Problem Set 6

1   Stochastic simulation of a bistable system (20 points)

In class and in the previous problem set we have begun exploring the consequences of stochasticity. We showed that because of stochasticity, identical systems can evolve differently in time despite having the same initial conditions. (This behavior is in stark contrast to the differential equations models we explored earlier in the course.)

The master equation offers an exact description of the time evolution of the probability distribution of the system. However, solving the master equation for all but the simplest systems is fairly difficult (even if we are just talking about the steady state). We showed that it is possible (and reasonable) to approximate the master equation at intermediate particle numbers by neglecting particle discreteness. This approximation is called the Fokker-Planck equation. By the end of this exercise you will learn to apply the Fokker-Planck equation to explore and gain intuition for more complicated systems.

Our playground will be the bistable system considered in problem 3 of Problem Set 2. We showed that the dynamics of the protein X were governed by the following differential equation:

$$\frac{dX}{dt} = \frac{v_0 + v_1 K_1 K_2 X^2}{1 + K_1 K_2 X^2} - \gamma X$$

Set $\gamma = 1$, $K_1 K_2 = 10^{-4}$, $v_0 = 12.5$, $v_1 = 200$. (These parameter values lead to a bistable system.)

a. *Sketch by hand* the shape of the production and the degradation terms on the same plot. Indicate the location of the stable fixed points on the plot. (No need to be fancy here.)

b. Calculate the values of X that correspond to the stable fixed points.

c. Write *explicitly* the expression for the potential of the system as derived from the Fokker-Planck equation. Specifically, what are $f(n)$ and $g(n)$? Don't forget to indicate the limits on the integral. (Page 61-62 of the supplementary notes "Stochastic Chemical Kinetics" by Alexander van Oudenaarden, which is listed under Lecture 10 reading, may prove useful).

d. The potential can be thought of as the potential energy of the system. Systems attempt to minimize their potential energy (i.e., basketballs roll downhill not vice-versa), seeking the state corresponding to the local minimum of potential energy. Noise can excite a system (make the basketball temporarily roll uphill) and as a result the system may end jumping between local minima.

   1. Plot the potential for the parameter values introduced above.
   2. Is the plot consistent with the idea that the system is bistable?
   3. Compare your results to the values of X calculated in part b.

e. Temporarily, set $K_1 K_2 = 1$, and re-plot the potential of the system.
  Based on the plot of the potential would you say that the system is monostable or bistable?

  Now, set $K_1 K_2$ back to its original value: 10^{-4}.

f. **COMPUTATION** Perform a *stochastic* simulation of this system to show that the expression level intermittently switches between the two stable states.

g. Use the simulation data to estimate the fraction of time that the system spends in each stable state.

h. In the notes the following expression is given for $p(n)$:

$$p(n) = \frac{A}{f+g} e^{-\varphi}$$

1. On a log-log scale plot $f + g$ vs. n and also $e^{-\varphi}$ vs. n. Which of the two affects the probability distribution more? Is it fair to say that $p(n) \propto e^{-\varphi}$?

2. Approximate the value of the constant A. (Useful functions: *quad* on matlab or *NIntegrate* on Mathematica.)

3. Calculate the fraction of time you expect to see the system in each stable state and compare it to the result you got from your simulation.

2   Life at low Reynolds number (10 points)

a. Dimensional analysis

Parameter	Meaning	Dimensions
ρ_m	Mass density of fluid	$[M][L]^{-3}$
v	Velocity of object	$[L][T]^{-1}$
a	Linear dimension of object	$[L]$
η	Viscosity of fluid	$[M][L]^{-1}[T]^{-1}$

1. Find a formula for the dimensionless Reynolds number R_e.

2. Show that the viscous critical force $f_{crit} = \frac{\eta^2}{\rho_m}$ has the dimensions of force.

3. An object in the fluid is dragged by an external force $f_{external}$ and moves with a constant velocity. In the limit of low Reynolds number ($R_e \ll 1$), compare the external force with the viscous critical force. How does the ratio $\frac{f_{external}}{f_{crit}}$ scale with R_e?

b. Coasting at low Reynolds[1]

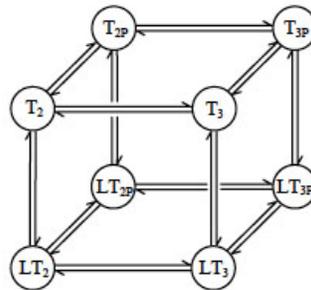 As discussed in class, tiny objects stop moving at once when we stop pushing them.

1. Consider a bacterium, idealized as a sphere of radius 1 μm, propelling itself at 1 $\frac{\mu m}{s}$. At time zero the bacterium suddenly stops swimming and coasts to a stop, following Newton's Law of motion with the Stokes drag force. How far does it travel before it stops? Comment.

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[1]Adapted from Nelson, P. Biological Physics: Energy, Information, Life. (**2008**), ISBN-13: 978-0-7167-9897-2.

2. Brownian motion assumes that each random step is independent of the previous one; thus for example we neglected the possibility of a residual drift speed left over from the previous step. In the light of (a), would you say that this assumption is justified for a bacterium?
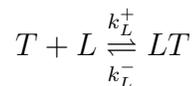
3   Biochemistry of the *E. coli* chemotaxis network-Spiro model[2] and Barkai model[3] (20 points)

The *E. coli* chemotaxis network is represented in the accompanying figure in a simplified form. T represents the Tar receptor and L the ligand or attractant. The receptor can by modified by phosphorylation (subscript P) or methylation (subscripts 2 or 3). For example,

Problem 3 and Images courtesy of Alexander van Oudenaarden. Used with permission.

- T_2: Tar receptor that is unmethylated, unphosphorylated and not bound with ligand

- LT_2: unmethylated, unphosphorylated, bound with ligand

- T_{2p}: unmethylated, phosphorylated, not bound with ligand

- T_3: methylated, unphosphorylated, not bound with ligand

a. The receptors, independently of their phosphorylation or methylation state, can bind an extracellular ligand L according to the scheme

$$T + L \underset{k_L^-}{\overset{k_L^+}{\rightleftharpoons}} LT$$

with the association constant $K_L = \frac{k_L^+}{k_L^-}$.
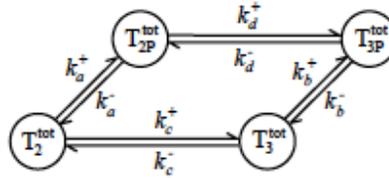
Calculate the fraction of receptors with a ligand bound to them.

b. We will assume that the ligand binding reaction is in rapid equilibrium and only consider total amounts of each modified form of receptor. So we will treat $T_{3P}^{tot} = T_{3P} + LT_{3P}$, etc, as the new relevant dynamical variables reducing the original problem to the analysis of the 4

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[2]P.A.Spiro et al. PNAS 94 , 7263-7268 (1997)

[3]N.Barkai and S.Leibler. Nature 387 , 913-917 (1997)

state system depicted below.

Problem 3 and Images courtesy of Alexander van Oudenaarden. Used with permission.

The assumed rates in the models of Spiro et al. and Barkai et al. are shown in the table below.

Write down explicitly the effective rate constants $k_a^+, ..., k_d^+$ and $k_a^-, ..., k_d^-$ for each model in terms of the symbols listed in the table.

Related effective rate constant	Spiro model	Spiro model	Barkai model	Barkai model
	L unbound	L bound	L unbound	L bound
k_a^+	k_8	0	0	0
k_a^-	k_y	k_y	k_0	k_0
k_b^+	$3k_8$	$1.1k_8$	k_{p1}^+	k_{p2}^+
k_b^-	k_y	k_y	k_{p1}^-	k_{p2}^-
k_c^+	k_1^+	k_3	k	k
k_c^-	k_1^-	k_1^-	0	0
k_d^+	k_1^+	k_3	0	0
k_d^-	k_1^-	k_1^-	k_m	k_m

c. Note that some effective rate constants are now functions of L. This is appropriate since we know, for example, that the receptors should become less phosphorylated as L increases.

   1. In the Spiro model, do $\frac{k_a^+}{k_a^-}$ and $\frac{k_b^+}{k_b^-}$ increase or decrease with L?

   2. In the Barkai model, we would like k_b^+ to decrease and k_b^- to increase with L. What does this imply about k_{p1}^+ , k_{p1}^- , k_{p2}^+ and k_{p2}^- ?
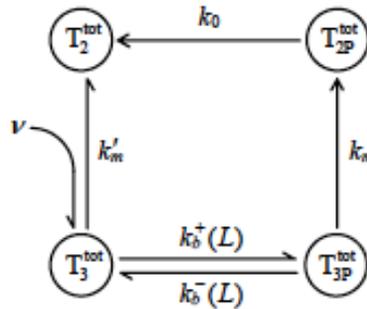
d. Spiro model. In steady state, after the slow methylation reactions have had time to equilibrate, let $\alpha(L)$ represent the fraction of receptors that are methylated. Consider now the total concentration of phosphorylated and unsphosphorylated receptors. Write out, in terms of $\alpha(L)$ and the relevant rate constants from the table shown in part c, the effective rates of phosphorylation (k_p^+) and dephosphorylation (k_p^-) using:

$$k_p^+ = [1 - \alpha(L)]k_a^+ + \alpha(L)k_b^+$$
$$k_p^- = [1 - \alpha(L)]k_a^- + \alpha(L)k_b^-$$

For perfect adaptation to be achieved the phosphorylated fraction of receptors must be independent of L in steady state. Show that this will hold if and only if k_p^+ is a constant (i.e. it is independent of L). We will name this constant κ.

Now set $\kappa = k_8 = 15$ s^{-1}, $K_L = 10^6$ M^{-1}.

1. Plot k_a^+ and k_b^+ for $L = 0$ to $2 / K_L$ and, on the same graph, draw a horizontal line showing the desired κ.

2. Set $k_p^+ = \kappa$ in the equation above, solve for $\alpha(L)$ and plot this function. This is the magical form of $\alpha(L)$ required for perfect adaptation. The model of Spiro *et al* is carefully "tuned" in order to achieve this result. W can contrast this situation with the Barkai model in part e, which has perfect adaptation but requires no fine tuning.

e. Barkai model. Biochemical evidence suggests that the methylation reaction (whose rate constant was written as k in part b) operates at saturation with rate ν. Show that under this assumption the entire model reduces to the following reaction scheme:

Note that ν is a constant rate per unit volume (measured in M s^{-1}) while k_m is a rate constant (measured in s^{-1}). According to the table in part b, what would the value of k_m' be?

Treat k_m' as an independent variable now. Write down the equation for $d(T_3^{tot} + T_{3P}^{tot})/dt$ and solve for T_{3P}^{tot} in steady state. Show that this value is independent of L if and only if $k_m' = 0$. This is the essence of the Barkai model: perfect adaptation is easy to achieve, as long as the phosphorylated receptors are demethylated by the CheB protein.

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