Exercise 4

In this exercise, we will focus on reaction-diffusion equations on growing domains.

1. **Review Material from the Lecture**

   - Plot the velocity field of a uniformly growing domain. How does it differ from the velocity field of a domain that expands only at the right boundary (tip growth)? What is the divergence of the velocity field?
   - What are advection and dilution?
   - How do advection and dilution affect a gradient on a domain that is growing either uniformly or only at the tip?
   - What is the difference between a Eulerian and a Lagrangian reference frame?

2. **Reaction-diffusion equations on a growing domain**. If the change of the concentration $c(\vec{x}, t)$ in a domain Ω is only due to diffusion with diffusion coefficient D and reactions $R(c)$, we have

$$\frac{d}{dt} \int_{\Omega} c(\vec{x}, t)\, d\Omega = \int_{\Omega} (D\triangle c + R(c))\, d\Omega. \tag{1}$$

On a static domain Ω, we can swap the differentiation and integral operators as long as $c(x, t)$ and its spatial derivative, ∇c, are continuous. We then obtain the reaction-diffusion equation for a diffusible component c

$$\frac{\partial c}{\partial t} = D\triangle c + R(c). \tag{2}$$

As part of this exercise, we will show that on growing domains, the reaction-diffusion equation reads

$$\frac{\partial c}{\partial t} + \nabla \cdot (c\vec{u}) = D\triangle c + R(c). \tag{3}$$

Here, $u = \frac{d\vec{x}}{dt}$ is the velocity field. For more details, see [1].

   i) Use Eq. 1 and map the time-dependent domain Ω_t to a stationary domain Ω_ξ. *Hint:* $d\Omega_t = \det(J) d\Omega_\xi$, where J is the matrix of the linear mapping.

   ii) Expand the total derivative in the integrand by using the chain rule and the fact that $\frac{d \det(J)}{dt} = \det(J)\nabla \cdot \vec{u}$.

   iii) Map the equation back to the time-dependent domain Ω_t. What is the physical meaning of the new terms? How will they affect the results of the simulation?

iv) Finally, consider a uniformly growing 1D domain, described by $x(t) \in [0,\, L(t)]$, that expands linearly with time, such that the domain length follows $L(t) = L(0) + v \times t$. Show that in the Lagrangian framework with $\zeta = \frac{x}{L(t)} \in [0,\, 1]$,

$$\frac{\partial c}{\partial t} = \frac{D}{L^2}\frac{\partial^2 c}{\partial \xi^2} + R(c) - \frac{\dot{L}}{L}c. \tag{4}$$

3. **Numerical solution of morphogen gradients on growing domains**. Eq. 4 allows you to solve the reaction-diffusion equation for the dynamics of a ligand c on a growing domain, while only requiring a static domain in the numerical solution. Exploit this to obtain a numerical solution using a PDE solver of your choice (for instance `pdepe` in MATLAB).

   i) Use zero-flux boundary conditions and neglect both the reaction term and diffusion. Use a uniform starting concentration $c(\xi, 0) = 1$ and investigate the behavior of the concentration profile caused by growth. What effect are you observing?

   ii) Implement a constant production rate and a concentration-dependent decay rate of 0.01 such that the steady state concentration is 1. Start with a uniform concentration of 0.1, how does the profile change on a growing domain for different growth speeds?

   iii) Implement a small constant production rate without degradation. Is there a steady-state concentration or will the ligand accumulate infinitely?

4. **Dynamic Scaling of Morphogen Gradients**. During the growth of the *Drosophila* wing disc, the Dpp gradient forms a gradient from the centre of the pouch to the outside region that can be described by $c(x,t) = c_0 \exp\left(-\frac{x}{\lambda(t)}\right)$ [1]. The wing disc domain grows uniformly and expands according to $L(t) = L(0) + v \times t$. The amplitude and length of the Dpp gradient increase such that $\lambda(t) \sim 0.11 \times L(t)$ and $c(x = 0, t) \propto A^{\beta}$ with $\beta = 0.59$ and $A \propto L^2$.

   i) What is gradient scaling? How could dynamic scaling be explained if the Dpp gradient was in steady state?

   ii) How can dynamic scaling be explained if the Dpp gradient is in pre-steady state? What is the key condition for a pre-steady state? (see [2] for details)

   iii) Explain the contributions of advection, dilution and diffusion to dynamic scaling of the gradient profile.

   iv) Use the PDE solver of choice (for instance pdepe in MATLAB) to solve Eq. 4 on the domain $\xi = [0, 1]$ with $D = 5$, $R(c) = 0$, $L(0) = 50$, $v = 2.5$ and $t = [0, 100]$. As boundary condition use $\left.\frac{\partial c}{\partial \xi}\right|_{\xi=0} = -0.1$ and $\left.\frac{\partial c}{\partial \xi}\right|_{\xi=1} = 0$. Plot $c(\xi,t)/\max(c(t))$ versus ξ, and plot $\sqrt{E[x^2]}$ as a measure of the length of the gradient versus the length of the domain $L(t)$ - what do you observe? Why?

v) How can the resulting, imperfectly scaling gradient be used for the threshold-dependent definition of gene expression boundaries? (see [3] for details)

vi) Do you expect the mechanism to apply generally in development? What are the limitations?

References

[1] Iber D, Tanaka S, Fried P, Germann P, Menshykau D. 21. In: Nelson CM, editor. Simulating Tissue Morphogenesis and Signaling. vol. 1189 of Methods in Molecular Biology (Springer). New York, NY: Springer New York; 2015. p. 323–338. Available from: http://link.springer.com/10.1007/978-1-4939-1164-6_21.

[2] Fried P, Iber D. Dynamic scaling of morphogen gradients on growing domains [Journal Article]. Nat Commun. 2014;5:5077. Available from: http://www.nature.com/doifinder/10.1038/ncomms6077.

[3] Fried P, Iber D. Read-Out of Dynamic Morphogen Gradients on Growing Domains [Journal Article]. PLoS One. 2015;10(11):e0143226. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26599604http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4657938/pdf/pone.0143226.pdf.