1. **Treadmilling Actin**: Actin filaments are long, asymmetric, polymers involved in a variety of cellular functions. In some cases the filaments are in a dynamic state in which monomers are removed from one end and added to the other. (The two ends are called minus and plus respectively, and this process is known as treadmilling.)

(a) Assume that monomers are added to the plus-end at rate $a$, and removed from the minus end at rate $b$. Write down the equations governing the rate of change of the probabilities $\{p(\ell, t)\}$, for finding a filament of length $\ell$ at time $t$. Note that $\ell = 1, 2, 3, \cdots$, and that the equation of $p(1, t)$ is different from the rest.

(b) It is possible to have a dynamic steady state with probabilities $p^*(\ell)$ that do not change with time. Find the (properly normalized) distribution $p^*(\ell)$ in such a case.

(c) What is the condition for the existence of a time independent steady state, and the mean length of the filament in such a case?

(d) For $a > b$, what is the average length of a filament at time $t$, starting from individual monomers at time $t = 0$? Calculate the fluctuations (variance) in length, and write down an approximate probability distribution $p(\ell, t)$ with the correct first and second moment.

2. **Growing/shrinking microtubules**: Consider a slightly generalized model of microtubule growth and shrinkage [M. Dogterom and S. Leibler, Phys. Rev. Lett. 70, 1347 (1993)], described by the equations

$$\partial_t p_+(x, t) = -f_-p_+ + f_+p_+ - \partial_x (v_+p_+) + d \partial_x^2 p_+$$

$$\partial_t p_-(x, t) = +f_-p_+ - f_+p_- + \partial_x (v_-p_-) + d \partial_x^2 p_-$$

(a) Such coupled linear equations are usually solved by first Fourier transforming to $\tilde{p}(k, \omega) = \int dx dt e^{i(kx - \omega t)} p(x, t)$. Find the dispersion relations for allowed $\omega(k)$.

(b) Expand the ‘slowly varying’ mode as $\omega(k) = \nu k + iDk^2 + O(k^3)$, and hence obtain the dependence of the drift velocity and diffusion coefficient of the microtubule length on the parameters describing the growing and shrinking states.

(c) Typical values of parameters for microtubules growing in a tubulin solution of concentration $c \approx 10\mu$M are $v_+ \approx 2 \mu$m/min, $v_- \approx 20 \mu$m/min, $f_{+-} \approx 0.004s^{-1}$, $f_{-+} \approx 0.05s^{-1}$. Use these parameters (along with $d = 0$) to estimate a time scale $\tau$ beyond which diffusion effects are less important than the average drift. (Hence microtubules that have survived to a time $\tau$ are unlikely to be completely eliminated by catastrophes.)

(d) Let us assume a microscopic model in which growth occurs by addition of discrete molecules of size $a$ at rates $r_+$ to the growing state, and detachment at rate $r_-$ shrinking state. Write the corresponding Master equations and construct their continuum limit.
3. **Internal states:** Consider a molecular motor modeled by an asymmetric hopping model with \( m \) internal states. Assume equal forward rates and no backward rates; i.e. \( u_i = u \) and \( w_i = 0 \) for \( i = 1, \cdots, m \). Visscher et al., in Nature 400, 184 (1999), use such a model to estimate the number of (rate limiting) internal states from observations of motion of kinesin on microtubules. In particular, they measure a ‘randomness parameter’ defined by

\[
r \equiv \lim_{t \to \infty} \frac{\langle x^2(t) \rangle - \langle x(t) \rangle^2}{d \langle x(t) \rangle},
\]

where \( x(t) \) is the displacement of the motor after a time \( t \), and \( d \) is the step size of kinesin along the microtubule.

(a) Relate \( r \) defined above to the parameters \( v \) and \( D \) of a drift–diffusion equation.

(b) Obtain \( v \) and \( D \) in terms of the parameters \( u, d, \) and \( m \) of the model.

(c) The experimental data (Fig. 4b of the above reference) indicate \( r \approx 1/2 \) at small force, and \( r \approx 1 \) at large force. What does this imply about the internal states of the motor?

4. **Two state motor:** Let us examine the two-state motor (with step length \( d \)) in more detail. At each site the motor can be in one of two states, indicated by \( n \) or \( n' \) for the \( n^{th} \) site. The forward transition rates are \( u_1 \) (for internal state change from \( n \) to \( n' \)) and \( u_2 \) (for hopping from \( n' \) to \( n + 1 \)), and the corresponding backward transition rates are \( w_1 \) and \( w_2 \).

(a) Write down the master equations governing the time evolution of the probabilities \( p(n, t) \) and \( p(n', t) \).

(b) Use Fourier transforms to obtain the dispersion relation \( \omega(k) \) for the slowly varying mode.

(c) Calculate the drift velocity \( v \), the diffusion coefficient \( D \), and the Einstein force \( f_E \), as a function of \( u_1, u_2, w_1, \) and \( w_2 \).

(d) Assume that under an external load \( F \), the forward hopping rate changes as \( u_2 \to u_2 \exp\left(-\frac{Fd}{k_BT}\right) \), while all the other rates remain unchanged. Calculate \( v(f) \), and obtain the stalling force \( f_s \).

(e) Direct observation of kinesin motors moving along microtubules (by Block’s group at Stanford using in vitro solution of [ATP]=2mM) indicate \( v \approx 670\text{nm/s}, D \approx 1400\text{nm}^2/\text{s}, \) and \( f_s \approx 5\text{pN}. \) Data from chemical analysis suggest that forward state changes occur at rates of \( u_1 \sim 2 \times 10^3\text{s}^{-1} \) and \( u_2 \sim 50\text{s}^{-1} \). The backward rates are harder to measure- assume values of \( w_1 \sim u_1/100 \) and \( w_2 \sim u_2/100 \). How consistent are these results with a two state model?

5. **Target site location:** Complex transcription machinery in cells is regulated by a set of protein molecules—transcription factors (TFs) whose functions can be described as:

- **Receiving a control signal**—This can be the binding or unbinding of a ligand, resulting in initiation or shutting down of the transcription machinery.
- **Finding a specific site on the DNA and binding to it**.
(a) Suppose the protein has to locate a unique binding site on a genome of length \( M \). It may do so by alternately diffusing in solution, and sliding along the DNA, as depicted in Fig. 1. Given a typical TF diameter of 10nm and cytoplasm dynamic viscosity of approximately 0.1 g s\(^{-1}\) cm\(^{-1}\), estimate \( D_{3d} \) for a TF in cytoplasm. (For 1D sliding, one can assume \( D_{1d} \approx 0.1 \times D_{3d} \).)

(b) Consider the mechanism of search by sliding and 3D diffusion discussed on the lecture. In addition to these processes, a protein can make occasional hops, i.e. once it dissociates from DNA, it associates again at the same place. Calculate the total search time, assuming that upon dissociation a protein will make a hop with a probability \( p \approx 0.9 \).

(c) Given the 1D diffusion coefficient \( D_{1d} \), obtain the optimal target location time \( t_{loc} \). The dissociation rate of the proteins from DNA is controlled by the nonspecific binding energy \( E_{ns} \). Estimate \( E_{ns} \) for the optimal target location time. Assume \( D_{1d} = 1 \mu m^2/sec \), \( \tau_{3d} = 10^{-3} sec \). Find the location time for \( M = 10^6 \) base-pairs.

6. (Optional) Chemotaxis: The motion of \textit{E. Coli} in a solution of nutrients consists of an alternating sequence of \textit{runs} and \textit{tumbles}. During a run the bacterium proceeds along a straight line for a time \( t_r \) with a velocity \( v \). It then tumbles for a time \( t_t \), after which it randomly chooses a new direction \( \hat{n} \) to run along. Let us assume that the times \( t_r \) and \( t_t \) are independently selected from probability distributions

\[
p_r(t_r) = \frac{4t_r}{\tau_r^2} \exp\left(-\frac{2t_r}{\tau_r}\right), \quad \text{and} \quad p_t(t_t) = \frac{4t_t}{\tau_t^2} \exp\left(-\frac{2t_t}{\tau_t}\right)
\]

(a) Assuming values of \( \tau_r \approx 2s, \tau_t \approx 0.2s \), and \( v \approx 30 \mu m/s \), calculate the diffusion coefficient \( D \) for the bacterium at long times.

(b) In the presence of a chemical gradient the run times become orientation dependent, and are longer when moving in a favorable direction. For preferred motion up the \( z \) axis, let us assume that the average run time depends on its orientation \( \hat{n} \) according to \( \tau_r(\hat{n}) = \tau_0 + g\hat{n} \cdot \hat{z} \). Calculate the average drift velocity at long times.