Bivariate Markov processes and immunology

Magic 042 – Lecture 8 (or lecture 14)

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Introduction I

• We model the number of T cells of two competing clonotypes by means of a bivariate competition Markov process.

• In what follows the index $i$ is used to label a given T cell clonotype and the index $q$ is used to label an antigen presentation profile (APP).

• We define the following sets:

1. $C$ is the set of all T cells extant in the naïve repertoire.
2. $C_q$ is the set of all T cells in the naïve repertoire that are capable of receiving a survival stimulus from APP $q$.
3. $Q$ is the set of all APPs which may occur on antigen presenting cells.
4. $Q_i$ is the set of all APPs from which T cells of clonotype $i$ can receive a survival stimulus.
Introduction II

- Previously we have assumed that $|Q_i \cap Q_{i'}| \ll |Q_i|$ for all $i \neq i'$.
- Even though T cells of a particular clonotype compete with T cells of many other clonotypes, competition between any two clones is typically small.
- We now consider the case where $|Q_i \cap Q_{i'}| \sim |Q_i|$, i.e., the sets of self-peptides that provide survival stimuli to T cells of clonotype $i$ and $i'$ overlap significantly.
- The number of T cells of clonotypes $i$ and $i'$ at time $t$ are modelled as a continuous-time stationary bivariate Markov process $\{(Y(t), Z(t)), t \geq 0\}$ on the state-space $S = \{(n, n') : n, n' = 0, 1, 2, \ldots\}$.
- Transitions are only allowed to adjacent states and so we have a two-dimensional analogue of the birth and death process, which we call a competition process (See Reference Reuter61).
Transition probabilities

- We introduce the transition probabilities

\[ p_{(n,n'),(m,m')}((\Delta t)) = \mathbb{P}\{Y(t+\Delta t) = m, Z(t+\Delta t) = m' | Y(t) = n, Z(t) = n'\}, \]

for \((n, n')\) and \((m, m')\) \(\in S\).

- As \(\Delta t \to 0\), these probabilities satisfy:

\[
p_{(n,n'),(m,m')}((\Delta t)) = \begin{cases} 
\lambda_{nn'} \Delta t + o(\Delta t) & (m, m') = (n + 1, n') \\
\lambda'_{nn'} \Delta t + o(\Delta t) & (m, m') = (n, n' + 1) \\
\mu_{nn'} \Delta t + o(\Delta t) & (m, m') = (n - 1, n') \\
\mu'_{nn'} \Delta t + o(\Delta t) & (m, m') = (n, n' - 1) \\
1 - (\lambda_{nn'} + \lambda'_{nn'} + \mu_{nn'} + \mu'_{nn'}) \Delta t + o(\Delta t) & \text{otherwise}
\end{cases}
\]

where \(f(\Delta t) = o(\Delta t)\) as \(\Delta t \to 0^+\) if \(\lim_{\Delta t \to 0^+} \frac{f(\Delta t)}{\Delta t} = 0\).

- \(p_{(n,n'),(m,m')}((\Delta t)) = 0\) for \((n, n')\) \(\notin S\) or \((m, m')\) \(\notin S\).
Transition probabilities II

- $\lambda_{nn'}$ is the birth rate for T cells of clonotype $i$ and is the rate of transition from state $(n, n')$ to $(n + 1, n')$.
- Similarly, the birth rate for T cells of clonotype $i'$, $\lambda'_{nn'}$, is the rate of transition from state $(n, n')$ to $(n, n' + 1)$.
- The death rate for T cells of clonotype $i$, $\mu_{nn'}$, is the rate of transition from state $(n, n')$ to $(n - 1, n')$.
- The death rate for T cells of clonotype $i'$, $\mu'_{nn'}$, is the rate of transition from state $(n, n')$ to $(n, n' - 1)$.
- Setting $\mu_{0n} = \mu'_{n0} = 0$ for all $n$ ensures that transitions outside of the state-space cannot occur.
- The transitions between states are illustrated schematically below:

\[
\begin{array}{cccc}
(0, 0) \overset{\lambda_{10}}{\rightleftharpoons} (1, 0) & (1, 0) \overset{\lambda'_{10}}{\rightleftharpoons} (2, 0) & \ldots \\
(0, 1) \overset{\mu_{10}}{\rightarrow} (1, 1) & (1, 1) \overset{\lambda'_{11}}{\rightarrow} (2, 1) & \ldots \\
(0, 2) \overset{\mu_{12}}{\rightarrow} (1, 2) & (1, 2) \overset{\lambda'_{12}}{\rightarrow} (2, 2) & \ldots \\
\end{array}
\]
Transition probabilities III

- We assume that after the initial time there is no further thymic input.
- We define the infinitesimal generator matrix,
  \[ Q = (q_{(nn'),(mm')}) = (p'_{(nn'),(mm')}(0)) \], of the process in terms of three square matrices.
- Define \( A_n \) to be the infinite square tridiagonal matrix given by
  \[
  A_n = \begin{pmatrix}
  -(\lambda_{0n} + \lambda'_{0n} + \mu_{0n} + \mu'_{0n}) & -\lambda_{1n} + \lambda'_{1n} + \mu_{1n} + \mu'_{1n} & 0 & \cdots \\
  \mu_{1n} & -(\lambda_{2n} + \lambda'_{2n} + \mu_{2n} + \mu'_{2n}) & \cdots & \\
  \vdots & \vdots & \ddots & \\
  \end{pmatrix}.
  \]
- We define the infinite diagonal matrix \( B_n \) by
  \[
  B_n = \begin{pmatrix}
  \lambda'_{0n} & 0 & 0 & \cdots \\
  0 & \lambda'_{1n} & 0 & \cdots \\
  0 & 0 & \lambda'_{2n} & \cdots \\
  \vdots & \vdots & \vdots & \ddots \\
  \end{pmatrix}.
  \]
- We define the infinite diagonal matrix \( C_n \) by
  \[
  C_n = \begin{pmatrix}
  \mu'_{0n} & 0 & 0 & \cdots \\
  0 & \mu'_{1n} & 0 & \cdots \\
  0 & 0 & \mu'_{2n} & \cdots \\
  \vdots & \vdots & \vdots & \ddots \\
  \end{pmatrix}.
  \]
Transition probabilities IV

- The matrix $Q$ has the following form:

$$Q = \begin{pmatrix} A_0 & B_0 & 0 & 0 & \cdots \\ C_1 & A_1 & B_1 & 0 & \cdots \\ 0 & C_2 & A_2 & B_2 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}.$$
Birth and death rates I

- $C$ is the set of all T cells extant in the naïve repertoire.
- $C_q$ is the set of all T cells in the naïve repertoire that are capable of receiving a survival stimulus from APP $q$.
- $Q$ is the set of all APPs which may occur on antigen presenting cells.
- $Q_i$ is the set of all APPs from which T cells of clonotype $i$ can receive a survival stimulus.
- We denote by $n_i$ the number of T cells of clonotype $i$ and by $n_i'$ the number of T cells of clonotype $i'$.
- The total number of T cells receiving stimuli from APP $q$ is given by $|C_q| = n_q$. 
Birth and death rates II

- We assume the survival stimuli emanating from APP $q$ are distributed equably among all naïve T cells that are capable of forming a stimulatory synapse with an APC upon encountering $q$.

- Let $\gamma_q$ denote the rate of survival stimuli emanating from APCs that present APP $q$ and let $\lambda_i$ be the stimulus rate received by a single T cell of clonotype $i$. Then

$$\lambda_i = \sum_{q \in Q} \frac{\gamma}{n_q},$$

(1)

where for the sake of simplicity we have assumed that $\gamma$ is independent of $q$.

- Let $n_{iq} = n_q - n_i$ so that

$$\lambda_i = \sum_{q \in Q} \frac{\gamma}{n_i + n_{iq}},$$

(2)

which depends on time through $n_i$ and $n_{iq}$. 

Birth and death rates III

- We now define the following sets, where $\bar{A}$ denotes the complement of $A$:
  1. $Q_{ii'} \overset{\text{def}}{=} Q_i \cap Q_i'$ is the set of APPs which provide a survival stimulus to T cells of both clonotype $i$ and $i'$.
  2. $Q_{i/i'} \overset{\text{def}}{=} Q_i \cap \bar{Q}_{i'}$ is the set of APPs which provide a survival stimulus to T cells of clonotype $i$ but not T cells of clonotype $i'$.

- By construction $Q_i = Q_{ii'} \cup Q_{i/i'}$ and $Q_{ii'} \cap Q_{i/i'} = \emptyset$.

- Define $n_{ii'q} = n_q - n_i - n_{i'}$.

- We write

$$\lambda_i = \sum_{q \in Q_{ii'}} \frac{\gamma}{n_i + n_{i'} + n_{ii'q}} + \sum_{q \in Q_{i/i'}} \frac{\gamma}{n_i + n_{iq}}.$$ (3)
Birth and death rates IV

- To proceed further we sub-divide the set $Q_{ii'}$ as follows.
- Let $Q_{ii'r}$ denote the set of APPs which provide a survival stimulus to T cells of clonotypes $i$ and $i'$ and to T cells of $r$ distinct clonotypes in the naïve repertoire other than $i$ and $i'$.
- The sets $Q_{ii'r}$ are disjoint: $\bigcup_{r=0}^{\infty} Q_{ii'r} = Q_{ii'}$ and $Q_{ii'r} \cap Q_{ii'r'} = \emptyset$ for $r \neq r'$.
- Similarly, we can subdivide $Q_{i/i'}$ into disjoint sets.
- Let $Q_{ir/i'}$ denote the set of APPs which provide a survival stimulus to T cells of clonotype $i$ and to $r$ other distinct clonotypes other than $i$, none of which is $i'$.
- We have $\bigcup_{r=0}^{\infty} Q_{ir/i'} = Q_{i/i'}$ and $Q_{ir/i'} \cap Q_{ir'/i'} = \emptyset$ for $r \neq r'$ by construction.
- Hence

$$\lambda_i = \gamma \sum_{r=0}^{\infty} \left( \sum_{q \in Q_{ii'r}} \frac{1}{n_i + n_{i'i} + n_{ii'q}} + \sum_{q \in Q_{ir/i'}} \frac{1}{n_i + n_{iq}} \right).$$  (4)
Birth and death rates $V$

- Let

$$\mathbb{E}_{ii'r}[n_{ii'q}] = \frac{1}{|Q_{ii'r}|} \sum_{q \in Q_{ii'r}} n_{ii'q},$$  \hspace{1cm} (5)$$

$$\mathbb{E}_{ir/i'[ri'[n_{iq}] = \frac{1}{|Q_{ir/i'[ri'|}} \sum_{q \in Q_{ir/i'[ri'|}} n_{iq},$$  \hspace{1cm} (6)$$

$$\mathbb{V}_{ii'r}[n_{ii'q}] = \frac{1}{|Q_{ii'r}|} \sum_{q \in Q_{ii'r}} (n_{ii'q} - \mathbb{E}_{ii'r}[n_{ii'q}])^2,$$  \hspace{1cm} (7)$$

$$\mathbb{V}_{ir/i'[ri'[n_{iq}] = \frac{1}{|Q_{ir/i'[ri'|}} \sum_{q \in Q_{ir/i'[ri'|}} (n_{iq} - \mathbb{E}_{ir/i'[ri'[n_{iq}])^2.\hspace{1cm} (8)$$
Birth and death rates VI

- We have
  \[
  \sum_{q \in \mathcal{Q}_{ii'}r} \frac{1}{n_i + n_{i'} + n_{ii'q}} = |\mathcal{Q}_{ii'}r| \left( \frac{1}{n_i + n_{i'} + \mathbb{E}_{ii'}r[n_{ii'q}]} + \frac{\mathbb{V}_{ii'q}[n_{ii'q}]}{(n_i + n_{i'} + \mathbb{E}_{ii'}r[n_{ii'q}])^3 + \cdots} \right)
  \approx \frac{|\mathcal{Q}_{ii'}r|}{n_i + n_{i'} + \mathbb{E}_{ii'}r[n_{ii'q}]}.
  \]
  (9)

- We can write
  \[
  \sum_{q \in \mathcal{Q}_{ir/i'}} \frac{1}{n_i + n_{iq}} = |\mathcal{Q}_{ir/i'}| \left( \frac{1}{n_i + \mathbb{E}_{ir/i'}[n_{iq}]} + \frac{\mathbb{V}_{ir/i'}[n_{iq}]}{(n_i + \mathbb{E}_{ir/i'}[n_{iq}])^3 + \cdots} \right)
  \approx \frac{|\mathcal{Q}_{ir/i'}|}{n_i + \mathbb{E}_{ir/i'}[n_{iq}]}.
  \]
  (10)
The mean field approximation is based on the following two assumptions:

(i) the second term in Eqs. (9) and (10) is small,

(ii) \( \mathbb{E}_{ii'r}[n_{ii'q}] = r\langle n \rangle \) and \( \mathbb{E}_{ir/i'}[n_{iq}] = r\langle n \rangle \).

For a given \( q \in Q_{ii'r} \) there are exactly \( r \) distinct clonotypes that compete with clones \( i \) and \( i' \) for survival stimuli from APP \( q \) and for \( q \in Q_{ir/i'} \) there are exactly \( r \) distinct clonotypes that compete with \( i \) for survival stimuli.

The second assumption is that the average number of T cells per clonotype in these sets, corrected for the strength of the competition, \( r \), is the same as the repertoire average clonotype size, denoted by \( \langle n \rangle \).

These approximations are reasonable if \(|Q_i \cap Q_j| \ll |Q_i|\) for \( j \neq i' \).

With this mean field approximation we have that

\[
\lambda_i = \gamma \sum_{r=0}^{+\infty} \left( \frac{|Q_{ii'r}|}{n_i + n_{i'} + r\langle n \rangle} + \frac{|Q_{ir/i'}|}{n_i + r\langle n \rangle} \right). \tag{11}
\]
Mean field approximation II

- It remains to determine $|Q_{i' r}|$ and $|Q_{ir/i'}|$.
- To do this we define the following quantities:

  1. $p_i \stackrel{\text{def}}{=} \mathbb{P}(q \in Q_i)$ is the probability that a randomly chosen APP $q$ provides survival stimuli to T cells of clonotype $i$ so that $|Q_i| = |Q|p_i$.
  
  2. $p_{i' \mid i} \stackrel{\text{def}}{=} \mathbb{P}(q \in Q_{i'} \mid q \in Q_i)$ is the probability that a randomly chosen APP $q$ provides survival stimuli to T cells of clonotype $i'$, given that it provides survival stimuli to T cells of clonotype $i$.
  
  3. $p_{\cdot \mid i / i'} \stackrel{\text{def}}{=} \mathbb{P}(q \in Q_i \mid q \in Q_{i / i'})$ is the probability that a randomly chosen APP $q$ provides survival stimuli to a randomly selected clonotype other than $i$, given that the APP provides survival stimuli to T cells of clonotype $i$ but not $i'$.
  
  4. $p_{i^\prime \mid i / i^\prime} \stackrel{\text{def}}{=} \mathbb{P}(q \in Q_{i'} \mid q \in Q_{i^\prime / i'})$ is the probability that a randomly chosen APP $q$ provides survival stimuli to a randomly selected clonotype other than $i$ or $i'$, given that the APP provides survival stimuli to T cells of clonotype $i$ and $i'$.
  
  5. $N_c \stackrel{\text{def}}{=} \text{the total number of clonotypes extant in the peripheral repertoire.}$
Mean field approximation III

- The number of competing clones follows the binomial distribution so that

\[
|Q_{ii'}|^r = |Q_{ii'}| \left( \frac{N_c - 2}{r} \right) (p_{i|i'})^r (1 - p_{i|i'})^{N_c - 2 - r}.
\]

(12)

- Similarly

\[
|Q_{ir/i'}| = |Q_{i/i'}| \left( \frac{N_c - 2}{r} \right) (p_{i/i'})^r (1 - p_{i/i'})^{N_c - 2 - r}.
\]

(13)

- Since \( N_c \gg 1 \) and \( p_{i|i'} \ll 1 \), \( p_{i/i'} \ll 1 \) we use a Poisson approximation and define \( \nu_{ii'} = (N_c - 2)p_{i|i'} \) and \( \nu_{i/i'} = (N_c - 2)p_{i/i'} \).

- We have

\[
|Q_{ii'}|^r = |Q_{ii'}| \frac{\nu_{ii'}^r e^{-\nu_{ii'}}}{r!} = p_{i'i}|i|Q_i \frac{\nu_{ii'}^r e^{-\nu_{ii'}}}{r!} = p_{i'i}|i_1|p_i|Q| \frac{\nu_{ii'}^r e^{-\nu_{ii'}}}{r!}.
\]

(14)

- We also have

\[
|Q_{ir/i'}| = |Q_{i/i'}| \frac{\nu_{i/i'}^r e^{-\nu_{i/i'}}}{r!} = (1 - p_{i'|i})|Q_i| \frac{\nu_{i/i'}^r e^{-\nu_{i/i'}}}{r!} = (1 - p_{i'|i})p_i|Q| \frac{\nu_{i/i'}^r e^{-\nu_{i/i'}}}{r!}.
\]

(15)
Mean field approximation IV

- Substituting Eqs. (14) and (15) into Eq. (11) gives

\[
\lambda_i = \gamma p_i |Q| \left\{ p_{i|i'} e^{-\nu_{ii'}} \sum_{r=0}^{\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n_i + n_{i'}} + (1 - p_{i|i'}) e^{-\nu_{ii'} / i'} \sum_{r=0}^{\infty} \frac{\nu_{i/i'}^r}{r!} \frac{1}{r\langle n \rangle + n_i} \right\}
\]

where \( \varphi_i \overset{\text{def}}{=} \gamma p_i |Q| \) is a parameter representing the strength of stimulation.

- \( \lambda_i \) is the stimulus rate per T cell of clonotype \( i \).

- The birth rate for \( n_i \) T cells of clonotype \( i \)

\[
\lambda_{n_i,n_{i'}} = \varphi_i n_i \left\{ p_{i|i'} e^{-\nu_{ii'}} \sum_{r=0}^{\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n_i + n_{i'}} + (1 - p_{i|i'}) e^{-\nu_{ii'} / i'} \sum_{r=0}^{\infty} \frac{\nu_{i/i'}^r}{r!} \frac{1}{r\langle n \rangle + n_i} \right\}.
\]

- By a similar derivation the birth rate for T cells of clonotype \( i' \) is given by:

\[
\lambda'_{n_i,n_{i'}} = \varphi_{i'} n_{i'} \left\{ p_{i|i'} e^{-\nu_{ii'}} \sum_{r=0}^{\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n_i + n_{i'}} + (1 - p_{i|i'}) e^{-\nu_{ii'} / i'} \sum_{r=0}^{\infty} \frac{\nu_{i/i'}^r}{r!} \frac{1}{r\langle n \rangle + n_i} \right\}.
\]

- We assume a constant death rate per cell of \( \mu \) for T cells of clonotype \( i \) and \( \mu' \) for T cells of clonotype \( i' \).

- \( \mu_{n_i,n_{i'}} = \mu n_i \) and \( \mu'_{n_i,n_{i'}} = \mu' n_{i'} \).
Summary I

- The number of T cells of clonotype $i$ and $i'$ are modelled as a bivariate process $(\mathcal{Y}(t), \mathcal{Z}(t)) : t \geq 0$ with $S = \{(n, n') : n, n' = 0, 1, 2, \ldots \}$.
- The birth and death rates are given by:

$$\lambda_{nn'} = \varphi n \left\{ pe^{-\nu_{ii'}^r} \sum_{r=0}^{+\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n + n'} + (1 - p)e^{-\nu_{ii'}^i} \sum_{r=0}^{+\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n} \right\},$$

(16)

$$\lambda_{nn'}' = \varphi' n' \left\{ p'e^{-\nu_{ii'}^r} \sum_{r=0}^{+\infty} \frac{\nu_{ii'}^{r'}}{r!} \frac{1}{r\langle n \rangle + n + n'} + (1 - p')e^{-\nu_{ii'}^{i'}} \sum_{r=0}^{+\infty} \frac{\nu_{ii'}^{r'}}{r!} \frac{1}{r\langle n \rangle + n} \right\},$$

(17)

$$\mu_{nn'} = n \mu,$$

(18)

$$\mu_{nn'}' = n' \mu' \ ,$$

(19)

where we have defined the following for notational convenience:

- $n \equiv n_i$, $n' \equiv n'_i$,
- $\varphi \equiv \varphi_i$, $\varphi' \equiv \varphi_i'$,
- $p \equiv p_{i'|i}$, $p' \equiv p_{i|i'}$: constraint $p = \varphi' p'$,
- $\lambda_{nn'} \equiv \lambda_{n_i,n'_i}$, $\lambda_{nn'}' \equiv \lambda'_{n_i,n'_i}$,
- $\mu_{nn'} \equiv \mu_{n_i,n'_i}$, $\mu_{nn'}' \equiv \mu'_{n_i,n'_i}$. 
Summary II

- From Eqs. (16)–(17), \( \lambda_{0j} = \lambda'_{j0} = 0 \) for all \( j \) and so \((0, 0)\) is the only absorbing state.
- We also have that \( \mu_{0j} = \mu_{j0} = 0 \) so that transitions out of the state space cannot occur.
- All other birth and death rates are strictly positive and so the states \((n, n') \in \{S - (0, 0)\}\) form a communicating class.
- The model now includes 11 parameters: \( \varphi, \varphi', p, p', \nu_{ii'}, \nu_{i'i}, \nu_{i'i'}/i', \langle n \rangle, \mu \) and \( \mu' \).
- Note that we have the constraint \( \varphi p = \varphi' p' \).
- The single clonotype model has only 4 parameters.
Summary III

- The birth rates are bounded as follows:

\[
\lambda_{n'n'} = \varphi n \left\{ pe^{-\nu_{ii'}} \sum_{r=0}^{+\infty} \frac{\nu_{ii'}^r}{r!} \frac{1}{r\langle n \rangle + n + n'} + (1 - p)e^{-\nu_{i'i'}} \sum_{r=0}^{+\infty} \frac{\nu_{i'i'}^r}{r!} \frac{1}{r\langle n \rangle + n} \right\}
\]

\[
\leq \varphi n \left\{ pe^{-\nu_{ii'}} \frac{1}{n} + (1 - p)e^{-\nu_{i'i'}} \right\}
\]

\[
= \varphi p + \varphi (1 - p)
\]

Similarly we have that \( \lambda_{n'n'}' \leq \varphi' \).
Absorption I

- We now consider the probability of eventual absorption into state $(0, 0)$.
- We show that this is equal to 1 for all values of the parameters.
- This corresponds physically to extinction of both clonotypes.
Absorption II

• The only absorbing state is $(0, 0)$.
• Define the following subsets of $S$ for $k = 0, 1, 2, \ldots$
  
  $$S_0 = \emptyset \text{ and } S_k = \{(n, n') : n + n' = k\} \text{ for } k \geq 1.$$ 
• We now define

$$\lambda_k = \max_{(n,n') \in S_k} \{\lambda_{nn'} + \lambda'_{nn'}\}, \quad (21)$$

$$\mu_k = \min_{(n,n') \in S_k} \{\mu_{nn'} + \mu'_{nn'}\}. \quad (22)$$

• $\lambda_k$ and $\mu_k$ are not defined when $S_k$ is empty.
• Let $k_0$ be the smallest integer $k$ for which $S_k$ is non-empty.
• In this case $k_0 = 1$ because $S_0$ is empty and $S_1 = \{(0, 1), (1, 0)\}$.
• For the process to pass from one set $S_k$ to another $S_{k'}$ it must pass through all intervening sets.
Absorption III

- $\lambda_k$ is the maximum rate the process moves upwards through the sets $S_k$ and $\mu_k$ is the minimum rate the process moves downwards though the sets $S_k$.

- We also define
  \[
  \pi_1 = 1, \quad \pi_k = \frac{\lambda_1 \lambda_2 \ldots \lambda_{k-1}}{\mu_2 \mu_3 \ldots \mu_k} \quad \text{for } k \geq 2.
  \]

- By Theorem 3 of [Iglehart64](#), a sufficient condition for guaranteed absorption is that the series
  \[
  \sum_{k=k_0}^{+\infty} \frac{1}{\lambda_k \pi_k}
  \]  
  diverges.
Absorption IV

- We prove that the series diverges for the birth and death rates.
- We have: \( \lambda_k = \max_{(n,n') \in S_k} \{ \lambda_{nn'} + \lambda'_{nn'} \} \leq \varphi + \varphi' \).
- We also have: \( \mu_k = \min_{(n,n') \in S_k} \{ n\mu + n'\mu' \} = k \min(\mu, \mu') \).
- We can write

\[
\sum_{k=k_0}^{+\infty} \frac{1}{\lambda_k \pi_k} = \sum_{k=1}^{+\infty} \frac{\mu_2 \mu_3 \ldots \mu_k}{\lambda_1 \lambda_2 \ldots \lambda_k} \geq \sum_{k=1}^{+\infty} \frac{k!\left[\min(\mu, \mu')\right]^{k-1}}{(\varphi + \varphi')^k}.
\]
Absorption V

- Let
  \[ a_k = \frac{k!\min(\mu, \mu')^{k-1}}{(\varphi + \varphi')^k}. \]

- We have
  \[ \frac{a_{k+1}}{a_k} = \frac{(k + 1) \min(\mu, \mu')}{(\varphi + \varphi')} \rightarrow +\infty \text{ as } k \rightarrow +\infty, \]
  so
  \[ \sum_{k=1}^{+\infty} \frac{k!\min(\mu, \mu')^{k-1}}{(\varphi + \varphi')^k} \]
  diverges by the ratio test.

- Hence \( \sum_{k=1}^{+\infty} \frac{1}{\lambda_k \pi_k} \) also diverges by comparison and so absorption is guaranteed for all parameter values.

- The process is regular and so the birth and death rates uniquely specify the process.
Time to extinction

- Let $\tau_{nn'}$ be the mean time to absorption from the initial state $(n, n')$.
- $\tau_{nn'} < +\infty$ for all $(n, n') \in \{S - (0, 0)\}$ if the series
  \[\sum_{k=k_0}^{+\infty} \pi_k\]
  converges.
- For our birth and death rates
  \[\sum_{k=k_0}^{+\infty} \pi_k = \sum_{k=1}^{+\infty} \frac{\lambda_1 \lambda_2 \ldots \lambda_{k-1}}{\mu_2 \mu_3 \ldots \mu_k} \leq \sum_{k=1}^{+\infty} \frac{(\varphi + \varphi')^{k-1}}{k! [\min(\mu, \mu')]^{k-1}}.\]
- Let
  \[b_k = \frac{(\varphi + \varphi')^{k-1}}{k! [\min(\mu, \mu')]^{k-1}}.\]
- Then
  \[\frac{b_{k+1}}{b_k} = \frac{\varphi + \varphi'}{(k + 1) \min(\mu, \mu')} \to 0\] as \(k \to +\infty\), so
  \[\sum_{k=1}^{+\infty} \frac{(\varphi + \varphi')^{k-1}}{k! [\min(\mu, \mu')]^{k-1}}\]
  converges by the ratio test.
Time to extinction II

- Hence $\sum_{k=1}^{+\infty} \tau_k$ converges by the comparison test and so the mean time to absorption from all initial states $(n, n') \in \{S - (0, 0)\}$ is finite.

- The two-dimensional competition process is bounded by a one-dimensional birth and death process with birth rate $\lambda_k$ and death rate $\mu_k$ which moves to infinity at a faster rate than the two-dimensional process.

- For a one-dimensional birth and death process with birth rate $\lambda_k$ and death rate $\mu_k$, the mean time until absorption from state $m$, $\tau_m$, is given by:

$$
\tau_m = \sum_{l=1}^{+\infty} \frac{1}{\lambda_l \rho_l} + \sum_{j=1}^{m-1} \rho_j \sum_{k=j+1}^{+\infty} \frac{1}{\lambda_k \rho_k},
$$

(24)

where $\rho_k = \prod_{j=1}^{k} \frac{\mu_j}{\lambda_j}$.

- Hence $\tau_m$, with $\lambda_k$ and $\mu_k$ as defined in (21) and (22), is an upper bound on the mean time to absorption at $(0, 0)$ from initial states in $S_m$. 
Define $p_{nn'}(t) = \mathbb{P}(Y(t) = n, Z(t) = n'|Y(0) = n_0, Z(0) = n'_0)$, the probability that the process is in state $(n, n')$ at time $t$ given that the initial state of the process is $(n_0, n'_0) \in S$.

Let $\mathbf{P}(t) = (p_{00}(t), p_{10}(t), \ldots, p_{01}(t), p_{11}(t), \ldots)$.

These probabilities satisfy the following system of differential equations:

$$
\frac{dp_{nn'}(t)}{dt} = \lambda_{n-1,n'} p_{n-1,n'}(t) + \lambda'_{n,n'-1} p_{n,n'-1}(t) + \mu_{n+1,n'} p_{n+1,n'}(t)
+ \mu'_{n,n'+1} p_{n,n'+1}(t) - (\lambda_{nn'} + \lambda'_{nn'} + \mu_{nn'} + \mu'_{nn'}) p_{nn'}(t)
$$

for $(n, n') \in S$.

$p_{nn'}(t) = 0$ for $(n, n') \notin S$.

These equations can be written in matrix form as $\frac{d\mathbf{P}(t)}{dt} = \mathbf{P}(t)\mathbf{Q}$.
We now consider the limiting distribution of the process as $t \to +\infty$.

The probability of being in state $(n, n')$ for large $t$ is given by

$$\bar{p}_{nn'} = \lim_{t \to +\infty} p_{(m,m'),(n,n')} (t).$$  \hfill (26)

For the process we consider here the limiting distribution has all its mass at the origin since absorption is guaranteed for all values of the parameters.

Hence we consider instead the behaviour of the process before extinction occurs.

Define

$$q_{nn'} (t) = \frac{p_{nn'} (t)}{1 - p_{00} (t)}, \quad (n, n') \in \{S - (0, 0)\},$$  \hfill (27)

which is the probability that the process is in state $(n, n')$ at time $t$ conditioned on the event that absorption has not yet occurred.
Quasi-stationary distribution III

- We have that \( \sum_{n=0}^{+\infty} \sum_{n'=0}^{+\infty} q_{nn'}(t) = 1 \) and \( q_{nn'}(t) \geq 0 \) for \((n, n') \in \{S - (0, 0)\}\). \( q_{nn'}(t) = 0 \) for \((n, n') \notin \{S - (0, 0)\}\).

- These probabilities satisfy the following system of differential equations:

\[
\frac{dq_{nn'}(t)}{dt} = \lambda_{n-1,n'}q_{n-1,n'}(t) + \lambda'_{n,n'-1}q_{n,n'-1}(t) + \mu_{n+1,n'}q_{n+1,n'}(t) \\
+ \mu'_{n,n'+1}q_{n,n'+1}(t) - (\lambda_{nn'} + \lambda'_{nn'} + \mu_{nn'} + \mu'_{nn'})q_{nn'}(t) \\
+ \mu_{10}q_{10}(t)q_{nn'}(t) + \mu'_{01}q_{01}(t)q_{nn'}(t) .
\]

(28)

- A quasi-stationary distribution, \( \bar{q}_{nn'} \), if it exists, satisfies the equations

\[
0 = \lambda_{n-1,n'}q_{n-1,n'} + \lambda'_{n,n'-1}q_{n,n'-1} + \mu_{n+1,n'}q_{n+1,n'} + \mu'_{n,n'+1}q_{n,n'+1} \\
- (\lambda_{nn'} + \lambda'_{nn'} + \mu_{nn'} + \mu'_{nn'})\bar{q}_{nn'} + \mu_{10}\bar{q}_{10}\bar{q}_{nn'} + \mu'_{01}\bar{q}_{01}\bar{q}_{nn'} ,
\]

(29)

for \((n, n') \in \{S - (0, 0)\}\), where \( \sum_{n=0}^{+\infty} \sum_{n'=0}^{+\infty} \bar{q}_{nn'} = 1 \), \( \bar{q}_{nn'} \geq 0 \) for \((n, n') \in \{S - (0, 0)\}\) and \( \bar{q}_{nn'} = 0 \) for \((n, n') \notin \{S - (0, 0)\}\).
Back to some more immunology
Lymphocyte recirculation through peripheral lymphoid organs

- Pathogens generally enter the body through an epithelial surface, usually through the skin, gut, or respiratory tract.
- To induce an adaptive immune response, microbial antigens must travel from these entry points to a peripheral lymphoid organ, such as a lymph node or the spleen, the sites where lymphocytes are activated.
- The route and destination depend on the site of entry.
- Lymphatic vessels carry antigens that enter through the skin or respiratory tract to local lymph nodes.
- Antigens that enter through the gut end up in gut-associated peripheral lymphoid organs such as Peyer’s patches.
- The spleen filters out antigens that enter the blood.
Lymphocyte recirculation through peripheral lymphoid organs II

Figure 25-5  Molecular Biology of the Cell 5/e (© Garland Science 2008)
Dendritic cells will carry the antigen from the site of infection to the peripheral lymphoid organ, where they play a crucial part in activating T cells.

Only a tiny fraction of the total lymphocyte population can recognise a particular microbial antigen in a peripheral lymph organ (estimated to be between $10^{-4}$ and $10^{-5}$ of each class of lymphocyte).

How do these rare cells find an antigen presenting cell displaying their antigen?

Lymphocytes continuously circulate between one peripheral lymphoid organ and another via the lymph and blood.

The continuous recirculation between the blood and lymph ends only if a lymphocyte is activated by its specific antigen in a peripheral lymphoid organ.

The lymphocyte remains in the peripheral lymphoid organ, where it proliferates and differentiates into either effector cells or memory cells.

Many of the effector T cells leave the lymphoid organ via the lymph and migrate through the blood to the site of infection, whereas others stay in the lymphoid organ and help activate B cells or other T cells there.
Some effector B cells (plasma cells) remain in the peripheral lymphoid organ and secrete antibodies into the blood for days until they die.

Others migrate to the bone marrow, where they secrete antibodies into the blood for months or years.

The memory T and B cells produced join the recirculating pool of lymphocytes.

Lymphocyte recirculation depends on specific interactions between the lymphocyte cell surface and the surface of the endothelial cells lining the blood vessels in the peripheral lymphoid organs.

Lymphocytes adhere and then migrate out of the bloodstream into the nodes.

The lymphocytes initially adhere to the endothelial cells via homing receptors that bind to specific ligands (often called counter-receptors) on the endothelial cell surface.

Lymphocyte migration into lymph nodes depends on a homing receptor protein called L-selectin.
Lymphocyte recirculation through peripheral lymphoid organs V

- The lymphocytes adhere weakly to the endothelial cells and roll slowly along their surface.
- The rolling continues until another, much stronger adhesion system is called into play by the chemoattractant proteins (chemokines) secreted by endothelial cells.
- This strong adhesion is mediated by members of the integrin family of cell adhesion molecules, which become activated on the lymphocyte surface.
- The lymphocytes stop rolling and crawl out of the blood vessel into the lymph node.
Lymphocyte recirculation through peripheral lymphoid organs VI

- The T and B cells initially enter the same region of a lymph node, but then different chemokines guide them to separate regions of the node.
- Unless they encounter their antigen, both T and B cells soon leave the lymph node via efferent lymphatic vessels.
- If they encounter their antigen, however, they are stimulated to display adhesion receptors that trap the cells in the node.
- The cells accumulate at the junction between the T cell and B cell areas, where the rare specific T and B cells can interact, leading to their proliferation and differentiation.
B cells and antibodies I

- Antibodies defend us against infection by binding to viruses and microbial toxins, thereby inactivating them.
- When antibodies bind to invading pathogens, they also recruit some of the components of the innate immune system.
B cells and antibodies II

• Synthesised exclusively by B cells, antibodies are produced in billions of forms, each with a different amino acid sequence.

• Collectively called immunoglobulins (abbreviated as Ig), they are among the most abundant protein components in the blood.

• Mammals make five classes of antibodies, each of which mediates a characteristic biological response following antigen binding.

• In this section, we discuss the structure and function of antibodies and how they interact with antigen.

• All antibody molecules made by an individual B cell have the same antigen-binding site.
The first antibodies made by a newly formed B cell are not secreted but are instead inserted into the plasma membrane, where they serve as receptors for antigen.

Each B cell has approximately $10^5$ such receptors in its plasma membrane.

Each B cell clone produces a single species of antibody, with a unique antigen-binding site.

When an antigen (with the aid of a helper T cell) activates a naive or a memory B cell, that B cell proliferates and differentiates into an antibody-secreting effector cell.

Such effector cells make and secrete large amounts of soluble (rather than membrane-bound) antibody, which has the same unique antigen-binding site as the cell-surface antibody that served earlier as the antigen receptor.
B cells and antibodies IV

- **Antigen receptor**
- **Proliferation and differentiation**
- **Effector B cells**
- **Secreted antibodies**

**Figure 25-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)**
B cells and antibodies V

- Effector B cells can begin secreting antibody while they are still small lymphocytes, but the end stage of their maturation pathway is a large plasma cell.
- Plasma cells continuously secrete antibodies at the astonishing rate of about 5000 molecules per second.
- Although most plasma cells die after several days, some survive in the bone marrow for months or years and continue to secrete antibodies into the blood, helping to provide long-term protection against the pathogen that stimulated their production.
The antibody molecule I

- The simplest antibodies are Y-shaped molecules with two identical antigen-binding sites, one at the tip of each arm of the Y.

- The basic structural unit of an antibody molecule consists of four polypeptide chains, two identical light (L) chains (each containing about 220 amino acids) and two identical heavy (H) chains (each usually containing about 440 amino acids).

- The molecule is composed of two identical halves, each with the same antigen-binding site.

- Both light and heavy chains usually cooperate to form the antigen-binding surface.
The antibody molecule II

Figure 25-21  Molecular Biology of the Cell 5/e (© Garland Science 2008)
B cell development

Development in bone marrow

Circulation through peripheral lymphoid organs

Figure 25-22 Molecular Biology of the Cell 5/e (© Garland Science 2008)
T cells versus B cells

- Like antibody responses, T cell-mediated immune responses are exquisitely antigen-specific, and they are at least as important as antibodies in defending vertebrates against infection.
- Most adaptive immune responses, including most antibody responses, require helper T cells for their initiation.
- Unlike B cells, T cells can help eliminate pathogens that would otherwise be invisible inside host cells.
- T cell responses differ from B cell responses in at least two crucial ways.
  - First, T cells are activated by foreign antigen to proliferate and differentiate into effector cells only when the antigen is displayed on the surface of antigen-presenting cells, usually dendritic cells in peripheral lymphoid organs.
  - T cells require antigen-presenting cells for activation because the form of antigen they recognise is different from that recognized by B cells.
T cells versus B cells II

- Whereas B cells recognise intact protein antigens, for example, T cells recognise fragments of protein antigens that have been partly degraded inside the antigen-presenting cell.

- Special proteins, called MHC proteins, bind to the peptide fragments and carry them to the surface of the antigen-presenting cell, where T cells can recognise them.

- The second difference is that, once activated, effector T cells act only at short range, either within a secondary lymphoid organ or after they have migrated into a site of infection.

- Effector B cells, by contrast, secrete antibodies that can act far away.

- Effector T cells interact directly with another host cell in the body, which they either kill (as in the case of an infected host cell, for example) or signal in some way (as in the case of a B cell or macrophage, for example).

- We shall refer to such host cells as target cells.
T cells versus B cells III

- Target cells must display an antigen bound to an MHC protein on their surface for a T cell to recognise them, they are also antigen-presenting cells.
- There are three main classes of T cells: cytotoxic T cells, helper T cells, and regulatory (suppressor) T cells.
- Effector cytotoxic T cells directly kill cells that are infected with a virus or some other intracellular pathogen.
- Effector helper T cells help stimulate the responses of other cells: mainly macrophages, dendritic cells, B cells, and cytotoxic T cells.
- Effector regulatory T cells suppress the activity of other cells, especially of self-reactive effector T cells.
• T cell responses depend on direct contact with an antigen-presenting cell or a target cell.

• T cell receptors (TCRs), unlike antibodies made by B cells, exist only in membrane-bound form and are not secreted.

• For this reason, TCRs were difficult to isolate, and it was not until the 1980s that researchers identified their molecular structure.
T cell receptor (TCR) II

- TCRs resemble antibodies.
- The three-dimensional structure of the extracellular part of a TCR has been determined by x-ray diffraction, and it looks very much like one arm of a Y-shaped antibody molecule.
- Various co-receptors and cell-cell adhesion proteins greatly strengthen the binding of a T cell to an antigen-presenting cell or a target cell.
Antigen presentation by dendritic cells I

- Naive cytotoxic or helper T cells must be activated to proliferate and differentiate into effector cells before they can kill or help their target cells, respectively.
- This activation occurs in peripheral lymphoid organs on the surface of activated dendritic cells that display foreign antigen complexed with MHC proteins on their surface, along with co-stimulatory proteins.
- Memory T cells can be activated by other types of antigen-presenting cells, including macrophages and B cells, as well as by dendritic cells.
- Dendritic cells interact with T cells to present antigens that either activate or suppress the T cells.
- Dendritic cells are located in tissues throughout the body, including the central and peripheral lymphoid organs.
- Wherever they encounter invading microbes, they endocytose the pathogens or their products.
- If the encounter is not in a lymphoid organ, the dendritic cells carry the foreign antigens via the lymph to local lymph nodes or gut-associated lymphoid organs.
Antigen presentation by dendritic cells II

INNATE IMMUNE RESPONSE

Figure 25-5  Molecular Biology of the Cell 5/e (© Garland Science 2008)
Antigen presentation by dendritic cells III

- The encounter with a pathogen activates pattern recognition receptors of the dendritic cell, which is thereby induced to mature from an antigen-capturing cell to an activated antigen-presenting cell that can activate T cells.
- Dendritic cells have to be activated in order to activate naive T cells, and they can also be activated by tissue injury or by effector helper T cells.
- Tissue injury is thought to activate dendritic cells by the release of heat shock proteins and uric acid crystals when cells die by necrosis rather than by apoptosis.
- Activated dendritic cells display three types of protein molecules on their surface that have a role in activating a T cell to become an effector cell or a memory cell.
Antigen presentation by dendritic cells IV

- (1) MHC proteins, which present foreign antigen to the TCR,
- (2) co-stimulatory proteins, which bind to complementary receptors on the T cell surface, and
- (3) cell-cell adhesion molecules, which enable a T cell to bind to the antigen-presenting cell for long enough to become activated, which is usually hours.

Activated dendritic cells secrete a variety of cytokines that can influence the type of effector helper T cell that develops, as well as where the T cell migrates after it has been stimulated.

- Non-activated dendritic cells also have important roles.
- They help induce self-reactive T cells to become tolerant, both in the thymus and in other organs.
- Such dendritic cells present self-antigens in the absence of the co-stimulatory molecules required to activate naive T cells.
Antigen presentation by dendritic cells V

Figure 25-45  Molecular Biology of the Cell 5/e (© Garland Science 2008)
Effector cytotoxic T cells I

- Cytotoxic T cells protect vertebrates against intracellular pathogens such as viruses and some bacteria and parasites that multiply in the host-cell cytoplasm, where they are sheltered from antibody-mediated attack.

- Cytotoxic T cells do this by killing the infected cell before the microbes can proliferate and escape from the infected cell to infect neighboring cells.

- Once a cytotoxic T cell has been activated by an infected antigen-presenting cell to become an effector cell, it can kill any target cell harboring the same pathogen.

- Using its TCR, the effector cytotoxic T cell first recognises a microbial antigen bound to an MHC protein on the surface of an infected target cell.

- This causes the T cell to reorganize its cytoskeleton and focus its killing apparatus on the target.

- Focus is achieved when the TCRs actively aggregate, along with various co-receptors, adhesion molecules, and signaling proteins at the T cell/target cell interface, forming an immunological synapse.
A similar synapse forms when an effector helper T cell interacts with its target cell.

In this way, effector T cells avoid delivering their signals to neighboring cells.

Once bound to its target cell, an effector cytotoxic T cell can employ one of two strategies to kill the target, both of which operate by inducing the target cell to kill itself by undergoing apoptosis.

In killing an infected target cell, the cytotoxic T cell usually releases a pore-forming protein called perforin.

In the second killing strategy, the cytotoxic T cell activates a death-inducing cascade in the target cell less directly.

A homotrimeric protein on the cytotoxic T cell surface, called Fas ligand, binds to transmembrane receptor proteins on the target cell called Fas.
Effector cytotoxic T cells III

A Perforin-dependent killing

B Fas-dependent killing

Figure 25-47 Molecular Biology of the Cell S/e (© Garland Science 2008)
In contrast to cytotoxic T cells, helper T cells are crucial for defense against both extracellular and intracellular pathogens.

They help stimulate B cells to make antibodies that help inactivate or eliminate extracellular pathogens and their toxic products.

They also activate macrophages to destroy any intracellular pathogens multiplying within the macrophage’s phagosomes, and they help activate cytotoxic T cells to kill infected target cells.

They can also stimulate a dendritic cell to maintain it in an activated state.

Once an antigen-presenting cell activates a helper T cell to become an effector cell, the helper cell can then help activate other cells.

It does this both by secreting a variety of co-stimulatory cytokines and by displaying co-stimulatory proteins on its surface.
Effector helper T cells II

- When activated by its binding to an antigen on a dendritic cell, a naive helper T cell usually differentiates into either of two distinct types of effector helper cell, called TH1 and TH2.
- TH1 cells are mainly involved in immunity to intracellular microbes and help activate macrophages, cytotoxic T cells, and B cells.
- TH2 cells are mainly involved in immunity to extracellular pathogens, especially multicellular parasites, and they help activate B cells to make antibodies against the pathogen.
- The nature of the invading pathogen and the types of innate immune responses it elicits largely determine which type of helper T cell develops.
Effector helper T cells III

- Naïve helper T cells
- Activated dendritic cells
- Effector helper T cells

Th1 activates macrophages, cytotoxic T cells, and B cells

Th2 activates B cells

Figure 25-48 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Let us consider two cell populations and their bivariate competition process.

Let \( n \equiv \text{number of cells of type 1} \) and \( n' \equiv \text{number of cells of type 2} \).

The master equation for the process is given by

\[
\frac{\partial P(n, n', t)}{\partial t} = \lambda_{n-1,n'} P(n-1, n', t) + \lambda'_{n,n'-1} P(n, n'-1, t) + \mu_{n+1,n'} P(n+1, n', t) + \mu'_{n,n'+1} P(n, n'+1, t) - (\lambda_{nn'} + \lambda'_{nn'} + \mu_{nn'} + \mu'_{nn'}) P(n, n', t). \tag{30}
\]

We introduce the difference operators:

\[
\mathbb{E}_n f(n, n') = f(n+1, n'), \tag{31}
\]

\[
\mathbb{E}_{n'} f(n, n') = f(n, n'+1), \tag{32}
\]

\[
\mathbb{E}_n^{-1} f(n, n') = f(n-1, n'), \tag{33}
\]

\[
\mathbb{E}_{n'}^{-1} f(n, n') = f(n, n' - 1). \tag{34}
\]
The master equation can be written as:

\[
\frac{\partial P(n, n', t)}{\partial t} = (E_{n}^{-1} - 1)\lambda_{nn'} P(n, n', t) + (E_{n'}^{-1} - 1)\lambda'_{nn'} P(n, n', t) \\
+ (E_n - 1)\mu_{nn'} P(n, n', t) + (E_{n'} - 1)\mu'_{nn'} P(n, n', t).
\]  

(35)

We are going to define a suitable transformation of variables that will allow us to go from the discrete set of variables \((n, n')\) to the continuous set of variables \((\xi, \xi')\).

The large N expansion allows us to go from a stochastic description to a deterministic one.
We expect $n$ to consist of a deterministic part plus fluctuations.

We introduce $\Omega$ – a parameter measuring the volume of the system, such that for large $\Omega$ the fluctuations are relatively small.

We define the following transformation ($n \rightarrow \xi$)

$$n = \Omega x(t) + \Omega^{\frac{1}{2}} \xi.$$ 

We assume the fluctuations are of order $\Omega^{\frac{1}{2}}$.

We define the following transformation ($n' \rightarrow \xi'$)

$$n' = \Omega y(t) + \Omega^{\frac{1}{2}} \eta.$$
Expansion of the master equation II

• Now, rather than a probability distribution $P$ of $n$ and $n'$, we have a probability distribution $\Pi$ of $\xi$ and $\eta$.

\[
\Pi(\xi, \eta, t) = P(\Omega x + \Omega\frac{1}{2} \xi, \Omega y + \Omega\frac{1}{2} \eta, t) .
\] (36)

• We can write

\[
\frac{\partial P}{\partial t} = \frac{\partial \Pi}{\partial t} - \Omega\frac{1}{2} \frac{dx}{dt} \frac{\partial \Pi}{\partial \xi} - \Omega\frac{1}{2} \frac{dy}{dt} \frac{\partial \Pi}{\partial \eta} ,
\] (37)

where we have made use of the chain rule.