BE 159 Winter 2019
Homework #2
Due at the start of class, January 30, 2019

Problem 2.1 (Means of scaling)**.**
Our discussions about the Ben-Zvi, et al. paper established that scaling is an important concept in morphogenetic patterning. The paper presented a mechanism for scaling of the dorsal-ventral activation profile of BMP and did a careful analysis of it. In this homework, you will investigate other possible mechanisms for scaling of a simple pattern that is high in one region (near $x = 0$) and low in another (near $x = L$). We will consider one-dimensional models in all cases.

a) In 1970, Francis Crick proposed a simple mechanism for formation of a morphogen gradient. He postulated that a source of morphogen might exist at position $x = 0$ and a sink at position $x = L$. To clarify what Crick means by "sink," I'll use his own words.

> "It is particularly easy to make a sink, if the sink holds the concentrations of the morphogen near zero, since then all that is required is an enzyme in the sink cells to destroy the morphogen very rapidly, even at very low concentrations."

   i) Derive an expression for the steady state profile of morphogen for this model.

   ii) Does the steady state distribution scale? If not, what can be modulated to make it scale?

b) Suppose that all of the cells in the tissue being patterned produce a diffusible mobilizing molecule (with concentration $m(x,t)$ and diffusion coefficient D_m) at constant rate q (in units of concentration of unit time). The mobilizer affects the diffusion coefficient of the morphogen as

$$D = D_0 f(m), \tag{2.1}$$

where $f(m)$ is some function of the mobilizer concentration, m. We can write $f(m)$ as a Taylor series to first order, $f(m) \approx 1 + am$. We assume that the mobilizer has no effect on the reaction rates involving the morphogen. So, the complete reaction-diffusion equation for the morphogen concentration $c(x,t)$ is

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D_0(1+am)\frac{\partial c}{\partial x}\right) + r(c). \tag{2.2}$$

Suppose further that there are sinks for this mobilizer on each end of the tissue. That is, $m(x = 0) = m(x = L) = 0$, where $m(x)$ is the concentration of mobilizer, as Crick proposed.

i) Solve for the mobilizer concentration, $m(x)$.

ii) Provided $r(c)$ does not have any strange L-dependence, does the morphogen profile scale? More specifically, does it scale exactly, approximately, or not at all? Discuss in which limits scaling might be most effective.

c) The concept of a globally secreted molecule that affects diffusion can be analogously applied to one that affects the reaction rate. Imagine that the mobilizer from part (b) is instead an inhibitor. That is, it inhibits the rate that reactions involving the morphogen can occur, for example by transiently binding it to protect it. Approximating this slowdown as a first order inhibiting Hill function, the reaction-diffusion equation for the morphogen is

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} + \frac{r(c)}{1+bh}, \tag{2.3}$$

where h represents the concentration of the reaction inhibitor. If the inhibitor has analogous dynamics as the mobilizer from part (b), does the steady state profile scale? Discuss appropriate limits.

d) In an earlier paper from the Barkai group, Eldar, et al. (*Nature*, **419**, 304, 2002) proposed a model for BMP-based patterning in *Drosophila*, which lacks the Admp BMP ligand. In Drosophila, the BMP ortholog *screw* (*scw*) is involved in dorsal-ventral patterning. It has a binding partner, *short gastrulation* (*sog*) that is a chordin ortholog. In a simple model for Scw patterning, Sog binds irreversibly to Scw to form a complex. The complex can be destroyed by the protease Tolloid (Tld) which cleaves Sog. Tld is uniformly distributed throughout the embryo and has constant concentration. In that paper, the authors demonstrate that this results in patterning that is robust to changes in ligand concentration. Here, we will see how that model performs with respect to scaling.

i) Write down reaction diffusion equations for the Sog, Scw, and the Sog/Scw complex. Assume mass action kinetics. Denote the concentrations of the respective species by s, b, and c. Denote the constant Tld concentration as τ. Define the diffusion constants for Soc, Scw, and the Sog/Scw complex to respectively be D_s, D_b, and D_c.

ii) If we assume that Sog *greatly* mobilizes Scw by forming the complex, such that $D_b \approx 0$, we can solve for the steady state Scw concentration analytically. As a first step toward doing that, show that, at steady state the concentration of the Sog/Scw complex is uniform in space, $c = c_0$. *Hint*: This system describes dorsal-ventral patterning, so we have periodic boundary conditions. It is also more convenient to work on the domain $x \in [-L/2, L/2]$. Then, $s(-L/2) = s(L/2)$, and similar conditions for b and c.

ii) Show that

$$\frac{\partial^2 b^{-1}}{\partial x^2} = \lambda^{-2}, \tag{2.4}$$

where λ is some length scale (be sure to define what it is in terms of the other parameters).

iii) Solve equation (2.4) to get the Scw profile. Your answer will be

$$b(x) = \frac{2\lambda^2}{x^2 + \varepsilon^2}, \tag{2.5}$$

where ε^2 is an undetermined constant of integration.

iv) Write ε in terms of the average total concentration of Scw, b_0, which can presumably be regulated.

$$b_0 \equiv \bar{b} + \bar{c} = \frac{1}{L}\int_{-L/2}^{L/2} \mathrm{d}x\ (b(x) + c(x))\,. \tag{2.6}$$

In doing this calculation, assume that $L/\varepsilon \gg 1$, such that $\tan^{-1}(L/2\varepsilon) \approx \pi/2$. For what values of b_0 is this assumption valid?

v) Does the Scw profile scale? If not, what is missing from the model and why? *Hint:* think about what is additionally in the model presented in the Ben-Zvi et al. paper we read in class.

e) For 10 points extra credit, invent your own mechanism that can give approximate or exact scaling and demonstrate that it does.