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LM Advanced Mathematical Biology 31128

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Disclaimer: *These notes have not been subjected to the usual scrutiny reserved for formal publications. The material is based on a similar course previously taught by Tom Montenegro-Johnson at the University of Birmingham*

Part 3: Biological transport models

In this part of the course we will look at several different models of biological transport that are described using special cases of the reaction-advection-diffusion equation.

3.1 Krogh-Erlang tissue cylinder model

In this section, we will consider the Krogh-Erlang model for the diffusion of oxygen through tissue surrounding a capillary. Krogh was awarded the Nobel Prize in Physiology or Medicine for the discovery of the mechanism of regulation of the capillaries in skeletal muscle. He mostly worked experimentally, meticulously recording many physiological phenomenon and building up a theory based on these observations. He is also known for developing the subsequent model of oxygen transport, which was motivated by his experimental discoveries. This mathematical model is not attributed entirely to him, however. Rather of his time, in the article presenting his model[1], he says: "The mathematician Mr K. Erlang has shown me

[1] The Journal of Physiology Vol. 52, Issue 6. 391-474

the kindness to work out such a formula which runs...", and so we must credit Erlang also.

3.1.1 Diffusion through tissue

We begin with a slightly simpler model of oxygen diffusion in one dimension through a slab of tissue of length L. Oxygen is assumed to be supplied at $x = 0$ at fixed concentration c_0 and consumed within tissue at a constant rate of F_0, which gives rise to the reaction-diffusion equation

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - F_0 \tag{3.1}$$

where $c(x,t)$ is the concentration of oxygen at x at time t, and D is the diffusion coefficient for oxygen in tissue. The general solution at steady state $\partial c/\partial t = 0$ is

$$c(x) = \frac{F_0}{D}x^2 + Ax + B \tag{3.2}$$

since

$$\frac{F_0}{D} = \frac{\partial^2 c}{\partial x^2} \Rightarrow \frac{\partial c}{\partial x} = \frac{F_0}{D}x + A \Rightarrow \frac{F_0}{D}x^2 + Ax + B. \tag{3.3}$$

Imposing that there is no flux of oxygen in or out of tissue at $x = L$, leads to the mixed boundary conditions

$$c(0) = c_0, \quad \frac{\partial c}{\partial x}(L) = 0. \tag{3.4}$$

From these, the values of constants A, B are determined

$$c_0 = c(0) = B \tag{3.5}$$

and

$$0 = \frac{\partial c}{\partial x}(L) = 2\frac{F_0}{D}L + A \Rightarrow A = -\frac{2F_0L}{D} \tag{3.6}$$

so that

$$c(x) = \frac{F_0}{D}\left(\frac{x^2}{2} - Lx\right) + c_0. \tag{3.7}$$

We can now ask: "given a fixed oxygen uptake rate by the tissue, how far can oxygen travel through it?". Equivalently, this is the same as determining the largest L such that $c(L) \geq 0$ for all $0 \leq x \leq L$. We therefore rearrange the equation

$$0 = c(L) = \frac{F_0}{D}\left(\frac{L^2}{2} - L^2\right) + c_0 = -\frac{L^2 F_0}{2D} + c_0 \tag{3.8}$$

to obtain

$$L = \sqrt{\frac{2Dc_0}{F_0}}, \tag{3.9}$$

which gives us the largest length L where the oxygen concentration remains positive throughout the tissue.

3.1.2 Cylindrical tissue model

Here we assume that tissue is arranged cylindrically around a blood vessel (capillary) and that the system is radially symmetric. In this case, the steady state diffusion equation is given in cylindrical coordinates r, z (θ not included due assumption of radial symmetry) by

$$F_0 = \nabla \cdot (D\nabla c) = D\left[\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} + \frac{\partial^2}{\partial z^2}\right] c(r, z) \tag{3.10}$$

where $0 \leq z \leq L$, $R_1 \leq r \leq R_2$ (tissue starts at some radius R_1 and ends at some larger radius R_2, with the tissue-capillary interface at $r = R_1$). The boundary conditions on this model are

$$\frac{\partial c}{\partial z}(r, 0) = \frac{\partial c}{\partial z}(r, L) = 0 \tag{3.11}$$

and

$$c(R_1, z) = c_T(z), \quad \frac{\partial c}{\partial r}(R_2, z) = 0 \tag{3.12}$$

where $c_T(z)$ denotes the concentration of oxygen at position z of the tissue-capillary interface.

Oxygen is supplied by blood that flows through the capillary in the centre of the tissue cylinder. We assume the advective flow of oxygen in the capillary implies we can effectively ignore diffusion of oxygen in the axial (z) direction. This means that, for every fixed value of z, equation 3.8 reduces to

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{dc}{dr}\right) = \frac{F_0}{D}, \tag{3.13}$$

which has general solution

$$c(r, z) = \frac{F_0}{4D}r^2 + A(z)\log r + B(z) \tag{3.14}$$

since

$$\frac{F_0 r}{D} = \frac{d}{dr}\left(r\frac{dc}{dr}\right) \Rightarrow r\frac{dc}{dr} = \frac{F_0}{2D}r^2 + A \Rightarrow \frac{F_0}{4D}r^2 + A\log r + B. \tag{3.15}$$

Since the boundary conditions 3.11 hold for each fixed value of z, we obtain

$$0 = \frac{\partial c}{\partial r}(R_2, z) = \frac{F_0}{2D}R_2 + \frac{A(z)}{R_2} \Rightarrow A(z) = -R_2^2\frac{F_0}{2D} = \text{const.} \tag{3.16}$$

and

$$c_T(z) = c(R_1, z) = \frac{F_0}{4D}R_1^2 - R_2^2\frac{F_0}{2D}\log R_1 + B(z) \tag{3.17}$$

$$\Rightarrow B(z) = c_T(z) - \frac{F_0}{2D}\left[\frac{R_1^2}{2} - R_2^2\log R_1\right] \tag{3.18}$$

so that

$$c(r, z) = \frac{F_0}{2D}\left[\frac{(r^2 - R_1^2)}{2} + R_2^2 \log\frac{R_1}{r}\right] + c_T(z). \tag{3.19}$$

3.1.3 Axial oxygen flow in the capillary

We now derive a final equation for the flow of oxygen within the capillary. Using both radial and angular symmetry, integrating over a cross-section identifies $\bar{c}_T(z) = R_1^2 \pi c_T(z)$ with the total concentration of oxygen within the capillary at point z. Assuming as before that, compared to diffusion, the flow of blood is the dominant oxygen transport mechanism along z, this implies $\bar{c}_T(z)$ obeys a one-dimensional reaction-advection equation at steady state

$$0 = \frac{\partial \bar{c}_T}{\partial t} = -v\frac{\partial \bar{c}_T}{\partial z} + 2\pi R_1 D\frac{\partial c}{\partial r}(R_1, z) \tag{3.20}$$

where $0 \leq z \leq L$, $R_1 \leq r \leq R_2$. Here v is the velocity of blood flow, and the reaction term describes the diffusive flux of oxygen out of the capillary and into tissue at position z (Fick's law times the circumference of the capillary). Equivalently, for $c_T(z)$ this gives

$$v\frac{\partial c_T}{\partial z} = \frac{2D}{R_1}\frac{\partial c}{\partial r}(R_1, z) \tag{3.21}$$

with initial condition $c_T(0) = c_0$.

To evaluate the reaction term explicitly, we differentiate 3.19 with respect to r at $r = R_1$ to obtain

$$\frac{2D}{R_1}\frac{\partial c}{\partial r}(R_1, z) = \frac{2D}{R_1}\frac{F_0}{2D}\left(R_1 - \frac{R_2^2}{R_1}\right) = -\frac{F_0(R_2^2 - R_1^2)}{R_1^2} = -F_0\frac{V_T}{V_C} \tag{3.22}$$

where we have identified $V_T = \pi(R_2^2 - R_1^2)L$ and $V_C = \pi R_1^2 L$ with the volume of the tissue and capillary, respectively. The equation for c_T then becomes

$$\frac{dc_T}{dz} = -\frac{F_0}{v}\frac{V_T}{V_C}, \tag{3.23}$$

which has the solution

$$c_T(z) = c_0 - \frac{F_0}{v}\frac{V_T}{V_C}z. \tag{3.24}$$

Substitution for $c_T(z)$ in 3.19 then gives the complete solution for the concentration of oxygen throughout the tissue

$$c(r,z) = \frac{F_0}{2D}\left[\frac{(r^2 - R_1^2)}{2} + R_2^2 \log\frac{R_1}{r} - \frac{2D}{v}\frac{V_T}{V_C}z\right] + c_0. \tag{3.25}$$

3.2 Linear reaction terms and boundary conditions

In the Krogh-Erlang tissue cylinder model the reaction term (in that case the rate of oxygen uptake by tissue) was taken to be perhaps the simplest possible: constant in time and space. We also did not consider temporal dynamics, working only with the steady state solutions. The next step up would be to take linear dependance in the concentration variable that could correspond, for example, to a spatio-temporal extension of the exponential growth or decay model we considered in the introduction. In the simplest model for exponential growth or decay in time and space we have

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) \pm kc \tag{3.26}$$

where $-kc$ corresponds to decay while $+kc$ to growth, which is a suitable approximation for small populations. We can substitute the ansatz $c(\mathbf{x},t) = e^{\pm kt} \cdot u(\mathbf{x},t)$ to find that u must satisfy the diffusion equation

$$\frac{\partial u}{\partial t} = \nabla \cdot (D\nabla u). \tag{3.27}$$

Thus, the solution of the reaction-diffusion system 3.26 is entirely determined by the solution to 3.27 with appropriate boundary conditions. While this is something the student has likely studied in previous courses on PDEs we take the time to revisit here for completeness.

3.2.1 Growth or decay in one spatial dimension

Taking the diffusion equation 3.27 in one spatial dimension

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} \tag{3.28}$$

we have a range of boundary conditions that correspond to different physical interpretations. We shall study the solutions associated with these boundary conditions using the method of *similarity solutions*. That is to say, we first make the re-scaling $x = \epsilon^{-a}x^*$, $t = \epsilon^{-b}t^*$ and $u = \epsilon^{-c}u^*$ for some real numbers ϵ, a, b, c to obtain

$$\epsilon^{b-c}\frac{\partial u^*}{\partial t^*} = D\epsilon^{2a-c}\frac{\partial^2 u^*}{\partial (x^*)^2} \tag{3.29}$$

and see that we must have $b = 2a$ for the PDE to remain unchanged. This implies that, if $u(x,t)$ was a solution to the diffusion equation, then so is $\epsilon^c u(\epsilon^a x, \epsilon^b t)$. In particular, since

$$u^*(t^*)^{-c/b} = u\epsilon^c(t\epsilon^b)^{-c/b} = ut^{-c/b} \quad \text{and} \quad x^*(t^*)^{-a/b} = x\epsilon(t\epsilon^b)^{-a/b} = xt^{-a/b} \tag{3.30}$$

we postulate that a solution that combines these variables would be suitable, which leads to the ansatz

$$u(x,t) = t^{c/b} f(xt^{-a/b}). \tag{3.31}$$

Using the condition $b = 2a$ this is

$$u = t^{c/b} f(z) \quad \text{with} \quad z = \frac{x}{\sqrt{t}}. \tag{3.32}$$

Substituting we have

$$\begin{aligned}
\frac{\partial u}{\partial t} &= \frac{\partial}{\partial t} t^{c/b} f(z) = \frac{c}{b} t^{c/b-1} f(z) + t^{c/b} \frac{df}{dz}\frac{\partial z}{\partial t} \\
&= \frac{c}{b} t^{c/b-1} f(z) + t^{c/b} \frac{df}{dz} \left(-\frac{1}{2}\frac{x}{\sqrt{t}}\frac{1}{t} \right) \\
&= \frac{c}{b} t^{c/b-1} \left(\frac{c}{b} f(z) - \frac{1}{2} z \frac{df}{dz} \right)
\end{aligned}$$

and

$$\frac{\partial^2 u}{\partial x^2} = t^{c/b} \frac{\partial^2}{\partial x^2} f(z) = t^{c/b} \left(\frac{\partial z}{\partial x} \right)^2 \frac{d^2 f}{dz^2} = t^{c/b-1} \frac{d^2 f}{dz^2}$$

such that

$$0 = \frac{1}{t^{c/b-1}} \left(\frac{\partial u}{\partial t} - D \frac{\partial^2 u}{\partial x^2} \right) = D \frac{d^2 f}{dz^2} + \frac{1}{2} z \frac{df}{dz} - \frac{c}{b} f(z). \tag{3.33}$$

Thus, we have obtained a second-order ODE for f as a function of z.

Turning to the set of boundary and initial value conditions we could have originally imposed on u, leads to a restricted set of values for c/b. To see this, let us first consider the diffusion equation defined on the spatial domain $x \in [0, \infty)$ with the following boundary conditions

$$u(0,t) = u_0 \quad \text{and} \quad u(x,t) \to 0 \quad \text{as} \quad x \to \infty \tag{3.34}$$

with initial condition

$$u(x,0) = 0 \quad \text{for all} \quad x > 0. \tag{3.35}$$

In terms of the original variable $c(x,t) = e^{-kt}u(x,t)$ (here for decay), this would correspond to an initial concentration $c_0 = u_0$ of a species isolated at the point $x = 0$, which decays exponentially according to $c(0,t) = c_0 e^{-kt}$ while also diffusing outward into regions with $x > 0$. In terms of the new variables, we have

$$t^{c/b} f(0) = u_0 \quad \text{and} \quad t^{c/b} f(z) \to 0 \quad \text{as} \quad z \to \infty, \tag{3.36}$$

which implies that we must have $c/b = 0$ and $u = f(z)$ with f satisfying

$$D\frac{d^2 f}{dz^2} + \frac{1}{2} z \frac{df}{dz} = 0. \tag{3.37}$$

Treating this as a first-order ODE for df/dz and integrating once we obtain

$$\log\left(\frac{df}{dz}\right) = -\frac{1}{2D}\int z dz + C_1 = -\frac{1}{4D}z^2 + C_1, \tag{3.38}$$

or

$$\frac{df}{dz}(z) = A\exp\left(-\frac{z^2}{4D}\right), \tag{3.39}$$

which we can integrate again to yield the general solution

$$f(z) = A\int \exp\left(-\frac{z^2}{4D}\right) dz + C_2 = A\sqrt{D\pi}\cdot \operatorname{erf}\left(\frac{z}{2\sqrt{D}}\right) + C_2, \tag{3.40}$$

where erf is the Gauss error function. The boundary conditions $f(0) = u_0$ and $f(z) \to 0$ as $z \to \infty$ imply that $C_2 = u_0$ and $A = -C_2 = -u_0$ since $\operatorname{erf}(0) = 0$ and $\operatorname{erf}(z) \to 1$ as

$z \to\to \infty$. Thus, substituting $z = x/\sqrt{t}$ we have that

$$u(x,t) = u_0 \left[1 - \text{erf}\left(\frac{x}{2\sqrt{Dt}}\right)\right] \tag{3.41}$$

and in terms of the original variable

$$c(x,t) = c_0 e^{-kt} \left[1 - \text{erf}\left(\frac{x}{2\sqrt{Dt}}\right)\right]. \tag{3.42}$$

In the above, we took a particular set of boundary conditions on the half-interval $[0, \infty)$. One is perhaps more familiar with the "free-space" boundary and initial conditions on the entire interval $(-\infty, \infty)$. In this case, we have

$$u(x,t) \to 0 \quad \text{as} \quad x \to \pm\infty \quad \text{and} \quad u(x,0) = \delta(x) \tag{3.43}$$

where $\delta(x)$ is the Dirac delta function (for a point source at 0). In terms of the original variable $c(x,t) = e^{kt}u(x,t)$ (here for growth), this would correspond to having an initial point source at $x = 0$ and imposing that the solution must decay as we go infinitely far away from it. To determine the value of c/b in this case, we use the definition of a *mollifier*[2] as a function f that satisfies

$$\int_{-\infty}^{\infty} f(x) = 1 \quad \text{and} \quad \lim_{\tau \to 0} \frac{1}{\tau} f\left(\frac{x}{\tau}\right) = \delta(x) \tag{3.44}$$

to see that, in terms of the f we used before, the initial condition

$$\delta(x) = \lim_{t \to 0} u(x,t) = \lim_{t \to 0} t^{c/b} f\left(\frac{x}{\sqrt{t}}\right) \tag{3.45}$$

[2]The mathematical rigour associated with this definition is beyond the scope of what we will do here.

will be satisfied if f is a mollifier and $c/b = -1/2$. Thus, in terms of z, the corresponding f must satisfy the second-order ODE

$$0 = D\frac{d^2 f}{dz^2} + \frac{1}{2}z\frac{df}{dz} + \frac{1}{2}f(z) = D\frac{d^2 f}{dz^2} + \frac{1}{2}\frac{d}{dz}zf(z) = \frac{d}{dz}\left(D\frac{df}{dz} + \frac{1}{2}zf\right) \tag{3.46}$$

or, equivalently,

$$D\frac{df}{dz} + \frac{1}{2}zf = C_1 \tag{3.47}$$

for some constant C_1 that we are free to take as $C_1 = 0$ since we are looking for just one solution. Solving the resulting first-order ODE we have

$$\log f(z) = -\frac{1}{2D}\int z dz + C_2 = -\frac{z^2}{4D} + C_2 \tag{3.48}$$

and therefore

$$f(z) = A\exp\left(-\frac{z^2}{4D}\right). \tag{3.49}$$

Using

$$1 = \int_{-\infty}^{\infty} f(x) = \int_{-\infty}^{\infty} A\exp\left(-\frac{z^2}{4D}\right) = 2\sqrt{\pi D}A \tag{3.50}$$

we find that $A = 1/\sqrt{4\pi D}$ and from $u(x,t) = f(x/\sqrt{t})/\sqrt{t}$ we have the solution

$$u(x,t) = \frac{1}{\sqrt{4\pi Dt}}\exp\left(-\frac{x^2}{4Dt}\right). \tag{3.51}$$

We recognise this as the fundamental solution in dimension $d = 1$ introduced for the corresponding boundary problem previously. The full solution in terms of the original variable is

$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}}\exp\left(kt - \frac{x^2}{4Dt}\right), \tag{3.52}$$

which describes exponential growth coupled with diffusion in a one-dimensional environment.

3.2.2 Absorbing and non-flux spatial boundary conditions

We have derived the fundamental solution over infinite spatial domains and now want to consider spatial domains that are finite. Examples include a constrained spatial domain for growth, i.e. zero resources outside a prescribed region of space. We shall consider two types of boundary conditions: perfectly reflecting or perfectly absorbing boundary conditions. Mathematically, given a solution $c(\mathbf{x}, t)$ the *perfectly reflecting boundary condition* is the Neumann condition at boundary ∂B that

$$\nabla c \cdot \mathbf{n}|_{\partial B} = 0 \tag{3.53}$$

where $\mathbf{n}$ is the outward normal direction from ∂B. By comparison, the *perfectly absorbing boundary condition* is the Dirichlet condition

$$c|_{\partial B} = 0. \tag{3.54}$$

We can use linear combinations of the fundamental solution over infinite spatial domains to construct specific solutions that satisfy these boundary conditions, the so-called *method of images.*

In one spatial dimension, we take $\psi(x - x_0, t)$ to be our fundamental solution derived in the previous subsection corresponding to a point source at $x_0 > 0$. That is to say,

$$\psi(x - x_0, t) = \frac{1}{\sqrt{4\pi D t}} \exp\left(kt - \frac{(x - x_0)^2}{4Dt}\right). \tag{3.55}$$

First consider a perfectly reflecting boundary at the point $x = 0$, which means

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = 0. \tag{3.56}$$

We can show that $c(x,t) = \psi(x - x_0, t) + \psi(-x - x_0, t)$ satisfies this boundary condition since

$$\left.\frac{\partial\psi(x - x_0, t)}{\partial x}\right|_{x=0} + \left.\frac{\partial\psi(-x - x_0, t)}{\partial x}\right|_{x=0} = \left.\frac{\partial\psi(z, t)}{\partial z}\right|_{z=-x_0} - \left.\frac{\partial\psi(z', t)}{\partial z'}\right|_{z'=-x_0} = 0 \quad (3.57)$$

where we made substitutions $z = x - x_0$ in the first term and $z' = -x - x_0$ in the second. Then, since linear superposition returns another solution to a linear differential equation, the linear combination is also solution to 3.26

$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp(\pm kt) \left[\exp\left(-\frac{(x - x_0)^2}{4Dt}\right) + \exp\left(-\frac{(x + x_0)^2}{4Dt}\right)\right]. \quad (3.58)$$

For a perfectly absorbing boundary condition at $x = 0$ it is easy to see that $c(x,t) = \psi(x - x_0, t) - \psi(-x - x_0, t)$ provides a solution since

$$c(0,t) = \psi(-x_0, t) - \psi(-x_0, t) = 0 \quad (3.59)$$

and therefore

$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp(\pm kt) \left[\exp\left(-\frac{(x - x_0)^2}{4Dt}\right) - \exp\left(-\frac{(x + x_0)^2}{4Dt}\right)\right]. \quad (3.60)$$

When we move to higher dimensions we can use the fundamental solution in dimension d to perform the same procedure, depending on the layout of boundary conditions. For example, for $d = 2$ the fundamental solution corresponding to a point source at $(0, y_0)$ is given by

$$\psi(x, y - y_0, t) = \frac{1}{4\pi Dt} \exp\left(kt - \frac{x^2 + (y - y_0)^2}{4Dt}\right). \quad (3.61)$$

If we take a perfectly reflecting boundary at the line $y = 0$, the corresponding superposition solution corresponds to

$$
\begin{aligned}
c(x,y,t) &= \psi(x, y-y_0, t) + \psi(x, -y-y_0, t) \\
&= \frac{1}{4\pi Dt}\exp(\pm kt)\left[\exp\left(-\frac{x^2+(y-y_0)^2}{4Dt}\right) + \exp\left(-\frac{x^2+(y+y_0)^2}{4Dt}\right)\right].
\end{aligned}
$$

From this simple procedure, we can systematically build up a collection of solutions to the problem specified over a range of multi-dimensional domains.

Exercise 3.1 We can approximate a tumour as a spherically-symmetric ball of cells in three dimensions with radius R. Cells within the tumour are supplied with oxygen by diffusion, and there is some critical oxygen concentration c^* below which cells die. Assume oxygen is supplied outside the tumour at fixed concentration c_0 and that living cells consume oxygen at a constant rate F_0.

(a) Solve the spherically-symmetric reaction-diffusion equation for oxygen concentration c within the tumour at steady state

$$
0 = D\frac{1}{r^2}\left(r^2\frac{dc}{dr}\right) - F_0
$$

subject to the boundary conditions

$$
\frac{dc}{dr}(0) = 0, \quad c(R) = c_0.
$$

(b) Determine the critical radius, R^*, for which any tumour of radius R^* or larger will contain dead cells.

Exercise 3.2 In this example, instead of taking c to represent the concentration of oxygen, we use it to describe the "concentration" of tumour cells in three-dimensional space and time. The fundamental solution for exponential tumour growth in dimensions $d = 3$ from a point source centred at the origin is given by

$$\phi(x, y, z, t) = \frac{1}{(4\pi Dt)^{3/2}} \exp\left(kt - \frac{x^2 + y^2 + z^2}{4Dt}\right).$$

Find a solution that describes tumour growth from a point source located at $(x_0, y_0, z_0) > 0$ in the case where no oxygen available for growth (and therefore no cells can exist) below the surface $z = 0$.