CALIFORNIA INSTITUTE OF TECHNOLOGY
BioEngineering

BE 150

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Problem Set #8

Issued: 5 Mar 12

Winter 2012

Due: 14 Mar 12

1. *Pattern formation by lateral inhibition. Based on Collier et al., Journal of theoretical biology, 1996*

   The Notch-Delta signaling pathway allows communication between neighboring cells during development. It has a critical role in the formation of 'fine-grained' patterns, generating distinct cell fates among groups of initially equivalent neighboring cells and sharply delineating neighboring regions in developing tissues. In this problem, we investigate the pattern-forming potential and temporal behavior of the Collier model through numerical simulation.

   The dynamics of Notch (n_p) and Delta (d_p) for each individual cell p are governed by:

$$\dot{n_p} = f(\bar{d_p}) - n_p$$

$$\dot{d_p} = \nu(g(n_p) - d_p)$$

   where $\bar{d_p}$ denotes the mean of the levels of Delta activity in the cells adjacent to cell p, and

$$f(x) = \frac{x^k}{a + x^k}, g(x) = \frac{1}{1 + bx^h}$$

   Consider a two dimensional array of cells, where each cell is modeled by a square. The parameters for the simulation are $a = 0.01, b = 100, \nu = 1, k = h = 2,$. Simulate Notch-Delta dynamics for a 15×15 array of cells, using initial conditions chosen randomly from a uniform distribution. Use the code provided in in *NotchDeltaGui.m* to provide a visualization of your simulation. Color cells with high Notch activity (if Notch activity is >= 0.995) in red, and low Notch activity level in black. Provide an illustration of the steady state of your simulation.

2. *Scaling of morphogen gradients. Based on Ben-Zvi, Barkai, PNAS, 2010*

   Consider the feedback "expansion-repression" model for morphogen gradient scaling in which the range of the morphogen gradient, [M] increases with the abundance of some diffusible molecule [E], whose production, in turn, is repressed by morphogen signaling. The partial differential equations

$$\frac{d[M]}{dt} = D_M \nabla^2 [M] - (1 + [E])^{-1_1} \alpha_M^1 [M] - (1 + [E])^{-1} \alpha_M^2 [M]^2$$

$$\frac{d[E]}{dt} = D_E \nabla^2 [E] - \alpha_E^1 [E] + \beta_E \frac{1}{1 + ([M]/T_{rep})^h}$$

   and boundary conditions:

$$D_M \nabla [M]_{x=0} = -\eta_M$$

$$D_M \nabla [M]_{x=L} = 0$$

$$D_E \nabla [E]_{x=0} = 0$$

$$D_E \nabla [E]_{x=L} = 0$$

represent the dynamics of morphogen/expander concentrations with respect to position and time.

a) Implement the system above using the technique discussed in class. Use the parameters below in addition to $L = 15$ grid points, $h = 4$, cell size 100 μm and time at steady state 5×10^5 sec.

Morphogen diffusion, D_M	10 $\mu m^2 \cdot sec^{-1}$
E diffusion, D_E	1 $\mu m^2 \cdot sec^{-1}$
Morphogen linear degradation rate, α_M^1	10^{-1} sec^{-1}
Morphogen quadratic degradation rate, α_M^2	1 $\mu M^{-1} \cdot sec^{-1}$
E degradation rate, α_E	10^{-5} sec^{-1}
Morphogen flux from proximal pole, η_M	10 $\mu m \cdot \mu M \cdot sec^{-1}$
E production rate, β_E	10^{-2} $\mu M \cdot sec^{-1}$
Threshold for E repression, T_{rep}	10^{-3} μM

Figure 1: Parameters for problem 4 a)

b) Plot the dynamics of the expansion-repression mechanism at three different times: when the morphogen gradient is sharp, when the gradient expands, and at steady state, along with the threshold. Explain the dynamics of the system in the three situations.

c) Run the simulation with parameters in figure 2 for two different cell sizes and plot the morphogen concentration in μM vs relative length x/L. Do the same using parameters from figure 1 and compare.

d) What is the condition on the diffusion of the expander that allows for scaling of the gradient?

Morphogen diffusion, D_M	10 $\mu m^2 \cdot sec^{-1}$
E diffusion, D_E	10^{-1} $\mu m^2 \cdot sec^{-1}$
Morphogen linear degradation rate, $\alpha_M{}^1$	10^{-5} sec^{-1}
Morphogen quadratic degradation rate, $\alpha_M{}^2$	1 $\mu M^{-1} \cdot sec^{-1}$
E degradation rate, α_E	10^{-4} sec^{-1}
Morphogen flux from proximal pole, η_M	1 $\mu m \cdot \mu M \cdot sec^{-1}$
E production rate, β_E	10^{-3} $\mu M \cdot sec^{-1}$
Threshold for *E* repression, T_{rep}	10^{-3} μM
Time points (Fig. 1*B*)	

Figure 2: Parameters for problem 4 b)