Chapter 4

Introduction to spatial variation

Both in the Part A *Mathematical Modelling in Biology* course, and this course so far, we have considered biological, biochemical and ecological phenomena for which spatial effects are not important. This is, however, often not the case. Consider a biochemical reaction as an example. Suppose this reaction involves solutes in a relatively large, *unstirred* solution. Then the system dynamics are governed not only by the rates at which the biochemicals react, but also by possible spatial variation in solute concentrations; in such cases, diffusion of the reactants can occur. Modelling such systems requires that we account for both reaction and diffusion.

A similar problem arises in population and ecological models when we wish to describe the tendency of a species to spread into a region it has not previously populated. Notable examples include ecological invasions, where one species invades another's territory (as with grey and red squirrels in the UK [11]), or the spread of disease. When developing mathematical descriptions of some, though by no means all, of these ecological and disease-spread systems, the appropriate transport mechanism is again diffusion; when modelling such systems we must include both reaction and diffusion. In addition, motile cells can move in response to external influences, such as chemical concentrations, light, mechanical stress and electric fields, among others. Of particular interest is modelling when motile cells respond to gradients in chemical concentrations, a process known as *chemotaxis*; we will also consider this scenario.

In the following chapters, we will learn how to model such phenomena and how (when possible) to solve and / or analyse the resulting partial differential equations, for a range of models drawn from biology, biochemistry and ecology. Most of the partial differential equations that we will

study can be written in the general form

$$\begin{pmatrix} \text{rate of change} \\ \text{of species} \end{pmatrix} = \begin{pmatrix} \text{net movement/flux} \\ \text{of species} \end{pmatrix} + \begin{pmatrix} \text{net rate of production} \\ \text{of species} \end{pmatrix}. \tag{4.1}$$

This is the **Principle of Mass Balance**.

4.1 Derivation of the reaction-diffusion equations

Let $i \in \{1, \ldots, m\}$. Suppose the chemical species C_i, of concentration c_i, is undergoing a reaction such that, in the absence of diffusion, one has

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = R_i(c_1, c_2, \ldots, c_m). \tag{4.2}$$

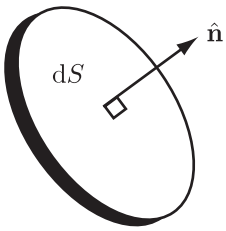
In Equation (4.2), $R_i(c_1, c_2, \ldots, c_m)$ is the total rate of production/destruction of C_i *per unit volume*, *i.e.* it is the rate of change of the concentration c_i.

Let t denote time, and $\boldsymbol{x}$ denote the position vector of a point in space. We define

- $c(\boldsymbol{x}, t)$ to be the concentration of a chemical (typically measured in mol m^{-3}).
- $\boldsymbol{q}(\boldsymbol{x}, t)$ to be the flux of the same chemical (typically measured in mol m^{-2} s^{-1}).

Now the flux of a chemical is defined such that, for a given infinitesimal surface element, of area $\mathrm{d}S$ and unit normal $\hat{\mathbf{n}}$, the amount of chemical flowing through the surface element in an infinitesimal time interval, of duration $\mathrm{d}t$, is given by

$$\hat{\mathbf{n}} \cdot \boldsymbol{q} \, \mathrm{d}S\mathrm{d}t. \tag{4.3}$$



Definition. *Fick's Law of Diffusion* relates the flux $\boldsymbol{q}$ to the gradient of c via

$$\boldsymbol{q} = -D\nabla c, \tag{4.4}$$

where D, the diffusion coefficient, is independent of c and ∇c.

Using the Principle of Mass Balance, we have, for any closed volume V (fixed in time and space), with bounding surface ∂V,

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_V c_i \, \mathrm{d}V = -\int_{\partial V} \boldsymbol{q} \cdot \mathbf{n} \, \mathrm{d}S + \int_V R_i(c_1, c_2, \ldots, c_m) \, \mathrm{d}V, \quad i \in \{1, \ldots, m\}. \tag{4.5}$$

Hence

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_V c_i \,\mathrm{d}V = -\int_V \nabla\cdot\boldsymbol{q}\,\mathrm{d}V + \int_V R_i(c_1,c_2,\ldots,c_m)\,\mathrm{d}V \tag{4.6}$$

$$= \int_V \{\nabla\cdot(D_i\nabla c_i) + R_i(c_1,c_2,\ldots,c_m)\}\,\mathrm{d}V, \tag{4.7}$$

and thus for any closed volume, V, with surface ∂V, we have

$$\int_V \left\{\frac{\partial c_i}{\partial t} - \nabla\cdot(D_i\nabla c_i) - R_i\right\}\mathrm{d}V = 0, \quad i\in\{1,\ldots,m\}. \tag{4.8}$$

Hence

$$\frac{\partial c_i}{\partial t} = \nabla\cdot(D_i\nabla c_i) + R_i, \quad \boldsymbol{x}\in\mathcal{D}, \tag{4.9}$$

which constitutes a system of reaction-diffusion equations for the m chemical species in the finite domain $\mathcal{D}$. Such equations must be supplemented with initial and boundary conditions for each of the m chemicals.

Warning. Given, for example, that

$$\int_0^{2\pi}\cos\theta\,\mathrm{d}\theta = 0 \quad \not\Rightarrow \quad \cos\theta = 0, \quad \theta\in[0,2\pi], \tag{4.10}$$

are you sure one can deduce Equation (4.9)?

Suppose

$$\frac{\partial c_i}{\partial t} - \nabla\cdot(D_i\nabla c_i) - R_i \neq 0, \tag{4.11}$$

at some $\boldsymbol{x} = \boldsymbol{x}^*$. Without loss of generality, we can assume the above expression is positive *i.e.* the left-hand side of Equation (4.11) is positive. Then $\exists\,\epsilon > 0$ such that

$$\frac{\partial c_i}{\partial t} - \nabla\cdot(D_i\nabla c_i) - R_i > 0, \tag{4.12}$$

for all $\boldsymbol{x}\in\mathcal{B}_\epsilon(\boldsymbol{x}^*)$. In this case

$$\int_{\mathcal{B}_\epsilon(\boldsymbol{x}^*)}\left[\frac{\partial c_i}{\partial t} - \nabla\cdot(D_i\nabla c_i) - R_i\right]\mathrm{d}V > 0, \tag{4.13}$$

contradicting our original assumption, Equation (4.8). Hence our initial supposition is false and Equation (4.9) holds for $\boldsymbol{x}\in\mathcal{D}$.

Remark. With one species that has a constant diffusion coefficient, in the absence of reactions, we have the diffusion equation. In one spatial dimension this reduces to

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}. \tag{4.14}$$

For a given length scale, L, and diffusion coefficient, D, the timescale of the system is $T = L^2/D$. For a cell, $L \sim 10^{-5}\text{m} = 10^{-3}\text{cm}$, and for a typical protein $D \sim 10^{-7}\text{cm}^2\text{s}^{-1}$ would not be unreasonable. Thus the timescale for diffusion to homogenise spatial gradients of a typical protein within a cell is

$$T \sim \frac{L^2}{D} \sim \frac{10^{-6}\ \text{cm}^2}{10^{-7}\ \text{cm}^2\ \text{s}^{-1}} \sim 10\ \text{s}, \tag{4.15}$$

therefore we can often neglect diffusion in a cell. However, as the length scale doubles, the time scale squares *e.g.* $L \mapsto L \times 10 \Rightarrow T \mapsto T \times 10^2$ and $L \mapsto L \times 10^2 \Rightarrow T \mapsto T \times 10^4$.

Note. The derivation of the reaction-diffusion equations generalises to situations other than modelling chemical or biochemical diffusion. For example, let $I(x, y, t)$ denote the number of infected people per unit area. Assume the infectives, on average, spread out via a random walk and interact with susceptibles, as described by the Law of Mass Action (see Section 5.2.1). Then the flux of infectives, $\boldsymbol{q}_I$, is given by

$$\boldsymbol{q}_I = -D_I \nabla I, \tag{4.16}$$

where D_I is a constant, with dimensions of (length)^2 (time)$^{-1}$. Thus, via precisely the same ideas and arguments as above, we have that

$$\frac{\partial I}{\partial t} = \nabla \cdot (D_I \nabla I) + rIS - aI, \tag{4.17}$$

where $S(x, y, t)$ is the number of susceptibles per unit area, and r is the rate at which susceptibles become infected on contact with infecteds, and a is the rate at which infecteds recover from the disease (see Section 5.2.1 for more details).

Fisher–KPP equation. A common example is the combination of logistic growth and diffusion which, in one spatial dimension, gives rise to the Fisher–KPP equation:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru\left(1 - \frac{u}{K}\right). \tag{4.18}$$

This equation was first proposed to model the spread of an advantageous gene through a population. See Section 5.1 for more details.

4.2 Chemotaxis

As briefly mentioned earlier, motile cells can move in response to spatial gradients in chemical concentrations, a process known as chemotaxis. This leads to slightly more complicated transport equations, as we shall see [6].

The diffusive flux for the population density of the cells, n, is as previously: $\boldsymbol{J}_D = -D_n \nabla n$. The flux due to chemotaxis (assuming it is an attractant rather than a repellent) takes the form

$$\boldsymbol{J}_C = n\chi(c)\nabla c = n\nabla\Phi(c), \tag{4.19}$$

where c is the chemical concentration and $\Phi(c)$ increases monotonically with c. Clearly $\chi(c) = \Phi'(c)$; the cells move in response to a gradient of the chemical in the direction in which the function $\Phi(c)$ is increasing at the fastest rate. Thus the total flux $\boldsymbol{J}$ is

$$\boldsymbol{J} = \boldsymbol{J}_D + \boldsymbol{J}_C = -D_n \nabla n + n\chi(c)\nabla c. \tag{4.20}$$

If we assume that the behaviour of the cells is dominated by their diffusive and chemotactic transport together with their rate of reproduction and/or death, then we can use the Principle of Mass Balance to derive a partial differential equation that describes how their distribution changes over time. We need an additional reaction-diffusion partial differential equation for the evolution of chemical concentration. We assume it diffuses and, typically, is secreted and degrades. In this way, we arrive at the following equations for the cells, n, and the cell-derived chemical, c:

$$\frac{\partial n}{\partial t} = \nabla \cdot (D_n \nabla n) - \nabla \cdot (n\chi(c)\nabla c) + f(n, c); \tag{4.21}$$

$$\frac{\partial c}{\partial t} = \nabla \cdot (D_c \nabla c) + \lambda n - \mu c. \tag{4.22}$$

In the above the above $f(n, c)$ is often taken to be a logistic growth term while the function $\chi(c)$ describing chemotaxis has many forms, including

$$\chi(c) = \frac{\chi_0}{c}, \tag{4.23}$$

$$\chi(c) = \frac{\chi_0}{(k + c)^2}, \tag{4.24}$$

where the latter represents a receptor law, with $\Phi(c)$ taking a Michaelis-Menten form [6].

4.3 Positional information and pattern formation

Patterns are ubiquitous in biology. Consider, for example, animal coat markings on tigers, leopards and tropical fish. Consider, also, the well-defined pattern of bones and digits (fingers, thumbs and toes) and teeth that appear during human development. There are two main theories about how such patterns arise:

- Alan Turing's concept of **diffusion-driven instability** which we will study in Chapter 6. Turing's original paper was published in 1952 [14]);
- Lewis Wolpert's theory of **positional information** which is often also known as the French Flag Model (see [17]). We will study this theory below.

4.3.1 The French Flag Model

Consider a one-dimensional chain of cells that occupies the region $0 \leq x \leq L$. Suppose that a morphogen (signalling molecule), $m(x,t)$, enters the domain through $x = 0$, diffuses across the domain (with diffusion coefficient D), and is removed at $x = L$. If we assume that initially there is no morphogen in the domain, then the distribution of $m(x,t)$ can be described by the following equation

$$\frac{\partial m}{\partial t} = D\frac{\partial^2 m}{\partial x^2}, \tag{4.25}$$

with

$$m(0,t) = m_0, \quad m(L,t) = 0, \quad m(x,0) = 0, \tag{4.26}$$

where the positive constant m_0 defines the morphogen concentration at $x = 0$.

We assume that the morphogen rapidly establishes a fixed spatial profile, $m_s(x)$, which we determine by setting $\partial m/\partial t = 0$ in Equation (4.25):

$$\frac{\mathrm{d}^2 m_s}{\mathrm{d}x^2} = 0 \quad \Longrightarrow \quad m_s(x) = m_0\left(1 - \frac{x}{L}\right). \tag{4.27}$$

The French Flag Model then assumes that cells on the left (near $x = 0$) sense high morphogen levels and respond in some way (*e.g.* they turn blue), whilst cells in the centre and on the right sense intermediate and low levels of morphogen, respectively, and response in different ways (*e.g.* they turn white and red, respectively). See Figure 4.1 for an illustration.

To determine the widths of the red, white and blue regions, we introduce the positive constants

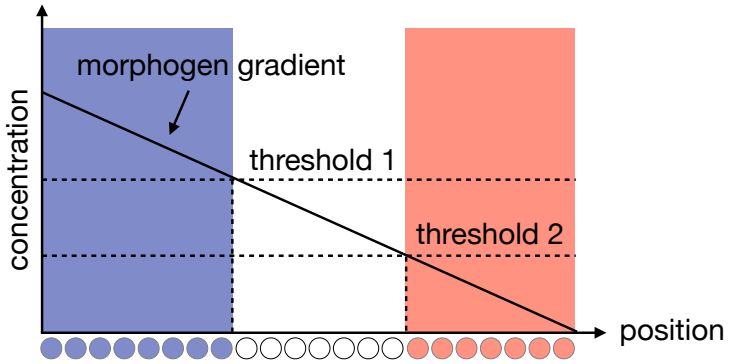


Figure 4.1: Schematic diagram of the French Flag Model. Cells that experience a morphogen concentration above threshold 1 turn blue, those that experience a morphogen concentration between threshold 1 and threshold 2 turn white, and those that experience a morphogen concentration below threshold 2 turn red.

$0 < m_W < m_B < m_0$ and define the spatial locations $0 < x_B < x_W < L$ such that

$$m_s(x = x_B) = m_B, \quad m_s(x = x_W) = m_W. \tag{4.28}$$

It is straightforward to show:

$$\text{width of blue region} = x_B = \left(1 - \frac{m_B}{m_0}\right) L; \tag{4.29}$$

$$\text{width of white region} = x_W - x_B = \left(\frac{m_B}{m_0} - \frac{m_W}{m_0}\right) L; \tag{4.30}$$

$$\text{width of red region} = L - x_W = \left(\frac{m_W}{m_0}\right) L. \tag{4.31}$$

Notes.

- The sizes of the red, white and blue regions are independent of the morphogen diffusion coefficient: do you think this is realistic?
- How do the widths of the different regions change as the domain size, L, and the right-hand boundary concentration, m_0, are varied? How do they depend on the threshold morphogen levels m_B and m_W?
- More complex models for positional information can be developed, to account for *e.g.* multiple morphogens, different boundary conditions and the decay of morphogens as they diffuse across the domain.
- In other biological applications (*e.g.* the intestinal crypt), positional information may determine whether cells proliferate, mature and/or die and, in this way, specify tissue size. In Chapter 6, we will study problems of this type, where the domain size depends on the distribution of a morphogen.

4.4 Minimum domains for spatial structure

Finally in this chapter, we explore whether there may be constraints on the size of a domain in terms of being able to support the growth of a population. To do so, we consider a dimensionless model for budworm dynamics. The budworm spread by diffusion on a one-dimensional domain, $0 \leq x \leq L$, and undergo logistic growth and predation by birds:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u), \quad \text{where} \quad f(u) = ru\left(1 - \frac{u}{q}\right) - \frac{u^2}{1+u^2}. \tag{4.32}$$

We suppose that exterior to the domain conditions are extremely hostile to budworm so that we have the boundary conditions

$$u(0,t) = 0, \quad u(L,t) = 0. \tag{4.33}$$

Clearly $u = 0$ is a solution of Equations (4.32)–(4.33). However, if we start with a small initial distribution of budworm, will the budworm die out, or will there be an outbreak of budworm? In particular, how does what happens depend on the domain size?

For initial conditions with $0 \leq u(x,0) \ll 1$, *i.e.* where there is initially a sufficiently small outbreak, we can approximate $f(u)$ by $f'(0)u = ru$, at least while $u(x,t)$ remains small. Then Equations (4.32)–(4.33) are, approximately,

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f'(0)u, \quad \text{with} \quad u(0,t) = 0, \quad u(L,t) = 0. \tag{4.34}$$

We look for a solution of the form (invoking completeness of Fourier series)

$$u(x,t) = \sum_{n=1}^{\infty} a_n(t) \sin\left(\frac{n\pi x}{L}\right). \tag{4.35}$$

This gives that the time-dependent coefficients satisfy

$$\frac{\mathrm{d}a_n}{\mathrm{d}t} = -\frac{Dn^2\pi^2}{L^2}a_n + f'(0)a_n = \sigma_n a_n, \tag{4.36}$$

and hence

$$u(x,t) = \sum_{n=1}^{\infty} a_n(0) \exp\left[\left(f'(0) - \frac{Dn^2\pi^2}{L^2}\right)t\right] \sin\left(\frac{n\pi x}{L}\right). \tag{4.37}$$

For the solution to decay to zero, *i.e.* for the outbreak to die out, we require that all Fourier modes decay to zero as $t \to \infty$. Hence, we require that

$$\sigma_n < 0 \quad \forall n \quad \Longrightarrow \quad f'(0) - \frac{Dn^2\pi^2}{L^2} < 0 \quad \forall n, \tag{4.38}$$

or, equivalently,

$$f'(0) < \frac{Dn^2\pi^2}{L^2} \quad \Longrightarrow \quad L \leq \sqrt{\frac{D\pi^2}{f'(0)}} \stackrel{\text{def}}{=} L_{\text{crit}}. \tag{4.39}$$

Hence there is a critical lengthscale, L_{crit}, beyond which an outburst of budworm is possible in a spatially distributed system.

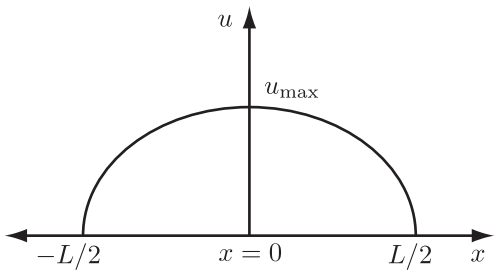
4.4.1 Domain size

On first inspection it is perhaps surprising that L_{crit} increases with the diffusion coefficient, *i.e.* diffusion is destabilising the zero steady state. We can further investigate how the nature of a steady state pattern depends on the diffusion coefficient.

Suppose $L > L_{\text{crit}}$, and we shift coordinates so that $x \in [-L/2, L/2]$ with

$$u(-L/2, t) = 0, \quad u(L/2, t) = 0, \tag{4.40}$$

and that the steady state is of the form shown in the right-hand figure.



At steady state we have

$$0 = D\frac{\partial^2 u}{\partial x^2} + f(u). \tag{4.41}$$

Multiplying by $\partial u/\partial x$ and integrating with respect to x gives

$$0 = \int D\frac{\partial u}{\partial x}\frac{\partial^2 u}{\partial x^2}\,\mathrm{d}x + \int \frac{\partial u}{\partial x} f(u)\,\mathrm{d}x. \tag{4.42}$$

Thus we have

$$\frac{1}{2}D\left(\frac{\partial u}{\partial x}\right)^2 + F(u) = \text{constant} = F(u_{\max}) \quad \text{where} \quad F'(u) = f(u). \tag{4.43}$$

We can therefore find a relation between L, D, integrals of

$$F(u) \stackrel{\text{def}}{=} \int_0^u f(y)\,\mathrm{d}y, \tag{4.44}$$

and $u_{\max}$, the maximum size of the outbreak. From Equation (4.43) we have

$$\frac{\partial u}{\partial x} = -\left(\frac{2}{D}\right)^{\frac{1}{2}} \sqrt{F(u_{\max}) - F(u)}, \tag{4.45}$$

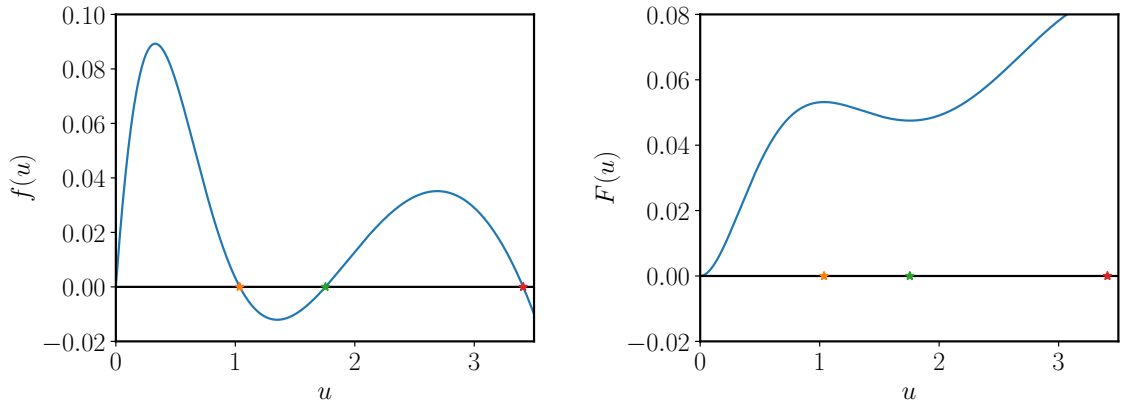


Figure 4.2: Plots of $f(u)$ and $F(u)$ with the three non-zero steady states indicated. Parameters are $r = 0.6$, $q = 6.2$ and $D = 0.1$.

since $x > 0$ and therefore $\partial u/\partial x < 0$. Plots of $f(u)$ and $F(u)$ are shown in Figure 4.2.

Integrating, gives

$$2\int_0^{L/2} \mathrm{d}x = -(2D)^{\frac{1}{2}} \int_{u_{\max}}^{0} \frac{1}{\sqrt{F(u_{\max}) - F(\bar{u})}}\,\mathrm{d}\bar{u}, \tag{4.46}$$

and hence

$$\frac{L}{\sqrt{2D}} = \int_0^{u_{\max}} \frac{1}{\sqrt{F(u_{\max}) - F(\bar{u})}}\,\mathrm{d}\bar{u}. \tag{4.47}$$

Therefore $u_{\max}$ is a function of $L/\sqrt{2D}$ and the root of Equation (4.47), as shown in Figure 4.3.

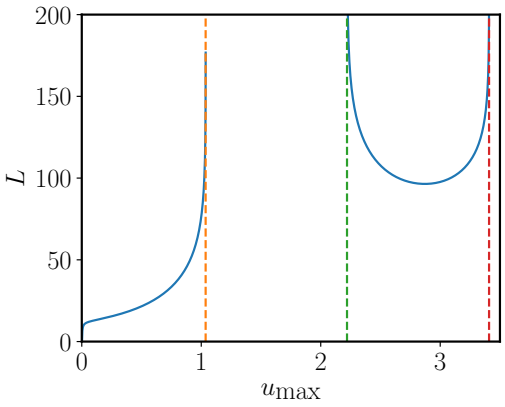


Figure 4.3: Numerical simulation of the $u_{\max}$-L space, given by Equation (4.47). Parameters are $r = 0.6$, $q = 6.2$ and $D = 0.1$.

Suggested reading.

- J. D. Murray, *Mathematical Biology, Volume I* – Chapter 11.
- N. F. Britton, *Essential Mathematical Biology* – Chapter 5.