Modelling motor proteins with random walk in a ratchet potential switched on and off

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Praktisk informasjon

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Innleveringsformat: Jupyter Notebook (lever kun én fil).

Notebooken skal være kjørt ved innlevering. For å sjekke om den er kjørt kan dere laste ned den endelige notebooken. Dere skal referere til oppgavenummer (for eksempel **2b**) i besvarelsen. Oppgavene skal besvares i riktig rekkefølge. Det er ikke nødvendig å skrive introduksjon, metode osv. som man vanligvis skriver i en labrapport. Svar kun på det oppgavene spør om.

Alle plott skal forklares/diskuteres, og alle akser skal ha navn ("labels"). Koden deres skal være enkel å lese og forståelig med informative variabelnavn. Bruk gjerne kommentarer. Godt dokumentert og strukturert kode vil trekke besvarelsen i positiv retning. Kjøretiden på koden deres vil variere avhengig av hvordan dere løser oppgavene, men vil ikke påvirke endelig karakter utover at rask/lur/godt strukturert kode vil telle i positiv retning. Det er fint mulig å få full uttelling med tregere kode. Dere oppfordres til å bruke lavere numerisk nøyaktighet (f.eks. færre partikler, tidssteg osv.) når dere tester koden for å slippe å vente på at den produserer feil resultater.

Karakteren blir satt ut fra hvor riktige resultatene er og diskusjonen av resultatene. Generelt vil de siste oppgavene telle mer på karakteren enn de første oppgavene. Resultater som åpenbart er ufysiske vil ikke gi maksimal poengsum, men diskusjonen av resultatene vil kunne trekke besvarelsen i positiv retning. Hvis dere forstår at svarene deres er ufysiske vil dere få en høyere poengsum hvis dere forklarer hva som er feil og hvorfor det er feil, ettersom dette viser fysisk intuisjon og forståelse.

Denne øvingen er basert på Haakon Krogstads biofysikkprosjekt "Modelling motor proteins as particles diffusing in parallel potentials" fra 2020.

Introduction

Motor proteins are, in short terms, proteins which are able to turn chemical energy into mechanical energy. Take for instance myosin. Myosin gets energy from ATP molecules, and turns this energy into mechanical movement by dragging a thin filament parallel to the myofilament they are attached to. The collective action of many such myosin proteins is what we know as muscle contractions! See Fig. 1 for an illustration of this process.

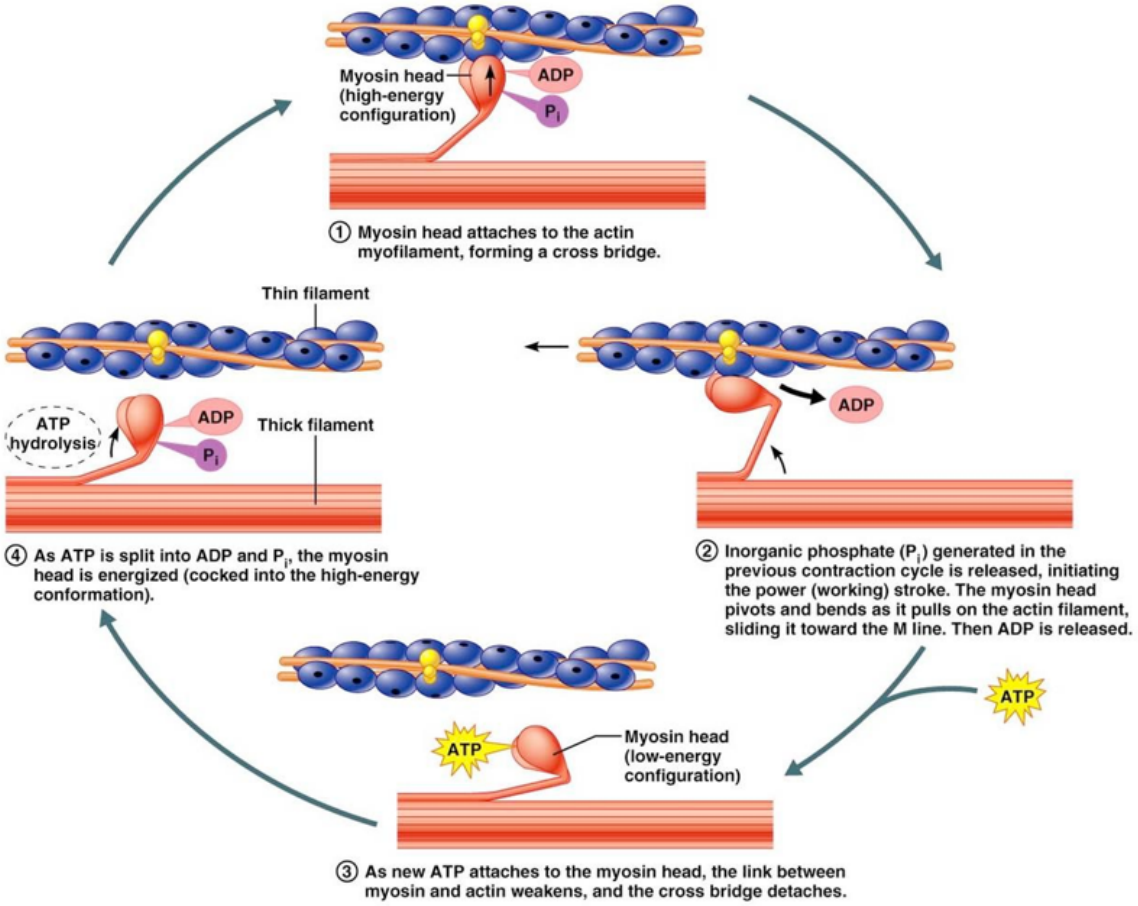

Figure 1: An illustration of myosin-ATPase, retrieved from here.

A common way to model such processes theoretically is to model the motor protein as particles moving in several, parallel and periodic potentials. Transitions between the potentials (or energy levels) are triggered by catching an ATP-molecule, or releasing ADP + P. If the periodic potentials are symmetric, one can easily form an argument for why the net particle current in this case must average to zero. The key to motor protein transport is therefore the (asymmetric) shape of the periodic potentials.

In this exercise, we will model the motor protein transport as a current of particles moving in a 1-dimensional, two-level potential landscape, using random walk simulations. Before digging into the full-scale problem, we will start with some theory and warm-up exercises to get you going. In the end, we will compare our results with one of the few analytic solutions which exists to this rather complex problem.

Theory

Mathematical introduction

Diffusion is a process where particles move down a concentration gradient. That is, particles move from areas with high concentration to areas with low concentration. The physical driving force of diffusion is simply random movement of each particle. Diffusion of a substance, of which distribution is given by $\phi(x,t)$, is described by the diffusion equation. In one dimension (1D) the diffusion equation takes the form

$$\frac{\partial\phi(x,t)}{\partial t} = \frac{\partial}{\partial x}\left(D(x)\frac{\partial\phi(x,t)}{\partial x}\right), \tag{1}$$

where $D(x)$ is the (position dependent) diffusion coefficient.

We will now show the correspondence between random walk in 1D and the diffusion equation. Random walk is defined as follows: let $X(t)$ be a stochastic process in time giving the position of a particle after a time t. At time $t = 0$, $X(0) = 0$. The particle makes a step in every time interval Δt. The particle can move left and right along an axis, or stay put, with the following probabilities

$$X(t+\Delta t) = \begin{cases} X(t)+h & \text{with probability } \frac{d}{2}, \\ X(t) & \text{with probability } 1-d, \\ X(t)-h & \text{with probability } \frac{d}{2}. \end{cases} \tag{2}$$

We now define the function $\phi(x,t) = P\{X(t) = x\}$. By conditional probabilities, we may straightforwardly write

$$\phi(x,t+\Delta t) = \frac{d}{2}\phi(x+h,t) + (1-d)\phi(x,t) + \frac{d}{2}\phi(x-h,t). \tag{3}$$

Slightly rewrite this to

$$\frac{\phi(x,t+\Delta t)-\phi(x,t)}{\Delta t} = \frac{dh^2}{2\Delta t}\frac{\phi(x+h,t)-2\phi(x,t)+\phi(x-h,t)}{h^2}. \tag{4}$$

Now suppose that $D = \frac{dh^2}{2\Delta t}$ is a constant. If we then let Δt and h^2 go simultaneously to zero, we find

$$\frac{\partial\phi(x,t)}{\partial t} = D\frac{\partial^2\phi(x,t)}{\partial x^2}. \tag{5}$$

This is the diffusion equation with constant diffusion coefficient. We have therefore shown that random walk in the limit of infinitesimal steps in time and space corresponds to diffusion.

1 Exercises

The diffusion equation

Exercise 1a)

Show that

$$\phi(x,t) = \frac{1}{\sqrt{4\pi D t}} \int_{-\infty}^{\infty} \mathrm{d}y \; h(y) e^{-\frac{(x-y)^2}{4Dt}} \tag{6}$$

is a solution of the diffusion equation.

Let $\phi(x,t)$ represent a distribution of particles along the x-axis at time $t \geq 0$. Give a physical interpretation of $h(y)$ (*Hint:* let $t \to 0$ in Eq. (6)).

Exercise 1b)

Assume that the probability of finding a particle at position x in a potential landscape $V(x)$ is given by[1]

$$P(x) = \frac{e^{-\beta V(x)}}{Z}, \tag{7}$$

where $V(x)$ is the particle's potential energy at position x, $\beta = (k_\mathrm{B}T)^{-1}$ where k_B is the Boltzmann's constant and T is the temperature, and Z is the canonical partition function of the system.

We now want to perform a random walk using these probabilities to determine the movement of the particles. At each step in the random walk, we allow the particle only to move one step to the right, one step to the left, or staying put. We define the probability of moving one step to the right as p^+, the probability of moving one step to the left as p^-, and the probability of staying put as p^0. Let the probability of a particle moving to position x from a position $x_0 \in \{x-1,\, x,\, x+1\}$ during one time step be proportional to $P(x)$, and assume that the proportionality constant is equal for all step options.

Show that, if the position of the particle before a random walk step is x_0, the probabilities $\{p^+,\, p^0,\, p^-\}$ are

$$\begin{aligned}
p^+ &= \frac{1}{1 + e^{-\beta[V(x_0-1)-V(x_0+1)]} + e^{-\beta[V(x_0)-V(x_0+1)]}}, \\
p^0 &= \frac{1}{1 + e^{-\beta[V(x_0-1)-V(x_0)]} + e^{-\beta[V(x_0+1)-V(x_0)]}}, \\
p^- &= \frac{1}{1 + e^{-\beta[V(x_0+1)-V(x_0-1)]} + e^{-\beta[V(x_0)-V(x_0-1)]}}.
\end{aligned} \tag{8}$$

Exercise 1c)

What happens to the probabilities $\{p^+,\, p^0,\, p^-\}$ given by Eq. (8) when the temperature T satisfies the following conditions:

- $k_\mathrm{B}T \gg |V(x+1) - V(x)|$ for any x?
- $k_\mathrm{B}T \ll |V(x+1) - V(x)|$ for any x?

[1] This is not a totally random probability distribution, but a well known (although slightly simplified) result from statistical physics.

An important tool for physicists is identifying the energy scales relevant to what we want to compute. In certain situations, we may ignore some interactions in a problem because the corresponding energy scale can be neglected compared to some other interaction. For example, when you compute the driving time from Trondheim to Oslo, you can with great precision ignore quantum effects and relativistic effects such as time dilation, as these effects are small on the relevant energy scale.

How can we simplify the random walk problem using an energy scale argument in the two limits given above?

2 Warm-up exercises

Random walk in a potential

We will now work through some examples of random walk in one dimension. In all examples, start with 10000 particles at $x = 0$. Let each of these particles be subject to a random walk for 200 time steps, where the step length is $h = 1$, and the time step is $\Delta t = 1$ (we use dimensionless time and space axes). Simulate the random walk by picking a random number between 0 and 1, and walk to the left if this number is equal to or less than p^-, walk to the right if it is greater than $(1 - p^+)$, and stay put otherwise. In each example a potential is defined, and you should use Eq. (8) to determine $\{p^+, p^0, p^-\}$ for each particle at each time step.

The quantity βk can to some extent be interpreted as the ratio between the potential energy scale and thermal energy scale relevant to a particle diffusing through the potentials below[2]. Plot the particle distribution along the x-axis after the random walk simulation for $\beta k \in \{0.01, 1, 100\}$ for each potential. Explain the different results for the different values of βk using your knowledge of the involved physics.

Programming exercise 2a)

$$V(x) = k$$

Fit a normal distribution to the resulting particle distribution (use for instance the function *fit* in scipy.norm), and explain the results using the theory section.

Programming exercise 2b)

$$V(x) = -kx$$

Fit a normal distribution to the resulting particle distribution.

Programming exercise 2c)

$$V(x) = k\left(\frac{x}{15} - \cos\left(\frac{x}{3}\right)\right)$$

As an additional task for this potential: try running the simulation at 200 time steps using $\beta k = 0.01$, and then set $\beta k = 100$ and run the simulation for an additional 200 time steps. What do you observe?

Programming exercise 2d)

$$V(x) = kx^4$$

Can βk alone be used as a ratio to determine whether the thermal energy or potential energy dominates the random walk behavior in this potential? Why, or why not?

[2] Remember that we operate with dimensionless position x, so that k is given in units of energy.

3 Random walk in a ratchet potential

We will now create a toy model for motor protein motion by modelling them as particles moving in two parallel and periodic potentials. Although the model is simplified, this is in fact one of the main theoretical principles used to model motor protein motion!

Define two potentials, $V_1(x)$ and $V_2(x)$. The particles can move inside the potential landscapes defined by $V_1(x)$ and $V_2(x)$, and they can be excited (de-excited) between these energy levels. $V_2(x)$ is a constant function of x, and its magnitude is not important. $V_1(x)$ is a periodic potential. Let the x-axis be discretized with step length $h = 1$, and let the spatial period of $V_1(x)$ be N_x steps. We then have $V_1(x + nN_x) = V_1(x)$ for $n \in \mathbb{Z}$. $V_1(x)$ is defined on the interval $x \in \langle -(1-\alpha)N_x,\, \alpha N_x]$ as

$$V_1(x) = \begin{cases} k\frac{x}{\alpha N_x} & 0 < x \leq \alpha N_x, \\ -k\frac{x}{(1-\alpha)N_x} & -(1-\alpha)N_x < x \leq 0, \end{cases} \tag{9}$$

where $0 \leq \alpha \leq 1$. The shape of this potential is a so-called sawtooth wave. α defines the x-positions of the teeth's peaks. In particular, $\alpha = 0.5$ results in a symmetric potential about $x = 0$. k determines the strength of the potential.

The particles living in this system are excited and de-excited between the energy levels 1 and 2 with respective potential landscapes $V_1(x)$ and $V_2(x)$ at even intervals T_p. That is, if the particles start in energy level 2 at $t = 0$, the particles are de-excited to energy level 1 at $t = T_p$. They live in the potential landscape defined by $V_1(x)$ in the time interval $T_p \leq t < 2T_p$, before the particles are excited to live in the potential landscape defined by $V_2(x)$ in the time interval $2T_p \leq t < 3T_p$, etc. In the (de-)excitation process, the x-coordinate is conserved, so that a particle situated at x_j before an excitation moves from $V_1(x_j) \to V_2(x_j)$.

Define the normalized particle current $J(t_i)$ as

$$J(t_i) = \frac{n^+(t_i) - n^-(t_i)}{N_p}, \tag{10}$$

where $n^+(t_i)$ is the number of particles moving to the right on the time interval $(t_i - t_{i-1})$, $n^-(t_i)$ is the number of particles moving to the left, and N_p is the total number of particles in the system.

Programming exercise 3a)

Let $\alpha = 0.1$ and $T_p = 200$. Use step length $h = 1$, $N_x = 100$ steps per potential period, time step $\Delta t = 1$ and $\beta k = 1000$. Define an x-axis that fits two full sawtooth peaks (in total $2N_x = 200$ discrete points), and use periodic boundary conditions. That is, if a particle moves to the left from the leftmost point x_0, it arrives at x_{199} (if we use zero-based numbering). Let the number of particles in the system be $N_p = 3$. Let the particles start in $V_2(x)$ at $x = 0$. They de-exite to $V_1(x)$ after $T_p = 200$ time steps, and stay there for $T_p = 200$ time steps. We will further on refer to two such periods as a cycle.

Run the random walk simulation for $150T_p = 30000$ time steps, that is 75 cycles. Plot the absolute positions X of the three particles at the end of each cycle. The absolute position is calculated by looking at the movement of the particle at each time step. If the particle moves left, its absolute position X decreases by $h = 1$. If the particle moves right, its absolute position X increases with $h = 1$. If the particle moves to the left from $X = 0$, its absolute position changes to $X = -1$ (and not X=199). What do you observe? Give a physical interpretation of the results.

Programming exercise 3b)

Let $\alpha = 0.8$ and $T_p = 500$. Let the number of particles in the system be $N_p = 12N_x$. Let the particles start in $V_2(x)$ and be evenly distributed along the x-axis at $t = 0$, so that there are six particles per discrete x-point to start with. Run the random walk simulation for $20T_p = 10000$ time steps, that is 10

cycles. Calculate the cycle-averaged current for each of the 10 cycles, $J_{\text{avg}}(n) = \frac{1}{2T_p}\sum_{i=1+2T_pn}^{2T_p(n+1)} J(t_i)$, where n labels the cycles. You should obtain negative average currents.

- Write down the 10 cycle-averaged currents you obtain.
- Why do we get non-zero currents? Give a physical interpretation of this.
- Compare $J_{\text{avg}}(0)$ with $J_{\text{avg}}(n)$ for $n > 0$. Give a physical interpretation of this difference.

Repeat this process, only this time with $\alpha = 0.1$. The cycle-averaged currents should now be positive. Give a physical interpretation of this result compared to what you obtained with $\alpha = 0.8$.

Programming exercise 3c)

From now on and in the rest of this project, start each simulation with half of the particles at each of the two x-coordinates which coincide with the minima of $V_1(x)$ (however, let the particles start in energy level 2 defined by $V_2(x)$). Reset the system into this state for every new set of parameters T_p or α.

Choose 50 values of T_p equally spaced between 1 and 1001, and run the random walk simulation for one cycle for each of these values. Let the number of particles in the system be $N_p = 40N_x$, and use $\alpha = 0.8$. Calculate one cycle-averaged current J_{avg} for all these values of T_p. Plot J_{avg} as function of T_p. What do you observe? Give a physical interpretation of the results.

Programming exercise 3d)

Now let $T_p = 500$, choose 50 equally spaced values of α between 0 and 1, and run the simulation for one cycle for each of these values of α. Let the number of particles in the system be $N_p = 12N_x$. Calculate the cycle-averaged current J_{avg} for all these values of α. Plot J_{avg} as function of α. What do you observe? Give a physical interpretation of the results.

4 Analytical solution

In the simple sawtooth-shaped potential which we encountered in the last section, there exists in fact an analytical solution to the current in certain parameter limits. Let us briefly go through the argument which leads to the solution:

When the particles find themselves in the sawtooth-shaped potential $V_1(x)$, they will relax towards the potential minima. Hence, as the particles are excited to the second energy level defined by $V_2(x)$, they start out localized at positions $x_n = nN_x$, $n \in \mathbb{Z}$. Since $V_2(x)$ is a constant potential, the particles will be subject to isotropic diffusion once excited to energy level 2. We learned in the theory section that random walk in a flat potential corresponds to diffusion with constant diffusion coefficient. If the particle distribution at $t = 0$ is $\phi(x, t = 0) \sim \delta(x)$, where $\delta(x)$ is the Dirac delta function, one can show that the normalized solution of the diffusion equation at $t > 0$ is

$$\phi(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}, \tag{11}$$

where $D = \frac{dh^2}{2\Delta t}$ (all these quantities are defined in the theory section). Random walk in a flat potential corresponds to $d = 2/3$. We moreover have $h^2/\Delta t = 1$, so that $D = 1/3$. After diffusion with duration $t = T_p$, the particles are de-excited into $V_1(x)$, where the particles once again move down the potential gradient into one of the minima. The particles on the interval $-(1-\alpha) \leq x < \alpha$ will therefore move towards $x = 0$. The particles having diffused to the right of αN_x will be caught in a minimum to the right, and the particles to the left of $-(1-\alpha)N_x$ will be caught in a minimum to the left.

The number of particles having moved to the right after a cycle of length $2T_p$ can be found by using Eq. (11),

$$n^+ = N_p \sqrt{\frac{3}{4\pi T_p}} \int_{\alpha N_x}^{\infty} \mathrm{d}x \; e^{-\frac{3x^2}{4T_p}}, \tag{12}$$

and the number of particles having moved to the left after the cycle of length $2T_p$ follows as

$$n^- = N_p \sqrt{\frac{3}{4\pi T_p}} \int_{-\infty}^{-(1-\alpha)N_x} \mathrm{d}x \; e^{-\frac{3x^2}{4T_p}}. \tag{13}$$

The normalized, cycle-averaged particle current can therefore be expressed as

$$J_{\mathrm{avg}} = \frac{N_x}{2T_p} \sqrt{\frac{3}{4\pi T_p}} \left(\int_{\alpha N_x}^{\infty} \mathrm{d}x \; e^{-\frac{3x^2}{4T_p}} - \int_{-\infty}^{-(1-\alpha)N_x} \mathrm{d}x \; e^{-\frac{3x^2}{4T_p}} \right). \tag{14}$$

Some algebra later, we arrive at

$$J_{\mathrm{avg}} = \frac{N_x}{4T_p} \left[\mathrm{erfc}\left(\frac{\alpha N_x}{2} \sqrt{\frac{3}{T_p}} \right) - \mathrm{erfc}\left(\frac{(1-\alpha)N_x}{2} \sqrt{\frac{3}{T_p}} \right) \right], \tag{15}$$

where $\mathrm{erfc}(x) = \frac{2}{\sqrt{\pi}} \int_x^{\infty} \mathrm{d}z \; e^{-z^2}$ is the "complimentary error function".

Programming exercise 4a)

Compare the results of Ex. 3d) with the analytical current [Eq. (15)] as function of α when $T_p = 500$. Plot both the numerical and analytical J_{avg} as function of α in the same figure. Compare and comment the graphs!

Programming exercise 4b)

Repeat Ex. 3c), but this time with 20 values of T_p equally space between 80 and 1500, and use $\alpha = 0.8$ and $N_x = 10$ (so that the system is discretized into 20 spatial steps). We use these parameters in order to avoid a very long computation time. Compare the numerical results with the analytical current [Eq. (15)]. Plot both the numerical and analytical J_{avg} as function of T_p in the same figure. Compare and comment the graphs!

Programming exercise 4c)

Repeat programming exercise 4a), but this time with $\beta k \in \{0.01, 1, 2, 3, 5, 10\}$. Compare the analytical and numerical results!

Exercise 4d)

Your results in 4b) and 4c) should indicate that the "analytical argument" presented above has some limitations. That is, the argument is not waterproof. Your last task in this exercise is to identify which parts of the argument contains implicit assumptions, and under what circumstances these assumptions do not hold!

Good luck!