BE 159 Winter 2021
Homework #2
Due at the start of class, January 27, 2021

Problem 2.1 (Means of scaling)**.**
In the Stapornwongkul, et al., paper, the authors established the first synthetic *in vivo* morphogen gradient, a remarkable achievement. To be clear in our definitions, by "gradient," we mean a steady state spatial profile of morphogen concentrations, where teh concentration is high in one region (near $x = 0$) and decay monotonically to be low in another region (near $x = L$, where L is the length of the tissue over which the morphgen ggradient is formed). We further refine this definition to mean a gradient in the gene-expression activity resulting from morphogen patterning. Importantly, Stapornwongkul and coworkers established some minimal components necessary to set up the gradient that had similar properties and apparent consequences of the Dpp gradient. To establish the gradient in the imaginal disc, they needed the following components.

1. A diffusible morphogen that is produced at a source at $x = 0$.
2. A signaling receptor that can not hop from cell to cell.
3. A nonsignaling receptor that can hop from cell to cell.

The dynamics of these species are described in equations 53–57 of the supplemental material of the paper, and also equations 67–81 for a model in which two signaling receptors are needed to affect gene expression.

As you can read in the supplement, the authors did a careful investigation of these models for morphogen gradient establishment. In this problem, we will address another important feature of morphogen gradients found in the living world, **scaling**.

Dobzhansky wrote an essay in 1973 entitled "Nothing in Biology Makes Sense Except in the Light of Evolution." In that spirit, we should consider what happens to the shape of a morphogen gradient if the size of an organism grows. As an example, consider the Bicoid gradient along the A-P axis in the early *Drosophia* embryo. In the figure below, we see the gradients of Bicoid in three different species of fruit fly, each with different embryo sizes. Each embryo shows an exponentially decaying gradient, but the decay length for each is different. When all of the gradients are plotted instead against the *fractional* distance along the A-P axis, they overlap. The decay length of the gradients therefore *scale* with the size of the embryo. Stated mathematically, this means that the observed length scale of the gradient λ is a linear function of the length of the tissue L. Another way of stating this is that the dynamics are only dependent on $\tilde{x} \equiv x/L$, at least over a substantial portion of the domain $0 \leq x \leq L$.

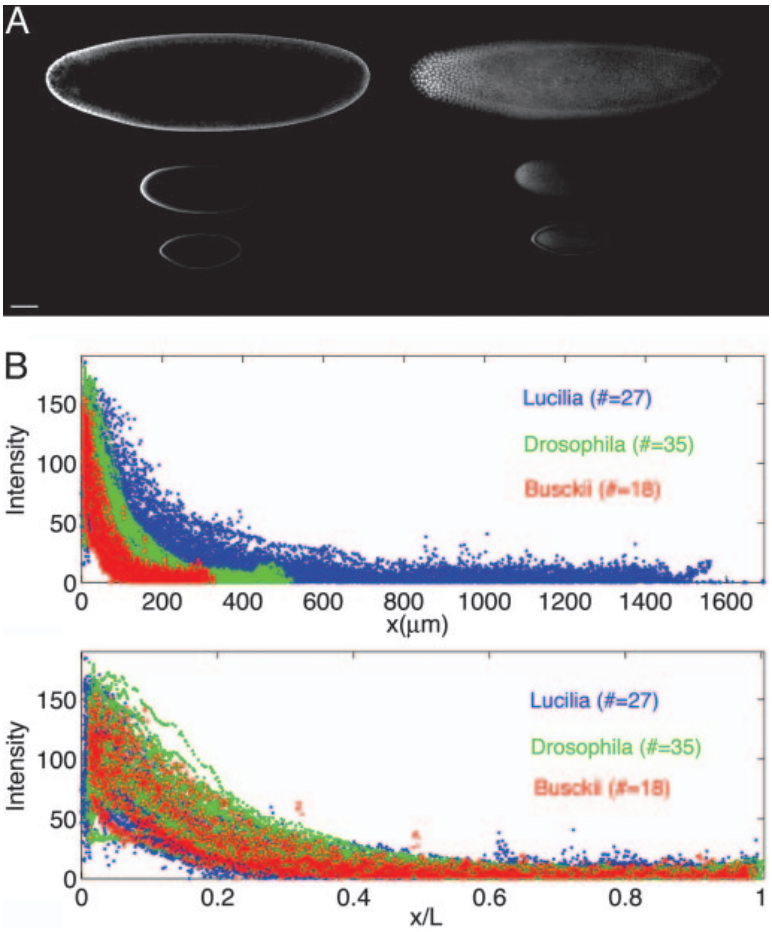

Figure 1: Fluorescence measurements of Bicoid gradients in three species of fruit fly, each with different embryo size. A. Representative images. B. Top, plots of measured gradients for each fly along the A-P axis. Bottom, the same data plotted versus the *fractional* distance along the A-P axis. Figure taken from Gregor, et al., Diffusion and scaling in early embryonic pattern formation, *PNAS*, 2005.

If you think in the context of evolution, mechanisms that produce gradients that scale might be more apt to survive selective pressure than those that do not. For example, if the size of the imaginal wing disc grows, if the gradient does not grow proportionately, then the wing will be disproportionate, possibly with more veins positioned toward the anterior of the wing. In this problem, we will explore mechanisms for gradient formation and investigate under what regimes they may exhibit scaling. (Note that in sections 4.3 and 4.4 of the lecture notes, we considered the scaling of a classic model for the Bicoid morphogen gradient and found that it does not scale.) 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) Does the model put forward in the paper exhibit scaling at steady state? They used several model variants. You may consider the model given by equations 53–57 in the supplemental text under the approximation that the receptors are far from saturated.

e) For 20 points extra credit, invent your own mechanism that can give approximate or exact scaling and demonstrate that it does.