Biophysics

Nathaniel D. Hoffman

May 5, 2021

Contents

1 Physics of the Cell **4**
- 1.1 *E. coli.* as the Model Organism . . . 4
  - 1.1.1 Coordination of Cell Growth with Division . . . 5
  - 1.1.2 Timer Model . . . 5
  - 1.1.3 Sizer Model . . . 6
  - 1.1.4 Adder Model . . . 6
- 1.2 The Adder Model, Again . . . 6
- 1.3 Generalized Model . . . 7
  - 1.3.1 Distribution of Cell Size and Division Parameters . . . 7
- 1.4 Fundamental Principles of Living Matter . . . 8

2 Statistical Physics of Cellular Processes **10**
- 2.1 Equilibrium as Free-Energy Minimization . . . 11
- 2.2 Entropy . . . 11
- 2.3 Can Entropy Drive Cellular Organization? . . . 12
- 2.4 Entropy and Information . . . 13
- 2.5 Partition Function Utilities . . . 14
  - 2.5.1 Ligand-Receptor Binding . . . 14

3 Two-State Biological Systems **16**

4 Structure of Macromolecules **18**
- 4.1 Structure of DNA . . . 18
  - 4.1.1 Random Walks . . . 18
- 4.2 End-to-end Length of DNA Strands . . . 19
  - 4.2.1 How Rigid is a Polymer? . . . 19
- 4.3 How is DNA Packaged? . . . 20
  - 4.3.1 Chromosome Conformation Capture (3C) . . . 21
  - 4.3.2 Statistics of Loop Formation in 3D . . . 21
  - 4.3.3 Chromosome Contact Map (Hi-C) . . . 21
  - 4.3.4 Force-Extension Curves of Macromolecules . . . 22

5 Mechanics of Biopolymers **23**
- 5.1 Mechanical Structure in Biological Cells . . . 23
- 5.2 Physics and Mathematics of Beam Theory . . . 23
- 5.3 Applications of Beam Theory . . . 25
  - 5.3.1 Elasticity and Entropy . . . 25
  - 5.3.2 Energetics of DNA Looping . . . 26
  - 5.3.3 Cytoskeletal Filaments . . . 26

6 Biological Fluid Dynamics **28**
  - 6.0.1 Stokes Flow . . . 29
  - 6.0.2 Fluid Dynamics of Blood . . . 29
  - 6.0.3 Stokes Drag . . . 30
- 6.1 Motion of Biological Organisms . . . 30

7 Diffusion in Cells **31**
  - 7.0.1 Fluorescence Recovery After Photobleaching (FRAP) . . . 32

7.1 Driven Diffusion . . . 32
7.2 Diffusion to Capture . . . 33

8 Chemical Reactions in Cells **35**
8.0.1 Polymerization of Directional Actin . . . 37

9 Molecular Motors **38**
9.1 Translational Motors . . . 38
9.2 Molecular Motors as Directed Random Walkers . . . 38
9.2.1 Two-State Motor Model . . . 39
9.3 Polymerisation as Motor Action . . . 40

10 Neural Signalling and Action Potentials **42**
10.1 Charge State of the Cell . . . 42
10.2 Two-State Model of Voltage Gating . . . 43
10.3 Current Across Membrane . . . 43
10.4 Cable Equation . . . 44
10.5 Fitzhugh-Nagumo Model . . . 46

11 Pattern Formation **48**
11.1 Morphogen Gradients . . . 48
11.2 Turing Patterns . . . 49
11.2.1 Activator-Inhibitor Models . . . 49

Chapter 1

Physics of the Cell

Lecture 1: Physics of the Cell I
Wednesday, February 03, 2021

Replication is one of the fundamental processes of living cells. *E. coli.* is a perfect example for understanding the physics of these biological processes because it is a very simple cell which is not as compartmentalized as our cells. When we examine cells dividing, we can start to ask questions, like how fast do cells grow, when do they divide, and how do the cells measure time and size? What is the biological clock that tells the cell when it needs to begin the next step of the replication process? What determines the structure of the cell colony, and how do the cells interact with each other?

1.1 *E. coli.* as the Model Organism

We can model *E. coli.* as a cylinder with a 1μm diameter and a length between 2-6μm. If you measure the area of the total group of cells as they grow, you will find that they grow exponentially:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \underbrace{\lambda}_{\text{growth rate}} N \implies N(t) = N(t=0)e^{\lambda t}$$

From this, we can compute the doubling time, the time in which the population size doubles:

$$t_{\text{doubling}} = \lambda^{-1}\ln(2) \approx 3000\text{s}$$

for *E. coli.* which is pretty fast, on the order of 40min or so. The basic flow of information in the cell is that DNA replicates, it is transcribed into RNA, and RNA is translated into proteins which carry out the physical metabolism of the cell.

If we now look at a single cell, naïvely, the cells divide when they roughly double in mass. This is actually an incorrect model, and we will discuss this later. The time from birth to division is called the cell cycle, and that is equal to the doubling time. In *E. coli.*, DNA is kind of spread out (not concentrated in a nucleus like in human cells). There isn't a lot of free space inside the cell. There are 4×10^6 base pares of DNA and 2×10^6 proteins, along with ribosomes, lipids, ions, water, and other molecules. Movement around the cell is relatively slow because of all these obstructions.

Given the doubling time, we can compute that the replication process operates at around 2000bp/s (base pairs per second). How do any of the molecules in the cell decide which daughter cell they'll end up in? We can say that each molecule has some probability p of ending up in daughter cell 1 and probability $q = 1 - p$ to end up in daughter cell 2. If we start with N molecules, we can calculate the probability of ending up with n_1 molecules in cell 1:

$$\Pr(n_1, N) = \frac{N!}{n_1!(N-n_1)!}p^{n_1}q^{N-n_1}$$

This is the equation of a simple binomial process, so we can calculate the mean to be $\langle n_1 \rangle = Np$ and the standard deviation as $\sqrt{\langle n_1^2 \rangle - \langle n_1 \rangle^2} = \sqrt{Npq}$. Is this a good model? Does this actually explain what we observe in living cells?

We could measure $\Delta N = n_1 - n_2$ and plot it against N, the total number of molecules. In an ideal case, $\Delta N = 0$, whereas in a case where one cell always gets everything, we would have $\Delta N \propto N$. In our model, we predict $\Delta N \propto \sqrt{N}$, like the standard deviation.

In reality, the individual cells don't grow exponentially. There is initially a lag phase where not much growth happens. Then there's an exponential face where the growth rate is constant. Finally comes a late exponential/early stationary stage followed by a stationary phase, where the cell mass stabilizes.

We can model such a system as a logistic curve:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \lambda N(N_{\max} - N) = \lambda N - \lambda_d N^2$$

where λ_d can be thought of as the "death" rate. This equation will have a "fixed point" at $N_{\max}$ where going to the right of that point in N will result in a negative growth rate, whereas moving to the left of it will result in a positive growth rate, both leading back to the fixed point.

If we write this equation as

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \lambda N \left(1 - \frac{N}{M}\right)$$

then we can solve this as

$$N(t) = N_0 e^{\lambda t} \frac{MN(0)}{M + N(0)(e^{\lambda t} - 1)}$$

1.1.1 Coordination of Cell Growth with Division

If the cell grows according to the logistic model, when will it divide? Even if we just assume exponential growth, at what time, τ would the cell split? If the cells elongate exponentially at a constant rate, we can write this as

$$l_i(t) = l_i(0)e^{\lambda t}$$

1.1.2 Timer Model

In a timer model, the cell divides at a constant time from birth ($\tau = \text{const}$). What this also implies is that the cell divides at a critical multiple of the initial size:

$$l_i(\tau) = l_i(0) \times \text{const.} = a l_i(0)$$

If $a = 2$, the cell separates when it doubles in size. Let's say the cell divides in a ratio r to $1 - r$. This means that

$$l_{i+1}(0) = r l_i(\tau) = ar l_i(0)$$

As a trivial example, we could say $r = \frac{1}{2}$. In other words, we have an iterative equation. What is l_{i+n}?

$$l_{i+n} = (ar)^n l_i$$

The problem with this model is that if $ar \neq 1$, the parent cell size will either grow or decay exponentially. This timer model is unstable. If you plot the generation time against the length of the cell, you find that it is not constant, as the timer model would suggest. Small cells will take longer to generate than larger cells.

1.1.3 Sizer Model

Maybe the cell is actually dividing at a constant size:

$$l_i(\tau) = l_i(0)e^{\lambda\tau} = \text{const.} \equiv \delta$$

such that

$$\tau = \lambda^{-1} \ln\left(\frac{\delta}{l(0)}\right)$$

This give us the proper generation plot discussed above, but this is also not the correct model. After n divisions, $l_{i+n} = r\delta$. However, this model would say that the length at which a cell divides is constant and doesn't depend on the newborn length, but data suggests that these variables are linearly dependent.

So if neither time nor size determines when the cell divides, what does?

1.1.4 Adder Model

Just fit the data!Let $l_\tau = l_0 + \delta$. This means the difference between the newborn size and division size is constant, so the cell "adds" a constant amount of material before it divides. Does this lead to stable size distributions?

$$l_i(\tau) = l_i(0) + \delta$$

so

$$\begin{aligned} l_{i+1}(0) &= r l_i(\tau) \\ &= r(l_i(0) + \delta) \end{aligned}$$

We make the Ansatz that as $i \to \infty$, $l_i \to l_s$, some stable size.

$$\begin{aligned} l_s &= r(l_s + \delta) \\ &= \frac{r\delta}{1-r} \end{aligned}$$

If $r = \frac{1}{2}$, then $l_s \to \delta$. By this adder principle, if a cell is born smaller or bigger, it will eventually converge to the size l_s (quite quickly, withing a few generations).

How does the cell know how much material it has added to itself? This is largely an open question. Some molecules inside that cell could encode this information, but we will discuss some possible explanations in the next class.

LECTURE 2: PHYSICS OF THE CELL II
Friday, February 05, 2021

1.2 The Adder Model, Again

Let us denote $l_i(0)$ as the cell length at time $t = 0$, where i is the index for generation. In the adder model,

$$l_i(\tau) = l_i(0) + \delta_i$$

where τ is the generation time (the splitting time) and δ_i is the added size, which for now we allow to be different between generations. After the next generation, after division by a ratio r, we have

$$l_{i+1}(0) = r l_i(\tau) = r\left(l_i(0) + \delta_i\right)$$

Let's say the mean of l_i is the "newborn size":

$$\langle l_i \rangle = l_b$$

and

$$\langle \delta_i \rangle = \delta$$

Then

$$l_b = r(l_b + \delta)$$

One of the assumptions made here is that when we take a mean, the value of r could technically fluctuate from generation to generation, but we assume that process is distinct and independent from when the cell actually decides to split. Solving for l_b:

$$l_b = \frac{r\delta}{1-r}$$

In the case of symmetric division, $r = 1/2$, which makes $l_b = \delta$.

Next, we may ask: how fast is the size convergence process? Does a large cell converge at the same rate as a small cell? We will address this later.

1.3 Generalized Model

It is surprising enough that such a simple model can explain the growth of *E. coli.*, but what about other bacteria? As it turns out, some other cells show a correlation to either the timer and sizer models, so we can write a more general model:

$$l(\tau) = al(0) + \delta$$

For an adder, $a = 1$ and $\delta > 0$. For a timer model, $a > 0$ and $\delta = 0$. For a sizer model, $a = 0$ and $\delta > 0$ (and δ is constant).

We know that with some conditions on this general model, we have size convergence, but others don't converge. We can study this model to understand the conditions on convergence:

$$\begin{aligned} l_i(\tau) &= al_i(0) + \delta \\ l_{i+1}(0) &= rl_i(\tau) \\ l_{i+1} &= arl_i + r\delta \\ l_{i+1} - l_i &= (ar-1)l_i + rd \end{aligned}$$

This last equation is like a finite difference, so we can approximate it as a differential equation:

$$\frac{\mathrm{d}l}{\mathrm{d}i} = -(1-ar)l + \delta r$$

This works approximately well with many generations, because technically i is an integer. Then the rate of convergence is the quantity $(1-ar)$. We can also see that $\frac{\mathrm{d}l}{\mathrm{d}i} = 0$ when

$$l = \frac{\delta r}{1-ar}$$

In the timer limit, where $\delta = 0$, there is no well-defined stable size (unless $ar = 1$ exactly, which is not a robust possibility for living systems).

1.3.1 Distribution of Cell Size and Division Parameters

If we look at the parameters that we can measure, there is some distribution that we could calculate for each parameter (such as r, $l(\tau)$, τ, $l_b = l(0)$, and δ, but also the elongation rate λ). Most of these are not independent of each other:

$$\left(\frac{\sigma_\delta}{\langle\delta\rangle}\right)^2 = 3\left(\frac{\sigma_{l_0}}{\langle l_0\rangle}\right)^2 \approx \frac{1}{\ln(2)}\left(\frac{\sigma_\tau}{\langle\tau\rangle}\right)^2$$

To derive the first equality here (the second is for homework), we can start with the adder model

$$l_{i+1}(0) = rl_i(0) + r\delta_i \tag{1}$$

Let's first square both sides:

$$l_{i+1}^2 = r^2 l_i^2 + r^2\delta_i^2 + 2rl_i\delta_i$$

Then, take an average, for now treating r as fixed:

$$\left\langle l_{i+1}^2 \right\rangle = r^2 \left\langle l_i^2 \right\rangle + r^2 \left\langle \delta_i^2 \right\rangle + 2r^2 \left\langle l_i\delta_i \right\rangle$$

We should have

$$\left\langle l_{i+1}^2 \right\rangle = \left\langle l_i^2 \right\rangle \equiv \left\langle l^2 \right\rangle$$

and we can define $\left\langle \delta_i^2 \right\rangle \equiv \left\langle \delta^2 \right\rangle$. We also know that

$$\langle \delta_i \rangle = \langle l_i \rangle = \langle l \rangle = \langle \delta \rangle$$

We can do this because this is an average across all generations, so looking at an average over $i+1$ and comparing it to an average over i doesn't cause a difference, because we are averaging over all i.

What about $\langle l_i\delta_i \rangle$? These are independent variables, so we can actually write

$$\langle l_i\delta_i \rangle = \langle l_i \rangle \langle \delta_i \rangle = \langle \delta \rangle^2$$

Now recall that we are just looking at the adder model here, but in the general case, these values could be dependent (in the sizer case, they certainly are). Nowe we have

$$\begin{aligned} \left\langle l^2 \right\rangle &= r^2 \left\langle l^2 \right\rangle + r^2 \left\langle \delta^2 \right\rangle + 2r^2 \langle \delta \rangle^2 \\ (1-r^2) \left\langle l^2 \right\rangle &= r^2 \left\langle \delta^2 \right\rangle + 2r^2 \langle \delta \rangle^2 \end{aligned}$$

Let's assume $r = 1/2$, so

$$\begin{aligned} \frac{3}{4} \left\langle l^2 \right\rangle &= \frac{1}{4} \left\langle \delta^2 \right\rangle + \frac{1}{2} \langle \delta \rangle^2 \\ 3 \left\langle l^2 \right\rangle &= \left\langle \delta^2 \right\rangle + 2 \langle \delta \rangle^2 \end{aligned}$$

We can now calculate the variance in l:

$$\left\langle l^2 \right\rangle - \langle l \rangle^2 = \frac{1}{3} \left(\left\langle \delta^2 \right\rangle - \langle \delta \rangle^2 \right)$$

since $\langle \delta \rangle = \langle l \rangle$.

1.4 Fundamental Principles of Living Matter

- **Living systems operate out of equilibrium**
- **Living systems self-organize** into heterogeneous component parts. Within this organization, there are four key functions which a cell has to perform:

  Structure (proteins)

  Energy—needed to maintain the structure (carbohydrates)

  Information/Memory—needed to replicate the structure (DNA/RNA—nucleic acids)

  Barrier/Environmental Sensing (lipids) These systems are built on macromolecules, which are mostly small molecules made almost entirely of the elements nitrogen, oxygen, phosphorus, carbon, and hydrogen. These macromolecules can assemble together to form organelles, which form cells, which form tissues, which form organisms.
- **Living systems have evolved**

- **Living systems are self-replicating.** Von Neumann, in his *Theory of Self-Reproducing Automata*, postulated that a self-replicating machine must have two fundamental requirements:

  A method of copying the machine

  A method of copying the instructions of the machine

  This is identical to the central dogma of molecular biology. DNA polymers copy the machine instructions, and ribosomes and RNA copy the machine (the proteins). The four *nucleotides*, adenine, thymine, guanine, and cytosine, can be thought of as letters which generate an alphabet of three-letter collections called *codons*. These words are used to tell ribosomes how to construct proteins out of amino acids. There are 23 amino acids (and two stop codes). The fact that multiple codons can give the same amino acid makes the system more protected from errors in the genetic code.

  Replication occurs when DNA polymerase copies DNA to create more DNA (double helix to double helix). Transcription is the process by which DNA generates RNA (double helix to single helix which can be read by a ribosome to chain together amino acids). The first step occurs on the order of less than a second, while the second step, called protein synthesis, occurs on the order of seconds. However, the cell itself grows on the order of hours.

  In a minimal cell, ribosomes make proteins, and proteins do all the other replication processes, but there needs to be additional amino acids (food) to grow. Also, as the cell grows, it needs more ribosomes to keep up with the rate of growth. If you look at the amount of ribosomes in a cell, r, it increases linearly with the growth rate of the cell: $r = r_{\min} + \frac{\lambda}{\kappa_t}$ (more on this *bacterial growth law* in a future lecture). A similar principle holds for the cell mass, the RNA, and the DNA. We call κ_t the "translational capacity".

  There is also a *nutrient growth law*, which states that larger cells grow faster (exponential dependence with growth rate: $s \propto e^{\lambda}$). What is the reason for this? It depends on what variable is being controlled in an experiment. If you control the size of the cell, there might be a different reason why the growth rate has this dependence as compared to controlling the amount of nutrients available.

Chapter 2

Statistical Physics of Cellular Processes

Lecture 3: Statistical Physics of Cellular Processes I
Wednesday, February 10, 2021

In biological systems, there are four different types of energy which we find relevant: chemical energy, which is used to generate mechanical energy and electromagnetic energy, and finally thermal energy. At the scale of cellular processes, we will mostly be concerned with the scale of Newtonian mechanics (and not quantum mechanics).

It is important to realize that biological systems are intrinsically out of equilibrium—system at equilibrium would be dead. Variables like force, entropy, and energy are dynamic and not necessarily conserved—living systems are open systems. Additionally, there are typically significant statistical fluctuations between observations of variables between experiments. Finally, energy consumption and dissipation typically occurs through irreversible processes.

However, if certain processes happen much faster than other, we can apply equilibrium models. Consider a reaction $A \leftrightarrow B \rightarrow C$ where the rate from A to B is k_+, from $B \rightarrow A$ is k_-, and from $B \rightarrow C$ is r. We can then write a system of differential equations:

$$\begin{aligned}
\frac{\mathrm{d}[A]}{\mathrm{d}t} &= -k_+[A] + k_-[B] \\
\frac{\mathrm{d}[B]}{\mathrm{d}t} &= k_+[A] - k_-[B] - r[B] \\
\frac{\mathrm{d}[C]}{\mathrm{d}t} &= r[B]
\end{aligned}$$

where $[X]$ refers to the concentration of chemical X. If we consider the case where $r \ll k_-$, we can ignore the $-r[B]$ in the second equation and find that

$$\frac{[A]}{[B]} = \frac{k_-}{k_+} = \text{constant}$$

and $[C]$ increases at a rate $\propto [B]$.

If we don't ignore r, the system is not in equilibrium and all three variables change in time. Eventually, $[A] \rightarrow 0$ and $[B] \rightarrow 0$ while $[C] \rightarrow$ constant.

2.1 Equilibrium as Free-Energy Minimization

The equilibrium state of a system minimizes the free energy,

$$F = E - TS \qquad \text{(Free Energy)}$$

where E is the potential energy, T is the temperature, and S is the entropy, which is naïvely the number of ways to rearrange a system. Mathematically it is

$$S = k_B \ln(W)$$

where W is the number of (equally likely) microstates and k_B is the Boltzmann constant.

What is a microstate? Let's take the example of ligand-receptor binding. Ligands are molecules which pair with receptor sites to trigger certain actions in the cell. If we imagine ligands arranged on a lattice with a receptor molecule, all the possible lattice configurations of the ligands enumerate the microstates. If the system is finite, there will be a finite number of microstates.

Another example could be microstates of DNA in a solution. DNA looks like some kind of curve, and such a curve can be drawn in an infinite number of ways, so the number of microstates is infinite.

2.2 Entropy

The theory of entropy was first thought of by Claude Shannon in his work on information theory. In his definition,

$$S \propto -\sum_{i=1}^{N} P_i \ln(P_i)$$

where P_i is the probability of being in state i. Since $\frac{\partial S}{\partial P_i} = 0$, $\sum_i(\ln(P_i) + 1) = 0$, so P_i is constant. We can normalize this to $P_i = \frac{1}{N}$ where N is the total number of microstates. Plugging this back in, $S \propto \ln(N)$.

Consider proteins binding onto a strand of DNA. We can simplify the DNA as a 1-dimensional chain of lattice sites which will have two states—they will be occupied by a protein or not. If the total number of binding sites is N and the total number of proteins is N_p, we can of course write the entropy as

$$S = k_B \ln(W(N_p, N))$$

where $W(N_p, N)$ is some function enumerating the number of ways N_p proteins can be arranged on N binding sites.

The first protein can occupy any N sites, the second can occupy $N - 1$, and so on:

$$W(N_p, N) = \frac{N!}{N_p!(N - N_p)!}$$

if we consider the proteins to be indistinguishable. Then

$$S = k_B \ln\left(\frac{N!}{N_p!(N - N_p)!}\right)$$

We can approximate logs of factorials (if N is large) as

$$\ln(N!) \approx N \ln(N) - N \qquad \text{(Stirling Approximation)}$$

How do we get this? $\ln(N!) \approx \ln(N(N-1)\ldots)$, or

$$\ln(N!) \approx \sum_{i=1}^{N} \ln(i) \sim \int_1^N \ln(x)\,\mathrm{d}x \sim N\ln(N) - N$$

Using this approximation, we can write

$$\begin{aligned} S/k_B &= \ln(N!) - \ln(N_p!) - \ln([N-N_p]!) \\ &\approx (n\ln(N) - N) - (N_p\ln(N_p) - N_p) - [(N-N_p)\ln(N-N_p) - (N-N_p)] \\ &\approx -(N-N_p)\ln\left(\frac{N-N_p}{N}\right) - N_p\ln\left(\frac{N_p}{N}\right) \end{aligned}$$

Let us now define $c \equiv \frac{N_p}{N}$, which we call the volume fraction, the fraction of the lattice which is occupied by proteins. With this definition,

$$S \approx -k_B N[c\ln(c) + (1-c)\ln(1-c)] \qquad \text{(Mixing Entropy)}$$

Now we can maximize S (to minimize $F = E - TS$):

$$\frac{\partial S}{\partial c} = \ln(c) + 1 - \ln(1-c) - 1 = 0 \implies c = \frac{1}{2}$$

We think of this point $c = \frac{1}{2}$ as being maximally mixed and having maximal entropy. In the other extremes, $c = 0$ and $c = 1$ have $S = 0$ because there is only one microstate present at this volume fraction.

2.3 Can Entropy Drive Cellular Organization?

A (eukaryotic) cell has organelles which perform certain functions, most of which are bound by membranes. These compartmentalize the cell, increase reaction rates, and store molecules. Ten years ago, there was a discovery of certain types of organelles without membranes. These membrane-less organelles appear to behave like liquid droplets which tend to condense over time (binding with other droplets).

The physics behind this behavior comes from entropy. Consider these organelles, called P-granules, in a solvent (cytoplasm). We can imagine that over time, this system will go to a high entropy state, where these two groups are mixed together and the droplets will dissolve into the cytoplasm. But we want to know if the reverse transition can happen. Consider the interaction between these particles. If the interaction between the granules and cytoplasm is much larger than the average of the granule-granule and cytoplasm-cytoplasm interaction, the low-entropy phase-separated state should be favored.

Let's go back to our example of mixing entropy with this new piece of information involved. In a 2D lattice, we can think of each lattice site as either being occupied by a P-granule or cytoplasm. We know the entropy which we just studied to be the entropy of mixing. On top of that, we need to add in an interaction energy:

$$U = k_B T N^2 \chi c(1-c)$$

where $\chi = \frac{\epsilon_{AB} - (\epsilon_{BB}+\epsilon_{AA})/2}{k_B T}$ is the energy cost of mixing. Then we can define the free energy of mixing as

$$F/Nk_BT = c\ln(c) + (1-c)\ln(1-c) + \chi N c(1-c)$$

What happens now if we minimize this free energy? If you begin with $\chi = 0$, you have the familiar minimum $c = \frac{1}{2}$. However, as you increase χ, you will find that this minimum slowly becomes a maximum, and phase-separated concentrations will become more favorable, particularly a low c "dilute" phase and a high c "condensed" phase. These minima will actually never be exactly 0 or 1, but can get arbitrarily close with larger χ. This is the physics underlying the formation of these membrane-less organelles—they interact in a way which favors phase separation. There is another problem, which is diffusion. Once these condensed particles form, why don't they diffuse away? This attractive interaction between these particles must be large enough to overcome diffusion.

LECTURE 4: STATISTICAL PHYSICS OF CELLULAR PROCESSES II
Friday, February 12, 2021

2.4 Entropy and Information

$$S(p_1, p_2, \cdots, p_N) = -\sum_{i=1}^{N} p_i \ln(p_i) \qquad \text{(Shannon/Information Entropy)}$$

This entropy is defined as the expectation value of the log of the probability distribution, p. We can say that the entropy of the ith microstate is $S_i = -\ln(p_i)$, then $S = \langle S_i \rangle$.

Let's define an entropy function as

$$S = \underbrace{-\sum_i p_i \ln(p_i)}_{\text{Shannon entropy}} - \lambda \left(\sum_i p_i - 1 \right)$$

The second part is a constraint that the sum of probabilities should add up to 1. Our goal is to find p_i in equilibrium, so lets find

$$\frac{\partial S}{\partial p_i} = 0$$

or

$$-\ln(p_i) - 1 - \lambda = 0$$

so

$$p_i = e^{-(1+\lambda)}$$

Now we impose a normalization constraint

$$\sum_{i=1}^{N} p_i = 1$$

so

$$e^{-(1+\lambda)} N = 1$$

or

$$p_i = \frac{1}{N}$$

In a **microcanonical ensemble**, all states are equally likely.

Now consider a subsystem S within a larger system R (reservoir) with energy E_R. The subsystem carries some energy E_i if it is in the state i. $E_i \ll E_R$, and we want to know the probability of being in microstate i, p_i. We can rewrite the entropy function in a slightly different form:

$$S = -\sum_i p_i \ln(p_i) - \lambda \left(\sum_i p_i - 1 \right) - \beta \left(\sum_i p_i E_i - \langle E \rangle \right)$$

We have added an energy constraint requiring the total average energy of the system to add up to be E. Let's maximize entropy:

$$\frac{\partial S}{\partial p_i} = 0 \implies p_i = e^{-1-\lambda-\beta E_i}$$

Again, we impose $\sum_i p_i = 1$, so

$$e^{-1-\lambda} = \frac{1}{\sum_i e^{-\beta E_i}}$$

so

$$p_i = \frac{e^{-\beta E_i}}{\sum_i e^{-\beta E_i}} \qquad \text{(Boltzmann Distribution)}$$

This means that the probability of being in state i decreases as the energy E_i increases. This is the **canonical ensemble**, and is often written

$$p(E_i) = \frac{1}{Z} e^{-\beta E_i} g(E_i)$$

where Z is a partition function (the normalization in the denominator) and g counts the multiplicity of each energy state:

$$Z = \sum_i e^{-\beta E_i}$$

Example. Ion channels can either be closed or open, so $Z = e^{-\beta\epsilon_{\text{closed}}} + e^{-\beta\epsilon_{\text{open}}}$. We can then say that the probability of having an open ion channel is

$$p_{\text{open}} = \frac{e^{-\beta\epsilon_{\text{open}}}}{e^{-\beta\epsilon_{\text{closed}}} + e^{-\beta\epsilon_{\text{open}}}}$$

◇

Example. In protein folding of a 4-amino acid chain, we can imagine three "open" states with energy ϵ and a compact state (like a horseshoe) with energy 0. The weight of the open state is $e^{-\beta\epsilon}$ with multiplicity 3 and the weight of the compact state will be 1 with multiplicity 1. Then

$$Z = 1 + 3e^{-\beta\epsilon}$$

◇

2.5 Partition Function Utilities

The partition function can be used in many ways. For example, the free energy can be written

$$F = -k_B T \ln(Z)$$

The average energy can be written

$$\langle E \rangle = \frac{1}{Z} \sum_{i=1}^{N} E_i g(E_i) e^{-E_i/k_B T}$$

so in our protein folding example, $\langle E \rangle = \frac{3\epsilon e^{-\beta\epsilon}}{1+3e^{-\beta\epsilon}}$. Alternatively, you could use

$$\langle E \rangle = -\frac{\partial \ln(Z)}{\partial \beta}$$

2.5.1 Ligand-Receptor Binding

Let's go back to the ligand lattice model from a previous lecture, where ligands can occupy points in a lattice, a receptor is somewhere on the lattice, and there is an unbound and a bound state for the receptor molecule. If we say there are L ligands and Ω lattice sites, we can take the scenario where $L \ll \Omega$.

Consider that each ligand has energy ϵ_{sol} in the solution, so in the unbound state, the energy is $L\epsilon_{\text{sol}}$. The multiplicity is

$$\frac{\Omega!}{L!(\Omega - L)!} \approx \frac{\Omega^L}{L!}$$

by Striling's approximation. Therefore, the weight in the partition function is

$$\frac{\Omega^L}{L!} e^{-\beta L \epsilon_{\text{sol}}}$$

In the bound state, we have a bound energy for one of the ligands:

$$E_{\text{bound}} = (L-1)\epsilon_{\text{sol}} + \epsilon_b$$

with multiplicity

$$\frac{\Omega!}{(L-1)!(\Omega-L+1)!} \approx \frac{\Omega^{L-1}}{(L-1)!}$$

so the weight is

$$\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\epsilon_{\text{sol}}+\epsilon_b]}$$

Technically, there is another approximation we have made here, which concerns the fact that the receptor occupies a lattice site, so really we should be using $\Omega - 1$ in these multiplicity factors.

The probability of being in a bound state can be calculated as (and simplified to)

$$p_{\text{bound}} = \frac{(L/\Omega)e^{-\beta\Delta\epsilon}}{1 + (L/\Omega)e^{-\beta\Delta\epsilon}}$$

where $\Delta\epsilon = \epsilon_b - \epsilon_{\text{sol}}$.

We can think of L/Ω as being related to the concentration of ligands:

$$\frac{L}{\Omega} = \frac{c}{c_0}$$

where c is the concentration of ligands and c_0 is some reference concentrations:

$$p_{\text{bound}} = \frac{(c/c_0)e^{-\beta\Delta\epsilon}}{1 + (c/c_0)e^{-\beta\Delta\epsilon}}$$

If we plot the probability vs. the concentration, we find that as we increase the number of ligands, the binding probability approaches 1, which is fairly obvious. What happens when we increase the binding energy (or equivalently, $\Delta\epsilon$)? You will have to go to higher and higher concentrations to approach the bound state because it is less favorable to be in the bound state.

Let's look at this from a different perspective: a chemical reaction

$$L + R \leftrightarrow LR$$

where L is the ligand, R is the receptor, and LR is the ligand-receptor bound complex. We can write down a differential equation

$$\frac{\mathrm{d}[LR]}{\mathrm{d}t} = k_{\text{on}}[L][R] - k_{\text{off}}[LR]$$

At equilibrium, $\frac{\mathrm{d}[LR]}{\mathrm{d}t} = 0$, so

$$\frac{[LR]}{[L][R]} = \frac{k_{\text{on}}}{k_{\text{off}}}$$

In this chemical-reaction perspective, the probability of being in the bound state is

$$p_{\text{bound}} = \frac{[LR]}{[R] + [LR]} = \frac{[L]/(k_{\text{off}}/k_{\text{on}})}{1 + [L]/(k_{\text{off}}/k_{\text{on}})}$$

From statistical physics,

$$p_{\text{bound}} = \frac{(c/c_0)e^{-\beta\Delta\epsilon}}{1 + (c/c_0)e^{-\beta\Delta\epsilon}} = \frac{([L]/c_0)e^{-\beta\Delta\epsilon}}{1 + ([L]/c_0)e^{-\beta\Delta\epsilon}}$$

so

$$\frac{k_{\text{off}}}{k_{\text{on}}} = c_0 e^{\beta\Delta\epsilon}$$

In the next lecture, we will consider multiple ligands binding to a single receptor.

Chapter 3

Two-State Biological Systems

Lecture 5: Two-State Biological Systems I
Wednesday, February 17, 2021

Lecture 6: Two-State Biological Systems II
Friday, February 19, 2021

Example. Phosphorylation can be described as a two-state system as proteins without a phosphate group can be thought of as being in an "off" state and proteins with phosphate are "on". This phosphate comes from ATP (adenosine triphosphate) which changes to ADP (adenosine diphosphate) through the process of protein kinase. A protein which is unphosphorylated exists in an "active" and "inactive" state with energies ϵ and 0 respectively (such that the energy to be in the active state is higher). In the phosphorylated state, the free energy landscape changes such that the active energy is $\epsilon - I_1$ and the inactive state has a higher energy $-I_2$. We can then define four states, (in)active (un)phosphorylated, which we can describe using two state variables. We will say $\sigma_P = 0, 1$ if the protein isn't/is phosphorylated. Additionally $\sigma_S = 0, 1$ if the state is inactive/active.

State	σ_P	σ_S	Energy	Weight
Inactive Unphosphorylated	0	0	0	1
Active Unphosphorylated	0	1	ϵ	$e^{-\beta\epsilon}$
Inactive Phosphorylated	1	0	$-I_2$	$e^{\beta I_2}$
Active Phosphorylated	1	1	$\epsilon - I_1$	$e^{-\beta(\epsilon - I_1)}$

We can describe the energy as

$$G(\sigma_P, \sigma_S) = \epsilon\sigma_S - I_2\sigma_P + (I_2 - I_1)\sigma_S\sigma_P$$

Then

$$p_{\text{active}} = \frac{e^{-\beta G(0,1)}}{\sum_{\sigma_S} e^{-\beta G(0,\sigma_S)}} = \frac{e^{-\beta\epsilon}}{1 + e^{-\beta\epsilon}}$$

We can also ask the probability of being in the active state when phosphorylated:

$$p^*_{\text{active}} = \frac{e^{-\beta G(1,1)}}{\sum_{\sigma_S} e^{-\beta G(1,\sigma_S)}} = \frac{e^{-\beta(\epsilon - I_1)}}{e^{-\beta I_2} + e^{-\beta(\epsilon - I_1)}}$$

Then

$$\frac{p^*_{\text{active}}}{p_{\text{active}}} = \frac{1 + e^{\beta\epsilon}}{1 + e^{\beta(\epsilon + I_2 - I_1)}}$$

If $\epsilon \sim 5k_BT$ and $I_2 - I_1 \sim -10k_BT$, then

$$\frac{p^*_{\text{active}}}{p_{\text{active}}} \sim 150$$

For enzymes found in cells,

$$\frac{p^*_{\text{active}}}{p_{\text{active}}} \sim 2 \text{ to } 1000$$

◇

Example. Haemoglobin: A case study in cooperative binding

Haemoglobin is a receptor molecule which has four binding sites for oxygen molecules. consider four sites described by σ_i where $i = 1, 2, 3, 4$ and $\sigma_i = 0$ for unbound and 1 for bound.

These binding sites are arranged in a square, and the entire state can be described by a string of numbers, like $\{0, 0, 0, 0\}$ or $\{0, 1, 1, 0\}$. There are $2^4 = 16$ states in this configuration, but not all are unique. We can imagine that the nearby binding energies are different than the diagonal binding energies. Consider a simpler model which we will call "dimoglobin"; haemoglobin but with only two states.

If one of the sites is occupied, it will have some binding energy ϵ. If both are occupied, there will also be some interaction energy J. In terms of state variables, we can write

$$E(\sigma_1, \sigma_2) = \epsilon(\sigma_1 + \sigma_2) + J\sigma_1\sigma_2$$

Additionally, $J < 0$ because we want cooperative binding, where the energy to bind more oxygen is lower with each additional bound site. We can now construct the partition function:

$$Z = 1 + 2e^{-\beta(\epsilon-\mu)} + e^{-\beta(2\epsilon+J-2\mu)}$$

where μ is the chemical potential for adding an oxygen molecule. We would now like to calculate the average occupancy, $\langle N \rangle$:

$$\langle N \rangle = \frac{1}{Z}\left[0 + 1e^{-\beta(\epsilon-\mu)+1e^{-\beta(\epsilon-\mu)}} + 2e^{-\beta(2\epsilon+J-2\mu)}\right]$$

Additionally,

$$\mu = \mu_0 + k_BT\ln(c/c_0)$$

where c is the concentration of oxygen, so

$$\langle N \rangle = \frac{2(c/c_0)e^{-\beta\Delta\epsilon} + 2(c/c_0)^2e^{-\beta(2\Delta\epsilon+J)}}{1 + 2(c/c_0)e^{-\beta\Delta\epsilon} + 2(c/c_0)^2e^{-\beta(2\Delta\epsilon+J)}}$$

where $\Delta\epsilon = \epsilon - \mu_0$.

Now back to the haemoglobin. How many non-degenerate microstates exist? There should be 5 if we consider all the interaction energies to be the same: one state for each occupancy number. In order of increasing number occupancy, we cna write the partition function as

$$Z = 1 + 4e^{-\beta(\epsilon-\mu)} + 6e^{-\beta(2\epsilon-2\mu+J)} + 4e^{-\beta(3\epsilon-3\mu+3J)} + e^{-\beta(4\epsilon-4\mu+6J)}$$

If we were to arrange this similarly to the dimoglobin model, we would see a faster phase transition to the completely occupied state with oxygen concentration in haemoglobin than with dimoglobin. ◇

Chapter 4

Structure of Macromolecules

Note

We had extra time at the end of this lecture, so we have started next week's lecture early.

4.1 Structure of DNA

We can characterize a strand of DNA by a curve in space, $\vec{\mathbf{r}}(x, y, z)$. Each random configuration defines a microstate, and if we imagine the curve to be continuous in space, there will be an infinite number of microstates, so we can't just count them like we did before.

One way we can represent the structure is a construction called a Kuhn segment. We can approximate the DNA as small, rigid, rod-like sections. The length of those segments depends on the physical properties of the molecule or material (not the length of the material). For example, the Kuhn segment of a rigid object, like a pen, is infinite in length. Spaghetti has a smaller Kuhn segment than copper wire. For DNA, the scale is around 50 to 100nm.

We can think of the structure as the path of a random walker. Each segment points in a direction independent of the previous one.

4.1.1 Random Walks

In 1D, if we want to know the average displacement (the mean-square displacement or variance), we find that

$$\left\langle R^2 \right\rangle = \left\langle \sum_{i=1}^{N} \sum_{j=1}^{N} x_i x_j \right\rangle = \sum_{i=1}^{N} \underbrace{\left\langle x_i^2 \right\rangle}_{a^2} + \sum_{i \neq j=1}^{N} \underbrace{\left\langle x_i x_j \right\rangle}_{0}$$

so

$$\left\langle R^2 \right\rangle = Na^2$$

or $\sqrt{\left\langle R^2 \right\rangle} = a\sqrt{N}$.

Lecture 7: Structure of Macromolecules I
Wednesday, February 24, 2021

4.2 End-to-end Length of DNA Strands

Let's define some statistical properties of a random walk. If we think of a DNA strand's ends as random walkers, we can talk about the end-to-end distance as a probability distribution. We could also talk about the radius of gyration, the average distance from each point to the center of mass. Let's simplify this end-to-end distance for a random walk in one dimension. You can think of each segment as either pointing to the left or right, so

$$R = (n_r - n_l)a = (2n_r - N)a$$

where n_r and n_l are the number of segments pointing right and left, a is the length of a segment, and N is the total number of segments. The probability distribution is then proportional to the number of ways you can realize the number of segments pointing to the right (or left):

$$W(n_r; N) = \frac{N!}{n_r!(N - n_r)!}$$

Again, in this we assume there is no "memory" of previous steps in the random walk, each segment's direction is independent of the previous. The probability distribution is then this times the probability of that many segments bing in the right-going state:

$$p(n_r; N) = W(n_r; N)\left(\frac{1}{2}\right)^N$$

Then we can turn this into a probability function of the end-to-end distance:

$$R = (n_r - n_l)a \implies p(R; N) = \frac{N!}{\left(\frac{N}{2} + \frac{R}{2a}\right)!\left(\frac{N}{2} - \frac{R}{2a}\right)!}\left(\frac{1}{2}\right)^N$$

This probability distribution peaks at $R = 0$, which means that the most common position for a 1D strand is a loop.

In the limit where $R \ll Na$, this binomial distribution becomes a Gaussian:

$$p(R; N) \approx \frac{2}{\sqrt{2\pi N}} e^{-R^2/2Na^2}$$

by the Central Limit Theorem.

We can generalize this Gaussian to 3D:

$$p(\vec{\mathbf{R}}; N) = \left(\frac{3}{2\pi N a^2}\right)^{3/2} e^{-3R^2/2Na^2}$$

4.2.1 How Rigid is a Polymer?

We can define a property called the "persistence length" which is a measure of the length scale over which a polymer remains relatively straight. Consider a curve of length L parameterized by $s \in (0, L)$. At each point, you can draw a tangent vector $\vec{\mathbf{t}}(s)$. If you take the dot product of two tangent vectors and average over all the possible tangent vectors,

$$\left\langle \vec{\mathbf{t}}(s) \cdot \vec{\mathbf{t}}(u) \right\rangle = e^{-|s-u|/\xi_p}$$

where ξ_p is the persistence length. In practice, this is done experimentally, although the relation can be derived from bending mechanics, which we will cover in the next chapter. For DNA, $L \gg \xi_p$.

If we consider a point on the curve to be $\vec{\mathbf{r}}(s)$, then $\vec{\mathbf{t}}(s) = \frac{\partial \vec{\mathbf{r}}}{\partial s}$. Experimentally, you can calculate the tangent-tangent correlation function and the width of this distribution will be the persistence length. The persistence length is also a measure of the "memory" of an object—how well each segment's orientation is correlated to the previous segments. Because $\xi_p \sim 50\text{nm} \ll L$ for DNA, it can be easily bent and twisted inside the nucleus.

How is persistence length related to Kuhn length? The end-to-end distance can be defined as

$$\vec{\mathbf{R}} = \int_0^L \mathrm{d}s\, \hat{t}(s)$$

and $\langle R^2 \rangle = Na^2$ where a is the Kuhn length.

$$\langle R^2 \rangle = \left\langle \int_0^L \mathrm{d}s\, \hat{t}(s) \cdot \int_0^L \mathrm{d}u\, \hat{t}(u) \right\rangle = \left\langle \int_0^L \mathrm{d}s \int_0^L \mathrm{d}u\, \hat{t}(s) \cdot \hat{t}(u) \right\rangle$$

We can divide the domain of integration into two parts, first integrating u and then s. For any value of s, the u quantity runs from s to L, so

$$\langle R^2 \rangle = 2 \int_0^L \mathrm{d}s \int_s^L \mathrm{d}u\, e^{-(u-s)/\xi_p}$$

Define $x = u - s$:

$$\langle R^2 \rangle = 2 \int_0^L \int_0^L \mathrm{d}x\, e^{-x/\xi_p}$$

We will now assume that $L \gg s$. This isn't a great assumption, because it clearly might not be true, but using it,

$$\langle R^2 \rangle \approx 2 \int_0^L \mathrm{d}s \int_0^\infty \mathrm{d}x\, e^{-x/\xi_p}$$

We could actually calculate the original integral exactly, but the higher-order corrections won't really matter much for the polymers we want to study.

$$\langle R^2 \rangle \approx 2L\xi_p$$

We can then compare this with $\langle R^2 \rangle = Na^2$ to show that

$$a = 2\xi_p$$

note that

$$\sqrt{\langle R^2 \rangle} = \sqrt{2L\xi_p} = \sqrt{aL}$$

The theory for semi-rigid objects is a lot more difficult because we cant make the assumption $L \gg s$.

Radius of gyration can be related to these metrics:

$$\langle R_G^2 \rangle = \frac{1}{N} \sum_{i=1}^{N} (\vec{\mathbf{R}} - \vec{\mathbf{R}}_{\mathrm{CM}})^2$$

$$\sqrt{\langle R_G^2 \rangle} = \sqrt{\frac{L\xi_p}{3}}$$

We can then use the length of a DNA strand along with the persistence length to calculate the average size of the molecule (the physical space it occupies in 3D).

4.3 How is DNA Packaged?

In the nucleus, DNA is tightly packed into nucleosomes, which are formed from histones which bind to the DNA ("beads-on-a-string"). These nucleosomes pack into a chromatin fiber, which is then looped and packaged with other proteins into chromosomes. Chromosomes are not always present, and generally only form during cell division. In the intermediate stages, the DNA becomes less organized.

Inside the nucleus, we can tag and view the individual chromosomes, and as it turns out, they are tethered at different locations on the edge of the nucleus. Because of these tethering sites, the statistical properties are very different than those of a free polymer.

Consider two florescent markers on a chromosome, one tethered and the other free to move. For the free marker, the distance from the nearest tether is Gaussian:

$$\Pr(\vec{\mathbf{r}}) = \left(\frac{3}{2\pi N a^2}\right)^{3/2} e^{-3\vec{\mathbf{r}}^2/2Na^2}$$

The tethered mark will follow a displaced distribution:

$$\Pr(\vec{\mathbf{r}}) = \left(\frac{3}{2\pi N' a^2}\right)^{3/2} e^{-3(\vec{\mathbf{r}}-\vec{\mathbf{R}})^2/2N'a^2}$$

Statistically, this tethered model fits experimental data better than a free polymer model. In the next lecture, we will discuss DNA looping—how DNA self-regulates its transcription.

Lecture 8: Structure of Macromolecules II

Friday, February 26, 2021

How is DNA actually packaged?

4.3.1 Chromosome Conformation Capture (3C)

Proteins connect to certain sections of DNA, connecting them and creating loops in a process called cell lysis. Then, these loops are killed (restriction) and the new ends are connected (ligation). This is a form of DNA purification. When we look at the probability of contacting the DNA in the correct place against the length L of the strand, we find a nearly exact $L^{-3/2}$ correlation, which is the correlation expected from a 3D random walk.

4.3.2 Statistics of Loop Formation in 3D

Using a continuous 3D distribution,

$$\Pr\left(\vec{\mathbf{R}}; N\right) = \left(\frac{3}{2\pi N a^2}\right)^{3/2} e^{-3R^2/2Na^2}$$

For a small distance $\delta \ll \sqrt{Na^2}$,

$$p_0 = \int_0^\delta 4\pi R^2 \Pr(R; N)\, \mathrm{d}R = \left(\frac{6}{\pi N^3}\right)^{1/2} \left(\frac{\delta}{a}\right)^3$$

so

$$p_0 \propto N^{-3/2}$$

4.3.3 Chromosome Contact Map (Hi-C)

Using another experiment, a contact map for a particular chromosome can be generated (a correlation plot). The diagonal will be colored because every point on the chromosome is in contact with itself, but this map can also tell us about the structure of DNA packaging. Square-like structures on this map are called domains, and these domains indicate that DNA in those areas contact each other much more than they contact other domains, so domains correspond to bundles of DNA inside the chromosome.

4.3.4 Force-Extension Curves of Macromolecules

Using atomic force microscopy, you can create force-extension curves for macromolecules. These are plots of the fractional extension of the DNA strand again the force applied by the cantilever. In experiment, there are multiple sloped regions, where the slopes give the stiffness. These increase with extension, which is quite common in biological polymers. A similar thing happens for RNA, but at some point of high extension, the force does not change but the polymer extends further. This could indicate that the structure has some folding which requires a certain amount of force to unfold. This is also common in other biological molecules, such as titin proteins in muscles.

If we imagine a force f pulling a molecule of length $L \to L + \delta L$, what is $f(\delta L)$? If we can write out the energy of the system, we can expand in δL and take the gradient to get the force:

$$f = -\frac{\partial G}{\partial L}$$

where $G = U - TS$. The potential energy is 0 for the system, so

$$f = T\frac{\partial S}{\partial L}$$

If we simplify the problem back to our 1D chain with segments pointing left and right, $S(L; L_{\text{tot}}) = k_B \ln(W(L; L_{\text{tot}}))$ where $L_{\text{tot}} = Na$. When you apply a force f, we need to factor that into the free energy:

$$G(L) = -fL - k_B T \ln(W)$$

$$W(n_R; N) = \binom{N}{n_R}$$

where $L = (2n_R - N)a$, so by Stirling's approximation,

$$G = -2fn_R a + k_B T \left[n_R \ln(n_R) + (N - n_R)\ln(N - n_R)\right]$$

$n_R \propto L$, so in equilibrium,

$$\frac{\partial G}{\partial n_R} = -2fa + k_B T \ln(n_R) - k_B T \ln(N - n_R) = 0$$

$$\frac{n_R}{n_L} = e^{2fa/k_B T}$$

You can then compute the extension as a function of force:

$$z = \frac{\langle L \rangle}{L_{\text{tot}}} = \frac{n_R - n_L}{n_R + n_L} = \tanh\left(\frac{fa}{k_B T}\right)$$

Expanding this ($fa \ll k_B T$), we find $z \approx \frac{fa}{k_B T}$, a linear response, which is experimentally true in force extension curves. Of course, the hyperbolic tangent plateaus at $z = 1$, which means the molecule isn't elastic and can't stretch more than the path length of the polymer. Some materials can, but biomolecules generally don't.

There are three fundamental modes of deforming an elastic material: bending, stretching, and twisting. However, if you think of the molecule as being composed of many layers, bending is just the result of stretching one side more than the other (or compressing one side).

Chapter 5

Mechanics of Biopolymers

Lecture 9: Mechanics of Biopolymers I
Wednesday, March 03, 2021

5.1 Mechanical Structure in Biological Cells

Beams are everywhere. In biology, they give cells structure: cytoskeletal filaments and microtubules define the shape and rigidity of a cell. Sterocilia on inner ear hair cells help us hear, flagella help sperm move, and histones wrap DNA.

Actin filaments cluster in different ways to perform different tasks in the cell. Sometimes they form filopodia, small clusters which push into the cell wall to probe the outside environment. When the cell divides, the actin forms a contractile ring, a belt which contracts to divide the cell wall. Neurons also consist of a network of filaments.

Actin is responsible for cell shape, polarity, movement, and muscle contraction. Microtubules are thicker, hollow tubes which provide tracks for cargo transport and aid in cell division. There is a third type of filament called intermediate filament (which we don't know much about) which is responsible for maintaining cell shape and providing tensile strength. These are all proteins that are found in eukaryotic cells, but prokaryotic cells have similar fibers.

5.2 Physics and Mathematics of Beam Theory

We can think about beam bending as stretching. In an unbent beam, we define an axis through the middle as the neutral axis with length L_0. When the beam is bent, material on one side of the neutral axis is stretched while material on the other side is compressed. Microscopically, we can think of this like two layers of springs with natural length a_0. When bent, the top layer gets stretched to $a_0 + \Delta a$ while the bottom layer is compressed to $a_0 - \Delta a$.

As a result of bending, different points along the beam may have different curvatures. We define curvature in terms of the reciprocal of the radius of curvature, the radius of a circle tangent to the curve: $\kappa = \frac{1}{r_c}$.

The first question we will ask is how do we define curvature elasticity? Hooke's law tells us that elastic strain energy is proportional to the square of the strain because in a spring, the energy is proportional to the square of the displacement, and we just said the beam can be thought of as a bunch of parallel springs. We can think of the strain of a fractional extension to be

$$\epsilon = \frac{\Delta L}{L_0}$$

where ΔL is the extension length and L_0 is the original length.

Let's imagine a rod of length L. If we divide the contour into small regions labeled by i, the total bending energy is

$$E_{\text{bend}} = \sum_i u^i_{\text{bend}} = \int_0^L \mathrm{d}l\, u_{\text{bend}}$$

where u^i_{bend} is the bending energy of each discrete section and u_{bend} is the energy density per unit length of the contour. If we look at an individual discrete section, we can define the radius of curvature as R. If we define the radial distance as z, then we can call the neutral axis $z = 0$, the stretched part $z = d$, and the compressed side as $z = -d$, such that the beam has thickness $2d$. We can use our definition of the energy above:

$$u_{\text{bend}} = \int \mathrm{d}A\, \frac{1}{2} E\epsilon^2$$

where E is Young's modulus and the integral is over the cross section of the beam. Note that because the strain is unitless, the Young's modulus has units of energy per unit volume, the same units as stress or pressure. Therefore,

$$E_{\text{bend}} = \int_0^L \mathrm{d}l \int \mathrm{d}A\, \frac{1}{2} E\epsilon^2$$

We now have to calculate the strain. What is the length of a longitudinal portion of the beam section as a function of z, $L(z)$? We can show geometrically that this is

$$L(z) = (R + z)\theta$$

where θ is the angle made by the arc of the beam section. We know that $\epsilon = \frac{\Delta L}{L_0} = \frac{L(z) - L_0}{L_0} = \frac{L(z)}{L_0} - 1$ and $L_0 = R\theta$, so

$$\epsilon(z) = \frac{(R + z)\theta}{R\theta} - 1 = \frac{z}{R}$$

The bending energy is therefore

$$\begin{aligned} E_{\text{bend}} &= \int_0^L \mathrm{d}l \int \mathrm{d}A\, \frac{E}{2} \left(\frac{z}{R}\right)^2 \\ &= \frac{E}{2} \int_0^L \mathrm{d}l\, \frac{1}{R^2} \underbrace{\int \mathrm{d}A\, z^2}_{\text{geometric momement } I} \\ &= \underbrace{\frac{EI}{2}}_{\text{bending modulus or stiffness}} \int_0^L \mathrm{d}l\, \frac{1}{R^2} \\ &= \frac{K_{\text{eff}}}{2} \int_0^L \mathrm{d}l \left(\frac{\mathrm{d}\hat{t}}{\mathrm{d}l}\right)^2 \end{aligned}$$

where $\hat{t}$ is the unit vector tangent to the curve. For uniform curvature,

$$E_{\text{bend}} = \frac{K_{\text{eff}} L}{2R^2} = \frac{EI\theta^2}{2L}$$

We can further relate persistence length of polymers to stress and strain. A polymer at a temperature T will fluctuate under thermal forces proportional to $k_B T$. Something with high persistence length ξ_p will not fluctuate a lot, while something with low ξ_p will. Lets imagine that

$$E_{\text{bend}} = \frac{1}{2} \frac{EIL}{R^2} = k_B T$$

If we suppose the radius of curvature is about the same as the length of the curved section and define this as ξ_p, we get

$$k_B T = \frac{1}{2} EI \frac{\xi_p}{\xi_p^2}$$

so

$$\xi_p = \frac{EI}{2k_BT}$$

Let's now examine some properties of tangent-tangent correlations. Let's define a function $g(s)$ parameterized by s along the length of the curve:

$$g(s) = \left\langle \hat{t}(s) \cdot \hat{t}(0) \right\rangle$$

Since the tangent vector is a unit vector, we can write this as

$$g(s) = \langle \cos(\theta(s)) \rangle$$

where θ is the angle between the tangent vectors. Let's approximate this by a series expansion:

$$g(s) aprox \left\langle 1 - \frac{\theta^2}{2} + \frac{\theta^4}{4!} + \cdots \right\rangle \sim 1 - \frac{1}{2}\left\langle \theta^2 \right\rangle$$

where

$$\left\langle \theta^2 \right\rangle = \int \mathrm{d}\varphi \int \mathrm{d}\theta \sin(\theta) \Pr(\theta, \varphi)\theta^2$$

where

$$\Pr(\theta) = \frac{1}{Z} e^{-\beta E_{\text{bend}}(\theta)} = \frac{1}{Z} e^{-\beta \frac{EI\theta^2}{2s}}$$

where $Z = \int \mathrm{d}\varphi \int \mathrm{d}\theta \sin(\theta) e^{-\beta E_{\text{bend}}(\theta)}$. From this, we can compute that

$$g(s) \approx 1 - \frac{k_BT}{EI} s = 1 - \frac{s}{\xi_p}$$

For $s \ll \xi_p$,

$$g(s) = e^{-s/\xi_p}$$

Lecture 10: Mechanics of Biomolecules II
Friday, March 05, 2021

5.3 Applications of Beam Theory

5.3.1 Elasticity and Entropy

The worm-like chain model accounts for both elastic energy and entropy of polymer chains. We can directly specify weight of a state i as

$$e^{-\frac{\xi_p}{2}\int_0^L \left|\frac{\mathrm{d}\hat{\mathbf{t}}_i(s)}{\mathrm{d}s}\right|^2 \mathrm{d}s}$$

where the partition function looks like

$$Z = \int \mathcal{D}\hat{\mathbf{t}}(s)^{-\frac{\xi_p}{2}\int_0^L \left(\frac{\mathrm{d}\hat{\mathbf{t}}}{\mathrm{d}s}\right)^2 \mathrm{d}s}$$

like the quantum mechanical path integral over all possible curved chains.

5.3.2 Energetics of DNA Looping

We can think of the bending energy of a loop to be

$$E_{\text{bend}} = \frac{\xi_p k_B T}{2} \underbrace{\int_0^L \mathrm{d}s}_{2\pi R} \underbrace{\frac{1}{R(s)^2}}_{R^{-2}}$$

so

$$E_{\text{loop}} = \frac{\xi_p \pi k_B T}{R}$$

For DNA, $\xi_p \sim 50\text{nm}$ and $R = (0.34 N_{bp}\text{nm}/2\pi$, so $E_{\text{loop}} \approx \frac{3000}{N_{bp}} k_B T$, where N_{bp} is the number of base pairs.

We can also look at the entropy:

$$\Delta S_{\text{loop}} = S_{\text{loop}} - S_{\text{total}} = k_B \ln()W_{\text{loop}}/W_{\text{total}})) = k_b \ln(p_0)$$

where p_0 is the probability of loop formation, which we showed earlier is proportional to

$$p_0 \propto N_{bp}^{-3/2}$$

so

$$\Delta S_{\text{loop}} = k_B \ln(p_0) = k_B \left(-\frac{3}{2} \ln(N_{bp}) + \text{const.} \right)$$

All together, we can compute the free energy of DNA looping:

$$\Delta G_{\text{loop}} = \Delta E_{\text{loop}} - T\Delta S_{\text{loop}} \approx k_B T \left(\frac{3000}{N_{\text{bp}}} + \frac{3}{2} \ln(N_{\text{bp}}) + \text{const.} \right)$$

If we plot this, we can see there is a minimum around 2000 base pairs.

5.3.3 Cytoskeletal Filaments

Microtubules provide tracks for molecular motors. That famous animation of kinesin "walking" a vesicle along a microtubule demonstrates this. Muscle contraction also works in a similar way, with multiple proteins walking along microtubules or actin pulling on other filaments to contract or extend the cell.

Let's think about a simple model. Motors moving along filaments have a "plus" and "minus" end, also called "barbed" and "pointed" respectively. These ends are defined by which way the motor moves along the filament (from minus to plus). Motors can be bound to more than one filament, and suppose they move at a constant velocity.

Actin will "buckle" when it is pushed into solid structure by a myosin motor, and sometimes can break. If we imagine a beam of length L, we can add a buckling force to both ends, deforming it to length x. Then $E = E_{\text{bend}} - F(L - x)$:

$$\begin{aligned} E &= \frac{\xi_p k_B T}{2} \frac{L}{R^2} - F(L - x) \\ &= \frac{\xi_p k_B T}{2} \frac{L}{R^2} - F(L - 2R\sin(\theta/2)) \\ &= \frac{\xi_p}{2} \frac{\theta^2}{L} - \frac{FL}{k_B T} \left(1 - \frac{2}{\theta} \sin(\theta/2) \right) \end{aligned}$$

We can define $f \equiv \frac{FL}{k_B T}$ like the bending force scaled by the thermal energy. If $f = 0$, $E = \frac{\xi_p K_B T \theta^2}{2L}$, which has a minimum at $\theta = 0$, a straight polymer. Otherwise, for $F < F_{\text{crit}}$, there will be no minimum other than $\theta = 0$, or no buckling. At some critical energy, a buckled state will have the lowest energy,

but how do we caalculate this F_{crit}? We can Taylor expand the $\sin(\theta/2)$ term and examine the coefficient of the θ^2 term:

$$\frac{E}{k_B T} = \frac{L}{24 k_B T}(F_{\text{crit}} - F)\theta^2$$

where

$$F_{\text{crit}} = 12\frac{k_B T \xi_p}{L^2}$$

In the homework, we will not ignore the higher-order terms.

Chapter 6

Biological Fluid Dynamics

Lecture 11: Biological Fluid Dynamics I
Wednesday, March 10, 2021

There are some scale-independent dynamics that happen in fluids which allow us to treat fluids as a continuous medium. Although they are composed of individual molecules, we can define continuous fields, like density and velocity, which describe the fluid. For the velocity field, the fluid is thought of as a blob with density ρ, and the state of motion is described by a vector at each point, $\vec{\mathbf{v}}(\vec{\mathbf{x}}, t)$.

Suppose a fluid has density $\rho(\vec{\mathbf{x}}, t)$. We can also define a continuity equation, because there must be some conservation of the overall amount of fluid:

$$\frac{\partial \rho}{\partial t} = \vec{\boldsymbol{\nabla}} \cdot \rho \vec{\mathbf{v}}$$

We will mostly be talking about fluids with constant density, where $\frac{\partial \rho}{\partial t} = 0$ so $\vec{\boldsymbol{\nabla}} \cdot \vec{\mathbf{v}} = 0$. Such a fluid is called "incompressible".

Imagine an experiment with two parallel plates of area A separated by a distance d with a fluid between them. If you move the top plate with a force F, then

$$\frac{F}{A} \propto \frac{v}{d}$$

A velocity gradient exists inside this gap. We call the constant of proportionality "viscosity" η:

$$\frac{F}{A} = \eta \frac{v}{d}$$

We can write Newton's second law for fluids, known as the Navier-Stokes equations:

where p is the scalar pressure field. σ is stress, which is defined as $\sigma = -pI + \eta \vec{\boldsymbol{\nabla}} \cdot \vec{\mathbf{v}}$. $\frac{D}{Dt}$ is the material derivative, taking into account the motion of the frame, $\frac{D}{Dt} = \frac{\partial}{\partial t} + \vec{\mathbf{v}} \cdot \vec{\boldsymbol{\nabla}}$. If we think of a cube of fluid moving at velocity v in the x-direction, then at time $t + \Delta t$, we will have to describe that block as $v(x + \Delta x, t + \Delta t)$. $a = \frac{\Delta v}{\Delta t}$, so we can Taylor expand:

$$\Delta v \approx v(x,t) + \partial_x v \Delta x + \partial_t v \Delta t - v(x,t) = \left(\frac{\partial v}{\partial x} \frac{\Delta x}{\Delta t} + \frac{\partial v}{\partial t} \right) \Delta t$$

With $\Delta x/\Delta t \equiv v$, we have $a = \frac{\Delta v}{\Delta t} = \left(v\frac{\partial v}{\partial x} + \frac{\partial v}{\partial t}\right)$. In three dimensions, this is $\vec{\mathbf{a}} = (\frac{\partial}{\partial t} + \vec{\mathbf{v}} \cdot \vec{\boldsymbol{\nabla}})\vec{\mathbf{v}} = \frac{D}{Dt}\vec{\mathbf{v}}$. Let's now consider the final term, the viscous force.

Viscous forces on each face of a fluid element is proportional to the change in flow rate perpendicular to the face. If we think of a shear flow $\vec{\mathbf{v}} = (0, 0, v_z(x))$, the viscous force is non-zero in the yz-plane. If we consider that the velocity is increasing along x, then the viscous force is an opposing force. The Laplacian comes from Taylor expanding the force to second order. The first order terms at x and $x + \Delta x$ will cancel, leaving only the second derivative terms.

Consider now an organism moving in fluid at some velocity v. Suppose the fluid is defined by fixed viscosity and density, η and ρ. If we suppose the size of the organism is approximately a (some length scale), we can write the Navier-Stokes equations as approximately

$$\rho\frac{\partial \vec{\mathbf{v}}}{\partial t} + \rho(\vec{\mathbf{v}} \cdot \vec{\boldsymbol{\nabla}})\vec{\mathbf{v}} = -\vec{\boldsymbol{\nabla}}p + \eta\nabla^2\vec{\mathbf{v}}$$
$$\rho \cdot \frac{v}{a/v} + \frac{\rho v^2}{a} = 0 + \frac{\eta v}{a^2}$$

If we want to compare the inertial term to the strength of the viscosity term, we can define the Reynolds number,

$$\mathrm{Re} = \frac{\rho v^2/a}{\eta v/a^2} = \frac{\rho a v}{\eta}$$

In biology, $\mathrm{Re} \ll 1$, which means the viscous force is much larger than the inertial force. if we consider *E. coli* swimming in water, $\mathrm{Re} \approx 10^5$. If we talk about a fish or a person swimming in water, that number is more like 10^5 or 10^6 respectively.

If you drop the inertial terms entirely (just the Stokes equation), you will have no time dependence. In this scenario, the organism will not really be able to go anywhere because the solutions are invariant under time reversal.

Lecture 12: Biological Fluid Dynamics II
Wednesday, March 24, 2021

6.0.1 Stokes Flow

In the last lecture (before the midterm), we discussed the concept of a Reynolds number, $\mathrm{Re} = \frac{\rho a v}{\eta}$ where η is the fluid viscosity, a is a length scale of the object, v is velocity, and ρ is the fluid density. This is a dimensionless value but is intrinsically scale-dependent. In biophysics, we are generally working with $\mathrm{Re} \ll 1$. In this regime, the Navier-Stokes equations become just the Stokes equation:

$$\vec{\boldsymbol{\nabla}}p = \eta\nabla^2\vec{\mathbf{v}} \qquad \text{(Stokes Equation)}$$

This equation defines Stokes flow and is much easier to solve than the full Navier-Stokes equation.

6.0.2 Fluid Dynamics of Blood

Suppose we have a capillary, which we can model as an infinitely long pipe. The physics will not depend on where we are along the length of the pipe, and we can write the equation in cylindrical coordinates, (r, θ, z). There also should be no angular dependence, since we are assuming an angularly-symmetric capillary. We want to compute the velocity profile at steady state. In this case, $\vec{\mathbf{v}} = v(r)\hat{\mathbf{z}}$ by cylindrical symmetry, $\frac{\partial \vec{\mathbf{v}}}{\partial t} = 0$ in the steady state, and $(\vec{\mathbf{v}} \cdot \vec{\boldsymbol{\nabla}})\vec{\mathbf{v}} = 0$, so we need to solve

$$\frac{\partial p}{\partial z} = \eta\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}v}{\mathrm{d}r}\right)$$

where the right-hand side is just the Laplacian in cylindrical coordinates. Here we are assuming the pressure is just z-dependent. The solution can be found to be

$$v(r) = \frac{\Delta p}{4\eta l}\left(\frac{d^2}{4} - r^2\right)$$

where Δp is the pressure difference across a length l and d is the diameter of the capillary. To solve this, we assume $v(d/2) = 0$, called a no-slip boundary condition at the wall of the capillary.

6.0.3 Stokes Drag

What is the drag force on a sphere of radius R through a viscous fluid at constant speed v (away from any boundaries). This force will depend on the geometry of the object:

$$F_S \propto \text{viscous stress} \times \text{surface area} \qquad \text{(Stokes Drag Force)}$$

In principle, this is a sort of complicated problem, but we will make a rough estimate. For the sphere, the viscous stress is about $\eta v/R$ while the surface area is $4\pi R^2$. Then $F_S \propto \eta v R$. The exact solution from solving the Stokes equation is $F_S = 6\pi\eta R v$. In two dimensions, it will be $F_S = 4\pi\eta R v$. What would the drag force on a cylinder be (the shape of many single-celled organisms)? First, this object is no longer isotropic, the drag force certainly depends on which direction we pull the cylinder. We will come back to this later, but essentially it will be very similar to the sphere, but with a prefactor which depends on direction.

For $\text{Re} < 10$, we generally get laminar flow (parallel lines) around a spherical object. For $\text{Re} \sim [10, 40]$, some vortices form and are generally maintained (stable). However, for $\text{Re} > 40$, vortices form and are periodically shed (unstable/chaotic). However, we can experimentally see vortex flows in cellular motion, despite having $\text{Re} \ll 1$. A cell contracting over a very short length of time can cause the Reynolds number to increase by several orders of magnitude, if only momentarily.

6.1 Motion of Biological Organisms

We can imagine a scallop as an animal with one degree of freedom (the opening and closing of its shell can be parametrized by θ, the angle of opening). Any motion created by opening should exactly cancel motion created by closing, so we are limited to motion along a linear phase space between two points (maximal open and closed states).

However, if we take an animal with two degrees of freedom, θ and φ, we can create cycles in a two-dimensional phase space which can lead to motion.

E. coli swim by rotating its flagellum. The force of propulsion is proportional to the drag coefficient along the z-axis times the velocity along that axis. If we imagine the flagellum oscillating in a plane, we can define a tangent at any point with an angle θ to the z-axis. Then the force of propulsion along the z-axis will be $F_p = F_\perp \sin(\theta) - F_\parallel \cos(\theta)$. If $F_\perp = \gamma_\perp v \cos(\theta)$ with $\gamma_\perp \sim 4\pi\eta l$ and $F_\parallel = \gamma_\parallel v \sin(\theta)$ with $\gamma_\parallel \sim 2\pi\eta l$, then $F_p = 2\pi\eta L v \cos(\theta)\sin(\theta)$ (here γ are the drag coefficients).

On Friday we will study diffusion in cells.

Chapter 7

Diffusion in Cells

Lecture 13: Diffusion in Cells I
Friday, March 26, 2021

Diffusion is a phenomenon which wants to homogenize concentrations of particles. This implies some flow from high-concentration to low-concentration. Diffusion is the continuum limit of random walks of each particle and is caused by thermal forces. In a cell, this is typically on the order of $\sim k_BT/\text{nm}$. We can think of the mean-squared displacement of a random trajectory $x(t)$:

$$\langle x \rangle = 0 \qquad \left\langle (x(t+\tau) - x(t))^2 \right\rangle = 2D\tau$$

in one dimension ($6D\tau$ in 3D), where D is the diffusion coefficient, which depends on the properties of the diffusive particle and the solvent.

We can define a concentration field c to describe the continuum limit of the amount of particles per unit volume in a system. Of course, this depends on how finely you define the unit volume. We can also define flux as the number of particles crossing a unit area per unit time. We can say that the flux is a vector $\vec{\mathbf{J}}$ where J_x is the number of particles crossing the y-z plane per unit area per unit time. The first law of mass transport is called Fick's Law:

$$\vec{\mathbf{J}} = -D\vec{\boldsymbol{\nabla}}c \qquad \text{(Fick's Law)}$$

If the concentration increases along the x-axis, the flux will be along the $-x$-axis, because it will try to oppose the concentration gradient. If we look at a box of volume $\Delta x \Delta y \Delta z$, we can see that the number of particles in the box will be $N_{\text{box}} = c\Delta x\Delta y\Delta z$. If we only look at the flux along one axis,

$$\begin{aligned}
\frac{\partial N_{\text{box}}}{\partial t} &= \frac{\partial c}{\partial t}\Delta x\Delta y\Delta z \\
&= j(x,y,z)\Delta y\Delta z - j(x+\Delta x, y, z)\Delta y\Delta z \\
&\approx j(x,y,z)\Delta y\Delta z - \left(j(x,y,z) + \frac{\partial j}{\partial x}\Delta x\right)\Delta y\Delta z \\
\implies \frac{\partial c}{\partial t} &= -\frac{\partial j}{\partial x}
\end{aligned}$$

Using Fick's Law, $j = -D\frac{\partial c}{\partial x}$, so we get the Diffusion Equation:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

Expanding this to all dimensions, we have to consider that the diffusion constant can differ throughout space:

$$\frac{\partial c}{\partial t} = -\vec{\boldsymbol{\nabla}} \cdot (D\vec{\boldsymbol{\nabla}}c)$$

Suppose for now that D is constant in space, so $\partial_t c = -D\nabla^2 c$. If we consider a 1D lattice with grid size a, let's suppose that a particle has three types of possible trajectories. In the first case, the particle travels to the left, so we consider the statistical weight to be $k\Delta t$ where k is the rate of motion (inverse time units). We can also consider a particle moving to the right, which also has weight $k\Delta t$. The third possibility is that the particle does not move. The statistical weight for this scenario is $1 - 2k\Delta t$, since all of these probabilities must add up to 1. Then

$$\langle x \rangle = \sum_i p_i x_i = ak\Delta t + (-a)k\Delta t + (0)(1 - 2k\Delta t) = 0$$

$$\left\langle x^2 \right\rangle = \sum_i p_i x_i^2 = 2a^2 k\Delta t \approx 2D\Delta t$$

where $D = ka^2$. We can say that $\Pr(x,t)$ is the probability density, so $\Pr(x,t)\Delta x$ is the probability of finding a particle in Δx at t. We can introduce a Master Equation:

$$\Pr(x, t + \Delta t) = (k\Delta t)\Pr(x + a, t) + (k\Delta t)\Pr(x - a, t) + (1 - 2k\Delta t)\Pr(x, t)$$

Then a Taylor expansion would show that

$$\Pr(x, t + \Delta t) \approx \Pr(x, t) + \Delta \frac{\partial \Pr}{\partial t}$$

and

$$\Pr(x \pm a, t) \approx \Pr(x, t) \pm a\frac{\partial \Pr}{\partial x} + \frac{a^2}{2}\frac{\partial^2 \Pr}{\partial x^2}$$

The solution to the diffusion equation is a Gaussian:

$$c(x,t) = \frac{N}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$$

(The easy way to find this is by using a Fourier transform)

7.0.1 Fluorescence Recovery After Photobleaching (FRAP)

An interesting method for measuring diffusive dynamics involves fluorescent molecules which are photobleached by a laser. Measuring the recovery time (time it takes for unbleached particles to re-enter the spot which was bleached) by diffusion can be used as a measurement of the diffusion constant. By computing the diffusion constant, people can infer transport properties of the cell, like how viscous the cytoplasm is.

Suppose we have a cell with Green Fluorescent Protein (GFP) inside it of length $2L$ ($x \in [-L, L]$) and we photobleach an area in the center, $[-a, a]$. The initial concentration is c_0 outside and 0 inside, and then we impose a no-flux boundary condition, $\frac{\partial c}{\partial x} = 0$ for $x = \pm L$, since there is no GFP entering or exiting the cell. We can integrate $c(x,t)$ over $[-a, a]$ and show that it eventually reaches some maximum concentration. Experimentally, one can measure curves and then fit them to this theoretical model to get D.

7.1 Driven Diffusion

We assumed that motion in one direction had the same statistical rate as motion in the other direction. However this doesn't have to be the case. If we assign $k_+(F)$ and $k_-(F)$ to be the rate at which the particle moves right and left respectively, the mean displacement will no longer be 0: $\langle \Delta x \rangle = a(k_+ - k_-)\Delta t$, so we can define a speed $v = \Delta x/\Delta t = a(k_+ - k_-)$. Then the variance will be $\mathrm{Var}(\Delta x) \approx a^2(k_+ + k_-)/(2\Delta t)$, so $D = a^2(k_+ + k_-)/2$. On a short timescale, the particle is diffusing, but on some longer timescale, it is drifting.

Doing a Taylor expansion like before, we get a slightly different equation:

$$\frac{\partial p}{\partial t} = -v\frac{\partial p}{\partial x} + D\frac{\partial^2 p}{\partial x^2} \qquad \text{(1D Smoluchowski Equation)}$$

where p is the probability density.

Solving this is also pretty easy by making a transformation $\bar{x} = x - vt$. Then we just have the usual diffusion equation which we can solve with a Gaussian and transform back. We can also write it as $\partial_t p = -\partial_x J$ where $J = vp - D\partial_x p$. At steady state, $J \equiv 0$, so $D\partial_x p = vp$, or $p \propto e^{\frac{vx}{D}}$.

Lecture 14: Diffusion in Cells II

Wednesday, March 31, 2021

In the last class, we discussed driven diffusion, where the concentration field (in one dimension) follows the equation

$$\frac{\partial c}{\partial t} + v\frac{\partial c}{\partial x} = D\frac{\partial^2 c}{\partial x^2}$$

We can rewrite this as

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x}$$

where

$$J = vc - D\frac{\partial c}{\partial x}$$

If we think of J as the current and v as a velocity, then we can also say that $v = F/\gamma$ where γ is a friction coefficient and F is the force which is moving the particles in the fluid.

$$J = \frac{F}{\gamma}c - D\frac{\partial c}{\partial x}$$

At equilibrium, we have $\frac{\partial c}{\partial t} = 0$ so $\frac{\partial J}{\partial x} = 0$ or $J = 0$, in which case

$$\begin{aligned} \frac{Fc}{\gamma} &= D\frac{\partial c}{\partial x} \\ \gamma D\frac{\mathrm{d}c}{c} &= F\,\mathrm{d}x = -\,\mathrm{d}U \\ \implies c &\propto e^{-\frac{U}{\gamma D}} \end{aligned}$$

Then the probability of finding a particle at x is proportional to the concentration field, so

$$\Pr \propto e^{-U/\gamma D} \sim e^{-U/k_B T}$$

since this should also have a Boltzmann distribution, so we find that

$$D\gamma = k_B T \qquad \text{(Einstein Relation)}$$

This means that the diffusion constant and the friction are not independent. Recall that Stoke's law tells us $\gamma = 6\pi\eta R$, so

$$D = \frac{k_B T}{6\pi\eta R} \qquad \text{(Fluctuation Dissipation Theorem)}$$

so diffusion is proportional to the inverse of viscosity.

7.2 Diffusion to Capture

Let's imagine monomers diffusing to attach to a polymer (or equivalently, some signaling molecule diffusing to a receptor site).

Suppose that far from a cell (which has receptors on the cell wall), the concentration is c_0. At the cell wall (take a spherically symmetric cell), $r = a$, the concentration is $c(a) < c_0$, since when they are caught by receptors, they enter the cell. We are interested in the capture rate at the surface.

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \text{flux} = J(r = a)4\pi a^2$$

$\vec{\mathbf{J}} = -D\vec{\boldsymbol{\nabla}}c$, and we then need to solve the diffusion equation at steady state, $D\nabla^2 c = 0$. However, we will assume the concentration field is spherically symmetric, which will simplify this greatly. In these coordinates,

$$D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) = 0$$

or

$$\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}c}{\mathrm{d}r}\right) = 0$$

so

$$r^2\frac{\mathrm{d}c}{\mathrm{d}r} = A \text{ (a constant)}$$

We can integrate to show that

$$c(r) = -\frac{A}{r} + B$$

We can use our boundaries:

$$c(r \to \infty) = c_0$$

and

$$c(r \to a) = c(a)$$

If $c(a) = 0$, we are describing "perfect capture". In this case, $c(r) = c_0\left(1 - \frac{a}{r}\right)$.

Then $J = -D\left.\frac{\mathrm{d}c}{\mathrm{d}r}\right|_{r=a} = -\frac{Dc_0}{a}$, and $\frac{\mathrm{d}n}{\mathrm{d}t} = 4\pi D c_0 a$.

In a reaction-limited scenario (no longer perfect capture),

$$\frac{\mathrm{d}n}{\mathrm{d}t} = MK_{\text{on}}c(a) = J(a)4\pi a^2$$

so

$$J(a) = -\left.\frac{\mathrm{d}c}{\mathrm{d}r}\right|_{r=a} = -\frac{D}{a}(c_0 - c(a))$$

Then

$$MK_{\text{on}}c(a) = D4\pi a(c_0 - c(a))$$

or

$$c(a) = \frac{c}{1 + \frac{MK_{\text{on}}}{4\pi Da}}$$

In the limit where $D \gg \frac{MK_{\text{on}}}{4\pi a}$, $c(a) = c_0$ and the distribution becomes limited. This is the reaction-limited limit. In the other direction, we have $c(a) = 0$, which is the diffusion-limited limit.

In reality, receptors are not always uniformly distributed. If receptors are localized in some area, would the capture be more efficient? It appears that real cells do have strong localization in their receptor proteins.

Chapter 8

Chemical Reactions in Cells

Lecture 15: Chemical Reactions in Cells I
Friday, April 02, 2021

Let's look at the example of a cell which crawls using actin fibers to extend its cell wall. Suppose the speed of migration is $v_{\text{cell}} = 200\text{nm/s}$ and the size of each monomer is $L_m = 3\text{nm}$. Then

$$\frac{\mathrm{d}N_{\text{actin}}}{\mathrm{d}t} = \frac{v_{\text{cell}}}{L_m} \sim 70\text{monomers/s}$$

(I might have gotten this wrong)

There is typically some nucleation (lag phase), an elongation phase, and a steady state equilibrium. While it's growing, the rate of adding monomers is greater than the rate of loss, and at equilibrium, the rates are equal (but never zero!). Actin is also directional, so there can be different rates for nucleation on the + end or − end. We can differentiate these rates by k_{on}^{+}, k_{off}^{+}, k_{on}^{-}, and k_{off}^{-}.

For a simple model, consider an actin filament without directionality, so the only rates we care about are k_{off} and k_{on}. Suppose P_n is a polymer with m monomers. The reaction we have is $P_n + P_1 \leftrightarrow P_{n+1}$, with the forward reaction happening at rate k_{on}. Let $[P_n]$ be the concentration of polymers with n subunits. In "equilibrium", we have

$$\frac{\mathrm{d}}{\mathrm{d}t}[P_{n+1}] = k_{\text{on}}[P_n][P_1] - k_{\text{off}}[P_{n+1}] = 0$$

or

$$\frac{[P_n][P_1]}{[P_{n+1}]} = \frac{k_{\text{off}}}{k_{\text{on}}} \equiv k_d$$

where k_d is called the dissociation constant. With $n = 1$, $k_d = \frac{[P_1]^2}{[P_2]}$, or the probability of having a dimer is the square of the probability of having a monomer. For $n = 2$, we get

$$k_d = \frac{[P_2][P_1]}{[P_3]} = \frac{[P_1]^3}{[P_3]k_d}$$

or $[P_3] = \frac{[P_1]^3}{k_d^2}$. We now start seeing the emerging pattern. We will eventually find that

$$[P_n] = \frac{[P_1]^n}{k_d^{n-1}} = k_d \left(\frac{[P_1]}{k_d}\right)^n$$

or

$$[P_n] = k_d e^{-\alpha n}$$

where

$$\alpha = -\ln\left(\frac{[P_1]}{k_d}\right)$$

If we plot $[P_n]$ as a function of n, we would get an exponential function. Is this true in a cell? Nobody knows. It works okay in-vitro.

If we derive the average polymer length vs monomer concentration, we find

$$\langle n \rangle = \frac{1}{\alpha}$$

but this blows up at high monomer concentration, so it might not be a great model.

In vitro, we find $k_{\text{on}} \sim 10\mu\text{mol}^{-1}\text{s}^{-1}$ and $k_{\text{off}} \sim 1\text{s}^{-1}$, then $k_d \sim 0.1\mu\text{mol}$. Above the critical concentration $c^* = k_d$, filaments will grow, but below this, they will shrink.

From a statistical view, we have some distribution of filaments with various lengths, and N_n is the number of filaments with n monomers. The probability a given filament has n monomers is

$$P_n(t) = \frac{N_n}{\sum_n N_n}$$

If we consider that $P_{n-1} + P_1 \leftrightarrow P_n$ and $P_n + P_1 \leftrightarrow P_{n+1}$ as two ways a polymer P_n can be created or destroyed, then

$$\frac{\mathrm{d}P_n}{\mathrm{d}t} = k_{\text{on}} P_{n-1} P_1 - k_{\text{off}} P_n + k_{\text{off}} P_{n+1} - k_{\text{on}} P_1 P_n$$

Then

$$\langle L \rangle = \sum_n anP_n$$

so

$$\frac{\mathrm{d}\langle L \rangle}{\mathrm{d}t} = \sum_n an \frac{\mathrm{d}P_n}{\mathrm{d}t} = \sum_n an \left[k_{\text{on}P_1(P_{n-1} - P_n)} + k_{\text{off}}(P_{n+1} - P_n) \right]$$

Let's examine the first term using the idea that

$$\sum_n nP_{n-1} = \sum (n+1)P_n$$

so

$$\begin{aligned} ak_{\text{on}} P_1 \sum_n n(P_{n-1} - P_n) &= ak_{\text{on}} P_1 \sum_n P_n(n+1-n) \\ &= ak_{\text{on}} P_1 \underbrace{\sum_n P_n}_{1} \\ &= ak_{\text{on}} P_1 \end{aligned}$$

The second term is just ak_{off}, so we get

$$\frac{\mathrm{d}\langle L \rangle}{\mathrm{d}t} = a(k_{\text{on}} P_1 - k_{\text{off}})$$

where a is the length of the monomer. Again we can define a critical point $c^* = k_{\text{off}}/k_{\text{on}}$ where $P_1 > c^*$ means the polymer will grow. c^* itself is an unstable equilibrium, and in biological systems these aren't robust. Again, this means this model isn't going to work well. One way to fix this is that we have a finite source of monomers. While a polymer grows, it depletes the concentration of monomers.

We can model this by adding in some negative feedback which takes away from the growth with the length of the polymer:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = k_{\text{on}} \left(c_0 - \frac{Mn(t)}{V} \right) - k_{\text{off}}$$

where M is the number of nuclei seeding growth and V is the volume of the solution. Solving this, we have

$$n(t) = \frac{V}{Mk_{\text{on}}} (k_{\text{on}} c_0 - k_{\text{off}}) \left(1 - e^{-k_{\text{on}} Mt/V} \right)$$

8.0.1 Polymerization of Directional Actin

Now we look at monomers and polymers with a + and − end. In experiment, the on-rate on the − end is lower than it is on the + end. Additionally, the polymer isn't necessarily uniform. On the − end, you add ATP-actin, but on the + end, you add ADP-actin. Let's consider a simple model:

$$\frac{\mathrm{d}n_\pm}{\mathrm{d}t} = k_{\mathrm{on}}^\pm c_0 - k_{\mathrm{off}}^\pm$$

we can write a critical concentration

$$c_\pm^* = \frac{k_{\mathrm{off}}^\pm}{k_{\mathrm{on}}^\pm}$$

However, if we deviate from equilibrium, there can be many different interesting possibilities. If $\frac{\mathrm{d}n_+}{\mathrm{d}t} = -\frac{\mathrm{d}n_-}{\mathrm{d}t}$, we get a "treadmill" effect. The length of the polymer will be constant, but it will appear to be moving. No forces are actually acting on the filament, but the motion is caused by the filament being grown in one direction at the same rate it shrinks in the other direction.

There are two critical concentrations c_+^* and c_-^*, where $c_+^* < c_-^*$ experimentally. Above c_-^*, both ends will grow. Below c_+^*, both ends will shrink. In between them, there is some concentration c^* which will result in treadmilling.

Chapter 9

Molecular Motors

Lecture 16: Molecular Motors I
Friday, April 09, 2021

9.1 Translational Motors

Many forms of molecular motion are driven by translational motors which operate by proteins walking along filaments. Even motors which appear to rotate typically operate via translational motors. Muscle myosin-II is formed from a coiled chain of two α-helicest which walk along actin filaments. These coils are then packaged into larger bundles, and the motion of individual fibers causes larger structured motion on the whole bundle. Once they reach the end of the actin filaments, the myosin proteins fall off and bind again somewhere else. This assembly of myosin motors generates muscle contraction.

How do myosin molecules "walk"? There are two possible scenarios. In a hand-over-hand method, the molecule twists, causing a stepping motion (like climbing a ladder). Alternatively, it could operate like an inchworm, extending one side and retracting the other. If we look at a plot of position vs time, we see many plateaus or steps. If the inchworm mechanism was correct, we would expect continuous motion. Additionally, the step sizes favor the hand-over-hand mechanism. If we place a tag on one "foot" of the myosin molecule and plot the step size as the displacement of that tag, we find three peaks, with average step sizes around 23nm, 52nm, and 74. This is because one of the steps hardly moves the marker at all, since it rotates on that leg, while the other step will move it quite a lot.

9.2 Molecular Motors as Directed Random Walkers

Molecular motors exist in multiple physical and chemical states. However, we would like to start with a simple model to see how few states we need to successfully explain experimental data. Consider a one-state model where motors exist in one state in each site. In one time step, the motor either moves left, right, or neither, so we can construct a master equation:

$$p(n, t + \Delta t) = k_+ \Delta t p(n-1, t) + k_- \Delta t p(n+1, t) + (1 - k_- \Delta t - k_+ \Delta t) p(n, t)$$

We can Taylor expand $p(n \pm a, t)$ and $p(n, t + \Delta t)$ to find a driven diffusion equation:

$$\frac{\partial p}{\partial t} = -V \frac{\partial p}{\partial x} + D \frac{\partial^2 p}{\partial x^2}$$

where

$$V = a[k_+(F) - k_-(F)] \qquad D = \frac{a^2}{2} [k_+(F) + k_-(F)]$$

The rates ideally depend on the force applied. We can solve the driven diffusion equation using the transformation $\bar{x} = x - Vt$ to find

$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-(x-Vt)^2/(4Dt)}$$

Now we need to figure out how the jump rates depend on force. Suppose the force is acting in the k_- direction. We can use a principle of detailed balance, which says there is no net flow of probability for a closed cycle of states:

$$k_+ p_n = k_- p_{n+1}$$

We could also say that

$$k_+ p_{n-1} = k_- p_n$$

We can then say that in equilibrium,

$$\frac{p_{n+1}}{p_n} = \frac{k_+}{k_-}$$

We also know that

$$p_n = \frac{1}{Z} e^{-\beta E_n}$$

so

$$\frac{p_{n+1}}{p_n} = e^{-\beta(E_{n+1} - E_n)} = \frac{k_+}{k_-}$$

We can write the energy to be in a state as a function of the force:

$$E_{n+1} - E_n = E^0_{n+1} + F(n+1)a - E^0_n + Fna = (E^0_{n+1} - E^0_n) + Fa = \Delta E + fa$$

so

$$\frac{k_+}{k_-} = e^{-\beta(\Delta E + Fa)}$$

We can have two possible scenarios, one where the forward rate is force-dependent and one where the backward rate is:

$$k_+(F) = k_- e^{-\beta(\Delta E + Fa)} \quad \text{or} \quad k_-(F) = k_+ e^{-\beta(\Delta E + Fa)}$$

Let's assume the first case. Then

$$V(F) = a k_- \left(1 - e^{-\beta(\Delta E + Fa)}\right)$$

When $V(F) = 0$, the force opposing the motion is large enough that no motion happens. It turns out that the second scenario, where the backward rate is force-dependent, agrees more with data.

9.2.1 Two-State Motor Model

Imagine we have two internal states, $|0\rangle$ and $|1\rangle$. These might correspond to whether or not the motor is bound to ATP. For example, $p_1(n,t)$ is the probability that the system is in state 1 at position n at time t. The homework asks us to derive $\frac{\mathrm{d}p_1}{\mathrm{d}t}$ or $\frac{\mathrm{d}p_2}{\mathrm{d}t}$.

Lecture 17: Molecular Motors II

Wednesday, April 14, 2021

Let's continue looking at the two-state motor model. $p_1(n,t)$ is the probability that the system is in state 1 at position n at time t, as mentioned in the previous class. For simplicity, we will drop any positional dependence.

We can consider transitions from $n \to n+1$ which change state, or transitions from $|0\rangle \to |1\rangle$ which don't change position. There are multiple ways for the motor to end up in state $|0\rangle$ or $|1\rangle$ for example:

Position	Internal State	Rate
$n-1 \to n$	$1 \to 0$	k_A^+
$n \to n$	$1 \to 0$	k_B^-
$n \to n-1$	$0 \to 1$	k_A^-
$n \to n$	$0 \to 1$	k_B^+

so

$$\frac{\mathrm{d}p_0}{\mathrm{d}t} = k_A^+ p_1 + k_B^- p_1 - k_A^- p_0 - k_B^+ p_0$$

We can also have

Position	Internal State	Rate
$n+1 \to n$	$0 \to 1$	k_A^-
$n \to n$	$0 \to 1$	k_B^+
$n \to n$	$1 \to 0$	k_A^+
$n \to n+1$	$1 \to 0$	k_B^-

which gives us

$$\frac{\mathrm{d}p_1}{\mathrm{d}t} = k_A^- p_0 + k_B^+ p_0 - k_A^+ p_1 - k_B^- p_1$$

We can now look at what happens at steady state, where $\frac{\mathrm{d}p_{0,1}}{\mathrm{d}t} = 0$. From this, we get

$$(k_A^+ + k_B^-)p_1 = (k_A^- + k_B^+)p_0$$

We also have the normalization condition that $p_0 + p_1 = 1$, so using this we can uniquely calculate

$$p_0 = \frac{k_A^+ + k_B^-}{k_A^+ + k_A^- + k_B^+ + k_B^-} \qquad p_1 = \frac{k_A^- + k_B^+}{k_A^+ + k_A^- + k_B^+ + k_B^-}$$

Consider that when the motor changes state from $|0\rangle \to |1\rangle$, it moves a physical distance δ, but when it jumps from $n \to n+1$ it moves a distance $a - \delta$. Then

$$V = \delta(p_0 k_B^+ - p_1 k_B^-) + (a-\delta)(p_1 k_A^+ - p_0 k_A^-)$$

Using p_0 and p_1 from above, we get the steady-state velocity

$$\langle V \rangle = a \frac{k_A^+ k_B^+ - k_A^- k_B^-}{k_A^+ + k_A^- + k_B^+ + k_B^-}$$

9.3 Polymerisation as Motor Action

Growing filaments can also generate forces. How does this happen? Suppose we have a cell membrane, and immediately below it we have some actin filament which is growing. To grow, it adds monomers primarily on the barbed end (+). To attach a monomer near the cell membrane, there needs to be some amount of space between the existing actin and the membrane. That space is generated by fluctuation in the cell membrane. This process is called a polymerization ratchet (or Brownian ratchet).

The probability that a monomer attaches, $\Delta p(\text{on})$

$$p(\text{allowed}) \times k_{\text{on}} m \Delta t$$

where p(allowed) is the probability that the attachment is allowed ($p(x > \delta)$), m is the concentration of monomers, and k_{on} is the rate of attachment.

$$p(x > \delta) = \int_{\delta}^{\infty} p(x)\,\mathrm{d}x$$

where

$$p(x) = \beta F e^{-\beta F x}$$

is the probability that the gap opens a distance x.

We can then consider the speed at which the monomer is moving as

$$v = \delta[k_{\text{on}} m e^{-\beta F \delta} - k_{\text{off}}]$$

In equilibrium, $v = 0$ and $k_{\text{on}} m e^{-\beta F \delta} = k_{\text{off}}$. Then we can see that

$$m = \left(\frac{k_{\text{off}}}{k_{\text{on}}}\right) e^{\beta F \delta}$$

if we consider $m^* = \frac{k_{\text{off}}}{k_{\text{on}}}$, then

$$m(F) = m^* e^{\beta F \delta}$$

or

$$F = \frac{1}{\beta\delta} \ln\left(\frac{m(F)}{m^*}\right)$$

The presence of force makes the transition less favorable by an amount $F\delta$, so the difference in free energy would be like $\Delta G = \Delta G_0 - F\delta$.

We can find $m \sim 20\mu$ and $m^* \sim 0.2\mu$ with $\delta \sim 2.7$nm, and this makes $F \sim 7$pN for F-actin. For microtubules, $m = 100m^*$ and $\delta \sim 0.6$nm, so $F \sim 30$pN. Is this enough force to buckle the microtubule? The buckling force depends on the length of the polymer, and by taking these forces above and knowing the persistence length, we can estimate the critical length of the polymers which would allow this polymerization process to cause buckling:

$$F_{\text{crit}} = 12\frac{\xi_p}{\beta L_c}$$

For F-actin, $L_c \sim 0.1\mu$m and for microtubules, $L_c \sim 0.6\mu$m. For lengths larger than L_c, the polymer will buckle upon adding new monomers.

Chapter 10

Neural Signalling and Action Potentials

Lecture 18: Neural Signalling and Action Potentials I
Wednesday, April 21, 2021

10.1 Charge State of the Cell

Neural signalling works on the idea that certain ions can diffuse across the cell membrane, carrying an electric charge gradient which carries a signal down the cell. Take a cell with potassium ions on the inside and outside. If there are more ions on one side of the membrane, there is an electric gradient created by the fact that these chemicals are ions, but there is also a chemical gradient formed due to diffusion and leak channels which allow for certain ions to move in only one direction. In cells, sodium ions are pumped into the cell and potassium ions are pumped out. In addition to the leak channels, there is a sodium-potassium pump which uses ATP hydrolysis to pump sodium out and potassium in, restoring equilibrium. When the cell is at equilibrium, $V_{\text{mem}} \sim -70\text{mV}$, the leak channels are closed.

Now let's discuss how potentials are generated by the flow of chemical species. Let's take a system with two subsystems, 1 and 2, connected by a channel. There is some charge $c_{1/2}$ and some potential $V_{1/2}$ in each subsystem. We want to figure out the equilibrium. The probability that an ion is in one of the subsystems is

$$p_1 = \frac{1}{Z} e^{-\beta q V_1} \qquad p_2 = \frac{1}{Z} e^{-\beta q V_2}$$

where $q = ze$ is the total charge. Then the charge concentration in each subsystem will be

$$c_1 = \frac{N p_1}{\mathcal{V}} \qquad c_2 = \frac{N p_2}{\mathcal{V}}$$

and the ratio of concentrations is

$$\frac{c_1}{c_2} = \frac{p_1}{p_2} = e^{-ze(V_1 - V_2)/k_B T}$$

or

$$V_1 - V_2 = \frac{k_B T}{ze} \ln\left(\frac{c_2}{c_1}\right)$$

or

$$V_1 - V_2 = \Delta V = \frac{k_B T}{Q} \ln\left(\frac{c_1}{c_2}\right) \qquad \text{(Nernst Potential)}$$

There are regular fluctuations around the -70mV equilibrium due to leak channels, but once the fluctuations pass -55mV, voltage-gated (sodium) channels are opened. From here, sodium ions (positive) will leak into the cell and the cell will become positively charged.

10.2 Two-State Model of Voltage Gating

We can imagine the voltage-gated channels as a spring. In the open state, we can say that the spring is in a relaxed state, and in the closed state, the spring is compressed. Then the closed state has a higher potential because it takes energy to compress the spring. For a two-state system, we know that the probability for the open state is given by

$$p_{\text{open}} = \frac{e^{-\beta\Delta\epsilon}}{1 + e^{-\beta\Delta\epsilon}}$$

In this case, $\Delta\epsilon = \epsilon_{\text{open}} - \epsilon_{\text{closed}}$. In the open state, the spring is relaxed, so we can say

$$\epsilon_{\text{open}} = E_{\text{relaxed}} - QV_{\text{membrane}}$$

where V_{membrane} is the potential difference across the membrane. It comes with a negative sign because if the difference is lower, it will favor an open channel. Similarly, we can say

$$\epsilon_{\text{closed}} = \left(E_{\text{relaxed}} + \frac{1}{2}kx^2\right) - Q(1-f)V_{\text{membrane}}$$

Then

$$\begin{aligned}\Delta\epsilon &= -\frac{1}{2}kx^2 - QfV_{\text{membrane}} \\ &= \Delta\epsilon_{\text{conf}} - QfV_{\text{mem}}\end{aligned}$$

We can then say

$$\begin{aligned}p_{\text{open}} &= \frac{1}{1 + e^{\beta(\Delta\epsilon_{\text{conf}} - QfV_{\text{mem}})}} \\ &= \frac{1}{1 + e^{a(V^* - V_{\text{mem}})}}\end{aligned}$$

where $a = \beta Qf$ and $V^* = \frac{\Delta\epsilon_{\text{conf}}}{Qf}$. $p_{\text{open}} \sim 0$ for low voltages, but at $V \sim V^*$, $p_{\text{open}} \to 1$ for values above V^* very quickly.

This model only discusses the opening probability, but doesn't mention the transition back into the closed state. In reality, there is another threshold at +30mV which opens potassium channels that release potassium ions from the cell, causing the potential to decrease again (depolarization to repolarization).

10.3 Current Across Membrane

We can figure out the total difference in chemical potential across the membrane:

$$\Delta\mu = \left(\mu_0 + k_BT\ln\left(\frac{c_{\text{in}}}{c_0} + zeV_{\text{in}}\right)\right) - \left(\mu_0 + k_BT\ln\left(\frac{c_{\text{out}}}{c_0} + zeV_{\text{out}}\right)\right)$$

Then $I = g\Delta\mu/ze$ gives us $I = g(V_{\text{mem}} - V_{\text{Nernst}})$ where

$$V_{\text{Nernst}} = -\frac{k_BTt}{ze}\ln\left(\frac{c_{\text{in}}}{c_{\text{out}}}\right)$$

and

$$V_{\text{mem}} = V_{\text{in}} - V_{\text{out}}$$

We can measure the actual current I, and experimentally, we see that g is likely some nonlinear function of V_{mem} for the sodium voltage and a mostly linear function of V_{mem} for the potassium voltage.

We want to figure out what causes the nonlinearity for sodium channels. We actually know that it is due to the opening of channels, so we can suppose that the total function is composed out of the summation of many channels with a probability distribution:

$$g_{\text{Na}} = Ng_1 p_{\text{open}} = Ng_1 \frac{1}{1 + e^{a(V^* - V_{\text{mem}})}}$$

g now has a sigmoid-like shape as a function of V_{mem}.

If we imagine g is constant with V_{mem}, then by Ohm's law, $I = g(V_{\text{mem}} - V_{\text{Nernst}})$ gives a linear function with an zero at V_{Nernst}.

If g is a step function which switches at V^*, then we have two lines with two different slopes that are disconnected around V^*. When we approach the sigmoid function, we get something similar to the nonlinear response function in the current.

Lecture 19: Neural Signalling and Action Potentials II
Friday, April 23, 2021

Next, we will describe cell signaling as a circuit to understand the dynamics of the system. We can think of both gates as battery-resistors connected in parallel, each with resistance g_{Na} or g_K and voltage V_N^{Na} and V_N^K (the Nernst potentials). These are in parallel with a capacitor which represents the cell membrane. Let I_{Na} be the current passing through the sodium channel and I_K be the current in the potassium channel. Then the charge difference set up across the membrane is

$$\Delta Q = -(I_k + I_{Na})\Delta t = C\Delta V_{\text{mem}}$$

or

$$c\frac{\mathrm{d}V_{\text{mem}}}{\mathrm{d}t} = -(I_K + I_{Na})$$

We also know that

$$I_K = g_K(V_{\text{mem}} - V_N^K)$$
$$I_{Na} = g_{Na}(V_{\text{mem}})(V_{\text{mem}} - V_N^{Na})$$

Recall from the previous class that

$$g_{Na} = g_{Na}^0 \frac{1}{1 + e^{a(V^* - V_{\text{mem}})}}$$

so (relabeling $V \equiv V_{\text{mem}}$),

$$c\frac{\mathrm{d}V}{\mathrm{d}t} = g_k(V_N^K - V) + g_{Na}(V)(V_N^{Na} - V)$$

Let's examine the steady-state:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0 \implies V = \frac{g_K V_N^K + g_{Na} V_N^{NA}}{g_K + g_{Na}}$$

If we take $V < V^*$, then $g_{Na} \sim 0 \ll g_K$, so $V \approx V_N^K$. However, if $V > V^*$, $g_{Na} \gg g_K$, so $V \approx V_N^{Na}$, so we get two steady states of the system. This system acts like a bistable switch.

10.4 Cable Equation

We can now imagine that at each point in space along the neuron, there is an equivalent circuit connected in parallel with some internal resistance ΔR_{int}, the resistance of the lipid. We can think of the potential as an effective potential V_N for each patch, with Δg_{patch} resistence and ΔC_{patch} capacitance. The current in each patch is $i_r(x)$. How does such a circuit work?

$$V(x+\Delta x) - V(x) = -i(x)\Delta R_{\text{int}}$$

and

$$i(x-\Delta x) = i_r(x) + i(x)$$

with

$$i_r = \Delta g(V(x) - V_N)$$

Then

$$i(x-\Delta x) - i(x) = \Delta g(V(x) - V_N)$$

We can use the first equation to see that

$$\frac{\mathrm{d}V}{\mathrm{d}x} = -i(x)\frac{\Delta R_{\text{int}}}{\Delta x}$$

so

$$-\frac{\mathrm{d}i}{\mathrm{d}x} = \frac{\Delta g}{\Delta x}(V - V_N)$$

and

$$\left(\frac{\Delta x}{\Delta R_{\text{int}}}\right) - \frac{\mathrm{d}}{\mathrm{d}x}\left(-\frac{\mathrm{d}V}{\mathrm{d}x}\right) = \left(\frac{\Delta g}{\Delta x}\right)(V - V_N)$$

which gives us

$$\frac{\mathrm{d}^2V}{\mathrm{d}x^2} = \frac{\Delta g \Delta R_{\text{int}}}{\Delta x \Delta x}(V - V_N)$$

Letting $\Delta g = g\pi d\Delta x$ (a cylindrical cell wall with channels uniformly distributed), $\frac{\Delta g}{\Delta x} = g\pi d$, and $\Delta R_{\text{int}} = \frac{\rho \Delta x}{\pi d^2/4}$, we get

$$\frac{\mathrm{d}^2V}{\mathrm{d}x^2} = \lambda^2(V - V_N) \qquad \lambda = \sqrt{\frac{d}{4\rho g}} \qquad \text{(Cable Equation)}$$

This is the steady-state solution. The next thing we want to do is find a time-dependent cable equation that can describe signals moving along this neuron. If we add a term $\Delta C\frac{\partial V(x,t)}{\partial t}$ to our first equation, we end up with something like

$$\lambda^2\frac{\partial^2 V}{\partial x^2} - \tau\frac{\partial V}{\partial t} = \frac{g_{Na}V}{g_K}(V - V_N^{Na}) + (V - V_N^K)$$

where $\tau = \Delta C/g_K$. The propagation speed is then $v \approx \lambda/\tau$.

If we take a boundary condition, say $V(x=0) = V_0$ at $t = 0$, what happens? Unfortunately, this equation is rather difficult to solve exactly, but we can input some of the known values for the free parameters and solve it numerically. For sub-threshold voltages which can't excite the sodium channels, the signal will decay to the potassium Nernst potential. However, super-threshold voltages will form a propagating wave-front. Unfortunately, the circuits won't turn off, like the propagating pulse expected of an action potential. The cable equation is not a good model for this because it only has one time derivative (equivalently, one time scale).

Lecture 20: Neural Signalling and Action Potentials III

Wednesday, April 28, 2021

We mentioned that there needs to be two time scales for pulse propagation. One of these it the time scale related to the motion of the signal. The other is a time scale related to the rate at which ion channels close after they are opened. The Hodgkin-Huxley model describes this process, a mathematical model for the circuit, which later won the Nobel Prize. Their insight was that the inactivation of sodium channels leads to propagating spikes. Consider that the Na channel can have three states, closed, open + active, and open + inactive. Before going to the closed state, the open state must pass from active to inactive:

$$\frac{\mathrm{d}p_c}{\mathrm{d}t} = -k_{\text{open}}p_c$$

$$\frac{\mathrm{d}p_o}{\mathrm{d}t} = k_{\text{open}} p_c - k_{\text{inactive}} p_o$$
$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = k_{\text{inactive}} p_o$$

The rate of opening is related to the conductance:

$$k_{\text{open}} = k_{\text{open}}^{\max} \frac{1}{1 + e^{\beta q [V^* - V(x,t)]}}$$

k_{inactive} can be seen as a constant, experimentally. We can couple this to the time-dependent cable equation via the conductance variable:

$$g_{\text{Na}} = g_{\text{Na}}^{\text{open}} p_o + g_{\text{Na}}^{\text{closed}} p_c$$

Two important features of this system: 1. The response is fairly robust. The traveling pulse size doesn't depend on the initial voltage (above threshold) and 2. In real life, at high voltages, the signal won't propagate (called blocking).

10.5 Fitzhugh-Nagumo Model

The Fitzhugh-Nagumo model for neural firing is a toy model which describes nerve potentials:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = V - V^3/3 - W + I$$
$$\frac{\mathrm{d}W}{\mathrm{d}t} = \phi(V + a - bW)$$

Fitzhugh started with the van der Pol oscillator system:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = V - V^3/3 - W$$
$$\frac{\mathrm{d}W}{\mathrm{d}t} = \phi V$$

(this is the limit of the Fitzhugh-Nagumo model when $a = b = I = 0$). We can take a time derivative of the first equation to eliminate W:

$$\frac{\mathrm{d}^2V}{\mathrm{d}t^2} + (V^2 - 1)\frac{\mathrm{d}V}{\mathrm{d}t} + \phi V = 0$$

which is just an oscillator with a nonlinear damping term, $V^2 - 1$. We will choose (for simplicity) $\phi \ll 1$.

Let's go back to the coupled first-order system. If $\phi \ll 1$, W is a "slow" variable compared to V. The first thing we can do to study this system is to figure out the fixed points, where $V' = 0$ and $W' = 0$. This implies

$$V - V^3/3 = W$$

or

$$\phi V = 0$$

Note that in nonlinear dynamics, these are called "nullclines". The fixed point is $V = 0$, $W = 0$. We want to test if this is a stable fixed point. If we linearize the system, we get

$$\frac{\mathrm{d}V}{\mathrm{d}t} \approx V - W$$

so

$$\frac{\mathrm{d}^2V}{\mathrm{d}t^2} \approx \frac{\mathrm{d}V}{\mathrm{d}t} - \phi V$$

This is an unstable oscillator because the damping term is negative. Therefore, this fixed point is unstable. If we look at numerical solutions, we can see that V has oscillatory behavior (W does too) but it is not uniform. There is a fast increase to the top of each peak and a slower falloff.

In the Fitzhugh-Nagumo model, the fixed point is no longer $V = W = 0$, and the $V = 0$ nullcline becomes a sloped line. It can further be shown that this new fixed point is no longer unstable. Fixed points happen wherever the nullclines cross, so there can be up to three fixed points (the middle one will always be unstable while the others will be stable).

The behavior of this model is very similar to that of an action potential. Changing the value of I changes the point at which voltages will allow for the system to travel around the oscillatory phase space.

Neurons contain both an analog portion, the dendrites, which build up action potentials. Once these potentials pass a threshold, the signal moves along the axon in a more digital manner, where the amplitudes don't matter, just the existence or absence of a signal.

Chapter 11

Pattern Formation

Lecture 21: Pattern Formation I
Friday, April 30, 2021

11.1 Morphogen Gradients

How do we encode positional information in a group of cells? Consider fly embryos. How do some cells know to become the head and others become the wings, etc? The French Flag Model (due to the distribution of morphogens resembling a tricolor flag) proposed by Lewis Wolpert posits that morphogens in the embryo have a spatial gradient, and at certain threshold values, different cell behaviors will develop.

Suppose our embryo has an oval shape with the long axis called the A-P axis (anterior/posterior) representing the head to tail length. Bicoid morphogens are more present at the anterior side and form a gradient which diminishes towards the posterior side. A simple model of this would be

$$\frac{\partial[B]}{\partial t} = D\frac{\partial^2[B]}{\partial x^2} - \frac{[B]}{\tau}$$

which is just diffusion with some decay parameter with a timescale τ. We need some initial conditions, like

$$\left.\frac{\partial[B]}{\partial x}\right|_{x=-L,L} = 0$$

and

$$[B](x, t=0) = \begin{cases} B_0 & x = 0 \\ 0 & x \neq 0 \end{cases}$$

At steady state, you get an equation that looks like

$$D\tau\frac{\partial^2[B]}{\partial x^2} = [B]$$

which has solutions

$$[B] = B_0 e^{-x/\lambda}$$

where $\lambda = \sqrt{D\tau}$ is the length scale of the decay. Experimentally, we can see that the length scale λ increases linearly with the length of the embryo. This is unexpected, since D and τ shouldn't depend on the size of the system, they are just molecular properties. To understand this, let's look at a discrete, one-dimensional model. Some sites are cytoplasm sites, which have no morphogen, and others are nucleus sites which do. We can turn the partial differential equation into a difference equation to numerically solve:

$$[B](x, t+\Delta t) = [B](x,t) + \Delta t\left(\frac{D}{\Delta x^2}\left\{[B](x+\Delta x, t) - 2[B](x,t) + [B](x-\Delta x, t)\right\} - \frac{1}{\tau}[B](x,t)\right)$$

We assume that $\tau^{-1} = 0$ in the cytoplasm and $\tau^{-1} \neq 0$ in the nucleus. We can model this by saying

$$\frac{1}{\tau_{\text{eff}}} = \frac{N_{\text{nuc}}\nu}{V}\frac{1}{\tau}$$

where N_{nuc} is the number of nuclei, ν is the volume of each nucleus, and V is the volume of the cell. Then

$$\lambda = \sqrt{D\tau_{\text{eff}}} = \sqrt{\frac{D\tau V}{N_{\text{nuc}}\nu}}$$

We can write

$$V = 2\pi RLt = \pi\alpha L^2 t$$

where t is the thickness of the embryo shell and $\alpha = 2RL$ is an aspect ratio, which organisms tend to maintain, even across similar species. This tells us that λ is related to α due to the distribution of nuclei sites, which explains the scale dependence:

$$\lambda = \sqrt{D\tau\frac{\pi\alpha t}{N_{\text{nuc}}\nu}}L$$

11.2 Turing Patterns

Alan Turing gave a model which generalizes pattern formation from diffusion:

$$\partial_t u = D\partial_x^2 u + R(u)$$

One component equations like this cannot result in periodic patterns, only gradients. We need two component models to get more interesting patterns.

11.2.1 Activator-Inhibitor Models

Suppose chemical X produces itself and produces a chemical Y which inhibits production of X and itself. For example,

$$\frac{\mathrm{d}X}{\mathrm{d}t} = 5X - 6Y + 1$$
$$\frac{\mathrm{d}Y}{\mathrm{d}t} = 6X - 7Y + 1$$

At steady state, $\frac{\mathrm{d}X}{\mathrm{d}t} = \frac{\mathrm{d}Y}{\mathrm{d}t} = 0$, we have a fixed point at $X = Y = 1$. If we examine small perturbations away from this fixed point,

$$X = 1 + \varepsilon_x \qquad Y = 1 + \varepsilon_y$$

then

$$\frac{\mathrm{d}\varepsilon_x}{\mathrm{d}t} = 5\varepsilon_x - 6\varepsilon_y$$
$$\frac{\mathrm{d}\varepsilon_y}{\mathrm{d}t} = 6\varepsilon_x - 7\varepsilon_y$$

which we can write in a matrix form as

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix}\varepsilon_x \\ \varepsilon_y\end{pmatrix} = \begin{pmatrix}5 & -6 \\ 6 & -7\end{pmatrix}\begin{pmatrix}\varepsilon_x \\ \varepsilon_y\end{pmatrix}$$

We can get the solutions as

$$\varepsilon_x(t) = \varepsilon_x^0 e^{\lambda t} \qquad \varepsilon_y(t) = \varepsilon_y^0 e^{\lambda t}$$

where λ are the eigenvalues of the matrix:

$$\begin{vmatrix}5-\lambda & -6 \\ 6 & -7-\lambda\end{vmatrix} = 0 \implies \lambda^2 + 2\lambda + 1 = 0 \implies \lambda = -1$$

so the steady-state is always stable to perturbations.

What happens when we couple this kind of reaction to diffusion? Consider two cells, cell 1 and cell 2:

$$\begin{aligned}
\frac{\mathrm{d}X_1}{\mathrm{d}t} &= 5X_1 - 6Y_1 + 1 + D_X(X_2 - X_1) \\
\frac{\mathrm{d}Y_1}{\mathrm{d}t} &= 6X_1 - 7Y_1 + 1 + D_Y(Y_2 - Y_1) \\
\frac{\mathrm{d}X_2}{\mathrm{d}t} &= 5X_2 - 6Y_2 + 1 + D_X(X_1 - X_2) \\
\frac{\mathrm{d}Y_2}{\mathrm{d}t} &= 6X_2 - 7Y_2 + 1 + D_Y(Y_1 - Y_2)
\end{aligned}$$

In more cells, we could imagine

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = 5X_i - 6Y_i + 1 + D_X\left(X_{i+1} + X_{i-1} - 2X_i\right)/(2a^2)$$

We get the two-cell version by imagining a periodic boundary condition on the cells, since we technically need more than two cells to model the second derivative in the diffusion equation. What will happen if the rate of diffusion is very different between the two molecular species? Suppose $D_Y \gg D_X$. If we have a small perturbation in the concentration of X, it will begin to produce more X and also some Y. However, Y will diffuse away faster, so it will eat away at parts of the X distribution which haven't actually been perturbed yet. This will give a "W" shaped concentration of X, and these sorts of patterns can grow more complicated for different kinds of interplay between molecular species.

Lecture 22: Pattern Formation II

Wednesday, May 05, 2021

We can add small perturbations to our activator-inhibitor system:

$$\begin{aligned}
X_i &= 1 + x_i \\
Y_i &= 1 + y_i
\end{aligned}$$

since $X = Y = 1$ is the steady-state solution. Doing this results in a matrix form for the linearized system, and the solutions are given by exponentials of eigenvalues of the matrix, like $x_i(t) = x_{i,0}e^{\lambda t}$:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} x_1 \\ y_1 \\ x_2 \\ y_2 \end{pmatrix} = \begin{pmatrix} 5 - D_X & -6 & D_X & 0 \\ 6 & -7 - D_Y & 0 & D_Y \\ D_X & 0 & 5 - D_X & -6 \\ 0 & D_Y & 6 & -7 - D_Y \end{pmatrix}\begin{pmatrix} x_1 \\ y_1 \\ x_2 \\ y_2 \end{pmatrix}$$

with solutions

$$\begin{aligned}
x_i(t) &= x_{i,0}e^{\lambda t} \\
y_i(t) &= y_{i,0}e^{\lambda t}
\end{aligned}$$

Only the largest eigenvalue is really important here, since it will determine the behavior over large timescales. Real eigenvalues will correspond to exponentially growing or decaying solutions, while imaginary eigenvalues will have oscillatory behavior.

Consider an activator-inhibitor system in a linear array of cells labeled by the index r. We can model

$$\begin{aligned}
\frac{\mathrm{d}X_r}{\mathrm{d}t} &= f(X_r, Y_r) \\
\frac{\mathrm{d}Y_r}{\mathrm{d}t} &= g(X_r, Y_r)
\end{aligned}$$

where f and g are some functions which model the behavior of the chemical reactions. We can then add diffusion in a discrete form:

$$\frac{\mathrm{d}X_r}{\mathrm{d}t} = f(X_r, Y_r) + D_X(X_{r+1} + X_{r-1} - 2X_r)$$
$$\frac{\mathrm{d}Y_r}{\mathrm{d}t} = g(X_r, Y_r) + D_Y(Y_{r+1} + Y_{r-1} - 2Y_r)$$

Assume some steady-state solution $(X_r, Y_r) = (h, k)$ which satisfies $f(h, k) = g(h, k) = 0$. Next, consider small perturbations about that steady state:

$$(X_r, Y_r) = (h + x_r, k + y_r)$$

$$\frac{\mathrm{d}x_r}{\mathrm{d}t} = \cancelto{0}{f(h,k)} + A_1 x_r + B_1 y_r + D_X(x_{r+1} + x_{r-1} - 2x_r)$$
$$\frac{\mathrm{d}y_r}{\mathrm{d}t} = \cancelto{0}{g(h,k)} + A_2 x_r + B_2 y_r + D_Y(y_{r+1} + y_{r-1} - 2y_r)$$

where

$$A_1 = \left.\frac{\partial f}{\partial X_r}\right|_{(h,k)} \qquad B_1 = \left.\frac{\partial f}{\partial Y_r}\right|_{(h,k)}$$
$$A_2 = \left.\frac{\partial g}{\partial X_r}\right|_{(h,k)} \qquad B_2 = \left.\frac{\partial g}{\partial Y_r}\right|_{(h,k)}$$

We'll assume an ansatz of

$$x_r(t) = x(t)e^{\imath(2\pi r/\lambda)}$$
$$y_r(t) = y(t)e^{\imath(2\pi r/\lambda)}$$

Plugging this in, we get

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \left[A_1 + D_X\left(e^{\imath(2\pi/\lambda)} + e^{-\imath(2\pi/\lambda)} - 2\right)\right]x + B_1 y$$
$$\frac{\mathrm{d}y}{\mathrm{d}t} = \left[B_2 + D_Y\left(e^{\imath(2\pi/\lambda)} + e^{-\imath(2\pi/\lambda)} - 2\right)\right]y + A_2 x$$

We can make an approximation:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \left[A_1 - D_X\left(\frac{2\pi}{\lambda}\right)^2\right]x + B_1 y \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = \left[B_2 - D_Y\left(\frac{2\pi}{\lambda}\right)^2\right]y + A_2 x$$

and write it in matrix form:

$$\mathcal{R} = \begin{pmatrix} A_1 - D_X(2\pi/\lambda)^2 & B_1 \\ A_2 & B_2 - D_Y(2\pi/\lambda)^2 \end{pmatrix}$$

so

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} x \\ y \end{pmatrix} = \mathcal{R}\begin{pmatrix} x \\ y \end{pmatrix}$$

Letting $q = \frac{2\pi}{\lambda}$, we can write the characteristic polynomial:

$$\det(\mathcal{R} - \sigma I) = 0$$

where solutions should have the form

$$x(t) = x_0 e^{\sigma t} \qquad y(t) = y_0 e^{\sigma t}$$

For any 2-by-2 matrix, we can use

$$\sigma^2 - (\operatorname{Tr}\mathcal{R})\sigma + \det\mathcal{R} = 0$$

which has the solution

$$\sigma = \frac{1}{2}\operatorname{Tr}\mathcal{R} \pm \frac{1}{2}\sqrt{(\operatorname{Tr}\mathcal{R})^2 - 4\det\mathcal{R}}$$

Then we can work out a condition on the stability of the system. We require the real part of the eigenvalue to be negative for the system to be stable (otherwise small perturbations will grow unchecked). For $\mathrm{Re}[\sigma] < 0$ for both eigenvalues, we must have $\det\mathcal{R} > 0$ and $\operatorname{Tr}\mathcal{R} < 0$.

$$\begin{aligned}\operatorname{Tr}\mathcal{R} &= A_1 + B_2 - (D_X + D_Y)q^2 < 0\\ \det\mathcal{R} &= (A_1 - D_X q^2)(B_2 - D_Y q^2) - B_1 A_2 > 0\end{aligned}$$

First, let's consider $D_X = D_Y = 0$. Then for stability,

$$A_1 + B_2 < 0 \quad \text{and} \quad A_2 B_2 - B_1 A_2 > 0$$

must both be true.

$\operatorname{Tr}\mathcal{R} < 0$ is always true in the presence of diffusion. Instability is still possible when $\det\mathcal{R} < 0$:

$$\det\mathcal{R} = (A_1 B_2 - B_1 A_2) + D_X D_Y q^4 - (D_X B_2 + D_Y A_1)q^2$$

The first and second terms are positive, so the third term must be large and negative for the system to be unstable: $D_X B_2 + D_Y A_1 > 0$.

From these conditions, one possible scenario that is unstable is where $A_1 > 0$ and $B_2 < 0$. This is the activator-inhibitor system. Note that A_1 is the rate at which X produces X, A_2 is the rate at which X produces Y, and so on.

We can then see $D_Y > \frac{(-B_2)D_X}{A_1} \implies D_Y \gg D_X$ for $-B_2 > A_1$.

If we look back at the determinant, we can see that the dependence on q will cause a certain region to have a negative determinant. At small q, the first term dominates, and at large q, the q^4 term dominates.