Chapter 1

1.1 Week 1 Activities and Assignments Set 1

There will be another set of activities for this week called "Set 2". Stay tuned.

Most of the exercises and activities of this "Set 1" are based on material that is available in short lectures and slides on our website

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

Exercise 1.1.1 (Biochemical Background, bistability, etc)

(a) Go over the biochemical "Modeling Preliminaries". Michaelis-Menten enzyme kinetics is a very standard kind of modeling assumption. But where does it come from? Look at the chemical reaction scheme and differential equations. If you have not done so before, find out how the MM kinetics are derived from this model for enzyme-substrate interactions. (This is fairly standard and can be found in many sources.) See if you can also understand the related "cooperativity" scheme and its approximation by "sigmoidal kinetics". Bring questions to class.

For further thought (optional): Can you formulate or the ordinary differential equations for competitive inhibition? How would you use this scheme to find the resulting rate of reaction shown on the last slide?

(b) Optional: Get familiar with the software XPP - see first few tutorials. Download XPP to your ipad or laptop and try out some examples.. Bring questions to class. [NOTE: If you know and are comfortable with other software such as Matlab etc, it is OK to use that instead. Note however, that XPP can produce bifurcation diagram, as shown in the online tutorial, that may or may not be a standard feature of other software packages.]

(c) See slides and pre-recorded lecture on "Biochemical motifs 1". Consider the production-decay process for which the concentration of product is $x(t)$, which satisfies

$$\frac{dx}{dt} = I(x) - \gamma x, \qquad (1.1)$$

Suppose

$$I(x) = \frac{I_{max}x^m}{k_n^m + x^m}$$

where m is the Hill coefficient. Find the steady states of the system for $m = 1$ and $m = 2$. For which Hill coefficient can this system have the property of bistability? Determine for what value of the parameter γ there are exactly 2 steady states in the case $m = 2$. (Your answer will be in terms of the other parameters.) You have just figured out the "bifurcation" values of γ. What is the range of values of γ that are consistent with bistability of Eqn (1.1) (that is, where there are 2 stable steady states).

(d) See slides and pre-recorded lecture on "Biochemical motifs 1". Consider the ODE

$$\frac{dx}{dt} = c(x - (1/3)x^3 + A)$$

determine for what value(s) of A this equation has exactly two steady states. Draw a little diagram of dx/dt versus x to show how this can happen. These values of A are the bifurcation values. Write an XPP .ode file to produce the bifurcation diagram for this system with A as bifurcation parameter. (See tutorial 2 on XPP for instructions.) Bring questions to class.

Exercise 1.1.2 (Genetic Switches)

   This material is related to the slides/pre-recorded lecture on "Biochemical Motifs 2 and 2.5", respectively. The idea of this exercise is to get you to think about how a cellular "circuit" can act as a switch. Here the "circuit" is a genetic circuit (rather than a biochemical circuit). Part (a) involves 2 interacting genes, part (b) involves a single gene interacting with several copies of the protein that it produces. Do one of the following parts. If you are particularly motivated, try both.

(a) Find the Collins and Gardner Toggle switch paper [1] and get more details about what the authors did. Note the link between model and their designed gene circuit. Either simulate their pair of ODEs for the toggle switch and display your diagram on a uv phase plane (e.g. using XPP) or show time plots of $u(t), v(t)$ that illustrate how each of the two steady

states can be obtained depending on initial conditions. [Remark: extensions of this exercise and/or study of related papers could be suitable for later class project.]

(b) Get the Hasty "phage lambda" paper, and get more details about what the authors did [2]. Pay particular attention to how the authors reduced a fairly complex system to a single ODE with bistability. Their paper also focuses on noise, not here discussed. Can you construct the bifurcation diagram shown in the slides? Compare to the system in problem (c). [Remark: extensions and/or related papers suitable for later class project.]

Exercise 1.1.3 (Activation-inactivation and sharpness of response)

This material is related to the slides/pre-recorded lecture on "Biochemical Motifs 3."

(a) Phosphorylation of a protein and its de-phosphorylation can be modeled as

$$\frac{dR_p}{dt} = \frac{k_1 S R}{K_{m1} + R} - \frac{k_2 R_p}{K_{m2} + R_p}. \tag{1.2}$$

Here the first term is the signal-dependent conversion of R to R_p, and k_2 is the rate of the reverse reaction.

Why do we see terms here that look like Michaelis-Menten kinetics?

(b) Conservation of the total amount of the protein R_T, implies that

$$R_T = R + R_p = \text{ constant.} \tag{1.3}$$

Use the rescaling $r_p = R_p/R_T$ and conservation to obtain the equation shown in the slides.

Then show that the steady state value of the "response" r_p depends on the "signal" S as a "Goldbeter-Koshland" function. It is OK to do this numerically, as the expression is messy.

(c) Suitable as a part of later project: see the paper by Tyson et al (2003) [3] where this and related example of "switches, oscillators, and adaptors" are presented and discussed comprehensively.

Bibliography

[1] T.S. Gardner, C.R. Cantor, and J.J. Collins. Construction of a genetic toggle switch in Escherichia coli. *Nature*, 403(6767):339–342, 2000.

[2] J. Hasty, J. Pradines, M. Dolnik, and JJ Collins. Noise-based switches and amplifiers for gene expression. *Proceedings of the National Academy of Sciences of the United States of America*, 97(5):2075, 2000.

[3] J.J. Tyson, K. Chen, and B. Novak. Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. *Current Opinion in Cell Biology*, 15(2):221–231, 2003.