \tilde{\varphi} - \mu x .
\] (4.126)

As above, define \( X_d(t) \) to be the solution of

\[
\frac{dX_d(t)}{dt} = F(x) ,
\] (4.127)
so that $X_d(t)$ is the deterministic process representing the time evolution of the
density of cells, $x$. Let $x_0 = X_d(t = 0)$ and suppose that $\lim_{\Omega \to +\infty} \frac{X(t=0)}{\Omega} = x_0$, so
that the initial condition of the deterministic process and the initial state of the
stochastic process are the same in the limit $\Omega \to +\infty$. As before, the state-space of
the process $\{X(t)/\Omega : t \geq 0\}$ is denoted by $S_\Omega$. Then for each compact set $K \subset S_\Omega$,

$$\sup_{x \in K} (\beta_1(x)) + \sup_{x \in K} (\beta_{-1}(x)) = \sup_{x \in K} (\tilde{\phi}) + \sup_{x \in K} (\mu x)$$

$$= \tilde{\phi} + \mu \sup_{x \in K} (x)$$

$$< +\infty,$$  \hspace{1cm} (4.128)

because $K$ is compact and therefore bounded, which means that $\sup_{x \in K}(x)$ exists
and is finite. Also, for all $x, y \in K$

$$|F(x) - F(y)| = \mu |x - y|,$$  \hspace{1cm} (4.129)

from Eq. (4.126), and so taking $M_K = \mu > 0$ satisfies condition (4.111). Therefore,
in the limit $\Omega \to +\infty$, $X(t)/\Omega$ converges to the deterministic process $X_d(t)$ according
to Eq. (4.112).

The deterministic process, $X_d(t)$, has a unique steady state at $\tilde{\phi}/\mu$ which is stable for
all values of the parameters (see Section 4.4.1). The distribution of the fluctuations,
$V_\Omega(t)$, about the deterministic steady state $\bar{x} = \tilde{\phi}/\mu = x_0$ in the limit $\Omega \to +\infty$ is
now determined. Since $\frac{dF}{dx}$, $\beta_1(x)$, $\beta_{-1}(x)$ are continuous and condition (4.116) holds,
then $V_\Omega(t) \to V(t)$ in distribution as $\Omega \to +\infty$, assuming that $V_\Omega(t = 0) = V(t = 0)$.

From Eqs. (4.119)–(4.120),

$$\sum_{l \in \mathbb{Z}} lW_l \left( \int_0^t \beta_l(X_d(s)) ds \right) = \sqrt{2\beta_1(\bar{x})} W(t) = \sqrt{2\tilde{\phi}} W(t).$$  \hspace{1cm} (4.130)
Also,
\[ \frac{dF}{dx} \bigg|_{x=\bar{x}} = -\mu , \]
and so the distribution \( V(t) \) is defined according to Eq. (4.114) by
\[ V(t) = V(0) + \sqrt{2\tilde{\varphi}} W(t) - \mu \int_0^t V(s) ds , \]
or equivalently,
\[ dV = -\mu V dt + \sqrt{2\tilde{\varphi}} dW , \]
which is an Ornstein-Uhlenbeck process whose stationary probability distribution is normal with mean zero and variance \( \tilde{\varphi}/\mu \). Hence, the LCD of the process \( \mathcal{X}(t) \) can be approximated by a normal distribution with mean \( \varphi/\mu \) and variance \( \varphi/\mu \), as in Section 4.4.1.

4.5.3 The diffusion approximation in the special case \( \nu \gg 1 \)

In the case \( \nu \gg 1 \), the birth and death rates of the process are given by
\[ \lambda_n = \frac{\varphi n}{n + \nu \langle \bar{n} \rangle} = \frac{\Omega \tilde{\varphi} x}{x + \nu \langle \bar{n} \rangle} , \]
\[ \mu_n = \mu n = \mu \Omega x , \]
where \( \varphi = \tilde{\varphi} \Omega \) and \( \langle \bar{n} \rangle = \langle \bar{n} \rangle \Omega \). Hence, the process is density dependent with \( \beta_1(x) = \tilde{\varphi} x / (x + \nu \langle \bar{n} \rangle) \), \( \beta_{-1}(x) = \mu x \) and \( \beta_l(x) = 0 \) for \( l \neq 1, -1 \). Next let
\[ F(x) = \frac{\tilde{\varphi} x}{x + \nu \langle \bar{n} \rangle} - \mu x , \]
and define \( \mathcal{X}_d(t) \) to be the solution of
\[ \frac{d\mathcal{X}_d(t)}{dt} = F(x) , \]
so that $\mathcal{X}_d(t)$ is the deterministic process representing the time evolution of the density of cells, $x$. Define $x_0 = \mathcal{X}_d(t = 0)$ and suppose that $\lim_{\Omega \to +\infty} \frac{\mathcal{X}(t = 0)}{\Omega} = x_0$, so that the initial condition of the deterministic process and the initial state of the stochastic process are the same in the limit $\Omega \to +\infty$. As before, the state-space of the process $\{\mathcal{X}(t)/\Omega : t \geq 0\}$ is denoted by $S_\Omega$. Then for each compact set $K \subset S_\Omega$

$$
\sup_{x \in K} (\beta_1(x)) + \sup_{x \in K} (\beta_{-1}(x)) = \bar{\phi} \sup_{x \in K} \left( \frac{x}{x + \nu(\bar{n})} \right) + \mu \sup_{x \in K} (x) < +\infty,
$$

(4.138)

because $K$ is compact and therefore bounded, and so $\sup_{x \in K} \left( \frac{x}{x + \nu(\bar{n})} \right)$ and $\sup_{x \in K} (x)$ exist and are finite. Also, for all $x, y \in K$

$$
|F(x) - F(y)| = \left| \frac{\bar{\phi} x}{x + \nu(\bar{n})} - \mu x - \frac{\bar{\phi} y}{y + \nu(\bar{n})} + \mu y \right|
\leq \left| \frac{\bar{\phi} (x - y)}{\nu(\bar{n})} - \mu (x - y) \right|
= \left( \frac{\bar{\phi}}{\nu(\bar{n})} - \mu \right) |x - y|,
$$

(4.139)

and so taking $M_K = \frac{\bar{\phi}}{\nu(\bar{n})} - \mu$ satisfies condition (4.111). Note that $M_K > 0$ when the stable steady state $\bar{x} = \bar{\phi}/\mu - \nu(\bar{n})$ exists (see Section 4.4.2). Therefore, in the limit $\Omega \to +\infty$, $\mathcal{X}(t)/\Omega$ converges to the deterministic process $\mathcal{X}_d(t)$ according to Eq. (4.112).

The distribution of the fluctuations, $V_{\Omega}(t)$, about the deterministic stable steady state $\bar{x} = \bar{\phi}/\mu - \nu(\bar{n}) = x_0$ in the limit $\Omega \to +\infty$ is now determined. Since $\frac{dF}{dx}$, $\beta_1(x)$, $\beta_{-1}(x)$ are continuous and condition (4.116) holds, then $V_{\Omega}(t) \to V(t)$ in distribution as $\Omega \to +\infty$, assuming that $V_{\Omega}(t = 0) = V(t = 0)$. From Eqs. (4.119)–(4.120) it can be shown that,

$$
\sum_{l \in \mathbb{Z}} lW_l \left( \int_0^t \beta_1(\mathcal{X}_d(s)) ds \right) = \sqrt{2\beta_1(\bar{x})}W(t) = \sqrt{2(\bar{\phi} - \mu \nu(\bar{n}))}W(t).
$$

(4.140)
Also,
\[
\left. \frac{dF}{dx} \right|_{x=\bar{x}} = \mu \left( \frac{\mu \nu \langle \tilde{n} \rangle}{\tilde{\phi}} - 1 \right),
\] (4.141)
which is negative when the steady state $\bar{x}$ is stable. Hence, the distribution $V(t)$ is defined according to Eq. (4.114) by
\[
V(t) = V(0) + \sqrt{2(\tilde{\phi} - \mu \nu \langle \tilde{n} \rangle)} W(t) - \mu \left( 1 - \frac{\mu \nu \langle \tilde{n} \rangle}{\tilde{\phi}} \right) \int_0^t V(s) ds ,
\] (4.142)
or equivalently
\[
dV = -\mu \left( 1 - \frac{\mu \nu \langle \tilde{n} \rangle}{\tilde{\phi}} \right) V dt + \sqrt{2(\tilde{\phi} - \mu \nu \langle \tilde{n} \rangle)} dW ,
\] (4.143)
which is an Ornstein-Uhlenbeck process whose stationary probability distribution is normal with mean zero and variance $\tilde{\phi}/\mu$. Hence, the LCD of the process $\mathcal{X}(t)$ can be approximated by a normal distribution with mean $\varphi/\mu - \nu \langle n \rangle$ and variance $\varphi/\mu$, as in Section 4.4.2.

### 4.6 A Poisson approximation

In this section, a partial differential equation (PDE) for the cumulant generating function of the process is derived and this is used to obtain a further approximation to the LCD in the case $\nu \ll 1$. The first step is to introduce the moment generating function (mgf) [66] of the process. This is denoted by $\mathcal{M}_{\mathcal{X}}(\theta,t)$ and is defined by
\[
\mathcal{M}_{\mathcal{X}}(\theta,t) \equiv E[e^{\theta \mathcal{X}(t)}] = \sum_{n=1}^{+\infty} p_n(t) e^{n \theta} ,
\] (4.144)
for some $\theta \in \mathbb{R}$. Note that the LCD is defined for $n \in \mathcal{S} \setminus \{0\}$ and so the state $n = 0$ is excluded from the approximation. In the case $\nu \ll 1$, the forward Kolmogorov
equations for \( n \in S \setminus \{0\} \) are given by

\[
\frac{dp_1(t)}{dt} = 2\mu p_2(t) - (\varphi + \mu)p_1(t), \tag{4.145}
\]

\[
\frac{dp_n(t)}{dt} = \varphi p_{n-1}(t) + \mu(n+1)p_{n+1}(t) - (\varphi + \mu n)p_n(t), \quad n \geq 2. \tag{4.146}
\]

Multiplying Eqs. (4.145)–(4.146) by \( e^{n\theta} \) and summing over all values of \( n \in S \setminus \{0\} \) results in

\[
\frac{\partial}{\partial t} \sum_{n=1}^{+\infty} p_n(t)e^{n\theta} = \sum_{n=1}^{+\infty} \mu(n+1)p_{n+1}(t)e^{n\theta} + \sum_{n=2}^{+\infty} \varphi p_{n-1}(t)e^{n\theta} - \sum_{n=1}^{+\infty} (\varphi + \mu n)p_n(t)e^{n\theta} - \mu p_1(t) \\
\simeq \sum_{n=0}^{+\infty} \mu(n+1)p_{n+1}(t)e^{n\theta} + \sum_{n=2}^{+\infty} \varphi p_{n-1}(t)e^{n\theta} - \sum_{n=1}^{+\infty} (\varphi + \mu n)p_n(t)e^{n\theta}.
\]

(4.147)

In this approximation, it is assumed that the term \( \mu p_1(t) \) is small and can be neglected. Therefore, this approximation is expected to be reasonable for small values of \( \mu \). With this assumption, Eq. (4.147) is equivalent to the following PDE:

\[
\frac{\partial M_X(\theta, t)}{\partial t} = \varphi(e^\theta - 1)M_X(\theta, t) + \mu(e^{-\theta} - 1)\frac{\partial M_X(\theta, t)}{\partial \theta}. \tag{4.148}
\]

The cumulant generating function (cgf) is denoted by \( K_X(\theta, t) \) and is defined in terms of the mgf by

\[
K_X(\theta, t) = \log[M_X(\theta, t)], \tag{4.149}
\]

so that

\[
\frac{\partial M_X(\theta, t)}{\partial t} = e^{K_X(\theta, t)}\frac{\partial K_X(\theta, t)}{\partial t}, \tag{4.150}
\]

\[
\frac{\partial M_X(\theta, t)}{\partial \theta} = e^{K_X(\theta, t)}\frac{\partial K_X(\theta, t)}{\partial \theta}. \tag{4.151}
\]
Therefore, from Eq. (4.148), the PDE satisfied by the cgf is
\[
\frac{\partial K_X(\theta,t)}{\partial t} = \varphi(e^\theta - 1) + \mu(e^{-\theta} - 1) \frac{\partial K_X(\theta,t)}{\partial \theta} .
\] (4.152)

The cumulants, \( \kappa_n(t) \), are the coefficients of the power series
\[
K_X(\theta,t) = \sum_{n=1}^{+\infty} \kappa_n(t) \frac{\theta^n}{n!} ,
\] (4.153)
and the first two cumulants of a probability distribution give its mean and variance, respectively. Expanding Eq. (4.152) in powers of \( \theta \) results in
\[
\sum_{n=1}^{+\infty} \frac{d\kappa_n(t)}{dt} \frac{\theta^n}{n!} = \varphi\left(\theta + \frac{\theta^2}{2!} + \frac{\theta^3}{3!} + \ldots\right) + \mu\left(-\theta + \frac{\theta^2}{2!} - \frac{\theta^3}{3!} + \ldots\right) \sum_{n=1}^{+\infty} \kappa_n(t) \frac{\theta^{n-1}}{(n-1)!} .
\] (4.154)

Equating coefficients of \( \theta^n \) from the above equation results in a set of ordinary differential equations (ODEs) for the cumulants, the first few of which are
\[
\frac{d\kappa_1(t)}{dt} = \varphi - \mu\kappa_1(t) ,
\] (4.155)
\[
\frac{d\kappa_2(t)}{2dt} = \frac{\varphi}{2} + \frac{\mu}{2}\kappa_1(t) - \mu\kappa_2(t) ,
\] (4.156)
\[
\frac{d\kappa_3(t)}{3!dt} = \frac{\varphi}{3!} + \frac{\mu}{3!}\kappa_1(t) + \frac{\mu}{2}\kappa_2(t) - \frac{\mu}{2}\kappa_3(t) ,
\] (4.157)
and in general,
\[
\frac{1}{n!} \frac{d\kappa_n(t)}{dt} = \frac{\varphi}{n!} + \mu \sum_{j=1}^{n} \kappa_{n-j+1}(t) \frac{(-1)^j}{j!(n-j)!} .
\] (4.158)

Solving these equations for their stationary values, denoted by \( \kappa_n \) for \( n \in S \setminus \{0\} \), results in an approximation to the cumulants of the LCD of the process. It is now shown that the stationary solution of Eq. (4.158) is given by \( \kappa_1 = \kappa_2 = \ldots = \kappa_n = \varphi/\mu \) for all \( n \in S \setminus \{0\} \). This requires use of the binomial theorem for \( n = 1, 2, \ldots \).
which states that

$$
(1 - x)^n = \sum_{j=0}^{n} (-1)^j \binom{n}{j} x^j \quad \text{for } -\infty < x < +\infty .
$$

(4.159)

Now assume that \( \kappa_1 = \kappa_2 = \ldots = \kappa_n = \varphi/\mu \). Then, from Eq. (4.158)

$$
\frac{1}{n!} \frac{d\kappa_n(t)}{dt} = \frac{\varphi}{n!} + \varphi \sum_{j=1}^{n} \frac{(-1)^j}{j!(n-j)!} \\
= \varphi \sum_{j=0}^{n} \frac{(-1)^j}{j!(n-j)!} \\
= \frac{\varphi}{n!} \sum_{j=0}^{n} (-1)^j \binom{n}{j} \\
= 0 ,
$$

(4.160)

by substituting \( x = 1 \) into Eq. (4.159). Therefore \( \kappa_1 = \kappa_2 = \ldots = \kappa_n = \varphi/\mu \) is a stationary solution to Eq. (4.158) for \( n \in S \setminus \{0\} \) and hence the LCD can be approximated by a Poisson distribution on the state-space \( S \setminus \{0\} \) with parameter \( \varphi/\mu \) because, for a Poisson distribution, all the cumulants are equal to the parameter of the distribution. For \( \varphi/\mu \) large, this distribution may be approximated by a normal distribution with mean and variance equal to \( \varphi/\mu \), which is the approximation to the LCD given by the large \( N \) expansion and diffusion approximation in Sections 4.4.1 and 4.5.2.

In the case considered here, the birth and death rates are linear and so the ODE for \( \kappa_n(t) \) contains no terms of order \( \kappa_{n+1}(t) \) or higher. This means that assumptions about the form of the LCD are not needed in order to close the hierarchy of equations [90, 91]. If the birth or death rates of the process contain non-linear terms in the variable \( n \), the ODE for \( \kappa_n(t) \) contains terms proportional to \( \kappa_{n+1}(t) \) and so moment closure techniques are needed in order to close the hierarchy of equations. There are several methods of doing this. One approach is to assume that the LCD
has a normal distribution which means that the stationary cumulants of order three and above are zero i.e., $\kappa_3 = \kappa_4 = \ldots = 0$. Solving Eqs. (4.155)–(4.156) for the stationary values $\kappa_1$ and $\kappa_2$ with this assumption results in $\kappa_1 = \kappa_2 = \varphi/\mu$. Then, the LCD of the process is approximated by a normal distribution with mean and variance given by $\varphi/\mu$. This is the same approximation that was derived in Sections 4.4.1 and 4.5.2 of this chapter using the large $N$ expansion and the diffusion approximation.

In this section, a further approximation for the LCD has been derived using the cumulants of the unconditioned process. It may seem more appropriate to condition on non-extinction of the given T cell clonotype in order to approximate the LCD. However, if instead the cumulants of the process conditioned on non-extinction are used, Eqs. (4.148) and (4.152) contain additional terms which are proportional to $\mu q_1(t)$. As this quantity is unknown, analytical progress can only be made if these terms are neglected, as above. This is reasonable if $q_1(t)$ or $\mu$ is small and so the approximation is expected to be reasonable when the mean time to extinction is long. This is illustrated in Fig. 4.5, where the Poisson approximation and the LCD are plotted for several values of the parameter $\frac{\varphi}{\mu}$ in the case $\nu \ll 1$.

### 4.7 Accuracy of the three approximations

The accuracy of the various approximations to the LCD ($\bar{p}^{(1)}, \bar{p}^{(2)}$, the normal approximation and the Poisson approximation) is now compared in the special cases $\nu \ll 1$ and $\nu \gg 1$. The state-space of the process is first truncated to be finite, i.e., $S = \{0, 1, \ldots, N\}$ to allow numerical computation. Here, $N = 5000$ was taken, which was large enough so that $q_N = 0$. The LCD was then computed numerically, using the iterative procedure described in Section 3.2.3, and then the probability distributions of each approximation were calculated using the results from the previous
Figure 4.5: The LCD $q$ and the Poisson approximation in the case $\nu \ll 1$ with $\mu = 1$ and (a) $\varphi = 1$, (b) $\varphi = 5$, (c) $\varphi = 10$, (d) $\varphi = 50$. In plots (c) and (d) the two probability distributions are almost indistinguishable.

sections. The approximations $\tilde{p}^{(1)}$, $\tilde{p}^{(2)}$ and the Poisson approximation are discrete distributions, while the normal approximation is continuous. Therefore, the normal approximation was discretised by calculating the value of the probability density function at each point $n \in S \setminus \{0\}$. The difference between the LCD, $q$, and approximating probability distribution $\tilde{p}^{(1)}$ may be quantified using the Jenson-Shannon divergence [84], which is defined by

$$D_{JS}(q, \tilde{p}^{(1)}) = \frac{1}{2} \sum_{n=1}^{+\infty} \tilde{p}_n^{(1)} \log \left( \frac{\tilde{p}_n^{(1)}}{r_n} \right) + \frac{1}{2} \sum_{n=1}^{+\infty} q_n \log \left( \frac{q_n}{r_n} \right) , \quad (4.161)$$
where \( r_n = (\bar{p}_n^{(1)} + q_n)/2 \) for \( n \geq 1 \) is the arithmetic mean of the two probability distributions. The Jensen-Shannon divergence is defined similarly for the approximating probability distribution \( \bar{p}^{(2)} \), the normal approximation and the Poisson approximation.

Fig. 4.6 shows the Jensen-Shannon divergence for each approximation in the case \( \nu \ll 1 \) as a function of the stable deterministic steady state value, \( \bar{n} = \varphi/\mu \). For large values of \( \varphi/\mu \) (which correspond to long mean extinction times), \( \bar{p}^{(1)} \) and the Poisson approximation are very similar and provide the best approximations to the LCD, while for small \( \varphi/\mu \) (when the mean time to extinction is short), \( \bar{p}^{(2)} \) is the best approximation. As expected, the normal approximation is poor when the deterministic steady state is close to the origin (because the clonotype is on the brink of extinction) and improves as \( \varphi/\mu \) increases.

Fig. 4.7 shows the Jensen-Shannon divergence for each approximation in the case \( \nu \gg 1 \). The normal approximation is only defined when the stable deterministic steady state is positive \( i.e., \varphi/\mu - \nu\langle n \rangle > 0 \). Again, approximation \( \bar{p}^{(1)} \) is the most accurate when the deterministic steady state takes large values corresponding to long mean extinction times, while \( \bar{p}^{(2)} \) is the most accurate when \( \nu\langle n \rangle \) is large compared to \( \varphi/\mu \), corresponding to short mean extinction times.

### 4.8 Discussion

Although the terms “quasi-stationary probability distribution” and “limiting conditional probability distribution” are used almost interchangeably by some authors, this is only true for processes which have a finite state-space. If the state-space of the process is infinite, a difficulty arises because a QSD may not exist, and even if it does, it may not be unique. In this chapter it has been shown that, although there are an infinite number of QSDs, there exists a unique LCD for the process \( \{X(t) : t \geq \tilde{t}\} \)
Figure 4.6: The Jenson-Shannon divergence between the LCD and the various approximations as a function of $\varphi/\mu$ in the case $\nu \ll 1$.

Figure 4.7: The Jenson-Shannon divergence between the LCD and the various approximations as a function of $\varphi/\mu - \nu \langle n \rangle$ in the case $\nu \gg 1$. 
on the state-space $S = \{0, 1, 2, \ldots\}$. It is not possible to find an explicit analytic expression for the LCD, but there are a variety of methods of approximation that can be used. It has also been shown how two of these approximations provide upper and lower bounds to the LCD in terms of likelihood ratio ordering, and the regions over which the LCD is increasing and decreasing have been determined for some special cases of the model.

Which approximation is the most appropriate depends on the parameters of the system. In particular, as conjectured by Nåsell [101], the mean time until extinction occurs determines how accurate a particular approximation is. When the parameters of the model are such that the mean time until extinction occurs is short, $\bar{p}^{(2)}$ provides the best approximation to the LCD, while the Poisson and the normal approximations are poor. The approximation $\bar{p}^{(1)}$ performs better than the Poisson and normal approximations, but not as well as the approximation $\bar{p}^{(2)}$. However, in the case when the mean time to extinction is short, the LCD is less physically relevant as numerical results suggest that the process becomes extinct before it relaxes to the LCD.

As the mean time to extinction increases, so does the mean of the LCD of the process and the approximations $\bar{p}^{(1)}$, the Poisson and the normal approximation become more accurate and the two approximations, $\bar{p}^{(1)}$ and the Poisson approximation, become very similar in the case $\nu \ll 1$. This is to be expected because $\bar{p}^{(1)}$ is given by a Poisson distribution with expectation value $\varphi/\mu$ conditioned not to take the value zero. The Poisson distribution with expectation value $\varphi/\mu$ may be approximated by a normal distribution with mean and variance $\varphi/\mu$ for $\varphi/\mu$ large and so in the case $\nu \ll 1$, the Poisson and the normal approximations become more similar as the mean time until extinction increases.

Hence, the numerical results indicate that $\bar{p}^{(1)}$ is a good approximation to the LCD when the mean time to extinction is long, while $\bar{p}^{(2)}$ is a good approximation when
the mean time to extinction is short, in agreement with the results of Nåsell [101]. If $\nu \langle n \rangle$ is very large, the mean time to extinction is short and the expressions for the birth and death rates (3.21)–(3.22) are approximately linear. The results can be mathematically justified as follows. For a linear birth and death process with an absorbing state at zero, i.e., $\lambda_n = \lambda n$ and $\mu_n = \mu n$ for $n \geq 0$, the QSD can be determined explicitly and is given by $\bar{q}_n = \left(1 - \frac{\lambda}{\mu}\right)\lambda^{n-1}$ when $\frac{\lambda}{\mu} < 1$ (this condition guarantees that the absorbing state is reached with certainty) [101]. For this process, the approximation $\bar{p}^{(2)}$ is given by

$$\bar{p}^{(2)}_1 = \frac{1}{1 + \sum_{n=2}^{+\infty} \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_1 \mu_2 \cdots \mu_{n-1}}} = 1 - \frac{\lambda}{\mu}, \quad (4.162)$$

$$\bar{p}^{(2)}_n = \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_1 \mu_2 \cdots \mu_{n-1}} \bar{p}^{(2)}_1 = \left(1 - \frac{\lambda}{\mu}\right)\frac{\lambda^{n-1}}{\mu} \quad \text{for } n \geq 2. \quad (4.163)$$

Hence, for a process with linear birth and death rates $\bar{p}^{(2)} = \bar{q}$. This provides theoretical support to the observation that $\bar{p}^{(2)}$ is a good approximation in the case $\nu \gg 1$ when $\nu \langle n \rangle$ is large.
Chapter 5

A stochastic model for a pair of competing clonotypes

In Chapter 3, the number of T cells belonging to a particular T cell clonotype was modelled by means of a univariate birth and death process. This model relies upon mean field assumptions regarding the competition between T cells of the given clonotype and other T cell clonotypes in the repertoire. More specifically, it was assumed that individual competitive interactions between pairs of clonotypes are small, even though T cells of the given clonotype may compete with many other clonotypes for access to survival signals from APPs. Recall that $Q_i$ denotes the set of APPs which are able to provide survival signals to T cells of clonotype $i$. In terms of this set, the assumption is that $|Q_i \cap Q_j| \ll |Q_i|$ for all $i \neq j$. While this is a plausible assumption for the majority of clonotype pairs in the naive T cell repertoire, clonotypes with very similar TCRs do occur [76, 145] and it is possible that these clonotypes may overlap significantly in terms of the APPs from which they are able to receive survival signals. If this is the case, the influence of the T cells belonging to the competing clonotype cannot be treated as part of the “background” of competitive interactions.
In this chapter, a model is formulated for a pair of T cell clonotypes $i$ and $j$ for which $|Q_i \cap Q_j| \sim |Q_i|$ but $|Q_i \cap Q_k| \ll |Q_i|$ and $|Q_j \cap Q_k| \ll |Q_j|$ for all $k \neq i,j$. A schematic representation of these sets is given in Fig. 5.1. This structure means that the influence of clonotypes $k \neq i,j$ can be included as part of the “general background” of competition, but the number of T cells belonging to both clonotypes $i$ and $j$ must be explicitly included in the model, and so the number of T cells belonging to clonotypes $i$ and $j$ is modelled using a two-dimensional analogue of the birth and death process, which is referred to as a bivariate competition process. It is proved that the extinction of both clonotypes occurs with certainty within a finite time and an upper bound on the mean time until extinction occurs is given. Two ways of defining the QSD of the process are introduced and the existence of both these distributions is investigated. A general method of proving the existence of a QSD for a bivariate competition process with a single absorbing state is described. It is anticipated that this method may be applied to many such bivariate competition processes as well as the particular process that will be introduced in this chapter.
5.1 A competition process modelling the number of T cells belonging to a pair of clonotypes

It is assumed that the thymus produces T cells of clonotype $i$ within a very short space of time, and the time at which this “burst” occurs is denoted by $\tilde{t}_i$. After this time it is assumed that no further T cells of clonotype $i$ are produced by the thymus and so production of T cells of this specificity occurs only through the process of homeostatic proliferation. Then the number of T cells belonging to clonotype 1 initially produced by the thymus is given by $n_1(\tilde{t}_1)$ and the number of T cells belonging to clonotype 2 produced by the thymus is given by $n_2(\tilde{t}_2)$. Without loss of generality, it is assumed that $\tilde{t}_1 \leq \tilde{t}_2$. Then, for $\tilde{t}_1 \leq t < \tilde{t}_2$ T cells of clonotype 1 are present in the naïve repertoire, but T cells of clonotype 2 are not, in which case the univariate model described in Chapter 3 may be applied.

The number of T cells belonging to clonotypes 1 and 2 at time $t$, which is denoted by $(n_1(t), n_2(t))$, is modelled by means of a continuous-time bivariate Markov process $\{(X_1(t), X_2(t)) : t \geq \tilde{t}_2\}$ on the state-space $S = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots\}$. Let $\tilde{n}_1 = n_1(\tilde{t}_2)$ and $\tilde{n}_2 = n_2(\tilde{t}_2)$. Then the initial state of the process is given by $(\tilde{n}_1, \tilde{n}_2)$.

Transitions are only allowed to adjacent states, resulting in a two-dimensional analogue of the birth and death process, which is referred to as a bivariate competition process [110]. The transition probabilities are defined by

$$p_{n,m}(\Delta t) = \mathbb{P}\{X_1(t + \Delta t) = m_1, X_2(t + \Delta t) = m_2 | X_1(t) = n_1, X_2(t) = n_2\} \quad (5.1)$$

for $n = (n_1, n_2) \in S$ and $m = (m_1, m_2) \in S$. For a competition process, these
probabilities satisfy the following as $\Delta t \to 0^+$:

$$p_{n,m}(\Delta t) = \begin{cases} 
\lambda_{n_1,n_2}^{(1)} \Delta t + o(\Delta t) & m = (n_1 + 1, n_2) , \\
\lambda_{n_1,n_2}^{(2)} \Delta t + o(\Delta t) & m = (n_1, n_2 + 1) , \\
\mu_{n_1,n_2}^{(1)} \Delta t + o(\Delta t) & m = (n_1 - 1, n_2) , \\
\mu_{n_1,n_2}^{(2)} \Delta t + o(\Delta t) & m = (n_1, n_2 - 1) , \\
1 - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) \Delta t + o(\Delta t) & m = (n_1, n_2) , \\
o(\Delta t) & \text{otherwise}.
\end{cases}$$

(5.2)

A schematic representation of the competition process is given in Fig. 5.2. The quantity $\lambda_{n_1,n_2}^{(1)}$ is the birth rate for T cells of clonotype 1 and is the rate of transition from state $(n_1, n_2)$ to $(n_1 + 1, n_2)$. Similarly, the birth rate for T cells of clonotype 2, denoted by $\lambda_{n_1,n_2}^{(2)}$, is the rate of transition from state $(n_1, n_2)$ to $(n_1, n_2 + 1)$. The death rate for T cells of clonotype 1 is given by $\mu_{n_1,n_2}^{(1)}$ and this is the rate of transition from state $(n_1, n_2)$ to $(n_1 - 1, n_2)$. The death rate for T cells of clonotype 2, $\mu_{n_1,n_2}^{(2)}$, is the rate of transition from state $(n_1, n_2)$ to $(n_1, n_2 - 1)$. Expressions for the birth and death rates are derived in the next section. The infinitesimal generator matrix of the process, $Q$, can be written in terms of three square matrices [97]. Define $A_n$ to be the infinite square tridiagonal matrix given by

$$A_n = \begin{pmatrix} 
-r_{0,n} & \lambda_{0,n}^{(1)} & 0 & \ldots \\
\mu_{1,n}^{(1)} & -r_{1,n} & \lambda_{1,n}^{(1)} & \ldots \\
0 & \mu_{2,n}^{(1)} & -r_{2,n} & \ldots \\
& \vdots & \vdots & \ddots
\end{pmatrix},$$

where $r_{n_1,n_2} = \lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}$. Next, define the infinite square
diagonal matrices $B_n$ and $C_n$ by

$$B_n = \begin{pmatrix}
\lambda_{0,n}^{(2)} & 0 & 0 & \ldots \\
0 & \lambda_{1,n}^{(2)} & 0 & \ldots \\
0 & 0 & \lambda_{2,n}^{(2)} & \ldots \\
\vdots & \vdots & \vdots & \ddots 
\end{pmatrix},$$

and

$$C_n = \begin{pmatrix}
\mu_{0,n}^{(2)} & 0 & 0 & \ldots \\
0 & \mu_{1,n}^{(2)} & 0 & \ldots \\
0 & 0 & \mu_{2,n}^{(2)} & \ldots \\
\vdots & \vdots & \vdots & \ddots 
\end{pmatrix}.$$ 

Then $Q$ has the following block tridiagonal form:

$$Q = \begin{pmatrix}
A_0 & B_0 & 0 & 0 & \ldots \\
C_1 & A_1 & B_1 & 0 & \ldots \\
0 & C_2 & A_2 & B_2 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \ddots 
\end{pmatrix}.$$

### 5.1.1 Derivation of the birth and death rates

As in Chapter 3, it is assumed that the survival signals from any particular APP are shared equally among all the T cells that are capable of receiving them. Recall that $C$ is the set of all T cells in the naïve repertoire, $C_q$ is the subset of all T cells that are able to receive survival signals from APP $q$ and $n_q = |C_q|$ is the total number of T cells that the survival signals from APP $q$ are shared between. The set of all APPs in the periphery is denoted by $Q$ and $Q_i$ is the subset of APPs from which T cells of clonotype $i$ can receive survival signals. As described in Chapter 3, these survival
Figure 5.2: A schematic representation of the bivariate competition process and the transitions between different states.
signals are signals for homeostatic proliferation in that they trigger a single round of cell division. Let $\lambda^{(1)}$ denote the per cell birth rate for T cells of clonotype 1 and $\gamma$ denote the rate of survival signals emanating from APP $q$, which is assumed to be the same for all APPs. Then, as in Eq. (3.1),

$$
\lambda^{(1)} = \sum_{q \in Q_1} \frac{\gamma}{n_q} = \sum_{q \in Q_1} \frac{\gamma}{n_1 + n_{1q}} ,
$$

(5.3)

where $n_{1q} = n_q - n_1$. Next, the set $Q_1$ is divided into two disjoint subsets. The first subset is defined by

$$
Q_{12} = Q_1 \cap Q_2 ,
$$

(5.4)

which is the set of APPs from which T cells of both clonotype 1 and clonotype 2 can receive survival signals, while the second subset is given by

$$
Q_{1/2} = Q_1 \cap \bar{Q}_2 ,
$$

(5.5)

which is the set of APPs from which T cells of clonotype 1 receive survival signals but T cells of clonotype 2 do not. Here, $\bar{A}$ denotes the complement of the set $A$ in $Q$. By construction, $Q_1 = Q_{12} \cup Q_{1/2}$ and $Q_{12} \cap Q_{1/2} = \emptyset$. Therefore,

$$
\lambda^{(1)} = \sum_{q \in Q_{12}} \frac{\gamma}{n_1 + n_2 + n_{12q}} + \sum_{q \in Q_{1/2}} \frac{\gamma}{n_1 + n_{1q}} ,
$$

(5.6)

where $n_{12q} = n_q - n_1 - n_2$. The sets $Q_{12}$ and $Q_{1/2}$ are further partitioned as follows. Let $Q_{12r}$ denote the set of APPs which provide survival signals to T cells of clonotype 1, clonotype 2 and a further $r$ distinct clonotypes in the repertoire. Similarly, let $Q_{1r/2}$ be the set of APPs which provide survival signals to T cells of clonotype 1 and to $r$ other distinct clonotypes in the repertoire, none of which are
clonotype 2. Hence,
\[
\lambda^{(1)} = \gamma \sum_{r=0}^{\infty} \left( \sum_{q \in Q_{12r}} \frac{1}{n_1 + n_2 + n_{12q}} + \sum_{q \in Q_{1r/2}} \frac{1}{n_1 + n_{1q}} \right).
\] (5.7)

In principle, \(\lambda^{(1)}\) depends not only on the number of T cells of clonotypes 1 and 2, but also on the numbers of T cells belonging to all other clonotypes which compete with clonotype 1 for access to an APP in the sets \(Q_{12r}\) and \(Q_{1r/2}\), through the terms \(n_{12q}\) and \(n_{1q}\), respectively. In order to obtain an approximation that simplifies the expression for \(\lambda^{(1)}\) so that it only depends explicitly on \(n_1\) and \(n_2\), the following quantities are defined:

\[
\mathbb{E}_{12r}[n_{12q}] = \frac{1}{|Q_{12r}|} \sum_{q \in Q_{12r}} n_{12q},
\] (5.8)

\[
\mathbb{E}_{1r/2}[n_{1q}] = \frac{1}{|Q_{1r/2}|} \sum_{q \in Q_{1r/2}} n_{1q},
\] (5.9)

\[
\mathbb{V}_{12r}[n_{12q}] = \frac{1}{|Q_{12r}|} \sum_{q \in Q_{12r}} (n_{12q} - \mathbb{E}_{12r}[n_{12q}])^2,
\] (5.10)

\[
\mathbb{V}_{1r/2}[n_{1q}] = \frac{1}{|Q_{1r/2}|} \sum_{q \in Q_{1r/2}} (n_{1q} - \mathbb{E}_{1r/2}[n_{1q}])^2.
\] (5.11)

Then, performing a Taylor expansion about \(\mathbb{E}_{12r}[n_{12q}]\) results in

\[
\sum_{q \in Q_{12r}} \frac{1}{n_1 + n_2 + n_{12q}} = |Q_{12r}| \mathbb{E}_{12r} \left[ \frac{1}{n_1 + n_2 + \mathbb{E}_{12r}[n_{12q}]} \right]
\]

\[
= |Q_{12r}| \left( \frac{1}{n_1 + n_2 + \mathbb{E}_{12r}[n_{12q}]} + \frac{\mathbb{V}_{12r}[n_{12q}]}{(n_1 + n_2 + \mathbb{E}_{12r}[n_{12q}])^2} + \cdots \right)
\]

\[
\approx \frac{|Q_{12r}|}{n_1 + n_2 + \mathbb{E}_{12r}[n_{12q}]],
\] (5.12)
and similarly,

\[ \sum_{q \in Q_{1r/2}} \frac{1}{n_1 + n_{1q}} = \left| Q_{1r/2} \right| \mathbb{E}_{1r/2} \left( \frac{1}{n_1 + n_{1q}} \right) \]

\[ = \left| Q_{1r/2} \right| \left( \frac{1}{n_1 + \mathbb{E}_{1r/2}[n_{1q}]} + \frac{\mathbb{V}_{1r/2}[n_{1q}]}{(n_1 + \mathbb{E}_{1r/2}[n_{1q}])^3} + \ldots \right) \]

\[ \simeq \frac{\left| Q_{1r/2} \right|}{n_1 + \mathbb{E}_{1r/2}[n_{1q}]} . \] (5.13)

The mean field approximation used here is similar to that introduced in Chapter 3 and consists of two assumptions. The first is that the second and subsequent terms in the Taylor expansions in Eqs. (5.12)–(5.13) are small and can be neglected. The second assumption is that

\[ \mathbb{E}_{12r}[n_{12q}] = r\langle n \rangle \] and \( \mathbb{E}_{1r/2}[n_{1q}] = r\langle n \rangle \). (5.14)

This means that the average number of cells belonging to a T cell clonotype across the \( r \) competing clonotypes in the sets \( Q_{12r} \) and \( Q_{1r/2} \) is the same as the average number of T cells belonging to a clonotype across the whole repertoire, which is denoted by \( \langle n \rangle \). These approximations are reasonable if \( |Q_1 \cap Q_j| \ll |Q_1| \) for \( j \neq 2 \).

Then,

\[ \lambda^{(1)} = \gamma \sum_{r=0}^{+\infty} \left( \frac{|Q_{12r}|}{n_1 + n_2 + r\langle n \rangle} + \frac{|Q_{1r/2}|}{n_1 + r\langle n \rangle} \right) . \] (5.15)

Eq. (5.15) depends on the number of T cells of clonotypes 1 and 2 but not explicitly on the number of other T cell clonotypes in the naïve repertoire. Instead, competition with other clonotypes is included in the terms \( r\langle n \rangle \), allowing the number of T cells of clonotype 1 to be modelled using a bivariate competition process.

The final stage in the specification of the birth rate, \( \lambda^{(1)} \), is to derive expressions for \( |Q_{12r}| \) and \( |Q_{1r/2}| \) for a fixed value of \( r \). Let \( p_1 \) denote the probability that a randomly chosen APP provides survival signals to T cells of clonotype 2, given that
it provides survival signals to T cells of clonotype 1, i.e., \( p_1 = \mathbb{P}(q \in Q_2|q \in Q_1) \).

This parameter provides a measure of the overlap between the sets of APPs that provide survival signals to each clonotype since the definition implies that

\[
p_1 = \frac{|Q_{12}|}{|Q_1|} = \frac{|Q_1 \cap Q_2|}{|Q_1|}.
\]

(5.16)

Then \( |Q_{12}| = p_1 |Q_1| \) and \( |Q_{1/2}| = (1 - p_1) |Q_1| \). In order to estimate the size of the sets \( Q_{1r} \) and \( Q_{1r/2} \) it is necessary to introduce two further probabilities. Let \( p_{j,12} \) denote the probability that a randomly chosen APP from the set \( Q_{12} \) is able to provide survival signals to T cells of another clonotype, \( j \neq 1, 2 \), chosen at random from the repertoire and let \( p_{j,1/2} \) denote the probability that a randomly chosen APP from the set \( Q_{1/2} \) is able to provide survival signals to T cells of another clonotype, \( j \neq 1, 2 \), chosen at random from the repertoire. Then the number of clonotypes competing with T cells of clonotype 1 can be computed using the binomial distribution as follows:

\[
|Q_{12}| = |Q_{12}| \left( \begin{array}{c} N_C - 2 \\ r \end{array} \right) (p_{j,12})^r (1 - p_{j,12})^{N_C - 2 - r},
\]

(5.17)

and

\[
|Q_{1/2}| = |Q_{1/2}| \left( \begin{array}{c} N_C - 2 \\ r \end{array} \right) (p_{j,1/2})^r (1 - p_{j,1/2})^{N_C - 2 - r}.
\]

(5.18)

Since \( N_C \gg 1 \) and \( p_{j,12} \ll 1, p_{j,1/2} \ll 1 \) [87], the Poisson approximation to the binomial distribution may be applied. Defining \( \nu_{12} = (N_C - 2)p_{j,12} \) and \( \nu_1 = (N_C - 2)p_{j,1/2} \) the following approximations are obtained:

\[
|Q_{12}| = |Q_{12}| \frac{\nu_{12}^r e^{-\nu_{12}}}{r!} = p_1 |Q_1| \frac{\nu_{12}^r e^{-\nu_{12}}}{r!},
\]

(5.19)

and

\[
|Q_{1/2}| = |Q_{1/2}| \frac{\nu_1^r e^{-\nu_1}}{r!} = (1 - p_1) |Q_1| \frac{\nu_1^r e^{-\nu_1}}{r!}.
\]

(5.20)
Substituting Eqs. (5.19)–(5.20) into Eq. (5.15) results in

\[ \lambda^{(1)} = \gamma |Q_1| \left( p_1 e^{-\nu_2} \sum_{r=0}^{+\infty} \frac{\nu_2^r}{r!} \frac{1}{n_1 + n_2 + r \langle n \rangle} + (1 - p_1) e^{-\nu_1} \sum_{r=0}^{+\infty} \frac{\nu_1^r}{r!} \frac{1}{n_1 + r \langle n \rangle} \right) \]

\[ = \varphi_1 \left( p_1 e^{-\nu_1} \sum_{r=0}^{+\infty} \frac{\nu_1^r}{r!} \frac{1}{n_1 + n_2 + r \langle n \rangle} + (1 - p_1) e^{-\nu_1} \sum_{r=0}^{+\infty} \frac{\nu_1^r}{r!} \frac{1}{n_1 + r \langle n \rangle} \right), \quad (5.21) \]

where \( \varphi_1 = \gamma |Q_1| \). Similarly, the per cell birth rate for T cells of clonotype 2 is given by

\[ \lambda^{(2)} = \varphi_2 \left( p_2 e^{-\nu_2} \sum_{r=0}^{+\infty} \frac{\nu_2^r}{r!} \frac{1}{n_1 + n_2 + r \langle n \rangle} + (1 - p_2) e^{-\nu_2} \sum_{r=0}^{+\infty} \frac{\nu_2^r}{r!} \frac{1}{n_2 + r \langle n \rangle} \right), \quad (5.22) \]

where \( \varphi_2 = \gamma |Q_2| \), \( p_2 = P(q \in Q_1 | q \in Q_2) \) and \( \nu_2 = (N_C - 2)p_{12}/1 \). The per cell death rate for a given clonotype is assumed to be constant and is denoted by \( \mu \) for T cells of clonotypes 1 and 2, respectively.

Thus, the birth and death rates for the bivariate competition process, as defined in Eq. (5.2), are given by \( \lambda_{n_1, n_2}^{(1)} = \lambda^{(1)} n_1 \), \( \lambda_{n_1, n_2}^{(2)} = \lambda^{(2)} n_2 \), \( \mu_{n_1, n_2}^{(1)} = \mu n_1 \) and \( \mu_{n_1, n_2}^{(2)} = \mu n_2 \).

### 5.1.2 Summary of the model

The number of T cells belonging to clonotypes 1 and 2 is modelled as a bivariate competition process \( \{(X_1(t), X_2(t)) : t \geq \tilde{t}_2\} \) on the state-space \( S = \{(n_1, n_2) : \)
CHAPTER 5. STOCHASTIC MODEL FOR A PAIR OF CLONOTYPES

\( n_1, n_2 = 0, 1, 2, \ldots \) with the birth and death rates

\[
\lambda_{0,n_2}^{(1)} = 0 \quad \text{for} \quad n_2 \geq 0 , \\
\lambda_{n_1,n_2}^{(1)} = \varphi_1 n_1 \left( p_1 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r(n)} + (1 - p_1) e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r(n)} \right) \\
\quad \text{for} \quad n_1 \geq 1 \quad \text{and} \quad n_2 \geq 0 , \\
\lambda_{n_1,0}^{(2)} = 0 \quad \text{for} \quad n_1 \geq 0 , \\
\lambda_{n_1,n_2}^{(2)} = \varphi_2 n_2 \left( p_2 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r(n)} + (1 - p_2) e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r(n)} \right) \\
\quad \text{for} \quad n_1 \geq 0 \quad \text{and} \quad n_2 \geq 1 , \\
\mu_{n_1,n_2}^{(1)} = \mu_1 n_1 \quad \text{for} \quad n_1 \geq 0 \quad \text{and} \quad n_2 \geq 0 , \\
\mu_{n_1,n_2}^{(2)} = \mu_2 n_2 \quad \text{for} \quad n_1 \geq 0 \quad \text{and} \quad n_2 \geq 0 .
\]

It is clear that \( Q_{12} \cap Q_{21} = Q_{21} \cap Q_{1} = Q_{12} \). Therefore, \( \gamma|Q_{12}| = \gamma p_1|Q_1| = p_1 \varphi_1 \) and similarly \( \gamma|Q_{21}| = \gamma p_2|Q_2| = p_2 \varphi_2 \), and so the parameters are constrained to obey the equation

\[
\varphi_1 p_1 = \varphi_2 p_2 ,
\]

where \( 0 \leq p_1 \leq 1 \) and \( 0 \leq p_2 \leq 1 \). Thus, the model has nine independent parameters compared to the four parameters of the model for a single T cell clonotype that was introduced in Chapter 3. These nine parameters are defined as follows:

(i) \( \varphi_1 \) is a parameter proportional to the number of APPs which can provide survival signals to T cells of clonotype 1 and to \( \gamma \), which is the rate of survival signals emanating from the APPs.

(ii) \( \varphi_2 \) is a parameter proportional to the number of APPs which can provide survival signals to T cells of clonotype 2 and to \( \gamma \), which is the rate of survival signals emanating from the APPs.
(iii) $\nu_{12}$ is the mean niche overlap for APPs in the set $Q_{12}$ and is the average number of clonotypes that are competing with T cells of clonotype 1 and clonotype 2 for an APP, where the average is taken over all the APPs belonging to the set $Q_{12}$.

(iv) $\nu_1$ is the mean niche overlap for APPs in the set $Q_1$ and is the average number of clonotypes that are competing with T cells of clonotype 1 for an APP, where the average is taken over all the APPs belonging to the set $Q_{1/2}$.

(v) $\nu_2$ is the mean niche overlap for APPs in the set $Q_2$ and is the average number of clonotypes that are competing with T cells of clonotype 2 for an APP, where the average is taken over all the APPs belonging to the set $Q_{2/1}$.

(vi) $p_1$ is the probability that an APP which provides survival signals to T cells of clonotype 1 also provides survival signals to T cells of clonotype 2.

(vii) $\langle n \rangle$ is the average clonotype size over the naïve T cell repertoire.

(viii) $\mu_1$ is the death rate per T cell of clonotype 1.

(ix) $\mu_2$ is the death rate per T cell of clonotype 2.

The parameters $\varphi_1$, $\varphi_2$, $\nu_1$, $\nu_2$, $\mu_1$ and $\mu_2$ are specific to either clonotype 1 or clonotype 2, while the parameters $p_1$ and $\nu_{12}$ depend on the nature of both clonotypes and the overlap between them, in terms of the APPs from which they are able to receive survival signals. The parameter $\langle n \rangle$ is a parameter of the repertoire as a whole. Note that $\mu_{0,j}^{(1)} = \mu_{j,0}^{(2)} = 0$ for all $j \geq 0$ so that transitions out of the state-space $S$ cannot occur. Since it is assumed that no T cells of either clonotype 1 or 2 are produced from the thymus after the time $\tilde{t}_2$, $\lambda_{0,j}^{(1)} = \lambda_{j,0}^{(2)} = 0$ for all $j \geq 0$. Hence, the set of states $A = \{(n_1, n_2) : n_1 = 0 \text{ or } n_2 = 0\}$ forms an absorbing set, meaning that once the process enters the set $A$, it will never move to a state in $S \setminus A$, while the set of states $S \setminus A$ forms a transient communicating class. The
state \((n_1, n_2) = (0, 0)\) is an absorbing state which corresponds to the extinction of both clonotypes from the repertoire.

This section is concluded with a bound on the birth rates. The birth rates are bounded from above as follows:

\[
\lambda_{n_1, n_2}^{(1)} = \varphi_{1n_1} \left( p_1 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r\langle n \rangle} + (1 - p_1) e^{-\nu_{11}} \sum_{r=0}^{+\infty} \frac{\nu_{11}^r}{r!} \frac{1}{n_1 + r\langle n \rangle} \right) \\
\leq \varphi_{1n_1} \left( p_1 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1} + (1 - p_1) e^{-\nu_{11}} \sum_{r=0}^{+\infty} \frac{\nu_{11}^r}{r!} \frac{1}{n_1} \right) \\
= \varphi_{1n_1} \left( p_1 e^{-\nu_{12}} e^{\nu_{11}} \frac{1}{n_1} + (1 - p_1) e^{-\nu_{11}} e^{\nu_{11}} \frac{1}{n_1} \right) \\
= \varphi_{1n_1} (1 - p_1) \\
= \varphi_1.
\]

(5.30)

Similarly, \(\lambda_{n_1, n_2}^{(2)} \leq \varphi_2\).

**5.1.3 The limits \(p_1 = p_2 = 0\) and \(p_1 = p_2 = 1\)**

For a pair of clonotypes with \(\varphi_1 = \varphi_2\), \(p_1 = p_2\) and \(\mu_1 = \mu_2\), there are two limits in which the bivariate competition process can be simplified to give a univariate birth and death process. Firstly, let \(p_1 = p_2 = 0\). Then the birth rates (5.24) and (5.26) become

\[
\lambda_{n_1, n_2}^{(1)} = \varphi_{1n_1} e^{-\nu_{11}} \sum_{r=0}^{+\infty} \frac{\nu_{11}^r}{r!} \frac{1}{n_1 + r\langle n \rangle}, \\
\lambda_{n_1, n_2}^{(2)} = \varphi_{2n_2} e^{-\nu_{22}} \sum_{r=0}^{+\infty} \frac{\nu_{22}^r}{r!} \frac{1}{n_2 + r\langle n \rangle},
\]

(5.31) 

(5.32)

which are of the form of the birth rates for a single clonotype under the mean field approximation, as given by Eq. (3.14). In this case, the decoupling occurs because
Q_1 \cap Q_2 = \emptyset$, and therefore the two T cell clonotypes have independent dynamics.

Now let $p_1 = p_2 = 1$, which means that the sets of APPs from which each clonotype receives survival signals overlap completely, i.e., $Q_1 \cap Q_2 = Q_{12} = Q_{21} = Q_1 = Q_2$. Then the birth rates (5.24) and (5.26) become

$$
\lambda_{n_1,n_2}^{(1)} = \varphi_1 n_1 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r\langle n \rangle},
$$

(5.33)

$$
\lambda_{n_1,n_2}^{(2)} = \varphi_1 n_2 e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r\langle n \rangle}.
$$

(5.34)

Hence,

$$
\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} = \varphi_1 (n_1 + n_2) e^{-\nu_{12}} \sum_{r=0}^{+\infty} \frac{\nu_{12}^r}{r!} \frac{1}{n_1 + n_2 + r\langle n \rangle},
$$

(5.35)

so that the two clonotypes together behave in the same way as a single clonotype in the mean field approximation. For $0 < p_1 < 1$ and $0 < p_2 < 1$, the bivariate analysis presented in this and the next chapter is required.

### 5.2 Guaranteed extinction and finite mean extinction times

In this section it is proved that the probability of absorption at the state $(n_1, n_2) = (0, 0)$ occurring is one for all parameter values of the model. In order to do this, the bivariate competition process is bounded by a univariate birth and death process which has the property that it moves towards the origin at a slower rate than the bivariate process, following the method of Iglehart [70]. It is then shown that absorption at the origin is certain for the univariate process. This implies that the bivariate process reaches state $(0, 0)$ with probability one [70]. An upper bound on the mean time until extinction is also computed using this method.
5.2.1 The ultimate fate of both clonotypes is extinction

In order to prove that extinction is guaranteed, a univariate birth and death process which moves towards the origin at a slower rate than the bivariate process is defined. The state-space $S$ is divided into the disjoint subsets

$$S_j' = \{(n_1, n_2) : n_1 + n_2 = j\} \text{ for } j \geq 0,$$

which define the states of the univariate process and are depicted schematically in Fig. 5.3. Next, the birth and death rates of the univariate process are defined. If the process is in the state $(n_1, n_2) \in S'_j$ at the current time, with the next transition it moves to a state in the set $S'_{j+1}$ with probability $(\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)})/r_{n_1,n_2}$ or to a state in the set $S'_{j-1}$ with probability $(\mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)})/r_{n_1,n_2}$, where $r_{n_1,n_2} = \lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}$. Let

$$\lambda_j' = \max_{(n_1,n_2) \in S_j'} \left\{\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)}\right\}, \quad (5.37)$$

$$\mu_j' = \min_{(n_1,n_2) \in S_j'} \left\{\mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}\right\}, \quad (5.38)$$
with \( \lambda_j' = \mu_j' = 0 \) when \( j = 0 \). The rate \( \lambda_j' \) is the maximum rate for the process to move upwards from the set \( S_j' \) to \( S_{j+1}' \) and the rate \( \mu_j' \) is the minimum rate for the process to move downwards from the set \( S_j' \) to \( S_{j-1}' \). These rates define a univariate birth and death process on the state-space \( S' = \{ S_0', S_1', S_2', \ldots \} \), where \( S_0' \) is an absorbing state and \( S_j' \) is now treated as a single state rather than a set of states. This process can be represented as follows:

\[
S_0' \xleftarrow{\mu_1'} S_1' \xleftarrow{\mu_2'} S_2' \ldots S_j' \xleftarrow{\mu_{j+1}'} S_{j+1}' \ldots
\]

Let

\[
\pi_1' = 1 \quad \text{and} \quad \pi_j' = \frac{\lambda_1' \lambda_2' \ldots \lambda_{j-1}'}{\mu_2' \mu_3' \ldots \mu_j'} \quad \text{for} \quad j \geq 2 . \tag{5.39}
\]

Theorem 1 of [70] and Proposition 9.3.1 of [4] state that the bivariate competition process is regular if

\[
\sum_{n=1}^{\infty} \frac{1}{\lambda_n} \sum_{j=1}^{\infty} \pi_j' = +\infty . \tag{5.40}
\]

This is also the sufficient condition for the univariate birth and death process to be regular. To prove that condition (5.40) holds for the birth and death rates (5.37)–(5.38), it is first observed that

\[
\lambda_j' = \max_{(n_1,n_2) \in S_j} \{ \lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} \} \leq \varphi_1 + \varphi_2 , \tag{5.41}
\]

from Eq. (5.30) and

\[
\mu_j' = \min_{(n_1,n_2) \in S_j} \{ \mu_1 n_1 + \mu_2 n_2 \} = j \min(\mu_1, \mu_2) . \tag{5.42}
\]
For the birth and death rates (5.37)–(5.38) the terms $\pi'_j$ are all strictly positive for $j \geq 1$ and so

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda'_n} \sum_{j=1}^{n} \pi'_j > \sum_{n=1}^{+\infty} \frac{1}{\lambda'_n} \pi'_n = \sum_{n=1}^{+\infty} \frac{1}{\lambda'_n} \geq \sum_{n=1}^{+\infty} \frac{1}{\varphi_1 + \varphi_2} = +\infty ,$$

(5.43)

and, hence, the process is regular. Then by Theorem 3 of Iglehart [70], a sufficient condition for guaranteed absorption of the bivariate process at $(n_1, n_2) = (0, 0)$ is that the series

$$\sum_{j=1}^{+\infty} \frac{1}{\lambda'_j \pi'_j}$$

(5.44)

diverges. Note that this is a sufficient condition for the univariate process to reach the absorbing state $S'_0$ with certainty. Then, for the birth and death rates (5.37)–(5.38),

$$\sum_{j=1}^{+\infty} \frac{1}{\lambda'_j \pi'_j} = \sum_{j=1}^{+\infty} \frac{\mu'_j \mu'_3 \ldots \mu'_j}{\lambda'_1 \lambda'_2 \ldots \lambda'_j} \geq \sum_{j=1}^{+\infty} \frac{j!\min(\mu_1, \mu_2)}{(\varphi_1 + \varphi_2)^j} .$$

(5.45)

Let

$$a_j = \frac{j!\min(\mu_1, \mu_2)}{(\varphi_1 + \varphi_2)^j} ,$$

(5.46)

so that

$$\frac{a_{j+1}}{a_j} = \frac{(j + 1) \min(\mu_1, \mu_2)}{(\varphi_1 + \varphi_2)} \rightarrow +\infty \text{ as } j \rightarrow +\infty .$$

(5.47)

Hence, the series $\sum_{j=1}^{+\infty} a_j$ diverges by the ratio test and therefore $\sum_{j=1}^{+\infty} \frac{1}{\lambda'_j \pi'_j}$ also diverges by comparison. Thus, absorption at $(n_1, n_2) = (0, 0)$ is guaranteed for all parameter values of the model. This means that the ultimate fate of both clonotypes is extinction from the repertoire.
5.2.2 A bound on the mean time until extinction

Let \( \tau_{n_1,n_2} \) be the mean time until both clonotypes become extinct when the initial state of the process is given by \((n_1, n_2)\). Theorem 4 of Iglehart [70] states that, for a regular competition process, \( \tau_{n_1,n_2} < +\infty \) for all \((n_1, n_2) \in \mathcal{S} \setminus \{(0,0)\} \) if the series \( \sum_{j=1}^{+\infty} \pi'_j \) converges. This is a sufficient condition for the mean time to extinction to be finite for the univariate process defined above. For the birth and death rates (5.37)–(5.38),

\[
\sum_{j=1}^{+\infty} \pi'_j = \sum_{j=1}^{+\infty} \frac{\lambda'_1\lambda'_2\cdots\lambda'_{j-1}}{\mu'_2\mu'_3\cdots\mu'_j} \leq \sum_{j=1}^{+\infty} \frac{(\varphi_1 + \varphi_2)^{j-1}}{j! \min(\mu_1, \mu_2)^{j-1}}. \tag{5.48}
\]

Let

\[
b_j = \frac{(\varphi_1 + \varphi_2)^{j-1}}{j! \min(\mu_1, \mu_2)^{j-1}}. \tag{5.49}
\]

Then

\[
\frac{b_{j+1}}{b_j} = \frac{\varphi_1 + \varphi_2}{(j+1) \min(\mu_1, \mu_2)} \rightarrow 0 \text{ as } j \rightarrow +\infty, \tag{5.50}
\]

so that the series \( \sum_{j=1}^{+\infty} b_j \) converges by the ratio test. Hence \( \sum_{j=1}^{+\infty} \pi'_j \) converges by comparison. Therefore the mean time to absorption from all initial states \((n_1, n_2) \in \mathcal{S} \setminus \{(0,0)\}\) is finite.

The bivariate competition process introduced in Section 5.1 is bounded by the univariate birth and death process with birth and death rates given by \( \lambda'_j \) and \( \mu'_j \) respectively, in the sense that the univariate process moves towards the absorbing state at a slower rate than the bivariate competition process \( \{(\mathcal{X}_1(t), \mathcal{X}_2(t)) : t \geq \tilde{t}_2\} \).

For a univariate birth and death process with birth rates \( \lambda'_j \) and death rates \( \mu'_j \), the mean time until absorption from an initial state \( j, \tau_j \), is given by Eq. (2.57) as

\[
\tau_j = \sum_{n=1}^{+\infty} \frac{1}{\lambda'_n \mu'_n} + \sum_{k=1}^{j-1} \rho'_k \sum_{n=k+1}^{+\infty} \frac{1}{\lambda'_n \mu'_n}, \tag{5.51}
\]
where $\rho'_k = \prod_{n=1}^k (\mu'_n / \lambda'_n)$. Hence $\tau_j$, with $\lambda'_j$ and $\mu'_j$ as defined in Eqs. (5.37)–(5.38), is an upper bound on the mean time to absorption at state $(0, 0)$ from all initial states $(n_1, n_2) \in S'_j$ for $j \geq 1$.

5.3 The quasi-stationary probability distribution of the bivariate competition process

In this section, the quasi-stationary probability distribution of the bivariate competition process is introduced in order to study the behaviour of the process before extinction occurs. This distribution can be defined in several ways. Firstly, the stationary probability distribution of the process conditional on the event that at least one of the pair of clonotypes is still present in the repertoire is introduced. Secondly, the stationary probability distribution of the process conditional on the event that both clonotypes 1 and 2 are still present in the repertoire is defined. The existence of both these probability distributions, and which is the most appropriate, is then discussed. It is possible to define the QSD in other ways, for example by conditioning on the event that T cells of clonotype 1 are still present in the repertoire, but such distributions are not considered here.
5.3.1 The stationary probability distribution of the process conditional on the event that at least one of the pair of clonotypes is present in the repertoire

Let $p_{n_1,n_2}(t)$ be the probability that there are $n_1$ T cells of clonotype 1 and $n_2$ T cells of clonotype 2 at time $t$, i.e.,

$$p_{n_1,n_2}(t) = \mathbb{P}(X_1(t) = n_1, X_2(t) = n_2 | X_1(\tilde{t}_2) = \tilde{n}_1, X_2(\tilde{t}_2) = \tilde{n}_2), \quad (5.52)$$

where $p_{n_1,n_2}(t) \geq 0$ for $(n_1, n_2) \in S$, $p_{n_1,n_2}(t) = 0$ for $(n_1, n_2) \notin S$ and

$$\sum_{n_1=0}^{+\infty} \sum_{n_2=0}^{+\infty} p_{n_1,n_2}(t) = 1 \text{ for } t \geq \tilde{t}_2. \text{ These probabilities satisfy the following system of differential equations}
$$

$$\frac{dp_{n_1,n_2}(t)}{dt} = \lambda_{n_1-1,n_2}^{(1)} p_{n_1-1,n_2}(t) + \lambda_{n_1,n_2-1}^{(2)} p_{n_1,n_2-1}(t) + \mu_{n_1+1,n_2}^{(1)} p_{n_1+1,n_2}(t)$$

$$+ \mu_{n_1,n_2+1}^{(2)} p_{n_1,n_2+1}(t) - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) p_{n_1,n_2}(t), \quad (5.53)$$

for all $(n_1, n_2) \in S$, which are the forward Kolmogorov equations for a bivariate competition process. The limiting solution of these equations as $t \to +\infty$ is given by $p_{0,0} = 1$ and $p_{n_1,n_2} = 0$ for all $(n_1, n_2) \neq (0, 0)$, since extinction of both clonotypes ultimately occurs with probability one. In order to study the behaviour of the process before both clonotypes become extinct, the above equations are written in terms of a new variable. Let

$$q'_{n_1,n_2}(t) = \frac{p_{n_1,n_2}(t)}{1 - p_{0,0}(t)}, \quad (5.54)$$

which is the probability that there are $n_1$ T cells of clonotypes 1 and $n_2$ T cells of clonotype 2 at time $t$, conditional on the event that at least one of the pair of clonotypes is still present in the naïve T cell repertoire. For all $t \geq \tilde{t}_2$, $q'_{n_1,n_2}(t) \geq 0$ for
(n_1, n_2) \in S \setminus \{(0,0)\}, \quad q'_{n_1,n_2}(t) = 0 \text{ for } (n_1, n_2) \notin S \setminus \{(0,0)\} \text{ and } \sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} q'_{n_1,n_2}(t) = 1. \text{ From Eq. (5.53), these probabilities satisfy}

\[
\frac{dq'_{n_1,n_2}(t)}{dt} = \lambda_{n_1-1,n_2}^{(1)} q'_{n_1-1,n_2}(t) + \lambda_{n_1,n_2-1}^{(2)} q'_{n_1,n_2-1}(t) + \mu_{n_1+1,n_2}^{(1)} q'_{n_1+1,n_2}(t) \\
+ \mu_{n_1,n_2+1}^{(2)} q'_{n_1,n_2+1}(t) - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) q'_{n_1,n_2}(t) \\
+ \mu_{1,0}^{(1)} q_{1,0}(t) q'_{n_1,n_2}(t) + \mu_{0,1}^{(2)} q_{0,1}(t) q'_{n_1,n_2}(t),
\]

for \((n_1, n_2) \in S \setminus \{(0,0)\}\). A probability distribution \(q'\), assuming it exists, is called a quasi-stationary probability distribution (QSD) if it satisfies

\[
0 = \lambda_{n_1-1,n_2}^{(1)} q'_{n_1-1,n_2} + \lambda_{n_1,n_2-1}^{(2)} q'_{n_1,n_2-1} + \mu_{n_1+1,n_2}^{(1)} q'_{n_1+1,n_2} \\
+ \mu_{n_1,n_2+1}^{(2)} q'_{n_1,n_2+1} - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) q'_{n_1,n_2} \\
+ \mu_{1,0}^{(1)} q_{1,0} q'_{n_1,n_2} + \mu_{0,1}^{(2)} q_{0,1} q'_{n_1,n_2},
\]

where \(q'_{n_1,n_2} \geq 0 \text{ for } (n_1, n_2) \in S \setminus \{(0,0)\}\), \(q'_{n_1,n_2} = 0 \text{ for } (n_1, n_2) \notin S \setminus \{(0,0)\}\) and \(\sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} q'_{n_1,n_2} = 1\). The limiting conditional probability distribution (LCD) is denoted by \(q'\) and is defined by

\[
q'_{n_1,n_2} = \lim_{t \to +\infty} q'_{n_1,n_2}(t),
\]

where \(q'_{n_1,n_2} \geq 0 \text{ for } (n_1, n_2) \in S \setminus \{(0,0)\}\), \(q'_{n_1,n_2} = 0 \text{ for } (n_1, n_2) \notin S \setminus \{(0,0)\}\) and \(\sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} q'_{n_1,n_2} = 1\). The LCD does not depend on time and so is, by definition, a QSD. However, the converse is not necessarily true. For a process with finite state-space, \emph{i.e.}, \(S = \{(n_1, n_2): n_1 = 0, 1, 2, \ldots, N_1; n_2 = 0, 1, 2, \ldots, N_2\}\) a unique QSD exists, which is also the unique LCD of the process [33]. However, if the state-space of the process is denumerably infinite, a QSD might not exist [29], or if it does exist, it may not be unique. In the next section, it is shown that at least one QSD of the type defined above exists for the process \(\{(X_1(t), X_2(t)): t \geq \hat{t}_2\}\) on the state-
space $\mathcal{S} = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots \}$. It is not in general possible to find an explicit solution to the non-linear equations given by Eq. (5.56), but the QSD may be calculated numerically from the infinitesimal generator matrix of the process, $Q$, restricted to the set of states $\mathcal{S} \setminus \{(0,0)\}$. Then, as described in Section 3.2.3, the QSD is given by the left eigenvector corresponding to the eigenvalue with maximal real part, normalised so that $\sum_{n_1=0}^{\infty} \sum_{n_2=0}^{\infty} \bar{q}_{n_1,n_2} = 1$ [105]. This can be computed in the MATLAB package [69], taking advantage of the sparse structure of $Q$.

5.3.2 Existence of the stationary probability distribution conditional on the event that at least one of the pair of clonotypes is present in the repertoire

In this section it is proved that a QSD (as defined by Eq. (5.56)) exists for the bivariate competition process introduced in Section 5.1. The existence of a QSD for a bivariate Markov process is often simply assumed [97, 100, 102]. Indeed, the only known previous work on this subject is by Clancy [28], where it is proved that a QSD exists for a bivariate Markov process where the state-space of the process is finite in one direction, i.e., $\mathcal{S} = \{(n_1, n_2) : n_1 = 0, 1, 2, \ldots, N; n_2 = 0, 1, 2, \ldots \}$. In this section a method of proving the existence of a QSD for a process with a state-space of the form $\mathcal{S} = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots \}$ is introduced. The method involves relabeling the states along the diagonals of the two-dimensional lattice in order to obtain a univariate Markov process $\{\mathcal{Y}(t) : t \geq \tilde{t}_2\}$ on the state-space $\tilde{\mathcal{S}} = \{0, 1, 2, \ldots \}$. The criteria of Ferrari et al. [47], introduced in Chapter 4, are then used to prove that a QSD exists.

Firstly, define the Markov process $\{\mathcal{Y}(t) : t \geq \tilde{t}_2\}$ so that

$$\mathcal{Y}(t) = \frac{1}{2}(\mathcal{X}_1(t) + \mathcal{X}_2(t))(\mathcal{X}_1(t) + \mathcal{X}_2(t) + 1) + \mathcal{X}_1(t).$$

(5.58)
This mapping defines a one-to-one correspondence between states \((n_1, n_2) \in S\) and \(x \in \tilde{S}\) according to the function \(g: \mathbb{N} \times \mathbb{N} \rightarrow \mathbb{N}\) which is defined by
\[
g(n_1, n_2) = \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1 = x, \tag{5.59}
\]
where the absorbing state at \((n_1, n_2) = (0, 0)\) is mapped uniquely to the state \(x = 0\). This function is known as the Cantor pairing function [85] and it is proved in Appendix A that Eq. (5.59) defines a bijective function. This means that the bivariate competition process \(\{(X_1(t), X_2(t)) : t \geq \tilde{t}_2\}\) on the state-space \(S = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots\}\) may be transformed into a univariate Markov process \(\{\mathcal{Y}(t) : t \geq \tilde{t}_2\}\) on the state-space \(\tilde{S} = \{0, 1, 2, \ldots\}\) using this relation. Therefore, proving that a QSD exists for the bivariate competition process is equivalent to proving that a QSD exists for this univariate Markov process. Note that \(\{\mathcal{Y}(t) : t \geq \tilde{t}_2\}\) is not a birth and death process. However, the criteria for the existence of a QSD given by Ferrari et al. [47] and used in Section 4.1.1, Method 2, apply to all univariate Markov processes and so can be used in the present situation.

Let
\[
R = \inf\{t \geq 0 : \mathcal{Y}(t) = 0\}, \tag{5.60}
\]
which is the time at which extinction of both clonotypes occurs. In Section 5.2.2 it was shown that the expected time to extinction from an initial state \((n_1, n_2) \in S \setminus \{(0, 0)\}\) is finite, as required. The first part of the proof is to show that
\[
\lim_{x_0 \to +\infty} \mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_2) = x_0) = 0 \quad \text{for all} \ t \geq \tilde{t}_2, \tag{5.61}
\]
i.e., the mean time until extinction of both clonotypes can be made arbitrarily large by taking the initial state of the process, \(x_0\), to be sufficiently far away from the origin. Recall from Chapter 4 that condition (5.61) is referred to as the “asymptotic remoteness” condition. The time until death of a T cell of clonotype 1 is an inde-
pendent exponential random variable with expected value $\mu_1^{-1}$. If the initial state of the process is given by $(\mathcal{X}_1(\tilde{t}_2), \mathcal{X}_2(\tilde{t}_2)) = (\tilde{n}_1, \tilde{n}_2)$ then prior to extinction of both clonotypes occurring, all of the $\tilde{n}_1$ T cells of clonotype 1 initially present must die. Extinction occurs at the time of death of the last of these $\tilde{n}_1$ initial cells if none of them has divided and there are no T cells of clonotype 2 present, and will occur strictly later otherwise. Hence, for any $t \geq \tilde{t}_2$,

$$\mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_2) = x_0) \leq (1 - e^{-\mu_1})^{\tilde{n}_1} \rightarrow 0 \text{ as } \tilde{n}_1 \rightarrow +\infty , \quad (5.62)$$

and, similarly,

$$\mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_2) = x_0) \leq (1 - e^{-\mu_2})^{\tilde{n}_2} \rightarrow 0 \text{ as } \tilde{n}_2 \rightarrow +\infty , \quad (5.63)$$

and so the “asymptotic remoteness” condition given by Eq. (5.61) holds. This is because the mapping given by Eq. (5.59) is defined in such a way that as the initial state, $x_0$, of the process increases, it becomes further away from the absorbing state at $(0, 0)$.

Next, a function $f$ on $S$ is defined with the constants $D_1, D_4, D_5 > 0$, $D_2, D_3, D_6 < +\infty$, where $D_6$ is an integer, which satisfies the conditions (4.13)–(4.17), where $q_{n,m}$ are the entries of the infinitesimal generator matrix defined by Eq. (5.1).
These are given by

\[
q(n_1, n_2), (n_1 + 1, n_2) = \varphi_1 n_1 (p_1 e^{-n_1 \bar{a}_{n_1, n_2}} + (1 - p_1) e^{-\bar{b}_{n_1}}), \quad (5.64)
\]

\[
q(n_1, n_2), (n_1, n_2 + 1) = \varphi_2 n_2 (p_2 e^{-n_2 \bar{a}_{n_1, n_2}} + (1 - p_2) e^{-\bar{d}_{n_2}}), \quad (5.65)
\]

\[
q(n_1, n_2), (n_1 - 1, n_2) = \mu_1 n_1 \quad (5.66)
\]

\[
q(n_1, n_2), (n_1, n_2 + 1) = \mu_2 n_2 \quad (5.67)
\]

\[-q(n_1, n_2), (n_1, n_2) = \varphi_1 n_1 (p_1 e^{-n_1 \bar{a}_{n_1, n_2}} + (1 - p_1) e^{-\bar{b}_{n_1}})
\]

\[+ \varphi_2 n_2 (p_2 e^{-n_2 \bar{a}_{n_1, n_2}} + (1 - p_2) e^{-\bar{d}_{n_2}})
\]

\[+ \mu_1 n_1 + \mu_2 n_2 \quad (5.68)
\]

\[
q(n_1, n_2), (m_1, m_2) = 0 \quad \text{otherwise ,} \quad (5.69)
\]

where \(\bar{a}_{n_1, n_2} = \sum_{r=0}^{+\infty} \frac{\nu_2^r}{r! n_1 + n_2 + r(n_1)}\), \(\bar{b}_{n_1} = \sum_{r=0}^{+\infty} \frac{\nu_1^r}{r! n_1 + r(n_1)}\), \(\bar{d}_{n_2} = \sum_{r=0}^{+\infty} \frac{\nu_2^r}{r! n_2 + r(n_2)}\).

This matrix is conservative as the total of each row is equal to zero and it is also regular from Eq. (5.43), as required. Recall that \(x = \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1\) defines a one-to-one correspondence between states \((n_1, n_2) \in S\) and states \(x \in S\) and so \(x\) and \((n_1, n_2)\) are used interchangeably in what follows (so that \(-q_{x,x}\) denotes \(-q(n_1, n_2), (n_1, n_2)\) and so on). Now, let \(f(x) = n_1 + n_2\) so that \(x \geq f(x)\) for all \(x \in S\).

(i) For \(x \in S\), the function \(f(x) = n_1 + n_2 \geq 0\) and \(f(x) \to +\infty\) as \(x \to +\infty\), satisfying condition (4.13).

(ii)

\[
\sum_{y \neq x} \frac{q_{x,y}}{-q_{x,x}} f(y) - f(x) \leq \frac{\varphi_1 + \varphi_2 - \mu_1 n_1 - \mu_2 n_2}{-q_{x,x}}, \quad (5.70)
\]

using the bound (5.30) and definitions (5.64)–(5.69). Thus,

\[
\sum_{y \neq x} \frac{q_{x,y}}{-q_{x,x}} f(y) - f(x) < 0, \quad (5.71)
\]
when

\[ \varphi_1 + \varphi_2 < \mu_1 n_1 + \mu_2 n_2 \leq (n_1 + n_2) \max(\mu_1, \mu_2) \]

\[ \Rightarrow x \geq n_1 + n_2 > \frac{\varphi_1 + \varphi_2}{\max(\mu_1, \mu_2)}. \]  

(5.72)

Then \( D_1 > 0 \) and an integer \( D_6 < +\infty \) can be found such that

\[ \sum_{y \neq x} \frac{q_{x,y}}{-q_{x,x}} f(y) \leq f(x) - D_1 \text{ for } x \geq D_6, \]  

(5.73)

and condition (4.14) is thus satisfied.

(iii) For the competition process, transitions are only allowed to neighbouring states and so \( n_1 + n_2 \) can only increase or decrease by one with each transition. Thus, for all values of \( y \) such that \( q_{x,y} > 0 \),

\[ |f(x) - f(y)| \leq 1 \text{ for all } x \in \tilde{S}. \]  

(5.74)

Then condition (4.15) is satisfied by taking \( D_2 = 1 \).

(iv) Now \( x \) is fixed. Then for \( 1 \leq x \leq D_6 - 1 \) the following bound is obtained:

\[ \sum_{y \neq x} q_{x,y} \leq \varphi_1 + \varphi_2 + \mu_1 n_1 + \mu_2 n_2 \leq \varphi_1 + \varphi_2 + (n_1 + n_2) \max(\mu_1, \mu_2) \]

\[ \leq \varphi_1 + \varphi_2 + (D_6 - 1) \max(\mu_1, \mu_2). \]  

(5.75)

Now, \( D_3 \) is chosen such that \( 0 < \frac{1}{D_3} (\varphi_1 + \varphi_2 + (D_6 - 1) \max(\mu_1, \mu_2)) < 1 \) and then, for \( z \geq 1 \), define

\[ D_4 = -\frac{1}{z} \log\left( \frac{1}{D_3} (\varphi_1 + \varphi_2 + (D_6 - 1) \max(\mu_1, \mu_2)) \right) > 0. \]  

(5.76)

Therefore, \( D_3 e^{-D_4 z} = \varphi_1 + \varphi_2 + (D_6 - 1) \max(\mu_1, \mu_2) \) and hence condition (4.16)
holds.

(v) Finally,

$$-q_{x,x} \geq \mu_1 n_1 + \mu_2 n_2 \geq (n_1 + n_2) \min(\mu_1, \mu_2) \geq \min(\mu_1, \mu_2), \quad (5.77)$$

for $x \geq 1$ and so in order to satisfy condition (4.17), define $D_5 = \min(\mu_1, \mu_2) > 0$.

Hence, by Lemma 4.3 and Theorem 1.1 of Ferrari et al. [47], a QSD exists for the process $\{\mathcal{Y}(t) : t \geq \tilde{t}_2\}$ on the state-space $\tilde{S}$. Therefore, it can be concluded that a QSD exists for the process $\{(X_1(t), X_2(t)) : t \geq \tilde{t}_2\}$ on the state-space $S$, as the two processes are equivalent. However, nothing can be concluded about whether or not the QSD is unique as the criterion used in Section 4.1.2 applies only to univariate birth and death processes.

Examples of the QSD, as defined by Eq. (5.56), are shown in Figs. 5.4–5.5 for two sets of parameter values where the state-space of the process has been truncated so that $S = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots, N\}$ in order to allow numerical computation. This means that, in both cases, the QSD is unique and is equal to the LCD of the process. All of the weight of the distribution is at states where $n_1 = 0$ or $n_2 = 0$. This is because, for this process, the set of states $A = \{(n_1, n_2) : n_1 = 0 \text{ or } n_2 = 0\}$ forms an absorbing set and so once the process reaches this set (which, from Section 5.2.1, it does eventually with probability one), it remains there forever. Hence, this form of the QSD provides information on the process after one clonotype has become extinct but before both clonotypes disappear from the repertoire. In the next section, the stationary probability distribution of the process conditional on the event that both clonotypes are present in the repertoire is introduced.
Figure 5.4: The limiting probability distribution of the process conditional on the event that at least one of the pair of clonotypes is present in the repertoire with $\nu_{12} = \nu_1 = \nu_2 = 0.001, \varphi_1 = \varphi_2 = 10, p_1 = p_2 = 0.5, \langle n \rangle = 10, \mu_1 = \mu_2 = 1$ and $N = 500$.

5.3.3 The stationary probability distribution of the process conditional on the event that both clonotypes are present in the repertoire

For some values of the model parameters, the time until the process reaches the absorbing set is large (see Chapter 6) and before the process reaches the absorbing set it wanders stochastically according to a probability distribution which is stationary for most of the time before the absorbing set is reached. Hence, in this case, there are two timescales to consider. Firstly, after a relatively short period of time, the process relaxes to this probability distribution, which represents the homeostatic
number of T cells before extinction occurs. Subsequently, one of the clonotypes becomes extinct and the process reaches the absorbing set. In this section, a QSD is defined by conditioning on the event that T cells of both clonotypes 1 and 2 are still present in the repertoire.

Recall that \( \mathcal{A} = \{(n_1, n_2) : n_1 = 0 \text{ or } n_2 = 0\} \) is the absorbing set and let \( p_{\bar{A}}(t) \) be the probability that the process is not in set \( \mathcal{A} \) at time \( t \). Then for all \( (n_1, n_2) \in \mathcal{S} \setminus \mathcal{A} \), define

\[
q_{n_1, n_2}(t) = \frac{p_{n_1, n_2}(t)}{p_{\bar{A}}(t)}
\]  

(5.78)

which is the probability that the process is in state \( (n_1, n_2) \) at time \( t \), conditional on
the event that the absorbing set has not been reached. For all $t \geq \tilde{t}_2$, $q_{n_1,n_2}(t) \geq 0$ for $(n_1, n_2) \in S \setminus A$, $q_{n_1,n_2}(t) = 0$ for $(n_1, n_2) \notin S \setminus A$ and $\sum_{n_1=1}^{+\infty} \sum_{n_2=1}^{+\infty} q_{n_1,n_2}(t) = 1$.

From Eq. (5.78),

$$\frac{dq_{n_1,n_2}(t)}{dt} = \frac{1}{p_{\bar{A}}(t)} \frac{dp_{n_1,n_2}(t)}{dt} - \frac{p_{n_1,n_2}(t)}{(p_{\bar{A}}(t))^2} \frac{dp_{\bar{A}}(t)}{dt}.$$  \hspace{1cm} (5.79)

By the law of total probability

$$p_{\bar{A}}(t) = 1 - \sum_{n_2=0}^{+\infty} p_{0,n_2}(t) - \sum_{n_1=0}^{+\infty} p_{n_1,0}(t) + p_{0,0}(t).$$ \hspace{1cm} (5.80)

Substituting $n_1 = 0$ in Eq. (5.53) and summing over all values of $n_2$ and then substituting $n_2 = 0$ in Eq. (5.53) and summing over all values of $n_1$ results in

$$\frac{d}{dt} \sum_{n_2=0}^{+\infty} p_{0,n_2}(t) = \mu_1 \sum_{n_2=0}^{+\infty} p_{1,n_2}(t),$$ \hspace{1cm} (5.81)

$$\frac{d}{dt} \sum_{n_1=0}^{+\infty} p_{n_1,0}(t) = \mu_2 \sum_{n_1=0}^{+\infty} p_{n_1,1}(t),$$ \hspace{1cm} (5.82)

and substituting $n_1 = n_2 = 0$ in Eq. (5.53) gives

$$\frac{d}{dt} p_{0,0}(t) = \mu_1 p_{1,0}(t) + \mu_2 p_{0,1}(t).$$ \hspace{1cm} (5.83)

Then

$$\frac{dp_{\bar{A}}(t)}{dt} = -\mu_1 \sum_{n_2=1}^{+\infty} p_{1,n_2}(t) - \mu_2 \sum_{n_1=1}^{+\infty} p_{n_1,1}(t).$$ \hspace{1cm} (5.84)
Hence, the system of differential equations satisfied by $q_{n_1,n_2}(t)$ is

$$
\frac{dq_{n_1,n_2}(t)}{dt} = \lambda_{n_1-1,n_2}^{(1)} q_{n_1-1,n_2}(t) + \lambda_{n_1,n_2-1}^{(2)} q_{n_1,n_2-1}(t) + \mu_{n_1+1,n_2}^{(1)} q_{n_1+1,n_2}(t) \\
+ \mu_{n_1,n_2+1}^{(2)} q_{n_1,n_2+1}(t) - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) q_{n_1,n_2}(t) \\
+ \mu_1 q_{n_1,n_2}(t) \sum_{n_2=1}^{+\infty} q_{1,n_2}(t) + \mu_2 q_{n_1,n_2}(t) \sum_{n_1=1}^{+\infty} q_{n_1,1}(t),
$$

(5.85)

for $(n_1,n_2) \in S \setminus A$. A probability distribution $\bar{q}$, assuming it exists, is called a quasi-stationary probability distribution (QSD) if it satisfies

$$
0 = \lambda_{n_1-1,n_2}^{(1)} \bar{q}_{n_1-1,n_2} + \lambda_{n_1,n_2-1}^{(2)} \bar{q}_{n_1,n_2-1} + \mu_{n_1+1,n_2}^{(1)} \bar{q}_{n_1+1,n_2} \\
+ \mu_{n_1,n_2+1}^{(2)} \bar{q}_{n_1,n_2+1} - (\lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}) \bar{q}_{n_1,n_2} \\
+ \mu_1 \bar{q}_{n_1,n_2} \sum_{n_2=1}^{+\infty} \bar{q}_{1,n_2} + \mu_2 \bar{q}_{n_1,n_2} \sum_{n_1=1}^{+\infty} \bar{q}_{n_1,1},
$$

(5.86)

where $\bar{q}_{n_1,n_2} \geq 0$ for $(n_1,n_2) \in S \setminus A$, $\bar{q}_{n_1,n_2} = 0$ for $(n_1,n_2) \notin S \setminus A$ and $\sum_{n_1=1}^{+\infty} \sum_{n_2=1}^{+\infty} \bar{q}_{n_1,n_2} = 1$. The limiting conditional probability distribution (LCD) of the process is denoted by $q$ and is defined by

$$
q_{n_1,n_2} = \lim_{t \to +\infty} q_{n_1,n_2}(t),
$$

(5.87)

where $q_{n_1,n_2} \geq 0$ for $(n_1,n_2) \in S \setminus A$, $q_{n_1,n_2} = 0$ for $(n_1,n_2) \notin S \setminus A$ and $\sum_{n_1=1}^{+\infty} \sum_{n_2=1}^{+\infty} q_{n_1,n_2} = 1$. The LCD does not depend on time and so is, by definition, a QSD. However, the converse is not necessarily true. For a process with a finite state-space, i.e., $S = \{(n_1,n_2) : n_1 = 0,1,2,\ldots,N_1; n_2 = 0,1,2,\ldots,N_2\}$ a unique QSD exists, which is also the unique LCD of the process [33]. However, if the state-space of the process is denumerably infinite, a QSD might not exist [29], or if it does exist, it may not be unique. In the next section, it is conjectured that at least one QSD of the type defined by Eq. (5.86) exists for the process $\{(X_1(t),X_2(t)) : t \geq \tilde{t}_2\}$.
on the state-space $S = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots\}$. It is not in general possible to find an explicit solution to the non-linear equations given by Eq. (5.86), but the QSD may be calculated numerically from the infinitesimal generator matrix of the process, $Q$, restricted to the set of states $S \setminus \mathcal{A}$. Then, as described previously, the QSD is given by the left eigenvector corresponding to the eigenvalue of this matrix with maximal real part, normalised so that \[
_{n_1=1}^{\infty} \n_{n_2=1}^{\infty} q_{n_1,n_2} = 1 \] [105].

### 5.3.4 Existence of the stationary probability distribution conditional on the event that both clonotypes are present in the repertoire

In this section it is conjectured that a QSD (as defined by Eq. (5.86)) exists for the bivariate competition process introduced in Section 5.1. It is not possible to relabel the states to form a univariate Markov process, as in Section 5.3.2, in such a way that the “asymptotic remoteness” condition (5.61) holds. This condition requires that the states adjacent to the absorbing set $\mathcal{A} = \{(n_1, n_2) : n_1 = 0 \text{ or } n_2 = 0\}$ are labelled first, but there are an infinite number of such states. Hence, a one-to-one mapping between the states in $S$ and the set of states $\{0, 1, 2, \ldots\}$ in such a way that the asymptotic remoteness condition holds is not possible.

Recall that in Section 5.2 the bivariate competition process was bounded by a univariate birth and death process, in the sense that the univariate process moves to the origin at a slower rate than the competition process. A similar approach is taken here. The state-space of the competition process, $S$, is divided into the following disjoint subsets:

\[ S_j = \{(n_1, n_2) : n_1 = j \text{ or } n_2 = j \text{ and } n_1, n_2 \geq j\} \text{ for } j \geq 0. \] (5.88)
These sets are represented schematically in Fig. 5.6. Hence, $S_0$ corresponds to the absorbing set and with each transition the process either stays in the same set or moves from $S_j$ to either $S_{j-1}$ or $S_{j+1}$. These sets correspond to the states of the univariate birth and death process that will be defined here. In order to define the birth and death rates of this new process, the transitions that may occur from three disjoint subsets of $S_j$ are considered, where $r_{n_1,n_2} = \lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)}$ for notational convenience:

1. States belonging to the set $\{(n_1,n_2) : n_1 = j, n_2 > j\}$. The following transitions may occur:
   (i) with probability $(\lambda_{j,n_2}^{(2)} + \mu_{j,n_2}^{(2)})/r_{j,n_2}$ the process stays in $S_j$,
   (ii) with probability $\lambda_{j,n_2}^{(1)}/r_{j,n_2}$ the process moves to a state in $S_{j+1}$,
   (iii) with probability $\mu_{j,n_2}^{(1)}/r_{j,n_2}$ the process moves to a state in $S_{j-1}$.

2. States belonging to the set $\{(n_1,n_2) : n_1 > j, n_2 = j\}$. The following transitions may occur:
   (i) with probability $(\lambda_{n_1,j}^{(1)} + \mu_{n_1,j}^{(1)})/r_{n_1,j}$ the process stays in $S_j$,
   (ii) with probability $\lambda_{n_1,j}^{(2)}/r_{n_1,j}$ the process moves to a state in $S_{j+1}$.
(iii) with probability $\mu_{n_1,j}^{(2)}/r_{n_1,j}$ the process moves to a state in $S_{j-1}$.

(3) States belonging to the set $\{(n_1, n_2) : n_1 = n_2 = j\}$. The following transitions may occur:

(i) with probability $(\lambda_{j,j}^{(1)} + \lambda_{j,j}^{(2)})/r_{j,j}$ the process stays in $S_j$,

(ii) with probability $(\mu_{j,j}^{(1)} + \mu_{j,j}^{(2)})/r_{j,j}$ the process moves to a state in $S_{j-1}$.

Hence, the birth and death process $\{Z(t) : t \geq \tilde{t}_2\}$ on the state-space $\{S_0, S_1, S_2, \ldots\}$ with birth and death rates given by

$$\lambda_j = \max(\varphi_1, \varphi_2),$$

$$\mu_j = j \min(\mu_1, \mu_2),$$

(5.89)

(5.90)

for $j \geq 1$ and $\lambda_0 = \mu_0 = 0$, is a univariate birth and death process which moves towards the absorbing set at a slower rate than the bivariate competition process.

Let

$$\pi_1 = 1 \text{ and } \pi_j = \frac{\lambda_1 \lambda_2 \ldots \lambda_{j-1}}{\mu_2 \mu_3 \ldots \mu_j}.$$ 

(5.91)

The process $\{Z(t) : t \geq \tilde{t}_2\}$ is regular because

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda_n} \sum_{j=1}^{n} \pi_j > \sum_{n=1}^{+\infty} \frac{1}{\lambda_n} \pi_n = \sum_{n=1}^{+\infty} \frac{1}{\lambda_n} = \sum_{n=1}^{+\infty} \frac{1}{\max(\varphi_1, \varphi_2)} = +\infty.$$ 

(5.92)

Then, if the series

$$\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j}$$

(5.93)
diverges, the univariate process reaches the state $S_0$ with certainty. For the birth and death rates (5.89)–(5.90),

$$\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} = \sum_{j=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_j}{\lambda_1 \lambda_2 \ldots \lambda_j} = \frac{j! [\min(\mu_1, \mu_2)]^{j-1}}{[\max(\varphi_1, \varphi_2)]^j}. \tag{5.94}$$

Let

$$a_j = \frac{j! [\min(\mu_1, \mu_2)]^{j-1}}{[\max(\varphi_1, \varphi_2)]^j}, \tag{5.95}$$

so that

$$\frac{a_{j+1}}{a_j} = \frac{(j + 1) \min(\mu_1, \mu_2)}{\max(\varphi_1, \varphi_2)} \rightarrow +\infty \text{ as } j \rightarrow +\infty. \tag{5.96}$$

Hence, the series $\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j}$ diverges by the ratio test. Therefore, the process $\{Z(t) : t \geq \tilde{t}_2\}$ reaches $S_0$ with certainty. Since this process moves towards the absorbing set at a slower rate than the competition process, it is concluded that the competition process reaches the absorbing set with probability one [70].

For the birth and death rates (5.89)–(5.90),

$$\lambda_j \rightarrow \max(\varphi_1, \varphi_2) \text{ and } \mu_j \rightarrow +\infty \text{ as } j \rightarrow +\infty, \tag{5.97}$$

and so, by Theorem 5.3 of van Doorn [131], $\sigma > 0$ for this process, and hence the decay parameter of the process, $\alpha$, is also positive (see Section 4.1.1, Method 1). Therefore, at least one QSD exists for the process $\{Z(t) : t \geq \tilde{t}_2\}$. This QSD is not
unique because

\[
\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \sum_{n=j+1}^{+\infty} \pi_n > \sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \pi_{j+1}
\]

\[
= \sum_{j=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_j \lambda_1 \lambda_2 \ldots \lambda_j}{\lambda_1 \lambda_2 \ldots \lambda_j \mu_2 \mu_3 \ldots \mu_{j+1}}
\]

\[
= \sum_{j=1}^{+\infty} \frac{1}{\mu_{j+1}}
\]

\[
= \frac{1}{\min(\mu_1, \mu_2)} \sum_{j=1}^{+\infty} \frac{1}{j+1} = +\infty ,
\]

and so there exists a one-parameter family of QSDs [132].

Since the bivariate competition process \( \{(X_1(t), X_2(t)) : t \geq \tilde{t}_2 \} \) is “better behaved” than the birth and death process \( \{Z(t) : t \geq \tilde{t}_2 \} \), in the sense that the bivariate process moves towards the absorbing set at a faster rate, it is conjectured that the existence of a QSD for \( \{Z(t) : t \geq \tilde{t}_2 \} \) implies that a QSD also exists for the bivariate competition process. For a univariate Markov process, the necessary and sufficient conditions for the existence of a QSD are that eventual absorption occurs with certainty and that the rate of absorption is exponential [47]. If these are also the necessary and sufficient conditions for the existence of a QSD for a bivariate process, the properties of the univariate process \( \{Z(t) : t \geq \tilde{t}_2 \} \) would imply existence of a QSD for the bivariate process also. Examples of the QSD, as defined by Eq. (5.86), are shown in Figs. 5.7–5.8 for two different sets of parameter values, where the state-space of the process has been truncated so that \( S = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots, N \} \) in order to allow numerical computation. This means that, in both cases, the QSD is unique and is equal to the LCD of the process.
Figure 5.7: The limiting probability distribution of the process conditional on the event that both of the pair of clonotypes are present in the repertoire with $\nu_1 = \nu_2 = 0.001$, $\varphi_1 = \varphi_2 = 10$, $p_1 = p_2 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$.

5.4 Discussion

In this chapter, the QSD of the process has been defined in two different ways. The QSD defined in Section 5.3.3 describes the late-time behaviour of the process when T cells of both clonotype 1 and clonotype 2 are still present in the repertoire, while the QSD defined in Section 5.3.1 describes the late-time behaviour of the process after one clonotype has become extinct but before both clonotypes disappear from the repertoire. Therefore, the latter is most useful when one of the pair of clonotypes becomes extinct from the repertoire very quickly (see Chapter 6).

There has been little previous work on the existence of a QSD for bivariate Markov
processes with infinite state-spaces. The relabelling method introduced in Section 5.3.2 provides for the first time a general method of proving the existence of a QSD for a bivariate competition process with an infinite state-space and may be widely applied. The method may also be extended to prove the existence of a QSD for competition processes in higher dimensions (see Chapter 7).

The bivariate competition process introduced in this chapter has a state-space consisting of an absorbing set, \( \mathcal{A} \), and a transient communicating class of states, \( \mathcal{S} \setminus \mathcal{A} \).

For a bivariate competition process on the state-space \( \mathcal{S} = \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots \} \) where \((0, 0)\) is an absorbing state and the remaining states form a transient communicating class of states, the absorbing set consists only of the state
(0, 0). This means that the QSD defined in Section 5.3.1 models the late-time behaviour of the process before extinction occurs and the definition of the QSD given in Section 5.3.3 is not applicable. An example of such a process is the Ross malaria model [97]. Hence, the method presented in Section 5.3.2 for proving the existence of a QSD for a bivariate competition with an infinite state-space may be applied to such processes.

Existence of a QSD is a necessary condition for the existence of the LCD because the LCD is independent of time and so is, by definition, a QSD. Therefore, if the initial probability distribution of the process is a QSD, this will also be the LCD of the process. However, for the bivariate competition process presented in Section 5.1, the biologically realistic initial condition is such that the initial probability distribution has all its weight at one state, \((\tilde{n}_1, \tilde{n}_2)\), which corresponds to the number of T cells belonging to clonotypes 1 and 2 at time \(\tilde{t}_2\). For such initial conditions, nothing can be concluded about the existence of an LCD in the infinite state-space case and this is an area for future work. Of course, in reality, there is an upper bound on the number of T cells that can belong to each clonotype (i.e., it cannot be larger than the number of cells in an adult human), which is denoted by \(N\), resulting in a finite state-space process. For such processes, there exists a unique QSD, which is also the unique LCD of the process [33].
Chapter 6

Special cases of the bivariate competition process

In the univariate birth and death process introduced in Chapter 3, which models the number of T cells belonging to a single clonotype, two special cases were defined corresponding to $\nu \ll 1$ and $\nu \gg 1$ (see Section 3.1.3). For the bivariate competition process defined in Chapter 5, which models the number of cells belonging to a pair of clonotypes for which the assumption $|Q_1 \cap Q_2| \ll |Q_1|$ does not hold, there are six such special cases. These cases are determined by the values of the parameters $\nu_{12}$, $\nu_1$ and $\nu_2$. The special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ is the focus of this chapter, as it provides an upper bound on all other cases in the sense that it is associated with the longest mean time until extinction occurs. This case also has the smallest number of parameters and it is possible to obtain some analytical results. It is shown that as the commonality between the pair of clonotypes increases (in terms of the APPs from which they are able to receive survival signals), one clonotype quickly becomes extinct from the repertoire by a mechanism which resembles the classical competitive exclusion principle of ecology [11]. The LCD of the process is approximated by means of a bivariate normal distribution, which is derived using
both van Kampen’s large $N$ expansion [134] and a diffusion approximation [46]. The other special cases are also briefly considered.

6.1 The six special cases

In this section, the six special cases of the bivariate competition process are defined and the form taken by the birth rates (5.24) and (5.26) is given.

(1) The case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1$. 

In this case the $r = 0$ term in the sums in Eqs. (5.24) and (5.26) dominates and so the birth rates become

\[
\lambda_{n_1,n_2}^{(1)} = \varphi_1 \left( 1 - \frac{p_1 n_2}{n_1 + n_2} \right), \quad (6.1)
\]
\[
\lambda_{n_1,n_2}^{(2)} = \varphi_2 \left( 1 - \frac{p_2 n_1}{n_1 + n_2} \right). \quad (6.2)
\]

In this case, the birth and death rates are symmetric under the exchange of the clonotype labels 1 and 2.

(2) The case $\nu_{12} \gg 1, \nu_1 \ll 1, \nu_2 \ll 1$. 

Using the same method of approximating the birth rates (5.24) and (5.26) for $\nu_{12} \gg 1$ as for $\nu \gg 1$ in Section 3.1.3, it can be shown that

\[
\lambda_{n_1,n_2}^{(1)} = \frac{\varphi_1 n_1 p_1}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \varphi_1 (1 - p_1), \quad (6.3)
\]
\[
\lambda_{n_1,n_2}^{(2)} = \frac{\varphi_2 n_2 p_2}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \varphi_2 (1 - p_2), \quad (6.4)
\]

so that the birth and death rates are symmetric under the exchange of the clonotype labels.
(3) The case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$.

Using the same method of approximating the birth rate (5.26) when $\nu_2 \gg 1$ as for $\nu \gg 1$ in Section 3.1.3, the birth rates (5.24) and (5.26) become

$$\lambda^{(1)}_{n_1,n_2} = \varphi_1 \left(1 - \frac{p_1 n_2}{n_1 + n_2}\right),$$  
(6.5)

$$\lambda^{(2)}_{n_1,n_2} = \varphi_2 n_2 \left(\frac{p_2}{n_1 + n_2} + \frac{1 - p_2}{n_2 + \nu_2 \langle n \rangle}\right).$$  
(6.6)

Similarly to case (3), the birth rates (5.24) and (5.26) become

$$\lambda^{(1)}_{n_1,n_2} = \varphi_1 n_1 \left(\frac{p_1}{n_1 + n_2} + \frac{1 - p_1}{n_1 + \nu_1 \langle n \rangle}\right),$$  
(6.7)

$$\lambda^{(2)}_{n_1,n_2} = \varphi_2 \left(1 - \frac{p_2 n_1}{n_1 + n_2}\right).$$  
(6.8)

Swapping the clonotype labels 1 and 2, it is clear that cases (3) and (4) are equivalent to one another.

(4) The case $\nu_{12} \ll 1$, $\nu_1 \gg 1$, $\nu_2 \ll 1$.

Here, the birth rates (5.24) and (5.26) are

$$\lambda^{(1)}_{n_1,n_2} = \varphi_1 n_1 \left(\frac{p_1}{n_1 + n_2 + \nu_1 \langle n \rangle}\right) + \varphi_1 (1 - p_1),$$  
(6.9)

$$\lambda^{(2)}_{n_1,n_2} = \varphi_2 n_2 \left(\frac{p_2}{n_1 + n_2 + \nu_2 \langle n \rangle}\right) + \frac{1 - p_2}{n_2 + \nu_2 \langle n \rangle}. $$  
(6.10)

(5) The case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$.

Similarly to case (3), the birth rates (5.24) and (5.26) become

(6) The case $\nu_{12} \gg 1$, $\nu_1 \gg 1$, $\nu_2 \ll 1$. 

In this case, the birth rates (5.24) and (5.26) are

\[
\lambda^{(1)}_{n_1,n_2} = \varphi_1 n_1 \left( \frac{p_1}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \frac{1 - p_1}{n_1 + \nu_1 \langle n \rangle} \right), \quad (6.11)
\]

\[
\lambda^{(2)}_{n_1,n_2} = \frac{\varphi_2 n_2 p_2}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \varphi_2 (1 - p_2). \quad (6.12)
\]

This case is equivalent to case (5).

(7) The case \( \nu_{12} \ll 1, \nu_1 \gg 1, \nu_2 \gg 1 \).

The birth rates (5.24) and (5.26) become

\[
\lambda^{(1)}_{n_1,n_2} = \varphi_1 n_1 \left( \frac{p_1}{n_1 + n_2} + \frac{1 - p_1}{n_1 + \nu_1 \langle n \rangle} \right), \quad (6.13)
\]

\[
\lambda^{(2)}_{n_1,n_2} = \varphi_2 n_2 \left( \frac{p_2}{n_1 + n_2} + \frac{1 - p_2}{n_2 + \nu_2 \langle n \rangle} \right). \quad (6.14)
\]

In this case, the birth and death rates are symmetric under the exchange of the clonotype labels 1 and 2.

(8) The case \( \nu_{12} \gg 1, \nu_1 \gg 1, \nu_2 \gg 1 \).

Finally, in this case the birth rates (5.24) and (5.26) are

\[
\lambda^{(1)}_{n_1,n_2} = \varphi_1 n_1 \left( \frac{p_1}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \frac{1 - p_1}{n_1 + \nu_1 \langle n \rangle} \right), \quad (6.15)
\]

\[
\lambda^{(2)}_{n_1,n_2} = \varphi_2 n_2 \left( \frac{p_2}{n_1 + n_2 + \nu_{12} \langle n \rangle} + \frac{1 - p_2}{n_2 + \nu_2 \langle n \rangle} \right). \quad (6.16)
\]

so that the birth and death rates are symmetric under the exchange of the clonotype labels.

Therefore, due to the equivalent nature of cases (3) and (4) and cases (5) and (6), there are only six different special cases to consider.
6.2 Mean extinction times in the case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1$

A pair of clonotypes with $\nu_{12} \ll 1, \nu_1 \ll 1$ and $\nu_2 \ll 1$ has TCRs that are very different (in terms of their recognition of APPs) from the other clonotypes in the naive repertoire, even though they overlap significantly with each other in terms of the APPs from which they are able to receive survival signals. Recall that these survival signals are signals for homeostatic proliferation which result in the T cell undergoing a single round of cell division. This case is the focus of the current chapter because the region of parameter space $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1$ is associated with the longest lifespan of a pair of clonotypes in the peripheral repertoire for which $|Q_1 \cap Q_2| \sim |Q_1|$, since competition with other T cell clonotypes is small. Therefore, this case provides an upper bound on the mean time to extinction for the general bivariate competition process $\{(X_1(t), X_2(t)) : t \geq \tilde{t}_2\}$ where the parameters $\nu_{12}, \nu_1$ and $\nu_2$ take arbitrary values. Furthermore, the number of model parameters is reduced from the nine listed in Section 5.1.2 to the five parameters $\varphi_1, \varphi_2, p_1, \mu_1$ and $\mu_2$ with the use of the constraint (5.29), which states that $\varphi p_1 = \varphi_2 p_2$, to eliminate $p_2$.

Before extinction at the absorbing state $(n_1, n_2) = (0, 0)$ occurs, the bivariate competition process enters the absorbing set $\mathcal{A} = \{(n_1, n_2) : n_1 = 0$ or $n_2 = 0\}$ when one of the pair of T cell clonotypes becomes extinct. Let $\hat{\tau}_{n_1, n_2}$ be the mean time until the process enters the absorbing set $\mathcal{A}$ given that the initial state of the process is $(n_1, n_2) \in \mathcal{S} \setminus \mathcal{A}$. It can be shown by first-step analysis [126] that this quantity satisfies the following two-dimensional difference equation (where
\[ r_{n_1,n_2} = \lambda_{n_1,n_2}^{(1)} + \lambda_{n_1,n_2}^{(2)} + \mu_{n_1,n_2}^{(1)} + \mu_{n_1,n_2}^{(2)} \]

for notational convenience:

\[ \hat{\tau}_{n_1,n_2} = \lambda_{n_1,n_2}^{(1)} r_{n_1,n_2} + \lambda_{n_1,n_2}^{(2)} r_{n_1,n_2} \hat{\tau}_{n_1,n_2} + \mu_{n_1,n_2}^{(1)} r_{n_1,n_2} \hat{\tau}_{n_1,n_2} + \mu_{n_1,n_2}^{(2)} r_{n_1,n_2} \hat{\tau}_{n_1,n_2} + \frac{1}{r_{n_1,n_2}}, \]

with the boundary conditions \( \hat{\tau}_{j,0} = \hat{\tau}_{0,j} = 0 \) for all \( j \geq 1 \) and \( \hat{\tau}_{N+1,j} = \hat{\tau}_{j,N+1} = 0 \) for all \( j \geq 1 \) where the state-space of the process is truncated to be finite, i.e., \( S = \{(n_1,n_2) : n_1,n_2 = 0,1,2,\ldots,N\} \) in order to allow numerical computation.

Eq. (6.17) can be rearranged to give

\[ -1 = \lambda_{n_1,n_2}^{(1)} \hat{\tau}_{n_1,n_2} + \lambda_{n_1,n_2}^{(2)} \hat{\tau}_{n_1,n_2} + \mu_{n_1,n_2}^{(1)} \hat{\tau}_{n_1,n_2} + \mu_{n_1,n_2}^{(2)} \hat{\tau}_{n_1,n_2} - r_{n_1,n_2} \hat{\tau}_{n_1,n_2}. \]

This set of equations can be written in the form

\[ A \hat{\tau} = b, \]

where \( \hat{\tau} = [\hat{\tau}_{1,1}, \hat{\tau}_{1,2}, \ldots, \hat{\tau}_{N,1}, \hat{\tau}_{N,2}, \ldots, \hat{\tau}_{N,N}]^T \in \mathbb{R}^{N^2}, b = [-1, -1, \ldots, -1]^T \in \mathbb{R}^{N^2} \) and \( A \) is an \( N^2 \times N^2 \) block tridiagonal matrix defined by

\[
\begin{pmatrix}
B_1 & C_1 & 0 & \cdots & 0 \\
D_2 & B_2 & C_2 & \cdots & 0 \\
0 & D_3 & B_3 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & \cdots & B_N
\end{pmatrix},
\]
with

\[
B_n = \begin{pmatrix}
-r_{1,n} & \lambda_{1,n}^{(1)} & 0 & \ldots & 0 \\
\mu_{2,n}^{(1)} & -r_{2,n} & \lambda_{2,n}^{(1)} & \ldots & 0 \\
0 & \mu_{3,n}^{(1)} & -r_{3,n} & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & 0 \\
0 & 0 & 0 & \ldots & -r_{N,n}
\end{pmatrix},
\]

and

\[
C_n = \begin{pmatrix}
\lambda_{1,n}^{(2)} & 0 & 0 & \ldots & 0 \\
n & \lambda_{2,n}^{(2)} & 0 & \ldots & 0 \\
0 & 0 & \lambda_{3,n}^{(2)} & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & 0 \\
0 & 0 & 0 & \ldots & \lambda_{N,n}^{(2)}
\end{pmatrix},
\]

and

\[
D_n = \begin{pmatrix}
\mu_{1,n}^{(2)} & 0 & 0 & \ldots & 0 \\
n & \mu_{2,n}^{(2)} & 0 & \ldots & 0 \\
0 & 0 & \mu_{3,n}^{(2)} & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & 0 \\
0 & 0 & 0 & \ldots & \mu_{N,n}^{(2)}
\end{pmatrix}.
\]

The matrix equation (6.19) can be solved numerically using the MATLAB package [69], where the sparse nature of the matrix \(A\) is exploited to increase the speed of the computation.

Figs. 6.1–6.3 show that the time until the absorbing set is reached decreases as \(p_1\) increases. In Fig. 6.1, \(\hat{\tau}_{n_1,n_2}\) is plotted as a function of \(p_1\) for various initial states \((n_1, n_2)\) with \(n_1 + n_2 = 10\), so that the initial total number of cells remains fixed. In Fig. 6.2, \(\hat{\tau}_{n_1,n_2}\) is plotted as a function of \(p_1\) for different initial total numbers of cells with \(n_1 = n_2\). Taken together, these plots show that \(\hat{\tau}_{n_1,n_2}\) depends on the initial state of the process and increases as the initial state becomes further away from the absorbing set \(A\). In Fig. 6.3, \(\hat{\tau}_{n_1,n_2}\) is plotted as a function of \(p_1\) for several
values of $\varphi_1$, with all other parameters and the initial conditions remaining fixed. Figs. 6.4–6.5 show the time for which both clonotypes are present in the repertoire, $\hat{\tau}_{n_1,n_2}$, compared to the time until both clones become extinct, $\tau_{n_1,n_2}$, as a function of $p_1$. This is measured by $\hat{\tau}_{n_1,n_2}/\tau_{n_1,n_2}$ which is the proportion of the time before the absorbing state $(0,0)$ is reached for which both clonotypes 1 and 2 are present in the repertoire and, by definition, $0 < \hat{\tau}_{n_1,n_2}/\tau_{n_1,n_2} < 1$ because $\hat{\tau}_{n_1,n_2} < \tau_{n_1,n_2}$. The quantity $\hat{\tau}_{n_1,n_2}/\tau_{n_1,n_2}$ takes a value close to zero when extinction of one of the pair of clonotypes occurs very quickly. On the other hand, the quantity approaches one when both clonotypes persist for a long time in the repertoire and then both become extinct within a short space of time. Figs. 6.4–6.5 show that this quantity decreases as $p_1$ increases. Therefore, as $p_1 \to 1$, one of the pair of clonotypes quickly becomes extinct by a process that resembles the competitive exclusion principle of classical ecology, which states that two species competing for the same set of resources cannot stably coexist [11]. The numerical results indicate that the quantity $\hat{\tau}_{n_1,n_2}/\tau_{n_1,n_2}$ is maximal when both clonotypes have access to the same number of APPs from which they can receive survival signals, i.e., $\varphi_1 = \varphi_2$, and decreases as one clonotype gains a competitive advantage over the other, i.e., $\varphi_1 > \varphi_2$ or vice versa.

Another quantity of interest is the probability that T cells of clonotype 1 become extinct from the repertoire before T cells of clonotype 2 given that the process starts from an initial state $(n_1, n_2) \in S \setminus A$, which is denoted by $\wp_{n_1,n_2}$. This probability satisfies the difference equation

\[
\wp_{n_1,n_2} = \frac{(1)}{r_{n_1,n_2}} \wp_{n_1+1,n_2} + \frac{(2)}{r_{n_1,n_2}} \wp_{n_1,n_2+1} + \frac{(1)}{r_{n_1,n_2}} \wp_{n_1-1,n_2} + \frac{(2)}{r_{n_1,n_2}} \wp_{n_1,n_2-1},
\]

with the boundary conditions $\wp_{0,j} = 1$ for all $j \geq 1$, $\wp_{j,0} = 0$ for all $j \geq 1$, $\wp_{N+1,j} = \wp_{j,N+1} = 0$ for all $j \geq 1$, where the state space of the process is truncated to be finite in order to allow numerical computation (as above). The probability of clonotype 2 becoming extinct before clonotype 1 with the initial state $(n_1, n_2) \in S \setminus A$ is given
Figure 6.1: The quantity $\hat{\tau}_{n_1,n_2}$ as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = 5$, $\varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ for various initial states where $n_1 + n_2 = 10$.

Figure 6.2: The quantity $\hat{\tau}_{n_1,n_2}$ as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = 5$, $\varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ for various initial states where $n_1 = n_2$. 
Figure 6.3: The quantity $\hat{\tau}_{n_1,n_2}$ as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = 5, 8, 10, 20$, $\varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ with the initial state $n_1 = n_2 = 10$. Note that for $\varphi_1 = 20$ it is required that $p_1 \leq 0.5$ so that the condition $p_2 \leq 1$ is satisfied because of the constraint $\varphi_1 p_1 = \varphi_2 p_2$.

Figure 6.4: The quantity $\frac{\hat{\tau}_{n_1,n_2}}{\tau_{n_1,n_2}}$ as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = 5, 8, 10, 20$, $\varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ with the initial state $n_1 = n_2 = 10$. 
by $1 - \varphi_{n_1,n_2}$, because extinction is guaranteed (see Section 5.2.1).

In Fig. 6.6 the probability that clonotype 1 becomes extinct before clonotype 2 is plotted as a function of $p_1$ for different values of the parameter $\varphi_1$. This probability decreases as $\varphi_1$ increases, due to an increasing level of survival signals for T cells of clonotype 1, causing them to gain a competitive advantage over T cells of clonotype 2. Again, this quantity depends on the initial state of the process, as illustrated in Fig. 6.7. As $p_1$ increases, the effect of the advantage gained from a clonotype having a higher initial number of cells than its competitor increases. In the case $\varphi_1 = \varphi_2$, $p_1 = p_2$, $\mu_1 = \mu_2$ where $n_1 = n_2$, neither clonotype has a competitive advantage, as shown by the straight line in Fig. 6.7. However, it can also be seen that changes in the initial conditions such that $n_1 \neq n_2$ break this symmetry.
Figure 6.6: The probability that T cells of clonotype 1 becomes extinct before T cells of clonotype 2 as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = 5, 10, 20$, $\varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ with the initial state $n_1 = 9$, $n_2 = 1$.

Figure 6.7: The probability that T cells of clonotype 1 becomes extinct before T cells of clonotype 2 as a function of $p_1$ for the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\varphi_1 = \varphi_2 = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$ for various initial states.
6.3 A normal approximation to the LCD in the case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1$

In this section van Kampen’s “large $N$ expansion” [133, 134] is used to formulate a deterministic approximation to the stochastic model and to study the fluctuations about the stable steady state of this deterministic system for the special case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1$. This provides an approximation to the LCD of the process defined in Section 5.3.3. Recall from Section 4.4 that in the large $N$ expansion, it is expected that the number of T cells belonging to clonotype $i$ consists of a deterministic component plus fluctuations and that $\Omega$ is a parameter measuring the volume of the system, such that for large $\Omega$ the fluctuations are relatively small. Hence, the following change of variables is defined for $i = 1, 2$:

$$n_i = \Omega x_i(t) + \Omega^{\frac{1}{2}} \eta_i(t), \quad (6.21)$$

so that the fluctuations are of order $\Omega^{\frac{1}{2}}$. The forward Kolmogorov equation (5.53) is now expanded systematically as a power series in the parameter $\Omega$. The following difference operators are required:

$$M^{\pm 1}_{n_1} f(n_1, n_2) = f(n_1 \pm 1, n_2), \quad (6.22)$$

$$M^{\pm 1}_{n_2} f(n_1, n_2) = f(n_1, n_2 \pm 1). \quad (6.23)$$

In terms of these operators, the forward Kolmogorov equation (5.53) can be written as

$$\frac{dp_{n_1,n_2}(t)}{dt} = (M^{-1}_{n_1} - 1)\lambda^{(1)}_{n_1,n_2} p_{n_1,n_2}(t) + (M^{-1}_{n_2} - 1)\lambda^{(2)}_{n_1,n_2} p_{n_1,n_2}(t)$$

$$+ (M^{+1}_{n_1} - 1)\mu^{(1)}_{n_1,n_2} p_{n_1,n_2}(t) + (M^{+1}_{n_2} - 1)\mu^{(2)}_{n_1,n_2} p_{n_1,n_2}(t). \quad (6.24)$$
The change of variables given by Eq. (6.21) means that, rather than a probability distribution \( p(n_1, n_2) \), there is a probability distribution \( \Pi(\eta_1, \eta_2) \), i.e.,

\[
\Pi(\eta_1, \eta_2, t) = p_{n_1, n_2}(t) = p_{\Omega x_1 + \Omega x_2, \Omega x_2 + \Omega^2 \eta_2}(t),
\]

and so by the chain rule

\[
\frac{dp_{n_1, n_2}(t)}{dt} = \frac{\partial \Pi(\eta_1, \eta_2, t)}{\partial t} - \Omega^2 \frac{dx_1(t)}{dt} \frac{\partial \Pi(\eta_1, \eta_2, t)}{\partial \eta_1} - \Omega^2 \frac{dx_2(t)}{dt} \frac{\partial \Pi(\eta_1, \eta_2, t)}{\partial \eta_2},
\]

because \((n_1, n_2)\) is fixed in Eq. (6.24) and

\[
\frac{dn_i}{dt} = 0 \Rightarrow \Omega \frac{dx_i(t)}{dt} = -\Omega^2 \frac{d\eta_i(t)}{dt},
\]

for \(i = 1, 2\). As in Section 4.4, the same change of variables implies the following Taylor expansions for the difference operators defined by Eqs. (6.22)–(6.23):

\[
M^{+1}_{n_i} = 1 + \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_i} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_i^2} + \ldots, \quad (6.28)
\]

\[
M^{-1}_{n_i} = 1 - \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_i} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_i^2} + \ldots. \quad (6.29)
\]

In terms of the new variables, Eq. (6.24) can be written as

\[
\frac{\partial \Pi}{\partial t} - \Omega^2 \frac{dx_1}{dt} \frac{\partial \Pi}{\partial \eta_1} - \Omega^2 \frac{dx_2}{dt} \frac{\partial \Pi}{\partial \eta_2} = \left( -\Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_1} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_1^2} + \ldots \right) \left( \lambda^{(1)}_{\Omega x_1 + \Omega x_2 + \Omega^2 \eta_2} \Pi \right) + \left( -\Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_2} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_2^2} + \ldots \right) \left( \lambda^{(2)}_{\Omega x_1 + \Omega x_2 + \Omega^2 \eta_2} \Pi \right) + \left( \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_1} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_1^2} + \ldots \right) \left( \mu^{(1)}_{\Omega x_1 + \Omega x_2 + \Omega^2 \eta_2} \Pi \right) + \left( \Omega^{-\frac{1}{2}} \frac{\partial}{\partial \eta_2} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_2^2} + \ldots \right) \left( \mu^{(2)}_{\Omega x_1 + \Omega x_2 + \Omega^2 \eta_2} \Pi \right),
\]

(6.30)
and in the special case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$, this becomes

$$
\frac{\partial \Pi}{\partial t} - \Omega^{\frac{1}{2}} \frac{dx_1}{dt} \frac{\partial \Pi}{\partial \eta_1} - \Omega^{\frac{1}{2}} \frac{dx_2}{dt} \frac{\partial \Pi}{\partial \eta_2} = \left( -\Omega^{\frac{1}{2}} \frac{\partial}{\partial \eta_1} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_1^2} + \ldots \right) \Omega \tilde{\varphi}_1 \frac{\Omega x_1 + x_2}{x_1 + x_2} \left[ x_1 + x_2 - p_1 x_2 \right] \Pi \\
+ \left( -\Omega^{\frac{1}{2}} \frac{\partial}{\partial \eta_2} + \frac{1}{2} \Omega^{-1} \frac{\partial^2}{\partial \eta_2^2} + \ldots \right) \Omega \tilde{\varphi}_2 \frac{\Omega x_2 + x_1}{x_1 + x_2} \left[ x_1 + x_2 - p_2 x_1 \right] \Pi \\
+ \left( \Omega^{\frac{1}{2}} \frac{\partial}{\partial \eta_1} \right) \mu_1 (\Omega x_1 + \Omega^{\frac{1}{2}} \eta_1) \Pi \\
+ \left( \Omega^{\frac{1}{2}} \frac{\partial}{\partial \eta_2} \right) \mu_2 (\Omega x_2 + \Omega^{\frac{1}{2}} \eta_2) \Pi ,
$$

(6.31)

where $\Omega \tilde{\varphi}_1 = \varphi_1$ and $\Omega \tilde{\varphi}_2 = \varphi_2$ in order to ensure dimensional consistency. Note that the variables $x_1$ and $x_2$ represent densities of cells and, as such, are continuous variables.

### 6.3.1 A deterministic approximation

The deterministic equations for the process are obtained by collecting terms of order $\Omega^{\frac{1}{2}}$ from Eq. (6.31). The deterministic process can be thought of as an approximation to the stochastic model when the number of cells of both clonotypes is large. For the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ the deterministic equations are

$$
\frac{dx_1}{dt} = \tilde{\varphi}_1 \left( 1 - \frac{p_1 x_2}{x_1 + x_2} \right) - \mu_1 x_1 ,
$$

(6.32)

$$
\frac{dx_2}{dt} = \tilde{\varphi}_2 \left( 1 - \frac{p_2 x_1}{x_1 + x_2} \right) - \mu_2 x_2 .
$$

(6.33)
The number of parameters can be reduced to 3 by non-dimensionalising the above equations and using the constraint on the parameters given by Eq. (5.29). Let

\[ \tau = \mu_1 t , \]  
\[ x_i = \frac{\tilde{\varphi}_1 u_i}{\mu_1} , \]  

for \( i = 1, 2 \), so that \( \tau \) and \( u_i \) are dimensionless variables. In terms of these new variables, the deterministic equations (6.32)–(6.33) become

\[ \frac{du_1}{d\tau} = 1 - \frac{p_1 u_2}{u_1 + u_2} - u_1 , \]  
\[ \frac{du_2}{d\tau} = \tilde{\varphi} - \frac{p_1 u_1}{u_1 + u_2} - \bar{\mu} u_2 , \]  

where \( \tilde{\varphi} = \varphi_2/\varphi_1 \) and \( \bar{\mu} = \mu_2/\mu_1 \). It is shown in Appendix B that a unique steady state solution \((\bar{u}_1, \bar{u}_2)\) to Eqs. (6.36)–(6.37) exists, where \( 1 - p_1 < \bar{u}_1 < 1 \) and \( \frac{1}{\bar{\mu}}(\tilde{\varphi} - p_1) < \bar{u}_2 < \frac{\tilde{\varphi}}{\bar{\mu}} \), which is locally asymptotically stable for all values of the parameters.

It does not appear possible to write down an expression for the number of T cells of each clonotype at the stable steady state in the most general case. However, if it is assumed that the per cell death rates for both clonotypes are equal, \( i.e., \mu_1 = \mu_2 \) then, in terms of the original variables \( n_1 \) and \( n_2 \), the unique steady state of the system is given by

\[ \bar{n}_1 = \Omega \bar{x}_1 = \frac{\varphi_1}{\mu_1} \left(1 - p_1 + \frac{\varphi_2}{\bar{\varphi}_1}(1 - p_1) \right) , \]  
\[ \bar{n}_2 = \Omega \bar{x}_2 = \frac{\varphi_1}{\mu_1} \left(1 - p_1 + \frac{\varphi_2}{\bar{\varphi}_1}(\bar{\varphi}_2 - p_1) \right) . \]  

Hence, if \( \varphi_2 > \varphi_1 \) the number of T cells of clonotype 2 at the steady state is greater than the number of T cells of clonotype 1, as T cells of clonotype 2 have greater
access to resources in the form of a larger set of APPs from which they are able to receive survival signals which cause them to undergo a single round of cell division.

While the stochastic model predicts that both clonotypes will become extinct within a finite time, the deterministic model predicts that both clonotypes will persist indefinitely. Therefore, questions regarding extinction cannot be addressed within the deterministic framework. However, if the mean time to extinction is large, the maximum of the corresponding LCD defined by Eq. (5.87) can be approximated by the stable steady state of the deterministic process. For the parameter values \( \varphi_1 = \varphi_2 = 10, p_1 = p_2 = 0.5 \) and \( \mu_1 = \mu_2 = 1 \), the deterministic steady state is given by \((7\frac{1}{2}, 7\frac{1}{2})\), which corresponds closely to the maximum of the LCD at state \((7, 7)\) as shown in Fig. 5.7, while for the parameter values \( \varphi_1 = 5, \varphi_2 = 10, p_1 = 0.5, p_2 = 0.25 \) and \( \mu_1 = \mu_2 = 1 \), the deterministic steady state is given by \((3\frac{1}{8}, 9\frac{3}{8})\) and the maximum of the LCD is at state \((3, 9)\) as shown in Fig. 5.8.

6.3.2 Fluctuations about the stable steady state and an approximation to the limiting conditional probability distribution

If the large \( N \) expansion is carried out to the next order, the fluctuations about the deterministic stable steady state may be studied. This provides a method of approximating the LCD of the process. Collecting terms of order \( \Omega^0 \) from Eq. (6.31) results in the equation

\[
\frac{\partial \Pi}{\partial t} = \frac{\hat{\varphi}_1}{2} \frac{x_1 + x_2}{x_1 + x_2 - p_1 x_2} \frac{\partial^2 \Pi}{\partial \eta_1^2} + \frac{\hat{\varphi}_2}{2} \frac{x_1 + x_2}{x_1 + x_2 - p_2 x_1} \frac{\partial^2 \Pi}{\partial \eta_2^2} \\
- \frac{\hat{\varphi}_1 p_1}{(x_1 + x_2)^2} \frac{\partial}{\partial \eta_1} [(\eta_1 x_2 - \eta_2 x_1) \Pi] - \frac{\hat{\varphi}_2 p_2}{(x_1 + x_2)^2} \frac{\partial}{\partial \eta_2} [(\eta_2 x_1 - \eta_1 x_2) \Pi] \\
+ \frac{1}{2} \mu_1 x_1 \frac{\partial^2 \Pi}{\partial \eta_1^2} + \mu_1 \frac{\partial}{\partial \eta_1} (\eta_1 \Pi) + \frac{1}{2} \mu_2 x_2 \frac{\partial^2 \Pi}{\partial \eta_2^2} + \mu_2 \frac{\partial}{\partial \eta_2} (\eta_2 \Pi),
\]  

(6.40)
which is a linear multivariate Fokker-Planck equation for the probability distribution of the fluctuations, $\Pi(\eta_1, \eta_2, t)$, the solution of which is an Ornstein-Uhlenbeck process [134] and is therefore fully determined by its first and second moments. Multiplying Eq. (6.40) by $\eta_1$ and integrating over all values of $\eta_1 \in \mathbb{R}$ and $\eta_2 \in \mathbb{R}$ [134] results in the differential equation

$$
\frac{d}{dt} \langle \eta_1 \rangle = \left( \frac{\tilde{\varphi}_1 p_1 x_2}{(x_1 + x_2)^2} - \mu_1 \right) \langle \eta_1 \rangle - \frac{\tilde{\varphi}_1 p_1 x_1}{(x_1 + x_2)^2} \langle \eta_2 \rangle .
$$

Similarly, multiplying Eq. (6.40) by $\eta_2$, $\eta_1^2$, $\eta_2^2$ and $\eta_1 \eta_2$, respectively and integrating over all values of $\eta_1 \in \mathbb{R}$ and $\eta_2 \in \mathbb{R}$ results in

$$
\frac{d}{dt} \langle \eta_2 \rangle = -\frac{\tilde{\varphi}_2 p_2 x_2}{(x_1 + x_2)^2} \langle \eta_1 \rangle + \left( \frac{\tilde{\varphi}_2 p_2 x_1}{(x_1 + x_2)^2} - \mu_2 \right) \langle \eta_2 \rangle ,
$$

$$
\frac{d}{dt} \langle \eta_1^2 \rangle = 2 \left( \frac{\tilde{\varphi}_1 p_1 x_2}{(x_1 + x_2)^2} - \mu_1 \right) \langle \eta_1^2 \rangle - \frac{2\tilde{\varphi}_1 p_1 x_1}{(x_1 + x_2)^2} \langle \eta_1 \eta_2 \rangle + \frac{\tilde{\varphi}_1}{x_1 + x_2} (x_1 + x_2 - p_1 x_2) + \mu_1 x_1 ,
$$

$$
\frac{d}{dt} \langle \eta_2^2 \rangle = 2 \left( \frac{\tilde{\varphi}_2 p_2 x_1}{(x_1 + x_2)^2} - \mu_2 \right) \langle \eta_2^2 \rangle - \frac{2\tilde{\varphi}_2 p_2 x_2}{(x_1 + x_2)^2} \langle \eta_1 \eta_2 \rangle + \frac{\tilde{\varphi}_2}{x_1 + x_2} (x_1 + x_2 - p_2 x_1) + \mu_2 x_2 ,
$$

$$
\frac{d}{dt} \langle \eta_1 \eta_2 \rangle = -\frac{\tilde{\varphi}_2 p_2 x_2}{(x_1 + x_2)^2} \langle \eta_1 \rangle - \frac{\tilde{\varphi}_1 p_1 x_1}{(x_1 + x_2)^2} \langle \eta_2^2 \rangle + \left( \frac{\tilde{\varphi}_1 p_1}{x_1 + x_2} - \mu_1 - \mu_2 \right) \langle \eta_1 \eta_2 \rangle .
$$

For the remainder of this section, the focus will be on the case where the pair of clonotypes is symmetric so that $\varphi_1 = \varphi_2$, $p_1 = p_2$ and $\mu_1 = \mu_2$, as the algebra is somewhat simpler than in the more general situation. In this case, the deterministic stable steady state values are given by

$$
x_1 = x_2 = \frac{\tilde{\varphi}_1 (2 - p_1)}{2\mu_1} .
$$
CHAPTER 6. SPECIAL CASES OF THE COMPETITION PROCESS

Substituting these values of $x_1$ and $x_2$ into Eqs. (6.41)–(6.42) and integrating with the initial conditions $\langle \eta_1(0) \rangle = \langle \eta_1 \rangle_0$, $\langle \eta_2(0) \rangle = \langle \eta_2 \rangle_0$, results in

$$
\langle \eta_1 \rangle = \frac{\langle \eta_1 \rangle_0 + \langle \eta_2 \rangle_0}{2} e^{-\mu_1 t} + \frac{\langle \eta_1 \rangle_0 - \langle \eta_2 \rangle_0}{2} e^{-\frac{2\mu_1}{p_1} t},
$$

$$
\langle \eta_2 \rangle = \frac{\langle \eta_1 \rangle_0 + \langle \eta_2 \rangle_0}{2} e^{-\mu_1 t} - \frac{\langle \eta_1 \rangle_0 - \langle \eta_2 \rangle_0}{2} e^{-\frac{2\mu_1}{p_1} t}.
$$

These functions are plotted for one set of initial conditions in Fig. 6.8. Hence, the stable stationary values for the means of the fluctuations about the deterministic stable steady state are $\langle \eta_1 \rangle_s = \langle \eta_2 \rangle_s = 0$. The solution of the system of Eqs. (6.43)–(6.45), where $x_1$ and $x_2$ take their deterministic stable steady state values, is given by

$$
\langle \eta_1^2 \rangle = \frac{\tilde{\varphi}_1(2 - p_1)(3p_1 - 4)}{8\mu_1(p_1 - 1)} + c_1 e^{-\mu_1 t} + c_2 e^{-\frac{2\mu_1}{p_1} t} + c_3 e^{-\frac{4\mu_1}{2 - p_1} t},
$$

$$
\langle \eta_2^2 \rangle = \frac{\tilde{\varphi}_1(2 - p_1)(3p_1 - 4)}{8\mu_1(p_1 - 1)} + c_1 e^{-\mu_1 t} - c_2 e^{-\frac{2\mu_1}{p_1} t} + c_3 e^{-\frac{4\mu_1}{2 - p_1} t},
$$

$$
\langle \eta_1 \eta_2 \rangle = \frac{\tilde{\varphi}_1 p_1(2 - p_1)}{8\mu_1(p_1 - 1)} + c_1 e^{-\mu_1 t} - c_3 e^{-\frac{4\mu_1}{2 - p_1} t},
$$

where

$$
c_1 = \frac{1}{4} \langle \eta_1^2 \rangle_0 + \langle \eta_2^2 \rangle_0 + \frac{1}{2} \langle \eta_1 \eta_2 \rangle_0 - \frac{\tilde{\varphi}_1(2 - p_1)}{4\mu_1},
$$

$$
c_2 = \frac{1}{2} \langle \eta_1^2 \rangle_0 - \langle \eta_2^2 \rangle_0,
$$

$$
c_3 = \frac{1}{4} \langle \eta_1^2 \rangle_0 + \langle \eta_2^2 \rangle_0 - \frac{1}{2} \langle \eta_1 \eta_2 \rangle_0 + \frac{\tilde{\varphi}_1(2 - p_1)^2}{8\mu_1(p_1 - 1)},
$$

and $\langle \eta_1^2(0) \rangle = \langle \eta_1^2 \rangle_0$, $\langle \eta_2^2(0) \rangle = \langle \eta_2^2 \rangle_0$, $\langle \eta_1(0) \eta_2(0) \rangle = \langle \eta_1 \eta_2 \rangle_0$. It follows that the stable stationary values of the second moments are

$$
\langle \eta_1^2 \rangle_s = \langle \eta_2^2 \rangle_s = \frac{\tilde{\varphi}_1(2 - p_1)(3p_1 - 4)}{8\mu_1(p_1 - 1)} \geq 0,
$$
Figure 6.8: The quantities $\langle \eta_1 \rangle$ and $\langle \eta_2 \rangle$ as a function of time with $\tilde{\varphi}_1 = \tilde{\varphi}_2 = 10$, $p_1 = p_2 = 0.5$, $\mu_1 = \mu_2 = 1$, $\langle \eta_1 \rangle_0 = 3$ and $\langle \eta_2 \rangle_0 = 5$.

and

$$
\langle \eta_1 \eta_2 \rangle_s = \frac{\tilde{\varphi}_1 p_1 (2 - p_1)}{8 \mu_1 (p_1 - 1)} \leq 0,
$$

as shown in Fig. 6.9. Hence, the LCD of the bivariate competition process may be approximated by a bivariate normal distribution with mean

$$
\Omega(\bar{x}_1, \bar{x}_2) = (\bar{\eta}_1, \bar{\eta}_2) = \left( \frac{\varphi_1 (2 - p_1)}{2 \mu_1}, \frac{\varphi_1 (2 - p_1)}{2 \mu_1} \right),
$$

and covariance matrix

$$
\Omega \Sigma = \Omega \begin{pmatrix}
\langle \eta_1^2 \rangle_s & \langle \eta_1 \eta_2 \rangle_s \\
\langle \eta_1 \eta_2 \rangle_s & \langle \eta_2^2 \rangle_s
\end{pmatrix} = \begin{pmatrix}
\frac{3 p_1 - 4}{4 (p_1 - 1)} \bar{\eta}_1 & \frac{p_1}{4 (p_1 - 1)} \bar{\eta}_1 \\
\frac{p_1}{4 (p_1 - 1)} \bar{\eta}_1 & \frac{3 p_1 - 4}{4 (p_1 - 1)} \bar{\eta}_1
\end{pmatrix}.
$$

For this to be a good approximation it is required that the steady state $(\bar{n}_1, \bar{n}_2)$ is stable and that both $\bar{n}_1$ and $\bar{n}_2$ are large enough so that it is unlikely that the Ornstein-Uhlenbeck process will reach the absorbing boundary at either $n_1 = 0$ or $n_2 = 0$. As in Sections 4.4.1 and 4.4.2, it is expected that the normal approximation will be reasonable if the coefficients of variation (defined in Eq. (6.60) below) are less than $1/3$. 
The Pearson product moment correlation coefficient \([66]\) between the number of T cells of the two clonotypes, \(n_1\) and \(n_2\), at the LCD is given by

\[
\rho = \frac{\langle \eta_1 \eta_2 \rangle_s}{\sqrt{\langle \eta_1^2 \rangle_s \langle \eta_2^2 \rangle_s}} = \frac{p_1}{3p_1 - 4},
\]

(6.59)

from Eq. (6.58). As would be expected for two competing populations, this is always negative and, moreover, \(\rho \to -1\) as the two clonotypes overlap more completely with each other, \((i.e., p_1 \to 1)\), which is illustrated in Fig. 6.10.

The coefficient of variation for the number of T cells belonging to a particular clonotype at the LCD is a dimensionless measure of the dispersion of the marginal distribution and is given by its standard deviation, \(\sqrt{\Omega \langle \eta_1^2 \rangle_s}\), divided by the mean of the distribution, \(\bar{n}_1\). Thus, the coefficient of variation for T cells of clonotype 1 at the LCD can be approximated by

\[
\frac{\sqrt{\Omega \langle \eta_1^2 \rangle_s}}{n_1} = \sqrt{\frac{\mu_1(3p_1 - 4)}{2\varphi_1(p_1 - 1)(2 - p_1)}}.
\]

(6.60)

The coefficient of variation is an indicator of the size of the stochastic fluctuations.
As \( p_1 \to 0 \), the coefficient of variation tends to \( \sqrt{\mu_1/\varphi_1} \), in agreement with earlier results from analysis of the univariate process introduced in Chapter 3, and as \( p_1 \to 1 \) the coefficient of variation tends to \( +\infty \) indicating the breakdown of the deterministic approximation. In this case, the numerical results from Section 6.2 suggest that one clonotype would quickly out-compete the other before the process converged to the LCD, because the mean time to reach the absorbing set is small. Then the deterministic approximation is poor and the large \( N \) expansion is not valid. This is illustrated in Fig. 6.11, which shows the coefficient of variation for the number of T cells belonging to clonotype 1 at the numerically computed LCD and the coefficient of variation derived from the normal approximation to the LCD, given by Eq. (6.60), as a function of \( p_1 \).
Figure 6.11: The coefficient of variation for the number of T cells belonging to clonotype 1 at the LCD with \( \nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1, \varphi_1 = \varphi_2 = 10, p_1 = p_2 \) and \( \mu_1 = \mu_2 = 1 \).

6.4 The diffusion approximation in the case \( \nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1 \)

In this section, the normal approximation to the LCD is derived using the diffusion approximation method introduced in Section 4.5. This method of approximation may be applied to so-called density dependent processes. A bivariate Markov process is said to be density dependent if the infinitesimal transition probabilities are of the form
\[
q_{n,n+1} = \Omega \beta_1 \left( \frac{n}{\Omega} \right) = \Omega \beta_1(x),
\]
where \( \mathbf{l} \in \mathbb{Z}^2, n = (n_1, n_2), x = \left( \frac{n_1}{\Omega}, \frac{n_2}{\Omega} \right) \) and \( \beta_1(x) \) denotes that \( \beta_1 \) is a function of \( x \) only. Recall that \( \Omega \) is a parameter which represents the size of the system and so \( x \) is a vector representing the density of cells belonging to clonotypes 1 and 2.

Hence, the bivariate competition process, which is here denoted by \( \mathcal{X}(t) = \{(X_1(t), X_2(t)) : t \geq 0\} \) on the state-space \( \{(n_1, n_2) : n_1, n_2 = 0, 1, 2, \ldots\} \) is density dependent if the
birth and death rates are of the form

\begin{align}
\lambda^{(1)}_{n_1, n_2} &= \Omega \beta^{(1)}_{(1)}(x), \\
\lambda^{(2)}_{n_1, n_2} &= \Omega \beta^{(0)}_{(1)}(x), \\
\mu^{(1)}_{n_1, n_2} &= \Omega \beta^{(-1)}_{(-1)}(x), \\
\mu^{(2)}_{n_1, n_2} &= \Omega \beta^{(0)}_{(-1)}(x).
\end{align}

(6.62) (6.63) (6.64) (6.65)

In the case \( \nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1 \) the birth and death rates may be written in this form, with

\begin{align}
\beta^{(1)}_{(1)} &= \tilde{\varphi}_1 \left( 1 - \frac{p_1 x_2}{x_1 + x_2} \right), \\
\beta^{(0)}_{(0)} &= \tilde{\varphi}_2 \left( 1 - \frac{p_2 x_1}{x_1 + x_2} \right), \\
\beta^{(-1)}_{(-1)} &= \mu_1 x_1, \\
\beta^{(0)}_{(-1)} &= \mu_2 x_2,
\end{align}

(6.66) (6.67) (6.68) (6.69)

where \( \varphi_1 = \Omega \tilde{\varphi}_1 \) and \( \varphi_2 = \Omega \tilde{\varphi}_2 \). Therefore, the bivariate competition process \( X(t) \) is density dependent in this case. As transitions are only allowed to adjacent states, \( \beta_l = 0 \) for \( l \neq (1, 0)^T, (0, 1)^T, (-1, 0)^T, (0, -1)^T \). Next, let

\[ F(x) \equiv \begin{pmatrix} F_1(x) \\ F_2(x) \end{pmatrix} = \sum_{l \in \mathbb{Z}^2} \beta_l(x). \]

(6.70)

Now define \( X_d(t) \) to be the solution of

\[ \frac{dX_d(t)}{dt} = F(x), \]

(6.71)

so that \( X_d(t) \) is the deterministic process representing the time evolution of the density of T cells belonging to clonotypes 1 and 2, \( x = (x_1, x_2) \).
Let \( x_0 = \mathcal{X}_d(t = 0) \) and suppose that \( \lim_{\Omega \to +\infty} \frac{\mathcal{X}(t=0)}{\Omega} = x_0 \), so that the initial condition of the deterministic process and the initial state of the stochastic process are the same in the limit \( \Omega \to +\infty \). The state-space of the process \( \{\mathcal{X}(t) / \Omega : t \geq 0 \} \) is denoted by \( \mathcal{S}_\Omega \) and is given by \( \mathcal{S}_\Omega = \{(x_1, x_2) : x_1, x_2 = 0, 1/\Omega, 2/\Omega, \ldots \} \). Let \( ||l|| \) denote the Euclidean norm of the vector \( l \). For each compact set \( K \subset \mathcal{S}_\Omega \),

\[
\sum_{l \in \mathbb{Z}^2} ||l|| \sup_{x \in K} \beta_l(x) = \tilde{\varphi}_1 \sup_{x \in K} \left( 1 - \frac{p_1 x_2}{x_1 + x_2} \right) + \tilde{\varphi}_2 \sup_{x \in K} \left( 1 - \frac{p_2 x_1}{x_1 + x_2} \right) + \mu_1 \sup_{x \in K} (x_1) + \mu_2 \sup_{x \in K} (x_2) < +\infty , \quad (6.72)
\]

and there exists \( M_K > 0 \) such that

\[
||F(x) - F(y)|| \leq M_K ||x - y|| \text{ for } x, y \in K . \quad (6.73)
\]

Then, by Theorem 11.2.1 of [46],

\[
\lim_{\Omega \to +\infty} \sup_{s \leq t} \left| \frac{\mathcal{X}(s)}{\Omega} - \mathcal{X}_d(s) \right| = 0 , \quad (6.74)
\]

for all \( t \geq 0 \), which means that \( \mathcal{X}(t) / \Omega \) converges to the deterministic process \( \mathcal{X}_d(t) \) in the limit \( \Omega \to +\infty \).

Next, the fluctuations about the deterministic process are considered. Let

\[
V_\Omega(t) = \sqrt{\Omega} \left( \frac{\mathcal{X}(t)}{\Omega} - \mathcal{X}_d(t) \right) , \quad (6.75)
\]

where \( V_\Omega \) is the distribution of the fluctuations, which is the same change of variables
as that employed in Section 6.3. Now define

\[ V(t) = V(0) + \sum_{l \in \mathbb{Z}^2} W_l \left( \int_0^t \beta_l(X_d(s)) ds \right) + \int_0^t J(X_d(s)) V(s) ds, \tag{6.76} \]

where \( W_l(t) \) denotes a bivariate Wiener process with mean \((0, 0)\) and covariance matrix

\[ \begin{pmatrix} t & 0 \\ 0 & t \end{pmatrix}, \tag{6.77} \]

and \( J \) denotes the Jacobian matrix, which is derived from the system of ODEs (6.71) and defined by

\[ J(x) = \begin{pmatrix} \frac{\partial F_1}{\partial x_1} & \frac{\partial F_1}{\partial x_2} \\ \frac{\partial F_2}{\partial x_1} & \frac{\partial F_2}{\partial x_2} \end{pmatrix}. \tag{6.78} \]

From Eq. (6.72), the condition

\[ \sum_{l \in \mathbb{Z}^2} ||l||^2 \sup_{x \in K} \beta_l(x) < +\infty, \tag{6.79} \]

is satisfied for each compact set \( K \subset \mathcal{S}_\Omega \). Also, \( \beta_l(x) \) and the entries of \( J \) are continuous. Then, by Theorem 11.2.3 of [46], \( V_\Omega(t) \rightarrow V(t) \) in distribution as \( \Omega \rightarrow +\infty \), assuming that \( V_\Omega(t = 0) = V(t = 0) \).

The distribution of the fluctuations about the unique deterministic stable steady state \( \bar{x} \) in the case \( \varphi_1 = \varphi_2, p_1 = p_2, \mu_1 = \mu_2 \), which is given by Eq. (6.46), are now studied. Then, from Eq. (6.71),

\[ \beta^\prime_{(1)}(\bar{x}) = \beta^\prime_{(-1)}(\bar{x}) = \beta^\prime_{(0)}(\bar{x}) = \beta^\prime_{(-0)}(\bar{x}) = \frac{\hat{\varphi}_1 (2 - p_1)}{2}. \tag{6.80} \]

Let the initial state of the process be given by the deterministic stable steady state
so that
\[ x_0 = X_d(t = 0) = \frac{X(t = 0)}{\Omega} = \bar{x} = \left( \frac{\hat{\varphi}_1(2 - p_1)}{2\mu_1}, \frac{\hat{\varphi}_1(2 - p_1)}{2\mu_1} \right), \quad (6.81) \]
and, hence, \( X_d(t) = \bar{x} \) for all \( t \geq 0 \). Then,
\[
\sum_{l \in \mathbb{Z}^2} l W_1 \left( \int_0^t \beta_l(X_d(s))ds \right) = \sum_{l \in \mathbb{Z}^2} l W_1 \left( \frac{\hat{\varphi}_1(2 - p_1)t}{2} \right) \\
= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} W_{(1)}^{(1)} \left( \frac{\hat{\varphi}_1(2 - p_1)t}{2} \right) + \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} W_{(0)}^{(0)} \left( \frac{\hat{\varphi}_1(2 - p_1)t}{2} \right) + \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} W_{(-1)}^{(-1)} \left( \frac{\hat{\varphi}_1(2 - p_1)t}{2} \right), \quad (6.82)
\]
where \( W_{(1)}, W_{(0)}, W_{(1)}^{(-1)} \) and \( W_{(-1)}^{(0)} \) denote independent Wiener processes, each with mean \((0, 0)\) and covariance matrix
\[
\begin{pmatrix} \hat{\varphi}_1(2 - p_1)t/2 & 0 \\ 0 & \hat{\varphi}_1(2 - p_1)t/2 \end{pmatrix}.
\]
Therefore,
\[
\sum_{l \in \mathbb{Z}^2} l W_1 \left( \int_0^t \beta_l(X_d(s))ds \right) = \begin{pmatrix} \sqrt{\hat{\varphi}_1(2 - p_1)} & 0 \\ 0 & \sqrt{\hat{\varphi}_1(2 - p_1)} \end{pmatrix} W(t) \equiv GW(t), \quad (6.84)
\]
where \( W(t) \) denotes the standard bivariate Wiener process which has mean \((0, 0)\) and covariance matrix given by Eq. (6.77). Also,
\[
J(\bar{x}) = \begin{pmatrix} \frac{p_1\mu_1}{2(2 - p_1)} - \mu_1 & -\frac{p_1\mu_1}{2(2 - p_1)} \\ -\frac{p_1\mu_1}{2(2 - p_1)} & \frac{p_1\mu_1}{2(2 - p_1)} - \mu_1 \end{pmatrix}.
\]
(6.85)
In Appendix B it is proved that both eigenvalues of this matrix are negative. Then,

\[ V(t) = V(0) + GW(t) + J(\bar{x}) \int_0^t V(s)ds , \]  

(6.86)

or equivalently,

\[ dV = J(\bar{x})Vdt + GdW , \]  

(6.87)

which is an Ornstein-Uhlenbeck process whose stationary distribution is a bivariate normal distribution with mean \((0, 0)\) and covariance matrix \(\Sigma\) which satisfies the equation [56]

\[ J(\bar{x})\Sigma + \Sigma[J(\bar{x})]^T + GG^T = 0 . \]  

(6.88)

The solution of this equation is

\[ \Sigma = \begin{pmatrix} \frac{\bar{\phi}_1(2-p_1)(3p_1-4)}{8\mu_1(p_1-1)} & \frac{\bar{\phi}_1p_1(2-p_1)}{8\mu_1(p_1-1)} \\ \frac{\bar{\phi}_1p_1(2-p_1)}{8\mu_1(p_1-1)} & \frac{\bar{\phi}_1(2-p_1)(3p_1-4)}{8\mu_1(p_1-1)} \end{pmatrix} . \]  

(6.89)

Hence, the LCD of the process may be approximated by a bivariate normal distribution with mean \(\Omega\bar{x}\) and covariance matrix \(\Omega\Sigma\), in agreement with the results obtained from the large \(N\) expansion (see Eq. 6.58).

### 6.5 Other special cases

So far in this chapter, the case \(\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1\) has been analysed in detail. In this section, the other special cases defined in Section 6.1 are discussed. The analysis focuses on the deterministic model for each case. This is because, in the majority of cases, an analytic expression for the stable steady state of the system cannot be written down and so the fluctuations about this steady state cannot be studied analytically using the large \(N\) expansion, although numerical work is always possible.
6.5.1 The case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$

In the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$, the APPs which provide survival signals to T cells of both clonotypes 1 and 2 also provide survival signals to many other clonotypes in the repertoire and so competition for APPs in the set $Q_{12}$ is large. The amount of competition from other T cell clonotypes for APPs which are not shared by clonotypes 1 and 2 (i.e., those in the sets $Q_{1/2}$ and $Q_{2/1}$) is small.

Employing the same change of variables as that defined by Eq. (6.21), the deterministic equations for the densities of T cells belonging to clonotypes 1 and 2, denoted by $x_1$ and $x_2$ respectively, are given by

$$\frac{dx_1}{dt} = \frac{\tilde{\varphi}_1 x_1 p_1}{x_1 + x_2 + \nu_{12} \langle \tilde{n} \rangle} + \tilde{\varphi}_1 (1 - p_1) - \mu_1 x_1, \quad (6.90)$$

$$\frac{dx_2}{dt} = \frac{\tilde{\varphi}_2 x_2 p_2}{x_1 + x_2 + \nu_{12} \langle \tilde{n} \rangle} + \tilde{\varphi}_2 (1 - p_2) - \mu_2 x_2, \quad (6.91)$$

where $\Omega \tilde{\varphi}_1 = \varphi_1$, $\Omega \tilde{\varphi}_2 = \varphi_2$, $\Omega \langle \tilde{n} \rangle = \langle n \rangle$ in order to ensure dimensional consistency.

The number of parameters in this set of equations may be reduced to 4 by non-dimensionalising and using the constraint on the parameters given by Eq. (5.29). Let

$$\tau = \mu_1 t, \quad (6.92)$$

$$x_i = \frac{\tilde{\varphi}_1}{\mu_1} u_i, \quad (6.93)$$

$$\langle \tilde{n} \rangle = \frac{\tilde{\varphi}_1}{\mu_1} \bar{n}, \quad (6.94)$$

for $i = 1, 2$, so that $\tau$, $u_i$ and $\bar{n}$ are dimensionless variables. In terms of these new
variables, Eqs. (6.90)–(6.91) become

\[
\frac{du_1}{d\tau} = \frac{u_1 p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + 1 - p_1 - u_1 \equiv f(u_1, u_2), \tag{6.95}
\]

\[
\frac{du_2}{d\tau} = \frac{u_2 p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + \bar{\varphi} - p_1 - \bar{\mu} u_2 \equiv g(u_1, u_2), \tag{6.96}
\]

where \(\bar{\varphi} = \frac{\varphi_2}{\varphi_1}\) and \(\bar{\mu} = \frac{\mu_2}{\mu_1}\).

The steady states of this system of equations are now investigated. Since \(x_1\) and \(x_2\) represent densities of cells, only the region \(u_1, u_2 \geq 0\) is biologically relevant. Firstly, the possibility that a limit cycle exists in the region \(u_1, u_2 > 0\) is excluded. A limit cycle is any simple, oriented, closed curve trajectory that does not contain steady states. The presence of limit cycles may be ruled out using the Bendixson-Dulac criterion [43]. Let \(D\) be a simply connected region of the \(u_1, u_2\) plane and suppose that there exists a function \(B(u_1, u_2)\) which is continuously differentiable on \(D\) such that the quantity

\[
\frac{\partial (Bf)}{\partial u_1} + \frac{\partial (Bg)}{\partial u_2} \tag{6.97}
\]

is not identically zero and does not change sign in \(D\). Then the Bendixson-Dulac criterion states that there are no limit cycles in the region \(D\). Let \(B = \frac{1}{u_1 u_2}\). Now,

\[
\frac{\partial (Bf)}{\partial u_1} = \frac{-p_1}{u_2(u_1 + u_2 + \nu_{12} \bar{n})} - \frac{1 - p_1}{u_1^2 u_2} < 0, \tag{6.98}
\]

and

\[
\frac{\partial (Bg)}{\partial u_2} = \frac{-p_1}{u_1(u_1 + u_2 + \nu_{12} \bar{n})} - \frac{\bar{\varphi} - p_1}{u_1 u_2^2} < 0, \tag{6.99}
\]

on the region \(u_1, u_2 > 0\) because \(\bar{\varphi} > p_1\) by Eq. (5.29), and so no limit cycles can exist in this region.

From Eqs. (6.95)–(6.96) it can be seen that \(f(u_1, u_2) > 1 - p_1 - u_1\) and \(f(u_1, u_2) < 1 - u_1\) and so \(f(u_1, u_2) > 0\) for \(u_1 < 1 - p_1\) and \(f(u_1, u_2) < 0\) for \(u_1 > 1\). Similarly, \(g(u_1, u_2) > \bar{\varphi} - p_1 - \bar{\mu} u_2\) and \(g(u_1, u_2) < \bar{\varphi} - \bar{\mu} u_2\) and so \(g(u_1, u_2) > 0\) for \(u_1 < \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1)\)
and $g(u_1, u_2) < 0$ for $u_2 > \frac{\bar{\varphi}}{\bar{\mu}}$. An example of a possible phase-plane diagram for the system is illustrated in Fig. 6.12. Steady states occur when $f(u_1, u_2) = g(u_1, u_2) = 0$. By the intermediate value theorem, there exists at least one stable steady state $(\bar{u}_1, \bar{u}_2)$ in the region $1 - p_1 < \bar{u}_1 < 1$, $(\bar{\varphi} - p_1)/\bar{\mu} < \bar{u}_2 < \bar{\varphi}/\bar{\mu}$ (recall that the possibility of limit cycles occurring in this region has already been excluded). This region is denoted by $R$. No stable steady state can exist outside of this region. However, it is possible that an unstable steady state exists outside of $R$. It is proved in Appendix C that the stable steady state in $R$ is unique.

Hence, in this case, the deterministic model predicts that neither clonotype goes extinct, even though $\nu_{12} \gg 1$. This is because the level of competition for APPs in the sets $Q_{1/2}$ and $Q_{2/1}$ is low and so both clonotypes have enough resources to survive. The LCD of the process (as defined in Section 5.3.3) is shown in Fig 6.13 for one set of parameter values, where the state-space of the process has been truncated to be finite, i.e., $S = \{(n_1, n_2) : n_1, n_2 = 0, 1, \ldots, N\}$. The maximum of the LCD is at $(5, 5)$ which is very close to the stable steady state of the corresponding deterministic model at $(5.02, 5.02)$. This case differs from the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ only in the value of $\nu_{12}$ and these cases are similar in that the deterministic...
models make the qualitative prediction that both clonotypes persist indefinitely for all values of the parameters. This suggests that the value of the parameter $\nu_{12}$ may not have a crucial impact on the qualitative behaviour of the system. The effect of $\nu_{12}$ is investigated further in Section 6.6.

Figure 6.13: The LCD of the process in the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ with $\nu_{12} = 100$, $\nu_1 = \nu_2 = 0.001$, $\varphi_1 = \varphi_2 = 10$, $p_1 = p_2 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$.

6.5.2 The case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$

In the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$, the APPs which provide survival signals to T cells of clonotype 2 but not to T cells of clonotype 1 also provide survival signals to many other clonotypes in the repertoire. The amount of competition for all other APPs from which T cells of either clonotype 1 or 2 are able to receive survival signals
is small. Hence, T cells of clonotype 2 experience a greater degree of competition for the APPs from which they are able to receive survival signals compared to T cells of clonotype 1.

The deterministic equations for the densities of T cells belonging to clonotypes 1 and 2, denoted by \( x_1 \) and \( x_2 \) respectively, are now given. These may be derived using the same change of variables as that defined by Eq. (6.21). Then

\[
\frac{dx_1}{dt} = \tilde{\phi}_1 \left( 1 - \frac{p_1 x_2}{x_1 + x_2} \right) - \mu_1 x_1, \tag{6.100}
\]

\[
\frac{dx_2}{dt} = \tilde{\phi}_2 x_2 \left( \frac{p_2}{x_1 + x_2} + \frac{1 - p_2}{x_2 + \nu_2 \langle n \rangle} \right) - \mu_2 x_2, \tag{6.101}
\]

where \( \Omega \tilde{\phi}_1 = \phi_1, \Omega \tilde{\phi}_2 = \phi_2, \Omega \langle \tilde{n} \rangle = \langle n \rangle \) in order to ensure dimensional consistency.

In terms of the non-dimensional variables given by Eqs. (6.92)–(6.94) these equations become

\[
\frac{du_1}{d\tau} = 1 - \frac{p_1 u_2}{u_1 + u_2} - u_1 \equiv f(u_1, u_2), \tag{6.102}
\]

\[
\frac{du_2}{d\tau} = u_2 \left( \frac{p_1}{u_1 + u_2} + \frac{\tilde{\phi} - p_1}{u_2 + \nu_2 \tilde{n}} - \bar{\mu} \right) \equiv g(u_1, u_2), \tag{6.103}
\]

where the constraint on the parameters (5.29) has been utilised and \( \bar{\phi} = \phi_2 / \phi_1, \bar{\mu} = \mu_2 / \mu_1 \).

The steady states of this system of equations are now investigated, again only considering the region \( u_1, u_2 \geq 0 \) as it is the only biologically relevant one. The possibility of limit cycles existing in this region may be excluded using the Bendixson-Dulac criterion with \( B = \frac{1}{u_1 u_2} \), as in the previous section.

From Eq. (6.102), \( f(u_1, u_2) > 1 - p_1 - u_1 \) and \( f(u_1, u_2) < 1 - u_1 \) and so \( f(u_1, u_2) > 0 \) for \( u_1 < 1 - p_1 \) and \( f(u_1, u_2) < 0 \) for \( u_1 > 1 \). Also,

\[
g(u_1, u_2) > u_2 \left( \frac{\tilde{\phi} - p_1}{u_2 + \nu_2 \tilde{n}} - \bar{\mu} \right), \tag{6.104}
\]
which means that $g(u_1, u_2) > 0$ when $u_2 < \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}$, and

$$g(u_1, u_2) < u_2 \left( \frac{\bar{\varphi} - p_1}{u_2} + \frac{p_1}{u_2 - \bar{\mu}} \right),$$  \hspace{1cm} (6.105)

so that $g(u_1, u_2) < 0$ when $u_2 > \bar{\varphi}/\bar{\mu}$. A steady state solution to Eqs. (6.102)–(6.103) is given by $(\bar{u}_1, \bar{u}_2) = (1, 0)$ and an example of a possible phase-plane diagram for the system is illustrated in Fig. 6.14. The above analysis and the phase-plane diagram show that if $\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} > 0$ then at least one stable steady state exists in the region $1 - p_1 < u_1 < 1, \max(0, \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}) < u_2 < \frac{\bar{\varphi}}{\bar{\mu}}$, which is denoted by $R$.

It can be shown, using the same method as in Appendix C, that this steady state is unique. No stable steady state can exist outside of this region and, hence, $(1, 0)$ is unstable in this case.

The case when $\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < 0$ is considered next. Then, it is possible that $(1, 0)$ is a stable steady state. The parameter values for which this is the case are
now determined. The Jacobian matrix is given by

\[ J = \begin{pmatrix}
\frac{\partial f}{\partial u_1} & \frac{\partial f}{\partial u_2} \\
\frac{\partial g}{\partial u_1} & \frac{\partial g}{\partial u_2}
\end{pmatrix}. \tag{6.106} \]

At \((u_1, u_2) = (1, 0)\) this becomes

\[ J = \begin{pmatrix}
-1 & -p_1 \\
0 & p_1 + \frac{\tilde{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu}
\end{pmatrix}, \tag{6.107} \]

which has the eigenvalues

\[ \lambda_1 = -1, \tag{6.108} \]
\[ \lambda_2 = p_1 + \frac{\tilde{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu}, \tag{6.109} \]

and so \((1, 0)\) is a stable steady state when

\[ p_1 + \frac{\tilde{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} < 0. \tag{6.110} \]

Note that this condition implies that \(\frac{1}{\bar{\mu}}(\tilde{\varphi} - p_1) - \nu_2 \bar{n} < 0\), as expected. When \((1, 0)\) is unstable, the previous analysis has shown that there exists a unique stable steady state in the region \(R\). It is shown in Appendix D that when \((1, 0)\) is stable, a steady state does not exist in \(R\).

In this case \(\nu_2 \gg 1\) and so T cells of clonotype 2 are at a disadvantage unless \(\mu_1\) is greater than \(\mu_2\), or \(\varphi_2\) is greater than \(\varphi_1\). If the parameters are such that both clonotypes receive sufficient survival signals, \(i.e., p_1 + \frac{\tilde{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} > 0\), a steady state \((\bar{u}_1, \bar{u}_2)\) with \(\bar{u}_1, \bar{u}_2 > 0\) exists and is stable. However, if \(\nu_2\) becomes large enough, \(i.e., p_1 + \frac{\tilde{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} < 0\), then this steady state ceases to exist and \((1, 0)\) becomes a stable steady state, corresponding to extinction of T cells of clonotype 2 from the repertoire. The effect of the parameter \(\nu_2\) is considered again in Section 6.6. The
LCD of the process (as defined in Section 5.3.3) is shown in Fig 6.15 (where the state-space of the process has been truncated to be finite) for a set of parameter values where \((\bar{u}_1, \bar{u}_2) = (1, 0)\) is the deterministic stable steady state. In terms of the original variables, this steady state is given by \((\bar{n}_1, \bar{n}_2) = (\varphi_1/\mu_1, 0) = (10, 0)\), which is close to the maximum of the LCD. Fig. 6.16 shows the LCD of the process for a set of parameter values where the stable steady state of the process is at \((\bar{n}_1, \bar{n}_2) = (2.95, 13.37)\), which is close to the maximum of the LCD, as expected.

Figure 6.15: The LCD of the process in the case \(\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \gg 1\) with \(\nu_{12} = \nu_1 = 0.001, \nu_2 = 100, \varphi_1 = \varphi_2 = 10, p_1 = p_2 = 0.5, \langle n \rangle = 10, \mu_1 = \mu_2 = 1\) and \(N = 500\).
Figure 6.16: The LCD of the process in the case $\nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \gg 1$ with $\nu_{12} = \nu_1 = 0.001, \nu_2 = 100, \varphi_1 = 5, \varphi_2 = 10, p_1 = 0.5, \langle n \rangle = 10, \mu_1 = 1, \mu_2 = 0.2$ and $N = 500$.

6.5.3 The case $\nu_{12} \gg 1, \nu_1 \ll 1, \nu_2 \gg 1$

In the case $\nu_{12} \gg 1, \nu_1 \ll 1, \nu_2 \gg 1$, the APPs which provide survival signals to T cells of clonotype 2 also provide survival signals to many other clonotypes in the repertoire, while there is little competition from other T cell clonotypes for the APPs which provide survival signals to T cells of clonotype 1 but not to T cells of clonotype 2.

The deterministic equations for the densities of T cells of clonotypes 1 and 2, denoted
by $x_1$ and $x_2$, are given by

$$\frac{dx_1}{dt} = \frac{\tilde{\varphi}_1 x_1 p_1}{x_1 + x_2 + \nu_{12} \langle \tilde{n} \rangle} + \tilde{\varphi}_1 (1 - p_1) - \mu_1 x_1,$$

(6.111)

$$\frac{dx_2}{dt} = \tilde{\varphi}_2 x_2 \left( \frac{p_2}{x_1 + x_2 + \nu_{12} \langle \tilde{n} \rangle} + \frac{1 - p_2}{x_2 + \nu_2 \langle \tilde{n} \rangle} \right) - \mu_2 x_2,$$

(6.112)

where $\Omega \tilde{\varphi}_1 = \varphi_1$, $\Omega \tilde{\varphi}_2 = \varphi_2$, $\Omega \langle \tilde{n} \rangle = \langle n \rangle$ in order to ensure dimensional consistency. Non-dimensionalising these equations using the change of variables defined by Eqs. (6.92)–(6.94) and using the constraint (5.29) results in

$$\frac{du_1}{d\tau} = \frac{u_1 p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + 1 - p_1 - u_1 \equiv f(u_1, u_2),$$

(6.113)

$$\frac{du_2}{d\tau} = \frac{u_2 p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + \left( \frac{\bar{\varphi} - p_1}{u_2 + \nu_2 \bar{n}} \right) - \bar{\mu} u_2 \equiv g(u_1, u_2),$$

(6.114)

where $\bar{\varphi} = \varphi_2/\varphi_1$ and $\bar{\mu} = \mu_2/\mu_1$.

The steady states on the region $u_1, u_2 \geq 0$ are now investigated. As in previous sections, the possibility of a limit cycle existing in this region can be excluded using the Bendixson-Dulac criterion with $B = \frac{1}{u_1 u_2}$. From Section 6.5.1, $f(u_1, u_2) > 0$ for $u_1 < 1 - p_1$ and $f(u_1, u_2) < 0$ for $u_1 > 1$. Also,

$$g(u_1, u_2) > u_2 \left( \frac{\bar{\varphi} - p_1}{u_2 + \nu_2 \bar{n}} - \bar{\mu} \right),$$

(6.115)

which means that $g(u_1, u_2) > 0$ when $u_2 < \frac{1}{\bar{\mu}} (\bar{\varphi} - p_1) - \nu_2 \bar{n}$ and

$$g(u_1, u_2) < u_2 \left( \frac{p_1}{u_2 + \nu_{12} \bar{n}} + \frac{\bar{\varphi} - p_1}{u_2 + \nu_2 \bar{n}} - \bar{\mu} \right) \leq u_2 \left( \frac{\bar{\varphi}}{\bar{n} \min(\nu_{12}, \nu_2)} + \frac{\bar{\mu}}{u_2} \right).$$

(6.116)

Therefore, $g(u_1, u_2) < 0$ when $u_2 > \bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_{12}, \nu_2)$. A possible phase-plane diagram for the system is shown in Fig. 6.17. A steady state of the form $(\bar{u}_1^*, 0)$ always exists with $1 - p_1 < \bar{u}_1^* < 1$. If $\frac{1}{\bar{\mu}} (\bar{\varphi} - p_1) - \nu_2 \bar{n} > 0$ then this steady state is unstable and at least one stable steady state exists in the region $R$, which is defined
CHAPTER 6. SPECIAL CASES OF THE COMPETITION PROCESS

Figure 6.17: Possible phase-plane diagram for the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$.

by $1 - p_1 < u_1 < 1$, $\max(0, \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}) < u_2 < \max(0, \frac{\bar{\varphi}}{\bar{\mu}} - \bar{n} \min(\nu_{12}, \nu_2))$. Using the same method as that in Appendix C, it can be shown that this steady state is unique.

Next, the case when $\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < 0$ is considered. Analysis of the stability matrix shows that the steady state at $(\bar{u}_1^*, 0)$ is stable when

$$\frac{p_1}{\bar{u}_1^* + \nu_{12} \bar{n}} + \frac{\bar{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} < 0, \quad (6.117)$$

which implies that $\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < 0$, as expected. If this steady state is unstable, then a unique stable steady state of the form $(\bar{u}_1^*, \bar{u}_2)$ with $\bar{u}_1, \bar{u}_2 > 0$ exists in $R$.

Using the method of Appendix D, it can be shown that when $(\bar{u}_1^*, 0)$ is stable the steady state $(\bar{u}_1, \bar{u}_2)$ does not exist. Note that if $\frac{\bar{\varphi}}{\bar{\mu}} - \bar{n} \min(\nu_{12}, \nu_2) < 0$, condition (6.117) is automatically satisfied and so the unique stable steady state of the system is given by $(\bar{u}_1^*, 0)$. 
6.5.4 The case $\nu_{12} \ll 1$, $\nu_1 \gg 1$, $\nu_2 \gg 1$

In the case $\nu_{12} \ll 1$, $\nu_1 \gg 1$, $\nu_2 \gg 1$, the APPs which provide survival signals to T cells of one of the pair of clonotypes 1 and 2 but not the other, also provide survival signals to many other clonotypes in the repertoire and so there is a high level of competition for access to these APPs. There is little competition from other T cell clonotypes for APPs which provide survival signals to T cells of both clonotype 1 and clonotype 2.

The deterministic equations for the densities of T cells of clonotypes 1 and 2, denoted by $x_1$ and $x_2$, are given by

$$\frac{dx_1}{dt} = \tilde{\varphi}_1 x_1 \left( \frac{p_1}{x_1 + x_2} + \frac{1 - p_1}{x_1 + \nu_1 \langle \tilde{n} \rangle} \right) - \mu_1 x_1,$$

$$\frac{dx_2}{dt} = \tilde{\varphi}_2 x_2 \left( \frac{p_2}{x_1 + x_2} + \frac{1 - p_2}{x_2 + \nu_2 \langle \tilde{n} \rangle} \right) - \mu_2 x_2,$$

where $\Omega \tilde{\varphi}_1 = \varphi_1$, $\Omega \tilde{\varphi}_2 = \varphi_2$, $\Omega \langle \tilde{n} \rangle = \langle n \rangle$ in order to ensure dimensional consistency. Non-dimensionalising these equations using the change of variables given in Eqs. (6.92)–(6.94) and using the constraint (5.29) results in

$$\frac{du_1}{d\tau} = u_1 \left( \frac{p_1}{u_1 + u_2} + \frac{1 - p_1}{u_1 + \nu_1 \tilde{n}} - 1 \right) \equiv f(u_1, u_2),$$

$$\frac{du_2}{d\tau} = u_2 \left( \frac{p_1}{u_1 + u_2} + \frac{\varphi - p_1}{u_2 + \nu_2 \tilde{n}} - \bar{\mu} \right) \equiv g(u_1, u_2),$$

where $\bar{\varphi} = \varphi_2/\varphi_1$ and $\bar{\mu} = \mu_2/\mu_1$.

The steady states on the region $u_1, u_2 \geq 0$ are now considered. Firstly, the possibility of a limit cycle existing in this region can be excluded using the Bendixson-Dulac criterion with $B = \frac{1}{u_1 u_2}$. 
From Eqs. (6.120)–(6.121) it follows that

$$f(u_1, u_2) > u_1 \left( \frac{1 - p_1}{u_1 + \nu_1 \bar{n}} - 1 \right),$$

(6.122)

and so \(f(u_1, u_2) > 0\) when \(u_1 < 1 - p_1 - \nu_1 \bar{n}\), and

$$f(u_1, u_2) < u_1 \left( \frac{1 - p_1}{u_1} + \frac{p_1}{u_1} - 1 \right),$$

(6.123)

so that \(f(u_1, u_2) < 0\) when \(u_1 > 1\). As in Section 6.5.2, \(g(u_1, u_2) > 0\) when \(u_2 < \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}\) and \(g(u_1, u_2) < 0\) when \(u_2 > \frac{\bar{\varphi}}{\bar{\mu}}\). A possible phase-plane diagram for the system is shown in Fig. 6.18. Steady states of the form \((\bar{u}_1^*, 0)\) and \((0, \bar{u}_2^*)\) always exist with \(1 - p_1 - \nu_1 \bar{n} < \bar{u}_1^* < 1\) and \(\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < \bar{u}_2^* < \frac{\bar{\varphi}}{\bar{\mu}}\). If \(\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} > 0\) and \(1 - p_1 - \nu_1 \bar{n} > 0\) then these steady states are both unstable and at least one stable steady state exists in the region \(R\), which is defined by \(\max(0, 1 - p_1 - \nu_1 \bar{n}) < u_1 < 1\) and \(\max(0, \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}) < u_2 < \frac{\bar{\varphi}}{\bar{\mu}}\). As in Appendix C, it can be shown that this stable steady state is unique. No stable steady state can exist outside of this region.
If \( \frac{1}{\mu}(\bar{\phi} - p_1) - \nu_2 \bar{n} < 0 \) then it is possible that the steady state \((\bar{u}_1^*, 0)\) is stable. Analysis of the stability matrix shows that this steady state is stable when

\[
\frac{p_1}{\bar{u}_1^*} + \frac{\bar{\phi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} < 0 ,
\]

which implies that \( \frac{1}{\mu}(\bar{\phi} - p_1) - \nu_2 \bar{n} < 0 \), as expected. The previous analysis has shown that if \((\bar{u}_1^*, 0)\) is unstable then a unique stable steady state \((\bar{u}_1, \bar{u}_2)\) with \( \bar{u}_1, \bar{u}_2 > 0 \) exists in \( R \). Using the same method as that given in Appendix D it can be shown that when \((\bar{u}_1^*, 0)\) is stable, the steady state \((\bar{u}_1, \bar{u}_2)\) with \( \bar{u}_1, \bar{u}_2 > 0 \) does not exist.

The steady state \((0, \bar{u}_2^*)\) is stable when

\[
\frac{p_1}{\bar{u}_2^*} + \frac{1 - p_1}{\nu_1 \bar{n}} - 1 < 0 ,
\]

which implies that \( 1 - p_1 - \nu_1 \bar{n} < 0 \). As above, when \((0, \bar{u}_2^*)\) is stable, a steady state of the form \((\bar{u}_1, \bar{u}_2)\) with \( \bar{u}_1, \bar{u}_2 > 0 \) does not exist.

In this case, the deterministic analysis predicts that it is possible for both clonotypes to coexist if the parameters are such that each clonotype can receive a sufficiently high level of survival signals. However, if the value of \( \nu_2 \) is sufficiently high, this stable steady state ceases to exist and \((\bar{u}_1^*, 0)\) becomes stable, corresponding to extinction of T cells of clonotype 2 from the repertoire. On the other hand, if \( \nu_1 \) is sufficiently high, the steady state \((0, \bar{u}_2^*)\) becomes stable corresponding to extinction of T cells of clonotype 1 from the repertoire.

### 6.5.5 The case \( \nu_{12} \gg 1, \nu_1 \gg 1, \nu_2 \gg 1 \)

In the case \( \nu_{12} \gg 1, \nu_1 \gg 1, \nu_2 \gg 1 \), competition from other T cell clonotypes for the APPs in the sets \( Q_1 \) and \( Q_2 \) is high. This represents the greatest level of competition among all the cases introduced in this chapter.
The deterministic equations for the densities of T cells belonging to clonotypes 1 and 2, which are denoted by $x_1$ and $x_2$ are given by

\[
\frac{dx_1}{dt} = \tilde{\varphi}_1 x_1 \left( \frac{p_1}{x_1 + x_2 + \nu_{12} \langle n \rangle} + \frac{1 - p_1}{x_1 + \nu_1 \langle n \rangle} \right) - \mu_1 x_1 , \tag{6.126}
\]

\[
\frac{dx_2}{dt} = \tilde{\varphi}_2 x_2 \left( \frac{p_2}{x_1 + x_2 + \nu_{12} \langle n \rangle} + \frac{1 - p_2}{x_2 + \nu_2 \langle n \rangle} \right) - \mu_2 x_2 , \tag{6.127}
\]

where $\Omega \tilde{\varphi}_1 = \tilde{\varphi}_1, \Omega \tilde{\varphi}_2 = \tilde{\varphi}_2, \Omega \langle n \rangle = \langle n \rangle$ in order to ensure dimensional consistency. Non-dimensionalising this system using the change of variables defined by Eqs. (6.92)–(6.94) and using the constraint (5.29) results in

\[
\frac{du_1}{d\tau} = u_1 \left( \frac{p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + \frac{1 - p_1}{u_1 + \nu_1 \bar{n}} - 1 \right) \equiv f(u_1, u_2) , \tag{6.128}
\]

\[
\frac{du_2}{d\tau} = u_2 \left( \frac{p_1}{u_1 + u_2 + \nu_{12} \bar{n}} + \frac{\tilde{\varphi} - p_1}{u_2 + \nu_2 \bar{n}} - \tilde{\mu} \right) \equiv g(u_1, u_2) , \tag{6.129}
\]

where $\tilde{\varphi} = \varphi_2 / \varphi_1$ and $\tilde{\mu} = \mu_2 / \mu_1$.

The steady states of this system in the region $u_1, u_2 \geq 0$ are now investigated. The analysis of the steady states of this deterministic system was first carried out by Mikhail Ivanchenko. The possibility of limit cycles existing in this region can be excluded using the Bendixson-Dulac criterion with $B = \frac{1}{u_1 u_2}$. The regions over which $f(u_1, u_2)$ and $g(u_1, u_2)$ are always positive and negative are now determined.

\[
f(u_1, u_2) > u_1 \left( \frac{1 - p_1}{u_1 + \nu_1 \bar{n}} - 1 \right) , \tag{6.130}
\]

and

\[
f(u_1, u_2) < u_1 \left( \frac{p_1}{u_1 + \nu_{12} \bar{n}} + \frac{1 - p_1}{u_1 + \nu_1 \bar{n}} - 1 \right) < u_1 \left( \frac{1}{u_1 + \bar{n} \min(\nu_{12}, \nu_1)} - 1 \right) , \tag{6.131}
\]

so that $f(u_1, u_2) > 0$ when $u_1 < 1 - p_1 - \nu_1 \bar{n}$ and $f(u_1, u_2) < 0$ when $u_1 > 1 - \bar{n} \min(\nu_{12}, \nu_1)$. Similarly, $g(u_1, u_2) > 0$ when $u_2 < \frac{1}{\tilde{\mu}} (\tilde{\varphi} - p_1) - \nu_2 \bar{n}$ and $g(u_1, u_2) < 0$
Figure 6.19: Possible phase-plane diagram for the case $\nu_1 \gg 1, \nu_2 \gg 1, \nu_2 \gg 1$. when $u_2 > \bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_1, \nu_2)$. A possible phase plane diagram for the system is given in Fig. 6.19. $(0, 0)$ is a steady state of the system. Also, a steady state of the form $(\bar{u}_1, 0)$ with $\bar{u}_1 > 0$ exists and is unique if

$$1 - \frac{p_1}{\nu_2 \bar{n}} - \frac{1 - p_1}{\nu_1 \bar{n}} < 0.$$  \hspace{1cm} (6.132)

Similarly, a steady state of the form $(0, \bar{u}_2)$ with $\bar{u}_2 > 0$ exists and is unique if

$$\bar{\mu} - \frac{p_1}{\bar{\mu} \nu_1 \bar{n}} - \frac{\bar{\varphi} - p_1}{\bar{\mu} \nu_2 \bar{n}} < 0.$$  \hspace{1cm} (6.133)

From the above analysis, and from the phase-plane diagram, it is clear that if $1 - p_1 - \nu_1 \bar{n} > 0, \frac{1}{\bar{n}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} > 0$, the steady states $(0, 0), (\bar{u}_1, 0)$ and $(0, \bar{u}_2)$ are unstable and at least one stable steady state exists in the region $R$, which is defined by $\max(0, 1 - p_1 - \nu_1 \bar{n}) < u_1 < \max(0, 1 - \bar{n} \min(\nu_1, \nu_1)), \max(0, \frac{1}{\bar{n}}(\bar{\varphi} - p_1) - \nu_2 \bar{n}) < u_2 < \max(0, \bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_1, \nu_2))$. Using the same method as that presented in Appendix C, it can be shown that this steady state is unique. No stable steady state can exist outside of this region.
Next, the case when \( \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < 0, \bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_{12}, \nu_1) > 0 \) and \( 1 - p_1 - \nu_1 \bar{n} > 0 \) is considered. Then the steady state \((\bar{u}_1^*, 0)\) may be stable but both \((0, 0)\) and \((0, \bar{u}_2^*)\) are unstable. Analysis of its stability matrix shows that \((\bar{u}_1^*, 0)\) is stable when

\[
-1 + \frac{p_1 \nu_{12} \bar{n}}{(\bar{u}_1^* + \nu_{12} \bar{n})^2} + \frac{(1 - p_1) \nu_1 \bar{n}}{(\bar{u}_1^* + \nu_1 \bar{n})^2} < 0 ,
\]

and

\[
\frac{p_1}{\bar{u}_1^* + \nu_{12} \bar{n}} + \frac{1 - p_1}{\nu_2 \bar{n}} - \bar{\mu} < 0 .
\]

If \((\bar{u}_1^*, 0)\) is unstable, a unique stable steady state of the form \((\bar{u}_1, \bar{u}_2)\) with \(\bar{u}_1, \bar{u}_2 > 0\) exists in \(R\). Using the method given in Appendix D it can be shown that when \((\bar{u}_1^*, 0)\) is stable, the steady state \((\bar{u}_1, \bar{u}_2)\) does not exist.

If \(1 - p_1 - \nu_1 \bar{n} < 0, 1 - \bar{n} \min(\nu_{12}, \nu_1) > 0 \) and \( \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} > 0 \), the steady state \((0, \bar{u}_2^*)\) may be stable but both \((0, 0)\) and \((\bar{u}_1^*, 0)\) are unstable. Analysis of its stability matrix shows that \((0, \bar{u}_2^*)\) is stable when

\[
\frac{p_1}{\bar{u}_2^* + \nu_{12} \bar{n}} + \frac{1 - p_1}{\nu_1 \bar{n}} - 1 < 0 ,
\]

and

\[
-\bar{\mu} + \frac{p_1 \nu_{12} \bar{n}}{(\bar{u}_2^* + \nu_{12} \bar{n})^2} + \frac{(\bar{\varphi} - p_1) \nu_2 \bar{n}}{(\bar{u}_2^* + \nu_2 \bar{n})^2} < 0 .
\]

If \((0, \bar{u}_2^*)\) is unstable, a unique stable steady state of the form \((\bar{u}_1, \bar{u}_2)\) with \(\bar{u}_1, \bar{u}_2 > 0\) exists in \(R\). As in Appendix D, it can be shown that if \((0, \bar{u}_2^*)\) is stable, the steady state \((\bar{u}_1, \bar{u}_2)\) does not exist.

Now, if \(1 - p_1 - \nu_1 \bar{n} < 0, \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) - \nu_2 \bar{n} < 0, 1 - \bar{n} \min(\nu_{12}, \nu_1) > 0 \) and \( \bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_{12}, \nu_2) > 0 \), the steady state \((0, 0)\) may be stable. The eigenvalues of the linear stability matrix at \((u_1, u_2) = (0, 0)\) are given by

\[
\lambda_1 = \frac{p_1}{\nu_{12} \bar{n}} + \frac{1 - p_1}{\nu_1 \bar{n}} - 1 ,
\]
and

\[ \lambda_2 = \frac{p_1}{\nu_{12} \bar{n}} + \frac{\bar{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu}, \]  

(6.139)

so that the steady state \((0, 0)\) becomes stable when \(\lambda_1, \lambda_2 < 0\). Therefore, from Eqs. (6.132) and (6.133), the steady state \((0, 0)\) is stable when both of the steady states \((\bar{u}_1, 0)\) and \((0, \bar{u}_2)\) do not exist.

If \(1 - \bar{n} \min(\nu_{12}, \nu_1) < 0\) then \((0, \bar{u}_2^*)\) is stable if it exists, otherwise \((0, 0)\) is stable. Similarly, if \(\bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_{12}, \nu_2) < 0\) then \((\bar{u}_1^*, 0)\) is stable if it exists, otherwise \((0, 0)\) is stable. If both \(\bar{n} \min(\nu_{12}, \nu_1) < 0\) and \(\bar{\varphi}/\bar{\mu} - \bar{n} \min(\nu_{12}, \nu_2) < 0\) then \((0, 0)\) is the unique stable steady state of the system.

Even in this case, which represents the highest level of competition for survival signals among all the cases presented in this chapter, a stable steady state of the form \((\bar{u}_1, \bar{u}_2)\) with \(\bar{u}_1, \bar{u}_2 > 0\) exists if the parameters are such that both clonotypes receive sufficient survival signals. If \(\nu_1\) is large enough, the steady state \((\bar{u}_1, \bar{u}_2)\) ceases to exist and \((0, \bar{u}_2^*)\) becomes stable, corresponding to extinction of clonotype 1 from the repertoire. Similarly, if \(\nu_2\) is large enough, \((\bar{u}_1, \bar{u}_2)\) does not exist and \((\bar{u}_1^*, 0)\) becomes stable corresponding to extinction of clonotype 2. If both \(\nu_1\) and \(\nu_2\) are sufficiently large, the steady states \((\bar{u}_1^*, 0)\) and \((0, \bar{u}_2^*)\) do not exist and \((0, 0)\) becomes stable, corresponding to extinction of both clonotypes from the repertoire.

### 6.6 Arbitrary values of \(\nu_{12}, \nu_1\) and \(\nu_2\)

In this chapter, the special cases that have been analysed are defined by whether the values of the parameters \(\nu_{12}, \nu_1\) and \(\nu_2\) are much less than one or much greater than one. In this section, the effect of changing these parameters is considered. The results of Section 6.5 suggest that, at least for the deterministic process, increasing \(\nu_1\) and \(\nu_2\) has a greater effect than increasing \(\nu_{12}\), as shown by the qualitative similarity
of the cases $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ and $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$ and the cases $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ and $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$.

Figs. 6.20–6.23 show the mean time until the process reaches the absorbing set from an initial state $(n_1, n_2) \in S \setminus A$, $\hat{\tau}_{n_1, n_2}$, as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with all other parameters remaining fixed. It can be seen that $\hat{\tau}_{n_1, n_2}$ is independent of $\nu_{12}$, $\nu_1$ and $\nu_2$ for $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$, as predicted by Eqs. (6.1)–(6.2). As $\nu_{12}$, $\nu_1$ and $\nu_2$ increase, $\hat{\tau}_{n_1, n_2}$ decreases due to increased competition from T cells belonging to other clonotypes. However, the extent of this decrease is greater for increasing $\nu_1$ and $\nu_2$ than for increasing $\nu_{12}$. This is because increasing $\nu_{12}$ results in more competition for both clonotypes, while increasing $\nu_2$ results in more competition for T cells belonging to clonotype 2, meaning that T cells belonging to clonotype 1 gain a selective advantage. Similarly, increasing $\nu_1$ results in more competition for T cells belonging to clonotype 1 meaning that T cells belonging to clonotype 2 gain a selective advantage.

Figure 6.20: $\hat{\tau}_{n_1, n_2}$ as a function of $\nu_{12}$ and $\nu_2$ with $\nu_1 = 0.001$, $\varphi_1 = \varphi_2 = 10$, $p_1 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$, $n_1 = n_2 = 10$ and $N = 500$. $\nu_{12} = \nu_2 = 0.001$ when these parameters are fixed. The effect of increasing the parameter $\nu_1$ is the same as that given by increasing $\nu_2$ in this case because the parameter values are symmetric between clonotypes 1 and 2.

of clonotype 1 become extinct from the repertoire before T cells of clonotype 2
Figure 6.21: $\hat{\tau}_{n_1,n_2}$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = \varphi_2 = 10$, $p_1 = 0.5$, $\langle n \rangle = 10$, $n_1 = n_2 = 9$, $n_1 = n_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 0.001$ when these parameters are fixed.

Figure 6.22: $\hat{\tau}_{n_1,n_2}$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = 5$, $\varphi_2 = 10$, $p_1 = 0.5$, $p_2 = 0.25$, $\langle n \rangle = 10$, $n_1 = n_2 = 1$, $n_1 = n_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 0.001$ when these parameters are fixed.
from an initial state \((n_1, n_2) \in \mathcal{S} \setminus \mathcal{A}, \phi_{n_1,n_2}\), as a function of \(\nu_{12}, \nu_1\) and \(\nu_2\). For the set of parameter values shown in Fig. 6.24, varying \(\nu_{12}\) has no effect because \(\varphi_1 = \varphi_2, p_1 = p_2, \mu_1 = \mu_2, n_1 = n_2\) and so both clonotypes are equally likely to become extinct first, regardless of the value of \(\nu_{12}\) which affects both clonotypes to the same extent, while in Fig. 6.25, increasing \(\nu_{12}\) does have a slight effect because \(n_1 \neq n_2\). Figs. 6.24–6.25 show that increasing \(\nu_1\) results in an increase in \(\phi_{n_1,n_2}\) due to increased competition for survival signals between T cells of clonotype 1 and other clonotypes in the repertoire which results in T cells of clonotype 2 gaining a competitive advantage. On the other hand, increasing \(\nu_2\) results in T cells of clonotype 1 gaining a competitive advantage and so \(\phi_{n_1,n_2}\) decreases.

The marginal distribution of the number of T cells belonging to clonotype 1 at the LCD is defined by

\[
q_{n_1,-} = \sum_{n_2=1}^{+\infty} q_{n_1,n_2},
\]

and the mean of this distribution is denoted by \(E(q_{n_1,-})\). Figs. 6.26–6.28 show \(E(q_{n_1,-})\) as a function of \(\nu_{12}, \nu_1\) and \(\nu_2\). As \(\nu_{12}\) increases, the mean number of T cells belonging to clonotype 1 at the LCD decreases due to increased competition which results in lower levels of survival signals. As \(\nu_1\) increases, the mean number of T cells belonging to clonotype 1 at the LCD decreases also, while as \(\nu_2\) increases, the mean number of T cells belonging to clonotype 1 at the LCD increases. As in Figs. 6.20–6.25, the effect of increasing \(\nu_1\) is greater than the effect of increasing \(\nu_{12}\) because changes in \(\nu_{12}\) affect both clonotypes, while increasing \(\nu_1\) only affects T cells belonging to clonotype 1, leading to clonotype 2 gaining a competitive advantage.
CHAPTER 6. SPECIAL CASES OF THE COMPETITION PROCESS

2.2 2.4 2.6 2.8 3 3.2 3.4 3.6 3.8 4

\[ \tau_{n_1, n_2} \] as a function of \( \nu_{12} \) and \( \nu_2 \) with \( \nu_1 = 10, \varphi_1 = \varphi_2 = 10, p_1 = p_2 = 0.5, \langle n \rangle = 10, \mu_1 = \mu_2 = 1, n_1 = n_2 = 10 \) and \( N = 500. \nu_{12} = \nu_2 = 10 \) when these parameters are fixed.

Figure 6.23: \( \tau_{n_1, n_2} \) as a function of \( \nu_{12}, \nu_1 \) and \( \nu_2 \) with \( \varphi_1 = \varphi_2 = 10, p_1 = 0.5, \langle n \rangle = 10, \mu_1 = \mu_2 = 1, n_1 = n_2 = 10 \) and \( N = 500. \nu_{12} = \nu_1 = \nu_2 = 0.001 \) when these parameters are fixed.

Figure 6.24: \( \varphi_{n_1, n_2} \) as a function of \( \nu_{12}, \nu_1 \) and \( \nu_2 \) with \( \varphi_1 = \varphi_2 = 10, p_1 = 0.5, \langle n \rangle = 10, \mu_1 = \mu_2 = 1, n_1 = n_2 = 10 \) and \( N = 500. \nu_{12} = \nu_1 = \nu_2 = 0.001 \) when these parameters are fixed.
Figure 6.25: $\rho_{n_1, n_2}$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = \varphi_2 = 10$, $p_1 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$, $n_1 = 9$, $n_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 0.001$ when these parameters are fixed.

Figure 6.26: $\mathbb{E}(q_{n_1,-})$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = \varphi_2 = 10$, $p_1 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 0.001$ when these parameters are fixed.
Figure 6.27: $E(q_{n_1,-})$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = 5$, $\varphi_2 = 10$, $p_1 = 0.5$, $p_2 = 0.25$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 0.001$ when these parameters are fixed.

Figure 6.28: $E(q_{n_1,-})$ as a function of $\nu_{12}$, $\nu_1$ and $\nu_2$ with $\varphi_1 = \varphi_2 = 10$, $p_1 = 0.5$, $\langle n \rangle = 10$, $\mu_1 = \mu_2 = 1$ and $N = 500$. $\nu_{12} = \nu_1 = \nu_2 = 10$ when these parameters are fixed.
CHAPTER 6. SPECIAL CASES OF THE COMPETITION PROCESS

6.7 Discussion

In this chapter it has been shown that as the pair of T cell clonotypes 1 and 2 become more similar, in terms of the APPs from which they are able to receive survival signals, \( i.e., \) as \( p_1 \to 1 \), one of the pair of clonotypes quickly becomes extinct from the repertoire in a process which resembles the ecological principle of classical competitive exclusion. If \( p_1 = p_2 = 0 \) then both clonotypes can be modelled independently using the model introduced in Chapter 3. On the other hand, in the case \( p_1 = p_2 = 1 \), the pair of clonotypes behave as a single clonotype under the mean field approximation introduced in Chapter 3 (see Eq. (5.35)). In this case, which clonotype becomes extinct first does not affect the coverage of APP space. There is a gradual transition between these two extremes which has been described in detail in this chapter.

The coefficient of variation of T cells of clonotypes 1, \( \sqrt{\Omega \langle \eta_1^2 \rangle}/\bar{n}_1 \), the coefficient of variation of T cells of clonotypes 2, \( \sqrt{\Omega \langle \eta_2^2 \rangle}/\bar{n}_2 \) and the correlation coefficient, \( \rho \), can be estimated experimentally by means of analysis of time series data from observations of \( n_1 \) and \( n_2 \) obtained by repeated real-time PCR on peripheral blood samples [17] at subsequent points in time. For a pair of clonotypes in the case \( \nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1 \), where it is assumed that \( \mu \equiv \mu_1 = \mu_2 \), knowledge of \( \sqrt{\Omega \langle \eta_1^2 \rangle}/\bar{n}_1 \), \( \sqrt{\Omega \langle \eta_2^2 \rangle}/\bar{n}_2 \), and \( \rho \), allows estimation of three parameters of the model, \( \varphi_1, \varphi_2 \) (in units of \( \mu \)) and \( p_1 \).

The analysis also suggests that the values of the parameters \( \nu_1 \) and \( \nu_2 \) have a greater influence on the dynamics of the process than the parameter \( \nu_{12} \). This is because \( \nu_{12} \) affects both clonotypes whereas \( \nu_1 \) and \( \nu_2 \) affect only one of the pair of clonotypes. Analysis of the corresponding deterministic models for various special cases of the system shows that if \( \nu_1 \) is sufficiently large, T cells of clonotype 1 become extinct very quickly, while if \( \nu_2 \) is sufficiently large, T cells of clonotype 2 become extinct.
rapidly. If $\nu_1$ and $\nu_2$ are both sufficiently large then neither clonotype has access to the level of survival signals needed to maintain them in the repertoire. Thus, as in Chapter 3, it is seen that a selection mechanism operates so that clonotypes with $\nu_1 \ll 1$, $\nu_2 \ll 1$, $\nu_{12} \ll 1$ are associated with the longest lifespans in the repertoire. In this way, unnecessary overlap in terms of APP recognition is avoided, thus maximising naïve T cell repertoire diversity.
Chapter 7

Many competing clonotypes

In Chapter 5, a bivariate competition process was introduced which extended the univariate model presented in Chapter 3 to the situation where there exists a pair of clonotypes for which the mean field assumption $|Q_1 \cap Q_2| \ll |Q_1|$ does not hold. In principle, the method given in Section 5.1.1 can be used to formulate a multivariate competition process for any number of clonotypes which do not satisfy the mean field assumption. However, as the number of clonotypes increases, so does the number of model parameters, meaning that analysis becomes more difficult. For example, a model for three clonotypes, labelled clonotypes 1, 2 and 3, where $|Q_1 \cap Q_2| \sim |Q_1|$, $|Q_2 \cap Q_3| \sim |Q_2|$ and $|Q_1 \cap Q_3| \sim |Q_1|$, has 18 independent parameters and there are 40 distinct special cases of the model corresponding to the 6 special cases of the bivariate process discussed in Chapter 6. Thus, as the number of clonotypes increases, the model quickly becomes analytically intractable. However, it is possible to show that some properties of the univariate and bivariate models are preserved. In particular, in this chapter it is proved that for a multivariate competition model of $k$ clonotypes, where $k \in \mathbb{Z}^+$, all $k$ clonotypes become extinct within a finite amount of time with probability one. Two ways of defining the QSD for this process are described and the existence of both these distributions is investigated. It is possible
to perform an exact numerical simulation of the full T cell repertoire dynamics without the need for any type of mean field approximation, using a version of the Gillespie algorithm. With this simulation method, the model may be extended to a variety of situations where analysis is difficult. For example, the number of clonotypes may be large and the parameters of the model may be specified to be time-dependent rather than constant, if required.

### 7.1 A competition process modelling the number of T cells belonging to $k$ clonotypes

As in previous chapters, it is assumed that the thymus produces T cells of clonotype $i$ within a very short space of time, and the time at which this burst of production occurs is denoted by $\tilde{t}_i$. After this time, it is assumed that no further T cells of clonotype $i$ are produced by the thymus and the number of T cells of clonotype $i$ initially produced by the thymus is given by $n_i(\tilde{t}_i)$. Without loss of generality, it is assumed that $\tilde{t}_1 \leq \tilde{t}_2 \leq \ldots \leq \tilde{t}_k$.

The number of T cells belonging to clonotypes 1, 2, ..., $k$ at time $t$, which is denoted by $(n_1(t), n_2(t), \ldots, n_k(t))$, is modelled by means of a continuous-time Markov process $\{(X_1(t), X_2(t), \ldots, X_k(t)) : t \geq \tilde{t}_k\}$ on the state-space $S = \{(n_1, n_2, \ldots, n_k) : n_i = 0, 1, 2, \ldots; i = 1, \ldots, k\}$. Let $\tilde{n}_i = n_i(\tilde{t}_k)$ so that the initial state of the process is given by $(\tilde{n}_1, \tilde{n}_2, \ldots, \tilde{n}_k)$. As in previous models, transitions are only allowed to adjacent states, resulting in a $k$-dimensional analogue of the birth and death process. This is referred to a multivariate competition process [4, 110]. The transition probabilities are defined by

$$p_{n,m}(\Delta t) = \mathbb{P}\{X_1(t + \Delta t) = m_1, \ldots, X_k(t + \Delta t) = m_k | X_1(t) = n_1, \ldots, X_k(t) = n_k\}$$

(7.1)
for $\mathbf{n} = (n_1, n_2, \ldots, n_k) \in \mathcal{S}$ and $\mathbf{m} = (m_1, m_2, \ldots, m_k) \in \mathcal{S}$. These probabilities satisfy the following as $\Delta t \to 0^+$:

$$p_{\mathbf{n}, \mathbf{m}}(\Delta t) = \begin{cases} \lambda_n^{(1)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1 + 1, n_2, \ldots, n_k) \\ \lambda_n^{(2)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1, n_2 + 1, \ldots, n_k) \\ \vdots & \\ \lambda_n^{(k)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1, n_2, \ldots, n_k + 1) \\ \mu_n^{(1)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1 - 1, n_2, \ldots, n_k) \\ \mu_n^{(2)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1, n_2 - 1, \ldots, n_k) \\ \vdots & \\ \mu_n^{(k)} \Delta t + o(\Delta t) & \mathbf{m} = (n_1, n_2, \ldots, n_k - 1) \\ 1 - \sum_{i=1}^{k} (\lambda_n^{(i)} + \mu_n^{(i)}) \Delta t + o(\Delta t) & \mathbf{m} = \mathbf{n} \\ o(\Delta t) & \text{otherwise.} \end{cases}$$ (7.2)

The quantity $\lambda_n^{(i)}$ is the birth rate for T cells of clonotype $i$ and is the rate of transition from state $(n_1, n_2, \ldots, n_i, \ldots, n_k)$ to state $(n_1, n_2, \ldots, n_i + 1, \ldots, n_k)$ for $i = 1, 2, \ldots, k$. Similarly, $\mu_n^{(i)}$ is the death rate for T cells of clonotype $i$ and is the rate of transition from state $(n_1, n_2, \ldots, n_i, \ldots, n_k)$ to state $(n_1, n_2, \ldots, n_i - 1, \ldots, n_k)$. Setting $\mu_n^{(i)} = 0$ when $n_i = 0$ ensures that transitions outside of the state-space $\mathcal{S}$ cannot occur. Since it is assumed that no cells belonging to clonotypes $1, 2, \ldots, k$ are produced by the thymus after the time $\tilde{t}_k$, $\lambda_n^{(i)} = 0$ for $n_i = 0$. Hence, the set of states $\mathcal{A} = \{(n_1, n_2, \ldots, n_k) : n_i = 0 \text{ for at least one } i \in \{1, 2, \ldots, k\}\}$ forms an absorbing set, meaning that once the process enters set $\mathcal{A}$ it will never move to a state in $\mathcal{S} \setminus \mathcal{A}$, while the set of states $\mathcal{S} \setminus \mathcal{A}$ forms a transient communicating class.

The state $(n_1, n_2, \ldots, n_k) = (0, 0, \ldots, 0)$ is an absorbing state which corresponds to the extinction of all $k$ clonotypes from the repertoire.

As in the previous models, it is assumed that the survival signals from any particular APP are shared equally among all the T cells that are capable of receiving them.
Recall that $\mathcal{C}$ is the set of all T cells in the naïve repertoire, $\mathcal{C}_q$ is the subset of T cells that are able to receive survival signals from APP $q$ and $n_q = |\mathcal{C}_q|$ is the total number of T cells that the survival signals from APP $q$ are shared between. The set of all APPs in the periphery is denoted by $\mathcal{Q}$ and $\mathcal{Q}_i$ is the subset of APPs from which T cells of clonotypes $i$ can receive survival signals. As described in Chapter 3, these survival signals are signals for homeostatic proliferation in that they trigger a single round of cell division. Let $\lambda^{(i)}$ denote the per cell birth rate for T cells of clonotype $i$, where $i = 1, 2, \ldots, k$, and let $\gamma$ denote the rate of survival signals emanating from an APP $q$, which is assumed to be the same for all $q \in \mathcal{Q}$. Then, as in Eq. (3.1),

$$\lambda^{(i)} = \sum_{q \in \mathcal{Q}_i} \frac{\gamma}{n_q} = \sum_{q \in \mathcal{Q}_i} \frac{\gamma}{n_i + n_{iq}}, \quad (7.3)$$

where $n_{iq} = n_q - n_i$. Therefore,

$$\lambda^{(i)} = \sum_{q \in \mathcal{Q}_i} \frac{\gamma}{n_i + n_{iq}} \leq \gamma \sum_{q \in \mathcal{Q}_i} \frac{1}{n_i} = \frac{\gamma |\mathcal{Q}_i|}{n_i} = \frac{\varphi_i}{n_i}, \quad (7.4)$$

where $\varphi_i = \gamma |\mathcal{Q}_i|$ is a parameter that is proportional to $|\mathcal{Q}_i|$, the number of APPs from which T cells of clonotype $i$ can receive survival signals and to $\gamma$, which is the rate of survival signals emanating from the APPs. Thus, the birth rates for the multivariate competition process, as defined in Eq. (7.2), are bounded as follows:

$$\lambda_n^{(i)} = \lambda^{(i)} n_i \leq \varphi_i. \quad (7.5)$$

To obtain the corresponding death rates, it is assumed that the per cell death rate
for T cells of clonotype \( i \) is given by a constant, which is denoted by \( \mu_i \). Therefore,

\[
\mu^{(i)}_n = \mu_i n_i .
\] (7.6)

7.2 Guaranteed extinction and finite mean extinction times

In this section it is proved that the probability of ultimate absorption at the state \((n_1, n_2, \ldots, n_k) = (0, 0, \ldots, 0)\) occurring is one for all parameter values of the model. In order to do this, the same method as that presented in Section 5.2.1 is used. The multivariate competition process is bounded by a univariate birth and death process which has the property that it moves towards the origin at a slower rate than the multivariate competition process [70].

The state-space \( S \) of the multivariate competition process is divided into the following disjoint subsets:

\[
S'_j = \{(n_1, n_2, \ldots, n_k) : n_1 + n_2 + \ldots + n_k = j\} \quad \text{for } j \geq 0 , \quad (7.7)
\]

which define the states of the univariate process. Next, the birth and death rates for this process are defined. If the process is in the state \((n_1, n_2, \ldots, n_k) \in S'_j \) at the current time, with the next transition it moves to a state in the set \( S'_{j+1} \) with probability \((\lambda^{(1)}_n + \lambda^{(2)}_n + \ldots + \lambda^{(k)}_n) / r_n\) or to a state in the set \( S'_{j-1} \) with probability \((\mu^{(1)}_n + \mu^{(2)}_n + \ldots + \mu^{(k)}_n) / r_n\), where \( r_n = \sum_{i=1}^{k} (\lambda^{(i)}_n + \mu^{(i)}_n) \). Let

\[
\lambda'_j = \max_{n \in S'_j} \{\lambda^{(1)}_n + \lambda^{(2)}_n + \ldots + \lambda^{(k)}_n\} , \quad (7.8)
\]

\[
\mu'_j = \min_{n \in S'_j} \{\mu^{(1)}_n + \mu^{(2)}_n + \ldots + \mu^{(k)}_n\} , \quad (7.9)
\]
with \( \lambda'_j = \mu'_j = 0 \) when \( j = 0 \). The rate \( \lambda'_j \) is the maximum rate for the process to move upwards from the set \( S'_j \) to \( S'_{j+1} \) and the rate \( \mu'_j \) is the minimum rate for the process to move downwards from the set \( S'_j \) to \( S'_{j-1} \). These rates define a univariate birth and death process on the state-space \( S' = \{ S'_0, S'_1, S'_2, \ldots \} \), which moves towards the origin at a slower rate than the multivariate competition process, where \( S'_0 \) is an absorbing state and \( S'_j \) is now treated as a single state rather than a set of states. The process can be represented as follows:

\[
S'_0 \xleftarrow{\mu'_1} S'_1 \xrightarrow{\lambda'_1} S'_2 \cdots S'_{j-1} \xleftarrow{\mu'_j} S'_j \xrightarrow{\lambda'_j} S'_{j+1} \cdots .
\]

Let

\[
\pi'_1 = 1 \quad \text{and} \quad \pi'_j = \frac{\lambda'_1 \lambda'_2 \cdots \lambda'_{j-1}}{\mu'_2 \mu'_3 \cdots \mu'_j} \quad \text{for} \quad j \geq 2 .
\]

(7.10)

Theorem 1 of Iglehart [70] and Proposition 9.3.1 of [4] state that the multivariate competition process is regular if

\[
\sum_{l=1}^{+\infty} \frac{1}{\lambda'_l} \sum_{j=1}^{l} \pi'_j = +\infty .
\]

(7.11)

This is also the sufficient condition for the univariate birth and death process to be regular. To prove that condition (7.11) holds for the birth and death rates (7.8)–(7.9), it is first observed that

\[
\lambda'_j = \max_{n \in S'_j} \{ \lambda^{(1)}_n + \lambda^{(2)}_n + \cdots + \lambda^{(k)}_n \} \leq \varphi_1 + \varphi_2 + \cdots + \varphi_k ,
\]

(7.12)

from Eq. (7.5) and

\[
\mu'_j = \min_{n \in S'_j} \{ \mu_1 n_1 + \mu_2 n_2 + \cdots + \mu_k n_k \} = j \min(\mu_1, \mu_2, \ldots, \mu_k) .
\]

(7.13)

For the birth and death rates (7.8)–(7.9) the terms \( \pi'_j \) are all strictly positive for
$j \geq 1$ and so

$$
\sum_{l=1}^{+\infty} \frac{1}{\lambda'_l\pi'_l} \sum_{j=1}^l \pi'_j > \sum_{l=1}^{+\infty} \frac{1}{\lambda'_l\pi'_l} \pi'_l = \sum_{l=1}^{+\infty} \frac{1}{\lambda'_l} \geq \sum_{l=1}^{+\infty} \frac{1}{\varphi_1 + \varphi_2 + \ldots + \varphi_k} = +\infty, 
$$

(7.14)

and, hence, the multivariate competition process is regular. Then by Theorem 3 of Iglehart [70], a sufficient condition for guaranteed absorption of the multivariate competition process at $(n_1, n_2, \ldots, n_k) = (0, 0, \ldots, 0)$ is that the series

$$
\sum_{j=1}^{+\infty} \frac{1}{\lambda'_j\pi'_j} 
$$

(7.15)

diverges. Note that this is a sufficient condition for the univariate process to reach the absorbing state $S'_0$ with certainty. Then, for the birth and death rates (7.8)–(7.9),

$$
\sum_{j=1}^{+\infty} \frac{1}{\mu'_2\mu'_3 \cdots \mu'_j} = \sum_{j=1}^{+\infty} \frac{j!\min(\mu_1, \mu_2, \ldots, \mu_k)^{j-1}}{\lambda'_1\lambda'_2 \cdots \lambda'_j} \geq \sum_{j=1}^{+\infty} \frac{j!\min(\mu_1, \mu_2, \ldots, \mu_k)^{j-1}}{(\varphi_1 + \varphi_2 + \ldots + \varphi_k)^j}. 
$$

(7.16)

Let

$$
a_j = \frac{j!\min(\mu_1, \mu_2, \ldots, \mu_k)^{j-1}}{(\varphi_1 + \varphi_2 + \ldots + \varphi_k)^j}, 
$$

(7.17)

so that

$$
\frac{a_{j+1}}{a_j} = \frac{(j + 1)\min(\mu_1, \mu_2, \ldots, \mu_k)}{(\varphi_1 + \varphi_2 + \ldots + \varphi_k)^j} \rightarrow +\infty \text{ as } j \rightarrow +\infty. 
$$

(7.18)

Hence, the series $\sum_{j=1}^{+\infty} a_j$ diverges by the ratio test and therefore $\sum_{j=1}^{+\infty} \frac{1}{\lambda'_j\pi'_j}$ also diverges by comparison. Thus, absorption at $(n_1, n_2, \ldots, n_k) = (0, 0, \ldots, 0)$ is guaranteed for all parameter values of the model. This means that the ultimate fate of all clonotypes is extinction from the repertoire.
Let $\tau_n$ be the mean time until all $k$ clonotypes become extinct when the initial state of the process is given by $n = (n_1, n_2, \ldots, n_k)$. Theorem 4 of Iglehart [70] states that, for a regular multivariate competition process, $\tau_n < +\infty$ for all $n \in S \setminus \{(0, 0, \ldots, 0)\}$ if the series $\sum_{j=1}^{+\infty} \pi'_j$ converges. This is a sufficient condition for the mean time to extinction to be finite for the univariate process defined above. For the birth and death rates (7.8)–(7.9),

$$\sum_{j=1}^{+\infty} \pi'_j = \sum_{j=1}^{+\infty} \frac{\lambda'_1 \lambda'_2 \ldots \lambda'_{j-1}}{\mu'_2 \mu'_3 \ldots \mu'_j} \leq \sum_{j=1}^{+\infty} \frac{(\varphi_1 + \varphi_2 + \ldots + \varphi_k)^{j-1}}{j! \min(\mu_1, \mu_2, \ldots, \mu_k)^{j-1}}. \quad (7.19)$$

Let

$$b_j = \frac{(\varphi_1 + \varphi_2 + \ldots + \varphi_k)^{j-1}}{j! \min(\mu_1, \mu_2, \ldots, \mu_k)^{j-1}}. \quad (7.20)$$

Then

$$\frac{b_{j+1}}{b_j} = \frac{\varphi_1 + \varphi_2 + \ldots + \varphi_k}{(j + 1) \min(\mu_1, \mu_2, \ldots, \mu_k)} \rightarrow 0 \text{ as } j \rightarrow +\infty, \quad (7.21)$$

so that the series $\sum_{j=1}^{+\infty} b_j$ converges by the ratio test. Hence, the series $\sum_{j=1}^{+\infty} \pi'_j$ converges by comparison. Therefore the mean time to absorption from all initial states $n \in S \setminus \{(0, 0, \ldots, 0)\}$ is finite.

The multivariate competition process introduced in Section 7.1 is bounded by the univariate birth and death process with birth rates and death rates given by $\lambda'_j$ and $\mu'_j$, respectively, in the sense that the univariate process moves towards the absorbing state at a slower rate than the multivariate competition process. For a univariate birth and death process with birth rates $\lambda'_j$ and death rates $\mu'_j$, the mean time until absorption from an initial state $j$, $\tau_j$, is given by Eq. (2.57) as

$$\tau_j = \sum_{l=1}^{+\infty} \frac{1}{\lambda'_l \rho'_l} + \sum_{a=1}^{j-1} \rho'_a \sum_{l=a+1}^{+\infty} \frac{1}{\lambda'_l \rho'_l}, \quad (7.22)$$

where $\rho'_a = \prod_{j=1}^{a} (\mu'_j / \lambda'_j)$. Hence $\tau_j$, with $\lambda'_j$ and $\mu'_j$ as defined in Eqs. (7.8)–(7.9), is
an upper bound on the mean time to absorption at state \((0, 0, \ldots, 0)\) from all initial states \(n \in S_j'\) for \(j \geq 1\).

## 7.3 The quasi-stationary probability distribution of the multivariate competition process

In this section, the QSD of the multivariate competition process is introduced to represent the behaviour of the system before extinction occurs. As in the bivariate case, the QSD can be defined in more than one way. Firstly, the stationary probability distribution of the process conditional on the event that at least one clonotype is still present in the repertoire is defined. Secondly, the stationary probability distribution of the process conditional on the event that each of the \(k\) clonotypes are still present in the repertoire is introduced. The existence of these distributions is then discussed. It is possible to define the QSD in other ways by conditioning on the event that a particular combination of clonotypes are still present in the repertoire, but these distributions are not considered here.

### 7.3.1 The stationary probability distribution of the process conditional on the event that at least one of the \(k\) clonotypes is present in the repertoire

Let \(p_n(t)\) be the probability that the state of the process at time \(t\) is given by \(n = (n_1, n_2, \ldots, n_k)\), i.e.,

\[
p_n(t) = \mathbb{P}(X_1(t) = n_1, \ldots, X_k(t) = n_k | X_1(t_k) = \hat{n}_1, \ldots, X_k(t_k) = \hat{n}_k), \quad (7.23)
\]
where \( p_n(t) \geq 0 \) for \( n \in S \), \( p_n(t) = 0 \) for \( n \notin S \) and \( \sum_{n \in S} p_n(t) = 1 \) for \( t \geq \tilde{t}_k \).

These probabilities satisfy the following system of differential equations:

\[
\frac{dp_n(t)}{dt} = \sum_{i=1}^{k} \lambda^{(i)}_{(n_1, \ldots, n_{i-1}, \ldots, n_k)} p_{(n_1, \ldots, n_{i-1}, \ldots, n_k)}(t) + \sum_{i=1}^{k} \mu^{(i)}_{(n_1, \ldots, n_{i+1}, \ldots, n_k)} p_{(n_1, \ldots, n_{i+1}, \ldots, n_k)}(t) \\
- \sum_{i=1}^{k} (\lambda^{(i)}_n + \mu^{(i)}_n) p_n(t),
\]

(7.24)

for all \( n \in S \), which are the forward Kolmogorov equations for the multivariate competition process [26]. The limiting solution of these equations as \( t \to +\infty \) is given by \( p_{(0,0,\ldots,0)} = 1 \) and \( p_n = 0 \) for all \( n \neq (0,0,\ldots,0) \), since extinction of all clonotypes ultimately occurs with probability one. In order to study the behaviour of the process before all \( k \) clonotypes become extinct, the above equations are written in terms of a new variable. Let

\[
q'_n(t) = \frac{p_n(t)}{1 - p_{(0,0,\ldots,0)}(t)},
\]

(7.25)

which is the probability that the state of the process at time \( t \) is given by \( n \), conditional on the event that at least one of the \( k \) clonotypes is still present in the naïve T cell repertoire. For all \( t \geq \tilde{t}_k \), \( q'_n(t) \geq 0 \) for \( n \in S \setminus \{(0,0,\ldots,0)\} \), \( q'_n(t) = 0 \) for \( n \notin S \setminus \{(0,0,\ldots,0)\} \) and \( \sum_{n \in S \setminus \{(0,0,\ldots,0)\}} q'_n(t) = 1 \). From Eq. (7.24), these probabilities satisfy

\[
\frac{dq'_n(t)}{dt} = \sum_{i=1}^{k} \lambda^{(i)}_{(n_1, \ldots, n_{i-1}, \ldots, n_k)} q'_{(n_1, \ldots, n_{i-1}, \ldots, n_k)}(t) + \sum_{i=1}^{k} \mu^{(i)}_{(n_1, \ldots, n_{i+1}, \ldots, n_k)} q'_{(n_1, \ldots, n_{i+1}, \ldots, n_k)}(t) \\
- \sum_{i=1}^{k} (\lambda^{(i)}_n + \mu^{(i)}_n) q'_n(t) + \sum_{i=1}^{k} \mu^{(i)}_{(0,\ldots,n_i=1,\ldots,0)} q'_{(0,\ldots,n_i=1,\ldots,0)}(t) q'_n(t),
\]

(7.26)
for \( n \in S \setminus \{(0,0,\ldots,0)\} \). A probability distribution \( \bar{q}' \), assuming it exists, is called a QSD if it satisfies

\[
0 = \sum_{i=1}^{k} \lambda^{(i)}_{1}(n_{1},n_{i-1},n_{k}) \bar{q}'_{1}(n_{1},n_{i-1},n_{k}) + \sum_{i=1}^{k} \mu^{(i)}_{1}(n_{1},n_{i+1},n_{k}) \bar{q}'_{1}(n_{1},n_{i+1},n_{k})
- \sum_{i=1}^{k} (\lambda^{(i)}_{1} + \mu^{(i)}_{n}) \bar{q}'_{n} + \sum_{i=1}^{k} \mu^{(i)}_{0} \bar{q}'_{1}(0,\ldots,n_{i-1},n_{k}) - \sum_{i=1}^{k} (\lambda^{(i)}_{1} n + \mu^{(i)}_{n}) \bar{q}'_{n} + \sum_{i=1}^{k} \mu^{(i)}_{0} \bar{q}'_{1}(0,\ldots,n_{i}=1,\ldots,0) \bar{q}'_{n},
\]

(7.27)

where \( \bar{q}'_{n} \geq 0 \) for \( n \in S \setminus \{(0,0,\ldots,0)\} \), \( \bar{q}'_{n} = 0 \) for \( n \notin S \setminus \{(0,0,\ldots,0)\} \) and \( \sum_{n \in S \setminus \{(0,0,\ldots,0)\}} \bar{q}'_{n} = 1 \). The LCD is denoted by \( q' \) and is defined by

\[
q'_{n} = \lim_{t \to +\infty} q'_{n}(t),
\]

(7.28)

where \( q'_{n} \geq 0 \) for \( n \in S \setminus \{(0,0,\ldots,0)\} \), \( q'_{n} = 0 \) for \( n \notin S \setminus \{(0,0,\ldots,0)\} \) and \( \sum_{n \in S \setminus \{(0,0,\ldots,0)\}} q'_{n} = 1 \). The LCD does not depend on time and so is, by definition, a QSD. However, the converse is not necessarily true. For a process with a finite state-space, \( i.e., \ S = \{(n_{1},n_{2},\ldots,n_{k}) : n_{i} = 0,1,\ldots,N_{i}; i = 1,\ldots,k\} \), a unique QSD exists, which is also the unique LCD of the process [33]. However, if the state-space of the process is denumerably infinite, a QSD might not exist, or if it does exist, it may not be unique. In the next section, it is shown that at least one QSD of the type defined by Eq. (7.27) exists for the process \( \{(X_{1}(t),X_{2}(t),\ldots,X_{k}(t)) : t \geq \tilde{t}_{k}\} \) on the state-space \( S = \{(n_{1},n_{2},\ldots,n_{k}) : n_{i} = 0,1,2,\ldots ; i = 1,\ldots,k\} \).

### 7.3.2 Existence of the stationary probability distribution conditional on the event that at least one of the \( k \) clonotypes is present in the repertoire

In this section, it is proved that a QSD, as defined by Eq. (7.27), exists for the multivariate competition process introduced in Section 7.1. As in Section 5.3.2, in
order to achieve this the states of the process are relabelled to obtain a univariate Markov process \( \{Y(t) : t \geq \hat{t}_k\} \) on the state-space \( \tilde{S} = \{0, 1, 2, \ldots\} \). The criteria of Ferrari et al. [47], introduced in Chapter 4, are then used to prove that a QSD exists.

States \((n_1, n_2, \ldots, n_k) \in S\) are mapped to states \(x \in \tilde{S}\) by the function \(g^{(k)} : \mathbb{N}^k \rightarrow \mathbb{N}\) which is defined by

\[
g^{(k)}(n_1, n_2, \ldots, n_k) = \sum_{j=1}^{k} \left( j - 1 + \sum_{i=1}^{j} n_i \right) = x, \tag{7.29}
\]

where \(\left[\frac{x}{y}\right] = 0\) for \(x < y\). This function is known as the \(k\)-degree generalised Cantor pairing function [85]. When \(k = 2\), the function reduces to \(g^{(2)}(n_1, n_2) = x = \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1\), which is the function given by Eq. (5.59). The states \((n_1, n_2, \ldots, n_k) \in S\) are mapped to \(x = 0, 1, 2, \ldots\) by the function defined above in the following order. The absorbing state at \((0, 0, \ldots, 0)\) is first mapped uniquely to \(x = 0\). Then the states in \(S_1'\) (defined by Eq. (7.7)) are mapped, followed by the states in \(S_2'\) and so on. Within the sets \(S_1', S_2', \ldots\) the states are ordered so that \(g^{(k)}(n_1, n_2, \ldots, n_k) < g^{(k)}(n_1', n_2', \ldots, n_k')\) if \(n_k > n_k'\) or if \(n_k = n_k'\) and \(g^{(k-1)}(n_1, n_2, \ldots, n_{k-1}) < g^{(k-1)}(n_1', n_2', \ldots, n_{k-1}')\) [85]. For example, if \(k = 3\) the states are labelled in the following order: \((0, 0, 0), (0, 0, 1), (0, 1, 0), (1, 0, 0), (0, 0, 2), (0, 1, 1), (1, 0, 1), (0, 2, 0), (1, 1, 0), (2, 0, 0)\) and so on.

The function \(g^{(k)}\) defines a one-to-one correspondence between states \((n_1, n_2, \ldots, n_k) \in S\) and \(x \in \tilde{S}\) because \(g^{(k)}\) is a bijective function [85]. Hence, the multivariate competition process \(\{(X_1(t), X_2(t), \ldots, X_k(t)) : t \geq \hat{t}_k\}\) on the state-space \(S = \{(n_1, n_2, \ldots, n_k) : n_i = 0, 1, 2, \ldots ; i = 1, \ldots, k\}\) may be transformed into a univariate Markov process \(\{Y(t) : t \geq \hat{t}_k\}\) on the state-space \(\tilde{S} = \{0, 1, 2, \ldots\}\) using this relation. Therefore, proving that a QSD exists for the multivariate competition process is equivalent of proving that a QSD exists for the univariate Markov process,
which is possible using the criteria of Ferrari et al. [47].

Let

$$R = \inf\{t \geq 0 : \mathcal{Y}(t) = 0\} ,$$

(7.30)

which is the time at which extinction of all \(k\) clonotypes occurs. In Section 7.2 it was shown that the expected time to extinction from all initial states \(n \in S \setminus \{(0,0,\ldots,0)\}\) is finite, as required. The first part of the proof is to show that

$$\lim_{x_0 \to +\infty} \mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_k) = x_0) = 0 \text{ for all } t \geq \tilde{t}_k ,$$

(7.31)

i.e., the mean time to extinction can be made arbitrarily large by taking the initial state of the process, \(x_0\), to be sufficiently far away from the origin. This condition is known as the “asymptotic remoteness” condition. The time until death of a T cell belonging to clonotype 1 is an independent exponential random variable with expected value \(\mu_i^{-1}\). If the initial state of the process is given by \((X_1(\tilde{t}_k), X_2(\tilde{t}_k), \ldots, X_k(\tilde{t}_k)) = (\tilde{n}_1, \tilde{n}_2, \ldots, \tilde{n}_k)\) then prior to extinction of all \(k\) clonotypes occurring, all of the \(\tilde{n}_1\) T cells belonging to clonotype 1 must die. Extinction occurs at the time of death of the last of these \(\tilde{n}_1\) initial cells if none of them has divided and there are no T cells belonging to clonotypes 2, 3, \ldots, \(k\) present, and will occur strictly later otherwise. Hence, for any \(t \geq \tilde{t}_k\),

$$\mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_k) = x_0) \leq (1 - e^{-\mu_i t})^{\tilde{n}_1} \to 0 \text{ as } \tilde{n}_1 \to +\infty ,$$

(7.32)

and, similarly,

$$\mathbb{P}(R < t | \mathcal{Y}(\tilde{t}_k) = x_0) \leq (1 - e^{-\mu_i t})^{\tilde{n}_i} \to 0 \text{ as } \tilde{n}_i \to +\infty ,$$

(7.33)

for \(i = 2, 3, \ldots, k\), and so the “asymptotic remoteness” condition given by Eq. (7.31) holds. This is because relabelling of states defined by Eq. (7.29) orders the states in
such a way that as the initial state, $x_0$, of the process increases, it becomes further away from the absorbing state at $(0,0,\ldots,0)$.

Next, a function $f$ on $\tilde{S}$ is defined with the constants $D_1, D_4, D_5 > 0$, $D_2, D_4, D_6 < +\infty$, where $D_6$ is an integer, which satisfies the conditions (4.13)–(4.17) with

$$q_{n,m}(\Delta t) = \begin{cases} 
\lambda_n^{(i)} & m = (n_1, \ldots, n_i + 1, \ldots, n_k), \\
\mu_n^{(i)} & m = (n_1, \ldots, n_i - 1, \ldots, n_k), \\
-\sum_{i=1}^{k} (\lambda_n^{(i)} + \mu_n^{(i)}) & m = n, \\
o(\Delta t) & \text{otherwise},
\end{cases} \quad (7.34)$$

for $i = 1, \ldots, k$. Hence, the process is conservative and it is also regular from Eq. (7.14), as required. Recall that $g^{(k)}(n_1, n_2, \ldots, n_k) = x$ defines a one-to-one correspondence between states $n = (n_1, n_2, \ldots, n_k) \in S$ and states $x \in \tilde{S}$ and so $x$ and $(n_1, n_2, \ldots, n_k)$ are used interchangeably in what follows (so that $-q_{x,x}$ denotes $-q_{n,n}$ and so on). Now, let $f(x) = n_1 + n_2 + \ldots + n_k$. Then $x \geq f(x)$ for all $x \in \tilde{S}$.

(i) For $x \in \tilde{S}$, the function $f(x) = n_1 + n_2 + \ldots + n_k \geq 0$ and $f(x) \to +\infty$ as $x \to +\infty$, satisfying condition (4.13).

(ii)

$$\sum_{y \neq x} \frac{q_{x,y}}{-q_{x,x}} f(y) - f(x) = \frac{\lambda_n^{(i)} + \ldots + \lambda_n^{(k)} - \mu_n^{(1)} - \ldots - \mu_n^{(k)}}{-q_{x,x}} \leq \frac{\varphi_1 + \ldots + \varphi_k - \mu_1 n_1 - \ldots - \mu_k n_k}{-q_{x,x}}, \quad (7.35)$$

using the bound (7.5) and Eq. (7.34). Thus,

$$\sum_{y \neq x} \frac{q_{x,y}}{-q_{x,x}} f(y) - f(x) < 0 \quad (7.36)$$
when

\[ \varphi_1 + \varphi_2 + \ldots + \varphi_k < \mu_1 n_1 + \ldots + \mu_k n_k \]

\[ \Rightarrow \varphi_1 + \varphi_2 + \ldots + \varphi_k < (n_1 + n_2 + \ldots + n_k) \max(\mu_1, \ldots, \mu_k) \]

\[ \Rightarrow x \geq n_1 + n_2 + \ldots + n_k > \frac{\varphi_1 + \varphi_2 + \ldots + \varphi_k}{\max(\mu_1, \mu_2, \ldots, \mu_k)}. \tag{7.37} \]

Then \( D_1 > 0 \) and an integer \( D_6 < +\infty \) can be found such that

\[ \sum_{y \neq x} \frac{q_{x,y}}{q_{x,x}} f(y) \leq f(x) - D_1 \quad \text{for} \quad x \geq D_6, \tag{7.38} \]

and condition (4.14) is thus satisfied.

(iii) For the multivariate competition process, transitions are only allowed to neigh-
bouring states and so \( n_1 + n_2 + \ldots + n_k \) can only increase or decrease by one
with each transition. Thus, for all values of \( y \) such that \( q_{x,y} > 0 \),

\[ |f(x) - f(y)| \leq 1 \quad \text{for all} \quad x \in \tilde{S}. \tag{7.39} \]

Then condition (4.15) is satisfied by taking \( D_2 = 1 \).

(iv) Now \( x \) is fixed. Then for \( 1 \leq x \leq D_6 - 1 \) the following bound is obtained:

\[ \sum_{y \neq x} q_{x,y} = \lambda^{(1)}_n + \ldots + \lambda^{(k)}_n + \mu^{(1)}_n + \ldots + \mu^{(k)}_n \]

\[ \leq \varphi_1 + \ldots + \varphi_k + \mu_1 n_1 + \ldots + \mu_k n_k \]

\[ \leq \varphi_1 + \ldots + \varphi_k + (n_1 + \ldots + n_k) \max(\mu_1, \ldots, \mu_k) \]

\[ \leq \varphi_1 + \ldots + \varphi_k + (D_6 - 1) \max(\mu_1, \ldots, \mu_k). \tag{7.40} \]

Now, \( D_3 \) is chosen such that \( 0 < \frac{1}{D_3} (\varphi_1 + \ldots + \varphi_k + (D_6 - 1) \max(\mu_1, \ldots, \mu_k)) < 1 \).
and then, for \( z \geq 1 \), define
\[
D_4 = -\frac{1}{z} \log \left( \frac{1}{D_3} (\varphi_1 + \ldots + \varphi_k + (D_6 - 1) \max(\mu_1, \ldots, \mu_k)) \right) > 0. \tag{7.41}
\]
Therefore, \( D_3 e^{-D_4 z} = \varphi_1 + \ldots + \varphi_k + (D_6 - 1) \max(\mu_1, \ldots, \mu_k) \) and hence condition (4.16) holds.

(v) Finally,
\[
-q_{x,x} \geq \mu_1 n_1 + \ldots + \mu_k n_k \geq (n_1 + \ldots + n_k) \min(\mu_1, \ldots, \mu_k) \geq \min(\mu_1, \ldots, \mu_k), \tag{7.42}
\]
for \( x \geq 1 \) and so in order to satisfy condition (4.17), define \( D_5 = \min(\mu_1, \ldots, \mu_k) > 0 \).

Hence, by Lemma 4.3 and Theorem 1.1 of Ferrari et al. [47], a QSD exists for the process \( \{Y(t) : t \geq \tilde{t}_k\} \) on the state-space \( \tilde{S} \). Therefore, it can be concluded that a QSD exists for the process \( \{X_1(t), X_2(t), \ldots, X_k(t) : t \geq \tilde{t}_k\} \) on the state-space \( S \), as the two processes are equivalent. However, nothing can be concluded about the uniqueness of the QSD as the criterion used in Section 4.1.2 applies only to univariate birth and death processes.

### 7.3.3 The stationary probability distribution of the process conditional on the event that all \( k \) clonotypes are present in the repertoire

Recall that \( \mathcal{A} = \{(n_1, n_2, \ldots, n_k) : n_i = 0 \text{ for all least one } i \in \{1, 2, \ldots, k\}\} \) defines the absorbing set of the process. Now, let \( p_{\mathcal{A}}(t) \) be the probability that the process
CHAPTER 7. MANY COMPETING CLONOTYPES

is not in set $\mathcal{A}$ at time $t$. Then for all $\mathbf{n} \in \mathcal{S} \setminus \mathcal{A}$, define

$$q_n(t) = \frac{p_n(t)}{p_\mathcal{A}(t)},$$

(7.43)

which is the probability that the process is in state $\mathbf{n}$ at time $t$, conditional on the event that the absorbing set has not been reached. For all $t \geq \tilde{t}_k$, $q_n(t) \geq 0$ for $\mathbf{n} \in \mathcal{S} \setminus \mathcal{A}$, $q_n(t) = 0$ for $\mathbf{n} \notin \mathcal{S} \setminus \mathcal{A}$ and $\sum_{\mathbf{n} \in \mathcal{S} \setminus \mathcal{A}} q_n(t) = 1$. From Eq. (7.43),

$$\frac{dq_n(t)}{dt} = \frac{1}{p_\mathcal{A}(t)} \frac{dp_n(t)}{dt} - \frac{p_n(t)}{(p_\mathcal{A}(t))^2} \frac{dp_\mathcal{A}(t)}{dt}. $$

(7.44)

By the law of total probability,

$$p_\mathcal{A}(t) = 1 - \sum_{\mathbf{n} \in \mathcal{A}} p_n(t).$$

(7.45)

Summing Eq. (7.24) over all $\mathbf{n} \in \mathcal{A}$ results in

$$\frac{d}{dt} \sum_{\mathbf{n} \in \mathcal{A}} p_n(t) = \sum_{i=1}^{k} \mu_i \sum_{\mathbf{m} \in \mathcal{S}_i^*} p_m(t),$$

(7.46)

where $\mathcal{S}_i^* = \{(m_1, \ldots, m_k) : m_i = 1 \text{ and } m_j > 0 \text{ for all } j \neq i\}$, so that

$$\frac{dp_\mathcal{A}(t)}{dt} = - \sum_{i=1}^{k} \mu_i \sum_{\mathbf{m} \in \mathcal{S}_i^*} p_m(t).$$

(7.47)

Hence, the system of differential equations satisfied by $q_n(t)$ is

$$\frac{dq_n(t)}{dt} = \sum_{i=1}^{k} \lambda_{(n_1, \ldots, n_{i-1}, n_i, \ldots, n_k)}^{(n)} q_{(n_1, \ldots, n_{i-1}, n_i, \ldots, n_k)}(t) + \sum_{i=1}^{k} \mu_{(n_1, \ldots, n_{i+1}, \ldots, n_k)}^{(n)} q_{(n_1, \ldots, n_{i+1}, \ldots, n_k)}(t)$$

$$- \sum_{i=1}^{k} (\lambda_{n_i}^{(n)} + \mu_{n_i}^{(n)}) q_n(t) + \sum_{i=1}^{k} \mu_i q_n(t) \sum_{\mathbf{m} \in \mathcal{S}_i^*} q_m(t).$$

(7.48)
A probability distribution \( \bar{q} \), assuming it exists, is called a QSD if it satisfies

\[
0 = \sum_{i=1}^{k} \lambda^{(i)}(n_1, \ldots, n_{i-1}, \ldots, n_k) \bar{q}(n_1, \ldots, n_{i-1}, \ldots, n_k) + \sum_{i=1}^{k} \mu^{(i)}(n_1, \ldots, n_{i+1}, \ldots, n_k) \bar{q}(n_1, \ldots, n_{i+1}, \ldots, n_k) \\
- \sum_{i=1}^{k} (\lambda^{(i)} + \mu^{(i)}(n_i) - \sum_{m \in S^*_i} \bar{q}_m),
\]

(7.49)

where \( \bar{q}_n \geq 0 \) for \( n \in S \setminus A \), \( \bar{q}_n = 0 \) for \( n \notin S \setminus A \) and \( \sum_{n \in S \setminus A} \bar{q}_n = 1 \). The LCD of the process is denoted by \( q \) and is defined by

\[
q_n = \lim_{t \to +\infty} q_n(t),
\]

(7.50)

where \( q_n \geq 0 \) for \( n \in S \setminus A \), \( q_n = 0 \) for \( n \notin S \setminus A \) and \( \sum_{n \in S \setminus A} q_n = 1 \). The LCD does not depend on time and so it is, by definition, a QSD. However, the converse is not necessarily true. For a process with a finite state-space, \( i.e., S = \{(n_1, n_2, \ldots, n_k) : n_i = 0, 1, 2, \ldots, N_i; i = 1, \ldots, k \} \) a unique QSD exists, which is also the unique LCD of the process [33]. However, if the state-space of the process is denumerably infinite, a QSD might not exist, or if it does exist, it might not be unique. In the next section, it is conjectured that at least one QSD of the type defined by Eq. (7.49) exists for the process \( \{(X_1(t), X_2(t), \ldots, X_k(t)) : t \geq \tilde{t}_k \} \) on the state-space \( S = \{(n_1, n_2, \ldots, n_k) : n_i = 0, 1, 2, \ldots; i = 1, \ldots, k \} \).

### 7.3.4 Existence of the stationary probability distribution conditional on the event that all \( k \) clonotypes are present in the repertoire

In this section it is conjectured that a QSD (as defined by Eq. (7.49)) exists for the multivariate competition process introduced in Section 7.1 by extending the method introduced in Section 5.3.4 to \( k \geq 2 \). As in Section 5.3.4, it is not possible to relabel
CHAPTER 7. MANY COMPETING CLONOTYPES

the states using a one-to-one mapping to form a univariate Markov process in such a way that the “asymptotic remoteness” condition (7.31) holds, because there are an infinite number of states that are adjacent to the absorbing set. Recall that in Section 7.2 the multivariate competition process was bounded by a univariate birth and death process in the sense that the univariate process moves to the origin at a slower rate than the multivariate competition process. A similar approach is taken here. Eq. (5.88) is generalised to $k \geq 2$ by defining the following sets which divide the state-space of the multivariate competition process, $S$, into disjoint subsets:

$$S_j = \{ (n_1, n_2, \ldots, n_k) : n_i = j \text{ for some } i = 1, \ldots, k \text{ and } n_i \geq j \text{ for all } i = 1, 2, \ldots, k \}$$

(7.51)

for $j \geq 0$. These sets are disjoint because if $j < j'$, then for states in $S_{j'}$, $n_i \geq j'$ for $i = 1, 2, \ldots, k$. On the other hand, for states in $S_j$, $n_i = j < j'$ for some $i = 1, 2, \ldots, k$. Therefore $S_j \cap S_{j'} = \emptyset$. A similar argument holds for $j > j'$.

Here, $S_0$ corresponds to the absorbing set and with each transition the process either stays in the same set or moves from set $S_j$ to either $S_{j-1}$ or $S_{j+1}$. These sets correspond to the states of the univariate birth and death process that will be defined here. In a similar way to in Section 5.3.4, the transitions that may occur are now considered, where $r_n = \sum_{i=1}^{k} (\lambda_n^{(i)} + \mu_n^{(i)})$ for notational convenience:

1. States belonging to the set $\{ n : n_i = j \text{ for exactly one value of } i \in \{1, \ldots, k\} \text{ and } n_l > j \text{ for } l \in \{1, \ldots, k\} \setminus \{i\} \}$. The following transitions may occur:

   (i) with probability $\sum_{i \neq i}^{k} (\lambda_n^{(i)} + \mu_n^{(i)}) / r_n$ the process stays in $S_j$,

   (ii) with probability $\lambda_n^{(i)} / r_n$ the process moves to a state in $S_{j+1}$,

   (iii) with probability $\mu_n^{(i)} / r_n$ the process moves to a state in $S_{j-1}$.

2. States belonging to the set $\{ n : n_i = j \text{ for more than one } i \in \{1, \ldots, k\} \text{ and } n_l > j \text{ for } l \neq i \}$. The following transitions may occur:
(i) with probability \( \frac{\sum_i \lambda_n^{(i)} + \sum_l \lambda_n^{(l)} + \sum_l \mu_n^{(l)}}{r_n} \) the process stays in \( S_j \),

(ii) with probability \( \sum_i \mu_n^{(i)}/r_n \) the process moves to a state in \( S_{j-1} \).

Hence, the birth and death process \( \{Z(t) : t \geq \tilde{t}_k\} \) on the state-space \( \{S_0, S_1, S_2, \ldots\} \) with the birth and death rates

\[
\lambda_j = \max(\varphi_1, \varphi_2, \ldots, \varphi_k), \quad (7.52)
\]

\[
\mu_j = j \min(\mu_1, \mu_2, \ldots, \mu_k), \quad (7.53)
\]

for \( j \geq 1 \) and \( \lambda_0 = \mu_0 = 0 \), is a univariate birth and death process which moves towards the absorbing set at a slower rate than the multivariate competition process.

Let

\[
\pi_1 = 1 \quad \text{and} \quad \pi_j = \frac{\lambda_1 \lambda_2 \ldots \lambda_{j-1}}{\mu_2 \mu_3 \ldots \mu_j}. \quad (7.54)
\]

The process \( \{Z(t) : t \geq \tilde{t}_k\} \) is regular because

\[
\sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} \sum_{j=1}^{n} \pi_j > \sum_{n=1}^{+\infty} \frac{1}{\lambda_n \pi_n} = \sum_{n=1}^{+\infty} \frac{1}{\lambda_n} = \sum_{n=1}^{+\infty} \frac{1}{\max(\varphi_1, \varphi_2, \ldots, \varphi_k)} = +\infty. \quad (7.55)
\]

Then, if the series

\[
\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \quad (7.56)
\]

diverges, the univariate process reaches the state \( S_0 \) with certainty. For the birth
and death rates (7.52)–(7.53),

\[ \sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} = \sum_{j=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_j}{\lambda_1 \lambda_2 \ldots \lambda_j} = \frac{j! [\min(\mu_1, \mu_2, \ldots, \mu_k)]^{j-1}}{[\max(\varphi_1, \varphi_2, \ldots, \varphi_k)]^j}. \] (7.57)

Let

\[ a_j = \frac{j! [\min(\mu_1, \mu_2, \ldots, \mu_k)]^{j-1}}{[\max(\varphi_1, \varphi_2, \ldots, \varphi_k)]^j}, \] (7.58)

so that

\[ \frac{a_{j+1}}{a_j} = \frac{(j+1) \min(\mu_1, \mu_2, \ldots, \mu_k)}{\max(\varphi_1, \varphi_2, \ldots, \varphi_k)} \rightarrow +\infty \text{ as } j \rightarrow +\infty. \] (7.59)

Hence, the series \( \sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \) diverges by the ratio test. Therefore, the process \( \{Z(t) : t \geq \tilde{t}_k\} \) reaches \( S_0 \) with certainty. Since this process moves towards the absorbing set at a slower rate than the multivariate competition process, it is concluded that the multivariate competition process reaches the absorbing set with probability one [70].

For the birth and death rates (7.52)–(7.53),

\[ \lambda_j \rightarrow \max(\varphi_1, \varphi_2, \ldots, \varphi_k) \text{ and } \mu_j \rightarrow +\infty \text{ as } j \rightarrow +\infty, \] (7.60)

and so, by Theorem 5.3 of van Doorn [131], \( \sigma > 0 \) for this process, and hence the decay parameter of the process, \( \alpha \), is also positive (see Section 4.1.1, Method 1). Therefore, at least one QSD exists for the process \( \{Z(t) : t \geq \tilde{t}_k\} \). This QSD is not
unique because

\[
\sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \sum_{n=j+1}^{+\infty} \pi_n > \sum_{j=1}^{+\infty} \frac{1}{\lambda_j \pi_j} \pi_{j+1} \\
= \sum_{j=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_j \lambda_1 \lambda_2 \ldots \lambda_j}{\lambda_1 \lambda_2 \ldots \lambda_j \mu_2 \mu_3 \ldots \mu_{j+1}} \\
= \sum_{j=1}^{+\infty} \frac{1}{\mu_{j+1}} \\
= \frac{1}{\min(\mu_1, \mu_2, \ldots, \mu_k)} \sum_{j=1}^{+\infty} \frac{1}{j+1} = +\infty, \quad (7.61)
\]

and so there exists a one-parameter family of QSDs [132].

Since the multivariate competition process \( \{(X_1(t), X_2(t), \ldots, X_k(t)) : t \geq \tilde{t}_k\} \) is “better behaved” than the birth and death process \( \{Z(t) : t \geq \tilde{t}_k\} \), in the sense that the multivariate process moves towards the absorbing set at a faster rate, it is conjectured that the existence of a QSD for \( \{Z(t) : t \geq \tilde{t}_k\} \) implies that a QSD also exists for the multivariate competition process. For a univariate Markov process, the necessary and sufficient conditions for the existence of a QSD are that eventual absorption occurs with certainty and that the rate of absorption is exponential [47].

If these are also the necessary and sufficient conditions for the existence of a QSD for a multivariate process, the properties of the univariate process \( \{Z(t) : t \geq \tilde{t}_k\} \) would imply existence of a QSD for the multivariate competition process also.

There has been little previous work on the existence of a QSD for multivariate Markov processes with infinite state-spaces. Of course, in reality, there is an upper bound on the number of T cells that can belong to each clonotype (i.e., it cannot be larger than the number of cells in an adult human), which is denoted by \( N \), resulting in a finite state-space process. For such processes, there exists a unique QSD, which is also the unique LCD of the process [33].
7.4 An exact numerical simulation for $N_C$ clonotypes

An exact numerical simulation of the dynamics of the full T cell repertoire consisting of $N_C$ clonotypes may be carried out without the need for any type of mean field approximation using a Gillespie algorithm \[59, 60\], which was described for a univariate birth and death process in Section 2.2.5. The simulation for the full repertoire is carried out as follows:

1. The initial state of the system is specified. There are $N_C$ T cell clonotypes in the repertoire, each consisting of an initial number of cells, and $|Q|$ APPs. The connections between these two sets (as illustrated in Fig. 3.1) are defined in terms of an $N_C \times |Q|$ matrix, where an entry of 1 in the $i$th column and $j$th row indicates that T cells of clonotype $i$ are able to receive a survival signal from APP $j$, and an entry of 0 means that they are not.

2. The time at which the next transition occurs is obtained by generating a random number, $T_n$, from an exponential distribution with mean $1/r_n$, where $n = (n_1, n_2, \ldots, n_{N_C})$ is the state of the process at the current time, $t$, and $r_n = \sum_{i=1}^{N_C} (\lambda^{(i)}_n + \mu^{(i)}_n)$.

3. The birth and death rates for each clonotype, $i = 1, 2, \ldots, N_C$, are calculated according to the equations

$$\lambda^{(i)}_n = \lambda^{(i)} n_i = n_i \sum_{q \in Q} \frac{\gamma}{n_q}, \quad (7.62)$$

$$\mu^{(i)}_n = \mu^{(i)} n_i. \quad (7.63)$$

Then the probability of a T cell belonging to clonotype $i$ dividing at the next transition is $\lambda^{(i)}_n / r_n$ and the probability of a T cell belonging to clonotype $i$
dying is $\mu_n^{(i)}/r_n$. The interval $[0, 1]$ is divided into $2N_C$ sub-intervals of lengths $\lambda_n^{(1)}/r_n, \lambda_n^{(2)}/r_n, \ldots, \lambda_n^{(N_C)}/r_n, \mu_n^{(1)}/r_n, \mu_n^{(2)}/r_n, \ldots, \mu_n^{(N_C)}/r_n$. Which event happens at the next transition is determined according to these probabilities by generating a random number from a uniform distribution on the interval $[0, 1]$. For example, if the random number lies in the sub-interval of length $\mu_n^{(i)}/r_n$, a T cell of clonotype $i$ dies with the next transition. The state of the process is then updated to take account of this transition.

4. The time of the simulation is updated to $t + T_n$.

5. Steps 2 – 4 are repeated until the absorbing state at the origin is reached, or until the time of the simulation exceeds a predetermined maximum value.

### 7.4.1 Simulations of a repertoire where the mean field assumption holds for all pairs of clonotypes and a repertoire where it does not

The procedure described above is first used to simulate a naïve T cell repertoire where the condition $|Q_i \cap Q_j| \ll |Q_i|$ holds for all pairs of clonotypes. This repertoire initially consists of $N_C = 15$ clonotypes, each composed of 50 cells. The total number of APPs is $|Q| = 135$, each T cell clonotype is able to receive survival signals from 10 APPs and the connections between the set of T cell clonotypes and the set of APPs are defined in such a way that each clonotype competes with T cells belonging to other clonotypes for access to 2 of its 10 APPs, while the other 8 APPs are not shared. The intersection between any pair of clonotypes consists of at most one APP, i.e., $|Q_i \cap Q_j| \leq 1$. For convenience, the competition structure is exactly the same for all clonotypes, which means that they each exhibit similar dynamics. The number of T cells belonging to a typical clonotype from this repertoire is plotted as a
function of time in Fig. 7.1, where the data have been averaged over 10000 individual realisations of the process. The parameter $\gamma$ is given the value 1 and so time is measured in units of $\gamma^{-1}$. Also, $\mu_i = 0.1$ for all clonotypes in the repertoire. For these values of the parameters, the mean time to extinction is long ($\tau_{50} \simeq 8 \times 10^{36}$ in units of $\gamma^{-1}$) and the number of T cells belonging to this typical clonotype quickly reaches a steady state level, which corresponds to the mean of the LCD for the model of a single T cell clonotype introduced in Chapter 3. If the per cell death rate is increased to $\mu_i = 1$ for all clonotypes in the repertoire, the mean time until extinction occurs decreases to around $\tau_{50} \simeq 2500$ in units of $\gamma^{-1}$ for a clonotype with $\nu \ll 1$. This is shown in Fig. 7.2 where the mean number of cells belonging to a clonotype (averaged over 10000 realisations) decreases with time, as the probability of extinction having occurred increases.

Next, the repertoire described above is modified so that there exists a pair of clonotypes, denoted by $i$ and $j$, such that $|Q_i \cap Q_j| \ll |Q_i|$ but where $|Q_i \cap Q_k| \ll |Q_i|$ and $|Q_j \cap Q_k| \ll |Q_j|$ for all other clonotypes $k \neq i, j$ in the repertoire. The connections between the sets of APPs and T cell clonotypes are defined such that, as before,
Figure 7.2: The number of T cells belonging to a particular clonotype as a function of time for a repertoire where $|Q_i \cap Q_j| \ll |Q_i|$ for all pairs of clonotypes, averaged over 10000 individual realisations with $\gamma = 1$ and $\mu_i = 1$ for all clonotypes. Initially, there are 50 T cells belonging to each clonotype, but this number quickly declines.

Each clonotype is able to receive survival signals from 10 APPs. However, in this modified repertoire, clonotypes $i$ and $j$ compete with each other for access to 6 of their 10 APPs. Interactions between all other pairs of clonotypes remain as in the repertoire described above, but now $|Q| = 130$. Also, $\gamma = 1$ and $\mu_i = 0.1$ for all T cell clonotypes. The number of T cells belonging to clonotypes other than $i$ and $j$ remains the same as in the first simulation (see the number of T cells belonging to clonotype $k$ in Fig. 7.3). However, the number of T cells belonging to clonotypes $i$ and $j$ is reduced due to the increased competition, as expected. In this case, the large overlap between the sets $Q_i$ and $Q_j$ means that this pair behaves differently from the rest of the repertoire and when modelling the number of T cells belonging to one of these clonotypes, the influence of the other cannot be included as part of the general background of competition under the mean field approximation. Hence, the model introduced in Chapter 3 is invalid for this pair of clonotypes and the model introduced in Chapter 5 is needed.
7.4.2 Simulations of a randomly generated T cell repertoire

In the simulations of the full T cell repertoire described above and illustrated in Figs. 7.1–7.3, the connections between the set of T cell clonotypes, \( \mathcal{C} \), and the set of APPs, \( \mathcal{Q} \), were specified by hand so that the repertoire possessed a particular competition structure \( e.g. \), for the simulations illustrated in Figs. 7.1–7.2, \( |\mathcal{Q}_i \cap \mathcal{Q}_j| \ll |\mathcal{Q}_i| \) for all \( i \neq j \). In the simulations presented in this section, the connections between the sets \( \mathcal{C} \) and \( \mathcal{Q} \) are assigned randomly, so that no assumptions regarding the competition structure of the repertoire are made. Recall that \( p_i \) is the probability that T cells belonging to clonotype \( i \) are able to receive survival signals from an APP chosen at random from the set of all APPs, \( i.e., \ p_i = \mathbb{P}(q \in \mathcal{Q}_i) \). For simplicity, in what follows, \( p_i \equiv p \) is assumed to be the same for all clonotypes. Then, for each clonotype and APP pair, a random number is generated from a uniform distribution on the interval \([0, 1]\). If this number lies in the interval \([0, p]\) then the T cell clonotype is able to receive survival signals from this APP, while if the random number lies in the interval \((p, 1]\) it is not.
Thus, the simulation requires the specification of the parameters $|Q|$, $p$, $\gamma$ and $\mu_i$, the initial value of $N_C$, and the initial number of cells belonging to each clonotype. The values of some of these parameters are known e.g., $N_C = 10^7$ [6] and the varying estimates of $\mu_i$ were discussed in Section 3.2.2. The parameters $p$ and $|Q|$ may be computed using the combinatoric model presented in Section 4 of [122]. The parameter $\gamma$ has not yet been experimentally measured and reliable estimates of its value will be needed for the simulation algorithm to provide predictions of the timescales involved in clonotype extinction and loss of repertoire diversity.

The simulated repertoire initially consists of $N_C = 50$ clonotypes, each composed of 50 cells. The total number of APPs is $|Q| = 500$, $p = 0.01$ and $\mu_i = 0.1$ for all clonotypes. As above, $\gamma = 1$ so that time is measured in units of $\gamma^{-1}$. The number of T cells is under homeostatic control regulated by competition for limited survival signals from APPs which means that the total number of T cells in the repertoire, $N_C\langle n \rangle$ remains approximately constant as a function of time, as shown in Fig. 7.4. It can also be seen that if $\gamma^{-1}$ is 1 day/month then $\mu_i^{-1}$ is 10 days/months and the time to reach the steady state number of T cells is approximately 50 days/months. Fig. 7.5 shows the number of T cell clonotypes that are still present in the repertoire as a function of time, averaged over 200 individual realisations. As expected, $N_C$ decreases with time as clonotypes become extinct from the repertoire.

In previous chapters, the mean niche overlap $\nu_i$ was treated as a fixed parameter. For a particular T cell clonotype $i$, $\nu_i$ depends on the clonotype’s TCR and also on the existing peripheral repertoire. Therefore, as clonotypes become extinct from the repertoire, $\nu_i$ may change with time. In the simulations presented in this section, $\nu_i$ is not an input parameter of the model as no mean field approximation is necessary. However, this parameter may be calculated for each clonotype at each time point of the simulation. In Fig. 7.6, the repertoire average mean niche overlap, which is
Figure 7.4: The total number of T cells in the repertoire, $N_C(n)$, as a function of time averaged over 200 realisations with $|\mathcal{Q}| = 500$, $p = 0.01$, $\gamma = 1$ and $\mu_i = 0.1$ for all clonotypes.

Figure 7.5: $N_C$ as a function of time averaged over 200 realisations with $|\mathcal{Q}| = 500$, $p = 0.01$, $\gamma = 1$ and $\mu_i = 0.1$ for all clonotypes.
defined by
\[ \langle \nu \rangle = \frac{1}{N_C} \sum_{i=1}^{N_C} \nu_i, \quad (7.64) \]
is plotted as a function of time, where the data has been averaged over 200 realisations. In Fig. 7.7, the mean niche overlap value of a clonotype at the time when it becomes extinct from the repertoire is plotted for all extinction events that occur over the 200 realisations of the process. The solid line shows \( \langle \nu \rangle \) as a function of time. It can be seen that most clonotypes which become extinct have higher than average values of \( \nu_i \). This is because such clonotypes have a shorter mean times until extinction compared to clonotypes with lower \( \nu_i \) values, which is the basis of the selection mechanism described in Section 3.2.2. There are several points on the horizontal axis which represent clonotypes with \( \nu_i = 0 \) at the time when they become extinct. The majority of these points correspond to those T cell clonotypes which, due to the random nature of the connections between the set of APPs and the set of all T cell clonotypes, do not receive survival signals from any APPs in \( Q \), i.e., \( |Q_i| = 0 \) and so quickly become extinct from the repertoire. For these clonotypes, \( \nu_i = 0 \) by definition. The remainder of the points on the horizontal axis correspond to clonotypes for which \( |Q_i| > 0 \) but \( \nu_i = 0 \) because the given clonotype does not compete with any others in the repertoire and extinction takes place as part of a random event.

In the models presented in Chapters 3 and 5, the average clonotype size over the naïve repertoire, \( \langle n \rangle \), is treated as a fixed input parameter, whereas it is actually a time-dependent quantity and should be computed in a self-consistent way. However, in the special case \( \nu \ll 1 \) discussed in Chapters 3–4 and the case \( \nu_{12} \ll 1 \), \( \nu_1 \ll 1 \), \( \nu_2 \ll 1 \) introduced in Chapter 6, the birth rates of the process do not depend on \( \langle n \rangle \) and, in view of the bounds given by Eqs. (3.23), (3.33), (3.34), (5.30) and (7.5), taking \( \langle n \rangle \) as a fixed parameter should not affect the properties of the model such as guaranteed clonotype extinction within finite time and existence of a QSD. Moreover,
Figure 7.6: $\langle \nu \rangle$ as a function of time averaged over 200 realisations with $|\mathcal{Q}| = 500$, $p = 0.01$, $\gamma = 1$ and $\mu_i = 0.1$ for all clonotypes.

Figure 7.7: The points indicate the mean niche overlap value of a clonotype at the time it becomes extinct from the repertoire for all extinction events occurring over the 200 realisations with $|\mathcal{Q}| = 500$, $p = 0.01$, $\gamma = 1$ and $\mu_i = 0.1$ for all clonotypes. The solid line shows $\langle \nu \rangle$ as a function of time.
results from simulations of the full T cell repertoire without the need for any kind of mean field approximation (obtained using the Gillespie algorithm outlined above) show that the value of \( \langle n \rangle \) quickly reaches a steady state value, as shown in Fig. 7.8. Therefore, treating \( \langle n \rangle \) as a fixed parameter is expected to provide a reasonable approximation to the true behaviour of the system. However, as more clonotypes die out, the available resources are shared between fewer clonotypes and so \( \langle n \rangle \) will gradually increase. The input of new clonotypes from the thymus (which is not included in any of the simulations presented in this chapter) is likely to prevent this effect.

Simpson’s diversity index was introduced in Section 3.2.4 as a measure of the evenness of the number of T cells belonging to different clonotypes and is defined by

\[
D_S = \left( \frac{1}{N_C \langle n \rangle^2} \sum_{i=1}^{N_C} n_i^2 \right)^{-1}.
\] (7.65)

Fig. 7.9 shows Simpson’s diversity index as a function of time. Initially, all clonotypes are composed of 50 T cells and so \( D_S = 1 \). After an initial decrease, \( D_S \) slowly increases as \( \langle \nu \rangle \) decreases, because low values of \( \nu \) are associated with higher values of \( D_S \), as shown in Fig. 3.11.

Finally, a more realistic repertoire with a larger initial number of T cells clonotypes and APPs was simulated using the Gillespie algorithm. The initial size of the repertoire is limited to \( N_C = 1000 \) and \( |Q| = 2000 \) by the available memory of the desktop computer upon which the simulation was run, although it should be possible to increase these values with the use of a more powerful computer. Hence, the simulated repertoire initially consists of 1000 clonotypes, each composed of 50 cells. The total number of APPs is \( |Q| = 2000 \), \( p = 0.01 \) and \( \mu_i = 0.1 \) for all clonotypes. This means that \( \mu_i^{-1} \), the mean lifespan of a naïve T cell, is 10 units of time. Estimates of the parameter \( \gamma \) are currently unknown and so in the plots
Figure 7.8: $\langle n \rangle$ as a function of time averaged over 200 realisations with $|Q| = 500$, $p = 0.01$, $\gamma = 1$, $\mu_i = 0.1$ for all clonotypes.

Figure 7.9: $D_S$ as a function of time averaged over 200 realisations with $|Q| = 500$, $p = 0.01$, $\gamma = 1$, $\mu_i = 0.1$ for all clonotypes.
below, results for various values of $\gamma$ are shown ($\gamma = 0.01, 0.1, 1$ corresponding to $\varphi = \gamma p|Q| = 0.2, 2, 20$ respectively).

Fig. 7.10 shows the number of clonotypes present in the repertoire as a function of time for single realisations of the process, each with a different value of the parameter $\gamma$. It can be seen that clonotypes survive for longer in the repertoire for higher values of the parameter $\gamma$, as this corresponds to a greater rate of survival signals from the APPs presenting self-peptides. For $\gamma = 0.01$, all 1000 clonotypes are extinct from the repertoire by $t = 405$, while for $\gamma = 0.1$ and $\gamma = 1$ some clonotypes survive in the repertoire for the whole time of the simulation ($t=1000$). The results indicate that if the time units are years (so that $\mu_i^{-1} = 10$ years [140]), a large proportion of the initial T cell clonotypes can be maintained over the lifetime of an individual, at least for $\gamma = 0.1$ and $\gamma = 1$. However, if $\mu_i^{-1}$ is of the order of a few weeks [15], export of new clonotypes from the thymus will be needed in order to maintain a diverse T cell repertoire. Nevertheless, reliable estimates of $\gamma$ are needed in order to make better predictions.

![Figure 7.10: $N_C$ as a function of time for single realisations of the process with $|Q| = 2000$, $p = 0.01$, $\mu_i = 0.1$ for all clonotypes and $\gamma = 0.01, 0.1, 1$.](image)

Fig. 7.11 shows the distribution of the number of T cell clonotypes in the repertoire
that receive survival signals from an APP at several different timepoints during the simulation for a repertoire where $|Q| = 2000$, $N_C = 1000$ initially, $\gamma = 1$, $p = 0.01$ and $\mu_i = 0.1$ for all clonotypes. At the beginning of the simulation the distribution is wide and the most common number of T cell clonotypes that are able to receive survival signals from an APP is 10. As time increases, the distribution becomes progressively narrower and at $t = 1000$ the most common number of T cell clonotypes that are able to receive a survival signal from an APP is 3. This illustrates how, over time, competition for survival signals and clonotype extinction results in a reduction of the overlap in the coverage of APP space. As shown in Fig. 7.12, this happens more rapidly for lower values of the parameter $\gamma$ because the level of

Figure 7.11: The distribution of the number of T cell clonotypes in the repertoire that are able to receive survival signals from an APP at different timepoints of the simulation where $N_C = 1000$ initially, $|Q| = 2000$, $\gamma = 1$, $p = 0.01$ and $\mu_i = 0.1$ for all T cell clonotypes.
available survival signals is lower and so there is more competition. Figures 7.13–

![Graphs showing the distribution of the number of T cell clonotypes in the repertoire that are able to receive survival signals from an APP at different timepoints of the simulation.](image)

Figure 7.12: The distribution of the number of T cell clonotypes in the repertoire that are able to receive survival signals from an APP at different timepoints of the simulation where $N_C = 1000$ initially, $|Q| = 2000$, $\gamma = 0.1$, $p = 0.01$ and $\mu_i = 0.1$ for all T cell clonotypes.

7.14 show the distribution of the values of the parameter $\nu_i$ for all clonotypes in the repertoire at several different timepoints of the simulation. It can be seen that as time increases, the distribution shifts towards lower values of $\nu_i$ as clonotypes become extinct from the repertoire.

### 7.5 Discussion

In this chapter, a Gillespie algorithm has been described which allows a simulation of the full T cell repertoire to be performed without the need for any type of mean
Figure 7.13: The distribution of $\nu_i$ at different timepoints of the simulation for a repertoire where $N_C = 1000$ initially, $|Q| = 2000$, $\gamma = 0.1$, $p = 0.01$ and $\mu_i = 0.1$ for all T cell clonotypes.

Field assumptions regarding the nature of the competition for APPs between different clonotypes. The models presented in previous chapters represent an approximation to this full model, in that to derive the birth rates, mean field approximations are necessary and the parameters $\langle n \rangle$ and $\nu_i$ are treated as fixed parameters, when in actual fact they depend on time. However, these simplified models are needed to enable an understanding of the basic principles of the system and so that analytical results may be obtained. Indeed, it has been shown in this chapter that several properties of the univariate and bivariate models presented in Chapters 3–6, such as guaranteed extinction within a finite time and existence of a QSD, also hold for the multivariate competition process for $k$ competing clonotypes where $k = 1, 2, \ldots$. 
Figure 7.14: The distribution of $\nu_i$ at different timepoints of the simulation for a repertoire where $N_C = 1000$ initially, $|Q| = 2000$, $\gamma = 0.01$, $p = 0.01$ and $\mu_i = 0.1$ for all T cell clonotypes.

The relabelling method introduced in Section 7.3.2 provides for the first time a general method of proving the existence of a QSD for a multivariate competition process and may be widely applied to processes which have an absorbing state at the origin and where the remaining states form a transient communicating class. If this QSD defines the initial distribution of the process, then the initial distribution is also the LCD. However, nothing can be said about the existence of an LCD in the infinite state-space case for the biologically realistic initial condition where the initial probability distribution of the process has all its mass at one state $(\tilde{n}_1, \tilde{n}_2, \ldots, \tilde{n}_k)$.

The simulation of the full T cell repertoire should prove to be a useful tool in the analysis of how the repertoire is shaped in the periphery over time by homeostatic
mechanisms. This is particularly important because direct experimental analysis of the human T cell repertoire is difficult, partly due to the limited sample sizes of cells that can be obtained [137, 136]. It has been shown in this chapter that this full model can be used to obtain estimates of quantities such as the time until a given proportion of the clonotypes present in the repertoire become extinct and can show how competition for APPs is reduced over time leading to the elimination of unnecessary overlap in the repertoire. However, more reliable estimates of the parameters of the system are needed in order to make better quantitative predictions.

The full simulation procedure may also be used to model more complex and realistic situations than the one considered here. For example, it is possible to include the addition to the naïve repertoire of new T cell clonotypes from the thymus and also new APPs could enter the repertoire at a specified time to represent the entry of foreign antigen into the system. Also, the parameter \( \gamma \) which denotes the rate of survival signals emanating from an APP could be specified so that it varies between APPs. The parameters \( \gamma \) and \( \mu_i \) could also become time-dependent if required. Currently, it is assumed that the probability of a T cell clonotype receiving a survival signal from an APP chosen at random from \( Q \), denoted by \( p \), is the same for all clonotypes. The model could be extended so that \( p \) varies between different clonotypes, for example using the combinatoric model described in Section 3.3 of [122]. It is well known that cytokines, in particular IL-7, are important in the process of naïve T cell homeostasis [117]. However, these effects are excluded from the models described in this thesis. The simulation algorithm presented in this chapter could be extended to include cytokine signalling and, in this way, the effect of both TCR-specific and non-TCR-specific signals on the repertoire could be compared.
Chapter 8

Concluding Remarks

In this thesis, T cell homeostasis and TCR repertoire maintenance have been studied by means of a stochastic model of T cell death and proliferation, based on competition for survival signals from APPs composed of self-peptides. The aim of the study was to provide a quantitative approach to answering immunological questions associated with this process. For example, questions such as how does T cell lifespan impact on T cell homeostasis, how does competition for homeostatic proliferation signals from APPs presenting self-peptides shape the T cell repertoire in the periphery, what are the timescales for the failure of homeostatic mechanisms, and what are the key parameters that govern this system, have begun to be addressed.

This model differs from previous deterministic approaches [36, 37] in that it allows the calculation of both the probability of clonotype extinction and the mean time until extinction given the initial conditions. This is necessary as it has been observed that T cell repertoire diversity declines with age as clonotypes become extinct, causing gaps to appear in the repertoire [146]. Also, the number of T cells belonging to a particular clonotype may be small, in which case random fluctuations in clonotype sizes are important. Indeed, this model has been used by others, along with experimental data on cell turnover for an individual at age 20, to estimate that the
mean time until extinction for a clonotype initially composed of 1000 cells is 22 years [49]. Stochastic models have been used to study T cell repertoire diversity before. For example, Ciup{\v{e}} et al. [27] propose a stochastic model of T cell homeostasis including both TCR-specific and TCR-non-specific resources. However, an important difference between their model and the one presented here is that in [27], competition for TCR-specific resources between different clonotypes is not included, while in the model presented in this thesis it has been shown that this competition is important in optimising the coverage of APP space to avoid unnecessary overlap. Another stochastic model is that of Dowling and Hodgkin [40] which, although very different to the model presented here (it is based on the assumption that lifespan of a cell is a heritable trait upon homeostatic proliferation), leads to similar conclusions regarding the peripheral selection of an optimal T cell repertoire over time.

In Chapter 3, the number of T cells belonging to a particular clonotype was modelled by means of a birth and death process on the state-space $S = \{0, 1, 2, \ldots\}$. It was shown that, for all values of the parameters, ultimate extinction of the given clonotype occurs with probability one. The clonotypes that survive for the longest time in the na"ive repertoire are those with small mean niche overlap values, which correspond to clonotypes having the least in common with other clonotypes in the repertoire in terms of the APPs from which they are able to receive survival signals. On the other hand, those T cell clonotypes which compete with many other clonotypes for access to APPs quickly become extinct from the repertoire. This selection mechanism maximises T cell repertoire diversity and optimises the coverage of APP space to avoid unnecessary overlap.

The set of all T cell clonotypes forms a population that competes for a limited supply of resources, including survival signals from APPs. Thus, the T cell repertoire may be viewed as an ecosystem, where individual clonotypes correspond to different species. The TCR determines an ecological niche [11, 38] for T cells belonging to
a particular clonotype and T cells compete for this niche both with other T cells belonging to the same clonotype and T cells belonging to different clonotypes whose niches overlap [83]. Only those T cells with a small mean niche overlap survive for a long time in the repertoire. This result is similar to the ecological principle of classical competitive exclusion, which states that two species competing for the same ecological niche cannot stably coexist [68]. However, a crucial difference between the T cell repertoire and an ecosystem is that there are many T cell clonotypes (around $10^7$ in a healthy adult human) and the number of distinct APPs is also very large. An estimate of the number of APPs that the immune system can potentially generate is now given. Let $N_A$ be the number of self-peptides that can provide survival signals to T cells in the naïve repertoire and let $N_{APP}$ be the number of self-peptides that make up an APP. Then, the total number of distinct APPs in the set $Q$ that may be generated from the $N_A$ self-peptides is $\binom{N_A}{N_{APP}}$. For example, if $N_A = 1000$ and $N_{APP} = 10$ then the number of different APPs which can be generated is of the order of $10^{23}$. This combinatorial richness means that each clonotype competes with many other clonotypes for access to APPs but competition between any pair of clonotypes is typically small and so, by itself, has a negligible impact on the chances of survival of either clonotype. Also, in classical ecology the diversity of the system is largely determined by the number of distinct species, whereas in the immune system the reliability of the response to pathogenic challenge depends on the even coverage of antigen space, rather than on the number of different clonotypes in the repertoire, as shown in Section 3.2.4. Hence, rather than maximising the number of different clonotypes in the repertoire, unnecessary overlap in the coverage of APP space is minimised by the selection mechanism described in Section 3.2.2.

Despite guaranteed clonotype extinction, homeostatic levels of T cells are maintained prior to extinction occurring. It was proved in Chapter 4 that a unique LCD always exists for the univariate birth and death process modelling the number of T cells belonging to a given clonotype and this distribution represents the homeostatic
number of T cells of this clonotype. As this distribution cannot be analytically
determined, several methods of approximating the LCD have been described and it
has been shown that the length of the mean time until extinction determines which
approximation is the most accurate.

The model presented in Chapter 3 relies on mean field assumptions concerning the
competition between different clonotypes in the repertoire, which allow the number
of T cells belonging to a particular clonotype to be modelled as a univariate birth
and death process without explicitly including the numbers of T cells belonging
to other clonotypes. In particular, it is assumed that, although T cells belonging
to a particular clonotype may compete with many other clonotypes for access to
APPs, individual competitive interactions between pairs of clonotypes are small \( i.e., \)
\(|Q_i \cap Q_j| \ll |Q_i| \) for all \( i \neq j \). While it is expected that this assumption will hold for
the majority of clonotype pairs in the repertoire, clonotypes possessing very similar
TCRs do occur [76, 145]. If \(|Q_i \cap Q_j| \sim |Q_i| \) for a pair of clonotypes \( i \) and \( j \) then the
number of T cells belonging to either of these clonotypes cannot be modelled without
explicitly including the number of T cells belonging to the other clonotype. In this
case, the bivariate competition model derived in Chapter 5 is required, where the
influence of all T cell clonotypes other than \( i \) and \( j \) is included by making mean field
assumptions. As in the univariate case, the bivariate competition process reaches the
absorbing state at the origin within a finite time with probability one, corresponding
to certain extinction of both clonotypes.

In Chapter 6 it was shown that as the pair of clonotypes \( i \) and \( j \) become more simi-
lar, in terms of the APPs that they are able to receive survival signals from, one
of the pair quickly becomes extinct by a process which resembles the classical com-
petitive exclusion principle. In the experiments on competitive exclusion described
in Hardin [68], although one of the two competing species always becomes extinct
within the timescale of the experiment, it is not always the same one. Similarly, in
the bivariate competition model described in this thesis, although one of the two clonotypes is always completely eliminated, it is not always the same one due to the inherent stochasticity of the system. From the birth and death rates of the two clonotypes, the probability that one clonotype becomes extinct before the other starting from a given initial state, which is denoted by \( \varphi_{n_1,n_2} \), may be computed. When neither clonotype possesses an advantage over the other, \( \varphi_{n_1,n_2} = 0.5 \). As the parameters of the system change so that one clonotype gains a selective advantage, the probability of this clonotype becoming extinct from the repertoire before the other decreases. Recall that \( \nu_{12} \) is a measure of competition for APPs in the set \( Q_{12} \), while \( \nu_1 \) and \( \nu_2 \) are measures of competition for APPs in the sets \( Q_{1/2} \) and \( Q_{2/1} \), respectively. The values of the parameters \( \nu_1 \) and \( \nu_2 \) have a crucial role in determining which of the two clonotypes becomes extinct first. As \( \nu_1 \) increases, T cells of clonotypes 2 gain a selective advantage over T cells of clonotype 1 and so it becomes more likely that clonotype 1 will become extinct from the repertoire before clonotype 2, and vice versa. Results from a deterministic analysis suggest that these parameters have a greater impact on the fate of the clonotypes than the parameter \( \nu_{12} \) which affects both clonotypes.

In principle, the model can be extended to include \( k \in \mathbb{Z}^+ \) competing clonotypes. However, as the number of clonotypes being modelled increases, the number of parameters needed grows rapidly and the model becomes analytically intractable. However, it is still possible to prove that extinction of all \( k \) clonotypes occurs within a finite amount of time. In situations where \( k \) is large and analysis is difficult to perform, the Gillespie algorithm described in Chapter 7 can be used to numerically study the dynamics of the system. In this way it may also be shown that several properties of the univariate and bivariate models, such as the repertoire average value of \( \nu \) decreasing over time, hold in more complex situations. This method allows realistic simulations of the full naïve T cell repertoire dynamics to be performed, although more reliable estimates of the parameter \( \gamma \) are needed in order to obtain
better quantitative predictions.

The model presented in this thesis includes T cell proliferation which occurs when
the T cell receives a survival signal from an APP. T cells have a finite replicative
capacity [44, 104] and it has been observed that the telomeric length of naïve T cells
decreases with age [77, 142]. Hence, in elderly individuals an increasing number of
T cells will be close to reaching their replicative limit. This is likely to be one of
the reasons behind the abrupt failure of homeostatic mechanisms in old age [63].
The extinction of some clonotypes will lead to the homeostatic expansion of others
due to decreased competition, which may in turn lead to these cells reaching their
replicative limit, triggering a chain reaction of extinction [49]. Also, it may be the
case that extinction of clonotypes with the longest lifetimes in the repertoire, i.e.,
those with $\nu \ll 1$, coincides with the decline of T cell repertoire diversity. The
results presented in Section 3.2.2 on the mean time until extinction occurs for such
clonotypes will be of use in determining whether or not this is the case, if reliable
parameter estimates can be obtained.

Telomere erosion and T cell senescence may also be induced by the chronic stimula-
tion of T cells by persistent infections such as cytomegalovirus (CMV) and Epstein-
Barr virus (EBV). The expansion of CD8 T cells specific for these pathogens leads
to in a highly restricted T cell repertoire consisting of a few clonotypes which dom-
inate the peripheral T cell repertoire [141]. Around 60 – 70% of healthy adults are
asymptomatic carriers of CMV [109] and it has been suggested that CMV-specific
cells may comprise up to 45% of all CD8 T cells in elderly individuals [67]. This
loss of diversity means that the probability of “holes” developing in the repertoire
is much increased [144, 146], which leads to reduced effectiveness of the immune
response to pathogenic challenge. Indeed, CMV and EBV seropositivity have been
correlated with an “immune risk phenotype” which is associated with poor health
status and increased incidence of mortality [143, 67]. The effect of persistent infec-
tions on T cell repertoire diversity is not included in any of the models presented in this thesis and this is an area for future work. For example, in the simulation algorithm described in Section 7.4, at a given time point an extra APP could be added to the system which strongly stimulates a small subset of the T cell clonotypes present in the repertoire.

Experimental evidence also suggests that in advanced age, antigen presentation may be impaired because dendritic cells have reduced antigen trapping capacity [65]. A possible area for future research is to include these effects of ageing in the model, for example, by making the parameter $\gamma$ time-dependent in the full repertoire simulation algorithm described in Section 7.4. Also, the effect of the addition to the repertoire of new clonotypes from the thymus may be investigated using the simulation procedure.

In this thesis, the per cell death rate of a T cell belonging to clonotype $i$, which is denoted by $\mu_i$ has been assumed to be constant. There is some evidence supporting a density dependent death rate as a mechanism of T cell homeostasis [41] and in reality it is possible that some combination of density dependent proliferation and death occurs. Models of density dependent death based on T cell killing and activation induced cell death (AICD) have been proposed [21, 148]. Competition for other resources such as cytokines (in particular IL-7) also plays a complex role in peripheral T cell homeostasis [71, 18] and these effects are neglected in the models presented here. However, since the action of cytokines is non-TCR specific, it has been argued that competition for these resources controls the total number of T cells while competition for TCR specific survival signals from APPs presenting self-peptides regulates T cell repertoire diversity [87].

As explained in Section 1.3, a one-to-one correspondence between T cell clonotypes and pMHCs is not possible, as this would require far more T cells than can be accommodated in the human lymphoid system [89]. Instead, the situation is far more combinatorially rich [122], with T cells able to interact with many different APPs.
This means that it is more likely that memory T cells and naïve T cells will overlap in terms of the APPs which they are able to interact with. Indeed, there is evidence that the homeostatic mechanisms controlling the naïve and memory T cell pools may not be independent and it has been shown that naïve and memory T cells compete for self-peptides [57, 83]. Hence, it is possible that the model presented in this thesis may also be applicable to memory T cell homeostasis. However, the requirements for naïve and memory T cell homeostasis could be different, particularly in terms of the cytokine requirements, and this is an area for future work. The model for two competing clonotypes presented in Chapters 5 and 6 could potentially be adapted to model competition between naïve and memory T cells.

Whilst this thesis is concerned with T cell homeostasis and repertoire maintenance based on competition for survival signals from APPs presenting self-peptides, the methods used should be applicable to many other stochastic processes which possess an absorbing state at the origin. In particular, the methods described in Sections 5.3 and 7.3 for proving the existence of a QSD may be applied to a wide class of such bivariate and multivariate competition processes. However, in both of these cases nothing can be said about the existence of an LCD. Existence of a QSD is a necessary but not sufficient condition for the existence of an LCD. Identifying sufficient conditions for the existence of an LCD for competition processes with an absorbing state at the origin is an area for future research. Also, the identification of the sufficient conditions for the existence of a QSD for bivariate and multivariate competition processes where the boundary states form an absorbing set is needed to confirm the conjectured existence of a QSD for the bivariate and multivariate processes, in Sections 5.3.4 and 7.3.4, respectively, studied here.
References


REFERENCES


[141] B. Weinberger, D. Herndler-Brandstetter, A. Schwanninger, D. Weiskopf, and
REFERENCES


Appendices

A Proof that Eq. (5.59) defines a bijective mapping from $S$ to $\tilde{S}$

In this appendix, it is proved that the mapping given by Eq. (5.59) is bijective. A function $g: \mathbb{N} \times \mathbb{N} \to \mathbb{N}$ on the domain $S$ is injective if $g(n_1, n_2) = g(n'_1, n'_2) \Rightarrow (n_1, n_2) = (n'_1, n'_2)$ for $(n_1, n_2)$ and $(n'_1, n'_2) \in S$. Let $g(n_1, n_2) = \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1$. Then

$$g(n_1, n_2) = g(n'_1, n'_2) \Rightarrow \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1 = \frac{1}{2}(n'_1 + n'_2)(n'_1 + n'_2 + 1) + n'_1.$$  
(A.1)

There are three separate cases to consider:

(i) If $n_1 + n_2 = n'_1 + n'_2$ then

$$\frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1 = \frac{1}{2}(n'_1 + n'_2)(n'_1 + n'_2 + 1) + n'_1 \Rightarrow n_1 = n'_1 \text{ and } n_2 = n'_2.$$  
(A.2)
(ii) If \( n_1 + n_2 = n_1' + n_2' + x \), where \( x \geq 1 \) is an integer, then

\[
\frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1 = \frac{1}{2}(n_1' + n_2')(n_1' + n_2' + 1) + n_1'
\]

\[
\Rightarrow \frac{1}{2}(n_1' + n_2' + x)(n_1' + n_2' + x + 1) + n_1 = \frac{1}{2}(n_1' + n_2')(n_1' + n_2' + 1) + n_1'
\]

\[
\Rightarrow (n_1' + n_2')x + \frac{1}{2}x(x + 1) = n_1' - n_1
\]

\[
\Rightarrow n_1' + n_2' < n_1' - n_1 \text{ because } x \geq 1
\]

\[
\Rightarrow n_2' < -n_1 , \quad (A.3)
\]

which is a contradiction because \( n_2' \geq 0, n_1 \geq 0 \).

(iii) Similarly, putting \( n_1 + n_2 + x = n_1' + n_2' \), where \( x \geq 1 \) is an integer, leads to a contradiction.

Hence, \( n_1 = n_1' \) and \( n_2 = n_2' \) as required and so \( g \) is injective. To prove that \( g \) is surjective, it must be shown that for all \( x \in \tilde{S} \), there exist integers \( n_1 \) and \( n_2 \) such that \( x = \frac{1}{2}(n_1 + n_2)(n_1 + n_2 + 1) + n_1 \). Given \( x \in \tilde{S} \), find the largest integer \( j \) such that \( x \geq \frac{1}{2}j(j + 1) \). Then choose \( n_1 = x - \frac{1}{2}j(j + 1) \) and \( n_2 = j - n_1 \). Clearly, \( n_1 \geq 0 \). It remains to show that \( n_1 \leq j \) which is required so that \( n_2 \) does not take negative values.

\[
x < \frac{1}{2}(j + 1)(j + 2) \Rightarrow x - \frac{1}{2}j(j + 1) < \frac{1}{2}(j + 1)(j + 2) - \frac{1}{2}j(j + 1)
\]

\[
\Rightarrow n_1 < j + 1 , \quad (A.4)
\]

and, since \( j \in \mathbb{N} \), it is concluded that \( n_1 \leq j \).

Hence, the mapping given by Eq. (5.59) is bijective.
B Proof that there is a unique stable steady state in the case \( \nu_{12} \ll 1, \nu_1 \ll 1, \nu_2 \ll 1 \)

In this appendix, it is shown that a unique steady state solution to Eqs. (6.36)–(6.37) exists which is locally asymptotically stable for all values of the parameters.

Steady states are found by setting the derivatives in Eqs. (6.36)–(6.37) to be equal to zero so that

\[
0 = 1 - \frac{p_1 u_2}{u_1 + u_2} - u_1, \quad \text{(B.1)}
\]
\[
0 = \bar{\phi} - \frac{p_1 u_1}{u_1 + u_2} - \bar{\mu} u_2. \quad \text{(B.2)}
\]

Since \((0, 0)\) is not a solution, the \(u_1\) nullcline \([43]\) is given by

\[
u_2 = \frac{u_1(u_1 - 1)}{1 - p_1 - u_1}, \quad \text{(B.3)}
\]

and, similarly, the \(u_2\) nullcline is given by

\[
u_1 = \frac{u_2(u_2 - \frac{\bar{\phi}}{\bar{\mu}})}{\frac{1}{\bar{\mu}}(\bar{\phi} - p_1) - u_2}. \quad \text{(B.4)}
\]

Steady states occur at the intersection of the nullclines. Since \(u_1\) and \(u_2\) represent densities of cells, it is required that \(u_1, u_2 \geq 0\). Hence, \(1 - p_1 < u_1 < 1\) and \(\frac{1}{\bar{\mu}}(\bar{\phi} - p_1) < u_2 < \frac{\bar{\phi}}{\bar{\mu}}\). This leads to the definition of the following functions:

\[
f_1 : [1 - p_1, 1] \to \mathbb{R}^+ \text{ with } f_1(u_1) = \frac{u_1(u_1 - 1)}{1 - p_1 - u_1}, \quad \text{(B.5)}
\]
\[
f_2 : \left[\frac{1}{\bar{\mu}}(\bar{\phi} - p_1), \frac{\bar{\phi}}{\bar{\mu}}\right] \to \mathbb{R}^+ \text{ with } f_2(u_2) = \frac{u_2(u_2 - \frac{\bar{\phi}}{\bar{\mu}})}{\frac{1}{\bar{\mu}}(\bar{\phi} - p_1) - u_2}. \quad \text{(B.6)}
\]
Both $f_1(u_1)$ and $f_2(u_2)$ are decreasing and continuous on their domains with

$$f_1(1) = f_2\left(\frac{\bar{\varphi}}{\bar{\mu}}\right) = 0$$  \hspace{1cm} (B.7)

and

$$\lim_{u_1 \to (1-p_1)^+} f_1(u_1) = \lim_{u_2 \to \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1)^+} f_2(u_2) = +\infty.$$  \hspace{1cm} (B.8)

These functions must intersect once and therefore a unique steady state exists. This is now proved. Since $f_2(u_2)$ is continuous and decreasing on its domain, it has a unique inverse, $f_2^{-1}$, which is also decreasing:

$$f_2^{-1} : \mathbb{R}^+ \to \left[\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1), \frac{\bar{\varphi}}{\bar{\mu}}\right],$$  \hspace{1cm} (B.9)

where $f_2^{-1}(0) = \bar{\varphi}/\bar{\mu}$ and $\lim_{u_2 \to +\infty} f_2^{-1}(u_2) = (\bar{\varphi} - p_1)/\bar{\mu}$. The domain of $f_2^{-1}$ is now restricted to the domain of $f_1(u_1)$. Note that $f_1(1 - p_1) > f_2^{-1}(1 - p_1)$ and $f_1(1) < f_2^{-1}(1)$. Next, define a function

$$h : [1 - p_1, 1] \to \mathbb{R},$$  \hspace{1cm} (B.10)

such that $h(u_1) = (f_1 - f_2^{-1})(u_1)$, which is a continuous function. Now, $h(1 - p_1) = f_1(1 - p_1) - f_2^{-1}(1 - p_1) > 0$ and $h(1) = f_1(1) - f_2^{-1}(1) < 0$. Then, by the intermediate value theorem, there exists $\bar{u}_1 \in (1 - p_1, 1)$ such that $h(\bar{u}_1) = 0$ and so $f_1(\bar{u}_1) = f_2^{-1}(\bar{u}_1)$. This steady state is unique because $f_1$ and $f_2$ are bijective on their domains. Thus, there exists a unique steady state for the equations (6.32)–(6.33), which is denoted by $(\bar{u}_1, \bar{u}_2)$, where $1 - p_1 < \bar{u}_1 < 1$ and $\frac{1}{\bar{\mu}}(\bar{\varphi} - p_1) < \bar{u}_2 < \frac{\bar{\varphi}}{\bar{\mu}}$.

It is now proved that the steady state $(\bar{u}_1, \bar{u}_2)$ is locally asymptotically stable for all
values of the parameters. Let

\[
\frac{du_1}{d\tau} = 1 - \frac{p_1 u_2}{u_1 + u_2} - u_1 \equiv f(u_1, u_2), \quad (B.11)
\]

\[
\frac{du_2}{d\tau} = \bar{\varphi} - \frac{p_1 u_1}{u_1 + u_2} - \bar{\mu} u_2 \equiv g(u_1, u_2). \quad (B.12)
\]

Then

\[
\frac{\partial f}{\partial u_1} = \frac{p_1 u_2}{(u_1 + u_2)^2} - 1, \quad \frac{\partial f}{\partial u_2} = -\frac{p_1 u_1}{(u_1 + u_2)^2},
\]

\[
\frac{\partial g}{\partial u_1} = -\frac{p_1 u_2}{(u_1 + u_2)^2}, \quad \frac{\partial g}{\partial u_2} = \frac{p_1 u_1}{(u_1 + u_2)^2} - \bar{\mu}.
\]

The Jacobian matrix is given by

\[
J = \begin{pmatrix}
\frac{\partial f}{\partial u_1} & \frac{\partial f}{\partial u_2} \\
\frac{\partial g}{\partial u_1} & \frac{\partial g}{\partial u_2}
\end{pmatrix},
\]

where \(u_1\) and \(u_2\) take their steady state values, \(\bar{u}_1\) and \(\bar{u}_2\), respectively. For \((\bar{u}_1, \bar{u}_2)\) to be locally asymptotically stable it is required that \(\text{Tr}(J) < 0\) and \(\text{Det}(J) > 0\).

From Eq. (B.3)

\[
\bar{u}_1 + \bar{u}_2 = \frac{\bar{u}_1 p_1}{\bar{u}_1 - (1 - p_1)}, \quad (B.13)
\]

and, similarly, from Eq. (B.4)

\[
\bar{u}_1 + \bar{u}_2 = \frac{\bar{u}_2 p_1}{\bar{\mu} (\bar{u}_2 - \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1))}. \quad (B.14)
\]

Then

\[
\text{Tr}(J) = \frac{\partial f}{\partial u_1} + \frac{\partial g}{\partial u_2}
\]

\[
= \frac{p_1}{\bar{u}_1 + \bar{u}_2} - 1 - \bar{\mu}
\]

\[
= \frac{\bar{u}_1 - (1 - p_1)}{\bar{u}_1} - 1 - \bar{\mu} < 0, \quad (B.15)
\]
because $\bar{\mu} > 0$ and $\bar{u}_1 > 1 - p_1$. Also,

$$\text{Det}(J) = \frac{\partial f}{\partial u_1} \frac{\partial g}{\partial u_2} - \frac{\partial f}{\partial u_2} \frac{\partial g}{\partial u_1} = \bar{\mu} - \frac{p_1(\bar{u}_1 + \bar{\mu}\bar{u}_2)}{(\bar{u}_1 + \bar{u}_2)^2}.$$  \hfill (B.16)

Now Det$(J)$ is considered in the following three different cases:

(i) $\bar{\mu} = 1$

$$\text{Det}(J) = 1 - \frac{p_1}{\bar{u}_1 + \bar{u}_2}$$
$$= 1 - \frac{\bar{u}_1 - (1 - p_1)}{\bar{u}_1}$$
$$= \frac{1 - p_1}{\bar{u}_1} > 0.$$  \hfill (B.17)

(ii) $\bar{\mu} > 1$

$$\text{Det}(J) = \bar{\mu} - \frac{p_1(\bar{u}_1 + \bar{\mu}\bar{u}_2)}{(\bar{u}_1 + \bar{u}_2)^2}$$
$$> \bar{\mu} - \frac{p_1\bar{\mu}(\bar{u}_1 + \bar{u}_2)}{(\bar{u}_1 + \bar{u}_2)^2}$$
$$= \bar{\mu} \left[ 1 - \frac{\bar{u}_1 - (1 - p_1)}{\bar{u}_1} \right]$$
$$= \bar{\mu} \left( \frac{1 - p_1}{\bar{u}_1} \right) > 0.$$  

(iii) $\bar{\mu} < 1$

$$\text{Det}(J) = \bar{\mu} - \frac{p_1(\bar{u}_1 + \bar{\mu}\bar{u}_2)}{(\bar{u}_1 + \bar{u}_2)^2}$$
$$> \bar{\mu} - \frac{p_1(\bar{u}_1 + \bar{u}_2)}{(\bar{u}_1 + \bar{u}_2)^2}$$
$$= \bar{\mu} \left[ 1 - \frac{\bar{u}_2 - \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1)}{\bar{u}_2} \right] > 0,$$

because $\bar{u}_2 > \frac{1}{\bar{\mu}}(\bar{\varphi} - p_1)$. 

Hence, the steady state \((\bar{u}_1, \bar{u}_2)\) is locally asymptotically stable for all values of the parameters.
C Proof that there is a unique stable steady state in the case $\nu_{12} \gg 1$, $\nu_1 \ll 1$, $\nu_2 \ll 1$

In this appendix it is proved that the system of differential equations (6.95)–(6.96) has a unique steady state in the region $R$ defined in Section 6.5.1.

The $u_1$ nullcline is given by

$$P(u_1) = \frac{-u_1(u_1 + \nu_{12}\bar{n}) + u_1 + (1 - p_1)\nu_{12}\bar{n}}{u_1 - 1 + p_1}, \quad (C.1)$$

and the $u_2$ nullcline is given by

$$Q(u_2) = \frac{-u_2(u_2 + \nu_{12}\bar{n}) + \frac{\bar{\phi}}{\bar{\mu}}u_2 + \frac{1}{\bar{\mu}}(\bar{\phi} - p_1)\nu_{12}\bar{n}}{u_2 - \frac{1}{\bar{\mu}}(\bar{\phi} - p_1)}. \quad (C.2)$$

At a steady state, denoted by $(\bar{u}_1, \bar{u}_2)$, $P(\bar{u}_1) = \bar{u}_2$ and $Q(\bar{u}_2) = \bar{u}_1$ and so $\bar{u}_1$ is a solution of the equation

$$Q(P(u_1)) - u_1 \equiv H_1(u_1) = 0, \quad (C.3)$$

and $\bar{u}_2$ is a solution of

$$P(Q(u_2)) - u_2 \equiv H_2(u_2) = 0. \quad (C.4)$$

Differentiating $H_1$ with respect to $u_1$ results in

$$\frac{dH_1}{du_1} = \frac{dQ}{du_2} \frac{dP}{du_1} - 1. \quad (C.5)$$

Now,

$$\frac{dP}{du_1} = -1 - \frac{p_1(1 - p_1)}{(u_1 - 1 + p_1)^2} < -1, \quad (C.6)$$
and
\[
\frac{dQ}{du_2} = -1 - \frac{p_1(\bar{\varphi} - p_1)}{\bar{\mu}^2(u_2 - \frac{1}{\bar{\mu}(\bar{\varphi} - p_1))^2} < -1 .
\]  \tag{C.7}

Then \(\frac{dH_1}{du_1} > 0\) so that \(H_1\) is strictly increasing and there is a unique solution, \(\bar{u}_1\), to Eq. (C.3) on the region where \(P\) and \(Q\) are continuous. Also,
\[
\frac{dH_2}{du_2} = \frac{dP}{du_1} \frac{dQ}{du_2} - 1 > 0 ,
\]  \tag{C.8}

and so there exists a unique solution, \(\bar{u}_2\), to Eq. (C.4) on this region. Hence, it can be concluded that a unique stable steady state exists in the region \(R\) defined in Section 6.5.1.
D  A stable steady state does not exist in the region $R$ in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ when the steady state at $(1,0)$ is stable

In this appendix it is proved that, in the case $\nu_{12} \ll 1$, $\nu_1 \ll 1$, $\nu_2 \gg 1$ when the steady state at $(1,0)$ is stable, a steady state $\left(\bar{u}_1, \bar{u}_2\right)$ with $\bar{u}_1, \bar{u}_2 > 0$ does not exist. If such a steady state does exist, it is a solution to the equations

\[
\begin{align*}
1 - \frac{p_1 u_2}{u_1 + u_2} - u_1 &= 0, \\
\frac{p_1}{u_1 + u_2} + \frac{\bar{\varphi} - p_1}{u_2 + \nu_2 \bar{n}} - \bar{\mu} &= 0.
\end{align*}
\]  

(D.1)

Substituting $u_2 = 0$ into this system results in

\[
\begin{align*}
1 - u_1 &= 0, \\
\frac{p_1}{u_1} + \frac{\bar{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} &= 0.
\end{align*}
\]  

(D.2)

which implies that

\[
p_1 + \frac{\bar{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu} = 0,
\]  

(D.3)

and so the steady state $\left(\bar{u}_1, \bar{u}_2\right)$ becomes identical to the steady state $(1,0)$ exactly when $(1,0)$ becomes stable. It is now shown that as the quantity

\[
p_1 + \frac{\bar{\varphi} - p_1}{\nu_2 \bar{n}} - \bar{\mu}
\]  

(D.4)

decreases further, the solution $\left(\bar{u}_1, \bar{u}_2\right)$ to Eqs. (D.1) ceases to exists because $\bar{u}_2 < 0$. In order to do this, the parameter $\nu_2 \bar{n}$ is increased while all other parameters remain
fixed. Let $\bar{u}_2$ be a solution to the system of equations (D.1). Then, from Appendix C,

$$H_2(\bar{u}_2) \equiv P(Q(\bar{u}_2, \nu_2 \bar{n})) - \bar{u}_2 = 0 .$$

(D.5)

Taking the partial derivative of this equation with respect to $\nu_2 \bar{n}$ gives

$$\frac{\partial H_2}{\partial \nu_2 \bar{n}} = \frac{\partial P}{\partial u_1} \left( \frac{\partial Q}{\partial \bar{u}_2} \frac{\partial \bar{u}_2}{\partial \nu_2 \bar{n}} + \frac{\partial Q}{\partial \nu_2 \bar{n}} \right) - \frac{\partial \bar{u}_2}{\partial \nu_2 \bar{n}} = 0 ,$$

(D.6)

which implies that

$$\frac{\partial \bar{u}_2}{\partial \nu_2 \bar{n}} = \frac{\frac{\partial Q}{\partial \nu_2 \bar{n}} \frac{\partial P}{\partial u_1}}{1 - \frac{\partial Q}{\partial u_1} \frac{\partial P}{\partial \bar{u}_2}} .$$

(D.7)

In the previous section it was shown that

$$\frac{\partial P}{\partial u_1} < -1 \text{ and } \frac{\partial Q}{\partial \bar{u}_2} < -1 .$$

(D.8)

Also,

$$\frac{\partial Q}{\partial \nu_2 \bar{n}} = -\frac{p_1(\bar{\varphi}_1 - p_1)}{(\bar{\mu} \nu_2 \bar{n} - (\bar{\varphi}_1 - p_1) + \bar{\mu} \nu_2)^2} < 0 ,$$

(D.9)

and so

$$\frac{\partial Q}{\partial \nu_2 \bar{n}} \frac{\partial P}{\partial u_1} > 0 \text{ and } 1 - \frac{\partial P}{\partial u_1} \frac{\partial Q}{\partial \bar{u}_2} < 0 ,$$

(D.10)

which means that

$$\frac{\partial \bar{u}_2}{\nu_2 \bar{n}} < 0 ,$$

(D.11)

and so $\bar{u}_2$ is a decreasing function of $\nu_2 \bar{n}$ on $R$. Hence, after the point at which $(1, 0)$ becomes stable, further increases in $\nu_2 \bar{n}$ result in $\bar{u}_2 < 0$ and a steady state $(\bar{u}_1, \bar{u}_2)$ with $\bar{u}_1, \bar{u}_2 > 0$ does not exist.
Copies of the following papers, as published or submitted, are provided in this appendix:

- **Paper 1**

- **Paper 2**

- **Paper 3**