BE 159 Spring 2014
Homework #1
Due at the start of lecture, April 22, 2014.

Problem 1.1 (Properties of Turing patterns, 25 pts)**.**
We quickly recall results from our first class, since several people were absent. Let $u(\mathbf{x}, t)$ and $v(\mathbf{x}, t)$ be the concentrations of two morphogens at spacial position $\mathbf{x}$ and time t. Let $f_u(u, v)$ be the net rate of production of species u by chemical reaction, with $f_v(u, v)$ similarly defined for species v. Let D_u be the diffusion coefficient for species u and D_v be the diffusion coefficient for species v. The reaction diffusion equations are then

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + f_u(u, v) \tag{1.1}$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + f_v(u, v). \tag{1.2}$$

Let $u = u_0,\ v = v_0$ be a homogeneous steady state, i.e., $f_u(u_0, v_0) = f_v(u_0, v_0) = 0$. Finally, we define

$$f_{u,u} = \left.\frac{\partial f_u}{\partial u}\right|_{u_0,v_0} \tag{1.3}$$

$$f_{u,v} = \left.\frac{\partial f_u}{\partial v}\right|_{u_0,v_0}, \tag{1.4}$$

with $f_{v,u}$ and $f_{v,v}$ similarly defined. In class, we showed that if we make a small perturbation $\delta u, \delta v$ from the homogeneous steady state u_0, v_0, we get the following linear system of equations for periodic of infinite boundary conditions.

$$s \begin{pmatrix} \delta u \\ \delta v \end{pmatrix} = \mathsf{L} \cdot \begin{pmatrix} \delta u \\ \delta v \end{pmatrix} = \begin{pmatrix} -k^2 D_u + f_{u,u} & f_{u,v} \\ f_{v,u} & -k^2 D_v + f_{v,v} \end{pmatrix} \cdot \begin{pmatrix} \delta u \\ \delta v \end{pmatrix}. \tag{1.5}$$

Here $\mathbf{k}$ (with $k^2 \equiv \mathbf{k} \cdot \mathbf{k}$) is the vector of wave numbers of the growing perturbation. I.e., this is the wave number of the emergent pattern in the concentration profile. The solution to this system is

$$\begin{pmatrix} \delta u \\ \delta v \end{pmatrix} = \begin{pmatrix} \delta u_0 \\ \delta v_0 \end{pmatrix} \mathrm{e}^{st + i\mathbf{k}\cdot\mathbf{x}}. \tag{1.6}$$

The values of s are the eigenvalues of the matrix L, and δu_0 and δv_0 are spacial functions dependent on the initial conditions. The homogeneous steady state is stable if the real part of s is nonpositive.

a) Show that a necessary condition for linear stability of a homogeneous steady state in the absence of diffusion is that at least one of $f_{u,u}$ and $f_{v,v}$ is negative.

b) Show that at a stable homogeneous steady state in the absence of diffusion, a necessary condition for linear *instability* in the presence of diffusion is that exactly one of $f_{u,u}$ and $f_{v,v}$ is negative. Remember, when the system of equations is *unstable*, we get patterns that might be relevant to morphogenesis. Why is it physically relevant to consider only *stable* homogeneous steady states in the absence of diffusion?

c) Assuming that $f_{v,v}$ is the negative one, show that at a Turing bifurcation (i.e., at the onset of instability: if we were to continuously adjust parameters such as reaction rate constants of diffusivities until the homogeneous steady state just becomes unstable), the characteristic length of the emerging pattern from the homogeneous steady state scales like

$$\lambda^{-2} \sim \lambda_u^{-2} - \lambda_v^{-2},$$

where $\lambda_u \equiv \sqrt{D_u/f_{u,u}}$ and $\lambda_v \equiv \sqrt{D_y/(-f_{v,v})}$. *Hint:* This length scale corresponds to the wave number k for which the eigenvalue s is maximal.

d) Show that $\lambda_v > \lambda_u$ is a necessary condition for an unstable homogeneous steady state. Comment on the physical implications of these results. It is often said that Turing patterns result from "local activation with long ranged inhibition." How do your mathematical results relate to that statement? What must the relative magnitudes of the diffusion coefficients be in order to get spontaneous patterns?

Problem 1.2 (The ASDM model (25 pts + 10 pts extra credit))**.**
In this problem, we will investigate Turing patterns for the activator substrate depletion model (ASDM) in one dimension. In their full form, the equations for the ASDM model are

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} + \rho_a \frac{a^2 s}{1 + \kappa_a a^2} - \mu_a a + \sigma_a, \tag{1.7}$$

$$\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} - \rho_s \frac{a^2 s}{1 + \kappa_a a^2} + \sigma_s, \tag{1.8}$$

where a is the concentration of the "activator" and s is the concentration of the "substrate." Note the single spatial derivative on the diffusion term; this is a result of confining ourselves to one dimension.

a) Describe in words the physical meaning of each term in the reaction-diffusion equations for the ASDM. Draw a diagram similar to that of Figure 1e of the Howard, et al. paper for the ASDM. How does the substrate act as an "inhibitor"?

b) Show that for $\kappa_a = 0$ and $\sigma_a = 0$, we can non-dimensionalize the equations to read

$$\frac{\partial a}{\partial t} = d \frac{\partial^2 a}{\partial x^2} + a^2 s - a, \tag{1.9}$$

$$\frac{\partial s}{\partial t} = \frac{\partial^2 s}{\partial x^2} + \mu(1 - a^2 s), \tag{1.10}$$

where all variables are now dimensionless. Take special note of how d relates to D_a and D_s. This leaves only two parameters to consider, d and μ.

c) Show that the ASDM model has a unique homogeneous steady state of $a_0 = s_0 = 1$.

d) We will only consider $\mu > 1$. What must the value of d be (in terms of μ) to get spontaneous patterns from the homogeneous steady state for the ASDM model?

e) (10 pts extra credit) This part takes more effort than 10 points-worth. However, most of that effort is in numerically solving the reaction-diffusion equations. This will come up in a future homework, and putting that effort in now might be worth your time.

Consider a periodic domain $x \in [0, 6\pi)$. Start with the homogeneous steady state and numerically solve equations (1.9) and (1.10). Plot the steady state profiles you get for various values of μ and d_a. Only include those that give patterns.

Problem 1.3 (Toy gap gene profiles and mutual information (30 pts))**.**
This problem was inspired by some of the discussion in the Ph.D. thesis of Julien Dubuis, Princeton University, 2012. For this problem, as in the Dubuis, et al. paper, we will assume

$$P(g|x) \approx \frac{1}{\sqrt{2\pi\sigma_g^2}} \exp\left\{-\frac{(g-\bar{g}(x))^2}{2\sigma_g^2}\right\}. \tag{1.11}$$

We will assume σ_g is constant (not a function of x), but $\bar{g} = \bar{g}(x)$. Finally, as in the Dubuis, et al. paper, we will take $P_x(x)$ to be uniform, i.e., $P_x = 1$.

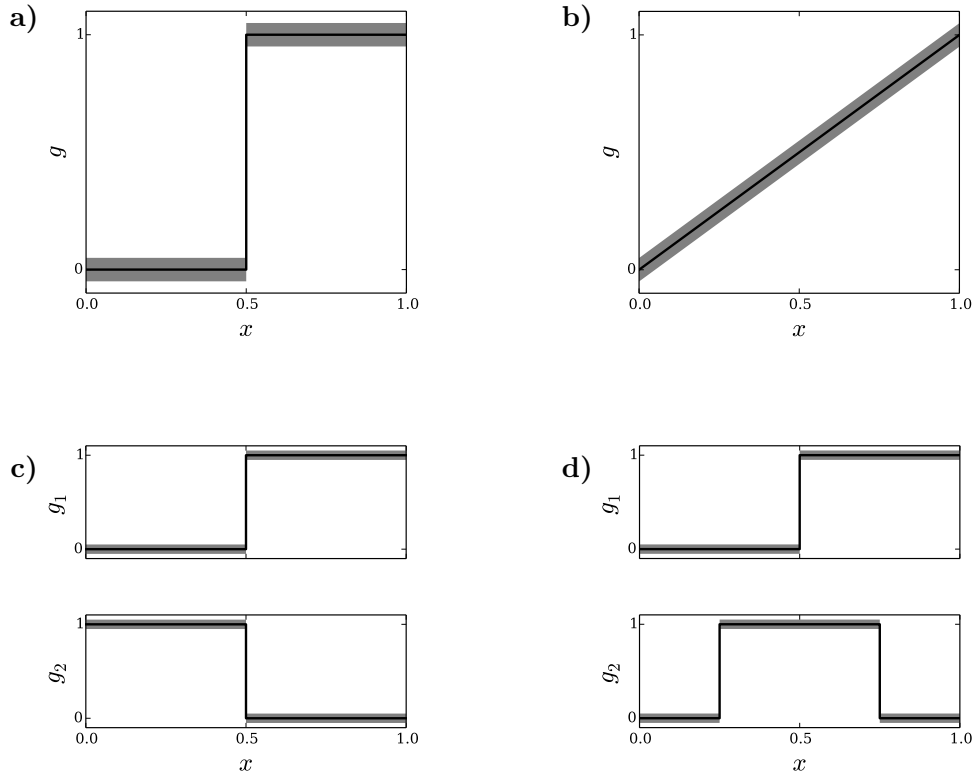

Figure 1: Figure adapted from the Ph.D. thesis of J. Dubuis, Princeton University, 2012. Each figure represents a gene expression profile. Lines represent $\bar{g}(x)$ and the shaded areas represent $\bar{g}(x) \pm \sigma_g$, where σ_g is a constant.

a) Compute the mutual information between normalized position x and normalized level of gene expression level g for the profile given in Fig. 1a in the limit of $\sigma_g = 0$. Is $I_{g\to x}$ for the case where $\sigma_g = 0$ an underestimate of overestimate of the mutual information when $\sigma_g > 0$? *Hint:* When $\sigma_g = 0$, g becomes a discrete variable.

b) Show that in the limit of low gene expression noise (small but nonzero σ_g), the mutual information for the expression profile in Fig. 1b is approximately

$$I_{g\to x} \approx -\frac{1}{2}\log_2\left(2\pi e\sigma_g^2\right). \tag{1.12}$$

Is this approximation an overestimate or an underestimate of the mutual information? *Hints:* The position x must strictly follow $0 \le x \le 1$, but g does not have to be between zero and one, since only $\bar{g}$ goes from zero to one. Let's say $g_{\min} \le g \le g_{\max}$. Because $P(g|x)$ is Gaussian, $P(g|x)$ is negligible for $|g| \gg \bar{g}$, so there is little error introduced by performing integrals with infinite bounds. In other words,

$$\begin{aligned} I_{g\to x} &= \int_0^1 \mathrm{d}x \int_{g_{\min}}^{g_{\max}} \mathrm{d}g\, P_x(x)P(g|x)\log_2\frac{P(g|x)}{P_g(g)} \\ &\approx \int_0^1 \mathrm{d}x \int_{-\infty}^{\infty} \mathrm{d}g\, P_x(x)P(g|x)\log_2\frac{P(g|x)}{P_g(g)}. \end{aligned} \tag{1.13}$$

Also, remember some identities for Gaussian integrals.

$$\int_{-\infty}^{\infty} \mathrm{d}u\, \mathrm{e}^{-u^2} = \sqrt{\pi}, \tag{1.14}$$

$$\int_{-\infty}^{\infty} \mathrm{d}u\, u^2\mathrm{e}^{-u^2} = \frac{\sqrt{\pi}}{2}. \tag{1.15}$$

c) Compute the mutual information between $\{g_1, g_2\}$ and x for the profiles shown in Figures 1c and d in the limit where $\sigma_{g_1} = \sigma_{g_2} = 0$.

d) In summary, what do the results of parts (a), (b), and (c) say about "design principles" for informative expression profiles?

Problem 1.4 (Mutual information from Hunchback profiles (20 pts))**.**
This problem is inspired by problem 137 of Bialek, Biophysics: Searching for Principles, *Princeton University Press, 2012*. In this problem we will investigate how the mutual information $I_{g\to x}$ is calculated from real data. We will do this for the profile of a single gap gene, Hunchback. On the website of Bialek's book, he made measurements of the Hunchback profile from 20 embryos available. (Note that these are not the same measured profiles from the Dubuis paper.) These can be downloaded here: `http://be159.caltech.edu/2014/handouts/hb.csv`. Each column gives the normalized profile of a single embryo. The data are evenly spaced, going from normalized position $x = 0$ to $x = 1$.

Your task is to use these data to compute the mutual information content between the gene expression level of Hunchback, g, and the position along the anterior-posterior axis in the embryo, x. As in the paper, use only the middle 80% of the profile in your analysis. We will not carry out the more sophisticated analysis used in the Dubuis papers, but will make the following approximations.

i) We assume that at each position x, the gene expression level is Gaussian. I.e.,

$$P(g|x) = \frac{1}{\sqrt{2\pi\sigma_g^2}}\exp\left\{-\frac{(g-\bar{g}(x))^2}{2(\sigma_g(x))^2}\right\}, \tag{1.16}$$

where $\bar{g}(x)$ and $\sigma_g(x)$ are computed directly from the experimental data.

ii) We assume the the data are of sufficient quality that both $\bar{g}(x)$ and $\sigma_g(x)$ vary smoothly with x such that we can naively use numerical quadrature as if the data accurately represent continuous functions.

We will not do further analysis to get an error bar on our mutual information, as done in the paper.

Compute $I_{g\to x}$ from the data you downloaded. How does it compare with the value reported in the paper? Comment on any discrepancies.