IX Stochastic Chemical Kinetics

Surprising things happen when we take the discreteness of molecule number seriously, abandoning the notion that chemical concentrations may be treated as continuous variables. Here we will show how ideas of discreteness force us into dealing with issues of noise and randomness. We will arrive at a probabilistic description of reaction kinetics which, in the limit of large numbers, will reproduce the familiar reaction-rate description. Finally, we will show how probabilistic systems may be treated numerically using Monte Carlo simulations.

Consider a simple chemical system in which a molecule $X$ is created at some constant rate $k$ and destroyed in a first-order reaction with rate $\gamma$. If the total number $n$ of molecules is large, as is the case in standard chemical systems (Avogadro’s number is about $10^{24}$), we can ignore the fact that $n$ is an integer, but treat it instead as a continuous variable (Fig. 20, dashed line), writing

$$\frac{dn}{dt} = k - \gamma n \equiv f_n - g_n.$$  \[IX.1\]

However, this is certainly not applicable in living cells, where there are typically thousands of molecules of a given protein, hundreds of free ribosomes and RNA polymerases, tens of mRNA molecules of each kind, and one or two copies of most

**Figure 20: Stochastic biochemical reactions.** Independent runs of the same reaction proceed differently, leading to a distribution of final states (histogram).
genes. Moving, then, to a discrete description, we might guess that the actual time evolution of \( n \) would be somewhat coarse, but still completely predictable. For example, we could imagine a situation in which creation events occurred, metronome-like, at time intervals \( \Delta t = \Delta n/(k-\gamma n) \), with \( \Delta n = 1 \). However, this is physically impossible: it would require the system to somehow keep track of the time that elapsed between event occurrences. But there is no internal clock in our simple system – there are only molecules which collide into one another. The system has no memory of the past, so its response can only depend on present conditions. (This is the defining property of a Markov process.) What therefore happens is that creation and destruction reactions occur with some probability per unit time, proportional to the reaction rates. This means that each time the reaction is run with fixed initial conditions, it will proceed somewhat differently: the system will be stochastic (Fig. 20, solid lines). If we ran several experiments of this kind, recording the number of molecules present after some fixed time had elapsed, we would find a distribution of possible values.

**Probabilistic formulation of reaction kinetics: the Master Equation**

If a reaction occurs at some rate \( r \), then in a large time interval \( T \) it will occur, on average, \( rT \) times. If this interval is divided into \( N \) smaller sub-intervals, the chance that the reaction occurred in any one of those sub-intervals is \( rT/N \). Writing \( dt = T/N \), this shows that the probability of a reaction with rate \( r \) occurring in a small time interval \( dt \) is just \( rdt \). (To be careful, we must eliminate the possibility that more than one reaction occurred in this interval; however, for small enough \( dt \), the likelihood of that outcome is negligible.)

We now consider an ensemble of identical systems, each having the same initial conditions, and define \( p_n(t) \) as the number of these systems which have precisely \( n \) molecules at time \( t \). This number can increase if a molecule of \( X \) is created in some system having \( n-1 \) molecules, or if a molecule of \( X \) is destroyed in some system having \( n+1 \) molecules; it can decrease if a molecule of \( X \) is created or destroyed in some system having \( n \) molecules. For clarity, consider just one of these for the moment. Suppose
there are \( p_{n-1} \) systems having \( n-1 \) molecules at some time \( t \). In a small time interval \( dt \), the probability that there will be a molecule created in any one of these systems is \( f_{n-1} \) \( dt \). Therefore, the total number of systems in which a molecule is created will be given by \( p_{n-1} f_{n-1} \) \( dt \). Each of these systems will then enter the pool of systems which have \( n \) molecules, adding to the number \( p_n \) that were there to begin with. Thus, 
\[
 p_n(t+dt) = p_n(t) + p_{n-1} f_{n-1} dt,
\]
and \( dp_n / dt = f_{n-1} p_{n-1} \). If we now include all four fluxes, we obtain the Master Equation:

\[
 \frac{dp_n}{dt} = -(f_n + g_n) p_n + f_{n-1} p_{n-1} + g_{n+1} p_{n+1}.
\]  \[\text{IX.2}\]

Note that this is actually an infinite set of equations, one for each \( n \). The Master Equation is linear in the quantities \( p_n \), so it remains unchanged when we divide the number of systems in a given state \( n \) by the fixed total number of systems. In that case, \( \Sigma_n p_n = 1 \), and we can think of \( p_n(t) \) as the probability for any given system to be in state \( n \). To connect with experiments: the ensemble of systems could be a population of cells, and \( p_n \) would represent the fraction of cells having \( n \) copies of some protein.

**Emergence of the deterministic law**

It is possible to obtain all the moments of the probability distribution \( p_n(t) \) without explicitly solving the Master Equation. For example, the mean number of molecules, calculated by averaging over all the systems at a given time, is \( \langle n \rangle = \Sigma n p_n \). Summing \[\text{IX.2}\] over \( n \), and using \( f_n \) and \( g_n \) from \[\text{IX.1}\], we obtain
\[
\frac{d}{dt} \langle n \rangle = -k \sum np_n + k \sum np_{n-1} - \gamma \sum n^2 p_n + \gamma \sum n(n+1) p_{n+1}
\]

where we have used the fact that \( \Sigma h(n) = \Sigma h(n+1) \) if the sum is carried over all \( n \). That is, the mean molecule number still obeys the deterministic equation. (This result is true whenever the rates \( f_n \) and \( g_n \) are linear functions of \( n \).)

**Steady state: the Poisson distribution**

Assume now that we are in steady state, so \( dp_n/dt = 0 \). Then,

\[
0 = -(k + \gamma)n p_n + k p_{n-1} + \gamma(n + 1) p_{n+1},
\]

or, setting \( \bar{n} = k / \gamma \),

\[
(n + 1)p_{n+1} - \bar{n} p_n = np_n - \bar{n} p_{n-1}.
\]

Since this is true for all \( n \), both sides must be equal to a constant; and because \( p_n \) must be normalizable, it can be shown that the constant is simply zero. Therefore,

\[
p_n = \frac{\bar{n}}{n} p_{n-1} = \frac{\bar{n}^2}{n(n-1)} p_{n-2} = \ldots = \frac{\bar{n}^n}{n!} p_0.
\]

\[
\Rightarrow \sum p_n = p_0 \sum \frac{\bar{n}^n}{n!} = p_0 e^{\bar{n}}.
\]

Setting \( \Sigma p_n = 1 \) gives \( p_0 = e^{-\bar{n}} \). The final steady state result is known as the Poisson distribution:

\[
p_n = \frac{\bar{n}^n}{n!} e^{-\bar{n}}, \quad \bar{n} = k / \gamma
\]
**The limit of large numbers**

The mean and variance of the Poisson distribution are given by:

\[ \langle n \rangle = \langle \delta n^2 \rangle = \bar{n}. \]  

[IX.8]

The relative standard deviation is therefore

\[ \frac{\sqrt{\langle \delta n^2 \rangle}}{\langle n \rangle} = \frac{1}{\sqrt{\langle n \rangle}}. \]  

[IX.9]

This gives us a precise notion of what it means to have a ‘large number’ of molecules in our system: we can expect deviations from deterministic behavior of the order of the inverse square root of the number of molecules involved. Therefore, an ensemble of systems with an average number of 20 molecules will show a spread of 22% about this value (Fig. 21, left), while one with 500 molecules will show a spread of just 4% (Fig. 21, right).

**Figure 21: The limit of large numbers.** Fluctuations can be neglected as the number of molecules involved increases.

**The Fokker-Planck equation**

For intermediate molecule numbers, when the difference between \( n \) and \( n+1 \) may be neglected but fluctuations must still be taken into account, there is a useful approximation to the Master Equation which provides some physical insight. We replace \( n \) by a continuous variable, and use the notation \( h(n) \) in place of the \( h_n \) used previously. Any function of \( n \) can be Taylor expanded:
\[ h(n + \Delta n) = h(n) + \frac{\partial h}{\partial n} \Delta n + \frac{1}{2} \frac{\partial^2 h}{\partial n^2} \Delta n^2 + \mathcal{O}(\Delta n^3). \]  

[IX.10]

Thus,

\[ f(n - 1)p(n - 1) = f(n)p(n) - \frac{\partial}{\partial n} f(n)p(n) + \frac{1}{2} \frac{\partial^2}{\partial n^2} f(n)p(n) + \ldots \]

\[ g(n + 1)p(n + 1) = g(n)p(n) + \frac{\partial}{\partial n} g(n)p(n) + \frac{1}{2} \frac{\partial^2}{\partial n^2} g(n)p(n) + \ldots. \]  

[IX.11]

Substituting this into [IX.2], we obtain the Fokker Planck equation:

\[ \frac{\partial p(n,t)}{\partial t} = -\frac{\partial}{\partial n} \left[ (f - g)p - \frac{1}{2} \frac{\partial}{\partial n} (f + g)p \right] = -\frac{\partial J}{\partial n}, \]  

[IX.12]

where \( J \) represents a probability flux. This can be thought of as a diffusion equation: every particle represents a system in our ensemble; the particle position is analogous to the number of molecules in the system; and \( J \) is the flux of particles across any boundary. In steady state, \( J \) must be a constant; however, the flux at \( n = 0 \) must be zero (no system can pass to having negative particle number), so the flux must be zero everywhere. This gives us the following equation:

\[ (f - g)p = \frac{1}{2} \frac{\partial}{\partial n} (f + g)p. \]  

[IX.13]

Setting \( q = (f + g)p \),

\[ \frac{1}{2} \frac{\partial q}{\partial n} = \frac{(f - g)}{(f + g)} q \quad \Rightarrow \quad \frac{1}{q} \frac{\partial q}{\partial n} = \frac{2}{(f + g)} (f - g) \quad \Rightarrow \quad q = Ae^{\frac{2(f-g)}{(f+g)} n} \]

Therefore,
\[ p(n) = \frac{A}{(f + g)^n} e^{-\varphi(n)}, \quad \text{with} \quad \varphi(n) = -\int 2\frac{(f - g)}{(f + g)} \, dn'. \]

That is, the reaction is analogous to a thermodynamic system in some potential \( \varphi \). (Fig. 22).

**Figure 22: A stochastic bistable system.** The system has the following dynamics:
\[
\frac{dx}{dt} = \frac{v_0 + v_1 K_1 K_2 x^2}{1 + K_1 K_2 x^2} - \gamma x^t
\]
with \( \gamma = 1, K_1 K_2 = 10^{-4}, v_0 = 12.5 \) and \( v_1 = 200 \). This results in a double well potential, with the two stable states separated by some energy barrier. The resulting distribution of expression levels is bimodal.

**Figure 23: Timecourse of a stochastic bistable system.**
The system is the same one that is shown in Fig. 17. The expression level intermittently switches between the two available states.

Waiting times between reaction events
Suppose a chemical reaction occurs with rate \( r \). What is the time interval between successive occurrences of the reaction? The probability that the reaction occurs in some
time interval $dt$ is $rdt$; the probability that it does not occur is therefore $1 - rdt$. The probability that it occurs only after some time $\tau$ can be calculated as follows:

$$
P(\tau) \equiv \wp(\text{next occurrence is in the interval } \tau \text{ to } \tau+\Delta \tau) = \\
\wp(\text{does not occur for } t < \tau) \wp(\text{occurs in } \tau \text{ to } \tau+\Delta \tau)
$$

[IX.15]

But

$$
\wp(\text{does not occur for } t < \tau) = \\
\wp(\text{does not occur for } t < \tau-d\tau) \wp(\text{does not occur in } \tau-d\tau \text{ to } \tau)
$$

[IX.16]

Setting $Q(\tau) = \wp(\text{does not occur for } t < \tau)$, this implies $\ln(Q(\tau))-\ln(Q(\tau-d\tau)) = \ln(1-rd\tau) \approx -rd\tau$. Therefore,

$$
\frac{d \ln(Q)}{d\tau} = -rd\tau \quad \Rightarrow \quad Q(\tau) = e^{-\tau r},
$$

[IX.17]

where we have used $Q(0) = 1$. Inserting this in [IX.15], we get

$$
P(\tau) = e^{-\tau r} rd\tau.
$$

[IX.18]

The waiting times between successive reactions are therefore exponentially distributed, with mean value $\langle \tau \rangle = 1/r$, and variance $\langle \delta \tau^2 \rangle = 1/r^2$. 

**Stochastic simulation of chemical reactions**

If \( u \) is a random number drawn from a uniform distribution between zero and one, then the following function of \( u \) is distributed precisely as \( \tau \) is in [IX.18]:

\[
\theta = \frac{1}{r} \ln \left( \frac{1}{u} \right) \quad [IX.19]
\]

This gives us a very simple prescription for numerically simulating the behavior of a stochastic system. Start with some initial condition for each molecule type. If there are \( m \) possible types of reactions (\( m = 2 \) for 2, as there are only creation and destruction events) occurring with rates \( r_i \) (\( i = 1, ..., m \)), then we can generate \( m \) random variables \( \theta_i \) which are the putative waiting times to the next occurrence of each reaction type. The smallest of these gives the time interval after which the first reaction which will actually occur. At this stage, simply update the variables (for [IX.2], we would increment \( n \) if a creation event occurred, or decrement it if a destruction event occurred), recalculate the rates, and repeat the generation of putative times. Continue this until some convenient time limit is reached. This procedure is a slight simplification of the Gillespie algorithm. This is how the timecourses in Fig. 20 were generated. To obtain a histogram, simply repeat this procedure several times (2,500 times for Fig. 20), recording the final state of the system, then calculate the histogram of final states. As a further example, Fig. 23 shows a simulated timecourse for the bistable system of Fig. 22. Notice that a single cell transitions stochastically between the two available states, so the distribution of expression levels in the population is bimodal.