# Modelling Morphogenesis

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In this project, we modelled the process of morphogenesis using a simple mathematical model of diffusion. We derived the model

## 1 The Idea of Morphogens

Morphogens are substances which occur in living systems which due to their non-uniform distribution in a particular medium give rise to patterning and spatially-specific tissue development of organs. Cells are able to respond to morphogens to produce a certain response depending on the localized morphogenic concentrations, meaning that where there is a higher concentration of morphogens at that point, the cell will produce a greater response which would manifest itself as, for instance, a darker patch of fur. This mechanism is hugely important to every biological organism as it is what ultimately determines the growth points of every component of the many biological organs found in organisms. An example of morphogenesis include Bicoid, which is a transcription factor which is ultimately responsible for the patterning of the head and thorax of the Drosophila fly. Another example of morphogenesis is in Sonic Hedgehog (Shh) signalling, which transmits information to cells in order to initiate cell differentiation. This is particularly applicable in the growth of digits and brain development in mammals. The applicability of morphogenesis across a wide variety of uses makes it an important biological concept to model.

## 2 Mathematically Modelling Morphogens

The diffusion of morphogens can be modelled using a coarse grain approach with a local morphogen concentration $\rho$ inside a system of a certain size and dimensions. This concentration is both dependent on the position within the system $(x, y, z)$ time $t$. Hence we can write the concentration $\rho$ as

$$\rho = \rho(x, y, z, t) \tag{1}$$

To simplify the model, one can assume that the morphogen concentration is dependent on only one spatial coordinate (in this case $x$) and time. This simplification is consistent with experimental data, hence the concentration function becomes

$$\rho = \rho(x, t) \tag{2}$$

By combining Fick's first law with the continuity equation, the diffusion equation is

$$\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2} \tag{3}$$

where $D$ is the diffusion constant. This equation states that the change in concentration is entirely passive and that there is no production/degradation rate. However in the case of modelling morphogens, they have to be produced (or injected) at a certain point, and then to diffuse and degrade throughout the system. The diffusion equation along with the boundary conditions will then have to be modified to account for this. To model degradation, we can assume that the rate

of degradation of morphogens is proportional to the amount of morphogens present at any given moment. This linear assumption is experimentally found to hold in the case of many biological systems. Mathematically, this can be written as

$$\frac{\partial \rho}{\partial t} = -\mu\rho \tag{4}$$

where the constant $\mu$ is the decay constant with units $\text{Time}^{-1}$. This equation can be combined with the diffusion equation to produce a modified diffusion equation:

$$\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2} - \mu\rho \tag{5}$$

One can model the production of morphogens at a certain point by imposing a boundary condition when solving the differential equation. If the system has a total length $L$, then one can assume that morphogens are entering the system as position $x = 0$ at a constant rate. Fick's first law gives states diffusion flux $J$ is proportional to the concentration gradient $\frac{\partial \rho}{\partial x}$:

$$J = -D\frac{\partial \rho}{\partial x} \tag{6}$$

This can be imposed at $x = 0$ when solving the equation, such that

$$\left.\frac{\partial \rho}{\partial x}\right|_{x=0} = -\frac{J}{D} \tag{7}$$

where $J$ is the constant morphogen flux at $x = 0$. We can assume that initially there is no morphogen concentration at any point across the domain, and that over time the morphogens are entering at the boundary with a constant flux $J$ and decaying at a certain decay rate linearly proportional to the concentration at that moment in time, with proportionality constant $\mu$.

# 3 Solving the Diffusion Equation with Linear Degradation

## 3.1 Discretisation of the Equation

To solve this equation numerically, a similar approach to solving the regular diffusion equation using the Euler method will be used. The first order time derivative can be approximated to be

$$\frac{\partial \rho}{\partial t} \approx \frac{\rho(x, t + \Delta t) - \rho(x, t)}{\Delta t} \tag{8}$$

Similarly, by writing down a similar expression for $\frac{\partial \rho}{\partial x}$ and evaluating it at two adjacent points $x - \Delta x$ and $x$, the second order derivative can be approximated as

$$\frac{\partial^2 \rho}{\partial x^2} \approx \frac{\rho(x - \Delta x, t) - 2\rho(x, t) + \rho(x + \Delta x, t)}{(\Delta x)^2} \tag{9}$$

These two results can be substituted into the diffusion equation with linear degradation (Equation 5), to produce the following equation for the next time step:

$$\rho(x, t + \Delta t) = \rho(x, t) - \frac{D\Delta t}{(\Delta x)^2}\Big(\rho(x - \Delta x, t) - 2\rho(x, t) + \rho(x + \Delta x, t)\Big) - \mu \Delta t \rho(x, t) \tag{10}$$

This approximation of the equation can be converted into code which then produces the subsequent value of $\rho(x, t)$ at each time step for a given initial value.
In addition to this, the boundary condition of there being a constant flux must also be discritised. At the position $x = 0$, there is a constant flux $J$ of morphogens entering the system. The boundary condition for this was given by Equation 7. To convert this into a boundary condition, the first order derivative approximation for $\frac{\partial \rho}{\partial x}$ can be used. This produces the following relationship between the two spatial steps at the boundary:

$$\rho(\Delta x, t) = \rho(0, t) + J\frac{\Delta x}{D} \tag{11}$$

Which can easily be translated into code and implemented at each time step.

## 3.2 Plotting The Solution

The morphogen concentration profile can be plotted over space and over time. The spatial profile is shown in Figure 1, with the solution over space shown in Figure 2a and the solution over time shown in Figure 2b.

From the plots, we can see that over time due to material being constantly added to the system, the concentration distribution continuously increases. At pre steady state, the two terms in the equation are comparable, and the solution to the diffusion equation is more complex than a simple exponential decay. The full analytic expression for $\rho$ as a function of space and time is given by

$$\rho(x, t) = \frac{JD}{2\lambda}\left(2e^{-\frac{x}{\lambda}} + e^{-\frac{x}{\lambda}}\operatorname{erfc}\left(\frac{\frac{2Dt}{\lambda} - x}{\sqrt{4Dt}}\right) - e^{\frac{x}{\lambda}}\left(\frac{\frac{2Dt}{\lambda} + x}{\sqrt{4Dt}}\right)\right) \tag{12}$$

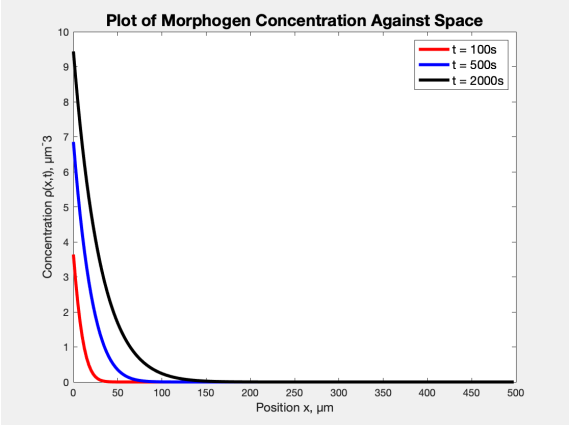
here $\operatorname{erfc}(x)$ is the complementary error function defined as

$$\operatorname{erfc}(x) = \frac{2}{\sqrt{\pi}}\int_x^\infty e^{-x^2} \tag{13}$$

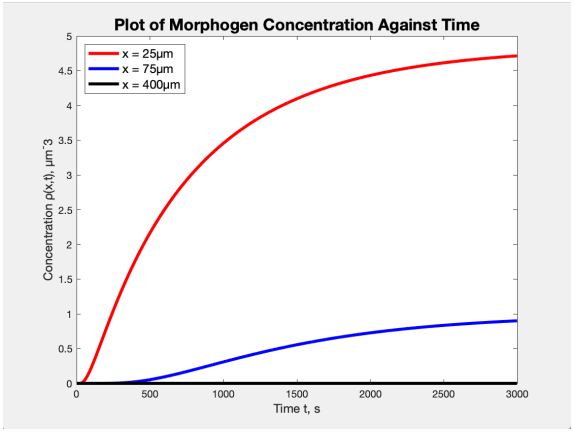
and $\lambda$ is the decay length, which is defined as

$$\lambda = \sqrt{\frac{D}{\mu}} \tag{14}$$

However, at much larger distances, the degradation term in Equation (5), $\mu\rho$ is much larger than the diffusive term $D\frac{\partial^2 \rho}{\partial x^2}$. Hence at large distances ($x \gg \lambda$), Equation (12) simply reduces to an




(a) Morphogen concentration profile $\rho(x,t)$ as a function of position $x$ at various different times.




(b) Morphogen concentration profile $\rho(x,t)$ as a function of position $t$ at various different spatial times.

Figure 1: Plots of both the solutions to the Morphogen concentration profile over space and time. Parameters: $L$ =500μm, $J = 0.3$ μm$^{-2}$s$^{-1}$, $D = 1$μm$^2$s$^{-1}$, $\mu = 10^{-4}$s$^{-1}$.

exponential decay at decay rate $\lambda$, which is the long term steady state solution of the equation. This is given by

$$\rho(x, t = \infty) = \frac{JD}{\lambda} e^{-\frac{x}{\lambda}} \tag{15}$$

which is the functional form of the curve in Figure 1.

# 4 Extension of Model to Flux at Both Ends

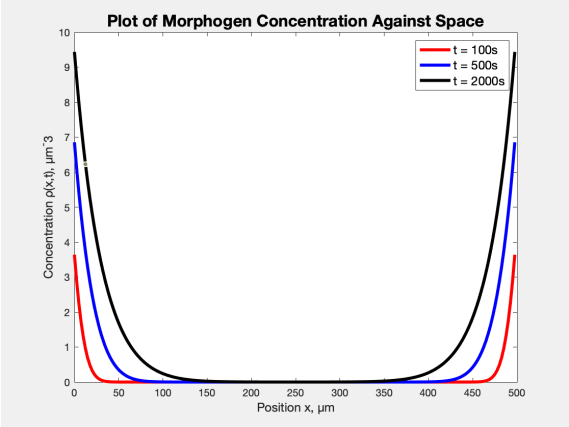
Instead of having just one flux term at $x = 0$, the Equation (5) will now be solved by including a flux of morphogens at the other side of the container, $x = L$. In practice, this will be implemented as a further boundary condition of the same constant flux, $J$ entering the system at that end. Mathematically, this is expressed as:

$$\left.\frac{\partial \rho}{\partial x}\right|_{x=L} = \frac{J}{D} \tag{16}$$

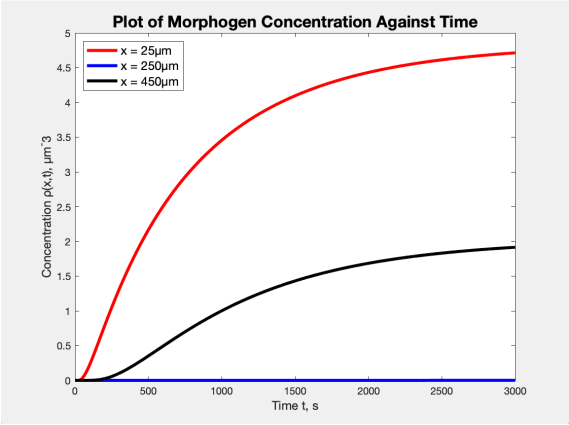
which when discretised in the same manner as before, gives the following equation which can readily be translated into code.

$$\rho(L, t) = \rho(L - \Delta x, t) - J\frac{\Delta x}{D} \tag{17}$$

When implementing this additional boundary condition, the concentration profile produced becomes different to that before. The new concentration profiles are shown in Figure 2.




(a) Morphogen concentration profile $\rho(x, t)$ as a function of position $x$ at various different times.




(b) Morphogen concentration profile $\rho(x, t)$ as a function of position $t$ at various different spatial times.

Figure 2: Plots of both the solutions to the morphogen concentration profile over space and time, with additional flux $J$ being imposed at $x = L$. Parameters: $L$ =500μm, $J$ = 0.3 μm$^{-2}$ s $^{-1}$, $D$ = 1μm$^2$s$^{-1}$, $\mu = 10^{-4}$s$^{-1}$.

From Figure 2, the difference made by implementing this additional boundary condition is clearly shown by an increase in concentration when $x \approx L$. It then shows a similar decay in concentration in the opposing direction, until the concentration at the mid point is virtually zero at all times.

# 5 Implementing Thresholding

Within the system, cells will only start producing the particular pattern if the morphogen concentration at a given position is above a certain threshold concentration, $\rho_{max}$. If we assume that patterning is performed at steady state, then this will lead to discrete regions in which patterning of a certain colour occurs. This is known as the French Flag model of morphogenesis. This section will investigate how a change in the flux $J$ will lead to a change in the boundary position $x^*$, which is the position at which the morphogen concentration crosses the threshold concentration. It is worth noting that this will be in the fixed time scenario, in which the time at which the concentration profile is measured $T$ is the same in each run of the solution. The same process will be carried out both in the case in which there is a flux at the left boundary and when there is a flux on both sides.

## 5.1 Single Flux Case

The same differential equation will be solved as before along with similar boundary conditions, only this time the value of the flux will vary between runs, by ± 20%. In this analysis, the threshold concentration value chosen will be $\rho_{max} = 5\mu m^{-3}$. For each case, the position $x^*$ at which the flux crosses the threshold will be observed. This is shown in Figure 3.

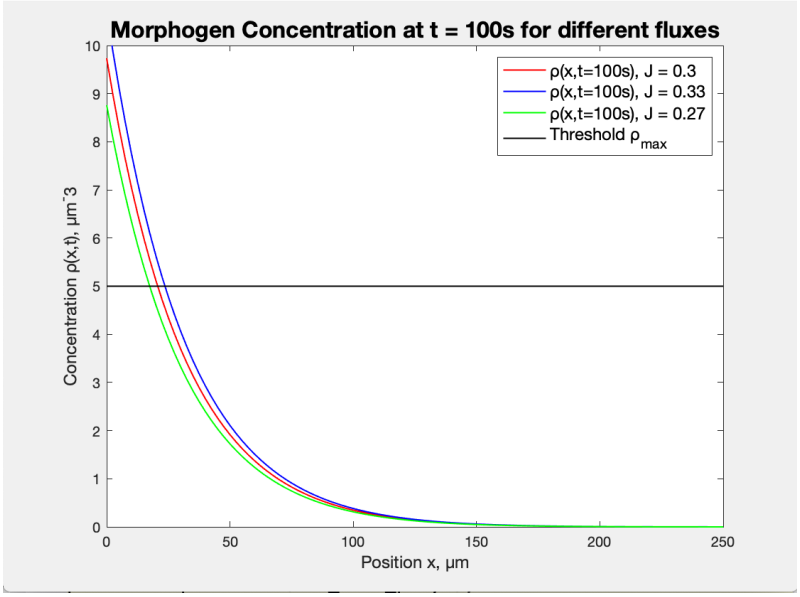



Figure 3: Morphogen concentration profile $\rho(x, t = 100\text{s})$ against position $x$ for different values of flux $J$ at the boundary $x = 0$, along with threshold concentration $\rho_{max}$. Other parameters $L$, $D$ and $\mu$ are the same as before.

From Figure 3, it is clear that changing the incident flux at the boundary has an effect on $x^*$. An increased flux leads to the boundary position shifted to the right, which would therefore result in the patterning going deeper into the system. The dependence of the boundary position on the incident flux can be found by setting the concentration to the constant threshold value:

$$\rho(x^* + \delta x^*, T) + \delta\rho(x^* + \delta x^*, T) = \rho(x^*, T) \tag{18}$$

which when solved analytically for small values of $\delta x^*$, gives the following functional dependence

$$\delta x^* = \frac{1}{\frac{\partial\rho}{\partial t}(x^*, T)} \frac{\partial\rho}{\partial J}(x^*, T)\delta J \tag{19}$$

## 5.2 Flux at Both Ends

In the case of a flux at both ends, there are now two boundary positions where the concentration crosses the threshold. The concentration profile is shown in Figure 4. This would have a similar

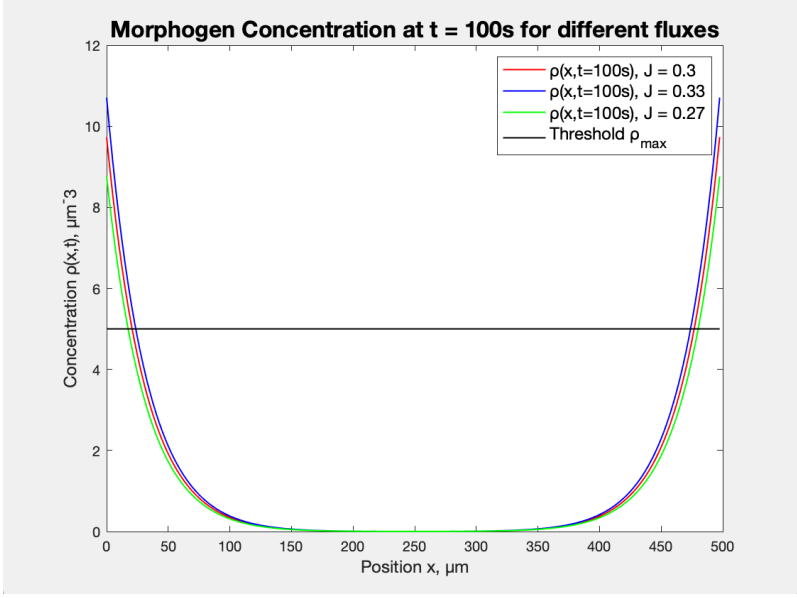



Figure 4: Morphogen concentration profile $\rho(x, t = 100\text{s})$ against position $x$ for different values of flux $J$ imposed at both boundaries $x = 0$ and $x = L$, along with threshold concentration $\rho_{max}$. Other parameters $L$, $D$ and $\mu$ are the same as before.

dependence on the boundary position as in the case with a single flux, except it would move in the opposite direction with an increased flux. In this double flux scenario, there would be patterning happening on both sides and it would be symmetrical about the mid-point.