Exercise 1

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. During development, tissues are typically growing. Therefore, it is important to understand how this can be taken into account in the model. In this exercise, we will consider the effect of growth on gradient dynamics.

1. **Reaction-diffusion equations on a growing domain**.

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

describes the spatio-temporal dynamics of the concentration $c(x,t)$ in a domain Ω due to diffusion with diffusion coefficient D and reactions $R(c)$. 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,

$$\frac{d}{dt}\int_{\Omega} c(x,t)\,d\Omega = \int_{\Omega} \frac{d}{dt} c(x,t)\,d\Omega. \tag{2}$$

We then obtain the reaction-diffusion equation

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

As part of this exercise, we will derive the reaction-diffusion equation for c on a growing domain. For more details on steps i-iii, see [1].

i) Use the Lagrangian approach 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) Solve the derivative in the integrand by using the chain rule and the fact that $\frac{d\det(J)}{dt} = \det(J)\nabla u$, where $u = \frac{\partial x}{\partial t}$ is the velocity field of the growing domain.

iii) Map the equation back to the time-dependent domain Ω_t. How do the time derivatives of c differ on the static and growing domains? What is the physical meaning of the new terms? How will they effect the results of the simulation?

iv) Consider a uniformly growing domain that expands linearly with time, i.e. $x = L(t)\xi$ and $L(t) = L(0)+v\times t$. Determine the reaction-diffusion equation for c in the Lagrangian framework. Note that the resulting formula now allows you to solve the reaction-diffusion equation for the dynamics of a ligand c on a growing domain, while operating on a static domain.

v) How can gradients scale on uniformly, linearly growing domains? For more details, see [2].

vi) How can imperfect scaling help with the read-out of the morphogen gradient? For more details, see [3]

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

References

[1] Dagmar Iber, Simon Tanaka, Patrick Fried, Philipp Germann, and Denis Menshykau. *Simulating Tissue Morphogenesis and Signaling*, volume 1189 of *Methods in Molecular Biology (Springer)*, book section 21, pages 323–338. Springer New York, New York, NY, 2015.

[2] P. Fried and D. Iber. Dynamic scaling of morphogen gradients on growing domains. *Nat Commun*, 5:5077, 2014.

[3] P. Fried and D. Iber. Read-out of dynamic morphogen gradients on growing domains. *PLoS One*, 10(11):e0143226, 2015.