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Chapter 1

Introduction

1.1 The Chapman Kolmogorov Equation

In these notes we study Markov stochastic processes. A stochastic process is a process by which a random variable X changes over time. The state space S over which $X(t)$ ranges can be discrete, or continuous or a combination of both discrete and continuous. So, for example, it could be the number of particles of a particular chemical (discrete), or the position in space of a molecule (continuous), or the position in space of a particle that can change its configuration (or chemical activity, such as an enzyme).

In all cases we are interested in learning something about $p(\mathbf{x}, t)$ where \mathbf{x} is the state space coordinate, and t is time. If the state space is discrete, then \mathbf{x} is an integer, $\mathbf{x} = j = 0, 1, 2, \dots$, and it is often convenient to write $p(\mathbf{x}, t)$ as a vector with components $p_j(t)$. If the state space is continuous, then $\mathbf{x} \in R^n$, for example, $\mathbf{x} = (x, y, z)$ with $0 \leq x, y, z \leq 1$, while if the state space is both continuous and discrete, then \mathbf{x} is the cross product of continuous and discrete coordinates, say $\mathbf{x} = (x, y, z, j)$.

An important feature of $p(\mathbf{x}, t)$ is that

$$\int_S p(\mathbf{x}, t) d\mathbf{x} = 1, \quad (1.1)$$

where integration is over all of the state space, and \mathbf{x} must be properly interpreted. That is, if \mathbf{x} is a continuous coordinate, the integral is the usual Riemann (or Lebesgue) integral, whereas if \mathbf{x} is discrete, then the integral is with respect to the Dirac measure, i.e.

$$\int_S p(\mathbf{x}, t) d\mathbf{x} \equiv \sum_j p_j(t). \quad (1.2)$$

Now, the goal of this study is to understand the joint probability function $p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \dots)$. An important identity for probabilities is that for conditional probabilities

$$p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \dots; \mathbf{y}_1, \tau_1; \mathbf{y}_2, \tau_2; \dots) = p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \dots | \mathbf{y}_1, \tau_1; \mathbf{y}_2, \tau_2; \dots) p(\mathbf{y}_1, \tau_1; \mathbf{y}_2, \tau_2; \dots). \quad (1.3)$$

The simplest example of a stochastic process is one for which there is complete independence, i.e.,

$$p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \cdots) = \prod_j p(\mathbf{x}_j, t_j). \quad (1.4)$$

This is true, for example, with repeated Bernoulli trials, such as a sequence of coin flips. However, for the processes studied here, we do not expect complete independence.

Now, from the definition of the marginal probability,

$$\begin{aligned} p(\mathbf{x}_1, t_1) &= \int_S p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2) d\mathbf{x}_2 \\ &= \int_S p(\mathbf{x}_1, t_1 | \mathbf{x}_2, t_2) p(\mathbf{x}_2, t_2) d\mathbf{x}_2, \end{aligned} \quad (1.5)$$

and

$$\begin{aligned} p(\mathbf{x}_1, t_1 | \mathbf{x}_3, t_3) &= \int_S p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2 | \mathbf{x}_3, t_3) d\mathbf{x}_2 \\ &= \int_S p(\mathbf{x}_1, t_1 | \mathbf{x}_2, t_2; \mathbf{x}_3, t_3) p(\mathbf{x}_2, t_2 | \mathbf{x}_3, t_3) d\mathbf{x}_2, \end{aligned} \quad (1.6)$$

where $t_1 > t_2 > t_3$. However, a Markov process is a process for which the probability depends only on the most recent history, i.e.

$$p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \cdots | \mathbf{y}_1, \tau_1; \mathbf{y}_2, \tau_2; \cdots) = p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2; \cdots | \mathbf{y}_1, \tau_1), \quad (1.7)$$

when $\tau_1 > \tau_2 > \cdots$.

It follows that for Markov processes,

$$\begin{aligned} p(\mathbf{x}_1, t_1 | \mathbf{x}_3, t_3) &= \int_S p(\mathbf{x}_1, t_1; \mathbf{x}_2, t_2 | \mathbf{x}_3, t_3) d\mathbf{x}_2 \\ &= \int_S p(\mathbf{x}_1, t_1 | \mathbf{x}_2, t_2) p(\mathbf{x}_2, t_2 | \mathbf{x}_3, t_3) d\mathbf{x}_2. \end{aligned} \quad (1.8)$$

This equation, called the Chapman-Kolmogorov equation, is foundational to all that is done in the following notes. Its importance cannot be overstated.

Chapter 2

Discrete State Space

2.1 The Master Equation

Suppose we have a discrete random variable X , that can take on discrete (possibly infinite) values x_i . We denote by $P_i(t)$ the probability that $X = x_i$ at time t . Let

$$p_{ij}(t, s) = P(X = x_i, t | x = x_j, s), \quad t > s \quad (2.1)$$

be the probability of a transition from state x_j to state x_i between times s and t . Note that

$$\sum_j P(X = x_i, t | x = x_j, s) = 1, \quad (2.2)$$

and

$$\sum_i P(X = x_i, t | x = x_j, s) = 1, \quad (2.3)$$

since X has to be somewhere at times t and s . According to the Chapman-Kolmogorov equation

$$P(x_i, t | x_k, u) = \sum_j P(x_i, t | x_j, s) P(x_j, s | x_k, u) \quad (2.4)$$

Now, observe that

$$\lim_{t \rightarrow s} P(x_i, t | x_j, s) = \begin{cases} 0 & i \neq j \\ 1 & i = j \end{cases}, \quad (2.5)$$

so that

$$P(x_i, t + \Delta t | x_j, t) = W_{ij}(t) \Delta t + o(\Delta t), \quad (2.6)$$

and

$$P(x_i, t + \Delta t | x_j, t) = W_{ij}(t) \Delta t + o(\Delta t), \quad (2.7)$$

and

$$P(x_i, t + \Delta t | x_i, t) = 1 - \sum_{j \neq i} W_{ij}(t) \Delta t + o(\Delta t). \quad (2.8)$$

Consequently, from the Chapman-Kolmogorov equation

$$P_i(t + \Delta t) = \sum_j P(x_i, t + \Delta t | x_j, s) P_j(t) \quad (2.9)$$

$$= \left(1 - \sum_{j \neq i} W_{ij}(t) \Delta t\right) P_i(t) + \sum_{j \neq i} W_{ij}(t) \Delta t P_j(t) + o(\Delta t). \quad (2.10)$$

Taking the limit as $\Delta t \rightarrow 0$, we find

$$\frac{dP_i}{dt} = \sum_{j \neq i} W_{ij} P_j - \left(\sum_{j \neq i} W_{ij}\right) P_i. \quad (2.11)$$

This can be represented in matrix form as

$$\frac{dP}{dt} = AP, \quad (2.12)$$

where A has off-diagonal entries $a_{ij} = W_{ij}$ and diagonal entries $a_{ii} = -\sum_{j \neq i} W_{ij}$. Consequently, $1^T A = 0$, which means that the column sums are zero. This also implies that $\frac{d}{dt} 1^T P = 0$ so that $1^T P = 1$ for all time, as it must be for a probability distribution.

2.2 Birth-Death processes

Here is the problem. Suppose we have a finite population of particles that can be created (birth) or decay (death). How does the population change over time, and will it go extinct, and if so when?

2.2.1 A Poisson process

To get started with a simpler problem, consider a waiting time problem (a Poisson process). How long does it take for n events to occur, if all events are independent, and if the probability of an event occurring in time dt is λdt ?

We let $P_j(t)$ be the probability that j events have taken place by time t . Then,

$$\frac{dP_0}{dt} = -\lambda P_0, \quad (2.13)$$

and

$$\frac{dP_n}{dt} = \lambda P_{n-1} - \lambda P_n, \quad (2.14)$$

for $n > 1$, with initial data $P_0(0) = 1$, $P_n(0) = 0$ for $n > 1$.

The conjecture is that the solution is of the form

$$P_n(t) = \frac{1}{n!} \lambda^n t^n \exp(-\lambda t). \quad (2.15)$$

This is certainly correct for $P_0(t)$. We check it inductively:

$$\frac{dP_n}{dt} = n \frac{1}{n!} \lambda^n t^{n-1} \exp(-\lambda t) - \lambda \frac{1}{n!} \lambda^n t^n \exp(-\lambda t) = \lambda P_{n-1} - \lambda P_n, \quad (2.16)$$

as desired.

It is also easy to find the generating function. Set $g(z, t) = \sum_{k=0}^{\infty} P_k z^k$ so that

$$\frac{\partial g}{\partial t} = \sum_{k=1}^{\infty} \lambda P_{k-1} z^k - \lambda \sum_{k=0}^{\infty} P_k z^k, \quad (2.17)$$

$$= z\lambda \sum_{k=0}^{\infty} P_k z^k - \lambda \sum_{k=0}^{\infty} P_k z^k, \quad (2.18)$$

$$= \lambda(z-1)g, \quad (2.19)$$

with initial data $g(z, 0) = 1$. This is actually an ordinary differential equation, with solution

$$g(z, t) = \exp((z-1)\lambda t), \quad (2.20)$$

and Taylor series

$$g(z, t) = \exp(-\lambda t) \sum_{k=0}^{\infty} \frac{1}{k!} (\lambda t)^k z^k \quad (2.21)$$

so that $P_n(t) = \frac{1}{n!} \lambda^n t^n \exp(-\lambda t)$, as stated above.

2.2.2 Stochastic Death process

Suppose we begin with N particles (e.g. carbon-14 molecules) that can undergo radioactive decay with rate constant λ . When will the population go extinct (i.e., every molecule has decayed)?

This process can be represented as the chemical reaction



or as the state diagram



where S_n is the state with n molecules.

Often this process is described using an ode of the form

$$\frac{du}{dt} = -\lambda u, \quad (2.24)$$

where u is a continuous variable describing the density or concentration of the molecules. However, with this equation the population never goes extinct, because the solution $u(t)$ cannot become zero. Of course, the difficulty is that we are using a continuous model when only a discrete model can work. So, we write the master equation for P_n , the probability that at time t the population has n members,

$$\frac{dP_n}{dt} = \lambda(n+1)P_{n+1} - \lambda n P_n, \quad (2.25)$$

with initial conditions $P_N(0) = 1$ and $P_n(0) = 0$ for $n \neq N$.

It takes some work, but one can show by induction, that the solution to this problem is

$$P_j(t) = \binom{N}{j} \exp(-\lambda j t) (\exp(\lambda t) - 1)^{N-j}. \quad (2.26)$$

The calculation is left to the reader. Notice that this is exactly the binomial distribution with $p(t) = \exp(-\lambda t)$.

A different idea to find the solution is to try a generating function, $g(z, t) = \sum_{k=0}^{\infty} P_k z^k$, and observe that

$$\begin{aligned} \frac{\partial g}{\partial t} &= \sum_{k=0}^{\infty} \lambda(k+1) P_{k+1} z^k - \sum_{k=0}^{\infty} \lambda k P_k z^k, \\ &= \lambda \sum_{k=0}^{\infty} (k+1) P_{k+1} z^k - \lambda z \sum_{k=0}^{\infty} k P_k z^{k-1}, \\ &= \lambda \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_{k+1} z^{k+1} - \lambda z \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_k z^k, \\ &= \lambda \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_k z^k - \lambda z \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_k z^k, \\ &= \lambda(1-z) \frac{\partial g}{\partial z}. \end{aligned} \quad (2.27)$$

The initial data for this are

$$g(z, 0) = z^N, \quad (2.28)$$

and the solution is found using the method of characteristics. The solution is constant along characteristics, satisfying

$$\frac{dz}{dt} = \lambda(z-1). \quad (2.29)$$

It follows easily that

$$\ln(z-1) = \ln(z_0-1) + \lambda t, \quad (2.30)$$

or

$$z_0 = 1 + (z-1) \exp(-\lambda t), \quad (2.31)$$

Thus, the solution is

$$g(z, t) = z_0^N = (1 - \exp(-\lambda t) + z \exp(-\lambda t))^N, \quad (2.32)$$

which can easily be expanded using the binomial expansion.

The mean and variance are easily calculated using facts about the binomial distribution, namely

$$\mu(t) = N \exp(-\lambda t), \quad (2.33)$$

which is the deterministic answer for the population size, and

$$var(t) = N(\exp(-\lambda t) - \exp(-2\lambda t)), \quad (2.34)$$

More generally, if λ is a function of time,

$$\ln(z - 1) = \ln(z_0 - 1) \int_0^t \lambda(s) ds, \quad (2.35)$$

or

$$z_0 = 1 + (z - 1) \exp\left(-\int_0^t \lambda(s) ds\right), \quad (2.36)$$

Thus, the solution is

$$g(z, t) = (1 + (z - 1) \exp\left(-\int_0^t \lambda(s) ds\right))^N, \quad (2.37)$$

which can easily be expanded using the binomial expansion.

There is yet another way to find a solution. Suppose we try a solution of the form

$$P_j(t) = \binom{N}{j} q^j (1 - q)^{N-j}, \quad (2.38)$$

where q is an unknown function of t .

We substitute this into the equation (2.25) and find

$$\binom{N}{j} (j - Nq) q_t = \lambda(j + 1) \binom{N}{j + 1} q^2 - \lambda j \binom{N}{j} q(1 - q), \quad (2.39)$$

which reduces to

$$q_t = -\lambda q. \quad (2.40)$$

In other words, the binomial distribution (2.38) is a solution of (2.25) provided $q(t)$ is a solution of (2.40), even if λ is a nonconstant function of time.

Now the extinction probability is

$$P_0(t) = g(0, t) = (1 - \exp(-\lambda t))^N, \quad (2.41)$$

and the expected time of going extinct is given by

$$E(t) = \int_0^\infty t P_0'(t) dt. \quad (2.42)$$

One can calculate this integral, however, below we show another way to determine the expected extinction time that is more generally applicable.

2.2.3 Stochastic Birth Process

Consider the stochastic birth problem where individual particles reproduce with birth rate b . This can be represented as the chemical reaction



or with the state diagram



The master equation for this process is

$$\frac{dp_n}{dt} = b(n-1)p_{n-1} - bp_n, \quad n = 1, 2, \dots, \quad (2.45)$$

and we suppose $p_a(0) = 1$, meaning that at the start $t = 0$ there are a molecules.

The solution is the negative binomial distribution

$$p_n(t) = \binom{n-1}{a-1} (\exp(-bt))^a (1 - \exp(-bt))^{n-a}, \quad n = a, a+1, \dots \quad (2.46)$$

The proof uses induction.

Mean and variance are $\mu = a \exp(bt)$ and $\sigma^2 = a \exp(bt)(\exp(bt) - 1)$.

We can also use a generating function, as follows:

$$g = \sum_{k=1}^{\infty} p_k z^k, \quad (2.47)$$

and then observe that

$$\frac{\partial g}{\partial t} = \sum_{k=1}^{\infty} b(k-1)p_{k-1}z^k - \sum_{k=1}^{\infty} bk p_k z^k \quad (2.48)$$

$$= bz^2 \sum_{k=2}^{\infty} (k-1)p_{k-1}z^{k-2} - bz \sum_{k=1}^{\infty} k p_k z^{k-1} \quad (2.49)$$

$$= bz^2 \frac{\partial}{\partial z} \sum_{k=2}^{\infty} p_{k-1}z^{k-1} - bz \frac{\partial}{\partial z} \sum_{k=1}^{\infty} p_k z^k \quad (2.50)$$

$$= b(z^2 - z) \frac{\partial g}{\partial z}, \quad (2.51)$$

$$(2.52)$$

with initial data $g(0, z) = z^a$.

The solution for g can be found using the method of characteristics. Set $\frac{dz}{d\tau} = b(z - z^2)$, $\frac{dt}{d\tau} = 1$, and then

$$\frac{dg}{d\tau} = \frac{\partial g}{\partial t} \frac{dt}{d\tau} + \frac{\partial g}{\partial z} \frac{dz}{d\tau} \quad (2.53)$$

$$= \frac{\partial g}{\partial t} + \frac{\partial g}{\partial x} b(z - z^2) = 0. \quad (2.54)$$

This we solve easily: $g = z_0^a$ along the curves

$$\ln\left(\frac{z}{z-1}\right) = \ln\left(\frac{z_0}{z_0-1}\right)bt, \quad (2.55)$$

or along

$$z_0 = \frac{z \exp(-bt)}{1 - z(1 - \exp(-bt))}. \quad (2.56)$$

From this we easily find the solution using the negative binomial expansion

$$(1-x)^{-a} = \sum_{k=0}^{\infty} \binom{a+k-1}{a-1} x^k. \quad (2.57)$$

The Negative Binomial Distribution

Question: What is the negative binomial distribution?

Consider the binomial distribution $p_{n,k}$, the probability of k successes in n trials,

$$p_{n,k} = \binom{n}{k} p^k (1-p)^{n-k}. \quad (2.58)$$

Now we ask, what is the probability of $n+k$ trials to achieve exactly n successes, with n fixed. The answer is closely related, namely

$$q_{n,k} = p_{k+n-1, n-1} p = \binom{n+k-1}{n-1} p^n (1-p)^k, \quad (2.59)$$

since the first $n-1$ successes in $n+k-1$ trials follow a binomial distribution.

Properties of the negative binomial follow from the identity

$$(1-x)^{-n} = \sum_{k=0}^{\infty} \binom{k+n-1}{n-1} x^k. \quad (2.60)$$

From this it follows that

$$\begin{aligned} \sum_{k=0}^{\infty} q_{n,k} &= \sum_{k=0}^{\infty} \binom{n+k-1}{n-1} p^n (1-p)^k, \\ &= p^n \sum_{k=0}^{\infty} \binom{n+k-1}{n-1} (1-p)^k, \\ &= p^n (1 - (1-p))^{-n} = 1. \end{aligned} \quad (2.61)$$

Now calculate the expected value:

$$\begin{aligned} E(k) &= \sum_{k=0}^{\infty} k \binom{n+k-1}{n-1} p^n (1-p)^k, \\ &= (1-p)^n p \sum_{k=0}^{\infty} k \binom{n+k-1}{n-1} (1-p)^{k-1}, \\ &= (1-p)^n p \frac{d}{dq} \sum_{k=0}^{\infty} \binom{n+k-1}{n-1} q^k, \\ &= (1-p)^n p \frac{d}{dq} (1-q)^{-n}, \\ &= nq(1-q)^{-1} = \frac{n}{p}(1-p). \end{aligned} \quad (2.62)$$

It follows that

$$E(n+k) = n + \frac{n}{p}(1-p) = \frac{n}{p}. \quad (2.63)$$

Next,

$$\begin{aligned}
E(k^2) &= \sum_{k=0}^{\infty} k^2 \binom{n+k-1}{n-1} p^n (1-p)^k, \\
&= \sum_{k=0}^{\infty} k(k-1) \binom{n+k-1}{n-1} p^n (1-p)^k + \sum_{k=0}^{\infty} k \binom{n+k-1}{n-1} p^n (1-p)^k, \\
&= (1-q)^n q^2 \sum_{k=0}^{\infty} k(k-1) \binom{n+k-1}{n-1} q^{k-2} + \frac{n}{p}(1-p), \\
&= (1-q)^n q^2 \frac{d^2}{dq^2} \sum_{k=0}^{\infty} \binom{n+k-1}{n-1} q^k + \frac{n}{p}(1-p), \\
&= (1-q)^n q^2 \frac{d^2}{dq^2} (1-q)^{-n} + \frac{n}{p}(1-p), \\
&= n(n+1) \frac{q^2}{(1-q)^2} + \frac{n}{p}(1-p) = n(n+1) \frac{(1-p)^2}{p^2} + \frac{n}{p}(1-p). \tag{2.64}
\end{aligned}$$

From this we calculate the variance as

$$Var(n+k) = E\left(\left(n+k - \frac{n}{p}\right)^2\right) = E(k^2 + 2k \frac{n}{p}(1-p) + \frac{n^2}{p^2}(1-p)^2) = \frac{n}{p^2}(1-p), \tag{2.65}$$

which is what it says in the books.

2.2.4 The Full Birth-Death Problem

Suppose we have a birth-death process

$$X \xrightarrow{\beta} 2X, \quad X \xrightarrow{\alpha} \phi, \tag{2.66}$$

$$S_n \xrightleftharpoons[\alpha(n+1)]{\beta n} S_{n+1}. \tag{2.67}$$

The master equation for this is

$$\frac{dP_n}{dt} = \alpha(n+1)P_{n+1} - \alpha n P_n + \beta(n-1)P_{n-1} - \beta n P_n. \tag{2.68}$$

Past experience suggests that there is a generating function $g(z, t) = \sum_{k=0}^{\infty} P_k z^k$, and that

$$\begin{aligned}
\frac{\partial g}{\partial t} &= \alpha \sum_{k=0}^{\infty} (k+1) P_{k+1} z^k - \sum_{k=0}^{\infty} \alpha k P_k z^k + \beta \sum_{k=1}^{\infty} (k-1) P_{k-1} z^k - \beta \sum_{k=0}^{\infty} k P_k z^k, \\
&= \alpha \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_{k+1} z^{k+1} - \alpha z \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_k z^k + \beta z^2 \frac{\partial}{\partial z} \sum_{k=1}^{\infty} P_{k-1} z^{k-1} - \beta z \frac{\partial}{\partial z} \sum_{k=0}^{\infty} P_k z^k, \\
&= (1-z)(\alpha - \beta z) \frac{\partial g}{\partial z}. \tag{2.69}
\end{aligned}$$

Of course, the solution is found using the method of characteristics, $g = z_0^N$ (assuming $P_N(0) = 1$ corresponding to N particles initially), where

$$\frac{dz}{dt} = (1-z)(\beta z - \alpha), \quad (2.70)$$

which we can solve to find

$$\ln\left(\frac{\beta z - \alpha}{z - 1}\right) = \ln\left(\frac{\beta z_0 - \alpha}{z_0 - 1}\right) - (\alpha - \beta)t, \quad (2.71)$$

from which we find that

$$\left(\frac{\beta z - \alpha}{z - 1}\right) \exp((\alpha - \beta)t) = \left(\frac{\beta z_0 - \alpha}{z_0 - 1}\right). \quad (2.72)$$

We solve for z_0 to find

$$z_0 = \frac{(\beta z - \alpha) \exp((\alpha - \beta)t) - \alpha(z - 1)}{(\beta z - \alpha) \exp((\alpha - \beta)t) - \beta(z - 1)}. \quad (2.73)$$

It is possible (but not easy) to find the Taylor series expansion of g , however, the original problem was to find $P_0(t)$, which we can easily do. In fact,

$$P_0(t) = \left(\frac{\alpha \exp((\alpha - \beta)t) - \alpha}{\alpha \exp((\alpha - \beta)t) - \beta}\right)^N. \quad (2.74)$$

It is interesting to calculate the probability of extinction: If $\alpha > \beta$, then

$$\lim_{t \rightarrow \infty} P_0(t) = 1, \quad (2.75)$$

i.e., the population is certain to go extinct, whereas if $\beta > \alpha$, then

$$\lim_{t \rightarrow \infty} P_0(t) = \left(\frac{\alpha}{\beta}\right)^N. \quad (2.76)$$

Consider now the special case $\alpha = \beta$. Here the characteristic equation becomes

$$\frac{dz}{dt} = -\alpha(z - 1)^2, \quad (2.77)$$

for which

$$\frac{dz}{(z - 1)^2} = -\alpha dt, \quad (2.78)$$

$$\frac{1}{(z - 1)} = \alpha t \frac{1}{(z_0 - 1)}, \quad (2.79)$$

from which it follows that

$$z_0 = \frac{\alpha t z - \alpha t - z}{\alpha t z - \alpha t - 1}. \quad (2.80)$$

It further follows that

$$P_0(t) = \left(\frac{\alpha t}{\alpha t + 1}\right)^N. \quad (2.81)$$

Some questions to answer (maybe):

- What is the expected time of extinction in a birth-death process? (as a function of initial population size, N)? (at least I can calculate this numerically, if not analytically)
- What is the variance in population size in a birth death process? (can the moment equations be solved? How about the moment generating function?)

2.2.5 A Simple Chemical Reaction

Consider the chemical reaction



where A is fixed (or does not change enough to matter much). Let $P_n(t)$ be the probability that there are n X molecules at time t . Then

$$\frac{dP_n}{dt} = \alpha(n+1)P_{n+1} - \alpha P_n + \beta a P_{n-1} - \beta a P_n, \quad (2.83)$$

where $a = [A]$.

The generating function for this equation satisfies

$$\frac{\partial g}{\partial t} = (z-1)(\beta a g - \alpha \frac{\partial g}{\partial z}). \quad (2.84)$$

Suppose $g(z, 0) = G(z)$.

In characteristic form this is

$$\frac{dg}{dt} = \beta a(z-1)g, \quad \frac{dz}{dt} = \alpha(z-1), \quad (2.85)$$

so that

$$z-1 = (z_0-1) \exp(\alpha t), \quad (2.86)$$

and

$$\frac{dg}{dt} = \beta a(z_0-1) \exp(\alpha t) g. \quad (2.87)$$

It follows that

$$\frac{dg}{g} = \beta a(z_0-1) \exp(\alpha t) dt, \quad (2.88)$$

or

$$\ln\left(\frac{g}{g_0}\right) = \frac{\beta a}{\alpha}(z_0-1) \exp(\alpha t) = \frac{\beta a}{\alpha}(z-1). \quad (2.89)$$

Hence,

$$g(z, t) = G(z_0) \exp\left(\frac{\beta a}{\alpha}(z-1)\right), \quad z_0 = 1 + (z-1) \exp(-\alpha t). \quad (2.90)$$

There is an interesting observation to make with this process. Suppose we try a solution of the form

$$P_n(t) = \frac{e^{-q} q^n}{n!}, \quad (2.91)$$

where q is an unknown function of t . Then,

$$g = \sum_n^{\infty} P_n z^n = \exp(q(z-1)). \quad (2.92)$$

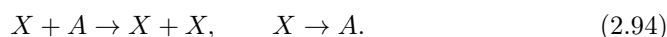
Substitute this into the equation (2.79) to find

$$q_t = \beta a - \alpha q. \quad (2.93)$$

In other words, the Poisson distribution (2.86) is a solution of the problem, provided $q(t)$ satisfies the ode (2.88), even if α and β are nonconstant functions of time. This is an example of a one dimensional invariant manifold. We will see more examples of these below.

2.2.6 Keizer's Paradox

Consider the chemical reaction



If N is the total number of molecules of X and A , then the master equation for the number n of X molecules is

$$\frac{dp_n}{dt} = -k_1 n(N-n)p_n + k_1(n-1)(N-n+1)p_n - k_2 n p_n + k_2(n+1)p_{n+1}. \quad (2.95)$$

Notice that the equation for $n = 0$ is

$$\frac{dp_0}{dt} = k_2 p_1. \quad (2.96)$$

This implies that it is possible to enter the state $n = 0$ but not leave it, i.e., $n = 0$ is an absorbing state. Consequently, regardless of initial data, this population is certain to go extinct eventually.

Now the reason there is a paradox here is that the differential equation model for this reaction is

$$\frac{dx}{dt} = k_1 x(A_0 - x) - k_2 x. \quad (2.97)$$

This equation has two steady state solutions, $x = 0$ which is unstable, and $x = A_0 - \frac{k_2}{k_1}$, which is stable (assuming $A_0 > \frac{k_2}{k_1}$). The contradiction is obvious. The differential equation model predicts that a steady positive solution will persist for all time, while the stochastic model predicts that x will go extinct no matter what the initial condition.

Which answer is correct?

An exploration and explanation of this can be found in [2].

2.3 The Gillespie Algorithm

Stochastic simulation of chemical reaction networks is readily accomplished using the Gillespie algorithm (also called the next reaction algorithm). Suppose we have a chemical reaction network consisting of K species, X_k , $k = 1, 2, \dots, K$, each of which can take on non-negative integer values. Associated with these species, there are J (state dependent) reaction rates R_j , $j = 1, 2, \dots, J$, and associated with each reaction there is a (state dependent) change of state $\Delta X_k = C_{kj}$ that occurs if reaction j takes place.

Suppose at a given time t , the state variables $X_k(t)$ are known. To determine the next reaction time, we let $\Sigma_m = \sum_{j=1}^m R_j(X)$ and then pick the time increment to the next reaction Δt to be

$$\Delta t = \frac{-1}{\Sigma_J} \ln \rho_1, \quad (2.98)$$

where ρ_1 is a uniformly distributed random number $0 \leq \rho_1 \leq 1$. Now, to decide which of the reactions takes place, pick j to be the integer for which

$$\Sigma_{j-1} \leq \rho_2 < \Sigma_j, \quad (2.99)$$

where ρ_2 is another uniformly distributed random number $0 \leq \rho_2 \leq 1$. Then increment the state variables by the change vector $\Delta X_k = C_{kj}$, i.e., let

$$X_k \rightarrow X_k + C_{kj}. \quad (2.100)$$

To illustrate this, suppose we wish to simulate the process



For this process, there are two reactions with rates of reaction

$$R_1 = \alpha x, \quad R_2 = \beta y, \quad (2.102)$$

and the associated change matrix is

$$\begin{array}{c|cc} & R_1 & R_2 \\ \hline x & -1 & 1 \\ y & 1 & -1 \end{array}. \quad (2.103)$$

Now suppose we have the reaction



The first reaction is the bimolecular reaction $X + Y \xrightarrow{\alpha} Z$, and if α is the reaction rate associated with the law of mass action for the two concentrations $[X]$, $[Y]$, then

$$\frac{d[X]}{dt} = -\alpha[X][Y]. \quad (2.105)$$

Since a concentration is number of molecules per volume, this implies that

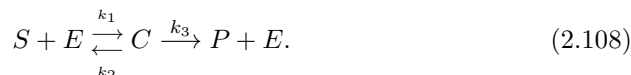
$$\frac{d}{dt} \frac{x}{V} = -\frac{\alpha}{V^2} xy. \quad (2.106)$$

where V is some reference volume. In other words, the reaction rate for the first reaction is $R_1 = \frac{\alpha}{V} xy$, where x and y are the integer numbers of molecules X and Y , respectively. The second reaction is a first order reaction, and so $R_2 = \beta z$. Finally the change matrix associated with this reaction network is

$$\begin{array}{c|cc} & R_1 & R_2 \\ \hline x & -1 & 1 \\ y & -1 & 1 \\ z & 1 & -1 \end{array} \quad (2.107)$$

Example - Michaelis Menten dynamics

Consider the enzyme reaction



We keep track of the number of molecules of each species denoted by x_S , x_E , and x_C , although it must be that $x_E + x_C = N_E$, a constant. The rates of the three possible reactions are

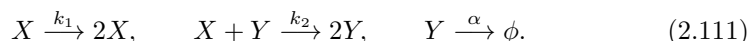
$$R_1 = k_1 x_S x_E, \quad R_2 = k_2 x_C, \quad R_3 = k_3 x_C, \quad (2.109)$$

and the change matrix is

$$\begin{array}{c|ccc} & R_1 & R_2 & R_3 \\ \hline x_S & -1 & 1 & 0 \\ x_E & -1 & 1 & 1 \\ x_C & 1 & -1 & -1 \end{array} \quad (2.110)$$

Example - Lotka Volterra Dynamics

Lotka Volterra dynamics can be viewed as coming from the chemical reactions



If we let x and y denote the integer number of X and Y species, respectively, then the three reaction rates are

$$R_1 = k_1 x, \quad R_2 = k_2 xy, \quad R_3 = k_3 y, \quad (2.112)$$

and the associated change matrix is

$$\begin{array}{c|ccc} & R_1 & R_2 & R_3 \\ \hline x & 1 & -1 & 0 \\ y & 0 & 1 & -1 \end{array} \quad (2.113)$$

Notice that the states $y = 0$ and $x = y = 0$ are absorbing states, so that at least one of the two populations is guaranteed to go extinct in finite time. A simulation of this is provided by the code `Lotka_volterra_master_eqn.m`.

2.4 Invariant Manifolds

A similar model (a birth-death process) describes the behavior of an ion channel with k independent subunits, all of which must be open in order for the ion channel to conduct ions. Here we have the state diagram



where j represents the number of open subunits.

Let p_j be the probability that j subunits are open. Then, the master equation is

$$\frac{dp_j}{dt} = \alpha(k-j+1)p_{j-1} + \beta(j+1)p_{j+1} - (\beta j + \alpha(k-j))p_j, \quad (2.115)$$

with appropriate restriction on the indices.

There are two interesting observations about this model. First, it is relatively easy to show that there is an invariant manifold given by

$$p_j = \binom{k}{j} q^j (1-q)^{k-j}, \quad (2.116)$$

with

$$\frac{dq}{dt} = \alpha(1-q) - \beta q. \quad (2.117)$$

This is a stable invariant manifold, the proof of which can be found in [3]. Second, we can find the equation for the generating function

$$g(t, z) = \sum_{j=0}^k p_j z^j, \quad (2.118)$$

to be

$$\begin{aligned} \frac{\partial g}{\partial t} &= \alpha \sum_{j=1}^{k+1} (k-j+1)p_{j-1}z^j + \beta \sum_{j=-1}^{k-1} (j+1)p_{j+1}z^j - \sum_{j=0}^k (\beta j + \alpha(k-j))p_j z^j \\ &= \alpha k \sum_{j=1}^{k+1} p_{j-1}z^j - \alpha \sum_{j=1}^{k+1} (j-1)p_{j-1}z^j + \beta \sum_{j=-1}^{k-1} (j+1)p_{j+1}z^j - (\beta - \alpha) \sum_{j=0}^k j p_j z^j - \alpha k \sum_{j=0}^k p_j z^j \\ &= \alpha k \sum_{j=0}^k p_j z^{j+1} - \alpha \sum_{j=0}^k j p_j z^{j+1} + \beta \sum_{j=0}^k j p_j z^{j-1} - (\beta - \alpha) \sum_{j=0}^k j p_j z^j - \alpha k \sum_{j=0}^k p_j z^j \\ &= \alpha k (z-1) \sum_{j=0}^k p_j z^j + (1-z)(\beta + \alpha z) \sum_{j=0}^k j p_j z^{j-1} \\ &= \alpha k (z-1)g + (1-z)(\beta + \alpha z) \frac{\partial g}{\partial z}. \end{aligned} \quad (2.119)$$

It is not hard to check that one solution of this pde is

$$g(z, t) = (qz + 1 - q)^k, \quad (2.120)$$

provided (2.112) holds. And, of course, (2.111) follows from the binomial expansion.

Notice also that if $q(0) = 0$, then $g(z, 0) = 1$, which implies all subunits are initially closed.

This is an interesting observation, that raises the question of when are there invariant manifolds. There are at least two kinds of invariant manifolds that are interesting.

2.4.1 Binomial Invariant Manifold

As we already saw above, if the transitions are

$$\alpha_k = a(N - k), \quad \beta_k = bk, \quad (2.121)$$

then p_k is the binomial distribution with parameter q where

$$\frac{dq}{dt} = \alpha(1 - q) - \beta q. \quad (2.122)$$

The important observation is that this is true even if α and β are time dependent.

2.4.2 Poisson Invariant Manifold

Suppose we look for a master equation whose solution is the Poisson distribution.

What must the birth-death process be? We let $p_k = \frac{q^k}{k!} \exp(-q)$ and then require

$$\frac{dp_k}{dt} = \alpha_{k-1}p_{k-1} - \alpha_k p_k + \beta_{k+1}p_{k+1} - \beta_k p_k. \quad (2.123)$$

We find

$$q_t = \frac{\alpha_{k-1}k - \alpha_k q}{k - q} + q \frac{\beta_{k+1}q - \beta_k(k+1)}{(k+1)(k-q)}, \quad (2.124)$$

which, if q is to be independent of k , requires that

$$\alpha_k = a, \quad \beta_k = kb, \quad (2.125)$$

in which case the equation governing q is

$$q_t = a - bq, \quad (2.126)$$

(even if a and b are time dependent). Correspondingly, the state diagram is

$$S_k \begin{array}{c} \xrightarrow{a} \\ \xleftarrow{b(k+1)} \end{array} S_{k+1}. \quad (2.127)$$

2.4.3 Multinomial Invariant Manifold

Suppose we have N identical independent k -state random variables, and suppose that the single random variable probabilities are $p_1(t)$, $p_2(t)$, ..., $p_k(t)$. Then, the

master equation for the probability of i_j random variables in state j , $j = 1, 2, \dots, k$ has an invariant manifold given by the multinomial distribution

$$p_{i_1, i_2, \dots, i_k} = \frac{n!}{i_1! i_2! \dots, i_k!} p_1^{i_1} p_2^{i_2} \dots p_k^{i_k}. \quad (2.128)$$

The proof is by a direct calculation. One must write out the master equation and then substitute (2.123) and somehow match up all the terms. To see how it works, we examine one of the possible reactions, between state j , and state k , say. Let's suppose that the rate of reaction from state j to state k is k_{jk} . Then, the master equation must have terms that look like

$$\frac{dP_{i_j i_k}}{dt} = (i_j + 1)k_{jk}P_{i_j+1, i_k-1} - i_j k_{jk}P_{i_j i_k} + (i_k + 1)k_{kj}P_{i_j-1, i_k+1} - i_k k_{kj}P_{i_j i_k}. \quad (2.129)$$

with all the other indices suppressed. Now substitution of (2.123) into (2.124) gives (after dividing by the multinomial)

$$\begin{aligned} \frac{i_j}{p_j} \frac{dp_j}{dt} + \frac{i_k}{p_k} \frac{dp_k}{dt} &= (i_j + 1)k_{jk} \frac{i_k}{i_j + 1} \frac{p_j}{p_k} - j k_{jk} + (i_k + 1)k_{kj} \frac{i_j}{i_k + 1} \frac{p_k}{p_j} - i_k k_{kj} \\ &= k_{jk} i_k \frac{p_j}{p_k} - i_j k_{jk} + k_{kj} i_j \frac{p_k}{p_j} - i_k k_{kj}. \end{aligned} \quad (2.131)$$

Because ultimately we want equations that are independent of i_j and i_k we take

$$\frac{dp_j}{dt} = k_{kj} p_k - k_{jk} p_j, \quad \frac{dp_k}{dt} = k_{jk} p_j - k_{kj} p_k. \quad (2.132)$$

In this way, we can see how the general case works, and the result is established.

2.4.4 The Negative Binomial Distribution

We ask what is the master equation (if any) whose invariant manifold is the negative binomial distribution with parameter q ? We begin with the negative binomial distribution

$$p_k = \frac{(n+k-1)!}{(n-1)! k!} q^n (1-q)^k. \quad (2.133)$$

Then substituting into a master equation with single jumps, to find

$$\frac{n}{q} \frac{dq}{dt} - \frac{k}{1-q} \frac{dq}{dt} = \alpha_{k+1} \frac{n+k}{k+1} (1-q) - \alpha_k + \beta_{k-1} \frac{k}{n+k-1} \frac{1}{1-q} - \beta_k. \quad (2.134)$$

We make the additional assumption that

$$\alpha_k = ak, \quad \beta_k = b(n+k), \quad (2.135)$$

and find that

$$\frac{n}{q} \frac{dq}{dt} - \frac{k}{1-q} \frac{dq}{dt} = a(n+k)(1-q) - ak + b \frac{k}{1-q} - b(n+k) \quad (2.136)$$

$$= \frac{n}{q} q(a(1-q) - b) - \frac{k}{1-q} q(a(1-q) - b), \quad (2.137)$$

$$= \left(\frac{n}{q} - \frac{k}{1-q} \right) q(a(1-q) - b). \quad (2.138)$$

Thus, if we set

$$\frac{dq}{dt} = q(a(1-q) - b), \quad (2.139)$$

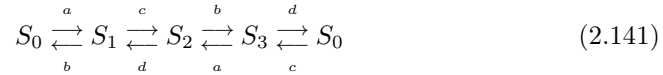
we have an invariant manifold. Notice that (2.134) is the logistic equation. Notice also, that as before, a and b can be time dependent. This process corresponds to the reaction scheme (or birth-death process)



Notice that with $n = 1$, this distribution is the geometric distribution. With $a = 0$ this is a standard birth process. In general, this is a rather strange birth-death process in which there are n individuals that do not die.

2.4.5 Other Invariants

We can generate lots of other processes with invariant structures. For example, the 4-state closed loop



has an invariant manifold of the form

$$p_0 = qs, \quad p_1 = q(1-s), \quad p_2 = (1-q)(1-s), \quad p_3 = (1-q)s, \quad (2.142)$$

provided

$$\frac{ds}{dt} = b(1-s) - as, \quad \frac{dq}{dt} = d(1-q) - cq. \quad (2.143)$$

More generally, suppose we have a system with two identical structures, with probabilities P and Q (vectors), and that the master equations are of the form

$$\frac{dP}{dt} = AP - aP + bQ, \quad \frac{dQ}{dt} = AQ + aP - bQ. \quad (2.144)$$

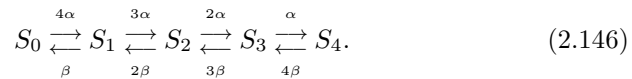
Then there is an invariant manifold reduction with $P = qS$, $Q = (1-q)S$ where

$$\frac{dS}{dt} = AS, \quad \frac{dq}{dt} = b(1-q) - aq. \quad (2.145)$$

Again, all of these invariant manifolds are correct, even if the rates are time dependent.

2.4.6 Applications- Ion Channel Dynamics

1. Potassium Ion Channel



The potassium ion channel is thought to have four independent subunits all of which must be open for conduction. The state diagram is shown above, with

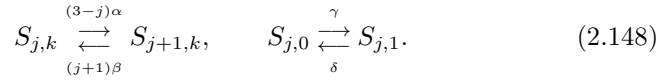
S_j corresponding to $j = 0, 1, 2, 3, 4$ open subunits. It follows that different states are binomially distributed with parameter n , where

$$\frac{dn}{dt} = \alpha(1 - n) - \beta n, \quad (2.147)$$

and the open probability is $P_o = n^4$.

2. Sodium Ion Channel

The sodium channel is thought to have three identical subunits that activate and one that inactivates. The eight different states are $S_{j,k}$ with $j = 0, 1, 2, 3$ and $k = 0, 1$. The two types of transitions are



Thus, the eight different states are double-binomially distributed

$$p_{j,k} = p_j^3(m)p_k^1(h), \quad (2.149)$$

where by $p_j^N(a)$ is meant a binomial distribution for N states with parameter a . The parameters m and h are governed by differential equations of the same form as above, namely,

$$\frac{dm}{dt} = \alpha(1 - m) - \beta m, \quad \frac{dh}{dt} = \gamma(1 - h) - \delta h, \quad (2.150)$$

3. Ryanodine receptors

One of the earliest models of the ryanodine receptor, due to Stern, is shown in Fig. 4.6.

This is a model of the type discussed above which can be described using two variables, say p and q with

$$\frac{dp}{dt} = k_{-1}(1 - p) - k_1 c^2 p, \quad \frac{dq}{dt} = k_{-2}(1 - q) - k_2 c q, \quad (2.151)$$

and then the open probability is $P_o = q(1 - p)$.

4. IP₃ receptors

The Keizer-DeYoung model for IP₃ receptors is shown in Fig. 2.2.

The thing to observe (and I don't think it has been observed before,) is that there is an invariant manifold here. In particular, if we let

$$X = \begin{pmatrix} x_{000} \\ x_{100} \\ x_{101} \\ x_{001} \end{pmatrix}, \quad Y = \begin{pmatrix} x_{010} \\ x_{110} \\ x_{111} \\ x_{011} \end{pmatrix}, \quad (2.152)$$

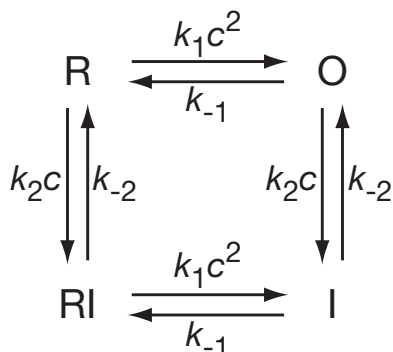


Figure 2.1: Model of the RyR due to Stern *et al.* (1999). R and RI are closed states, O is the open state, and I is the inactivated state. The rate constants depend on c , the Ca^{++} in the diadic cleft. Stern *et al.* used the parameters $k_1 = 35 \mu\text{M}^{-2} (\text{ms})^{-1}$, $k_{-1} = 0.06 (\text{ms})^{-1}$, $k_2 = 0.5 \mu\text{M}^{-1} (\text{ms})^{-1}$, $k_{-2} = 0.005 (\text{ms})^{-1}$.

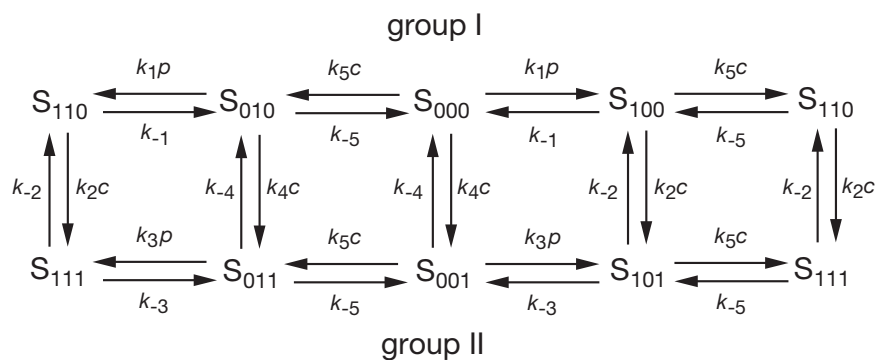


Figure 2.2: The binding diagram for the Keizer-DeYoung IP_3 receptor model. Here, c denotes Ca^{++} , and p denotes IP_3 .

$k_1 = 400 \mu\text{M}^{-1}\text{s}^{-1}$	$k_{-1} = 52 \text{s}^{-1}$
$k_2 = 0.2 \mu\text{M}^{-1}\text{s}^{-1}$	$k_{-2} = 0.21 \text{s}^{-1}$
$k_3 = 400 \mu\text{M}^{-1}\text{s}^{-1}$	$k_{-3} = 377.2 \text{s}^{-1}$
$k_4 = 0.2 \mu\text{M}^{-1}\text{s}^{-1}$	$k_{-4} = 0.029 \text{s}^{-1}$
$k_5 = 20 \mu\text{M}^{-1}\text{s}^{-1}$	$k_{-5} = 1.64 \text{s}^{-1}$

Table 2.1: Parameters of the eight-state IPR model (De Young and Keizer, 1992).

then the master equations are of the form

$$\frac{dX}{dt} = AX - k_5 cX + k_{-5}Y, \quad \frac{dY}{dt} = AQ + k_5X - k_{-5}Y. \quad (2.153)$$

It follows easily that if we set $X = \alpha S$, $Y = (1 - \alpha)S$, then

$$\frac{dS}{dt} = AS, \quad \frac{d\alpha}{dt} = k_{-5}(1 - \alpha) - k_5 c\alpha, \quad (2.154)$$

is an invariant manifold. Thus, it is not necessary to work with the full 8-state model (actually 7 because of conservation), but only a 4-state model.

2.5 Mean Exit Times and Splitting Probabilities

Suppose the master equation can be written as

$$\frac{d}{dt} \begin{pmatrix} Q \\ P \end{pmatrix} = \frac{d}{dt} \begin{pmatrix} 0 & B \\ 0 & A \end{pmatrix} \begin{pmatrix} Q \\ P \end{pmatrix}, \quad (2.155)$$

where the Q states are absorbing states. To find the splitting probability

$$Q^\infty = \int_0^\infty \frac{dQ}{dt} dt = B \int_0^\infty P dt \quad (2.156)$$

$$= BA^{-1} \int_0^\infty \frac{dP}{dt} dt = -BA^{-1}P(0). \quad (2.157)$$

The expected exit time is

$$E(t|Q) = \int_0^\infty t \frac{dQ}{dt} dt = BA^{-1} \int_0^\infty t \frac{dP}{dt} dt \quad (2.158)$$

$$= -BA^{-1} \int_0^\infty P dt = -BA^{-2} \int_0^\infty \frac{dP}{dt} dt = BA^{-2}P(0). \quad (2.159)$$

However, since $\mathbf{1}^T B + \mathbf{1}^T A = 0$, it follows that $\mathbf{1}^T B A^{-1} = -\mathbf{1}^T$, so that

$$E(t) = \mathbf{1}^T E(t|Q) = \mathbf{1}^T B A^{-2} P(0) = -\mathbf{1}^T A^{-1} P(0). \quad (2.160)$$

An example. Consider the death process



for which the master equations are

$$\frac{dP_n}{dt} = \lambda(n+1)P_{n+1} - \lambda n P_n, \quad (2.162)$$

with initial conditions $P_N(0) = 1$ and $P_n(0) = 0$ for $n \neq N$. The solution of the problem $Ax = -e_N$ is equivalent to

$$\lambda x_N = 1, \quad \lambda(n+1)x_{n+1} - \lambda n x_n = 0, \quad n < N \quad (2.163)$$

from which it follows that

$$x_n = \frac{1}{\lambda n}, \quad (2.164)$$

and the

$$E(t) = \frac{1}{\lambda} \sum_{n=0}^N \frac{1}{n}. \quad (2.165)$$

Now, consider an example in which there are $N + 1$ boxes with a particle that can jump from box to box with rate α , but if it enters box 0 or N , it cannot leave. This can be represented with the state diagram

$$S_0 \xleftarrow{\alpha} S_1 \xrightleftharpoons[\alpha]{\alpha} S_2 \cdots S_{N-2} \xrightleftharpoons[\alpha]{\alpha} S_{N-1} \xrightarrow{\alpha} S_N. \quad (2.166)$$

We would like to know the expected time to capture, starting from position k , as well as the splitting probabilities $\pi_0(k)$ and $\pi_N(k)$.

One can show directly that the solution of $Ax = -1$ is given by

$$x_k = \frac{k}{2\alpha}(N - k). \quad (2.167)$$

This is the mean first exit time starting from position k . Similarly, one can calculate directly that the splitting probabilities are

$$\pi_0(k) = \frac{N - k}{N}, \quad \pi_N(k) = \frac{k}{N}. \quad (2.168)$$

Chapter 3

Continuous State Space

3.1 Kolmogorov Forward Equations

3.2 Brownian Motion

The diffusion equation (??) was derived to describe the evolution of a chemical concentration, under the assumption that the concentration is a continuous variable, even though the number of molecules involved is necessarily an integer. Einstein recognized that the solution of the diffusion equation could also be interpreted as the probability distribution function for the location of a single particle undergoing some kind of a random walk. That is, if $p(x, t)$ is the solution of the diffusion equation

$$\frac{\partial p}{\partial t} = D\nabla^2 p, \quad (3.1)$$

then $\int_{\Omega} p(x, t) dx$ could be identified as the probability that a particle is in the region Ω at time t . More specifically, if $p(x, t|x_0, t_0)$ is the probability distribution function for the particle to be at position x at time t , given that it was at position x_0 at time t_0 , then

$$p(x, t_0|x_0, t_0) = \delta(x - x_0), \quad (3.2)$$

and solving the diffusion equation (in one spatial dimension) gives

$$p(x, t|x_0, t_0) = \frac{1}{2\sqrt{\pi D(t - t_0)}} \exp\left(-\frac{(x - x_0)^2}{4D(t - t_0)}\right), \quad (3.3)$$

provided $t > t_0$. It follows immediately that the mean and variance of this distribution are

$$\langle x \rangle = \int_{-\infty}^{\infty} xp(x, t|0, 0) dx = 0, \quad (3.4)$$

and

$$\langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 p(x, t|0, 0) dx = 2Dt. \quad (3.5)$$

Now suppose we let $X(t)$ represent the position as a function of time of a sample path. We can readily calculate that $X(t)$ is continuous, since for any $\epsilon > 0$, the probability of escaping from a region of size ϵ in time Δt is

$$\begin{aligned} \int_{|x-z|>\epsilon} p(x, t + \Delta t | z, t) dx &= 2 \int_{\epsilon}^{\infty} \frac{1}{2\sqrt{\pi D \Delta t}} \exp\left(-\frac{x^2}{4D\Delta t}\right) dx \\ &= \int_{\frac{\epsilon}{2\sqrt{D\Delta t}}}^{\infty} \exp(-x^2) dx, \end{aligned}$$

which in the limit $\Delta t \rightarrow 0$ approaches zero. On the other hand, the velocity of the particle is likely to be extremely large since

$$\begin{aligned} \text{Prob}\left(\frac{1}{\Delta t}(X(t + \Delta t) - X(t)) > k\right) &= \int_{k\Delta t}^{\infty} \frac{1}{2\sqrt{\pi D \Delta t}} \exp\left(-\frac{x^2}{4D\Delta t}\right) dx \\ &= \int_{\frac{k}{2}\sqrt{\frac{\Delta t}{\pi D}}}^{\infty} \exp(-x^2) dx \rightarrow \frac{1}{2}, \end{aligned} \quad (3.6)$$

in the limit that $\Delta t \rightarrow 0$. In other words, with probability 1 the absolute value of the velocity is larger than any number k , hence infinite.

If $D = 1$, the stochastic process $X(t)$ is known as a *Wiener process*, is usually denoted as $W(t)$, and is a model for Brownian motion.

Diffusion as a Markov process

A popular derivation of the diffusion equation is based on a Markovian random walk on a grid, as follows. We suppose that a particle moves along a one-dimensional line in discrete steps of length Δx at discrete times with time step Δt . At each step, however, the direction of motion is random, with probability $\frac{1}{2}$ of going to the left and probability $\frac{1}{2}$ of going to the right. If $p(x, t)$ is the probability of being at position x at time t , then

$$p(x, t + \Delta t) = \frac{1}{2}p(x + \Delta x, t) + \frac{1}{2}p(x - \Delta x, t). \quad (3.7)$$

Now we make the assumption that $p(x, t)$ is a smooth function of both x and t and find the Taylor series expansion of (3.7),

$$\Delta t \frac{\partial p}{\partial t} + O(\Delta t^2) = \frac{\Delta x^2}{2} \frac{\partial^2 p}{\partial x^2} + O(\Delta x^4). \quad (3.8)$$

In the limit that Δt and Δx both approach zero, keeping $\frac{\Delta x^2}{\Delta t} = 1$, we find the diffusion equation with diffusion coefficient $\frac{1}{2}$.

3.2.1 Sample Paths; the Langevin equation

The diffusion equation describes the probability distribution that a particle is at a particular place at some time, but does not describe how the particle actually moves. The challenge, of course, is to write (and solve) an equation for motion that

is random and continuous, but nowhere differentiable. Obviously, one cannot use a standard differential equation to describe the motion of such a particle. So, instead of writing $\frac{dx}{dt} = \text{something}$ (which does not make sense since the velocity $\frac{dx}{dt}$ of a Brownian particle is not finite), it is typical to write

$$dx = \sqrt{2D}dW. \quad (3.9)$$

To make careful mathematical sense of this expression requires a discussion of the Ito or Stratonovich calculus, topics which are beyond the scope of this text. However, a reasonable verbal description of what this means in practical terms is as follows. The term dW is intended to represent the fact that the displacement of a particle after a very short time interval, say dt , is a random variable having three properties, namely, it is uncorrelated with previous displacements (it has no memory and is therefore Markovian), it has zero mean, and it has variance dt , in the limit $dt \rightarrow 0$. This is also referred to as uncorrelated *Gaussian white noise*. In fact, this definition is rigged so that the probability distribution for this particle is described by the diffusion equation.

For this text, it is important to know how to numerically calculate representative sample paths, and to this end we write

$$dx = \sqrt{2Ddt}N(0, 1), \quad (3.10)$$

where $N(0, 1)$ represents the Gaussian (normal) distribution with zero mean and variance 1. The interpretation of this is that at any given time one randomly chooses a number n from a normal distribution, takes a step of size $dx = \sqrt{2Ddt}n$, and then increments time by dt . It can be shown that in the limit that $dt \rightarrow 0$, this converges to the Wiener process (3.9).

Equation (3.9) is an example of a stochastic differential equation, also called a Langevin equation. More generally, Langevin equations are of the form

$$dx = a(x, t)dt + \sqrt{2b(x, t)}dW, \quad (3.11)$$

or, in a form that suggests a numerical algorithm,

$$dx = a(x, t)dt + \sqrt{2b(x, t)dt}N(0, 1). \quad (3.12)$$

Here $a(x, t)$ represents the deterministic part of the velocity, since if there were no noise ($b(x, t) = 0$), this would be the same as the deterministic equation

$$\frac{dx}{dt} = a(x, t). \quad (3.13)$$

Thus, the displacement dx is a random variable, with mean value $a(x, t)dt$ and variance $2b(x, t)dt$, in the limit $dt \rightarrow 0$.

The special case $a(x, t) = -x$, $b(x, t) = 1$, called an *Ornstein-Uhlenbeck* process, is important in the study of molecular motors, for example, and shows up in many places throughout these notes.

3.2.2 The Fokker-Planck equation

The diffusion equation is the simplest example of an equation describing the evolution of the probability distribution function for the position of a particle. More generally, if we suppose that the position of the particle is continuous in time (no finite jumps are possible), that the Chapman-Kolmogorov equation (1.8) holds, and that the displacement of the particle in time dt has mean $a(x, t)dt$ and variance $2b(x, t)dt$, then one can derive that the probability distribution $p(x, t)$ for the position, x , of the particle at time t , is governed by

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}(a(x, t)p) + \frac{\partial^2}{\partial x^2}(b(x, t)p), \quad (3.14)$$

called the *Fokker-Planck* equation. Note that, since this equation models the motion of a particle, which must be at a single position y at the starting time, t_0 , the initial condition must therefore be $p(x, t_0|y, t_0) = \delta(x - y)$.

More generally, it is possible to start with the Chapman-Kolmogorov equation (1.8) and derive a general version of the Fokker-Planck equation that includes discrete jump processes. We visit this later with a discussion of jump-velocity processes.

An extremely important problem is the so-called *mean first exit time problem*, in which we wish to determine how long a particle stays in a particular region of space. Before we can solve this problem we must first determine the equation for the conditional probability, $p(x, t|y, \tau)$, as a function of y and $\tau < t$, with x and t fixed. That is, we want to know the probability distribution function for a particle with known position x at time t to have been at the location y at time $\tau < t$.

The equation governing this conditional probability is most easily derived by using the Chapman-Kolmogorov equation

$$p(x, t|z, s) = \int_S p(x, t|y, \tau)p(y, \tau|z, s)dy. \quad (3.15)$$

Differentiating this with respect to τ , we find

$$0 = \int_S \frac{\partial}{\partial \tau} p(x, t|y, \tau)p(y, \tau|z, s)dy + \int_S p(x, t|y, \tau) \frac{\partial}{\partial \tau} p(y, \tau|z, s)dy. \quad (3.16)$$

Using the forward Fokker-Planck equation (3.14), we find

$$0 = \int_S \frac{\partial}{\partial \tau} p(x, t|y, \tau)p(y, \tau, z, s)dy + \int_S p(x, t|y, \tau) \left(-\frac{\partial}{\partial y}(a(y, \tau)p(y, \tau, z, s)) + \frac{\partial^2}{\partial y^2}(b(y, \tau)p(y, \tau, z, s)) \right) dy. \quad (3.17)$$

Then, integrating by parts (and ignoring boundary contributions), we find

$$0 = \int_S \left(\frac{\partial}{\partial \tau} p(x, t|y, \tau) + a(y, \tau) \frac{\partial}{\partial y} p(x, t|y, \tau) + b(y, \tau) \frac{\partial^2}{\partial y^2} p(x, t|y, \tau) \right) p(y, \tau|z, s)dy. \quad (3.18)$$

Because this must be true regardless of what $p(y, \tau|z, s)$ is,

$$\frac{\partial}{\partial \tau} p(x, t|y, \tau) = -a(y, \tau) \frac{\partial}{\partial y} p(x, t|y, \tau) - b(y, \tau) \frac{\partial^2}{\partial y^2} p(x, t|y, \tau), \quad (3.19)$$

subject to the condition $p(x, t|y, t) = \delta(x - y)$. This equation for the backward conditional probability is called the *backward Kolmogorov equation*. Notice that this is a *backward* diffusion equation, which in forward time is ill-posed. However, it is well posed when solved for backwards times $\tau < t$.

3.2.3 Fluctuation Dissipation Balance

An important example of brownian motion is that of a small particle in water for which

$$m\dot{v} + \xi v = F, \quad (3.20)$$

where F is the random force coming from the brownian motion of the solute particles. Expressed as a Langevin equation, this is

$$dv = -\frac{\xi}{m}vdt + \sqrt{2D}dW, \quad (3.21)$$

where dW is normal brownian forcing, and D , as yet unknown, specifies the amplitude of the forcing. To determine D , we invoke the fact from statistical physics that at equilibrium, the average kinetic energy of a particle is $\frac{1}{2}k_B T$, i.e.,

$$\frac{1}{2}m \langle v^2 \rangle = \frac{1}{2}k_B T. \quad (3.22)$$

There are several arguments by which this can be imposed. Perhaps the most direct is to write the Fokker-Planck equation for the pdf of particle velocity $p(v, t)$ as

$$p_t = \frac{\partial}{\partial v} \left(\frac{\xi}{m} v p \right) + D \frac{\partial^2 p}{\partial v^2}, \quad (3.23)$$

an Ornstein-Uhlenbeck equation.

Set $E = \langle v^2 \rangle = \int_{-\infty}^{\infty} v^2 p(v, t) dv$, and calculate that

$$E_t = \int_{-\infty}^{\infty} v^2 \frac{\partial}{\partial v} \left(\frac{\xi}{m} v p \right) dv + \int_{-\infty}^{\infty} v^2 D \frac{\partial^2 p}{\partial v^2} dv \quad (3.24)$$

$$= -2 \frac{\xi}{m} E + 2D. \quad (3.25)$$

Accordingly, at equilibrium, $E = \frac{Dm}{\xi}$. It follows that

$$\frac{1}{2}mE = \frac{1}{2} \frac{Dm^2}{\xi} = \frac{1}{2}k_B T, \quad (3.26)$$

so that

$$D = \frac{\xi}{m^2} k_B T, \quad (3.27)$$

which is the velocity diffusion coefficient, with units of velocity²/time.

Now consider the situation of a small molecule attached to a spring, so that

$$m\dot{v} + \xi v + kx = F, \quad \dot{x} = v. \quad (3.28)$$

More generally, the restoring force could be the gradient of a potential $U'(x)$.

The Langevin equations for this is

$$dv = -\frac{\xi}{m}vdt - \frac{k}{m}xdt + \sqrt{2\frac{\xi}{m^2}k_B T}dW, \quad dx = vdt, \quad (3.29)$$

and the Fokker-Planck equation is

$$\frac{\partial p}{\partial t} = \frac{1}{m} \frac{\partial}{\partial v} ((\xi v + kx)p) - \frac{\partial}{\partial x} (vp) + \frac{\xi k_B T}{m^2} \frac{\partial^2 p}{\partial v^2}. \quad (3.30)$$

A nondimensionalization of this is to set $t = \tau \sqrt{\frac{m}{k}}$, $v = \sqrt{\frac{k_B T}{m}}u$, $x = \sqrt{\frac{k_B T}{k}}y$, and we find

$$\frac{\partial p}{\partial \tau} = \frac{\partial}{\partial u} (yp) - \frac{\partial}{\partial y} (up) + \frac{\xi^2}{km} \frac{\partial}{\partial u} (up + \frac{\partial p}{\partial u}). \quad (3.31)$$

Now an interesting question is what happens when $m \rightarrow 0$. A formal reduction of the Langevin equation (take $mdv = 0$) suggests that

$$dx = -\frac{k}{\xi}xdt + \sqrt{2\frac{k_B T}{\xi}}dW, \quad (3.32)$$

leading to the Fokker-Planck equation (an Ornstein-Uhlenbeck equation)

$$\frac{\partial p}{\partial \tau} = \frac{\partial}{\partial x} \left(\frac{k}{\xi}xp \right) + \frac{k_B T}{\xi} \frac{\partial^2 p}{\partial x^2}, \quad (3.33)$$

but is this correct? We will answer this later using adiabatic reduction.

3.2.4 Ornstein Uhlenbeck Equation

Consider the general Ornstein Uhlenbeck equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} ((k(x - y(t))p) + D(t) \frac{\partial^2 p}{\partial x^2}). \quad (3.34)$$

We try a solution of the form

$$p(x, t) = \frac{p_0}{\sqrt{a(t)}} \exp\left(-\frac{(x - b(t))^2}{a(t)}\right), \quad (3.35)$$

and upon substitution into the governing equation find the quadratic polynomial in x ,

$$\begin{aligned} 0 = & (4ak + 2\frac{da}{dt} - 8D)x^2 + (-4abk - 4aky + 4a\frac{db}{dt} - 4b\frac{da}{dt} + 16bD)x \\ & + 4abky - 2ka^2 - 4\frac{db}{dt}ab^2 + 2b\frac{da}{dt} - 8b^2D - a\frac{da}{dt} + 4aD. \end{aligned} \quad (3.36)$$

Consequently, we require each of the coefficients of this polynomial to be zero, which, it turns out, is equivalent to requiring

$$\frac{da}{dt} = 4D - 2ak \quad (3.37)$$

$$\frac{db}{dt} = k(y(t) - b). \quad (3.38)$$

The interpretation of this is clear. The parameter a goes exponentially to $\frac{2D}{k}$ (assuming D is constant), and b tracks y exponentially. Thus, the variance approaches the constant $\frac{D}{k}$, even if $y(t)$ is not constant.

3.3 Mean Exit Times

3.3.1 For Fokker-Planck Equations

Mean Exit Times

To find the mean first exit time from some region, say $a < y < b$, we note that

$$G(y, t) = \int_a^b p(x, t|y, 0)dx, \quad (3.39)$$

is the probability that the particle is in the domain at time t . Observe that, if $T(y)$ is the random variable for the time at which the particle first leaves the domain having started at y , then

$$P(T(y) > t) = G(y, t) = - \int_t^\infty G_t(y, t)dt, \quad (3.40)$$

and

$$P(T(y) < t) = - \int_0^t G_t(y, t)dt. \quad (3.41)$$

Thus, $-G_t(y, t)$ is the pdf for the random variable $T(y)$. Furthermore, the expected value of the random variable $T(y)$ is

$$E(T(y)) = - \int_0^\infty tG_t(y, t)dt = \int_0^\infty G(y, t)dt. \quad (3.42)$$

We also observe that, for a time-autonomous process, $p(x, t|y, 0) = p(x, 0|y, -t)$, so that

$$G_t(y, t) = \int_\Omega p_t(x, t|y, 0)dy = \int_\Omega p_t(x, 0|y, -t)dy. \quad (3.43)$$

Now, $p(x, 0|y, \tau)$ satisfies the backward Fokker-Planck equation

$$p_\tau = -a(y)p_y - b(y)p_{yy}, \quad (3.44)$$

so that

$$G_t = a(y)G_y + b(y)G_{yy}. \quad (3.45)$$

Finally, integrate this equation with respect to t to get

$$-1 = a(y)T_y + b(y)T_{yy}, \quad (3.46)$$

where for the sake of notational confusion, here $T \equiv E(T(y))$.

In addition, we must specify boundary conditions. The first thing to notice is that the boundary conditions on $T(y)$ are the adjoint boundary conditions associated with the adjoint operator for the backward Kolmogorov equation. To see what these are, notice that

$$\int p_t q dx = \int \left(-\frac{d}{dx}(a(x)p) + \frac{d^2}{dx^2}(b(x)p) \right) q dx \quad (3.47)$$

$$= \left(-a(x)p + \frac{d}{dx}(b(x)p)q - b(x)p \frac{dq}{dx} \right) \Big| \quad (3.48)$$

$$+ \int \left(a(x) \frac{dq}{dx} + b(x) \frac{d^2 q}{dx^2} \right) p dx, \quad (3.49)$$

so that the boundary term contribution is

$$\left(-a(x)p + \frac{d}{dx}(b(x)p)q - b(x)p \frac{dq}{dx} \right) \Big|. \quad (3.50)$$

Thus, if $p = 0$ at a boundary point, then $q = 0$ and hence $T = 0$ at the same point. However, if the process is reflecting, i.e., there is no flux, $J = a(x)p - \frac{d}{dx}(b(x)p) = 0$, then $\frac{dq}{dx} = \frac{dT}{dx} = 0$ at that boundary point. Other possible boundary conditions include the Robin boundary condition $-\frac{d}{dx}(b(x)p) = \alpha p$, which, if $a(x) = 0$, has the adjoint condition $-b(x) \frac{dq}{dx} = \alpha q$.

As an example, consider a pure diffusion process on a domain of length L with a reflecting boundary at $x = 0$ and an absorbing boundary at $x = L$. The mean first exit time satisfies the differential equation

$$DT_{xx} = -1, \quad (3.51)$$

subject to boundary conditions $T_x(0) = 0$, $T(L) = 0$. This has solution

$$T(x) = \frac{-x^2 + L^2}{2D}. \quad (3.52)$$

We readily calculate that $T(0) = \frac{L^2}{2D}$, as might be expected from (3.5). In addition, as x increases, $T(x)$ decreases, which again makes intuitive sense. The closer the particle starts to the absorbing boundary, the shorter is the mean first exit time.

We do not prove the statement here, but it can be shown that for any region Ω with boundary $\partial\Omega$, where the boundary is divided into two sub-boundaries $\partial\Omega_a$ and $\partial\Omega_r$, which are absorbing and reflecting, respectively, the expected escape time $T(x)$ for a particle starting at position x satisfies the boundary value problem

$$D\nabla^2 T = -1, x \in \Omega, \quad T \Big|_{\partial\Omega_a} = 0, \quad \mathbf{n} \cdot \nabla T \Big|_{\partial\Omega_r} = 0. \quad (3.53)$$

The solution of this problem is interestingly different for different spatial dimensions. For example, in one dimension, suppose the boundary at $x = 0$ is *reflecting*

(particles bounce off and cannot escape). Then, we must solve $D \frac{d^2 T}{dx^2} = -1$, subject to boundary conditions $T'(0) = 0$, $T(L) = 0$. The solution is

$$T(x) = \frac{L^2}{2D} \left(1 - \frac{x^2}{L^2}\right). \quad (3.54)$$

Compare this to the situation for escape from a circle of radius R , for which the escape time T satisfies

$$\frac{D}{r} \frac{d}{dr} \left(r \frac{dT}{dr} \right) = -1, \quad (3.55)$$

with $T(R) = 0$. The solution of this problem is

$$T(r) = \frac{R^2}{4D} \left(1 - \frac{r^2}{R^2}\right). \quad (3.56)$$

For escape from a sphere of radius R , T satisfies

$$\frac{D}{r^2} \frac{d}{dr} \left(r^2 \frac{dT}{dr} \right) = -1, \quad (3.57)$$

with $T(R) = 0$. The solution is

$$T(r) = \frac{R^2}{6D} \left(1 - \frac{r^2}{R^2}\right). \quad (3.58)$$

The obvious conclusion of this is that escape from the interior of a circle or from the interior of a sphere is two times, or three times, respectively, slower than along a line.

Consider now the capture problem: Consider the case where there is partial absorption at L , $-Dp_x = \alpha p$. We solve the equation (3.51) subject to the boundary conditions $T_x(0) = 0$, $-DT_x = \alpha T$. Remark: Notice that α has units of velocity. We find

$$T(x) = \frac{L^2 - x^2}{2D} + \frac{L}{\alpha}. \quad (3.59)$$

In three dimensions, the full absorption problem is

$$\frac{D}{r^2} \frac{d}{dr} \left(r^2 \frac{dT}{dr} \right) = -1, \quad (3.60)$$

subject to boundary conditions $T'(R) = 0$, $T(\rho) = 0$. Straightforward integration gives that

$$T(r) = \frac{1}{3D} \left(\frac{1}{2}(\rho^2 - r^2) + R^3 \left(\frac{1}{\rho} - \frac{1}{r} \right) \right). \quad (3.61)$$

Starting from $r = R$, this gives

$$T(R) = \frac{1}{3D} \left(\frac{1}{2}(\rho^2 - R^2) + R^3 \left(\frac{1}{\rho} - \frac{1}{R} \right) \right), \quad (3.62)$$

and in the limit $\rho \rightarrow 0$ this is unbounded. In other words, a particle of zero size cannot be found.

A similar calculation in 2 dimensions gives

$$T(r) = \frac{1}{2D} \left(\frac{1}{2}(\rho^2 - r^2) + R^2 \ln\left(\frac{r}{\rho}\right) \right). \quad (3.63)$$

Once again, this is infinite if $\rho \rightarrow 0$.

Binding to an interior point: Suppose there is a binding site in the interior of the domain. The probability density satisfies the forward Kolmogorov equations

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} - \alpha(x)p, \quad \frac{dq}{dt} = \int \alpha(x)p dx, \quad (3.64)$$

where $p(x, t)$ is the probability density for unbound particles, q is the density function for bound particles. The mean exit time for binding satisfies the equation

$$-1 = D \frac{d^2 T}{dx^2} - \alpha(x)T. \quad (3.65)$$

We suppose that there is reflection at $x = \pm L$ (i.e., $T'(\pm L) = 0$).

Suppose $\alpha(x) = \alpha\delta(x)$. Then,

$$T(x) = \begin{cases} \frac{1}{2D}(x^2 + 2Lx) + A & x < 0 \\ \frac{1}{2D}(x^2 - 2Lx) + A & x > 0 \end{cases}. \quad (3.66)$$

The constant A is determined by the jump condition

$$D \frac{\partial T}{\partial x} \Big|_{0^-}^{0^+} = \alpha A, \quad (3.67)$$

so that $A = \frac{2L}{\alpha}$.

Suppose that the boundary at $r = \rho$ is only partially absorbing so that $Dr^2 \frac{dp}{dr} = \alpha p$. Since, as noted above, $T(r)$ inherits the adjoint boundary conditions of p , the boundary condition for T is $Dr^2 \frac{dT}{dr} = \alpha p$ at $r = \rho$. We find directly that

$$T(r) = \frac{1}{3D} \left(\frac{1}{2}(\rho^2 - r^2) + R^3 \left(\frac{1}{\rho} - \frac{1}{r} \right) + \frac{R^3 - \rho^3}{3\alpha} \right). \quad (3.68)$$

Notice that the effect of partial binding is to simply increase the exit time by an amount inversely proportional to α , as one might expect, and in the limit $\alpha \rightarrow \infty$, we recover the fully absorbing result.

3.3.2 Reaction rates and Kramers' result

Here we consider the simple chemical reaction



with the goal of understanding something about the reaction rates k_+ , and k_- when the reaction is viewed as a stochastic process.

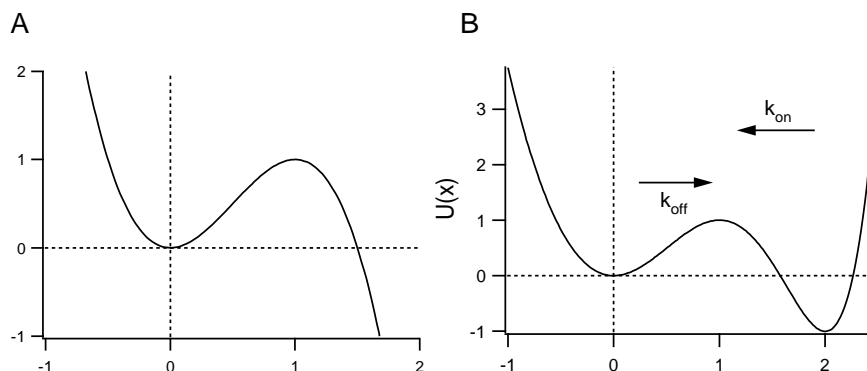


Figure 3.1: Potential energy profiles. A: a cubic profile, $U(x) = \Delta G(2x^2(3/2 - x))$, plotted for $\Delta G = 1$. B: a double well potential, $U(x) = \Delta G^0(\frac{19}{144}x^6 - \frac{1}{24}x^5 - \frac{77}{144}x^4 - \frac{4}{3}x^3 + \frac{25}{9}x^2)$, plotted for $\Delta G^0 = 1$.

One common model of a reaction rate is based on the mean first exit time of the time-dependent Fokker-Planck equation. This model assumes that a reactant particle can be modelled as a damped oscillator driven by a stochastic force, and that the reaction occurs once the particle reaches the peak of the energy profile between the reactant and product states. Although this model is based on a number of crude assumptions, it gives reasonably good results for a range of potential energy profiles, particularly those for which the energy wells are deep.

The mean first exit time is found from the solution of the ordinary differential equation

$$-U'(x)\frac{d\tau}{dx} + k_B T \frac{d^2\tau}{dx^2} = -\nu, \quad (3.70)$$

subject to $\tau(x_0) = 0$ at any boundary point x_0 where escape is allowed, or $\tau'(x_1) = 0$ at any boundary point where escape is not allowed, but instead there is reflection. The off-rate, or unbinding rate, is defined as the inverse of the mean first exit time from the bottom of the potential well.

To be specific, consider a potential $U(x)$ such as shown in Fig. 3.1A. Here $U(x)$ is a cubic polynomial, with a minimum at $x = 0$ and a maximum at $x = 1$, with $U(1) = \Delta G$. We expect the particle to spend most of its time near $x = 0$. However, if the particle gets to $x = 1$ it can escape to $x = \infty$, and is assumed to have reacted. Thus, the time to react (the inverse of the reaction rate) is approximated by the mean first passage time from $x = 0$ to $x = 1$.

More generally, suppose $U(x) = \Delta G u(\frac{x}{L})$ where $u'(0) = u'(1) = u(0) = 0$ and $u(1) = 1$, so that $x = 0$ is a local minimum and $x = L$ is a local maximum, and the height of the energy barrier is ΔG . The mean first passage time is the solution of (3.70) together with the boundary conditions $\tau(-\infty) = 0$ and $\tau(1) = 0$.

To find the solution it is useful to nondimensionalize (3.70). We set $y = \frac{x}{L}$ and

$\sigma = \alpha\tau$ and find

$$-au'(y)\frac{d\sigma}{dy} + \frac{d^2\sigma}{dy^2} = -1, \quad (3.71)$$

where $a = \frac{\Delta G}{k_B T}$, and $\alpha = \frac{\nu L^2}{k_B T}$. Now, using an integrating factor, it is easily shown that

$$\sigma(y) = \int_x^1 e^{au(s')} \left(\int_{-\infty}^{s'} e^{-au(s)} ds \right) ds', \quad (3.72)$$

and thus the time to react is $\tau(0) = \frac{\nu L^2}{k_B T} \sigma(0)$, where

$$\sigma(0) = \int_0^1 e^{au(s')} \left(\int_{-\infty}^{s'} e^{-au(s)} ds \right) ds'. \quad (3.73)$$

As we demonstrate below, this formula does not agree with the Arrhenius rate law for all parameter values. However, when the potential well at $x = 0$ is deep (i.e., when $a = \Delta G/(k_B T) \gg 1$), the two are in agreement. Here we provide a demonstration of this agreement.

Notice first that

$$\sigma(0) = \int_0^1 e^{au(s')} \left(\int_{-\infty}^1 e^{-au(s)} ds - \int_{s'}^1 e^{-au(s)} ds \right) ds'. \quad (3.74)$$

Clearly,

$$\begin{aligned} \int_0^1 e^{au(s')} \left(\int_{s'}^1 e^{-au(s)} ds \right) ds' &= \int_0^1 \left(\int_{s'}^1 e^{a(u(s')-u(s))} ds \right) ds' \\ &< \int_0^1 \left(\int_{s'}^1 ds \right) ds' = \frac{1}{2}. \end{aligned} \quad (3.75)$$

In fact, with a bit of work one can show that this integral approaches zero as $a \rightarrow \infty$. Thus,

$$\sigma(0) \approx \left(\int_0^1 e^{au(s')} ds' \right) \left(\int_{-\infty}^1 e^{-au(s)} ds \right). \quad (3.76)$$

We now use the fact that $y = 0$ and $y = 1$ are extremal values of $u(y)$ to approximate these integrals. When a is large, the integrands are well approximated by Gaussians, which decay to zero rapidly. Thus, near $y = 0$, $u(y) \approx \frac{1}{2}u''(0)y^2$ so that

$$\begin{aligned} \int_{-\infty}^1 e^{-au(s)} ds &\approx \int_{-\infty}^1 e^{-\frac{1}{2}au''(0)s^2} ds \\ &\approx \int_{-\infty}^{\infty} e^{-\frac{1}{2}au''(0)s^2} ds \\ &= \sqrt{\frac{2\pi}{au''(0)}}. \end{aligned} \quad (3.77)$$

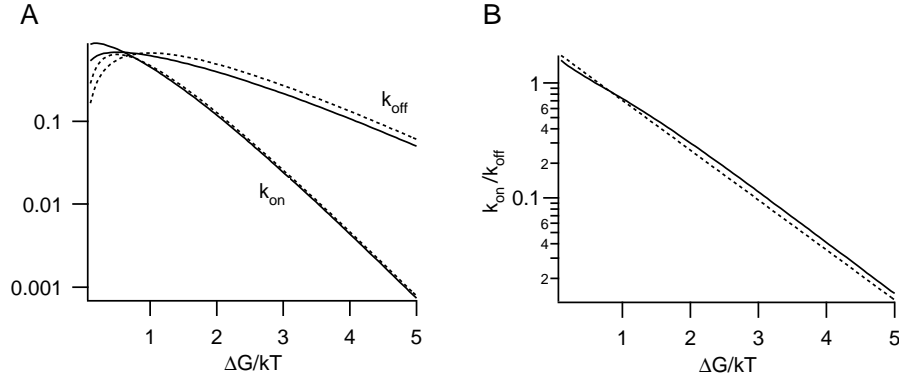


Figure 3.2: Reaction rates for the potential profile shown in Fig. 3.1B. A: exact (solid lines) and approximate (dashed lines) solutions for k_1 and k_{-1} , plotted as functions of $\Delta G^0/k_B T$. The exact solutions are calculated from (3.73), while the approximations are calculated from (3.79). For simplicity, we set $\nu L^2/k_B T = 1$. B: exact and approximate calculations of k_{-1}/k_1 . As in A, the exact solution is plotted as a solid line.

Similarly, near $y = 1$, $u(y) \approx 1 - \frac{1}{2}|u''(1)|(y-1)^2$, so that

$$\begin{aligned} \int_0^1 e^{au(s)} ds &\approx e^a \int_0^1 e^{-\frac{1}{2}|u''(1)|(s-1)^2} ds \\ &\approx e^a \int_{-\infty}^0 e^{-\frac{1}{2}|u''(1)|s^2} ds \\ &= \frac{1}{2} e^a \sqrt{\frac{2\pi}{a|u''(1)|}}. \end{aligned} \quad (3.78)$$

Combining (3.76), (3.77) and (3.78) gives

$$\tau(0) \approx \frac{\pi \nu L^2}{\Delta G \sqrt{|u''(0)||u''(1)|}} e^{\frac{\Delta G}{k_B T}}. \quad (3.79)$$

Since the reaction rate is the inverse of the mean first passage time, this gives the Arrhenius rate expression with

$$\kappa = \frac{\Delta G \sqrt{|u''(0)||u''(1)|}}{\pi \nu L^2}, \quad (3.80)$$

which is independent of T , but not ΔG . This formula was first derived by Kramers (1940).

A double well potential profile

Now suppose that $U(x)$ is a double well potential, such as that shown in Fig. 3.1B. In particular, suppose that $U(x) = \Delta G^0 u(\frac{x}{L})$, where $u(x)$ has two local minima at

$x = 0$ and $x = b > 1$, with a local maximum at $x = 1$. For the example in Fig. 3.1B, $\Delta G^0 = L = 1$ and $b = 2$. Note also that the potential profile is such that $\Delta G_{-1} = 2\Delta G^0$, $\Delta G_1 = \Delta G^0$.

According to Kramers' rate theory,

$$k_1 = \frac{\Delta G_1 \sqrt{u''(0)|u''(1)|}}{\pi\nu L^2} e^{-\frac{\Delta G_1}{k_B T}}, \quad (3.81)$$

$$k_{-1} = \frac{\Delta G_{-1} \sqrt{u''(b)|u''(1)|}}{\pi\nu L^2 (b-1)^2} e^{-\frac{\Delta G_{-1}}{k_B T}}, \quad (3.82)$$

To compare these with the exact solutions, in Fig. 3.2 we plot k_{-1} and k_1 for the double well potential shown Fig. 3.1B, calculated by numerical integration of (3.73), and using the approximation (3.81) and (3.82). Note that the reaction rates (both exact and approximate) are not exactly exponential functions of ΔG_i , and thus the curves in Fig. 3.2A are not straight lines (on a log scale). For the approximate rate constants this is because the prefactor is proportional to ΔG_i . Interestingly, the approximate solutions agree exactly with the Arrhenius rate law, when viewed as functions of T , while the exact solutions do not.

Next, we observe that using Kramers' formula, the equilibrium constant is

$$K_{\text{eq}} = \frac{k_{-1}}{k_1} = \frac{1}{(b-1)^2} \frac{u(1) - u(b)}{u(1) - u(0)} \sqrt{\frac{u''(b)}{u''(0)}} e^{-\frac{\Delta G^0}{k_B T}}. \quad (3.83)$$

In Fig. 3.2 we plot $\frac{k_{-1}}{k_1}$ for the double well potential shown in Fig. 3.1B, with the exact ratio shown as a solid curve and the approximate ratio from (3.83) shown as a dashed curve. As before, the exact ratio k_{-1}/k_1 (solid line, Fig. 3.1B) is not an exact exponential function of ΔG^0 , and thus does not give the correct equilibrium behavior. This results from the fact that, for small ΔG^0 , the mean first exit time of the Fokker-Planck equation is not a good model for the reaction rate.

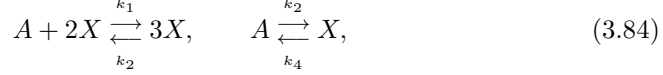
However, the ratio of the approximate expressions for the rate constants (3.83) is a true exponential function of ΔG^0 , as the dependence of ΔG^0 in the prefactors cancels out in the ratio. Hence, the dashed line in Fig. 3.2B is straight. Thus, paradoxically, the approximate solution gives better agreement to the correct equilibrium behavior than does the exact solution. However, one must be somewhat cautious with this statement, since there is a factor multiplying the exponential that is not equal to one (as it should be for correct equilibrium behavior), but depends on the details of the shape of the energy function. Thus, if the shape of the potential energy function is modified by, for example, an external voltage potential, this factor is modified as well, in a voltage dependent way.

3.3.3 Double Well Potentials - Examples

The Kramers result described above is but one example where exit from a double well potential is of interest. Here we describe other examples.

A trimolecular reaction

Consider the reaction



where A is assumed to be in sufficiently large quantities as to be fixed. We write the Master equation for this reaction using

$$t_+ = k_1 A x(x-1) + k_3 A, \quad t_- = k_2 x(x-1)(x-2) + k_4 x, \quad (3.85)$$

where x is the (integer) number of X molecules. Then, taking a large volume limit, we find the Fokker-Planck equation

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}((k_1 A x^2 + k_3 A - k_2 x^3 - k_4 x)p) + \frac{1}{N} \frac{\partial^2}{\partial x^2}(((k_1 A x^2 + k_3 A + k_2 x^3 + k_4 x)p). \quad (3.86)$$

The interesting feature of this is that for certain parameter values the deterministic dynamics are bistable. To determine when, we look for steady state solutions as

$$A = \frac{x(k_2 x^2 + k_4)}{k_1 x^2 + k_3}. \quad (3.87)$$

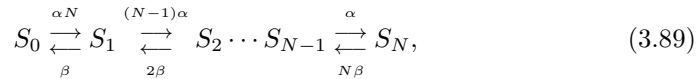
Then, using resultant analysis, we find that this is a monotone increasing function of x whenever $k_1 k_4 < 9k_2 k_3$, while it is a triphasic function whenever the opposite, $k_1 k_4 > 9k_2 k_3$.

Calcium Sparks

Here we present a model of calcium release dynamics from Ryanodine receptors (RyRs). We track the calcium concentration in the dyadic cleft, depicted in a yet to be drawn figure. Calcium is released into the cleft from the Endoplasmic Reticulum (ER) through RyRs, and it leaves the dyadic space to the cytoplasm via diffusion. The equation governing calcium concentration is straightforward,

$$\frac{dc}{dt} = gk(c_{ER} - c) + \delta(c_{cyl} - c), \quad (3.88)$$

where g is the single channel conductance, and k is the number of open channels. The channels are assumed to be independent, so the number of open channels is described by the state diagram



where

$$\alpha = f(c) = \frac{c^2}{K_c^2 + c^2}, \quad (3.90)$$

indicating that the open rate of RyRs is calcium concentration dependent. The full master equation for the number of open channels then has two rates,

$$a(k) = (N - k)f(c), \quad b(k) = k\beta. \quad (3.91)$$

Following a large N expansion, we find a Fokker Planck equation for the number of open channels to be

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x}((b(x) - a(x))p) + \frac{1}{2N} \frac{\partial^2}{\partial x^2}((a(x) + b(x))p). \quad (3.92)$$

Finally, we assume that δ is sufficiently large so that c can be taken to be in quasi-steady state, as

$$c(x) = \frac{gNx c_{ER} + \delta c_{cvt}}{gNx + \delta}. \quad (3.93)$$

The important observation is that the deterministic dynamics associated with this process is given by

$$\frac{dx}{dt} = a(x) - b(x) = (1-x)f(c(x)) - \beta x, \quad (3.94)$$

a function which for appropriate parameter values, is bistable. Thus, the spontaneous spark rate is understood as the rate at which x escapes from the leftmost well of a double well potential.

In the special case that $c_{cvt} = 0$, we can determine (using resultant analysis) that the bistable parameter region is that for which

$$4K_c^2 \beta^2 \delta^2 + 4K_c^2 \beta c_{ER} \delta gN + 4K_c^2 \beta \delta^2 - c_{ER}^2 g^2 N^2 < 0. \quad (3.95)$$

3.4 Splitting Probabilities

For the specific case of a Fokker-Planck equation on a line $a < x < b$, with the possibility of exit at either a or b , we want to know the probability of exiting through a , starting at position x , denoted $\pi_a(x)$, and the probability of exiting through b , starting from position x , denoted $\pi_b(x)$. Clearly, $\pi_a(x) + \pi_b(x) = 1$.

The Fokker-Planck equation for the evolution of $p(x, t|y, 0)$ is

$$\frac{\partial p}{\partial t} = -\frac{\partial J}{\partial x}, \quad (3.96)$$

where

$$J(x, t|y, 0) = a(x)p(x, t|y, 0) - \frac{\partial}{\partial x}(b(x)p(x, t|y, 0)), \quad (3.97)$$

is the flux of probability at position x , subject to absorbing boundary conditions $p(a, t) = p(b, t) = 0$. Now, the probability that the particle exits through b at a time greater than t is given by

$$g_b(y, t) = \int_t^\infty J(b, t'|y, 0) dt'. \quad (3.98)$$

Clearly,

$$\frac{\partial}{\partial t} g_b(y, t) = -J(b, t|y, 0) = \int_t^\infty \frac{\partial}{\partial t'} J(b, t'|y, 0) dt'. \quad (3.99)$$

Because this is a time invariant process, $p(x, t|y, 0) = p(x, 0|y, -t)$ and consequently, $J(x, t|y, 0) = J(x, 0|y, -t)$. It follows that both $p(x, 0|y, -t)$ and $J(x, 0|y, -t)$ satisfy the backward Kolmogorov equation

$$q_t = a(y) \frac{\partial}{\partial y} q(y, t|x, 0) + b(y) \frac{\partial^2}{\partial y^2} q(y, t|x, 0). \quad (3.100)$$

It follows that $g_b(y, t)$ satisfies the same equation, namely

$$\frac{\partial}{\partial t} g_b(y, t) = a(y) \frac{\partial}{\partial y} g_b(y, t) + b(y) \frac{\partial^2}{\partial y^2} g_b(y, t). \quad (3.101)$$

Observing that $g_b(y, 0) = \pi_b(y)$, we set $t = 0$ in (3.101) to find

$$0 = a(y) \frac{\partial}{\partial y} \pi_b(y) + b(y) \frac{\partial^2}{\partial y^2} \pi_b(y). \quad (3.102)$$

Finally, the boundary conditions on $\pi_b(y)$ are

$$\pi_b(a) = 0, \quad \pi_b(b) = 1. \quad (3.103)$$

More generally, suppose the boundary conditions are Robin conditions of the form

$$J = a(x)p(x, t|y, 0) - \frac{\partial}{\partial x} (b(x)p(x, t|y, 0)) = \alpha(x)p, \quad (3.104)$$

for $x = a, b$. Then, the boundary conditions for the backward equation are the adjoint conditions, given by

$$b(x) \frac{\partial q}{\partial x} + \alpha(x)q = 0. \quad (3.105)$$

Finally, this implies that the boundary conditions on π are given by

$$b(a) \frac{\partial \pi_a}{\partial x} + \alpha(a)\pi_a(a) = \alpha(a), \quad b(b) \frac{\partial \pi_a}{\partial x} + \alpha(b)\pi_a(b) = 0, \quad (3.106)$$

and

$$b(a) \frac{\partial \pi_b}{\partial x} + \alpha(a)\pi_b(a) = 0, \quad b(b) \frac{\partial \pi_b}{\partial x} + \alpha(b)\pi_b(b) = \alpha(b). \quad (3.107)$$

Example: Find the splitting probabilities for a diffusing particle with Robin conditions $-D \frac{\partial p}{\partial x} = \pm \alpha p$ at $x = \pm L$.

Solve the problem

$$D\pi_L'' = 0, \quad (3.108)$$

subject to boundary conditions

$$-D \frac{\partial \pi_L(-L)}{\partial x} = -\alpha \pi_L(-L), \quad -D \frac{\partial \pi_L(L)}{\partial x} = \alpha \pi_L(L) - \alpha. \quad (3.109)$$

We calculate directly that

$$\pi_L(x) = \frac{1}{2} \frac{\alpha x}{\alpha L + D} + \frac{1}{2}. \quad (3.110)$$

3.4.1 Exit through an interior point

Suppose that, in addition to exiting through the boundaries (i.e., $p(a) = p(b) = 0$), the particle can exit through an interior point, for example, by binding. The probability that the particle is unbound and at position x is given by the modified Fokker-Planck equation

$$\frac{\partial p}{\partial t} = -\frac{\partial J}{\partial x} - g(x)p(x, t|y, 0). \quad (3.111)$$

and the probability that the particle binds after time t is given by $Q(y, t)$ where

$$Q(y, t) = \int_t^\infty \left(\int_a^b g(x)p(x, t'|y, 0)dx \right) dt'. \quad (3.112)$$

arguing similar to above

$$\frac{\partial}{\partial t} Q(y, t) = - \int_a^b g(x)p(x, t|y, 0)dx = \int_t^\infty \left(\int_a^b g(x) \frac{\partial}{\partial t'} p(x, t'|y, 0)dx \right) dt' \quad (3.113)$$

and since this is a time autonomous process $p(x, t|y, 0) = p(x, 0|y, -t)$ and consequently, satisfies the backward equation (the adjoint)

$$q_t = a(y) \frac{\partial}{\partial y} q(y, t|x, 0) + b(y) \frac{\partial^2}{\partial y^2} q(y, t|x, 0) - g(y)q(y, t|x, 0). \quad (3.114)$$

It follows that $Q(y, t)$ satisfies the same equation. Then, setting $t = 0$, we find

$$-g(y) = a(y) \frac{\partial \pi_c}{\partial y} + b(y) \frac{\partial^2 \pi_c}{\partial y^2} - g(y)\pi_c, \quad (3.115)$$

where $\pi_c(y) = Q(y, 0)$, and $\frac{\partial}{\partial t} Q(y, 0) = - \int_a^b g(x)p(x, 0|y, 0)dx = - \int_a^b g(x)\delta(y-x)dx = -g(y)$. Boundary conditions are $\pi_c(a) = \pi_c(b) = 0$. The quantities π_a and π_b are similar (assuming $p(a) = p(b) = 0$) with

$$0 = a(y) \frac{\partial \pi_\alpha}{\partial y} + b(y) \frac{\partial^2 \pi_\alpha}{\partial y^2} - g(y)\pi_\alpha, \quad (3.116)$$

for $\alpha = a, b$, with boundary conditions $\pi_a(a) = \pi_b(b) = 1$, and $\pi_a(b) = \pi_b(a) = 0$. Notice that $u = \pi_a + \pi_b + \pi_c$ is a solution of

$$-g(y) = a(y) \frac{\partial u}{\partial y} + b(y) \frac{\partial^2 u}{\partial y^2} - g(y)u, \quad (3.117)$$

with $u(a) = u(b) = 1$, and clearly $u(y) = 1$ is the unique solution, as it must be.

Example: Suppose a diffusing particle can bind to a binding site at $x = \frac{L}{2}$ or can escape from the boundary at $x = L$, while the boundary at $x = 0$ is reflecting. Find the splitting probabilities.

We must solve the problem

$$D\pi_L'' - \lambda\delta(x - \frac{L}{2})\pi_L = 0, \quad (3.118)$$

subject to boundary conditions

$$\pi'_L(0) = 0, \quad \pi_L(L) = 1. \quad (3.119)$$

It follows easily that

$$\pi_L(x) = \begin{cases} A & x < \frac{L}{2} \\ B(x-L) + 1 & x > \frac{L}{2} \end{cases}, \quad (3.120)$$

and then requiring continuity and a jump condition at $x = \frac{L}{2}$ we find

$$\pi_L(x) = \begin{cases} \frac{2D}{2D+\lambda L} & x < \frac{L}{2} \\ \frac{2\lambda}{2D+\lambda L}(x-L) + 1 & x > \frac{L}{2} \end{cases}, \quad (3.121)$$

Example: Suppose instead that a particle can bind and unbind from the binding site at position $x = \frac{L}{2}$, and escape from $x = L$, reflect at $x = 0$. How does binding/unbinding delay the escape time?

The forward Kolmogorov equations are

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} - \lambda \delta(x - \frac{L}{2})p + \beta q, \quad (3.122)$$

$$\frac{\partial q}{\partial t} = \lambda \delta(x - \frac{L}{2})p - \beta q. \quad (3.123)$$

The equations for exit time are

$$-1 = D \frac{\partial^2 T_p}{\partial x^2} - \lambda \delta(x - \frac{L}{2})(T_p - T_q), \quad (3.124)$$

$$-1 = \beta(T_p - T_q), \quad (3.125)$$

with $T'_p(0) = 0$ and $T_p(L) = 0$.

It follows easily that

$$T_p(x) = \begin{cases} -\frac{x^2}{2D} + A & x < \frac{L}{2} \\ -\frac{(x-L)^2}{2D} + B(x-L) & x > \frac{L}{2} \end{cases}, \quad (3.126)$$

We apply continuity and jump condition at $x = \frac{L}{2}$ to find

$$T_p(x) = \begin{cases} -\frac{x^2}{2D} + \frac{L}{2D}(L + \frac{\lambda}{\beta}) & x < \frac{L}{2} \\ -\frac{(x-L)^2}{2D} + \frac{1}{D}(L + \frac{\lambda}{\beta})(x-L) & x > \frac{L}{2} \end{cases}, \quad (3.127)$$

Apparently the time that the particle is bound during this process is

$$T_b(x) = \begin{cases} \frac{\lambda L}{2D\beta} & x < \frac{L}{2} \\ \frac{\lambda}{D\beta}(x-L) & x > \frac{L}{2} \end{cases}, \quad (3.128)$$

and consequently the number of times the particle binds (and unbinds) is

$$N_b(x) = \begin{cases} \frac{\lambda L}{2D} & x < \frac{L}{2} \\ \frac{\lambda}{D}(x-L) & x > \frac{L}{2} \end{cases}, \quad (3.129)$$

3.5 Jump-Velocity Processes

In this section we examine the stochastic differential equation

$$\frac{dy}{dt} = f(y, x) \quad (3.130)$$

where x is a discrete random variable taking on values x_k , $k = 0, 1, \dots, n$. The process for x is a Markov process, and there are transition probabilities $W_{j,k}$ which is the transition probability of going from state k to state j . Following standard arguments, the forward Kolmogorov equation for the probability distribution function $p(y, x, t)$ is (following Gardiner)

$$\frac{\partial p_k}{\partial t} = -\frac{\partial}{\partial y}(f_k p_k) + \sum_j (W_{j,k} p_j - W_{j,k} p_k), \quad (3.131)$$

where $p_k = p(y, x_k, t)$ and $f_k = f(y, x_k)$. We can write this in vector notation as

$$\frac{\partial \mathbf{p}}{\partial t} = -\frac{\partial}{\partial y}(\mathbf{F}\mathbf{p}) + A\mathbf{p}, \quad (3.132)$$

where \mathbf{F} is the diagonal matrix with elements f_k .

It also follows that the backward Kolmogorov equation is

$$\frac{\partial q_k}{\partial t} = -f_k \frac{\partial q_k}{\partial y} - \sum_j W_{j,k}(q_k - q_j), \quad (3.133)$$

which in vector form is

$$\frac{\partial \mathbf{q}}{\partial t} = -\mathbf{F} \frac{\partial \mathbf{q}}{\partial y} - A^T \mathbf{q}. \quad (3.134)$$

To find the mean first exit time from some region, say $a < y < b$, we let

$$G_j(z, t) = \int_a^b \sum_k p_k(y, t|z, x_j, 0) dy = P(T \geq t), \quad (3.135)$$

where T is the exit time, starting from initial position z , x_j (so we denote it as $T_j(z)$). Note that $G_j(z, 0) = 1$. Because this process is autonomous,

$$p_k(y, t|z, x_j, 0) = p_k(y, 0|z, x_j, -t) = q_j(z|y, k), \quad (3.136)$$

which is governed by the backward Kolmogorov equation

$$\frac{\partial q_j}{\partial t} = f_j \frac{\partial q_j}{\partial z} + \sum_i W_{i,j}(q_j - q_i), \quad (3.137)$$

so that

$$\frac{\partial G_j}{\partial t} = f_j \frac{\partial G_j}{\partial z} + \sum_i W_{i,j}(G_j - G_i). \quad (3.138)$$

Now observe that

$$P(T_j(z) \leq t) = 1 - G_j(z, t), \quad (3.139)$$

so that

$$\langle T_j(z) \rangle = - \int_0^\infty t \frac{\partial G_j}{\partial t} dt = \int_0^\infty G_j(z, t) dt. \quad (3.140)$$

It follows from (3.138) that

$$-1 = f_j \frac{\partial \langle T_j(z) \rangle}{\partial z} + \sum_i W_{i,j} (\langle T_j(z) \rangle - \langle T_i(z) \rangle). \quad (3.141)$$

with appropriate boundary conditions.

At this juncture it is worth observing that this derivation extends naturally to *any* forward Kolmogorov equation of the form

$$p_t = L(\mathbf{x})p, \quad (3.142)$$

where $L(\mathbf{x})$ is a differential-matrix operator. It follows directly that the mean first exit time satisfies the equation

$$L^*(\mathbf{y})T = -\mathbf{1}, \quad (3.143)$$

where L^* is the adjoint operator for L defined formally by

$$\int_S q(\mathbf{x}, t) L(\mathbf{x}) p(\mathbf{x}, t) d\mathbf{x} = \int_S p(\mathbf{x}, t) L^*(\mathbf{x}) q(\mathbf{x}, t) d\mathbf{x}. \quad (3.144)$$

As an example, consider the process in which a particle randomly switches between traveling to the right and traveling to the left. The pdf is governed by the Kolmogorov system

$$\frac{\partial p_+}{\partial t} = -\frac{\partial V p_+}{\partial x} + \alpha(p_- - p_+), \quad (3.145)$$

$$\frac{\partial p_-}{\partial t} = \frac{\partial V p_-}{\partial x} + \alpha(p_+ - p_-), \quad (3.146)$$

and consequently, the mean first exit times are given by the solution of

$$V \frac{\partial T_+}{\partial x} + \alpha(T_- - T_+) = -1, \quad (3.147)$$

$$-V \frac{\partial T_-}{\partial x} + \alpha(T_+ - T_-) = -1, \quad (3.148)$$

with boundary conditions $T_+(L) = 0$, $T_-(-L) = 0$. Here $T_+(x)$ denotes the mean exit time starting in the + state at position x . We find the solution of this to be

$$T_+(x) = \frac{1}{V^2}(L-x)(\alpha(L+x)+V), \quad T_-(x) = \frac{1}{V^2}(x+L)(\alpha(L-x)+V), \quad (3.149)$$

Notice that $T_+(x) + T_-(x) = \frac{1}{V^2}(\alpha(2L^2 - 2x^2) + 2LV)$.

For this problem the splitting probabilities satisfy

$$V \frac{\partial \pi_+^+}{\partial x} + \alpha(\pi_-^+ - \pi_+^+) = 0, \quad (3.150)$$

$$-V \frac{\partial \pi_-^+}{\partial x} + \alpha(\pi_+^+ - \pi_-^+) = 0, \quad (3.151)$$

with $\pi_+^+(L) = 1$, $\pi_-^+(-L) = 0$ (for exit on the right). Here the notation is that $\pi_i^j(x)$ means the probability of exiting at j , starting in state i at position x . Then, we find

$$\pi_+^+(x) = \frac{\alpha(L+x) + V}{2L\alpha + V}, \quad \pi_-^+(x) = \frac{\alpha(L+x)}{2L\alpha + V}, \quad (3.152)$$

and the probability of exiting on the right is

$$\pi_+^+(x) + \pi_-^+(x) = \frac{2\alpha(L+x) + V}{2L\alpha + V}. \quad (3.153)$$

For exiting on the left,

$$\frac{\partial V \pi_+^-}{\partial x} + \alpha(\pi_-^- - \pi_+^-) = 0, \quad (3.154)$$

$$-\frac{\partial V \pi_-^-}{\partial x} + \alpha(\pi_+^- - \pi_-^-) = 0, \quad (3.155)$$

with $\pi_+^-(-L) = 0$, $\pi_-^-(-L) = 1$. The solution is

$$\pi_+^-(x) = \frac{\alpha(L-x)}{2L\alpha + V}, \quad \pi_-^-(x) = \frac{\alpha(L-x) + V}{2L\alpha + V}. \quad (3.156)$$

and

$$\pi_+^-(x) + \pi_-^-(x) = \frac{2\alpha(L-x) + V}{2L\alpha + V}, \quad (3.157)$$

and as it must

$$\pi_+^+(x) + \pi_-^+(x) + \pi_+^-(x) + \pi_-^-(x) = 1. \quad (3.158)$$

3.6 Adiabatic Reduction

We can reduce the system (3.134) to a standard Fokker-Planck equation in the limit that the transitions between x_k states are fast. If this is the case, then we can write the Kolmogorov forward system (3.134) as

$$\frac{\partial \mathbf{p}}{\partial t} = -\frac{\partial}{\partial y}(\mathbf{F}\mathbf{p}) + \frac{1}{\epsilon}A\mathbf{p}. \quad (3.159)$$

Now, it must be that the matrix A has a zero eigenvalue with eigenvector ϕ . (We assume that the null space of A is one dimensional, so that ϕ is unique.) The corresponding left eigenvector is ψ with entries $(\psi_j) = 1$. We assume that $\langle \phi, \psi \rangle = 1$. Using these, we split \mathbf{p} into two parts

$$\mathbf{p} = v\phi + w \quad (3.160)$$

where $\langle \mathbf{p}, \psi \rangle = v$, and $\langle w, \psi \rangle = 0$. It follows that

$$\frac{\partial v}{\partial t} = -\psi^T \frac{\partial}{\partial y}(\mathbf{F}(v\phi + w)), \quad (3.161)$$

and

$$\frac{\partial w}{\partial t} = \frac{1}{\epsilon}Aw - \frac{\partial}{\partial y}(\mathbf{F}\mathbf{p}) + \psi^T \frac{\partial}{\partial y}(\mathbf{F}\mathbf{p})\phi. \quad (3.162)$$

Here, the fast behavior of w is evident, so we take w to be in quasi-steady state. Thus, we take

$$Aw = \epsilon \frac{\partial}{\partial y}(v\mathbf{F}\phi) - \epsilon\psi^T \frac{\partial}{\partial y}(v\mathbf{F}\phi)\phi + O(\epsilon^2). \quad (3.163)$$

This equation can be solved uniquely for w subject to the constraint $\psi^T w = 0$; we denote this as

$$w = \epsilon A^\perp \frac{\partial}{\partial y}(v\mathbf{F}\phi) - \epsilon A^\perp \psi^T \frac{\partial}{\partial y}(v\mathbf{F}\phi)\phi + O(\epsilon^2), \quad (3.164)$$

where A^\perp is the inverse of the properly constrained A . Consequently,

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}(\psi^T \mathbf{F}v\phi) - \frac{\partial}{\partial y} \left(\epsilon \psi^T \mathbf{F}A^\perp \left(\frac{\partial}{\partial y}(v\mathbf{F}\phi) - \psi^T \frac{\partial}{\partial y}(v\mathbf{F}\phi)\phi \right) \right), \quad (3.165)$$

which is a Fokker-Planck equation.

More generally, consider the Kolmogorov forward system

$$\frac{\partial \mathbf{p}}{\partial t} = L_2 \mathbf{p} + \frac{1}{\epsilon} L_1 \mathbf{p}, \quad (3.166)$$

with $\epsilon \ll 1$. We suppose that L_1 has a one dimensional nullspace spanned by ϕ , so that

$$L_1 \phi = 0, \quad L_1^T \psi = 0, \quad \langle \psi, \phi \rangle = 1. \quad (3.167)$$

We define a projection P by

$$P\mathbf{p} = \langle \psi, \mathbf{p} \rangle \phi, \quad (3.168)$$

and then set $\mathbf{p} = v + w$ where

$$v = P\mathbf{p}, \quad w = (I - P)\mathbf{p}. \quad (3.169)$$

Notice that

$$PL_1\mathbf{p} = \langle \psi, L_1\mathbf{p} \rangle \phi = \langle L_1^T \psi, \mathbf{p} \rangle \phi = 0. \quad (3.170)$$

Projecting the governing equation,

$$\frac{\partial v}{\partial t} = PL_2\mathbf{p}, \quad \frac{\partial w}{\partial t} = (I - P)L_2w + (I - P)L_2v + \frac{1}{\epsilon}L_1w, \quad (3.171)$$

since $L_1v = 0$. We take the qss approximation for w as

$$\frac{1}{\epsilon}L_1w = -(I - P)L_2v. \quad (3.172)$$

Consequently,

$$\frac{\partial v}{\partial t} = PL_2(v - \epsilon L_1^{-1}(I - P)L_2v), \quad (3.173)$$

where L_1^{-1} is the properly constrained pseudo-inverse of L_1 .

3.6.1 Examples

Consider the simple example

$$\frac{dy}{dt} = kx, \quad (3.174)$$

where x is either 0 or 1, with transition probabilities α and β . The forward Kolmogorov equation is

$$\frac{\partial p}{\partial t} = \alpha q - \beta p - \frac{\partial kp}{\partial y}, \quad (3.175)$$

$$\frac{\partial q}{\partial t} = \beta p - \alpha q. \quad (3.176)$$

Suppose that α and β are large compared to k . Then the exchange between states is fast relative to the rate of change of y , and we should be able to do a qss reduction. To do so, we introduce dimensionless time (set $k = 1$) and let $\epsilon = \frac{1}{\alpha + \beta}$, and introduce $a = \frac{\alpha}{\alpha + \beta}$ and $b = \frac{\beta}{\alpha + \beta}$, so that $a + b = 1$. In terms of these variables, the F-P equations are

$$\frac{\partial p}{\partial t} = \frac{1}{\epsilon}(aq - bp) - \frac{\partial p}{\partial y}, \quad (3.177)$$

$$\frac{\partial q}{\partial t} = \frac{1}{\epsilon}(bp - aq). \quad (3.178)$$

We now introduce the change of variables

$$v = p + q, \quad w = bp - aq, \quad (3.179)$$

so that

$$p = av + w, \quad q = bv - w. \quad (3.180)$$

In terms of these variables the forward Kolmogorov equations are

$$\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} - \frac{\partial w}{\partial y}, \quad (3.181)$$

$$\frac{\partial w}{\partial t} = -\frac{1}{\epsilon}w - b\frac{\partial av}{\partial y} - b\frac{\partial w}{\partial y}. \quad (3.182)$$

Now we see the obvious fast-slow separation and take w to be in quasi-steady state, so that

$$w = -\epsilon b \frac{\partial av}{\partial y} + O(\epsilon^2), \quad (3.183)$$

from which it follows that

$$\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} + \frac{\partial}{\partial y}(\epsilon b \frac{\partial av}{\partial y}) + O(\epsilon^2), \quad (3.184)$$

which is the standard F-P equation we seek.

For the more general problem

$$\frac{dy}{dt} = xf(y) - g(y), \quad (3.185)$$

the forward Kolmogorov equations are

$$\frac{\partial p}{\partial t} = \frac{1}{\epsilon}(aq - bp) - \frac{\partial}{\partial y}((f - g)p), \quad (3.186)$$

$$\frac{\partial q}{\partial t} = \frac{1}{\epsilon}(bp - aq) + \frac{\partial}{\partial y}(gq). \quad (3.187)$$

We now introduce the change of variables (3.179) and find

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}((af - g)v + fw), \quad (3.188)$$

$$\frac{\partial w}{\partial t} = -\frac{1}{\epsilon}w - a\frac{\partial}{\partial y}(gq) - b\frac{\partial}{\partial y}((f - g)p). \quad (3.189)$$

Again, the fast-slow separation is apparent and we take w to be in quasi-steady state, so that

$$w = \epsilon(-a\frac{\partial}{\partial y}(gbv) - b\frac{\partial}{\partial y}((f - g)av)) + O(\epsilon^2), \quad (3.190)$$

from which it follows that

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}((af - g)v) + \frac{\partial}{\partial y}\left(\epsilon fb\frac{\partial}{\partial y}(fav) + \epsilon fgv\frac{\partial b}{\partial y}\right) + O(\epsilon^2), \quad (3.191)$$

which is the F-P equation we seek.

A second interesting example is the three state process with $x = -1, 0, 1$ and transitions



There are numerous physical situations where this might occur.

The master equations are

$$\frac{\partial p_{-1}}{\partial t} = \alpha_- p_0 - \beta p_{-1} + V\frac{\partial p_{-1}}{\partial x}, \quad (3.193)$$

$$\frac{\partial p_0}{\partial t} = \beta p_{-1} + \beta p_1 - (\alpha_- + \alpha_+)p_0 + D\frac{\partial^2 p_0}{\partial x^2}, \quad (3.194)$$

$$\frac{\partial p_1}{\partial t} = \alpha_+ p_0 - \beta p_1 - V\frac{\partial p_1}{\partial x}. \quad (3.195)$$

We assume that α_- , α_+ , and β are large so introduce the scaled parameters $a_{\pm} = \epsilon\alpha_{\pm}$, $b = \epsilon\beta$ where $\epsilon = \frac{1}{\alpha_- + \alpha_+ + \beta}$, so that $a_- + a_+ + b = 1$. Then, the equations become

$$\frac{\partial p_{-1}}{\partial t} = \frac{1}{\epsilon}(a_- p_0 - b p_{-1}) + V\frac{\partial p_{-1}}{\partial x}, \quad (3.196)$$

$$\frac{\partial p_0}{\partial t} = \frac{1}{\epsilon}(b p_{-1} + b p_1 - (a_- + a_+) p_0) + D\frac{\partial^2 p_0}{\partial x^2}, \quad (3.197)$$

$$\frac{\partial p_1}{\partial t} = \frac{1}{\epsilon}(a_+ p_0 - b p_1) - V\frac{\partial p_1}{\partial x}. \quad (3.198)$$

The nullspace of the matrix is spanned by the vector

$$\phi = \begin{pmatrix} a_- \\ b \\ a_+ \end{pmatrix}. \quad (3.199)$$

We set

$$p = \begin{pmatrix} p_{-1} \\ p_0 \\ p_1 \end{pmatrix} = v\phi + \begin{pmatrix} w_{-1} \\ w_0 \\ w_1 \end{pmatrix}, \quad (3.200)$$

and find the equation for v by projecting

$$\frac{\partial v}{\partial t} = V \frac{\partial p_{-1}}{\partial x} - V \frac{\partial p_1}{\partial x} + D \frac{\partial^2 p_0}{\partial x^2} \quad (3.201)$$

$$= V(a_- - a_+) \frac{\partial v}{\partial x} + V \frac{\partial}{\partial x} (w_{-1} - w_1) + D \frac{\partial^2}{\partial x^2} (bv + w_0). \quad (3.202)$$

The vector w must satisfy the equation

$$\frac{1}{\epsilon} \begin{pmatrix} -b & a_- & 0 \\ b & -(a_- + a_+) & b \\ 0 & a_+ & -b \end{pmatrix} w = \begin{pmatrix} -V a_- \frac{\partial v}{\partial x} \\ D b \frac{\partial^2 v}{\partial x^2} \\ V a_+ \frac{\partial v}{\partial x} \end{pmatrix} - C \begin{pmatrix} a_- \\ b \\ a_+ \end{pmatrix}, \quad (3.203)$$

where $C = -V(a_- - a_+) \frac{\partial v}{\partial x} + D b \frac{\partial^2 v}{\partial x^2}$. The solution of this problem is given by (ignoring D)

$$w_{-1} = \frac{\epsilon}{b} V a_- v_x (b^2 + 2a_+ b + 2a_+), \quad (3.204)$$

$$w_0 = \epsilon b V v_x (a_+ - a_-), \quad (3.205)$$

$$w_1 = -\frac{\epsilon}{b} V a_+ v_x (b^2 + 2a_- b + 2a_-), \quad (3.206)$$

so that

$$w_{-1} - w_1 = \frac{\epsilon}{b} V ((a_- + a_+) b^2 + 4(b+1)a_+ a_-) v_x. \quad (3.207)$$

Thus, the effective Fokker-Planck equation (ignoring all higher order derivatives) is

$$\frac{\partial v}{\partial t} = V(a_- - a_+) \frac{\partial v}{\partial x} + D_{eff} \frac{\partial^2 v}{\partial x^2}, \quad (3.208)$$

where

$$D_{eff} = bD + \frac{\epsilon}{b} V^2 ((a_- + a_+) b^2 + 4(b+1)a_+ a_-). \quad (3.209)$$

3.6.2 Higher Dimensional example

Consider the movement of a particle on a random microtubule network in 2-D. The random variables are the position and the angle of movement θ , so we seek the pdf $p(x, y, \theta, t)$. The Master Equations are

$$\frac{\partial p_b}{\partial t} = -\beta p_b + \alpha q(\theta, x) p_u - V \frac{\partial}{\partial x} (\cos \theta p_b) - V \frac{\partial}{\partial y} (\sin \theta p_b), \quad (3.210)$$

$$\frac{\partial p_u}{\partial t} = \beta p_b - \alpha q(\theta, x) p_u + D \frac{\partial^2 p_u}{\partial x^2} + D \frac{\partial^2 p_u}{\partial y^2}. \quad (3.211)$$

Rescaling, with $b = \frac{\beta}{\beta+\alpha q}$ and $a = \frac{\alpha}{\beta+\alpha q}$ (so that $a + b = 1$), we have

$$\frac{\partial p_b}{\partial t} = \frac{1}{\epsilon}(-bp_b + ap_u) - V \frac{\partial}{\partial x}(\cos \theta p_b) - V \frac{\partial}{\partial y}(\sin \theta p_b), \quad (3.212)$$

$$\frac{\partial p_u}{\partial t} = \frac{1}{\epsilon}(bp_b - ap_u) + D \frac{\partial^2 p_u}{\partial x^2} + D \frac{\partial^2 p_u}{\partial y^2}. \quad (3.213)$$

The adiabatic analysis of this problem is actually easier than for the 1-D problem. We set

$$\begin{pmatrix} p_b \\ p_u \end{pmatrix} = v \begin{pmatrix} a \\ b \end{pmatrix} + \begin{pmatrix} w \\ -w \end{pmatrix}. \quad (3.214)$$

Projecting, the equation for v is

$$\frac{\partial v}{\partial t} = -V \frac{\partial}{\partial x}(\cos \theta p_b) - V \frac{\partial}{\partial y}(\sin \theta p_b) + D \frac{\partial^2 p_u}{\partial x^2} + D \frac{\partial^2 p_u}{\partial y^2}, \quad (3.215)$$

and the equation for w is

$$\frac{\partial w}{\partial t} = -\frac{1}{\epsilon}w + b \left(-V \frac{\partial}{\partial x}(\cos \theta p_b) - V \frac{\partial}{\partial y}(\sin \theta p_b) \right) - a \left(D \frac{\partial^2 p_u}{\partial x^2} + D \frac{\partial^2 p_u}{\partial y^2} \right). \quad (3.216)$$

It follows that the qss solution for w is (ignoring D)

$$w = -V \epsilon b \left(\frac{\partial}{\partial x}(\cos \theta av) + \frac{\partial}{\partial y}(\sin \theta av) \right), \quad (3.217)$$

leading to the Fokker Planck equation

$$\begin{aligned} \frac{\partial v}{\partial t} &= -V \frac{\partial}{\partial x}(\cos \theta av) - V \frac{\partial}{\partial y}(\sin \theta av) \\ &+ V^2 \frac{\partial}{\partial x}(\cos \theta \epsilon b \frac{\partial}{\partial x}(\cos \theta av)) + V^2 \frac{\partial}{\partial x}(\cos \theta \epsilon b \frac{\partial}{\partial y}(\sin \theta av)) \\ &+ V^2 \frac{\partial}{\partial y}(\sin \theta \epsilon b \frac{\partial}{\partial y}(\cos \theta av)) + V^2 \frac{\partial}{\partial y}(\sin \theta \epsilon b \frac{\partial}{\partial x}(\sin \theta av)) + D \frac{\partial^2 av}{\partial x^2} + D \frac{\partial^2 av}{\partial y^2} \end{aligned} \quad (3.218)$$

which seems to be a reasonable extension of the 1-D example above.

Now let's apply this technology to a more general problem. Consider the stochastic differential equation

$$\frac{dy}{dt} = x_k f(y) - g(y), \quad (3.219)$$

where x_k can be an integer between 0 and N . For example, suppose that x_k represents the number of open ion channels and that channels act independently. (We can also consider cooperativity, but this may come later). For this we have the state diagram



where j represents the number of open channels. Thus, the transition probabilities are

$$P(x_k \rightarrow x_{k+1}) = (N - k)\alpha, \quad P(x_k \rightarrow x_{k-1}) = k\beta. \quad (3.221)$$

Thus,

$$W_{k+1,k} = (N - k)\alpha, \quad W_{k-1,k} = k\beta, \quad (3.222)$$

and all other transitions are impossible. The Kolmogorov forward equations are then

$$\frac{\partial p}{\partial t} = \frac{1}{\epsilon} Ap - \frac{\partial}{\partial y}(Bp), \quad (3.223)$$

where

$$a_{k,k-1} = a(N - k + 1), \quad a_{k,k} = -a(N - k) - bk, \quad a_{k,k+1} = b(k + 1), \quad (3.224)$$

for $k = 0, \dots, N$, and all other entries of A are zero, and where B is the diagonal matrix with entries $b_{k,k} = kf(y) - g(y)$.

Now to do the qss analysis, we observe that A has a one-dimensional nullspace spanned by the vector ϕ , and a one-dimensional adjoint nullspace spanned by ψ where

$$\phi_k = \binom{N}{k} a^k b^{N-k}, \quad \psi_k = 1. \quad (3.225)$$

We set $p = v\phi + w$, where $v = \langle p, \psi \rangle$ and $\langle w, \psi \rangle = 0$. Then,

$$\frac{\partial v}{\partial t} = -\psi^T \frac{\partial}{\partial y}(B(v\phi + w)), \quad (3.226)$$

and

$$\frac{\partial w}{\partial t} = \frac{1}{\epsilon} Aw - \frac{\partial}{\partial y}(Bp) + \psi^T \frac{\partial}{\partial y}(Bp)\phi, \quad (3.227)$$

Here the qss approximation is apparent. We take

$$Aw = \epsilon \frac{\partial}{\partial y}(Bv\phi) - \epsilon \psi^T \frac{\partial}{\partial y}(Bv\phi)\phi + O(\epsilon^2), \quad (3.228)$$

with $\psi^T w = 0$. Observe, that w is uniquely determined by this equation, although A is not invertible. Now the interesting question is if we can find analytical expressions for w .

Using Maple, I have been able to determine that

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}((Naf - g)v) + N \frac{\partial}{\partial y} \left(\epsilon b f \frac{\partial}{\partial y}(afv) + \epsilon(Ng - (N-1)af)fv \frac{\partial b}{\partial y} \right). \quad (3.229)$$

When $f = \frac{1}{N}$, $g = 0$, this reduces to

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y} \left(\left(1 + \epsilon \left(1 - \frac{1}{N} \right) \frac{\partial b}{\partial y} \right) av \right) + \frac{\partial}{\partial y} \left(\frac{\epsilon b}{N} \frac{\partial}{\partial y}(av) \right). \quad (3.230)$$

More Complicated Markov Processes

Suppose we have a more complicated gating behavior, such as

$$\frac{dy}{dt} = x_1 x_2 f(y) - g(y), \quad (3.231)$$

where both x_1 and x_2 are independent, identical, discrete random variables taking on values 0 and 1. Now there are four functions $p_{j,k}$ to be determined, and the Fokker-Planck equations are

$$\frac{\partial p_{00}}{\partial t} = -2\alpha p_{00} + \beta p_{10} + \beta p_{01} + \frac{\partial}{\partial y}(gp_{00}), \quad (3.232)$$

$$\frac{\partial p_{10}}{\partial t} = \alpha p_{00} - (\beta + \alpha)p_{10} + \beta p_{11} + \frac{\partial}{\partial y}(gp_{10}), \quad (3.233)$$

$$\frac{\partial p_{01}}{\partial t} = \alpha p_{00} - (\beta + \alpha)p_{01} + \beta p_{11} + \frac{\partial}{\partial y}(gp_{01}), \quad (3.234)$$

$$\frac{\partial p_{11}}{\partial t} = \alpha p_{10} + \alpha p_{01} - 2\beta p_{11} - \frac{\partial}{\partial y}((f - g)p_{11}). \quad (3.235)$$

We want to examine this in the limit that α and β are large, and so set (as before) $a = \frac{\alpha}{\alpha + \beta}$, $b = \frac{\beta}{\alpha + \beta}$, and $\epsilon = \frac{1}{\alpha + \beta}$, with the result that

$$\frac{\partial p_{00}}{\partial t} = \frac{1}{\epsilon}(-2ap_{00} + bp_{10} + bp_{01}) + \frac{\partial}{\partial y}(gp_{00}) \quad (3.236)$$

$$\frac{\partial p_{10}}{\partial t} = \frac{1}{\epsilon}(ap_{00} - p_{10} + bp_{11}) + \frac{\partial}{\partial y}(gp_{10}) \quad (3.237)$$

$$\frac{\partial p_{01}}{\partial t} = \frac{1}{\epsilon}(ap_{00} - p_{01} + bp_{11}) + \frac{\partial}{\partial y}(gp_{01}) \quad (3.238)$$

$$\frac{\partial p_{11}}{\partial t} = \frac{1}{\epsilon}(ap_{10} + ap_{01} - 2bp_{11}) - \frac{\partial}{\partial y}((f - g)p_{11}) \quad (3.239)$$

Now we want to apply the technology developed above to this system of equations. To do so we examine the matrix

$$A = \begin{pmatrix} -2a & b & b & 0 \\ a & -1 & 0 & b \\ a & 0 & -1 & b \\ 0 & a & a & -2b \end{pmatrix} \quad (3.240)$$

The nullspace of A is spanned by

$$\phi = \begin{pmatrix} b^2 \\ ab \\ ab \\ a^2 \end{pmatrix} \quad (3.241)$$

so we introduce the change of variables

$$v = \langle \psi, p \rangle, \quad w = p - \langle \psi, p \rangle \phi, \quad (3.242)$$

so that

$$p = v\phi + w \quad (3.243)$$

and find

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}((a^2 f - g)v) + \frac{\partial}{\partial y} \left(\frac{\epsilon}{2} f \left(b(3a + 1) \frac{\partial}{\partial y} (a^2 f v) - 2gv \frac{\partial a^2}{\partial y} \right) \right). \quad (3.244)$$

More generally, when there are N channels, we find (using Maple)

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial y}(N(a^2 f - g)v) + \frac{\partial}{\partial y} \left(\frac{N\epsilon}{2} f \left(b(3a + 1) \frac{\partial}{\partial y} (a^2 f v) - 2gv \frac{\partial a^2}{\partial y} + (N - 1)f \frac{\partial a^4}{\partial y} \right) \right). \quad (3.245)$$

3.6.3 Remarks on modeling

The above calculation requires amplification. As stated, if there are N channels, there are 2^N configurations. However, if the states are independent, a significant reduction can be made, without error (except for a small initial transient). Since each channel can be in one of three states, we let p_{ijk} be the probability that there are i channels in state 0_1 , j channels in state 0_2 and k channels in state 1 (open). Obviously, $i + j + k = N$, and i , j , and k are nonnegative. Now the possible transitions are

$$p_{i,k-i,N-k} \xrightarrow{(k-i)\alpha} p_{i,k-i-1,N-k+1}, \quad k \neq 0 \quad (3.246)$$

$$p_{i,k-i,N-k} \xrightarrow{(k-i)\beta} p_{i+1,k-i-1,N-k}, \quad k \neq i \quad (3.247)$$

$$p_{i,k-i,N-k} \xrightarrow{2i\alpha} p_{i-1,k-i+1,N-k}, \quad i \neq 0 \quad (3.248)$$

$$p_{i,k-i,N-k} \xrightarrow{2(N-k)\beta} p_{i,k-i+1,N-k-1}, \quad k \neq N \quad (3.249)$$

Furthermore, in state i, j, k , the deterministic dynamics are

$$\frac{dy}{dt} = kf(y) - g(y) \quad (3.250)$$

3.6.4 K-step processes

Suppose there are K closed states,

$$C_k \leftrightarrow C_{k-1} \leftrightarrow \cdots \leftrightarrow C_1 \leftrightarrow O \quad (3.251)$$

It is easy to determine that the mean value is

$$E(X) = \frac{a^k}{(a+b)^k} \quad (3.252)$$

The variance, on the other hand seems not to have such a nice formula. Here we list the first six:

$$V_1 = \frac{ab}{(a+b)^3}, \quad (3.253)$$

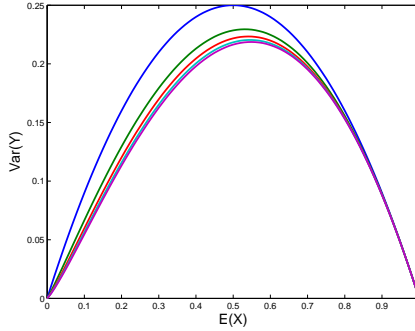


Figure 3.3: Variance of the process y as a function of K , plotted as a function of the mean of the process X .

$$V_2 = \frac{1}{2} \frac{a^2 b (4a + b)}{(a + b)^5}, \quad (3.254)$$

$$V_3 = \frac{1}{6} \frac{a^3 b (18a^2 + 9ab + 2b^2)}{(a + b)^7}, \quad (3.255)$$

$$V_4 = \frac{1}{12} \frac{a^4 b (3b^3 + 16ab^2 + 36a^2b + 48a^3)}{(a + b)^9}, \quad (3.256)$$

$$V_5 = \frac{1}{60} \frac{a^5 b (200b^2a^2 + 300ba^3 + 300a^4 + 75b^3a + 12b^4)}{(a + b)^{11}}. \quad (3.257)$$

The important observation is that the variance is a decreasing function of K , and it appears to be converging in the limit of large K .

3.6.5 Adiabatic reduction for a Brownian Particle

We begin with the two dimensional equation

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial y}(up) + \frac{\partial}{\partial u}(U'(y)p) + \gamma \frac{\partial}{\partial u}(up + \frac{\partial p}{\partial u}), \quad (3.258)$$

where $\gamma = \sqrt{\frac{\xi^2}{km}} \gg 1$. (k is the linear spring constant.) Set

$$L_1 p = \frac{\partial}{\partial u}(up + \frac{\partial p}{\partial u}), \quad L_2 p = -\frac{\partial}{\partial y}(up) + U'(y) \frac{\partial}{\partial u} p. \quad (3.259)$$

We want a projection operator based on the null-space of L_1 . Note that $L_1 \phi = 0$ implies that

$$\phi' + u\phi = 0, \quad (3.260)$$

so that

$$\phi(u) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{u^2}{2}\right). \quad (3.261)$$

The adjoint operator has a null space spanned by $\psi = 1$, so the projection operator we seek is

$$Pf = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{u^2}{2}\right) \int_{-\infty}^{\infty} f(u, y) du. \quad (3.262)$$

Now we set $p = Pp + (1 - P)p = v + w$ (so that $v = f(y, t)\phi(u)$) and observe that

$$L_2 Pp = -\frac{\partial}{\partial y}(uPp) + U'(y) \frac{\partial Pp}{\partial u} = (f'(y) + f(y)U'(y)) \frac{d\phi}{du} = g(y) \frac{d\phi}{du}, \quad (3.263)$$

so that $PL_2 Pp = 0$. Furthermore, by construction, $PL_1 = 0$. Thus,

$$\frac{\partial v}{\partial t} = P(\gamma L_1 + L_2)(v + w) = PL_2 w, \quad (3.264)$$

and

$$\frac{\partial w}{\partial t} = \gamma L_1 w + (1 - P)L_2 v + L_2 w. \quad (3.265)$$

Now we assume γ is large so take w to be in qss, so take

$$\gamma L_1 w = -(1 - P)L_2 v = -L_2 v, \quad (3.266)$$

or

$$\gamma \frac{\partial}{\partial u}(uw + \frac{\partial w}{\partial u}) = -g(y) \frac{d\phi}{du}. \quad (3.267)$$

Thus,

$$\gamma \frac{\partial}{\partial u}\left(\frac{w}{\phi}\right) = -g(y), \quad (3.268)$$

so that

$$\gamma w = -g(y)u\phi = g(y) \frac{\partial \phi}{\partial u}. \quad (3.269)$$

Now, notice that

$$L_2 w = \frac{\partial}{\partial y}\left(\frac{g}{\gamma}\right)u^2\phi - U'(y) \frac{g}{\gamma} \frac{\partial}{\partial u}(u\phi), \quad (3.270)$$

so that

$$PL_2 w = \phi \frac{\partial}{\partial y}\left(\frac{g}{\gamma}\right) \int_{-\infty}^{\infty} u^2 \phi du = \phi \frac{\partial}{\partial y}\left(\frac{g}{\gamma}\right). \quad (3.271)$$

It follows that

$$\frac{\partial f}{\partial t} = \frac{1}{\gamma} \frac{\partial}{\partial y}\left(\frac{\partial f}{\partial y} + U'(y)f\right), \quad (3.272)$$

the Fokker-Planck equation we were looking for. Put this back into dimensional units, with $t = \tau \sqrt{\frac{m}{k}}$, $v = \sqrt{\frac{k_B T}{m}} u$, $x = \sqrt{\frac{k_B T}{k}} y$, we find

$$\frac{\partial f}{\partial t} = \frac{k_B T}{\xi} \frac{\partial^2 f}{\partial y^2} + \frac{k}{\xi} \frac{\partial}{\partial x}(U'(x)f), \quad (3.273)$$

as expected.

3.6.6 Flashing Ratchets

Now we apply this technology to two state flashing ratchet. It is probably not correct that binding-unbinding reactions are fast, but it is still interesting to see what the answer is.

The F-P equations are

$$\frac{\partial p}{\partial t} = \frac{1}{\epsilon}(aq - bp) - \frac{\partial Fp}{\partial y} + D\frac{\partial^2 p}{\partial y^2}, \quad (3.274)$$

$$\frac{\partial q}{\partial t} = \frac{1}{\epsilon}(bp - aq) - \frac{\partial Gp}{\partial y} + D\frac{\partial^2 q}{\partial y^2}. \quad (3.275)$$

As before we introduce the change of variables

$$v = p + q, \quad w = bp - aq, \quad (3.276)$$

so that

$$p = av + w, \quad q = bv - w. \quad (3.277)$$

In terms of these variables the F-P equations are

$$\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} - \frac{\partial w}{\partial y} \quad (3.278)$$

$$\frac{\partial w}{\partial t} = -\frac{1}{\epsilon}w - b\frac{\partial av}{\partial y} - b\frac{\partial w}{\partial y} \quad (3.279)$$

Now we see the obvious fast-slow separation and take w to be in quasi-steady state, so that

$$w = -\epsilon b \frac{\partial av}{\partial y} + O(\epsilon^2), \quad (3.280)$$

from which it follows that

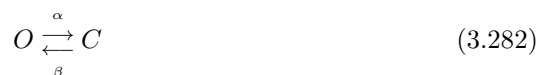
$$\frac{\partial v}{\partial t} = -\frac{\partial av}{\partial y} + \frac{\partial}{\partial y}(\epsilon b \frac{\partial av}{\partial y}) + O(\epsilon^2), \quad (3.281)$$

which is the standard F-P equation we seek.

3.7 Large Volume Expansion

All chemical reaction reactions are in some sense discrete state space Markov processes, and their dynamics can be represented by the chemical master equation. However, if the number of molecules is large, this representation of the process becomes impractical, if not impossible, to work with in any meaningful way. For this reason, the large volume expansion, or large N approximation is useful. We illustrate it here with specific examples.

Consider the situation with N independent objects, say ion channels, that can be in one of two states, open or closed, denoted S_0 and S_1 , respectively, and represented by the reaction



Let $P_k(t)$ be the probability that there are k open channels at time t . Then the master equation for this process is given by

$$\frac{dP_k}{dt} = \beta(N - k + 1)P_{k-1} + \alpha(k + 1)P_{k+1} - \beta(N - k)P_k - \alpha k P_k. \quad (3.283)$$

We suppose that N is large, so let $x = \frac{k}{N}$ and $dx = \frac{1}{N}$, and write the master equation in terms of x rather than k , with $P_k(t) = p(x, t)dx$ as

$$dx \frac{\partial p(x)}{\partial t} = \beta(1 - x + dx)p(x - dx) + \alpha(x + dx)p(x + dx) - \beta(1 - x)p(x) - \alpha x p(x). \quad (3.284)$$

Assuming that $p(x)$ is a sufficiently smooth function of x , we find the Taylor expansion of this equation to be

$$\begin{aligned} dx \frac{\partial p(x)}{\partial t} &= -\frac{\partial}{\partial x}(\beta(1 - x)p(x))dx + \frac{1}{2} \frac{\partial^2}{\partial x^2}(\beta(1 - x)p(x))dx^2 \\ &\quad + \frac{\partial}{\partial x}(\alpha x p(x))dx + \frac{1}{2} \frac{\partial^2}{\partial x^2}(\alpha x p(x))dx^2 + O(dx^3) \end{aligned} \quad (3.285)$$

Combining terms, we find the Fokker-Planck equation

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}((\beta(1 - x) - \alpha x)p) + \frac{1}{2N} \frac{\partial^2}{\partial x^2}((\beta(1 - x) + \alpha x)p) \quad (3.286)$$

ignoring terms of order $O(dx^2)$.

For this example, we have taken α and β to be independent of k , but they need not be, as the equation (3.286) is valid even if they are not independent of k .

There is a further useful approximation that can be made. Notice that the deterministic flux corresponds to the ode dynamics

$$\frac{dx}{dt} = \beta(1 - x) - \alpha x, \quad (3.287)$$

which has a stable equilibrium at $x = \frac{\beta}{\alpha + \beta} \equiv x_0$. Setting $x = x_0 + y$ and keeping only leading order terms in y , we find the Ornstein Uhlenbeck equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial y}((\alpha + \beta)yp) + \frac{1}{N} \frac{\partial^2}{\partial y^2} \left(\left(\frac{\alpha\beta}{\alpha + \beta} \right) p \right). \quad (3.288)$$

There is an important point to be made here about scaling. For the above example, N represents the total number of ion channels, so x is dimensionless and limited to be between 0 and 1, and represents the fraction of the total that is in the open state. However, if we are working with chemical reactions where k represents the number of a particular species, then it may be more appropriate to let x be the concentration of the first species, and there is interconversion between species. In this case, we set $u = \frac{k}{V}$, where V is a volume, and then $\frac{N}{V}$ is taken to be some fixed total concentration, say U_0 . Now, we can explore the consequences of allowing the volume to be large, keeping the total concentration X_0 fixed. Of course, for the above problem this simply represents a change of scale from the dimensionless

coordinate $x = \frac{k}{N}$ to the dimensional coordinate $u = \frac{k}{V}$. Expressed in terms of concentration u , the equation (3.286), is

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial u} \left((\beta(U_0 - u) - \alpha u)p \right) + \frac{1}{2V} \frac{\partial^2}{\partial u^2} \left((\beta(U_0 - u) + \alpha u)p \right), \quad (3.289)$$

and the equivalent Ornstein-Uhlenbeck equation is

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial u} \left((\alpha + \beta)up \right) + \frac{U_0}{V} \frac{\partial^2}{\partial u^2} \left(\left(\frac{\alpha\beta}{\alpha + \beta} \right) p \right). \quad (3.290)$$

While this conversion is straightforward for first order reactions as above, there is some additional subtlety when higher order chemical reactions are involved. For example, consider the dimerization reaction



It is important to understand the meaning of the rate constants α and β . Since β is the rate constant for a first order reaction, its units are inverse time. In contrast, α is a rate of dimerization and so it has units of inverse time times inverse concentration. It follows that the master equation for the evolution of $P_k(t)$, where k is the number of X molecules is

$$\frac{dP_k}{dt} = -\frac{\alpha}{V} k(k-1)P_k + \frac{\alpha}{V} (k+2)(k+1)P_{k+2} + \frac{\beta}{2}(N-k+2)P_{k-2} - \frac{\beta}{2}(N-k)P_k, \quad (3.292)$$

where N is the total number of X molecules in both forms X and Y , $N = X + 2Y$, and V is the reference volume that converts reaction rates in units of concentration to reaction rates in units of numbers of molecules. Now, to find the large N (large V) approximation, we set $u = \frac{k}{V}$, keeping $U_0 = \frac{N}{V}$ fixed, with $du = \frac{1}{V}$,

$$\begin{aligned} \frac{dp(u)}{dt} &= -\frac{\alpha}{V} V^2 u(u - du)p(u) + \frac{\alpha}{V} V^2 (u + 2du)(u + du)p(u + 2du) \\ &\quad + \frac{\beta}{2} V (U_0 - u + 2du)P(u - 2du) - \frac{\beta}{2} V (U_0 - u)p(u), \end{aligned} \quad (3.293)$$

Expanding the Taylor series we find to leading order

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial u} \left((2\alpha u^2 - \beta(U_0 - u))p \right) + \frac{1}{V} \frac{\partial^2}{\partial u^2} \left((2\alpha u^2 + \beta(U_0 - u))p \right). \quad (3.294)$$

The deterministic dynamics for this are given by

$$\frac{du}{dt} = \beta(U_0 - u) - 2\alpha u^2, \quad (3.295)$$

and linearizing around the steady state of these dynamics, we find the Ornstein-Uhlenbeck equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial y} (kyp) + D \frac{\partial^2 p}{\partial y^2}, \quad (3.296)$$

where $k = \sqrt{8\alpha\beta U_0 + \beta^2}$ and $D = \frac{\beta}{\alpha V} (4\alpha U_0 + \beta - k)$, with y in units of concentration.

Chapter 4

Applications

4.1 Stochastic Analysis of Action Potential Initiation

4.1.1 Introduction

Stochasticity plays an important role in many electrophysiological contexts. The onset of pathological dynamical behaviors such as epilepsy and cardiac fibrillation are most likely the result of random fluctuations that move an otherwise deterministic dynamical system from one basin of attraction to another. For example, spontaneous release of calcium from the sarcoplasmic reticulum of cardiac cells is thought to be related to delayed after-depolarizations (DAD's), which are in turn believed to initiate fatal cardiac arrhythmias [10, 11]. Stochastic opening and closing of high-conductance K-Ca channels is thought to be responsible for the highly stochastic bursting patterns of isolated pancreatic beta cells [14].

The Hodgkin-Huxley equations have been used successfully to describe many important features of the behavior of nerve cells. These equations, like most conductance-based ionic models, calculate average ionic currents using channel open probabilities. Although the expectation is that because of the law of large numbers, average channel behavior gives adequate accuracy in many situations, there are several questions that cannot be answered by averaged equations. For example, how often can an action potential be initiated spontaneously, i.e., without external stimulus? How big is big, that is, at what channel density can stochastic effects be ignored? Said another way, how fast do stochastic equations of action potential dynamics converge to their deterministic limit? What are the effects of stochastic behavior on the stimulus threshold?

The purpose of these notes is to examine the role of stochastic sodium channel openings and closings on the initiation of an action potential. While this analysis is carried out specifically for the Hodgkin-Huxley equations, the general problem can be described as follows:

Suppose the initial dynamics of an action potential are described by a determin-

istic bistable equation, say

$$\frac{dv}{dt} = F(v) + I(t), \quad (4.1)$$

where v is the transmembrane potential, and $F(v)$ represents the ionic currents and has three zeros, the smallest of which corresponds to the stable resting potential, and the largest of which corresponds to the excited state. A stochastic interpretation of this equation replaces the deterministic model with a Fokker-Planck equation of the form

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial v}((F(v) + I(t))p) + \frac{\partial}{\partial v}(D(v)\frac{\partial p}{\partial v}), \quad (4.2)$$

where $p(v, t)$ is the probability distribution function for the random variable v as a function of time t . In this context, the bistable function $F(v)$ is viewed as the derivative of a double well potential, and initiation of an action potential is viewed as the escape from the lower well to the upper well. This Fokker-Planck equation allows us to study the statistics of transitions between rest states, whether spontaneous or evoked, and to give a stochastic interpretation of the stimulus threshold. Furthermore, the size of $D(v)$ gives us an estimate of how far the stochastic behavior is from the deterministic model.

A primary question, then, is how to determine the "diffusion" coefficient $D(v)$. However, once this diffusion coefficient is determined, one can also address other questions of fundamental importance such as the rate of convergence to the deterministic limit as a function of parameters of the problem, such the size and number of discrete channels.

To derive a Fokker-Planck equation, we exploit the fact that sodium channels are "fast" channels, in that their open and close rates are typically large compared to other processes.

Suppose that we have a simple ionic conductance model of transmembrane potential of the form

$$\frac{dv}{dt} = \sum x_i f(v) + g(v), \quad (4.3)$$

where x_i is either zero or one, depending on whether the i^{th} ionic channel is closed (0) or open (1). The term $f(v)$ represents the current of a single gated ion channel, and $g(v)$ represents ungated currents. Suppose further that the state of the random variable $\sum x_i$ is determined by a Markov model with a finite number of states, denoted by the vector of indices I . We wish to determine the probability distribution function $\mathbf{p}_I(v, t)$, a function of the continuous random variable v and the discrete vector-valued random variable I .

Suppose the matrix $M(v)$ is the transition matrix for the Markov process and that in a given state I , the differential equation (4.3) can be written as

$$\frac{dv}{dt} = f_I(v), \quad (4.4)$$

Then, the Chapman-Kolmogorov equation for (4.3) is [5]

$$\frac{\partial \mathbf{p}_I}{\partial t} = -\frac{\partial}{\partial v}(\mathbf{F}_I \mathbf{p}_I) + M \mathbf{p}_I, \quad (4.5)$$

v_{Na}	$= 115\text{mV}$	$\frac{g_{Na}}{C_m}$	$= 120\text{ms}^{-1}$
v_K	$= -12\text{mV}$	$\frac{g_k}{C_m}$	$= 36\text{ms}^{-1}$
v_l	$= 10.5988\text{mV}$	$\frac{g_l}{C_m}$	$= 0.3\text{ms}^{-1}$

Table 4.1: Parameter values for the Hodgkin-Huxley equations.

where F_I is the diagonal matrix with entries $f_I(v)$ from (4.4).

If the transitions between discrete states are fast compared to the time scale of change of v , then the elements of M are typically much larger than the elements of F_I . This difference in time scale can be emphasized by rescaling the matrix M by a small dimensionless parameter ϵ , the ratio of typical time scales, setting $A = \epsilon M$. Our goal is to take advantage of this time scale difference to reduce (4.5) to a simpler equation describing the behavior on the slower time scale. This we do using adiabatic reduction, described earlier in these notes.

4.1.2 The Hodgkin-Huxley equations

The Hodgkin-Huxley equations are well-known to be

$$C_m \frac{dv}{dt} = g_{Na} m^3 h (v_{Na} - v) + g_k n^4 (v_K - v) + g_l (v_l - v) + I(t), \quad (4.6)$$

where m , n , and h are gating variables which satisfy the ordinary differential equations

$$\frac{du}{dt} = \alpha_u (1 - u) - \beta_u u, \quad (4.7)$$

for each of $u = m, n, h$. The functions α_m and β_m are given by

$$\alpha_m = \frac{25 - v}{10} / (\exp(\frac{25 - v}{10}) - 1) \text{ms}^{-1}, \quad (4.8)$$

$$\beta_m = 4 \exp(-\frac{v}{18}) \text{ms}^{-1}. \quad (4.9)$$

Since we do not make use of n and h in what follows, α_h , α_n , β_h and β_n are not listed here; they can be found in numerous places [8, 9]. The parameter values are listed in Table 4.1. It is an inconvenient fact of history that v , v_{Na} , v_k , and v_l are not the transmembrane or Nernst potentials, but have been adjusted so that the rest potential for (4.6) is zero.

Because the time constant for m is much smaller than for either n or h , it is typical to replace m in equation (4.6) by $m_\infty(v) = \frac{\alpha_m(v)}{\alpha(v) + \beta(v)}$. Then, the initial stages of an action potential are governed by the equation

$$C_m \frac{dv}{dt} = g_{Na} m_\infty^3 h_0 (v_{Na} - v) + g_k n_0^4 (v_K - v) + g_l (v_l - v) + I(t), \quad (4.10)$$

where n_0 and h_0 are the steady state values of n and h , respectively.

Instead of the deterministic model (4.10), we consider the stochastic model for activation of neural membrane

$$C_m \frac{dv}{dt} = \frac{g_{Na}}{N} \sum_i^{N_h} x_i (v_{Na} - v) + g_{eff} (v_{eff} - v) + I(t), \quad (4.11)$$

where x_i is either zero or 1, zero if the i^{th} sodium channel is closed, and 1 if it is open, N is the total number of sodium ion channels. Here,

$$g_{eff} (v_{eff} - v) \equiv g_k n_0^4 (v_K - v) + g_l (v_l - v). \quad (4.12)$$

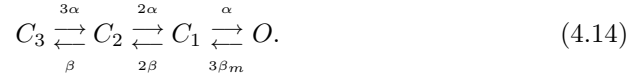
To simplify notation, we write (4.11) in the form of (4.3),

$$\frac{dv}{dt} = \sum_i^{N_h} x_i f(v) + g(v, t), \quad (4.13)$$

where $f(v) = \frac{g_{Na}}{NC_m} (v_{Na} - v)$, $g(v) = \frac{g_{eff}}{C_m} (v_{eff} - v) + \frac{1}{C_m} I(t)$.

Since sodium channels are the most important channels for initiation of an action potential, we do not include stochastic opening and closing of potassium channels, as was done in [4].

We use a Markov model for the opening and closing of a sodium channel



Since we are concerned only with the initial activation of excitable membrane via the opening of sodium channels, we do not include an inactivated state, nor do we include transitions to and from an inactivated state. Rather, we let $N_h = Nh$ be the (assumed to be an integer) number of activated channels, i.e., the number of channels that are not inactivated and are therefore available to open. The rates $\alpha = \alpha_m(v)$ and $\beta = \beta_m(v)$ are taken to be the voltage dependent transition rates for the gating variable m in standard Hodgkin-Huxley parlance. Thus, this model is based on the assumption that the opening of a sodium channel requires the opening of three independent subunits.

To analyze this stochastic differential equation, we must write down the corresponding Kolmogorov-Chapman equation [5]. The state space is a mixture of continuous and discrete variables, v the continuous voltage, and i, j, k, l , the integers that enumerate the number of channels in states C_3, C_2, C_1 , and O , respectively. These equations take the form

$$\begin{aligned} \frac{d}{dt} p_I(v, t) &= \sum_{I'} (W(I'|I) p_{I'}(v, t) - W(I|I') p_I(v, t)) \\ &\quad - \frac{\partial}{\partial v} ((lf + g) p_I(v, T)) \end{aligned} \quad (4.15)$$

where $I = (i, j, k, l)$ and $I' = (i', j', k', l')$ are vectors of indices, and $W(I|I')$ represents the transition rates from state I to state I' . There are a limited number of

transitions that are possible, as follows

$$W(i, j, k, l | i - 1, j + 1, k, l) = 3i\alpha \text{ for } i > 0, \quad (4.16)$$

$$W(i, j, k, l | i, j - 1, k + 1, l) = 2j\alpha \text{ for } j > 0, \quad (4.17)$$

$$W(i, j, k, l | i, j, k - 1, l + 1) = k\alpha \text{ for } k > 0, \quad (4.18)$$

$$W(i, j, k, l | i + 1, j - 1, k, l) = j\beta \text{ for } j > 0, \quad (4.19)$$

$$W(i, j, k, l | i, j + 1, k - 1, l) = 2k\beta \text{ for } k > 0, \quad (4.20)$$

$$W(i, j, k, l | i, j, k + 1, l - 1) = 3l\beta \text{ for } l > 0. \quad (4.21)$$

Since there are N_h total available channels, it must be that $i + j + k + l = N_h$. It follows that there are $N_T = \frac{1}{6}(N_h + 1)(N_h + 2)(N_h + 3)$ different states I . Clearly, it is not an easy matter to study the equation (4.15), and an approximate analysis is desirable. The relevant observation is that at rest ($v = 0$), the two time constants are $\tau_m = \frac{1}{\alpha_m + \beta_m} = 0.25$ ms, and $C_m g_{eff}^{-1} \equiv C_m (g_k n_0^4 + g_l)^{-1} = 1.5$ ms, which differ by a factor of 6. Thus, we introduce the dimensionless parameter

$$\epsilon = \frac{g_{eff}}{C_m(\alpha_m + \beta_m)}, \quad (4.22)$$

and carry out the calculation of Section 2 on (4.15), based on the assumption that ϵ is small.

The result of that calculation is (with heavy reliance on Maple), ignoring terms of order ϵ^2 ,

$$\begin{aligned} \frac{\partial q}{\partial t} = & -\frac{\partial}{\partial v} \left((N_h a^3 f + g + \epsilon \frac{C_m}{g_{eff}} h) q \right) \\ & + \frac{C_m}{g_{eff}} \frac{\partial}{\partial v} \left(\epsilon N_h d(v) f \frac{\partial}{\partial v} (a^3 f q) \right), \end{aligned} \quad (4.23)$$

where

$$d(v) = \frac{1}{6} b (18a^2 + 9ab + 2b^2), \quad (4.24)$$

and

$$h = \left(\frac{17}{2} N_h (N_h - 1) f^2 a^5 + 3 N_h f g a^2 \right) \frac{\partial a}{\partial v}, \quad (4.25)$$

with $a = \frac{\alpha}{\alpha + \beta} \equiv m_\infty$, $b = 1 - a$.

Equation (4.23) is the Fokker-Planck equation relevant to the Hodgkin-Huxley model. We can also express this as the Langevin equation

$$\begin{aligned} dv = & (N_h a^3 f + g + O(\epsilon)) dt \\ & + \sqrt{2\epsilon \frac{C_m}{g_{eff}} N_h d(v) a^3 f^2} dt \xi(t), \end{aligned} \quad (4.26)$$

where $\xi(t)$ is brownian white noise. The significant observation is that since the diffusion coefficient is proportional to $\frac{\epsilon}{N}$, this Langevin equation converges to the Hodgkin-Huxley model (4.10) in the limit $\epsilon \rightarrow 0$. In the limit $N \rightarrow \infty$ it converges to a deterministic equation that differs from (4.10) by a term of size $O(\epsilon)$, as expected.

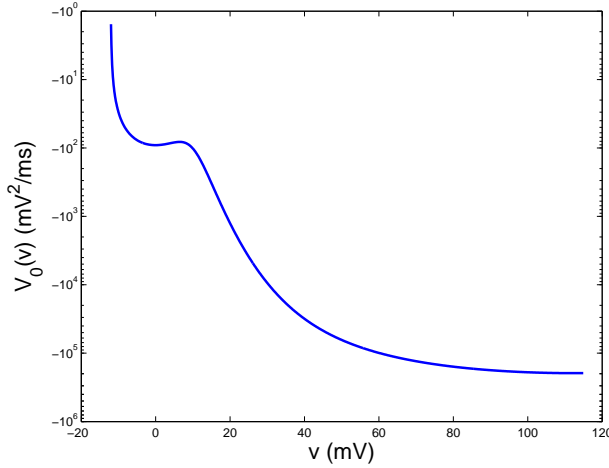


Figure 4.1: The double well potential $V_0(v)$ for the Hodgkin-Huxley version of the Fokker-Planck equation, plotted on a logarithmic scale.

Expected Firing Times and Strength-Duration Curves

Now that we have a Fokker-Planck version of the Hodgkin-Huxley model we can study initiation of action potentials in probabilistic terms. For this, we write (4.23) as

$$\frac{\partial q}{\partial t} = -\frac{\partial}{\partial v} (V'(v, t)q) + \frac{\partial}{\partial v} \left(D(v) \frac{\partial q}{\partial v} \right), \quad (4.27)$$

where

$$V'(v) = V'_0(v) + \frac{1}{C_m} I(t) + O(\epsilon) + O\left(\frac{\epsilon}{N}\right), \quad (4.28)$$

$$V'_0(v) = N_h a^3 f + g, \quad (4.29)$$

and

$$\begin{aligned} D(v) &= \epsilon \frac{C_m}{g_{eff}} N_h d(v) a^3 f^2 \\ &= \frac{h_0}{N} d(v) \frac{m_\infty^3}{\alpha + \beta} \left(\frac{g_{Na}}{C_m} (v_{Na} - v) \right)^2. \end{aligned} \quad (4.30)$$

Note that the function $V'_0(v) + \frac{1}{C_m} I(t)$ is the same as the right hand side of (4.10), divided by C_m . Hence the potential $V_0(v)$ is a double-well potential, shown plotted in Fig. 4.1. (The potential is plotted on a logarithmic scale so that the double-well can be easily seen.) This double well potential has extremal values at the zeros of $V'_0(v)$, denoted by $v_0 < v_1 < v_2$. For the parameter values used here, $v_0 = 0\text{mV}$, $v_1 = 6.5\text{mV}$, and $v_2 = 112.7\text{mV}$.

The parameter values for g_{eff} are slightly different than might be expected from the preceding discussion. In particular, $n_0 = 0.3754$ rather than 0.3177, which is

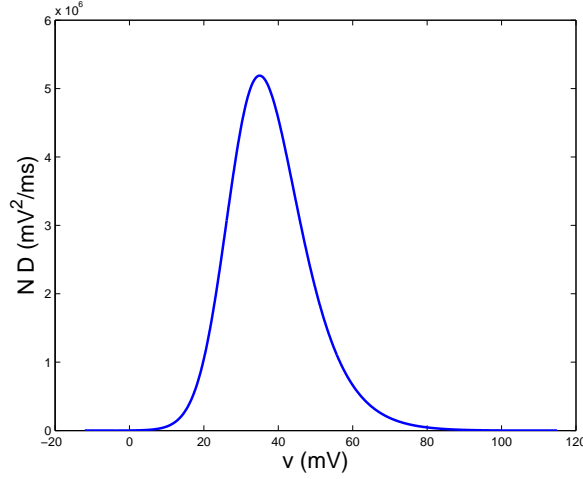


Figure 4.2: The diffusion coefficient $ND(v)$ for the Hodgkin-Huxley version of the Fokker-Planck equation.

the steady state value of n , and $\frac{gI}{C_m} = 0.6943\text{ms}^{-1}$ rather than 0.3ms^{-1} listed in Table 1. The reason for these particular choices was to adjust the intermediate zero of the function $V_0'(v)$ to be $v_1 = 6.5$, to correspond to the voltage threshold of the full Hodgkin-Huxley system.

In Fig. 4.2 is shown $ND(v)$, where $D(v)$ is the diffusion coefficient for the Fokker-Planck equation (4.27). It is significant that $D(v)$ is inversely proportional to N , the number of sodium channels. It is also noteworthy that $D(v)$ is highly variable over the range of interest. For example $D(v_K) = 10\text{mV}^2\text{ms}^{-1}$, $D(0) = 1.4 \times 10^3\text{mV}^2\text{ms}^{-1}$, and $D(v_1) = 1.7 \times 10^4\text{mV}^2\text{ms}^{-1}$.

The first thing to do with this is to determine the mean first passage time. It is well known that the mean first exit time $T(v)$ for a time autonomous process satisfies the ordinary differential equation

$$V'(v)\frac{dT}{dv} + \frac{d}{dv}\left(D(v)\frac{dT}{dv}\right) = -1, \quad (4.31)$$

subject to appropriate boundary conditions. Here we require $T'(v_K) = 0$ because in the original stochastic model, the voltage can never go below v_K , and we require $T(v_1) = 0$, because v_1 is the location of the potential maximum which defines the threshold in the deterministic problem. We are interested in determining $T_{exit} \equiv T(0)$ for different values of stimulus current.

It is straightforward to solve this boundary value problem numerically using a shooting method. We let $T(v) = T_0(v) + c$, where c is a constant, then $T_0(v)$ is the solution of the equation (4.31) subject to initial conditions $T_0(v_K) = 0$, $T_0'(v_K) = 0$, and $c = -T_0(v_1)$. Thus, the boundary value problem to find the mean exit time can be solved by simple integration of the equation (4.31) with zero initial data.

The results of this calculation are shown in Fig. 4.3. Here is shown the mean

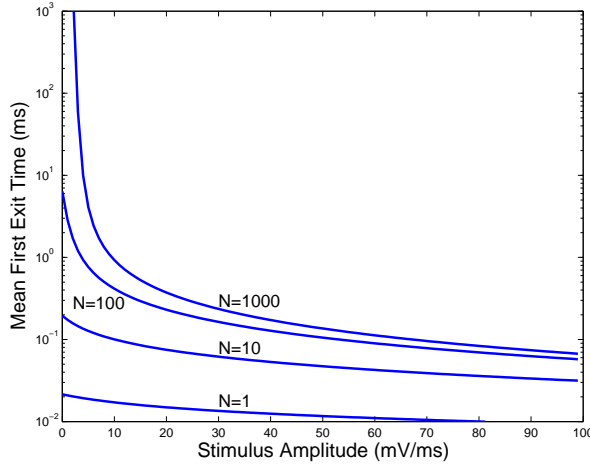


Figure 4.3: Mean first exit time as a function of stimulus amplitude for the stochastic Hodgkin-Huxley equation with number of channels $N = 1, 10, 100, 1000$.

first exit time, as a function of stimulus amplitude $\frac{I}{C_m}$. The four curves shown are for the total number of channels $N = 1, 10, 100, 1000$.

The spontaneous (i.e., with stimulus amplitude = 0) mean exit time is well fit by the function

$$\begin{aligned} T &= 0.5155 \times 10^{0.011N} \text{ms} \\ &= 0.5155 \exp(0.025N) \text{ms}, \end{aligned} \quad (4.32)$$

for N larger than about 50. This formula is reminiscent of the famous Arrhenius formula for escape from a double well potential

$$T_{off} \sim \kappa_0 \exp\left(\frac{\Delta G}{kT}\right), \quad (4.33)$$

which relates the time of escape from a quadratic potential well to the depth of the well (ΔG) and the amplitude of random noise (kT). The Arrhenius formula is an asymptotic formula derived assuming a constant diffusion coefficient, so the derivation is not applicable here. However, since the diffusion coefficient is inversely proportional to N , the N -dependence in (4.32) is exactly as would be expected from the Arrhenius formula.

The strength-duration curve for a deterministic model is the curve of stimulus amplitudes as a function of stimulus duration that is required to move the potential from rest to threshold. To be specific, for the bistable model (4.1), the strength-duration curve $I = I(T)$ is defined implicitly by

$$T = \int_{v_0}^{v_1} \frac{dv}{F(v) + I}. \quad (4.34)$$

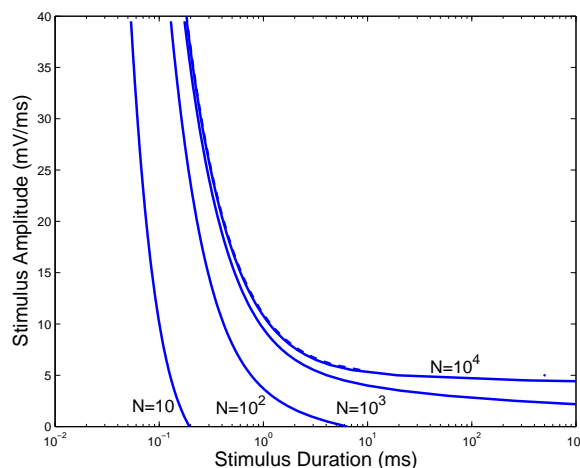


Figure 4.4: Strength-duration curves for the stochastic Hodgkin-Huxley equation with $N = 10, 10^2, 10^3$, and 10^4 . For $N = 10^4$, the curve is essentially converged to the strength-duration curve for the deterministic model.

For a stochastic model of action potential initiation, a natural definition of strength-duration curve is the mean first exit time vs. stimulus amplitude curve, plotted with stimulus amplitude as a function of mean first exit time. Thus, simply reversing the axes in Fig. 4.3 gives examples of stochastic strength-duration curves.

In Fig. 4.4 strength-duration curves are shown for several values of N . The important observation is that the stochastic strength-duration curves converge to the deterministic curve in the limit of large N . Here, for $N = 10^4$, the stochastic curve is essentially converged to the deterministic strength-duration curve.

4.1.3 Discussion

Dendritic spines are relatively noisy. In [1] it was estimated that a typical dendritic spine has 328 channels with channel conductance of 12 pS. The parameters used in [13] result in a slightly higher estimate. However, in [12], maximum per channel conductance was estimated as 22 pS. If the 22 pS conductance is used, then the number of channels would be about 180. Furthermore, the number of channels scales with the surface area of the spine, so one can expect some additional variation of these numbers. With these ranges for N , the rate of spontaneous action potential initiation is $10^{-3} - 10^{-2} \text{ms}^{-1}$. In a population of a million spines there would be between 1,000 and 10,000 spontaneous action potentials per ms.

On the other hand, squid axons are not very noisy. For a 1 cm^2 patch of axonal membrane with about 10^9 sodium channels, the mean time for spontaneous action potential initiation is on the order of 10^{10} ms, which is far larger than the age of our universe.

Stochastic effects are quite important in other contexts as well. For example,

calcium release through ryanodine receptors is highly stochastic owing to the fact that there are relatively few release channels per release site. The analysis presented here applies when channel transitions are fast compared to other processes. However, for ryanodine receptors, the time constants are exactly opposite, with the time constant for calcium uptake much smaller than the time constants for ryanodine receptor transitions. Consequently, a different asymptotic method is necessary [6, 7].

The diffusion coefficient calculated here is specific to the Markov channel model (4.14). Not surprisingly, different Markov channel models give different diffusion coefficients, even if the expected open probability remains unchanged.

Finally, a word about how the formulas for equation (4.23) were calculated. The original Chapman-Kolmogorov equation is a $N_T \times N_T$ matrix system, where $N_T = \frac{1}{6}(N_h + 1)(N_h + 2)(N_h + 3)$. For example, with $N_h = 5$, $N_T = 56$. Clearly, it is challenging, even for Maple, to calculate these formulas for large N_h . In fact, the formulas were calculated for $N_h = 1, 2, \dots, 6$, and the general formula was deduced from these results. A general proof of these is not known.

4.2 Brownian ratchets

(Remark: This section is excerpted from K&S, Volume II, Chapter 15)

Proteins live in a world that is being continually shaken by random movements. If these random motions could be rectified, or biased, then they could be used to perform work. For example, if a particle performs an unbiased random walk on a line then, if there are no outside influences, its mean displacement is zero. However, if every time the particle moves a certain distance in one direction it is prevented by some mechanism from moving back in the opposite direction (i.e., a ratchet), then the original random motion of the particle is “rectified”, and the particle experiences a net drift.

This concept can be understood in a simple way by the way in which a glucose transporter operates (see Chapters ?? and ??). In the absence of hexokinase, the transporter is merely an exchanger that reaches steady-state when the glucose concentrations are the same on either side of the membrane. However, ATP hydrolysis and phosphorylation of glucose by hexokinase is able to rectify the diffusional flux of glucose, eliminating the backflow, thus maintaining a net flux of glucose into the cytoplasm.

Another example is the provided by the translocation of macromolecules through a membrane. For example, the chaperone molecule HSP-70 (heat shock protein, molecular weight 70 kilodaltons) is required for translocation of proteins into the ER and mitochondria. In the absence of HSP-70, macromolecules move through pores in the membrane by simple diffusion, moving forward or backward via a random walk. It is not certain how HSP-70 works, but one proposal (Elston 2000, T. C. Elston, Models of Post-translational Protein Translocation, Biophysical J. 2235-2251, 2000.) is that HSP-70, which is located inside the organelle, binds to the diffusing protein as it enters the organelle, preventing it from sliding back through the pore, thus creating a ratchet.

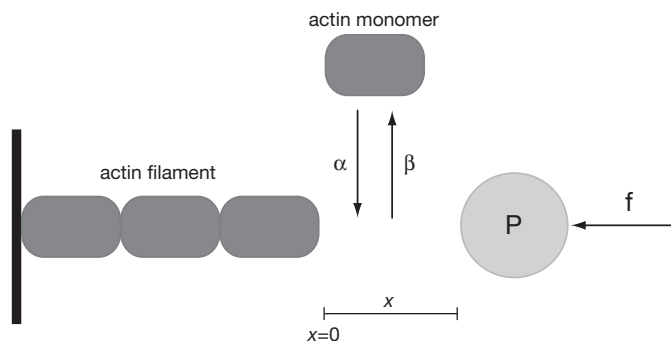


Figure 4.5: Diagram of a polymerization ratchet.

4.2.1 Polymerization Ratchets

Another important example of a Brownian ratchet is the polymerization ratchet, a diagram of which is shown in Fig. 4.5. An actin filament that is capable of polymerizing is in contact, from time to time, with a particle, P (which may also have an applied load f). Although P is diffusing it cannot move far to the left as the actin polymer is in the way. However, every so often the Brownian motion of P takes it far enough to the right, providing the opportunity for another actin monomer to polymerize onto the filament, extending the actin filament. The net effect is that the motion of P is biased to the right. Clearly, for this to happen a number of conditions must be satisfied; P must move randomly far enough to the right to make space for an actin monomer to join the filament, and it must stay there long enough to give actin time to bind; also, the polymerizing actin must remain strongly bound to the filament so that the process is not reversed, i.e., so that the collision of P with the actin polymer does not cause the actin at the end to unbind.

We wish to calculate the load-velocity relationship for this system (Peskin *et al.* (1993)). To do so, we let x denote the positive distance between the end of the actin filament and P , and let $p(x, t)$ be the probability density function for the location of the particle P . That is, $\int_a^b p(x, t) dx$ is the probability that the particle P lies in the interval $x \in [a, b]$.

There are only two ways that the distance between the end of the polymer and the particle can change; the particle can move to a different position or the length of the actin polymer can change. Correspondingly, $p(x, t)$ can change either because of movement of the particle or because of changes to the length of the polymer. The flux of p due to particle movement is given by

$$J = -D \left(\frac{\partial p}{\partial x} + \frac{f}{kT} p \right), \quad (4.35)$$

where k is Boltzmann's constant, T is absolute temperature, and D is the diffusion coefficient of P . This is the same as the Nernst-Planck relationship for movement

of ions in an electric field, where f replaces $qz \frac{\partial \phi}{\partial x}$. Notice that the sign of f is such that it is positive to the left.

Now suppose that monomers bind at rate α and unbind at rate β . Presumably unbinding can occur independent of x , but when it does so, the distance x is suddenly increased by the amount δ . Similarly, if binding occurs, the distance x is suddenly decreased by the amount δ . However, binding can occur only if there is enough room, i.e. only if $x > \delta$.

The rate of change of p depends on these reactions. If $x < \delta$, the rate of change of p is (in words)

$$\begin{aligned} \text{rate of change of } p &= \text{transport rate} \\ &\quad + \text{binding rate at position } x + \delta \\ &\quad - \text{unbinding rate at position } x, \end{aligned} \quad (4.36)$$

whereas, if $x > \delta$,

$$\begin{aligned} \text{rate of change of } p &= \text{transport rate} \\ &\quad + \text{binding rate at position } x + \delta \\ &\quad - \text{unbinding rate at position } x \\ &\quad - \text{binding rate at position } x \\ &\quad + \text{unbinding rate at position } x - \delta. \end{aligned} \quad (4.37)$$

In mathematical terms,

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} + \frac{Df}{kT} \frac{\partial p}{\partial x} + \alpha p(x + \delta, t) - \beta p(x, t), \quad x < \delta, \quad (4.38)$$

and

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} + \frac{Df}{kT} \frac{\partial p}{\partial x} + \alpha [p(x + \delta, t) - p(x, t)] + \beta [p(x - \delta, t) - p(x, t)], \quad x > \delta. \quad (4.39)$$

Since the particle cannot move across the boundary at $x = 0$, we impose the no-flux condition,

$$D \frac{\partial p(0, t)}{\partial x} + \frac{Df}{kT} p(0, t) = 0. \quad (4.40)$$

Finally, we require that p be continuously differentiable at $x = \delta$.

Although this is a fairly simple example of a Brownian ratchet, its full solution is highly non-trivial. This is because the steady state equation is a delay differential equation that must be solved on the infinite half-line, subject to boundary conditions at $x = 0$ and $x = \infty$. However, it is possible to gain an understanding of how this Brownian ratchet works in several limiting cases.

In the limit that α and β are small compared to $\frac{D}{\delta^2}$ (see Exercise ??) we can calculate the steady-state solution for p explicitly. In this case we have

$$\frac{d^2 p}{dx^2} + \frac{\omega}{\delta} \frac{dp}{dx} = 0, \quad x < \delta \text{ and } x > \delta, \quad (4.41)$$

$$\frac{dp(0)}{dx} + \frac{\omega}{\delta} p(0) = 0, \quad (4.42)$$

$$p \text{ continuous at } x = \delta, \quad (4.43)$$

where $\omega = \frac{f\delta}{kT}$. Furthermore, we require that $p \rightarrow 0$ as $x \rightarrow \infty$. This boundary value problem has solution

$$p = \frac{\omega}{\delta} e^{-\omega x/\delta}, \quad (4.44)$$

so that $\int_0^\infty p(x) dx = 1$.

We now can find the mean ratchet velocity, v . The proportion of positions at which a monomer can bind is $\int_\delta^\infty p(x) dx$, and thus the mean rate at which the length of the filament increases due to monomer binding is $\delta\alpha \int_\delta^\infty p(x) dx$. Similarly, all filaments can decrease in length due to unbinding of a monomer, and thus the mean rate at which the length of the filament decreases due to monomer unbinding is $\delta\beta$. Taking the difference between these two rates gives the net mean ratchet velocity

$$v = \delta \left(\alpha \int_\delta^\infty p(x) dx - \beta \right). \quad (4.45)$$

Substituting for p from (4.44) gives the remarkably simple expression for the force-velocity relation,

$$v = \delta \left[\alpha \exp\left(-\frac{f\delta}{kT}\right) - \beta \right]. \quad (4.46)$$

The stall force, f_0 , i.e., the force at which the ratchet velocity is zero, is given by

$$f_0 = -\frac{kT}{\delta} \ln\left(\frac{\beta}{\alpha}\right). \quad (4.47)$$

Note the similarity of this with the Nernst equation (??). Notice also that $\frac{\beta}{\alpha}$ is the equilibrium constant for binding of monomer, $\frac{\beta}{\alpha} = \exp\left(\frac{\Delta G^0}{RT}\right)$, so that

$$f_0 = -\frac{\Delta G^0}{\delta N_A}. \quad (4.48)$$

Thus, the energy used to move the particle against the load is the same as the free energy of binding of the monomer. Clearly, a necessary condition for this polymerization ratchet to push a load is that the binding rate be larger than the unbinding rate.

We can also easily examine this Brownian ratchet in another limit, the fast reaction limit. We suppose that we have an ideal ratchet for which binding of monomer takes place instantly ($\alpha \rightarrow \infty$) and irreversibly ($\beta = 0$) whenever there is sufficient space to bind, i.e., whenever x reaches δ . Thus, the mean velocity of the ratchet is δ divided by the time it takes the particle to diffuse to the right a distance δ starting from position $x = 0$. This time is the mean first exit time $T(0)$, where $T(x)$ satisfies the differential equation

$$D \left(\frac{d^2 T}{dx^2} - \frac{f}{kT} \frac{dT}{dx} \right) = -1, \quad (4.49)$$

subject to boundary conditions $T'(0) = 0$ (since the boundary at $x = 0$ is a reflecting boundary) and $T(\delta) = 0$. The solution is

$$T(0) = \frac{\delta^2}{D} \left(\frac{kT}{f\delta} \right)^2 \left[\exp\left(\frac{f\delta}{kT}\right) - \frac{f\delta}{kT} - 1 \right], \quad (4.50)$$

so that

$$v = \frac{D}{\delta} \frac{\left(\frac{f\delta}{kT}\right)^2}{\exp\left(\frac{f\delta}{kT}\right) - 1 - \frac{f\delta}{kT}}. \quad (4.51)$$

This load-velocity curve is a monotone decreasing function of load f . Notice, however, that for this model there is no stall velocity, because, since the bound monomer is assumed to bind irreversibly ($\beta = 0$), there is the implicit assumption that the binding energy is infinite, which of course, cannot be correct.

Peskin *et al.* (1993) applied this model to the study of filopod protrusion, as well as to propulsion of the bacteria *Listeria monocytogenes*, while a number of elaborations of the basic scheme have been constructed (Mogilner and Oster, 1996, 1999; Simon *et al.*, 1992).

Continuous Brownian Ratchet

Another useful way to model the polymerization ratchet is to think of binding and unbinding, not as providing a discrete jump in length, but as providing a continuous velocity. That is, binding produces a velocity of $-\delta\alpha$ while unbinding produces a velocity of $\delta\beta$. With this understanding, we can write the continuous brownian ratchet model has

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} \left(U'(x) + \frac{f}{\xi} \right) p + D \frac{\partial^2 p}{\partial x^2}, \quad (4.52)$$

where

$$U'(x) = \delta(\alpha H(x - \delta) - \beta), \quad (4.53)$$

and is defined for $0 < x < \infty$.

The velocity is defined as

$$v = \delta \int_0^\infty (\alpha H(x - \delta) - \beta) p(x) dx \equiv \int_0^\infty U'(x) p(x) dx. \quad (4.54)$$

In steady state,

$$p(x) = \exp\left(-\frac{U(x) + \frac{f}{\xi}x}{D}\right), \quad (4.55)$$

where

$$U(x) = -\delta\beta x + \delta\alpha(H(x - \delta)(x - \delta)). \quad (4.56)$$

We find that

$$S_1 = \int_0^\delta p dx = D \frac{(-1 + \exp(\frac{\delta}{D}(\delta\beta - \frac{f}{\xi})))}{(\delta\beta - \frac{f}{\xi})}, \quad (4.57)$$

and

$$S_2 = \int_\delta^\infty p dx = D \frac{-\exp(\frac{\delta}{D}(\delta\beta - \frac{f}{\xi}))}{(\delta\beta - \delta\alpha - \frac{f}{\xi})}, \quad (4.58)$$

then

$$v = \delta \frac{\alpha S_2 - \beta(S_1 + S_2)}{S_1 + S_2}. \quad (4.59)$$

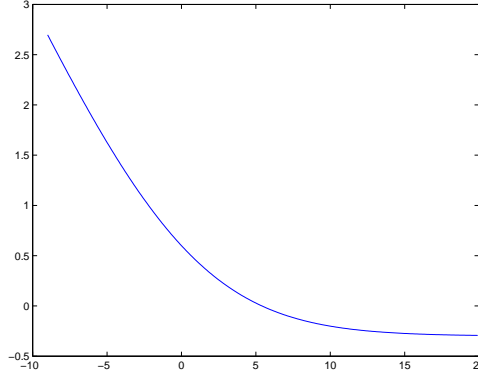


Figure 4.6: Load velocity curve with $\alpha = 10$, $\beta = 1$, $\delta = 0.3$.

4.2.2 The Tilted Potential

There is another approximate model of the Brownian ratchet that has proven to be quite useful. Rather than thinking of binding and unbinding of a monomer, we suppose that at the fixed positions $x = x_k = k\delta$, the particle P is given a “kick” of energy ΔG , but that it diffuses freely elsewhere, against a load f . Now the probability distribution function $p(x, t)$ for the location of the particle is the solution of the Fokker-Planck equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x}(V'(x)p) + D\frac{\partial^2 p}{\partial x^2}, \quad (4.60)$$

where $V(x)$ is the potential energy function with

$$V'(x) = \frac{Df}{kT} - D\frac{\Delta G}{kT} \sum_n \delta(x - n\delta). \quad (4.61)$$

The potential $V(x)$ shown plotted in Fig. 4.7 is a piecewise linear “staircase”, often called a tilted ratchet potential.

One feature of this that is immediately obvious is that the stall load is $f = \Delta G$, because it is the load at which the potential $V(x)$ is periodic. This also makes sense intuitively because at this value the load is exactly balanced by the energy expended.

The second feature of this model is that the load-velocity relationship can be calculated explicitly. To do so we look for a steady periodic solution of the Fokker-Planck equation (4.60). For $x \neq n\delta$, $p(x)$ must satisfy the differential equation

$$\frac{Df}{kT}p + D\frac{dp}{dx} = -J, \quad (4.62)$$

while at the points $x = n\delta$, the solution experiences a jump,

$$\ln p|_{x_n^-}^{x_n^+} = \frac{\Delta G}{kT}, \quad (4.63)$$

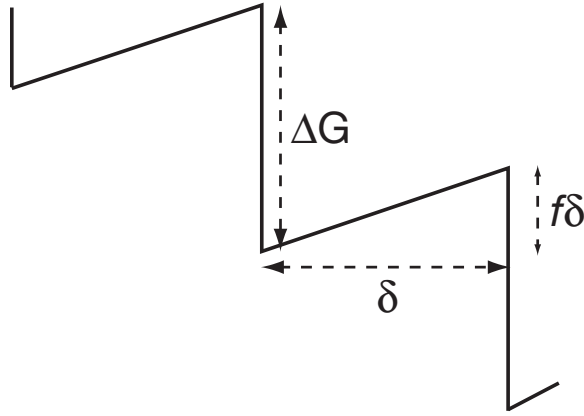


Figure 4.7: Diagram of a tilted ratchet potential (4.61)

so that

$$p(n\delta^+) = p(n\delta^-) \exp\left(\frac{\Delta G}{kT}\right). \quad (4.64)$$

For periodicity, it must be that

$$p(0) = p(\delta) \exp\left(\frac{\Delta G}{kT}\right). \quad (4.65)$$

In addition, we require $\int_0^\delta p(x)dx = 1$. The solution has

$$J = \frac{D}{\delta^2} \omega_l^2 \frac{1 - \exp(\omega_0 - \omega_l)}{(\exp(\omega_0) - 1)(\exp(-\omega_l) - 1) + \omega_l(\exp(\omega_0 - \omega_l) - 1)}, \quad (4.66)$$

where

$$\omega_0 = \frac{\Delta G}{kT}, \quad \omega_l = \frac{f\delta}{kT}. \quad (4.67)$$

Furthermore,

$$\lim_{f \rightarrow 0} J = 2 \frac{D}{\delta^2} \frac{\exp(\omega_0) - 1}{\exp(\omega_0) + 1}. \quad (4.68)$$

The mean velocity of the ratchet is given by

$$\left\langle \frac{dx}{dt} \right\rangle = \int_0^\delta J dx = \delta J. \quad (4.69)$$

A motor pulling cargo

The tilted potential Brownian ratchet was motivated as a model for a polymerization ratchet which is pushing a loaded particle. However, another interpretation is that it describes the movement of a molecular motor moving along a track, pulling a load. Elston and Peskin (2000) extended this idea by assuming that the molecular

motor moves in a tilted potential, but that the load is attached to the motor by a spring. They then addressed the question of how the velocity of the motor with its load was affected by the flexibility of the spring.

To study this problem, suppose that the molecular motor is a molecule with diffusion coefficient D_1 , the cargo molecule has diffusion coefficient D_2 , and that the two are connected by a spring with spring constant κ . Thus, the load on the molecular motor is not fixed but is determined by the distance between motor and cargo times the spring constant. One can readily write down the Fokker Planck equation for the location of this motor-cargo complex. Elston and Peskin used asymptotic analysis for large and small κ to determine the velocity of the motor, but their results can also be explained using intuitive physical reasoning.

Suppose the spring is very stiff $\kappa \rightarrow \infty$. With no flexibility, the motor-cargo complex is expected to move as a single molecule with an effective diffusion coefficient. Since (recall from Chapter 2) friction is inversely proportional to the diffusion coefficient $f = \frac{kT}{D}$, and we expect friction to be additive, it follows that the diffusion coefficient of the complex should be

$$D_c = \frac{1}{\frac{1}{D_1} + \frac{1}{D_2}} = \frac{D_1 D_2}{D_1 + D_2}. \quad (4.70)$$

The velocity of the complex should be that for a molecule with diffusion coefficient D_c , that is

$$v = 2 \frac{D_c \exp(\omega_0) - 1}{\delta \exp(\omega_0) + 1}. \quad (4.71)$$

In the opposite limit of a soft spring $\kappa \rightarrow 0$, one expects the load to be essentially constant. This is because small fluctuations in the separation between cargo and motor change the load very little. Since the load on the cargo must match the velocity times friction coefficient, it must be that

$$F_l = \frac{kT}{D_2} v. \quad (4.72)$$

so that

$$w_l = \frac{\delta}{D_2} v. \quad (4.73)$$

This same load is felt by the motor and the motor and cargo must have the same average velocity, so that

$$v = \frac{D_1 \omega_l^2}{\delta} \frac{1 - \exp(\omega_0 - \omega_l)}{(\exp(\omega_0) - 1)(\exp(-\omega_l) - 1) + \omega_l(\exp(\omega_0 - \omega_l) - 1)}, \quad (4.74)$$

as well. Here we have two relationships between load and velocity that must both be satisfied. Since (4.73) is a monotone increasing relationship between load and velocity and (4.74) is a monotone decreasing relationship between load and velocity, there is a unique intersection of these two curves, hence a unique velocity.

Plots of the velocities in the hard spring limit and in the soft spring limit as a function of the parameter ω_0 are shown in Fig. 4.8. The important observation is that the velocity in the soft spring limit is always larger than in the hard spring limit. Thus, a flexible spring allows a motor to transport its cargo much more efficiently than does a non-flexible spring.

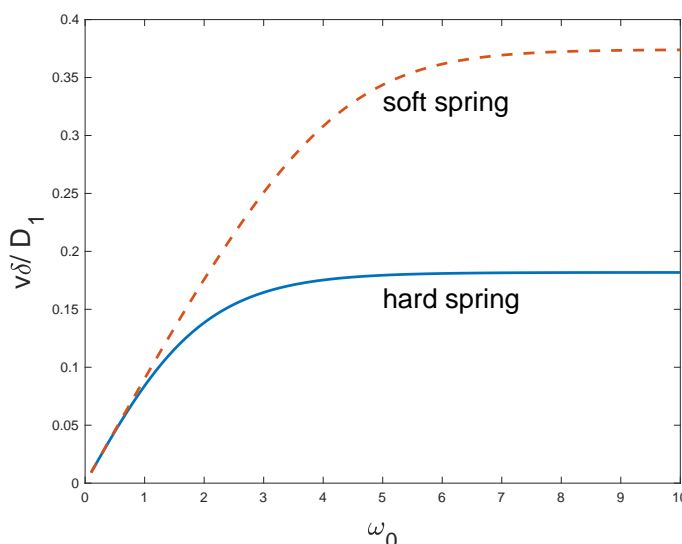


Figure 4.8: Plots of the velocities of the molecular motor-cargo complex in the hard spring limit ($\kappa \rightarrow \infty$) and soft spring limit ($\kappa \rightarrow 0$), plotted for $\frac{D_2}{D_1} = 0.1$.

4.2.3 Flashing Ratchets

The brownian ratchet model presented above is a reasonable qualitative model for a molecular motor, however, it does not provide any insight into the actual physical mechanisms by which a molecular motor works.

To build a more mechanistic model of molecular motors, reconsider how an actin-myosin crossbridge works. In the Huxley model, the crossbridge can be in one of two states, bound or unbound. If it is unbound its movement is governed by diffusion and any applied load. If it is bound, then its movement is additionally governed by a force the strength of which is proportional to its deviation from its preferred position.

This is this idea behind a flashing ratchet model. We suppose there are two conformations, bound and unbound, with binding and unbinding rate constants α and β , respectively. In the unbound state the particle (or motor protein) moves by simple diffusion, while in the bound state, it is also driven by the periodic potential $V(x)$. Since $V(x)$ is periodic, there can be no net movement if the protein is always bound. However, if the potential is asymmetric, then net drift is possible, even against a load.

The reason that net movement is possible can be understood as follows. When the particle is bound it is forced to be mostly near the location of the minimum of the potential well; the deeper the potential well, the more narrowly the particle is confined, and the faster it equilibrates. However, when the particle is unbound it is free to move away from the minimum, and the longer it stays unbound, the more uniform the distribution becomes. Now when the particle is bound again,

there is some probability that the particle will remain in the same attractive basin and there is some probability that it will be in an adjacent attractive basin. If the potential is asymmetric, then the probability that the particle falls into an adjacent attractive basin is biased, with one direction preferred over another, decided by the asymmetry of the potential. Thus, if the minimum of the potential well is biased to the left, the particle is more likely to move to the left.

The following is a simple model of an ideal flashing ratchet. We suppose that the periodic potential is deep with each attracting basin between $n\delta$ and $(n+1)\delta$ having its minimum at $x = n\delta + a$, so that binding has the effect of localizing the particle to exactly the minimum at position $x = n\delta + a$. Suppose we start the process with the particle localized at $x = a$. Then, when unbinding occurs, the probability distribution function for the position of the particle is exactly a delta function localized at $x = a$. Now, diffusion renders the distribution a Gaussian with mean $x = a$ and variance $2Dt$. When the next binding occurs, the probability of being in an attractive basin to the right, p_r , is the probability of being to the right of $x = \delta$, while the probability of moving to the left, p_l , is the probability of being to the left of $x = 0$. Thus,

$$p_r(t) = \frac{1}{2} \operatorname{erfc}\left(\frac{\delta - a}{\sqrt{2Dt}}\right), \quad p_l(t) = \frac{1}{2} \operatorname{erfc}\left(\frac{a}{\sqrt{2Dt}}\right). \quad (4.75)$$

Since the average time spent unbound is $\frac{1}{\alpha}$ and the average time spent bound is $\frac{1}{\beta}$, the average velocity is approximately (making the approximation that the particle moves no more than one position to the left or right),

$$V = \delta \frac{\alpha\beta}{\alpha + \beta} \left[p_r\left(\frac{1}{\alpha}\right) - p_l\left(\frac{1}{\alpha}\right) \right] \quad (4.76)$$

$$= \frac{\delta\alpha}{2} \frac{\beta}{\alpha + \beta} \left[\operatorname{erfc}\left(\sqrt{\frac{\alpha\delta^2}{2D}}\left(1 - \frac{a}{\delta}\right)\right) - \operatorname{erfc}\left(\sqrt{\frac{\alpha\delta^2}{2D}}\frac{a}{\delta}\right) \right] \quad (4.77)$$

$$= \frac{D}{\delta} \frac{\beta}{\alpha + \beta} v\left(\frac{\alpha\delta^2}{2D}\right), \quad (4.78)$$

where

$$v(\eta) = \eta \left[\operatorname{erfc}\left(\sqrt{\eta}\frac{a}{\delta}\right) - \operatorname{erfc}\left(\sqrt{\eta}\left(1 - \frac{a}{\delta}\right)\right) \right]. \quad (4.79)$$

The function $v(\eta)$ is shown in Fig. 4.9 with $\frac{a}{\delta} = \frac{3}{4}$. It is a nonmonotone function of η , with a maximum at about $\eta = 11.5$.

One can easily understand that there should be an optimal rate of switching between the bound and the unbound states. If the switching occurs rapidly (compared to the rate of diffusion), then there is not much time for the distribution to spread out from the localized minimum and hence there is little opportunity to move to an adjacent potential well. On the other hand, if switching is slow, then much of the time spent in the bound state is wasted, since once the asymmetric potential has localized the particle, there is no reason to remain bound.

It is typical in the literature on flashing ratchets that the driving potential is assumed to be asymmetric. If the binding and unbinding rates are independent of

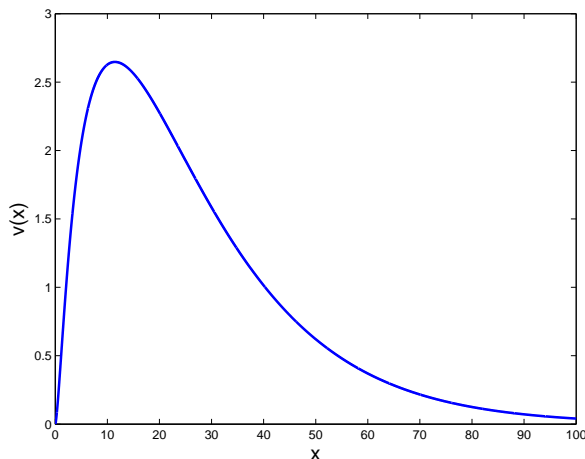


Figure 4.9: Plot of the function $v(x)$ given by (4.79), with $\frac{a}{b} = \frac{3}{4}$.

position, this is a necessary condition for net directional transport. However, if the binding and unbinding rates are spatially inhomogeneous, then it is not necessary that the potential be asymmetric. The symmetry can be broken by the arrangement of binding sites relative to the potential well locations. Thus, for example, actin-myosin crossbridge dynamics, wherein the force is assumed to be driven by a simple linear spring, has directed motion because the crossbridge binding site is shifted away from the minimum of the spring potential energy, due to the conformational change that occurs when a weakly bound crossbridge is transformed into a strongly bound crossbridge.

A more detailed analysis of flashing ratchets requires examination of the appropriate Fokker-Planck equations. Suppose that there are a number of chemical states, and that the transition rates between the states are given by $k_{ij}(x)$. Further, assume that in each chemical state the molecule is subject to the potential $\psi_j(x)$. The governing Fokker-Planck equations are then given by

$$\frac{\partial p_j}{\partial t} = \frac{\partial}{\partial x} \left(D \left(\left(\frac{\psi_j'(x)}{kT} + \frac{f}{kT} \right) p_j + \frac{\partial p_j}{\partial x} \right) \right) + \sum_i k_{ij}(x) p_i - \sum_i k_{ji} p_j, \quad (4.80)$$

where $p_j(x, t)$ is the probability distribution for being in state j at position x at time t .

For example, a model of the myosin motor that follows the Huxley crossbridge model would have two states, bound and unbound, with spatially periodic binding and unbinding rates $f(x)$ and $g(x)$, and with a periodic, symmetric potential $\psi(x)$.

This general framework has been used in many studies of real and generic molecular motors. See for example Howard (2001), Reimann (2002), Zwanzig (2001) and references therein.

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