Computational Biology

Chapter 3: Continuous modeling using PDEs

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Continuous modelling by PDEs

Reaction-diffusion equations

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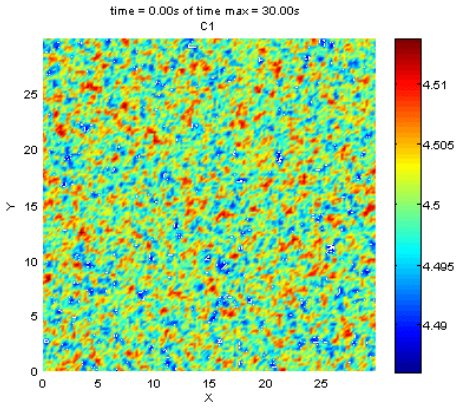
Biological processes in time and space

- Biological systems have complex internal structure capable of formation of intricate patterns on all levels of organization from individual cell to large scale patterns exhibited by populations.
- Science arrived at two seemingly contradictory conclusions: the biological processes are governed by the (old) physical/chemical principles; we continue to discover deeper levels of complexity which never stop to bewilder us.

Things moving around: reaction-diffusion equations

- One common method of quantitative description for spatial inhomogeneous systems which has enjoyed wide and successful applicability is through the use of PDEs (partial differential equations) known as reaction-diffusion equations.
- These equations are a natural extension for a spatial distributed case of the mass action laws.



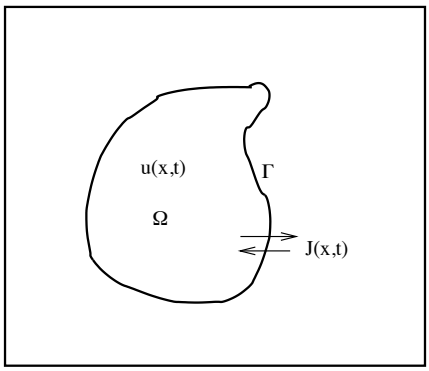
A biochemical reaction

- Suppose a biochemical reaction occurring among solutes in a relatively large, unstirred solution.
- The dynamics of the system is not only governed by the dynamics of the rate at which the biochemical react, but also by the fact there can be spatial variation in solute concentrations, which entails that diffusion of the reactants can occur.
- Modelling such a system requires taking into account both reaction and diffusion.
- We will study how to model such phenomena and how (when possible) to solve the resulting equations in detail.

Derivation of the reaction-diffusion equations

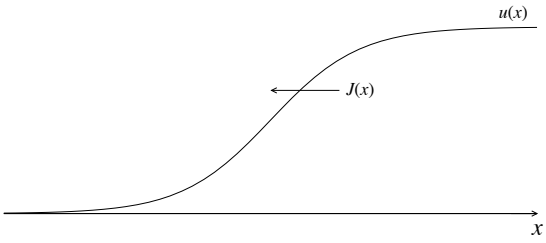
- Suppose a chemical species U, of concentration $u(x, t)$ – typically measured in mol m^{-3} –, is living (dependence on time) and moving (dependence on space) in a container.
- To describe the movement, we introduce another quantity: the flux $J(x, t)$ – typically measured in mol m^{-2} s^{-1}.

The flux



- At each location x and at each time t, the flux $J(x,t)$ is a vector which points in the general direction of movement at that location.
- Its magnitude, $|J(x,t)|$, is proportional to the amount of particles which flow in that direction per unit time.
- Specifically, the flux J plays the role of the heat flux in heat transport, or a concentration flux for a chemical reactor.

Ficks Law of Diffusion



- Ficks Law of Diffusion relates the flux J to the gradient of u via

$$J = -D\nabla u,$$

  where D, the diffusion coefficient, is independent of u and ∇u.
- The flux is proportional to the negative gradient of the concentrations.

Mass balance

- We consider a test volume Ω with boundary Γ and we balance the fluxes inward and outward through Γ

Change of u in Ω = flux through Γ+ changes due to reactions

- In mathematical terms, this is given by

$$\frac{\partial}{\partial t}\int_\Omega u(x,t)dV = -\int_\Gamma J(x,t)dS + \int_\Omega f(u(x,t))dV,$$

where $f(u(x,t))$ describes the rate of change of the concentration u.

- By the divergence theorem ($\int_\Gamma J(x,t)dS = \int_\Omega \text{div } J(x,t)dV$)

$$\int_\Omega \frac{\partial}{\partial t}u(x,t) + \text{div } J(x,t) - f(u(x,t))dV = 0$$

and so (if the mesure dV is not degenerate) the Mass Balance Law is

$$\frac{\partial u}{\partial t} + \text{div } J - f(u) = 0.$$

Reaction-Diffusion Equation

Combining:

- Mass Balance Law

$$\frac{\partial u}{\partial t} + \text{div } J - f(u) = 0$$

- Ficks Law of Diffusion

$$J = -D\nabla u,$$

we get a reaction-diffusion equation

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

where the Laplacian Δu is defined as

$$\Delta u(x,t) = \sum_{j=1}^{n} \frac{\partial^2}{\partial x_j^2}u(x,t).$$

The fundamental solution for the diffusion equation

- Consider the initial value problem in one dimension

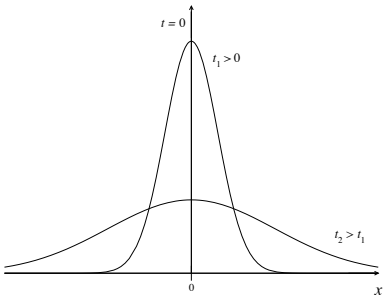
$$\frac{\partial g}{\partial t} = D\frac{\partial^2 g}{\partial x^2}, \qquad g(x,0) = \delta_0(x).$$

- The $\delta-$distribution $\delta_0(x)$ (a.k.a. Dirac-delta function) is not a function in the classical sense. It $f(x)$ is a smooth function, the $\delta_0(x)$ is the only object which satisfies

$$\int_{\mathbb{R}} \delta_0(x) f(x) dx = f(0), \qquad \int_{\mathbb{R}} \delta_0(x) dx = 1.$$

- The fundamental solution is given by

$$g(x,t) = \frac{1}{\sqrt{4\pi D t}} e^{-\frac{x^2}{4Dt}}.$$



Root-mean-square displacement (∗)

- From this we can obtain the root-mean-square displacement of a diffusion particle in one-dimension.
- From statistical physics we know that the average quadratic displacement of a particle starting at $(x,t) = (0,0)$ is given by

$$\langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 \underbrace{g(x,t)}_{\text{p.d.f.}} dx = 2Dt$$

then

$$x_{rms} = \sqrt{\langle x^2 \rangle} = \sqrt{2Dt}.$$

- In three dimensions this result converts to $x_{rms} = \sqrt{6Dt}$.
- This result can also be rewritten in the form convenient for calculation of time necessary for the particle to travel certain distance R

$$t = \frac{R^2}{6D}.$$

The fundamental solution for general initial condition

If we study the diffusion equation with a general initial condition,

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2}, \qquad u(x,0) = u_0(x).$$

then the solution can be found by convolution with g

$$u(x,t) = (u_0 * g(\cdot,t))(x),$$

where the convolution integral is given by

$$\begin{aligned}(u_0 * g(\cdot,t))(x) &= \int_{-\infty}^{\infty} u_0(y)g(x-y,t)dy \\ &= \frac{1}{\sqrt{4\pi Dt}}\int_{-\infty}^{\infty} u_0(y)e^{-\frac{(x-y)^2}{4Dt}}dy.\end{aligned}$$

What defines the diffusion coefficient D? $(*)$

- Theoretic estimates for the diffusion coefficient can be obtained from the Einstein theory of Brownian motion. For a spherical particle with radius r

$$D = \frac{k_b T}{6\pi\mu r},$$

where T is temperature, k_b is the Boltzmann's constant and μ is the dynamic viscosity.

- The radius of a molecule can be estimated from its molecular weight and density

$$M = \frac{4}{3}\pi r^3\rho \Rightarrow D = \frac{k_b T}{3\mu}\left(\frac{\rho}{6\pi^2 M}\right)^{1/3} \Rightarrow DM^{1/3} \approx CT,$$

where C is a constant. If $M < 1000$, $DM^{1/2} \approx CT$.

Molecular weight and diffusion coefficients (∗)

Molecular weight and diffusion coefficients of some biochemical substances in dilute aqueous solution at 20°C.

Substance	M (g/mol)	D (cm^2/s)
Glycine	75	9.34×10^{-6}
Glucose	192	6.60×10^{-6}
Insuline	5 734	2.10×10^{-6}
Cytochrome C	13 370	1.14×10^{-6}
Hemoglobine	64 500	0.69×10^{-6}
Catalase	247 500	0.41×10^{-6}
Myosin	524 800	0.105×10^{-6}
Tobacco mosaic virus	40 590 000	0.053×10^{-6}

Time scales

- For a given length scale, L, and diffusion coefficient, D, the timescale of the system is $t \approx L^2/D$.
- For a cell, $L \approx 10^{-3}$ cm and a typical protein $D \approx 10^{-7}$ cm^{2}s^{-1}, the time scale for diffusion to homogenise spatial gradients of this protein within a cell is

$$t \approx \frac{L^2}{D} \approx \frac{10^{-6}}{10^{-7}} = 10 \text{ s}.$$

- Therefore, we can often neglect diffusion in a cell.
- However, as the scale doubles the time scales squares e.g.

$$L_1 = L \times 10 \Rightarrow t_1 = t \times 100, \qquad L_2 = L \times 100 \Rightarrow t_2 = t \times 10^4.$$

Homework #9: Signaling in ant populations

Exercise 3.1: Certain ant species (such as *Pogonomyrmex badius*) use pheromones as a signal for danger. A good model for the spread of the pheromones in the tube is the one-dimensional diffusion equation. In experiments, Bossert and Wilson released ants in a long tube and stimulated one ant until it released a pheromone. They measured within which distance and after which time delay the other ants would react to the signal. Weassume that at time $t = 0$ a signal of strength α is released. The diffusion constant is $D = 1$. Other ants react to the stimulus if the concentration they perceive is 10% of α or higher.

1. For each $t > 0$, find the region in the tube $0 < x < x(t)$ where the ants would react to the stimulus (region of influence).
2. Sketch the time evolution of $x(t)$.
3. Find the time t^* such that the region of influence is empty for all $t > t^*$.