Exercise 9

1. **Ca^{2+} Waves on Amphibian Eggs.** Upon fertilization calcium waves can be observed on amphibian eggs. In the following we will assume that Ca^{2+} diffuses on the cortex (surface) of the egg. We thus have a reaction diffusion model where both the reaction and the diffusion take place on a spherical surface. Since the Ca^{2+} wavefront is actually a ring propagating over the surface its mathematical description will involve only one independent variable θ, the polar angle measured from the top of the sphere, so $0 \leq \theta \leq \pi$. We write

$$\frac{\partial u}{\partial t} = f(u) + D\Delta_s u$$

where $f(u) = A(u - u_1)(u_2 - u)(u - u_3)$, $A > 0$ describes the excitable Ca^{2+} kinetics. Δ_s is the spherical Laplace operator.

a) Show that the operator Δ_s is given by

$$\Delta_s = \frac{1}{r^2 \sin(\theta)} \frac{\partial}{\partial \theta}(\sin(\theta) \frac{\partial}{\partial \theta}) = \frac{1}{r^2} \left(\frac{\partial^2}{\partial \theta^2} + \cot(\theta) \frac{\partial}{\partial \theta} \right). \tag{1}$$

b) Show that for fixed θ we obtain a wavefront solution of the form

$$u(\theta, t) = U(z), \qquad z = R\theta - ct \tag{2}$$

with wave speed

$$c = \sqrt{\frac{AD}{2}}(u_1 - 2u_2 + u_3) - \frac{D}{R} \cot \theta. \tag{3}$$

c) Discuss how the wave speed changes as the wave propagates over the surface of the egg. How well does the model capture the biology?

2. **Wave Pinning.** Consider the equation

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} + f(a, b).$$

Suppose a develops a propagating front on $0 < x < L$, sufficiently far from the boundaries.

a) Use

$$A(z) = A(x - ct) = a(x, t).$$

to map $a(x,t)$ to the travelling wave reference frame (and thereby convert the PDE to a second order ODE).

b) Show that the wave speed is given by

$$c = \frac{\int_{a-}^{a+} f(a,b)da}{\int_{-\infty}^{\infty} \left(\frac{\partial A}{\partial z}\right)^2 dz}.$$

[*Hint: Multiply the resulting second order ODE by A' and integrate from* $-\infty$ to ∞. *Then use that* $A'(\pm\infty) = 0$ *(flat part of wave) and* $A(-\infty) = a_-$ and $A(\infty) = a_+$.]

c) What are the conditions for wave pinning? Under what conditions could wave pinning be observed for

$$f(a,b) = b\left(k_0 + \frac{\gamma a^2}{K^2} + a^2\right) - \delta a.$$

3. **Hes oscillations during vertebrate body segmentation.**

In 2003, Julian Lewis proposed a simple model that describes the dynamics of *her* genes (*Hes* in mammals) providing a mechanistic molecular model for the intracelular oscillator that controls body segmentation in zebrafish [**?**]. The model consists of the dynamics of *her* mRNA (m) and protein (p) given by the following delayed differential equations:

$$\frac{d}{dt}m = g[t-\tau] - bm, \tag{4}$$

$$\frac{d}{dt}p = am - bp, \tag{5}$$

where τ represents the delay, b represents mRNA and protein degradation rate, and a represents the translational rate. The production rate of *her* mRNA in the time t is defined by the following function:

$$g[t] = kH^-(p[t]) \tag{6}$$

where k is the basal production rate, $p[t]$ represents the amount of *her* proteins in the time t and H^- is a negative Hill function: $H^-(x) = \frac{1}{1+(x/x_0)^n}$.

a) Show that in the absence of delay ($\tau = 0$), the ODE system is a stable focus. Plot the nullclines.

b) Find the eigenvalues of the DDE system. Assuming small delays, show that the solution of the system has a Hopfield bifurcation (goes from has a stable focus to a oscillatory solution) when

$$\tau = \frac{2}{nbH^+(p^*)} \tag{7}$$

where $(m,p) = (m^*,p^*)$ is the equilibrium point of the ODE system.

c) Show that at the Hopfield bifurcation, the period of oscillations is given by:

$$T_{Hopf} = \frac{\pi}{b}\sqrt{\frac{1+\frac{nb^2}{2}H^+(p^*)\tau^2}{1+nH^+(p^*)}}. \tag{8}$$

Hint: The eigenvalues of the DDE system can be obtained by solving the determinant:

$$\det(-\lambda I + A_0 + A_1 e^{-\lambda\tau}) = 0 \tag{9}$$

where the caracteristic equation of the DDE system is:

$$\frac{d\mathbf{x}}{dt} = A_0\mathbf{x}(t) + A_1\mathbf{x}(t-\tau). \tag{10}$$

Also, assume that for small delays:

$$e^{-\lambda\tau} \simeq 1 - \lambda\tau + \frac{\lambda^2\tau^2}{2}. \tag{11}$$

References

[1] Lewis, J. Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator. *Current Biology.* 2003.