

Chapter 3

Week 2 Activities and Assignments Set 1

Most of the exercises and activities are based on material that is available in short lectures and slides on our website

<http://www.math.ubc.ca/~keshet/MCB2012/Week1.html>

or else, in some of the daily lectures recorded at PIMS. You can get to those recoded lectures by going through a link on our main Home Page.

<http://www.math.ubc.ca/~keshet/MCB2012/>

3.1 Actin and polymerization

Exercise 3.1.1 (Actin Basics)

Watch the video about actin basics and answer the following questions

- (a) Roughly how many actin filament barbed ends are at the edge of a cell (per μm)?
- (b) A single actin filament can grow and shrink at either end due to monomer addition or loss. Write down the equation for the rate of change of length $d\ell/dt$ of a single filament given (constant) actin monomer concentration a .
- (c) Explain what is treadmilling, and use (b) to determine the monomer concentration at which treadmilling can occur. Furthermore: determine the treadmilling rate, and estimate the speed at which the barbed end of an actin filament moves when the filament treadmills.

Exercise 3.1.2 (Actin Length Distribution)

Here we look at a simple model for length distribution. Let x_j be the number of actin filaments of “length” j , i.e. having j monomers. Let $k^+ = (k_b^+ + k_p^+)$, $k^- = (k_b^- + k_p^-)$ be the rates of monomer binding and unbinding to a filament (at both barbed and pointed ends). Here we will assume that the monomer concentration a is constant.

- (a) Explain the equation:

$$\frac{dx_j}{dt} = k^- x_{j+1} - (k^- + ak^+) x_j + k^+ a x_{j-1}$$

- (b) Show that if time is scaled using
- $t = t^* k^-$
- , the equation can be written in a simpler form

$$\frac{dx_j}{dt^*} = x_{j+1} - (1 + r)x_j + r x_{j-1}.$$

(Find the quantity r in terms of the other parameters and interpret what it represents.)

- (c) Find the steady state length distribution by solving the discrete difference equation obtained by setting
- $dx_j/dt = 0$
- . This solution will contain some arbitrary constant. (What else might we need to determine the value of such a constant?)

Exercise 3.1.3 (Actin and Motility)

Watch the iBioSeminar lecture by Julie Theriot Part 1: Cell motility (43:53 minutes) at

<http://ibioseminars.hhmi.org/lectures/bio-mechanisms/julie-theriot.html>

Then answer these questions. (A few others will be asked in class). It is OK to answer briefly (1 sentence or so each).

- Q7: What are differences in the motion of neutrophils and epithelial cells (such as keratocytes?)
- Q13: What is phalloidin? why is it useful in cell biology?
- Q16: What is needed to initiate the formation of an actin filament from monomers?
- Q18: What is typical life time of one actin filament in the cell?
- Q21: What is the maximal load that an actin filament can push against? What is actin’s critical concentration?

3.2 Integrin Dynamics and FRAP

The following problem is based on a lecture by Dodo Das on Friday May 4 (Week 1). You can view parts of that lecture again by going to the pre-recorded lectures via our web page (see above).

Exercise 3.2.4 (Integrin Receptors)

In a research project by Raibatak Das and Guy Tanenzapf's group, integrin receptors (cell surface receptors that transduce mechanical signals) were investigated by a FRAP technique to study the turnover and mobility of those receptors. Fig 3.1 is a theoretical FRAP recovery based on the two-state model for integrin turnover discussed in the lecture:

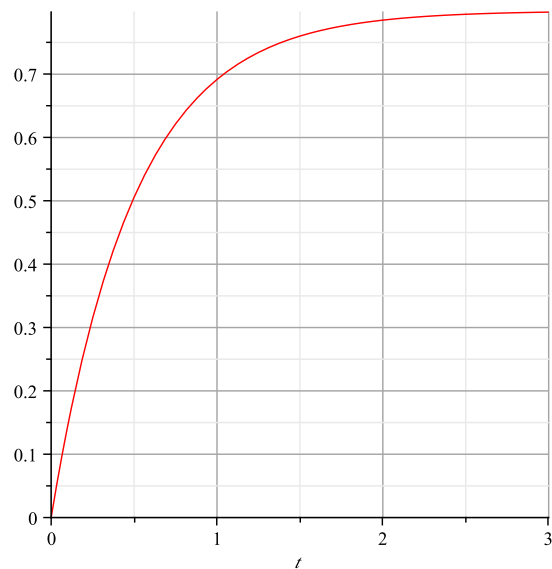
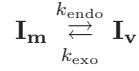


Figure 3.1: A model FRAP recovery curve for integrin receptors. Vertical axis: $f(t)$. Horizontal axis: time in minutes

- Briefly explain (2-3 sentences max) what is FRAP and how it was used in this investigation.
- The investigators noted that diffusion plays a very slight role in the integrin recovery dynamics. Explain on what basis they reached that conclusion.
- They next studied the endo- and exocytosis of these receptors, and created

a model to fit their FRAP data. Explain what is meant by endocytosis and exocytosis.

- (d) The two-state model for integrin turnover is represented by the process:



Note the connection of this practical example to the two-state biochemical reaction $A \rightleftharpoons B$ in our Biochemical Motifs lecture.

Let M = the number of fluorescently labeled integrin molecules in the cell membrane, and let V = the number of fluorescently labeled integrin receptors in vesicles, i.e. M and V are the number of \mathbf{I}_m and \mathbf{I}_v molecules, respectively. Suppose these are the only two states and that on the timescale of interest (seconds, minutes), integrin is neither synthesized, nor degraded. The rate law for this system is :

$$\frac{dM}{dt} = -k_{\text{endo}}M + k_{\text{exo}}V.$$

We assume that prior to applying the photobleaching perturbation, the system is at chemical equilibrium. Find a relationship between the equilibrium concentration of M and V (call these M_{eq} and V_{eq} , respectively).

- (e) Assume that at time $t = 0$, photobleaching instantaneously resets the concentration of the fluorescently labelled membrane integrins to zero, while not affecting the (labeled) integrins in vesicles. Explain how this gives rise to the conservation law:

$$M(t) + V(t) = V_{\text{eq}}$$

where t is the time after photobleaching.

- (f) Define the fractional recovery as, $f(t) = M(t)/M_{\text{eq}}$ and show that:

$$\frac{df}{dt} = -(k_{\text{endo}} + k_{\text{exo}})f(t) + k_{\text{endo}}, \quad f(0) = 0.$$

Solve this ODE for $f(t)$ and show that the recovery follows the time behaviour

$$f(t) = f_{\text{max}} \left(1 - e^{-t/\tau} \right)$$

What is the relationship of the maximal recovery, f_{max} , and the time scale τ , to the rate constants k_{endo} and k_{exo} .

- (g) Solve for k_{endo} and k_{exo} in terms of f_{max} , and τ . Use the sample recovery curve shown in Fig 3.1 to determine the approximate values of k_{endo} and k_{exo} .

- (h) Use the estimates above to compute the equilibrium ratio of membrane and vesicle integrin receptors $M_{\text{eq}}/V_{\text{eq}}$ in the cell.
- (i) If we compare experiments at two different temperatures and find that the maximal recovery increases upon increasing temperature, what does this tell us about the equilibrium distribution of integrins between the two states in response to a change in temperature?

3.3 Dimensional analysis

This is an important modeling tool. If you are not yet an expert, watch the short video clip on our website, based on an example related to a chemostat (device for growing cells in a continuous flow reactor). Several other detailed examples are provided in the Course Notes linked to Week 1 of the website, for your reference.

Exercise 3.3.5 (Beta Cells and nondimensionalization)

This is an exercise in dimensional analysis that is based on a paper by [1]. Watch the introductory clip about Beta cells, glucose, and insulin ($\beta(t)$, $G(t)$, $I(t)$) on our Week 2 web page, download the handwritten 2-page list of questions, and work on the questions.

The required part of the problem is to put the following model into dimensionless form:

$$\frac{dG}{dt} = R_o - (E_{G0} + S_I I)G \quad (3.1)$$

$$\frac{dI}{dt} = \beta\sigma \left(\frac{G^2}{\alpha + G^2} \right) - kI \quad (3.2)$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2)\beta \quad (3.3)$$

The parameters are explained and values provided in the paper [1] by Topp et al (2000).

An extended exercise would be to continue through parts 2-6 of the problems. This is optional. It would be a good practice if you would like extra practice with phase-plane methods. This can also be expanded into a project for the course.

Bibliography

- [1] B. Topp, K. Promislow, G. Devries, R.M. Miura, and D.T. Finegood. A model of beta-cell mass, insulin, and glucose kinetics: Pathways to diabetes. *Journal of Theoretical Biology*, 206(4):605–619, 2000.