Drift, Diffusion, and Dynamic Instability

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 ℓ at time t. Note that $\ell = 1,\ 2,\ ,3,\cdots$, and that the equation of $p(1,t)$ is different from the rest.

- For $\ell > 1$ the rate of change of the probabilities is:

$$\frac{\partial p(\ell,t)}{\partial t} = a\ p(\ell-1,t) + b\ p(\ell+1,t) - (a+b)\ p(\ell,t).$$

For $\ell = 1$ a monomer cannot be destroyed or created from nothing:

$$\frac{\partial p(1,t)}{\partial t} = b\ p(2,t) - a\ p(1,t).$$

Note that the total probability $\sum_\ell p(\ell,t)$ does not change with time.

(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.

- We are looking for a solution of the form $p^*(\ell) = ck^\ell$. In steady state rate of change is zero:

$$\frac{\partial p^*(\ell)}{\partial t} = ck^\ell \left(\frac{a}{k} + bk - (a+b)\right) = 0 \qquad \Longrightarrow \qquad bk^2 - (a+b)k + a = 0$$

with solutions $k = 1$ and $k = a/b$. $k = 1$ is not a good solution because distribution cannot be normalized. The only good solution is $k = a/b$, when $a < b$. If $a > b$ then we have exponentially increasing distribution that cannot be normalized. It is easy to verify that this ansatz also satisfy rate of change for $\ell = 1$. Normalization:

$$1 = \sum_{\ell=1}^{\infty} c\left(\frac{a}{b}\right)^\ell = c\frac{a/b}{1-a/b} \qquad \Longrightarrow \qquad c = \frac{b-a}{a}$$

Properly normalized distribution is thus:

$$p^*(\ell) = \frac{(b-a)}{a}\ \left(\frac{a}{b}\right)^\ell$$

(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?

• As mentioned in the previous item, the condition for the existence of a time independent steady state is $a < b$. To calculate the mean length we introduce the function $f(x)$:

$$\begin{aligned} f(x) &= \sum_{\ell=0}^{\infty} \left(\frac{a}{b}\right)^{x\ell} = \frac{1}{1-(a/b)^x} \\ f'(x) &= \sum_{\ell=0}^{\infty} \ell \ \ln(a/b) \left(\frac{a}{b}\right)^{x\ell} = \frac{(a/b)^x \ln(a/b)}{\left(1-(a/b)^x\right)^2} \end{aligned}$$

Note that excluding the term $\ell = 0$ from summation does not change the $f'(x)$.

$$\langle \ell \rangle = \sum_{l=1}^{\infty} \ell \ p^*(l) = \frac{(b-a)}{a} \ \frac{f'(1)}{\ln(a/b)} = \frac{1}{1-a/b} = \frac{b}{b-a}$$

(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.

• At $t = 0$ average length is $\langle \ell(t=0) \rangle = 1$ and variance is $\sigma^2(t=0) = 0$. First we derive the average length:

$$\begin{aligned} \frac{\partial \langle \ell(t) \rangle}{\partial t} &= \sum_{\ell=1}^{\infty} \ell \frac{\partial p(\ell,t)}{\partial t} \\ \frac{\partial \langle \ell(t) \rangle}{\partial t} &= \sum_{\ell=1}^{\infty} \ell \Big(a p(\ell-1,t) + b p(\ell+1,t) - (a+b) p(\ell,t) \Big) \\ \frac{\partial \langle \ell(t) \rangle}{\partial t} &= \sum_{\ell=1}^{\infty} \Big(a(\ell+1) + b(\ell-1) - (a+b)\ell \Big) p(\ell,t) \\ \frac{\partial \langle \ell(t) \rangle}{\partial t} &= a \langle \ell(t) \rangle + a + b \langle \ell(t) \rangle - b - (a+b) \langle \ell(t) \rangle = a - b \\ \langle \ell(t) \rangle &= (a-b)t + 1 \end{aligned}$$

In the same way we can calculate variance:

$$\begin{aligned} \sigma^2(t) &= \sum_{\ell=1}^{\infty} \ell^2 p(\ell,t) - \langle \ell(t) \rangle^2 \\ \frac{\partial \sigma^2(t)}{\partial t} &= \sum_{\ell=1}^{\infty} \ell^2 \Big(a p(\ell-1,t) + b p(\ell+1,t) - (a+b) p(\ell,t) \Big) - 2(a-b) \langle \ell(t) \rangle \\ \frac{\partial \sigma^2(t)}{\partial t} &= \sum_{\ell=1}^{\infty} \Big(a(\ell+1)^2 + b(\ell-1)^2 - (a+b)\ell^2 \Big) p(\ell,t) - 2(a-b) \langle \ell(t) \rangle \\ \frac{\partial \sigma^2(t)}{\partial t} &= a + b \\ \sigma^2(t) &= (a+b)t \end{aligned}$$

An approximate probability distribution with correct first and second moment is thus:

$$p(\ell,t) = \frac{1}{\sqrt{2\pi(a+b)t}} \exp\left[-\frac{(\ell-(a-b)t-1)^2}{2(a+b)t}\right]$$

The last result can be obtained also in the continuum limit of the Master equation:

$$\begin{aligned}
\frac{\partial p(\ell,t)}{\partial t} &= a\ p(\ell-1,t) + b\ p(\ell+1,t) - (a+b)\ p(\ell,t) \\
\frac{\partial p(\ell,t)}{\partial t} &= a\left[p(\ell,t) - \frac{\partial p(\ell,t)}{\partial \ell} + \frac{1}{2}\frac{\partial^2 p(\ell,t)}{\partial \ell^2}\right] + b\left[p(\ell,t) + \frac{\partial p(\ell,t)}{\partial \ell} + \frac{1}{2}\frac{\partial^2 p(\ell,t)}{\partial \ell^2}\right] - (a+b)\ p(\ell,t) \\
\frac{\partial p(\ell,t)}{\partial t} &= -v\frac{\partial p(\ell,t)}{\partial \ell} + D\frac{\partial^2 p(\ell,t)}{\partial \ell^2},
\end{aligned}$$

with $v = a - b$ and $D = (a+b)/2$. Average length and variance are thus:

$$\begin{aligned}
\langle \ell(t) \rangle &= vt + 1 = (a-b)t + 1 \\
\sigma^2(t) &= 2Dt = (a+b)t.
\end{aligned}$$

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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

$$\begin{aligned}
\partial_t p_+(x,t) &= -f_{+-}p_+ + f_{-+}p_- - \partial_x\left(v_+ p_+\right) + d\ \partial_x^2 p_+ \\
\partial_t p_-(x,t) &= +f_{+-}p_+ - f_{-+}p_- + \partial_x\left(v_- p_-\right) + d\ \partial_x^2 p_-
\end{aligned}$$

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

• First we invert the Fourier transform $p(x,t) = \int dk\ d\omega\ e^{-i(kx-\omega t)} p(k,w)$. Inserting this into equations above we obtain matrix equation:

$$i\omega \begin{pmatrix} \tilde{p}_+ \\ \tilde{p}_i \end{pmatrix} = \begin{pmatrix} -f_{+-} + ikv_+ - dk^2 & f_{-+} \\ f_{+-} & -f_{-+} - ikv_- - dk^2 \end{pmatrix} \begin{pmatrix} \tilde{p}_+ \\ \tilde{p}_i \end{pmatrix}$$

Dispersion relation is obtained from eigenvalues:

$$\begin{aligned}
\omega(k) &= \frac{1}{2}\Big(i(f_{+-}+f_{-+}) + k(v_+ - v_-) + 2idk^2 \\
&\quad \pm i\sqrt{(f_{+-}+f_{-+})^2 + 2ik(f_{-+}-f_{+-})(v_+ + v_-) - k^2(v_+ + v_-)^2}\Big)
\end{aligned}$$

We must choose the negative sign, because $\omega(k=0) = 0$.

(b) Expand the 'slowly varying' mode as $\omega(k) = vk + iDk^2 + \mathcal{O}(k^3)$, 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.

- Taylor expansion of dispersion relation

$$\omega(k) = k\frac{f_{-+}v_+ - f_{+-}v_-}{f_{-+}+f_{+-}} + ik^2\left(d + \frac{f_{-+}f_{+-}(v_- + v_+)^2}{(f_{-+}+f_{+-})^3}\right) + \mathcal{O}(k^3),$$

gives us velocity and diffusion coefficient:

$$\begin{aligned} v &= \frac{f_{-+}v_+ - f_{+-}v_-}{f_{-+}+f_{+-}}, \\ D &= d + \frac{f_{-+}f_{+-}(v_- + v_+)^2}{(f_{-+}+f_{+-})^3}. \end{aligned}$$

Note that the sign in front of D in dispersion relation ($\omega(k) = vk \pm iDk^2$), depends on the sign definition of the Fourier transform ($\tilde{p}(k,\omega) = \int dxdte^{\pm i(kx-\omega t)}p(x,t)$).

(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, $f_{+-} \approx 0.004\text{s}^{-1}$, $f_{-+} \approx 0.05\text{s}^{-1}$. Use these parameters (along with $d = 0$) to estimate a time scale τ beyond which diffusion effects are less important than the average drift. (Hence microtubules that have survived to a time τ are unlikely to be completely eliminated by catastrophes.)

- Plugging in the parameter values in results from previous parts gives velocity $v = 0.37\mu$m/min and diffusion coefficient $D = 10.2\mu\text{m}^2$/min. Using this coefficients we calculate typical timescale τ of the system

$$\tau = \frac{D}{v^2} = 150\text{min} = 2.5\text{hr}.$$

This time scale sets the persistence of surviving filaments; beyond τ, the mean drift dominates stochastic shrinkage.

(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.

- Master equation:

$$\begin{aligned} \partial_t p_+(x,t) &= -f_{+-}p_+(x,t) + f_{-+}p_-(x,t) + r_+p_+(x-a,t) - r_+p_+(x,t) \\ \partial_t p_-(x,t) &= +f_{+-}p_+(x,t) - f_{-+}p_-(x,t) + r_-p_-(x+a,t) - r_-p_-(x,t) \end{aligned}$$

Continuum limit is obtained by Taylor expansion of terms $p_\pm(x \mp a, t)$:

$$\begin{aligned} \partial_t p_+(x,t) &= -f_{+-}p_+(x,t) + f_{-+}p_-(x,t) - \partial_x\left(v_+p_+\right) + d_+\,\partial_x^2 p_+ \\ \partial_t p_-(x,t) &= +f_{+-}p_+(x,t) - f_{-+}p_-(x,t) + \partial_x\left(v_-p_-\right) + d_-\,\partial_x^2 p_-, \end{aligned}$$

where $v_\pm = ar_\pm$ and $d_\pm = a^2r_\pm/2$. Unlike in the previous parts in this microscopic model diffusion constants $d_\pm$ are different.

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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. r measures how regular or noisy the stepping is; $r = 1$ for a pure Poisson process, smaller r indicates internal substeps.

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

• For drift equation $\partial_t p(x,t) = -v\partial_x p(x,t) + D\ \partial_x^2\ p(x,t)$ we know that:

$$\begin{aligned} \partial_t \langle x(t)\rangle &= v, \\ \partial_t \left\langle x^2(t)\right\rangle_c &= 2D. \end{aligned}$$

Thus the randomness is:

$$r = \frac{2D}{dv}.$$

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

• Let us first consider the case $m = 1$. This is equivalent to problem 1 (d) with parameters $a = u$ and $b = 0$ and we find $v = du$ and $D = d^2u/2$. Introducing m internal variables is equivalent to rescaling the size of the step $d \to d/m$ in continuum limit of drift-diffusion equation.

$$v = \frac{ud}{m}, \qquad D = \frac{ud^2}{2m^2}, \qquad r = \frac{2D}{dv} = \frac{1}{m}.$$

(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?

• For small force there are two ($m = 2$) internal states (ADP + ATP processes). At large forces ATP process is dropped and there is only one ($m = 1$) internal state (ADP process).

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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 $p(n',t)$.

- Master equation:

$$\begin{aligned}\frac{\partial p(n,t)}{\partial t} &= -(u_1+w_2)p(n,t) + w_1 p(n',t) + u_2 p((n-1)',t)\\ \frac{\partial p(n',t)}{\partial t} &= +w_2 p(n+1,t) + u_1 p(n,t) - (u_2+w_1)p(n',t)\end{aligned}$$

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

- Using the same Fourier transform as in problem 2 and expanding probabilities at $n \pm 1$ into Taylor series to the second order (because we are interested in the solutions up to the second order in k), we get matrix equation:

$$i\omega \begin{pmatrix} \tilde{p} \\ \tilde{p}' \end{pmatrix} = \begin{pmatrix} -u_1 - w_2 & w_1 + u_2(1 + ikd - k^2d^2/2) \\ u_1 + w_2(1 - ikd + k^2d^2/2) & -u_2 - w_1 \end{pmatrix} \begin{pmatrix} \tilde{p} \\ \tilde{p}' \end{pmatrix}$$

Dispersion relation is obtained from eigenvalues:

$$\begin{aligned}\omega(k) &= \frac{i}{2}\Big(u_1+u_2+w_1+w_2 \\ &\quad \pm\sqrt{(u_1+u_2+w_1+w_2)^2 + 4ikd(u_1u_2 - w_1w_2) - 2k^2d^2(u_1u_2+w_1w_2) + k^4d^4u_2w_2}\Big)\end{aligned}$$

We have to choose the $-$ sign, to satisfy $\omega(k=0)=0$ condition.

(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.

- From Taylor series expansion of $\omega(k) = vk + iDk^2$ we find velocity v and diffusion coefficient D:

$$\begin{aligned} v &= d\frac{(u_1u_2 - w_1w_2)}{(u_1+u_2+w_1+w_2)} \\ D &= d^2\left(\frac{(u_1u_2+w_1w_2)}{2(u_1+u_2+w_1+w_2)} - \frac{(u_1u_2-w_1w_2)^2}{(u_1+u_2+w_1+w_2)^3}\right) \\ f_E &= \frac{k_BTv}{D} = \frac{k_BT}{d\left(\frac{(u_1u_2+w_1w_2)}{2(u_1u_2-w_1w_2)} - \frac{(u_1u_2-w_1w_2)}{(u_1+u_2+w_1+w_2)^2}\right)}\end{aligned}$$

(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.

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$$v(f) = d\frac{\left(u_1u_2\exp\left(-\frac{fd}{k_BT}\right) - w_1w_2\right)}{\left(u_1 + u_2\exp\left(-\frac{fd}{k_BT}\right) + w_1 + w_2\right)}$$

Stalling force is defined as $v(f_s) = 0$:

$$f_s = \frac{k_B T}{d} \ln\left(\frac{u_1 u_2}{w_1 w_2}\right)$$

(e) Direct observation of kinesin motors moving along microtubules (by Block's group at Stanford using in vitro solution of [ATP]=2mM) indicate $v \approx 670$nm/s, $D \approx 1400\text{nm}^2/\text{s}$, and $f_s \approx 5$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?

• From equations for v, D and f_s at room temperature we can calculate step size d and compare the results:

$$\begin{aligned} v &\Rightarrow d \sim 14\text{nm} \\ D &\Rightarrow d \sim 8\text{nm} \\ f_s &\Rightarrow d \sim 8\text{nm} \end{aligned}$$

Because our parameters are not very precise we can conclude that these results are consistent with two state model even though one of the values is off by factor ≈ 2.

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5. (Optional) *Entropy increase* is related to irreversibility. Consider a motor (or any other random walker), whose stochastic motion at long times can be described by a drift velocity v and diffusion constant D.

(a) What is the probability that the walker starting at the origin arrives to a position x after time t; and what is the probability of a reverse path from x to 0 in the same time?

• The forward and backward probabilities are simple gaussians, with mean vt and variance $2Dt$, and hence

$$p_{\text{forward}} = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-\frac{(x-vt)^2}{4Dt}\right] \quad \text{and} \quad p_{\text{backward}} = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-\frac{(-x-vt)^2}{4Dt}\right].$$

(b) The increase in entropy is quantitatively related to the ratio of forward and backward probabilities as $\Delta S = k_B \ln\left[p_{\text{forward}}/p_{\text{backward}}\right]$. Compute the entropy increase for the random walker described above.

• Using the expression for entropy change, and the computed probabilities, we find

$$\Delta S = k_B \ln\left[\frac{p_{\text{forward}}}{p_{\text{backward}}}\right] = k_B \ln\left[\frac{\exp\left[-\frac{(x-vt)^2}{4Dt}\right]}{\exp\left[-\frac{(x+vt)^2}{4Dt}\right]}\right] = k_B \frac{4xvt}{4Dt} = k_B \frac{vx}{D}.$$

(c) Assuming that the velocity and diffusion constant are related by the Einstein equation, how is the change in entropy related to work done by an external force F.

• In a dissipative system, the velocity and force are related by a mobility μ, such that $v = \mu F$. According to the Einstein relation, the mobility and diffusion constant are related by $D = \mu k_B T$; hence $v/D = F/(k_B T)$, and thus

$$\Delta S = \frac{Fx}{T} = \frac{W}{T},$$

where $W = Fx$ is the work done to move a distance x by the force F.

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6. (Optional) *Chemotaxis:* The motion of *E. Coli* in a solution of nutrients consists of an *alternating* sequence of *runs* and *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

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

(a) Assuming values of $\tau_r \approx 2$s, $\tau_t \approx 0.2$s, and $v \approx 30\mu$ms^{-1}, calculate the diffusion coefficient D for the bacterium at long times.

• Directions of runs are uniformly distributed, thus $\langle \vec{R}(t) \rangle = 0$, where $\vec{R}(t)$ presents relative displacement from origin after time t. After N runs and tumbles the average value of $\langle \vec{R}^2 \rangle = N \langle \ell^2 \rangle$ where $\langle \ell^2 \rangle$ is averaged square length of each run. For given distribution averaged square length of each run is:

$$\left\langle \ell^2 \right\rangle = v^2 \left\langle t_r^2 \right\rangle = \frac{3}{2} v^2 \tau_r^2$$

For a given distributions the average time spent for N runs and tumbles is $\langle T \rangle = N(\tau_r + \tau_t)$. For 3D random walk $\langle R^2 \rangle = 6Dt$, thus the diffusion coefficient is:

$$D = \frac{\langle \vec{R}^2 \rangle}{6\langle T \rangle} = \frac{3v^2\tau_r^2}{12(\tau_r + \tau_t)} = 410\mu\text{m}^2\text{s}^{-1},$$

(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.

• Because of the rotational symmetry around $\hat{z}$ axis the drift velocity is in the $\hat{z}$ direction. We need to calculate the average displacement along the $\hat{z}$ axis in each run:

$$\langle z \rangle = \frac{1}{2}\int_{-1}^{1} d(\cos\theta) v \cos\theta (\tau_0 + g\cos\theta) = \frac{vg}{3},$$

where we have already used the averaged time in each direction θ. The average time of run and tumble is:

$$\langle T \rangle = \tau_t + \frac{1}{2}\int_{-1}^{1} d(\cos\theta)(\tau_0 + g\cos\theta) = \tau_t + \tau_0$$

Finally average drift velocity along $\hat{z}$ is:

$$v_d = \frac{\langle z \rangle}{\langle T \rangle} = \frac{vg}{3(\tau_t + \tau_0)}$$

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