

Discrete and continuous stochastic modelling

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Some useful books are Stirzaker *Stochastic processes and models*

Taylor and Karlin *An Introduction to Stochastic Modelling*

Linda Allen *An introduction to stochastic processes with applications to biology*

2009

Summary

- 1** Markov processes: the Gillespie algorithm
 - Introduction: Gambler's ruin
 - Continuous-time Markov chains
 - The Gillespie algorithm
- 2** Stochastic processes in continuous space
 - Brownian motion or the Wiener process
 - A bit of immunology
- 3** T-cell homeostasis

Gambler's ruin: The rules of the game

A gambler tosses a fair coin. Each time the coin lands heads, the gambler gains a dollar and each time the coin lands tails, the gambler loses a dollar. The game continues until the gambler either loses B dollars (is ruined) or wins A dollars (wins overall).

Let \mathbf{S}_n be the net winnings after n tosses. Suppose $\mathbf{S}_0 = k$. Let τ be the number of steps it takes to end the game. If

$f(k) = \Pr[\text{hit } A \text{ before } -B]$ and $g(k) = \mathbb{E}(\tau)$

then $f(k) = \frac{1}{2}f(k-1) + \frac{1}{2}f(k+1)$

$$\text{and } g(k) = \frac{1}{2}g(k-1) + \frac{1}{2}g(k+1) + 1.$$

Continuous-time Markov chains

If time is now a continuous variable then we define the transition probability function as

$$P_{ij}(t+u) = \Pr[\mathbf{X}_{t+u} = j | \mathbf{X}_u = i] \quad t \geq 0.$$

Now $t \in \mathbb{R}^+$ but i and j are still integers.

If the $P_{ij}(t+u)$ do not depend on u , we say the Markov chain has stationary transition probabilities.

Birth processes

Birth processes are continuous-time Markov chains where

$$\Pr[\mathbf{X}_{t+h} - \mathbf{X}_t = 1 | \mathbf{X}_t = k] \rightarrow \lambda_k h \quad \text{as } h \rightarrow 0.$$

That is

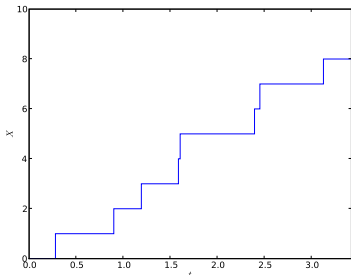
$$\lim_{h \rightarrow 0} \frac{\Pr[\mathbf{X}_{t+h} - \mathbf{X}_t = 1 | \mathbf{X}_t = k]}{h} = \lambda_k.$$

Notice that the process never decreases, and increases by one unit at a time.

We might call it a “pure” birth process.

If λ_k is in fact independent of k , the process is known as the Poisson process, because then

$$\Pr[\mathbf{X}_{t+s} - \mathbf{X}_s = k] = \frac{(\lambda t)^k}{k!} e^{-\lambda t}.$$



Time of the first jump

If τ is the time of the first jump, then

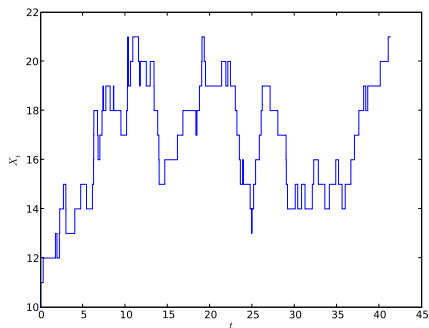
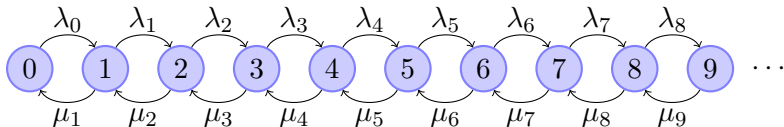
$$\frac{d}{dt}\Pr[\tau > t] = -\lambda\Pr[\tau > t]$$

and $\Pr[\tau > 0] = 1$. Thus

$$\Pr[\tau > t] = \exp(-\lambda t).$$

Birth and death processes

If \mathbf{X}_t can increase or decrease, the Markov chain is the continuous-time analogue of the random walk.



```
import random, math
tmax=100
x0=10
t=0
x=x0
while t <= tmax:
    lamb=1.0
    mu=2.0
    if x==0:
        mu=0
    rate=lamb+mu
    urv=random.random()
    if urv>=lamb/rate:
        x-=1
    else:
        x+=1
    t+=-math.log(random.random())/rate
```

The Gillespie algorithm

Starting from any state, each of the possible jumps occurs with constant probability per unit time, independent of the others. The probability that no jump has occurred before time t is the product of the probabilities of each jump not having occurred.

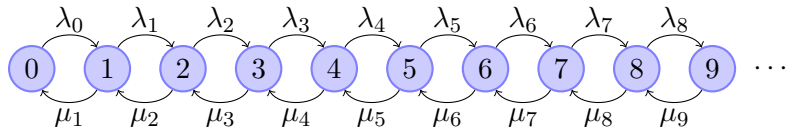
Given that the process is in state n at time t , the distribution of the time τ_n that it first leaves state n is exponential:

$$\Pr[\tau_n > t] = e^{-(\lambda_n + \mu_n)t}.$$

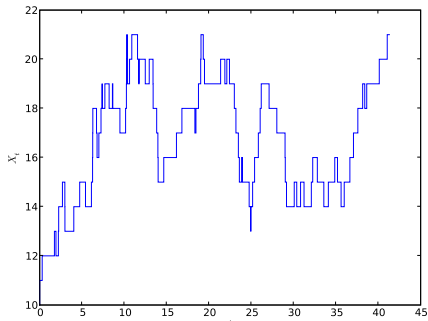
To generate numerical realisations of the birth-death process, **two random variables, uniformly distributed in $(0, 1)$, are needed for each jump**. Call them \mathbf{U}_1 and \mathbf{U}_2 .

- Time is incremented by $\Delta t = -(\lambda_n + \mu_n)^{-1} \ln \mathbf{U}_1$.
- If $\mathbf{U}_2 < \frac{\lambda_n}{\lambda_n + \mu_n}$ then $\mathbf{X}_{t+\Delta t} = n + 1$, otherwise $\mathbf{X}_{t+\Delta t} = n - 1$.

Birth and death processes



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Visualisation of multivalent receptor-ligand engagement

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Stochastic processes

- A stochastic process \mathbf{X} is a series of random variables labelled by time.
The value of the process at time t is a random variable that we write \mathbf{X}_t .
- When time is continuous (t is a real number) we say that \mathbf{X} is a continuous-time stochastic process.
- One realization of a stochastic process is a sample path. When we can draw these paths without lifting the pen from the paper, we say that the stochastic process has continuous paths.

Brownian motion or the Wiener process

The fundamental stochastic process in continuous space and time is standard Brownian motion, or the Wiener process.

The position at time t is the random variable denoted \mathbf{W}_t .

It is a Markov process with the property that, no matter how small Δt is,

$$\mathbf{W}_{t+\Delta t} - \mathbf{W}_t$$

has a Gaussian distribution with mean zero and variance Δt .

If $f(x, t)$ is the probability density function of \mathbf{W}_t then

$$\frac{\partial}{\partial t} f(x, t) = \frac{1}{2} \frac{\partial^2}{\partial x^2} f(x, t).$$

Wiener process: Python Code

```

from pylab import *
import random

nRealize = 10

while nRealize > 0:
    maxTime=10.0
    dt = 0.01
    x = 0.0
    t = 0.0
    ListTime = []
    ListX = []
    ListTime.append(t)
    ListX.append(x)

    while t <= maxTime:
        g1 = random.gauss(0,1)
        x += g1*math.sqrt(dt)
        t += dt
        ListTime.append(t)
        ListX.append(x)

    plot(ListTime, ListX)
    xlabel('$t$')
    ylabel('$X_t$')

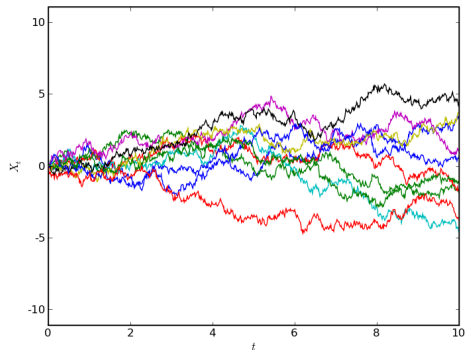
    nRealize -= 1

savefig('Wiener.png')
show()

```

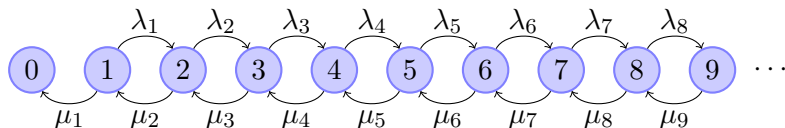
Exact algorithm:

$$\mathbf{W}_{t+\Delta t} = \mathbf{W}_t + \sqrt{\Delta t}\mathbf{G}.$$



Approximating a Markov chain

When realizations of a Markov chain move over a large number of states, we may seek a continuous-space approximation of the dynamics (and vice versa). To find the SDE, we need to consider the infinitesimal parameters. Consider a birth and death process that is in state n at time t .



As $\Delta t \rightarrow 0$,

$$\mathbb{E}(\mathbf{X}_{t+\Delta t} - n) = (\lambda_n - \mu_n)\Delta t \quad \text{and} \quad \mathbb{E}((\mathbf{X}_{t+\Delta t} - n)^2) = (\lambda_n + \mu_n)\Delta t^2.$$

Thus the appropriate SDE, that lets \mathbf{X}_t take real, rather than integer, values is

$$d\mathbf{X}_t = (\lambda(x) - \mu(x))dt + (\lambda(x) + \mu(x))^{\frac{1}{2}}d\mathbf{W}_t.$$

Immunology

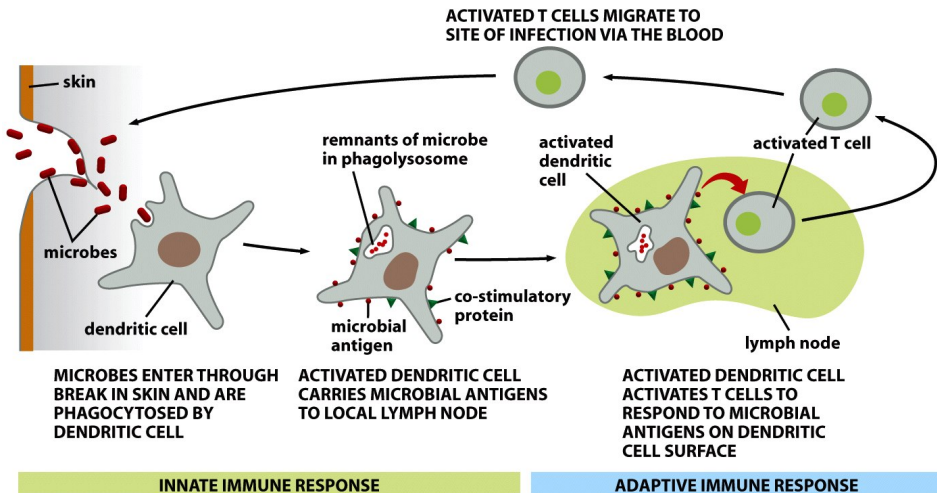
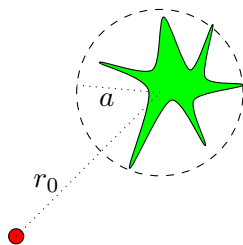


Figure 25-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

To hit or not to hit

If a T cell follows an unbiased Brownian path in three space dimensions, and starts a distance r_0 away from a spherical zone of attraction with radius a , the probability that it will hit the zone is

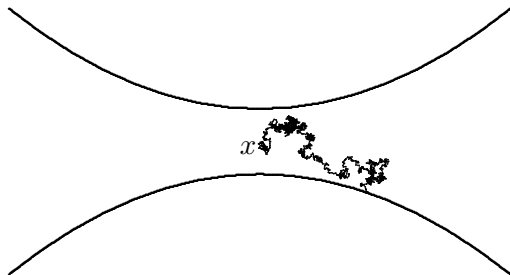
$$\Pr[\text{hit}] = \frac{a}{r_0}.$$



Hitting probability

If the initial condition $x \in \mathbb{R}^n$ is in a region $D \in \mathbb{R}^n$ with boundary ∂D , then the probability that the first intersection of \mathbf{B}_t with ∂D occurs in a subset, H , of the boundary satisfies

$$\nabla^2 p(x) = 0, \quad \text{with boundary conditions } \begin{cases} p(x) = 1, & x \in H \\ p(x) = 0, & x \in \partial D - H. \end{cases}$$

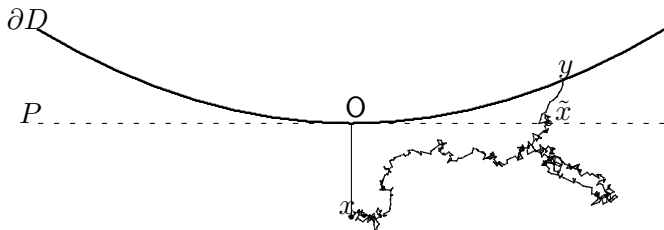


Hitting time

Let $\tau_D = \inf\{t : \mathbf{B}_t \in \partial D\}$.

If D is bounded, or such that $\Pr[\tau_D < \infty] = 1$, then the mean exit time $T(x) = \mathbb{E}(\tau_D | \mathbf{B}_0 = x)$ satisfies

$$\frac{1}{2}\nabla^2 T(x) = -1, \quad \text{with boundary condition } T(x) = 0, x \in \partial D.$$



Stochastics meets Electrostatics

Solutions of the Laplace and Poisson equations, can be written using the Green function, which is the occupation density at y . It is equal to the electrostatic potential at y due to a point charge at x .

The Green function, $G(x, y)$, for the Laplace equation on the domain D satisfies

$$\nabla^2 G(x, y) = \delta(x - y) + H(x, y),$$

where $\nabla^2 H(x, y) = 0$ on D . The function $H(x, y)$ is chosen to satisfy any boundary conditions.

If we choose $H(x, y)$ so that $G(x, y) = 0$ when $x \in A$, then

- The hitting probability density on ∂D is the electric field there:

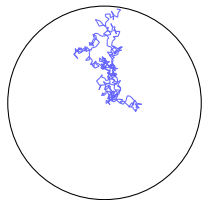
$$p(x) = \int_H \frac{\partial G(x, y)}{\partial n} dS.$$

- The mean exit time is obtained by integrating over the domain D :

$$T(x) = \int_D G(x, y) dy.$$

Finding the way out

If the cell is reflected everywhere except for a “polar cap” exit with radius a , then the mean time to escape is $\frac{\pi R^3}{3 Da}$.

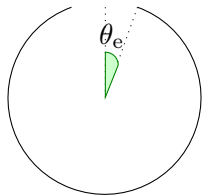


The time to hit an exit, that makes an angle θ_e , on the surface of a sphere is given by solving Laplace's equation:

$$\nabla^2 \tau = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \tau}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \tau}{\partial \theta} \right) = -D,$$

with boundary conditions;

$$\begin{aligned} \tau(R, \theta) &= 0 & \text{if } 0 \leq \theta < \theta_e \\ \frac{\partial \tau}{\partial r} &= 0 & \text{if } \theta_e \leq \theta \leq \pi. \end{aligned}$$



Immunology I

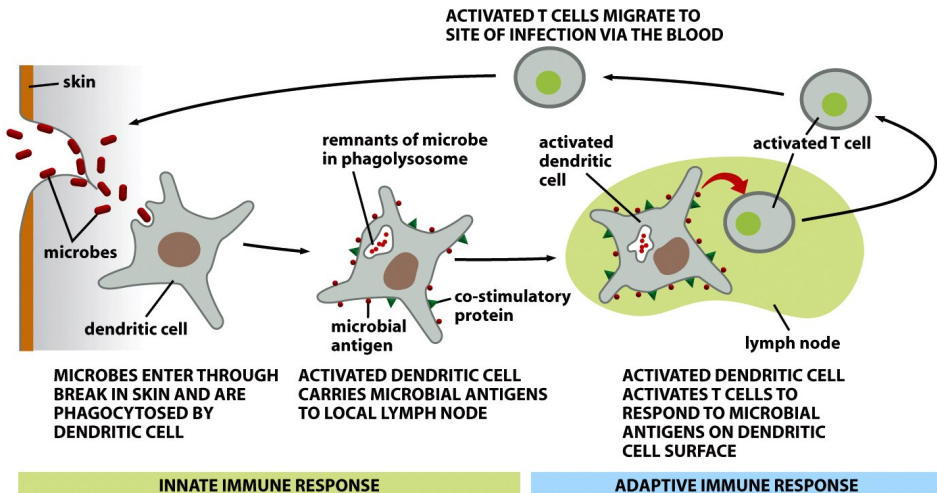


Figure 25-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Constant death rate

Assumption

Every T cell has a constant probability per unit time μ of dying, independent of all others.

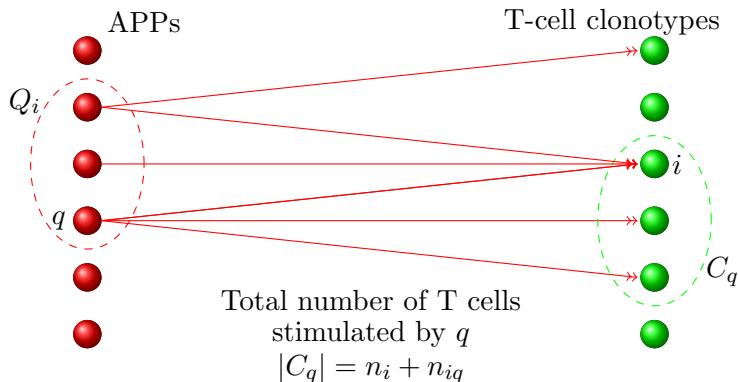
Consequence

If, at time t , there are n T cells of clonotype i then the probability that, at time $t + \Delta t$, there are $n - 1$ T cells of clonotype i is $n\mu\Delta t$, as $\Delta t \rightarrow 0$.

Assumption

Each APP stimulates at rate γ and the stimulus is shared equally among the T cells capable of recognising it.

Survival stimuli and clonotype competition



Stimulus rate received by a T cell of type i

$$\Lambda_i = \gamma \sum_{q \in Q_i} \frac{1}{|C_q|} = \gamma \sum_{q \in Q_i} \frac{1}{n_i + n_{iq}} = \gamma \sum_{r=0}^{\infty} \sum_{q \in Q_{ir}} \frac{1}{n_i + n_{iq}}$$

Stochastic modelling

