CALIFORNIA INSTITUTE OF TECHNOLOGY
BioEngineering

BE 150

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Problem Set #7

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1. *From Alon 8.1. Diffusion from both sides.* A morphogen is produced at both boundaries of a region of cells that ranges from x=0 to x=L. The morphogen diffuses into the region and is degraded at rate α. What is the steady state concentration of the morphogen as a function of position? Assume that the concentration at the boundaries is $M(0) = M(L) = M_o$. Under what conditions is the concentration of morphogen at the center of the region very small compared to M_o?

   Hint: The morphogen concentration obeys the diffusion-degradation equation at steady state:

   $$D\frac{d^2M}{dx^2} - \alpha M = 0$$

   The solutions of this equation are of the form:

   $$M(x) = Ae^{-x/\lambda} + Be^{x/\lambda}$$

   Fine λ, A, and B that satisfy the diffusion-degradation equation and the boundary conditions.

2. *Alon 8.3. Polynomial self-enhanced degradation.* Find the steady state concentration profile of a morphogen produced at x=0. The morphogen diffuses into a field of cells, with nonlinear self-enhanced degradation described by:

   $$\frac{dM}{dt} = D\frac{d^2M}{dx^2} - \alpha M^n$$

   When is patterning with this profile robust to the level of M at the boundary, M_o? *Hint:* Try a solution of the form $M(x) = a(x+b)^m$ and find the parameters a and b in terms of D, M_o, and α.

3. *Alon 8.4. Robust Timing.* A signaling protein X inhibits pathway Y. At time t=0, X production stops and its concentration decays due to degradation. The pathway Y is activated when X levels drop below a threshold T. The time at which Y is activated is t_Y. Our goal is to make t_Y as robust as possible to the tinitial level of X, $X(t=0) = X_o$.

   a) Compare the robustness of t_Y in two mechanisms, linear degradation and self-enhanced degradation (note that in this problem, all concentrations are spatially uniform).

   $$\frac{dX}{dt} = -\alpha X$$

   $$\frac{dX}{dt} = -\alpha X^n$$

   Which mechanism is more robust to fluctuations in X_o? Explain.

b) Explain why a robust timing mechanism requires a rapid decay of X at times close to t=0.

4. *Robustness of Morphogen Gradients. Based on Eldar, et al., Developmental Cell, 2003*

a) Consider a simplified version of the Hedgehog signaling model, a key regulator in development:

$$\frac{\partial[Hh]}{\partial t} = D\frac{\partial^2[Hh]}{\partial x^2} - k_+^{ph}[Hh][Ptc] + k_-^{ph}[PtcHh]$$

$$\frac{\partial[Ptc]}{\partial t} = \eta_{Ptc}^{end} + \eta_{Ptc}^{reg}\frac{[PtcHh]^n}{K_t^n + [PtcHh]^n} - \alpha_P[Ptc] - k_+^{ph}[Hh][Ptc] + k_-^{ph}[PtcHh] + \rho\alpha_{ph}[PtcHh]$$

$$\frac{\partial[PtcHh]}{\partial t} = k_+^{ph}[Hh][Ptc] - k_-^{ph}[PtcHh] - \alpha_{ph}[PtcHh]$$

represent the dynamics of morphogen/expander concentrations with respect to position and time.
Implement the system above with 10 discrete cells arranged in a line as discussed in class and plot concentrations of Ptc and Hh with respect to position. Use the parameters in table 1.

b) Now consider a model that incorporates Smoothened and is described by the following equations:

$$\frac{\partial[Hh]}{\partial t} = D\frac{\partial^2[Hh]}{\partial x^2} - k_+^{psh}[Hh][PtcSmo] + k_-^{psh}[PtcSmoHh] - k_+^{ph}[Hh][Ptc] - k_-^{ph}[PtcHh]$$

$$\frac{\partial[Ptc]}{\partial t} = \eta_{Ptc}^{end} + \eta_{Ptc}^{reg}\frac{[PtcSmoHh]^n}{K_t^n + [PtcSmoHh]^n} - \alpha_P[Ptc] - k_+^{ph}[Hh][Ptc] + k_-^{ph}[PtcHh] + \rho\alpha_{ph}[PtcHh] - -k_+^{ps}[Ptc][Smo] + k_-^{ps}[PtcSmo]$$

$$\frac{\partial[PtcHh]}{\partial t} = k_+^{ph}[Hh][Ptc] - k_-^{ph}[PtcHh] - \alpha_{ph}[PtcHh]$$

$$\frac{\partial[PtcSmo]}{\partial t} = k_+^{ps}[Ptc][Smo] - k_-^{ps}[PtcSmo] - k_+^{psh}[Hh][PtcSmo] + k_-^{psh}[PtcSmoHh]$$

$$\frac{\partial[PtcSmoHh]}{\partial t} = k_+^{psh}[Hh][PtcSmo] - k_-^{psh}[PtcSmoHh]$$

$$[Smo]^{tot} = [Smo] + [PtcSmo] + [PtcSmoHh]$$

where [Smo] is the concentration of Smoothed.
Implement the system above with 10 discrete cells arranged in a line as discussed in class and plot concentrations of Ptc and Hh with respect to position. Use the parameters in table 2 and table 1.

c) Explain the differences in the signaling profile between a) and b).

d) Plot the time response for 5 different initial conditions. What is the time to reach steady state in each case?

Table 1: Model parameters, problem 4, a)

Parameter	Value
D	$1\ \mu m^2 s^{-1}$
k_+^{ph}	$7.15 \times 10^{-2} \mu M^{-1} s^{-1}$
k_-^{ph}	$6.25 \times 10^{-4} s^{-1}$
η_{Ptc}^{end}	$6.2 \times 10^{-5} \mu M s^{-1}$
η_{Ptc}^{reg}	$1.1 \times 10^{-3} \mu M s^{-1}$
α_P	$6.25 \times 10^{-4} s^{-1}$
α_{ph}	$6.9 \times 10^{-2} s^{-1}$
η_{Hh}	$3.3 \times 10^{-3} \mu M s^{-1}$
L_P (length of organism)	$30 \mu m$
K_t	$4.8 \times 10^{-2} \mu M$
n	3
ρ	1

Table 2: Model parameters, problem 4, b)

Parameter	Value
α_{ph}	$2 \times 10^{-2} s^{-1}$
K_t	$5.7 \times 10^{-2} \mu M$
n	2
ρ	1
k_+^{ps}	$1.25 \mu M^{-1} s^{-1}$
k_-^{ps}	$6.25 \times 10^{-4} \mu M^{-1} s^{-1}$
k_+^{psh}	$2.1 \times 10^{-3} \mu M^{-1} s^{-1}$
k_-^{psh}	$6.25 \times 10^{-4} \mu M^{-1} s^{-1}$
Smo^{tot}	$0.3 \mu M$