Chem 163, Lecture 6

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1 Calculating rates

So far, we've been focused on equilibrium diffusion processes. But if you look inside a cell, you see all sorts of things moving around, whizzing too and fro. How do we get from simple Brownian jiggling to directional motion? We need to couple motion to chemistry.

[SHOW CHART OF MOLECULAR MOTORS] Today we're going to talk about molecular motors. The canonical molecular motors are the kinesins and dyneins. Kinesins walk along microtubules toward the (+) end (typically away from the nucleus), and dyneins walk toward the minus end. Axonemal dynein shears microtubules relative to each other and is responsible for the swimming of sperm and other flagellar motions. Kinesin and dynein both power their motion by eating ATP. The myosins are also widespread molecular motors. Myosin V walks along actin and carries a cargo. Myosin II forms centipede-like aggregates, and moves actin strands along each other's length. This is how muscle contracts. These types of molecular motors are only found in Eukaryotes. Bacteria are small enough that they don't need train tracks to move things around inside–diffusion does the job perfectly well.

The concept of a molecular motor is much broader than just these fancy walking machines. There are also rotary molecular motors, like the E. coli flagellar motor, or the F0F1 ATP synthase.

There are motors that walk along DNA: the polymerases and exonucleases can all be thought of as molecular motors, as can topoisomerase (passes one DNA strand through another), gyrase, and helicase. The ribosome is also a molecular motor.

There are also less obvious molecular motors. We shall see that polymerization of cytoskeletal elements can on its own generate pretty substantial forces. This is important in cell motility, and is how a nasty pathogen, Listeria monocytogenes, gets around inside cells.

There are also the transmembrane molecular motors, whose thermodynamics are similar to the mechanical ones, though the mechanisms are very different. These are the various transporters and pumps. These hugely diverse and important molecules can be broadly divided into two classes: electrogenic and non-electrogenic. The electrogenic transporters move a net charge across the membrane associated with their chemical cycle.

2 Brownian ratchet

Today we're going to start by considering a very simple molecular motor, which is a paradigm for one class of these devices. When bacteriophage infects an E. coli, the phage must inject its genome into the bacterium. There are several conceivable driving forces for this: electrostatic self-repulsion of the tightly packed DNA in the capsid; stored mechanical energy in the tightly wound DNA in the capsid; increased entropy in the DNA when it's free to wiggle in the bacterial cytoplasm vs. being cramped up in the capsid. Some simple quantitative experiments showed that these factors, while possibly important, weren't sufficient to explain all the data. If you tickle surface-bound phages just right, you can trick it into disgorging its DNA. In a gentle flow with a fluorescent label, you can then measure the length of the released DNA vs. time. The DNA doesn't completely exit the capsid! This tells us that there isn't enough stored free energy among all the ideas we listed above to get the DNA completely out of the package. Furthermore, the DNA seems to slow down as it progresses out of the capsid. Finally, capsids with truncated genomes show slower DNA release, and still don't release all their DNA.

In contrast, in an E. coli, the capsid always releases all of its DNA. The release is at a constant rate. Both short and long genomes are completely released. So things are quite different in the E. coli. The mechanism for this is quite subtle. The DNA does a random walk going into and out of the capsid. Once a certain length of bare DNA is exposed in the cytoplasm, DNA-binding proteins attach and rectify the motion. Once the DNA binding proteins are in place, there's no going back into the capsid (unless the proteins come off, but we'll assume for the moment that they don't).

For any molecular motor, we want to calculate the velocity as a function of force. For starters, let's calculate the velocity at zero force. Suppose the distance the DNA must diffuse to catch its next binding protein is s, and the DNA diffusion coefficient is D. Then the mean first-passage time to catch the next protein is:

$$\tau = s^2/2D. \tag{1}$$

We'll assume that the binding proteins are in high concentration and bind instantaneously. The velocity is a constant, $v = s/\tau = 2D/s$. The time for the whole strand to exit the capsid is $t = Ls/2D$. Compare this to the time if we were relying on diffusion alone, $L^2/2D$, where L is the length of the strand. So smaller step sizes helps a ton!

[Discuss application to actin or microtubule polymerization, and merit of having multiple strands out of registry (small s)].

If you want to calculate the force-velocity curve of the Brownian ratchet, you need to know how a constant force (ramp potential) affects a mean first-passage time. For a constant force, the answer is:

$$\tau = 2\left(\frac{s^2}{2D}\right)\left(\frac{k_BT}{Fs}\right)^2\left\{\exp\left(-\frac{Fs}{k_BT}\right) - 1 + \frac{Fs}{k_BT}\right\}. \tag{2}$$

Check that this gives $s^2/2D$ in the limit $F \to 0$. If the force is large and positive, then the particle is sliding downhill and the first-passage time approaches s/v, where $v = F/\gamma = FD/k_BT$ is the drift velocity. If the force is large an negative, the time grows exponentially

with the force because the probability of getting over a barrier of height Fs is exponentially suppressed. As before, you can calculate the velocity $v = s/\tau$.