Modelling Biochemical Reaction Networks

Lecture 12:
Stochastic modeling of a single ion channel

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Recommended reading

- Fall, Marland, Wagner and Tyson, section 11.1

Describing reactions involving small numbers of molecules

- Differential equations are appropriate for models involving a very large number of molecules, where the concentrations can be treated as continuous variables because a reaction event that (say) decreases the number of molecules of a particular species by 1 has an infinitesimal effect on the concentration.
- If, on the other hand, we have only a few molecules of a certain type, or maybe even a few thousand, a decrease by 1 is a (discontinuous) step change in the concentration.
- Better in these cases to count molecules than to use concentration

Stochasticity (randomness) in chemical reactions

▶ By way of illustration, consider a bimolecular elementary reaction $A + B \rightarrow C$.
Suppose that this is the only reaction that occurs at an appreciable rate in this system.

▶ In order for A and B to react, they first have to come together.

Boltzmann's Stosszahlansatz: Due to collisions with other molecules, the path of a molecule in the gas phase is essentially unpredictable. Thus, collisions occur at unpredictable (random) times.
The same is true in solution where frequent collisions with solvent molecules cause Brownian motion (paths with randomly directed sharp turns).

Stochasticity (randomness) in chemical reactions

- Molecules often have to collide in a specific orientation to react, so any rotational motion is an additional source of stochasticity.

- There is usually a minimum amount of energy required for reaction (activation energy). Molecules gain and lose energy in collisions, so the energetic state of the molecules is another random variable.

- Quantum mechanical factors often determine whether two molecules that have collided in the correct orientation will react, and quantum dynamics is intrinsically unpredictable.

Conclusion: The timing of reactive events is a random variable.

# *Reactions involving small numbers of molecules*

- ▶ We have two new issues to deal with:
  - ▶ Molecules as countable entities
  - ▶ Random reactive events
- ▶ Options:
  - ▶ Find some way to describe the statistical properties of the system $\implies$ CHEMICAL MASTER EQUATION
  - ▶ Simulate, i.e. generate some random reactive events, knowing that we will only get examples, called realizations, of the stochastic process

Dynamics of single ion channels

- The extreme case of a small number of molecules is one molecule.
- In electrically active cells (nerve cells, cardiac cells, some secretory cells like pancreatic beta cells), currents are generated by opening and closing channels that are permeable to a particular type of ion.
- The openings and closings happen randomly, with rates that are biased by various factors some of which can be manipulated experimentally, e.g. the membrane potential.

Dynamics of single ion channels

▶ The activity of a single channel can be monitored using a patch clamp.
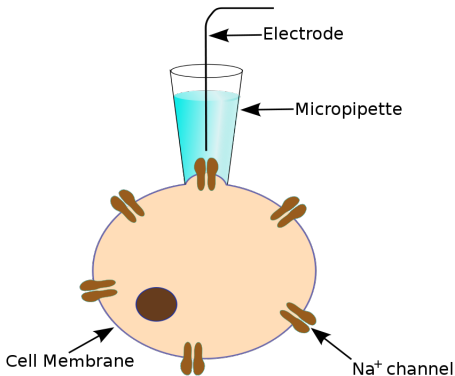
Source: Theresa Knott, Creative Commons license (`http://en.wikipedia.org/wiki/File:Patch_clamp.svg`)

A model for a single ion channel

- The channel has two states, open (O) and closed (C).
- Random transitions occur between these two states, which we represent as a conventional chemical reaction:

$$C \underset{k^-}{\overset{k^+}{\rightleftharpoons}} O$$
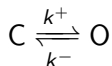
- When the channel is closed, there is a certain probability per unit time of making a transition to the open state, k^+.
- The probability that a closed channel makes a transition to the open state in time Δt is therefore $k^+ \Delta t$, provided we choose a Δt such that $k^+ \Delta t$ is small.
- Similarly, the probability that an open channel makes a transition to the closed state in time Δt is $k^- \Delta t$.

A model for a single ion channel

- The probability that the channel is closed at time $t + \Delta t$ is

$$P_C(t + \Delta t) = \left\{ \begin{array}{c} \text{Probability} \\ \text{channel} \\ \text{was closed} \\ \text{at } t \end{array} \right\}$$

$$+ \left\{ \begin{array}{c} \text{Probability} \\ \text{channel} \\ \text{was open} \\ \text{at } t \end{array} \right\} \left\{ \begin{array}{c} \text{Probability} \\ \text{an open channel} \\ \text{closes in } \Delta t \end{array} \right\}$$

$$- \left\{ \begin{array}{c} \text{Probability channel} \\ \text{was closed} \\ \text{at } t \end{array} \right\} \left\{ \begin{array}{c} \text{Probability} \\ \text{a closed channel} \\ \text{opens in } \Delta t \end{array} \right\}$$

$$= P_C(t) + P_O(t)k^- \Delta t - P_C(t)k^+ \Delta t$$

A model for a single ion channel

- Now rearrange:

$$P_C(t + \Delta t) - P_C(t) = P_O(t)k^- \Delta t - P_C(t)k^+ \Delta t$$

$$\therefore \frac{P_C(t + \Delta t) - P_C(t)}{\Delta t} = k^- P_O(t) - k^+ P_C(t)$$

- Take the limit as $\Delta t \to 0$:

$$\frac{dP_C}{dt} = k^- P_O - k^+ P_C$$

- Proceeding similarly for P_O, we find

$$\frac{dP_O}{dt} = k^+ P_C - k^- P_O$$

Chemical master equation

- The equations

$$\frac{dP_C}{dt} = k^- P_O - k^+ P_C$$

$$\frac{dP_O}{dt} = k^+ P_C - k^- P_O$$

  are an example of a chemical master equation.

- They tell us how the probability distribution (P_C, P_O) evolves with time.

Chemical master equation

- We are often interested in the steady state probability distribution, called the stationary probability distribution. The stationary probability distribution is the distribution you expect to see in an experiment that is long compared to the time it takes to make transitions between the two states (to be studied below).

- The stationary probability distribution is obtained by solving the equations $\frac{dP_C}{dt} = \frac{dP_O}{dt} = 0$, with the added condition that the probabilities add up to 1: $P_C + P_O = 1$.
  In this case, we get

$$P_C = \frac{k^-}{k^- + k^+} \qquad \text{and} \qquad P_O = \frac{k^+}{k^- + k^+}$$

Dwell time

- The dwell time is the average amount of time the system spends in a given state once it has reached that state.
- To calculate the dwell time in the closed state, imagine that we have prepared the system such that, at $t = 0$, the channel is closed. Thus, $P_C(0) = 1$.
- Since we are only interested in how long the channel stays in the closed state, we will treat the open state as an absorbing state.
  In other words, we won't allow transitions back out of this state.
  The master equation simplifies to

$$\frac{dP_C}{dt} = -k^+ P_C$$

  with solution

$$P_C(t) = e^{-k^+ t}$$

Dwell time

- $P_C(t)$ is the probability that the channel remains closed at time t.
- The dwell time is the average time of opening, so we want the probability that the channel opens between times t and $t + dt$.
- From the rate equation, this is $|dP_C| = k_+ P_C(t)\, dt$.
- The probability density p of a variable t is the amount of probability per unit t.
- The probability density of the opening time is therefore $p_O(t) = |dP_C|/dt = k_+ P_C(t)$.

Dwell time

- If we have a probability density $p(t)$, then statistical theory tells us that the average value of some quantity $f(t)$ is

$$\langle f \rangle = \int_{\mathcal{R}} f(t)p(t)\, dt$$

where $\mathcal{R}$ is the range of the variable t.

- The dwell time in the closed state is the average time to opening of the channel, so

$$\langle t_C \rangle = \int_0^\infty t k^+ e^{-k^+ t} dt = \frac{1}{k^+}$$

Standard deviation of dwell time

- The standard deviation is

$$\sigma_t = \sqrt{\langle t^2 \rangle - \langle t \rangle^2}$$

- For the dwell time in the closed state, we have

$$\langle t^2 \rangle = \int_0^\infty t^2 k^+ e^{-k^+ t} dt = \frac{2}{(k^+)^2}$$

$$\therefore \sigma_{t_C} = \sqrt{\frac{2}{(k^+)^2} - \left(\frac{1}{k^+}\right)^2} = \frac{1}{k^+}$$