Exercise 3

According to the French Flag model, morphogens form a gradient across a field of cells, and cells determine their fate according to the local concentration of the morphogen. In the previous exercise, you have studied models that lead to linear or exponential gradients in steady-state. In this exercise, you will solve a reaction-diffusion model that results in a power-law gradient. In the second part of the exercise you will study the effects of noise on the read-out of the morphogen gradient. In this context, you will learn about the advantages and disadvantages of different decay mechanisms.

1. **Review Material from the Lecture**
   - How do cells read out a morphogen gradient?
   - What affects the precision of a morphogen gradient read-out?
   - What happens to the morphogen read-out when the source strength varies?
   - Describe the problem of scaling! How could scaling be achieved with a steady-state exponential gradient?

2. **Gradient profiles.**

   In the previous exercise you determined the steady state solution of the PDE

$$\begin{aligned} \partial c/\partial t &= D\Delta c - k \cdot c^n \\ c(x=0,t) &= c_0, \qquad c(x \to \infty) = 0 \end{aligned} \tag{1}$$

   for $k = 0$ (no decay), and $n = 1$ (linear decay). Derive the (analytic) steady state solution for $n = 2$, i.e. non-linear decay.

   Hint. You should obtain a powerlaw gradient. You can transform the second order ODEs into a set of first order ODEs by writing $z = dc/dx$. You can then eliminate dx and solve the resulting equations by standard methods.

3. **Sensitivity of Gradients to a noisy Source**.

   Processes in biology are noisy, yet embryonic development is very precise. It is an open question how nature achieves this level of precision in spite of noise. In this exercise, we will quantify the expected shift in the pattern in response to a noisy morphogen source.

   In the previous exercise, you derived the steady state solutions of Eq. 1 for $n = 1$. Moreover, you showed that for $n = 1$, the position x_θ at which the concentration c_θ is obtained is given by

$$x_\theta = \lambda[\ln(c_\theta) - \ln(c_0)], \tag{2}$$

   and that a ψ-fold change in the left hand boundary value c_0 results in a shift in the position x_θ, at which c_θ is attained, by

$$\Delta x_\theta = \lambda \ln \psi. \tag{3}$$

i) Repeat the same analysis for $k = 0$, and $n = 2$.

ii) What is the steady state solution of c for $n > 2$? How does x_θ depend on c_0 for $n > 2$?

iii) Write the power-law solution from (ii) in terms of an exponential function. Note that you can make the transformation

$$C_0 x^{-m} = C_0 e^{-x\lambda(x)} \tag{4}$$

if you define $\lambda(x)$ accordingly. Sketch $\lambda(x)$ and calculate $\lim_{x\to\infty} \lambda(x)$.

iv) What are the (dis)advantages of linear ($n = 1$) or self-enhanced ($n > 1$) decay in buffering a noisy source? What effect does morphogen degradation have on the positional accuracy of the read-out in the presence of noise?

4. **Numerical Solution**. In the previous exercise, you obtained analytical and numerical solutions for

$$\begin{aligned} \partial c/\partial t &= D\Delta c - k \cdot c^n \\ c(x=0,t) &= c_0, \qquad c(x=L,t) = 0 \\ c(x=0,0) &= c_0, \qquad c(x>0,0) = 0. \end{aligned} \tag{5}$$

with $n = 1$ and default parameters $c_0 = 1$, $L = 50$, $D = 0.1$, $k = 10^{-5}$. You explored the effects of k, D, L, and the boundary condition on the shape and kinetics of the solution. We will now focus on the impact of non-linear decay ($n = 2$), and we will explore the impact of parameter variations on the read-out position x_θ. *Hint:* Use the Matlab function `pdepe` to obtain numerical solutions for the PDEs.

- *Impact of non-linear decay:* Solve Eq. 5 for $n = 2$ with the default parameters and compare your results to what you have previously obtained for $n = 1$. How does non-linear decay affect the solution?
- *Parameter dependency of the read-out position:* How is the read-out position, x_θ, with $c(x_\theta, t) = \exp(-1)$ and the relative read-out position, $\zeta_\theta = x_\theta/L$, affected by changes in D, k, or L? Do you observe differences for $n = 1$ and $n = 2$? Why?
- *Impact of the source strength on the read-out position:* The left hand side boundary condition reflects the contribution from the source. This contribution may differ between embryos.
  - Compare the shift in the read-out position, x_θ for the power-law gradient ($n = 2$) or the exponential gradient ($n = 1$) close to the source ($c(x_\theta, t) = \exp(-0.5)$) and far away from the source ($c(x_\theta, t) = \exp(-2)$), for a 2-fold increase or decrease in the left hand side boundary condition, c_0. Discuss your observations in light of your findings in Problem 3.
  - Plot the shift in the read-out position $\Delta x = x_\theta(c_0^*) - x_\theta(c_0)$ against $\ln\left(\frac{c_0^*}{c_0}\right)$ over the range $\frac{c_0^*}{c_0} \in [0.1, 10]$ for $n = 1$ and $n = 2$. Determine the slope. What does the slope correspond to? *Hint.* You can use the MATLAB function $\texttt{logspace}(-1, 1, 100)$ to define the range $\frac{c_0^*}{c_0} \in [0.1, 10]$.