Modelling Chick Embryogenesis

Math399 project

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Abstract

The purpose of this project was to study mechanisms of axis extension on chick embryo using mathematical modelling approach. The developed models were designed to describe migration of the stem zone and corresponding dynamics on concentration profiles of FGF8 gene and protein (denoted as u_G and u_A in a model) across the stem zone. The stem zone is an area on the blastodisc, a small region on top of the yolk in a developing egg, where all 4 main stages of embryogenesis take place. The concentration of this gene and protein are thought to be important as they may explain a biological phenomenon known as the progression of the primitive streak. This progression and subsequent regression takes place during the second stage of embryogenesis, gastrulation, and if it were not for this then there would never be a third stage, neurulation.

In my project I first investigated the concentration of the gene FGF8 inside a stem zone of length L moving with speed c using a one dimensional continuous model. I found that the concentration of the gene FGF8 was constant inside the stem zone, was non-existent in front, and decayed exponentially behind.

Since the concentration of the protein FGF8 depended on the concentration of the gene FGF8, I then investigated the concentration of the protein FGF8 using the results I had already obtained for gene FGF8. I found slightly more complicated solutions for protein FGF8 inside, in front of and behind the stem zone; they were superpositions of exponential functions. I plotted this on a graph, and found that the maximum concentration of protein FGF8 was found behind the stem zone. However, I wanted to know what factors made this the case.

I found an expression for L (the size of the stem zone) in terms of c (the speed with which it was moving), when the maximum concentration of the protein FGF8 is on the rear boundary of the stem zone. I found that when I plotted this expression on a graph, I could see that above this curve would mean that the maximum concentration of the protein FGF8 would be found inside the stem zone, but below this curve would ensure it was found behind the stem zone.

I then decided to use a different model- a 2D Cellular Potts model. This involved making swaps between cell sites to achieve a minimum energy within the stem zone. Looking at the graph I had produced for the concentration profile of protein FGF8 I saw that there would be a point where gene FGF8 was no longer produced, and therefore neither was protein FGF8 as the one depended upon the other. This meant that any cells behind this point would be different than the cells in front as they would essentially be different cells without this feature of producing gene FGF8. This gave me a clue as to possibly how Hensen's node (a group of cells within the stem zone) and the primitive streak were formed; the stem zone was moving as we had seen before, and the cells inside were constantly proliferating. However, at the point where the gene FGF8 is no longer produced, these cells turn into neurons and move much more slowly than the cells in front. The picture to be gained from this was Hensen's node, at the forefront of the primitive streak moving with speed c, proliferating cells that would eventually turn into neurons. If we coloured these neurons green as they are then different from the cells in Hensen's node, we would see a train of neurons preceded by the cells at Hensen's node- a good approximation of the primitive streak.

1. Biological Introduction/Overview

In my project I will be attempting to model specific features of a process known as Embryologenesis, the progression of stages an organism goes through during its early life from fertilization to birth. In particular I will be considering the case of a chick developing in an egg, which undergoes 4 main stages. One of these stages, gastrulation, I will be looking at in detail, where the progression and subsequent regression of the primitive streak takes place.

All animal life starts with a fertilised egg, scientifically known as a zygote. The zygote undergoes several processes which collectively make up Embryogenesis: **Cleavage**, **Gastrulation**, **Neurulation** and **Organogenesis**. We will consider these stages in some detail to give an overview of what occurs within them .

1.1 Cleavage

Cleavage, the first of these stages, takes place while the egg is still in the hen's oviduct. It has in itself two stages. The first**, mitosis**, is where the chromosones of the zygote duplicate themselves to produce identical daughter nuclei. After this comes the second stage, **cytokenesis**, where the cell membrane (the outer wall of the zygote) splits into two, and each half now contains one of each of the nuclei. These processes are repeated multiple times to increase the number of cells, increasing the size of the zygote.

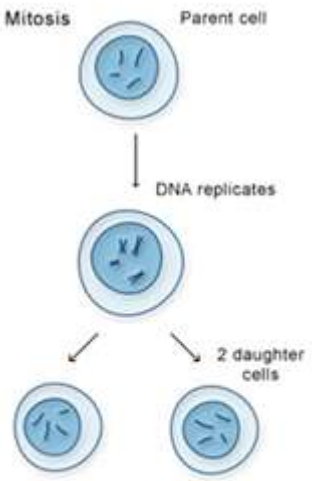


Fig 1.1 shows the parent cell replicating DNA and splitting into two cells (mitosis)

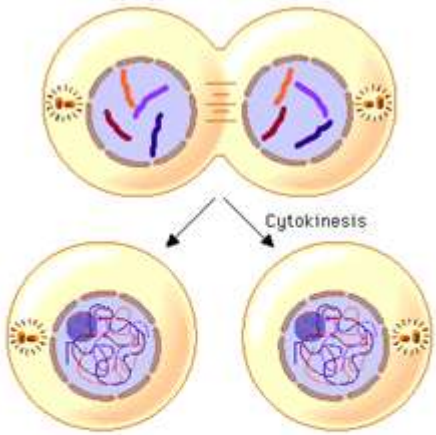


Fig 1.2 shows more clearly the process of Cytokenesis, where the cell membrane splits in two

The process of cleavage takes place on the **blastodisc,** a small circular region on top of the yolk. It lasts approximately 20 hours after fertilization, during which time the fertilized egg is travelling down the oviduct.

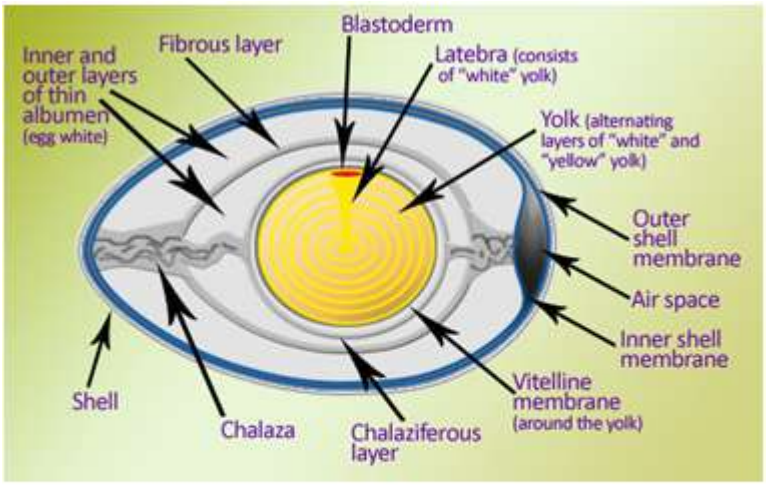


Fig 1.3 shows the various parts of the fertilised egg

After the 20 hours, the chick egg has been surrounded by albumen, shell membrane and the shell itself, and so it is laid with the chick still developing inside.

At this point, the central region of the blastodisc is translucent and is known as the **area pellucida**, and is a contrast to the outer region which is darker and known as the **area opaca** (see Fig 1.4). The area pellucida appears lighter as there exists a cavity below it which is filled with a secreted liquid; this area is known as subgerminal space, and does not exist beneath the area opaca hence why it appears darker. There is also a sickle shaped region of cells that has developed between the areas pellucida and opaca at the posterior of the blastodisc, known **as Koller's Sickle**. Once this has all taken place, the **primitive streak** will start to appear at Koller's Sickle, which signals the next stage of embryogenesis- Gastrulation.

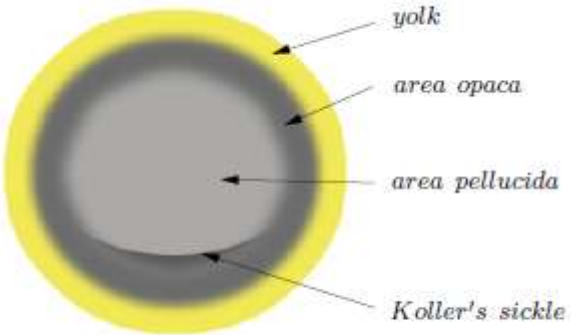


Fig 1.4 Shows the various parts of the blastodisc

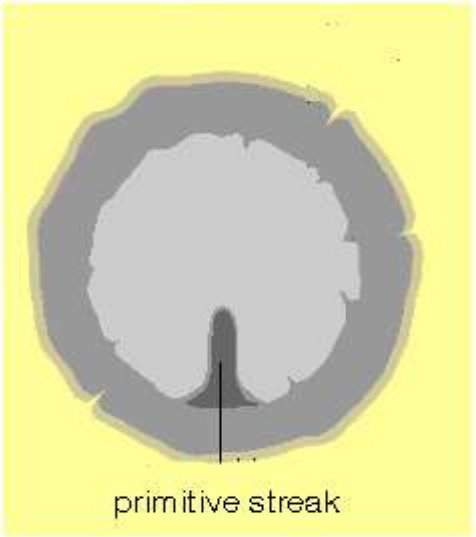


Fig 1.5 show the progression of the primitive streak across the blastodisc

1.2 Gastrulation

The cells on the surface of the blastodisc are collectively known as the **epiblast**, while the cells on the bottom are known as the **hypoblast.** Gastrulation is signalled by a movement of cells from Koller's Sickle in a posterior (what will be the tail of the chick) to anterior (the head) motion, marking the progression of the primitive streak across the area pellucida that forms a groove in the epiblast (shown in Fig 1.5). As the primitive streak progresses, some of the other cells are pushed outwards and then back towards the primitive streak in a circular motion. Imagine you have a bowl of honey and you pull a spoon through it in a straight line; the honey around this would behave in a similar way, as these are both viscous fluids. Some of the cells that return back towards the primitive streak will pass through it, and sink underneath, forming two germ layers. The first, **mesoderm**, is made up of the cells that settle beneath the surface. However some cells will move further downwards, and will displace the cells in the hypoblast. This then creates the second germ layer known as **endoderm**. Any remaining cells on the surface make up the third germ layer, **ectoderm**. This process is shown in Fig 1.7. These three germ layers will each determine the features of the chick that they will form later on, during organogenesis.

All this time the primitive streak is progressing across the area pellucida, and after around 16 hours it is fully extended. Now there comes an interesting change. The area pellucida changes shape, from circular to pear. At the same time a collection of cells begins to form at the anterior end of the primitive streak, known as **Hensen's node**. As the embryo starts to move into the next stage of embryogenesis, neurulation, the primitive streak together with Hensen's node begins to regress backwards towards the posterior end of the embryo, shown in Fig 1.6.

This stage of gastrulation is very interesting- why should the cells start to move at all? Why should Hensen's node progress one minute and begin the regress the next? Essentially the cells in Koller's Sickle differentiate from the rest of those on the epiblast, which is why they move and the rest do not. One theory is that there may be a chemical produced in the area pellucida that the cells in Koller's Sickle are either attracted to or repulsed from, and hence they start to move towards or away from it, forming the primitive streak and Hensen's node. This is known **as chemotaxis**, which can be considered in two cases: either as chemo-attraction (the case where the cells are attracted to the chemical) or chemo-repulsion (the case where the cells are repelled from the chemical).

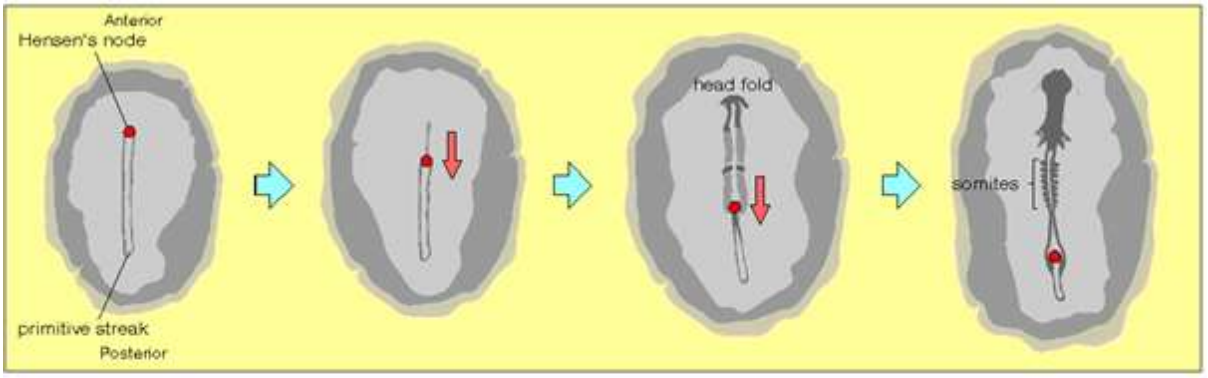


Fig 1.6 shows the fully extended primitive streak starting to regress, leading the embryo into the third stage of embryogenesis: neurulation

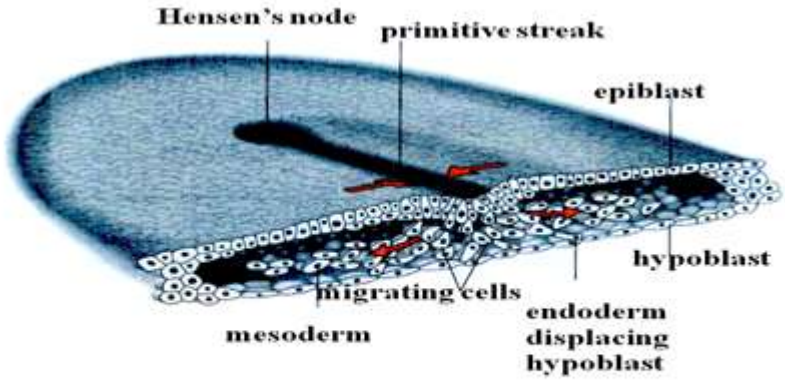


Fig 1.7 shows a cross section of the blastodisc to show the migration of cells on the surface

1.3 Neurulation

Neurulation, an early phase of the final stage organogenesis, is where the central nervous system and brain begin to develop. Cells from the ectodermal germ layer begin to form the **neural plate**, moving towards the midline of the blastodisc. The plate then starts to fold around the midline (or notochord), starting with a pair of neural folds and ultimately forming the **neural tube** in a process known as **primary neurulation**, which will eventually form the spinal cord, brain and the entire nervous system.

At the same time, Hensen's node and the primitive streak has begun to regress towards the posterior end of the embryo, resulting in the body axis beginning to extend along the central midline. It is Hensen's node that is in charge of forming the neural tube and production of other cells in the area.

By the end of neurulation, the zygote is in the **phylotypic** stage with the brain and spinal area clearly visible, and signals the final stage of embryogenesis.

1.4 Organogenesis

Now that the central nervous system and brain has been laid down, it is time for the internal organs (including the circulatory system) and limbs to develop from the three main germ layers (ectoderm, endoderm and mesoderm) created earlier during gastrulation. This final stage is known as organogenesis**.** The different germ layers contribute to the development of different features of the chick; for example, the nervous system that started to develop during neurulation was due to the ectoderm, the gastrointestinal tract is produced by the endoderm and the liver and heart by the mesoderm. During this time, the embryo grows in size, and also develops its beak, wings, and grows down feathers on the wings and body. 21 days after the egg is laid, the chick hatches.

a)

b)

c)

a) Shows the chick near the end of neurulation. The spinal area and brain are clearly visible.
b) Shows the chick towards the start of organogenesis; limbs have started to develop, as well as the beak.
c) Shows the chick almost ready to be hatched at the end of organogenesis; most of its features are now clearly defined, and it has grown down feathers on its wings and body.

2. Mathematical models

We need mathematical models to explore possible mechanisms for the progression and regression of the primitive streak during gastrulation. A feasible reason for this, as mentioned earlier in the biological introduction, is **chemo-repulsion**.

During gastrulation, the group of cells known collectively as Hensen's node is inside the '**stem zone**'. The stem zone is made up of around 1000 stem cells, which are cells that, under the right conditions, can become anything they like, such as skin, bone or muscle. It is these cells, whilst on the epiblast, that begin to move in a head to tail motion. As they progress, forming the primitive streak, the cells surrounding them are pushed first outwardly and then flow inwardly towards the midline, as was described above. This is similar to an unzipping motion along the midline, and some of the cells begin to sink eventually forming the mesodermal and ectodermal germ layers. When the primitive streak finally starts to regress, it is a similar action to 'zipping up the midline'; there is now no motion along the midline.

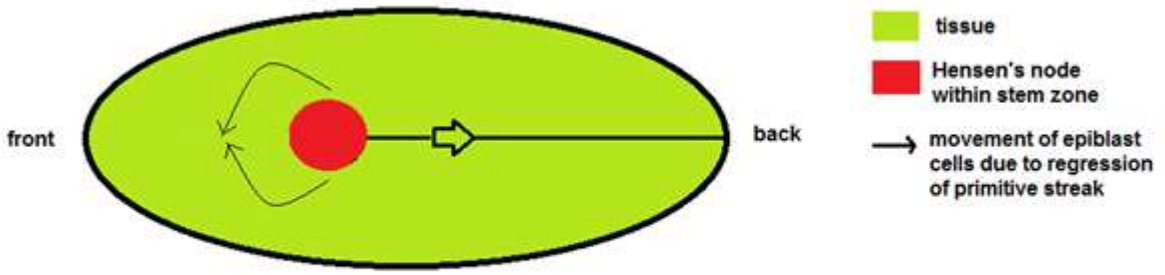


Fig 1.8 shows the primitive streak regressing across the blastodisc

The cells in the stem zone constantly proliferate, yet the number of cells inside always remains the same and so the size (also known as the **DOT**) remains constant. This happens because some cells will stop moving as others multiply, and be left behind (picture). These cells become neurons, which eventually form the nervous system during the embryonic stage of neurulation. This act of stem cells becoming neurons is what balances out the number of cells in the stem zone. Figure 1.9 below displays what is happening within the stem zone, as old stem cells stop moving and become neurons.

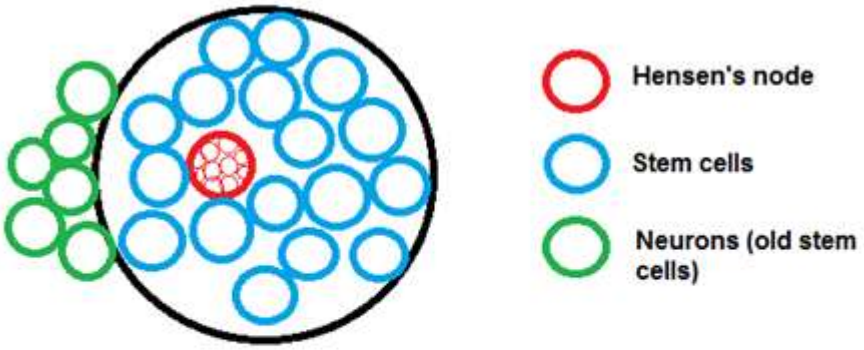


Fig 1.9 shows the cells within the stem zone; the stem cells (blue cells) proliferate, yet for the DOT to remain constant some cells are left behind and become neurons (green cells).

The stem cells express a gene called FGF8. It is thought that the gene FGF8 may regulate the mobility and differentiation of the surface cells on the area pellucida. Let's use a one-dimensional continuous model and take a section including the stem zone, considering the image above.

2.1 One-dimensional continuous model

In this model we will consider two variables representing the levels of gene FGF8 and a protein FGF8 which we will consider later.

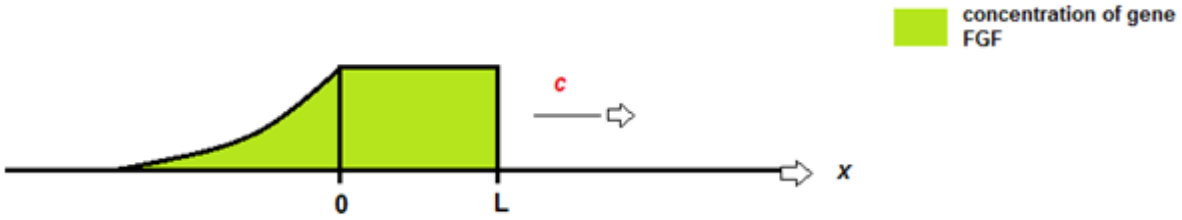


Fig 2.1 shows the stem zone of size L moving with speed c across a segment of line. The concentration of gene FGF8 is constant inside the stem zone, is 0 in front and decays exponentially behind.

Dynamics of gene FGF8 : a lab perspective

In this system of coordinates, the differential equation defining the level of gene FGF8 (herein called u_G) inside of the stem zone moving with speed c is

$$\frac{du_G}{dt} = k_0 - k_1 u_G$$

The moving stem zone is represented by a segment of line of length L moving to the right with speed c, i.e. in the range

$$0 < x < L + ct$$

k_0 and $k_1$are called kinetics constants: k_1 defines the rate of decay of u_G, and k_0 defines the rate of production of u_G.

Outside of this segment, i.e. within the ranges

$$x < 0, \;\; x > L + ct,$$

$$\frac{du_G}{dt} = -k_1 u_G$$

as k_0 (production) is 0.

We can approximate the level of gene inside the stem zone by a stationary solution:

$$\frac{du_G}{dt} = 0 = k_0 - k_1 u_G \Rightarrow u_G = \frac{k_0}{k_1}$$

We can see that u_G is a constant inside the stem zone. If we let $k_0 = k_1$, then $u_G = 1$ inside the stem zone.

As for the level of gene outside the stem zone, we can conclude that its level is zero in front of the stem zone and decreases exponentially behind, since the stationary solution is given by:

$$-k_1 u_G = 0$$

However, the ranges for the differential equations change over time, so this isn't the best way to represent the solution. Consider the case in a co-moving frame of reference, where we are moving with the stem zone.

Dynamics of gene FGF8 : In a co-moving frame of reference

In this system of coordinates, the partial differential equation defining the level of gene u_G inside the stem zone is

$$\frac{\partial u_G}{\partial t} = c\frac{\partial u_G}{\partial x} + k_0 - k_1 u_G$$

for the range $0 < x < L$, and outside the stem zone is

$$\frac{\partial u_G}{\partial t} = c\frac{\partial u_G}{\partial x} - k_1 u_G$$

for the ranges $x < 0$ and $x > L$.

These areas do not change over time, so we use this co-moving frame of reference to easily solve for u_G.

We can look for the stationary solutions representing the concentration of the gene, i.e.

$$\frac{\partial u_G}{\partial t} = 0$$

In front of the stem zone

$$0 = c\frac{\partial u_G}{\partial x} + 0 - 0.k_1 \Rightarrow u_G = const$$

In fact,

$$u_G(x > L) = 0$$

This is clearly true; there will be no concentration of u_G in front of the stem zone.

Inside the stem zone

$$0 = c\frac{\partial u_G}{\partial x} + k_0 - k_1 u_G \Rightarrow c\frac{\partial u_G}{\partial x} = k_0 - k_0 = 0$$

$$\Rightarrow u_G = const$$

u_G will clearly not be 0 as in front, but let

$$u_G(0 < x < L) = 1$$

Behind the stem zone

$$0 = c\frac{\partial u_G}{\partial x} - k_1 u_G \Rightarrow c\frac{\partial u_G}{\partial x} = k_1 u_G \Rightarrow \frac{\partial u_G}{u_G} = \frac{k_1}{c}\partial x$$

$$\Rightarrow \ln(u_G) = \frac{k_1 x}{c}$$

$$\Rightarrow u_G(x < 0) = u_0 e^{\frac{k_1 x}{c}}$$

Where u_0 is u_G at time 0, position 0.

We also need to model the amount of a diffusible protein FGF8 (herein called u_A), also produced in the stem zone wherever the gene FGF8 is produced.

Dynamics of protein FGF8 (also called protein A)

In a co-moving frame of reference the partial differential equation defining the level of u_A is

$$\frac{\partial u_A}{\partial t} = D_2\frac{\partial^2 u_A}{\partial x^2} + c\frac{\partial u_A}{\partial x} + k_2(2u_G - u_A)$$

where D_2 defines the diffusion constant and k_2 is a kinetic constant. $2k_2u_G$ represents the production of u_A and -k_2u_A represents the decay of u_A.

Remember, $u_G = 0$ in front of the stem zone, inside the stem zone it is a constant (say 1), and behind it is a decaying exponential.
We need to solve for u_A in three regions: u_1, u_2, u_3 (shown in Fig 2.3)

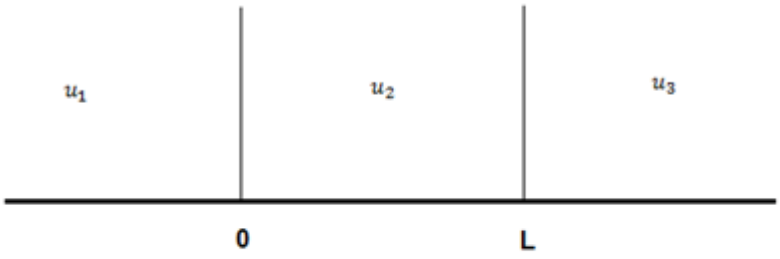


Fig 2.3 shows the 3 regions in which we need to solve the partial differential equation for the concentration of protein A; in front of the stem zone, inside the stem zone, and behind.

In front of the stem zone

$$u_G = 0$$

To find stationary solution,

$$D_2 \frac{\partial^2 u_3}{\partial x^2} + c \frac{\partial u_3}{\partial x} - k_2 u_3 = 0$$

This is a homogeneous second order differential equation, so choose a trial solution $u_A = e^{mx}$
If we substitute this into our differential equation we get

$$D_2 m^2 + cm - k_2 = 0$$
$$\Rightarrow m = \frac{-c \pm \sqrt{c^2 + 4D_2 k_2}}{2D_2}$$

Take

$$\lambda_1 = \frac{-c + \sqrt{c^2 + 4D_2 k_2}}{2D_2}$$

And

$$\lambda_2 = \frac{-c - \sqrt{c^2 + 4D_2 k^2}}{2D_2}$$

to be the roots of this quadratic equations, where $\lambda_1 > 0,\ \lambda_2 < 0$
So our general solution is

$$\boldsymbol{u_3 = Ae^{\lambda_1 x} + Be^{\lambda_2 x}}$$

Inside the stem zone

$$u_G = const = 1$$

To find stationary solution,

$$D_2 \frac{\partial^2 u_2}{\partial x^2} + c \frac{\partial u_2}{\partial x} - k_2 u_2 = -2k_2$$

Our general solution is the same as before, $u_2 = Ae^{\lambda_1 x} + Be^{\lambda_2 x}$
However we need to find the particular solution as well, as this is no longer a homogeneous second order differential equation.
Try

$$u_2(PI) = \alpha \Rightarrow u_2', u_2'' = 0$$

If we substitute this back into our differential equation we get

$$-k_2 \alpha = -2k_2$$
$$\Rightarrow \alpha = 2$$

So our solution is

$$\boldsymbol{u_2 = Ee^{\lambda_1 x} + Fe^{\lambda_2 x} + 2}$$

Behind the stem zone

$$u_G = e^{\frac{k_1 x}{c}}$$

From time to time we will refer to $\frac{k_1}{c}$ as $\boldsymbol{m}$ for simplicity.

To find a stationary solution,

$$D_2\frac{\partial^2 u_1}{\partial x^2}+c\frac{\partial u_1}{\partial x}-k_2u_1=-2k_2e^{mx}$$

Again our general solution is as before, but we need to find the particular solution.
Try

$$u_1(PI)=-\eta e^{\upsilon x}\Rightarrow {u_1}'=-\eta\upsilon e^{\upsilon x}\Rightarrow {u_1}''=-\eta\upsilon^2 e^{\upsilon x}$$

If we substitute this back into our differential equation we get

$$-\eta e^{\upsilon x}(D_2\upsilon^2+c\upsilon-k_2)=-2k_2e^{mx}$$

$$\Rightarrow \upsilon=m$$

$$-\eta=\frac{-2k_2}{D_2\upsilon^2+c\upsilon-k_2}=\frac{-2k_2}{D_2m^2+k_1-k_2}=\frac{-2k_2}{D_2m^2+cm-k_2}$$

$$\Rightarrow \eta=\frac{2k_2}{D_2m^2+cm-k_2}$$

We will leave η in this form as it is tedious to write out; but we must remember that η is a constant throughout our workings.

So our solution is

$$\boldsymbol{u_1=Ge^{\lambda_1 x}+He^{\lambda_2 x}-\eta e^{\frac{k_1 x}{c}}}$$

However, we need to find a continuous smooth solution for u_A, which means we have 6 conditions we need to fulfil:

$$u_1(0)=u_2(0)$$
$${u'}_1(0)={u'}_2(0)$$
$$u_2(L)=u_3(L)$$
$${u'}_2(L)={u'}_3(L)$$

and

$$u_3(\infty)=u_1(-\infty)=0$$

1) $u_1(0)=u_2(0)\Rightarrow \boldsymbol{G+H-\eta=E+F+2}$
2) ${u'}_1(0)={u'}_2(0)\Rightarrow \boldsymbol{G\lambda_1+H\lambda_2-\frac{\eta k_1}{c}=E\lambda_1+F\lambda_2}$
3) $u_2(L)=u_3(L)\Rightarrow \boldsymbol{Ee^{\lambda_1 L}+Fe^{\lambda_2 L}+2=Ae^{\lambda_1 L}+Be^{\lambda_2 L}}$
4) ${u'}_2(L)={u'}_3(L)\Rightarrow \boldsymbol{E\lambda_1 e^{\lambda_1 L}+F\lambda_2 e^{\lambda_2 L}=A\lambda_1 e^{\lambda_1 L}+B\lambda_2 e^{\lambda_2 L}}$
5) $u_3(\infty)=0\Rightarrow \boldsymbol{Ae^{\lambda_1\infty}+Be^{\lambda_2\infty}=0}$
6) $u_1(-\infty)=0\Rightarrow \boldsymbol{Ge^{-\lambda_1\infty}+He^{-\lambda_2\infty}-\eta e^{\frac{-k_1\infty}{c}}=0}$

Take 5):

$$Ae^{\lambda_1\infty}+Be^{\lambda_2\infty}=0$$

We have $\lambda_2<0$, so the term $Be^{\lambda_2\infty}=0$. To satisfy the whole equation, $A=0$

Take 6):

$$He^{-\lambda_2\infty}=0$$

This is true because $Ge^{-\lambda_1\infty}$ and $\eta e^{\frac{-k_1\infty}{c}}$ both equal zero, since λ_1 and $\frac{k_1}{c}$ are both positive.

$$\Rightarrow H=0$$

Take 1) and 2) and substitute in $H = 0$:

1)$\Rightarrow G = E + F + 2 + \eta$

2)$\Rightarrow\ G\lambda_1 = E\lambda_1 + F\lambda_2 + \frac{\eta k_1}{c}$

$$\Rightarrow G\lambda_1 = E\lambda_1 + F\lambda_2 + \frac{\eta k_1}{c} = (E + F + 2 + \eta)\lambda_1$$

$$\Rightarrow E\lambda_1 + F\lambda_2 + \frac{\eta k_1}{c} = E\lambda_1 + F\lambda_1 + 2\lambda_1 + \eta\lambda_1$$

$$\Rightarrow F\lambda_2 + \frac{\eta k_1}{c} = F\lambda_1 + 2\lambda_1 + \eta\lambda_1$$

$$\Rightarrow F\lambda_2 = F\lambda_1 + 2\lambda_1 + \eta\lambda_1 - \frac{\eta k_1}{c} \Rightarrow F(\lambda_2 - \lambda_1) = \lambda_1(2 + \eta) - \eta m$$

$$\Rightarrow F = \frac{\lambda_1(2 + \eta) - \eta m}{(\lambda_2 - \lambda_1)}$$

$$\Rightarrow F = \frac{-2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}$$

1) $\Rightarrow$

$$G = E - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)} + 2 - \eta$$

3) and 4) now become:

$$Ee^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}e^{\lambda_2 L} + 2 = Be^{\lambda_2 L}$$

And

$$E\lambda_1 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L} = B\lambda_2 e^{\lambda_2 L}$$

Multiply 3) by λ_2:

$$E\lambda_2 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L} + 2\lambda_2 = B\lambda_2 e^{\lambda_2 L}$$

Now we can equate 3) and 4):

$$E\lambda_2 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L} + 2\lambda_2 = E\lambda_1 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L}$$

$$\Rightarrow E\lambda_2 e^{\lambda_1 L} + 2\lambda_2 = E\lambda_1 e^{\lambda_1 L}$$

$$\Rightarrow E\lambda_2 e^{\lambda_1 L} - E\lambda_1 e^{\lambda_1 L} = Ee^{\lambda_1 L}(\lambda_2 - \lambda_1) = -2\lambda_2$$

$$\Rightarrow E = \frac{-2\lambda_2}{(\lambda_2 - \lambda_1)e^{\lambda_1 L}}$$

$$\Rightarrow E = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)$$

And so

$$G = E + F + 2 + \eta$$

$$\Rightarrow G = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right) - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)} + 2 + \eta$$

$$= \frac{e^{-\lambda_1 L}2\lambda_2 - 2\lambda_1 + \eta m - \eta\lambda_1 + (2 + \eta)(\lambda_1 - \lambda_2)}{\lambda_1 - \lambda_2}$$

$$= \frac{e^{-\lambda_1 L}2\lambda_2 - 2\lambda_1 + \eta m - \eta\lambda_1 + 2\lambda_1 - 2\lambda_2 + \eta\lambda_1 - \eta\lambda_2}{\lambda_1 - \lambda_2}$$

$$= \frac{e^{-\lambda_1 L}2\lambda_2 + \eta m - 2\lambda_2 - \eta\lambda_2}{\lambda_1 - \lambda_2}$$

$$\Rightarrow G = \left(\frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2}{\lambda_1 - \lambda_2}\right)$$

And 4)⇒

$$B\lambda_2 e^{\lambda_2 L} = E\lambda_1 e^{\lambda_1 L} + F\lambda_2 e^{\lambda_2 L}$$

$$\Rightarrow B\lambda_2 e^{\lambda_2 L} = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)\lambda_1 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L}$$

$$= \frac{2\lambda_2\lambda_1 - 2\lambda_1\lambda_2 e^{\lambda_2 L} + \lambda_2 e^{\lambda_2 L}\eta(m - \lambda_1)}{\lambda_1 - \lambda_2}$$

$$\Rightarrow B = \frac{2\lambda_2\lambda_1 - 2\lambda_1\lambda_2 e^{\lambda_2 L} + \lambda_2 e^{\lambda_2 L}\eta(m - \lambda_1)}{\lambda_2 e^{\lambda_2 L}(\lambda_1 - \lambda_2)}$$

$$= \frac{2\lambda_1 - 2\lambda_1 e^{\lambda_2 L} + e^{\lambda_2 L}\eta(m - \lambda_1)}{e^{\lambda_2 L}(\lambda_1 - \lambda_2)}$$

$$\Rightarrow B = \frac{2\lambda_1 e^{-\lambda_2 L} + \eta(m - \lambda_1) - 2\lambda_1}{\lambda_1 - \lambda_2}$$

Also remember that in these equations,

$$\frac{k_1}{c} = m$$

So we can say that:

$$\boldsymbol{u_1 = Ge^{\lambda_1 x} - \eta e^{mx}}$$
$$\boldsymbol{u_2 = Ee^{\lambda_1 x} + Fe^{\lambda_2 x} + 2}$$
$$\boldsymbol{u_3 = Be^{\lambda_2 x}}$$

Therefore, substituting in our constants of integration, the solution is

$$u_1 = \left(\frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2}{\lambda_1 - \lambda_2}\right)e^{\lambda_1 x} - \frac{2k_2}{D_2 m^2 + cm - k_2}e^{mx}, \qquad x \le 0$$

$$u_2 = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)e^{\lambda_1 x} + \left(\frac{-2\lambda_1 + \eta(m - \lambda_1)}{\lambda_1 - \lambda_2}\right)e^{\lambda_2 x} + 2, \qquad 0 \le x \le L$$

$$u_3 = \left(\frac{2\lambda_1 e^{-\lambda_2 L} + \eta(m - \lambda_1) - 2\lambda_1}{\lambda_1 - \lambda_2}\right)e^{\lambda_2 x}, \qquad x \ge L$$

Check using boundary conditions:

1) $\boldsymbol{G + H - \eta = E + F + 2}$

$$\frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2}{\lambda_1 - \lambda_2} - \eta = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right) - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)} + 2$$

$$\Rightarrow \frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2 - \eta(\lambda_1 - \lambda_2)}{\lambda_1 - \lambda_2} = \frac{2\lambda_2 e^{-\lambda_1 L} - 2\lambda_1 + \eta(m - \lambda_1) + 2(\lambda_1 - \lambda_2)}{\lambda_1 - \lambda_2}$$

$$\Rightarrow 2\lambda_2 e^{-\lambda_1 L} - \lambda_2\eta + \eta m - 2\lambda_2 - \eta\lambda_1 + \eta\lambda_2 = 2\lambda_2 e^{-\lambda_1 L} - 2\lambda_1 + \eta m - \lambda_1\eta + 2\lambda_1 - 2\lambda_2$$

All the terms cancel so this holds.

2) $\boldsymbol{G\lambda_1 + H\lambda_2 - \frac{\eta k_1}{c} = E\lambda_1 + F\lambda_2}$

$$\left(\frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2}{\lambda_1 - \lambda_2}\right)\lambda_1 - \eta m = e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)\lambda_1 - \frac{2\lambda_1\lambda_2 + \eta\lambda_2(m - \lambda_1)}{(\lambda_1 - \lambda_2)}$$

$$\Rightarrow \frac{2\lambda_2\lambda_1 e^{-\lambda_1 L} + \eta\lambda_1(-\lambda_2 + m) - 2\lambda_1\lambda_2 - \eta m(\lambda_1 - \lambda_2)}{\lambda_1 - \lambda_2} = \frac{2\lambda_2\lambda_1 e^{-\lambda_1 L} - 2\lambda_1\lambda_2 + \eta\lambda_2(m - \lambda_1)}{\lambda_1 - \lambda_2}$$

$$\Rightarrow 2\lambda_2\lambda_1 e^{-\lambda_1 L} - \eta\lambda_1\lambda_2 + \eta\lambda_1 m - 2\lambda_1\lambda_2 - \eta m\lambda_1 + \eta m\lambda_2 = 2\lambda_2\lambda_1 e^{-\lambda_1 L} - 2\lambda_1\lambda_2 + \eta\lambda_2 m - \eta\lambda_2\lambda_1$$

All the terms cancel so this holds.

3) $\boldsymbol{Ee^{\lambda_1 L} + Fe^{\lambda_2 L} + 2 = Ae^{\lambda_1 L} + Be^{\lambda_2 L}}$

$$e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}e^{\lambda_2 L} + 2 = \frac{2\lambda_1 e^{-\lambda_2 L} + \eta(m - \lambda_1) - 2\lambda_1}{\lambda_1 - \lambda_2}e^{\lambda_2 L}$$

$$\Rightarrow \frac{2\lambda_2 - 2\lambda_1 e^{\lambda_2 L} + \eta e^{\lambda_2 L}(m - \lambda_1) + 2(\lambda_1 - \lambda_2)}{\lambda_1 - \lambda_2} = \frac{2\lambda_1 + \eta e^{\lambda_2 L}(m - \lambda_1) - 2e^{\lambda_2 L}\lambda_1}{\lambda_1 - \lambda_2}$$

$$\Rightarrow 2\lambda_2 - 2\lambda_1 e^{\lambda_2 L} + \eta m e^{\lambda_2 L} - \lambda_1\eta e^{\lambda_2 L} + 2\lambda_1 - 2\lambda_2 = 2\lambda_1 + m\eta e^{\lambda_2 L} - \lambda_1\eta e^{\lambda_2 L} - 2e^{\lambda_2 L}\lambda_1$$

All the terms cancel so this holds.

4) $\boldsymbol{E\lambda_1 e^{\lambda_1 L} + F\lambda_2 e^{\lambda_2 L} = A\lambda_1 e^{\lambda_1 L} + B\lambda_2 e^{\lambda_2 L}}$

$$e^{-\lambda_1 L}\left(\frac{2\lambda_2}{\lambda_1 - \lambda_2}\right)\lambda_1 e^{\lambda_1 L} - \frac{2\lambda_1 + \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\lambda_2 e^{\lambda_2 L} = \frac{2\lambda_1 e^{-\lambda_2 L} + \eta(m - \lambda_1) - 2\lambda_1}{\lambda_1 - \lambda_2}\lambda_2 e^{\lambda_2 L}$$

$$\Rightarrow \frac{2\lambda_2\lambda_1 - 2\lambda_1\lambda_2 e^{\lambda_2 L} + \eta\lambda_2 e^{\lambda_2 L}(m - \lambda_1)}{\lambda_1 - \lambda_2} = \frac{2\lambda_1\lambda_2 + \eta\lambda_2 e^{\lambda_2 L}(m - \lambda_1) - 2\lambda_1\lambda_2 e^{\lambda_2 L}}{\lambda_1 - \lambda_2}$$

$$\Rightarrow 2\lambda_2\lambda_1 - 2\lambda_1\lambda_2 e^{\lambda_2 L} + \eta m\lambda_2 e^{\lambda_2 L} - \lambda_1\eta\lambda_2 e^{\lambda_2 L} = 2\lambda_1\lambda_2 + m\eta\lambda_2 e^{\lambda_2 L} - \lambda_1\eta\lambda_2 e^{\lambda_2 L} - 2\lambda_1\lambda_2 e^{\lambda_2 L}$$

All the terms cancel so this holds.

5) $\boldsymbol{Ae^{\lambda_1 \infty} + Be^{\lambda_2 \infty} = 0}$

6) $\boldsymbol{Ge^{-\lambda_1 \infty} + He^{-\lambda_2 \infty} + \eta e^{\frac{-k_1 \infty}{c}} = 0}$

These both obviously hold as we have shown before.

Location of maximum u_A

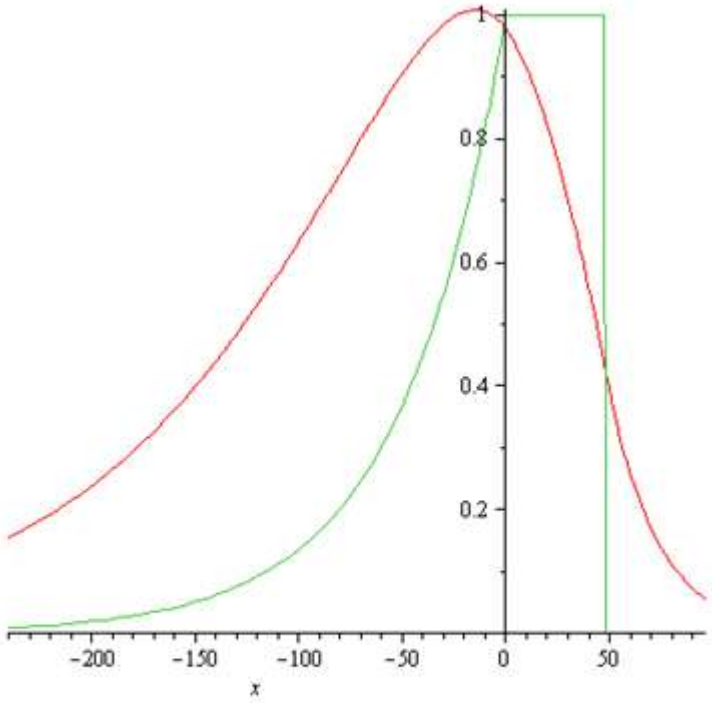


Fig 2.4 Location of maximum concentration of protein A

We now want to find the maximum point of u_A. The protein FGF8 is produced wherever the gene FGF8 is. Since there is no production of the gene FGF8 in the region u_3, i.e. in front of the stem zone, we will not consider this region. Instead we will search for $\max(u_A)$ inside regions u_1 and u_2. We can use Maple to plot the graph of the concentrations of the protein FGF8 (red line) and the gene FGF8 (green line), using the following parameters, acquired by experimentation:

$$k_1 = 0.0003$$
$$k_2 = 0.00025$$
$$c = 0.015$$
$$L = 48$$
$$D = 0.5$$

(See Fig 2.4 above for graph)

The green line represents the concentration of gene FGF8. It is at its highest concentration inside the stem zone with a concentration of 1, its lowest in front with zero concentration, and is exponentially decaying behind the stem zone. The red line represents the concentration of the protein FGF8 which is produced wherever the gene FGF8 is. It is clear that the maximum value of u_A is just behind the stem zone; however we must be able to prove this beyond any doubt, to check we have made no mistakes. To do this we must evaluate the x −position of u_A(max) both behind the stem zone and inside it.

Behind stem zone ($x < 0$):

$$\boldsymbol{u_1 = Ge^{\lambda_1 x} - \eta e^{\frac{k_1 x}{c}} = Ge^{\lambda_1 x} - \eta e^{mx}}$$

To find the x −position of u_A(max);

$$u_1{}' = G\lambda_1 e^{\lambda_1 x} - \eta m e^{mx} = 0$$
$$\Rightarrow G\lambda_1 e^{\lambda_1 x} = \eta m e^{mx} \Rightarrow \frac{\eta m}{G\lambda_1} = e^{(\lambda_1 - m)x}$$
$$\Rightarrow (\lambda_1 - m)x = ln\left(\frac{\eta m}{G\lambda_1}\right)$$

And so

$$\boldsymbol{x_1 = \frac{1}{(\lambda_1 - m)} ln\left(\frac{\eta m}{G\lambda_1}\right)}$$

Inside stem zone ($0 < x < L$):

$$\boldsymbol{u_2 = Ee^{\lambda_1 x} + Fe^{\lambda_2 x} + 2}$$

To find the x-position of u_A(max);

$$u_2{}' = E\lambda_1 e^{\lambda_1 x} + F\lambda_2 e^{\lambda_2 x} = 0$$
$$\Rightarrow E\lambda_1 e^{\lambda_1 x} = -F\lambda_2 e^{\lambda_2 x} \Rightarrow -\frac{F\lambda_2}{E\lambda_1} = e^{(\lambda_1 - \lambda_2)x}$$

We can find that

$$\boldsymbol{F\lambda_2 = \lambda_2\left[\frac{-2\lambda_1 - \eta(m - \lambda_1)}{(\lambda_1 - \lambda_2)}\right]}$$

And

$$\boldsymbol{E\lambda_1 = \lambda_1 e^{-\lambda_1 L}\frac{2\lambda_2}{\lambda_1 - \lambda_2}}$$

$$\Rightarrow -\frac{F\lambda_2}{E\lambda_1} = \frac{-\lambda_2(-2\lambda_1 + \eta(m - \lambda_1))}{2\lambda_2\lambda_1 e^{-\lambda_1 L}} = \frac{2\lambda_1\lambda_2 - \eta\lambda_2(m - \lambda_1)}{2\lambda_2\lambda_1 e^{-\lambda_1 L}} = \frac{2\lambda_1 - \eta(m - \lambda_1)}{2\lambda_1 e^{-\lambda_1 L}}$$

$$= \frac{e^{\lambda_1 L}(2\lambda_1 - \eta(m - \lambda_1))}{2\lambda_1} = e^{\lambda_1 L}\left[1 - \frac{\eta(m - \lambda_1)}{2\lambda_1}\right]$$

This gives

$$e^{(\lambda_1 - \lambda_2)x} = e^{\lambda_1 L}\left[1 - \frac{\eta(m - \lambda_1)}{2\lambda_1}\right] \Rightarrow (\lambda_1 - \lambda_2)x = \lambda_1 L + ln\left|1 - \frac{\eta(m - \lambda_1)}{2\lambda_1}\right|$$

And so

$$\boldsymbol{x_2 = \frac{\lambda_1 L}{\lambda_1 - \lambda_2} + \frac{1}{\lambda_1 - \lambda_2} ln\left|1 - \frac{\eta(m - \lambda_1)}{2\lambda_1}\right|}$$

We now have two points where u_A(max) could be found, and of course only one of these will be correct. Using Maple, we will evaluate them. To be a true maximum point, the x −coordinate must exist within the ranges we have chosen.

The maximum found in u_1 (i.e. behind the stem zone) is given by the coordinates (-14.70668504, 1.009018583). The x coordinate is at -14.706 (approximately), which is within the range $(-\infty, 0]$. However, the maximum found in u_2 (i.e. inside the stem zone) is given by the coordinates

(-10.35744445, 1.002809479),which is not within the range of the stem zone, (0, 48). Therefore, the true maximum must be

$$x_1 = \frac{1}{(\lambda_1 - m)} ln\left(\frac{\eta m}{G\lambda_1}\right)$$

which is behind the stem zone, as was shown in Fig 2.4.

The next question we would like to answer is what conditions on the parameters ensure that u_A(max) will be found behind the stem zone?

The extreme case is on the border between the sections $x < 0$ and $0 < x < L$, i.e. when $x = 0$. So we put $x_1 = 0$ (we could also put $x_2 = 0$, and we should still find the same answer)

$$x_1 = \frac{1}{(\lambda_1 - m)} ln\left(\frac{\eta m}{G\lambda_1}\right) = 0 \Rightarrow \frac{\eta m}{G\lambda_1} = 1$$

$$\Rightarrow \eta m = \frac{2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2}{\lambda_1 - \lambda_2}\lambda_1$$

$$\Rightarrow \frac{\eta m(\lambda_1 - \lambda_2)}{\lambda_1} = 2\lambda_2 e^{-\lambda_1 L} + \eta(-\lambda_2 + m) - 2\lambda_2$$

$$\Rightarrow \frac{\eta m(\lambda_1 - \lambda_2)}{\lambda_1} - \eta(-\lambda_2 + m) + 2\lambda_2 = 2\lambda_2 e^{-\lambda_1 L}$$

$$\Rightarrow \frac{\eta m(\lambda_1 - \lambda_2) - \eta\lambda_1(-\lambda_2 + m) + 2\lambda_1\lambda_2}{2\lambda_2\lambda_1} = \frac{\eta m\lambda_1 - \eta m\lambda_2 - \eta\lambda_1 m + \lambda_2\eta\lambda_1 + 2\lambda_1\lambda_2}{2\lambda_2\lambda_1} = e^{-\lambda_1 L}$$

$$\Rightarrow -\lambda_1 L = \ln\left(1 + \frac{\eta\lambda_1 - \eta m}{2\lambda_1}\right) \Rightarrow L = -\frac{1}{\lambda_1}\ln\left(1 + \frac{\eta(\lambda_1 - m)}{2\lambda_1}\right)$$

So we have found an expression for the same of the stem zone in terms of the speed with which it is moving (remember, λ_1, η and m are all functions of c)

Using to Maple to plot L as a function of c, using the same parameters as before, we obtain the following graph:

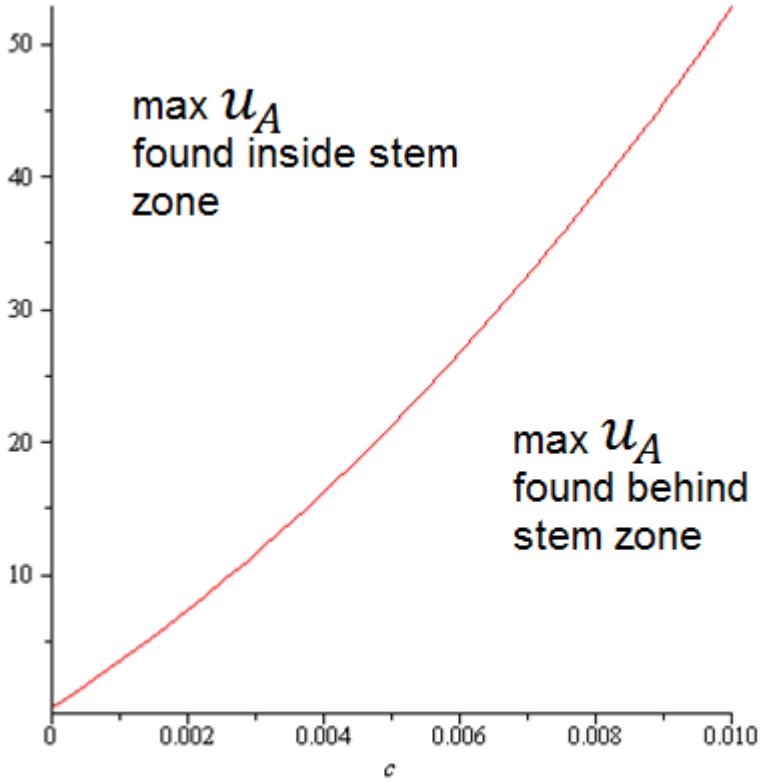


Fig 2.5 shows a graph of L plotted against c. Above this curve, max UA will be found inside the stem zone. Below the curve, max UA will be found behind the stem zone.

Along this red curve, max(u_A) will always be found on the line $x = 0$. Now we can find what happens above and below this curve.

<u>For a maximum to be found behind the stem zone:</u>

$$x_1 = \frac{1}{(\lambda_1 - m)} ln\left(\frac{\eta m}{G\lambda_1}\right) \leq 0$$

We need to consider two cases; $(\lambda_1 - m) > 0$ and $(\lambda_1 - m) < 0$:

$$(\boldsymbol{\lambda_1 - m}) > 0 \Rightarrow ln\left(\frac{\eta m}{G\lambda_1}\right) \leq 0 \Rightarrow \frac{\eta m}{G\lambda_1} \leq 1$$

$$\Rightarrow L \geq -\frac{1}{\lambda_1} \ln\left(1 + \frac{\eta(\lambda_1 - m)}{2\lambda_1}\right)$$

$$(\boldsymbol{\lambda_1 - m}) < 0 \Rightarrow ln\left(\frac{\eta m}{G\lambda_1}\right) \geq 0 \Rightarrow \frac{\eta m}{G\lambda_1} \geq 1$$

$$\Rightarrow L \leq -\frac{1}{\lambda_1} \ln\left(1 + \frac{\eta(\lambda_1 - m)}{2\lambda_1}\right)$$

Using the parameters from before, we can find that $(\lambda_1 - m) < 0$; it is -0.0080741759. Therefore, being below the curve on the graph will ensure that a maximum value of u_A is found behind the stem zone.

For a maximum to be found inside the stem zone:

$$x_2 = \frac{\lambda_1 L}{\lambda_1 - \lambda_2} + \frac{1}{\lambda_1 - \lambda_2} ln \left| 1 - \frac{\eta(m - \lambda_1)}{2\lambda_1} \right| \geq 0$$

$\lambda_1 - \lambda_2 > 0$ (it is 0.05385164808)

$$\Rightarrow \lambda_1 L \geq ln \left| 1 - \frac{\eta(m - \lambda_1)}{2\lambda_1} \right| \Rightarrow L \geq \frac{1}{\lambda_1} ln \left| 1 - \frac{\eta(m - \lambda_1)}{2\lambda_1} \right|$$

So being above the curve on the graph will ensure that a maximum value of u_A is found inside the stem zone.

2.2 Potts Model

2.21 Cellular Potts model

In the last chapter we used a 1-dimensional continuous model considering a segment on a line to represent a stem zone, which gave accurate results. We can also use a 2-dimensional model that considers individual cells, and is more representative of what is happening biologically.
The Cellular Potts model developed by Graner and Grazier is a computational method using lattices, used to simulate the behaviour of cellular structures. The lattice was originally created as a model of ferromagnetism (the mechanism by which certain materials are attracted to magnets) in ferrous crystalline (or lattice) materials.

The lattice L can be thought of as a 2D matrix, with each entry representing a 'cell site'. Many squares make up a single cell, as shown below in Fig 2.6.

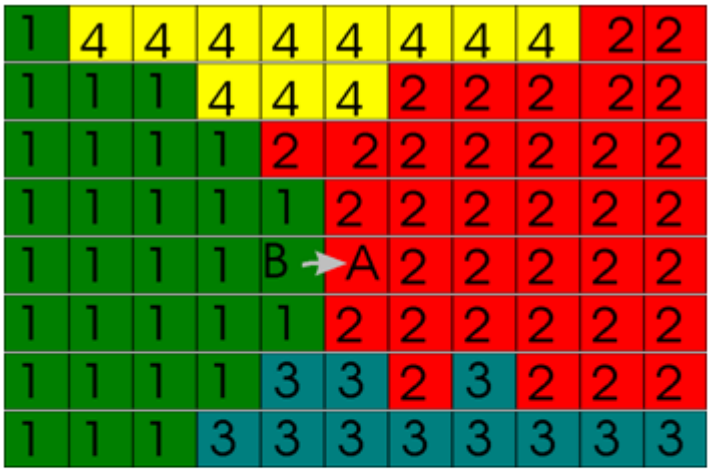


Fig 2.6 shows the lattice used in the 2D Cellular Potts model. Each entry represents a cell site. All the cells coloured red and numbered '2' represent one whole cell, and similarly for blue, green and yellow. The arrow shows a potential cell site swap between B and A.

So for example, all the red entries numbered 2 make up one single cell; the same goes for all the green entries, yellow entries, and blue entries.
Biologically, cells explore their boundaries in an attempt to minimise the overall energy. We have an expression for the energy of the system:

$$E = E_{adhesive} + E_{cell\_size} + E_{chemotaxis} + \ldots$$

where the energy terms somehow relate to forces existing within the system. The first term relates to the adhesive forces existing between the cells. The second term is related to the cell size, which must always remain constant. The third term is related to chemotaxis- this describes the movement of cells due to the gradient of a chemical that may be present within the cells. This is the case we looked at in the one dimensional model, where we considered chemotaxis due to the presence of a gene FGF8.
We could consider more energy terms, but for the problem we want to solve these will be enough.

The energy is defined in such a way as to mimic the desired biological behaviour of cells; in our case we shall consider the stem cells within the stem zone.
First we shall consider a case with no chemotaxis (i.e. we will obtain a stationary solution), and will consider the evolution of the system towards minimisation of energy. So for this we only need consider the first two terms of the energy,

$$E = E_{adhesive} + E_{cell\_size}$$

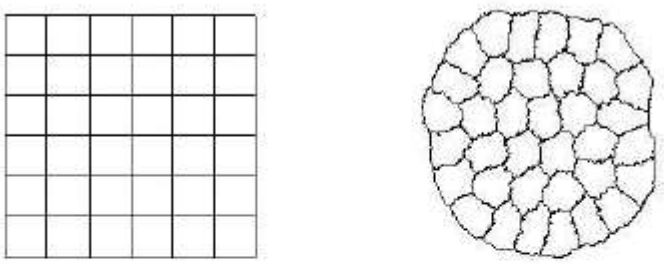
To mimic the behaviour of the cells, the CPM uses an algorithm to choose a particular site; for example it picks site B in the image above. It then uses a random sampling method to pick a neighbouring site, for example site A. It then calculates the probability that site B will choose to inhabit the space where site A currently resides.

It the CPM finds that by site B invading site A the overall energy of the system decreases, the probability is 1 and site B will definitely invade site A. If the CPM finds that the overall energy does not decrease, it calculates the probability that site B will invade site A using a Boltzmann probability function:

$$P(\Delta E) = e^{-\frac{\Delta E}{\mathrm{T}}}$$

where T is the "temperature" of the system, and ΔE is a change in energy. So there is still a probability that site B will inhabit site A, but it is not definite that this will happen.

The CPM repeats this process until the solution stabilises as it has found the minimised energy state. By doing so, the CPM eventually changes the lattice to a desired biological representation, i.e. the cells in the stem zone. We would expect the lattice to reduce to a circular group of cells as this would represent a minimised energy state. The picture below illustrates this. Figure a) shows a regular 2-D lattice before any steps have been taken. Figure b) shows the lattice after maximum number of cell site invasions; it shows the lattice in a minimized energy state, that now more closely resembles the cells in the stem zone. These cells will have little motility now that the energy is at a minimum.



a) - Initial b) - Minimized

Fig 2.7; a) shows the lattice before any cell site swaps have taken place; b) shows the lattice after the maximum number of cell site swap have taken place, where the energy is minimum.

If we now consider the case with chemotaxis involved, we now consider the first three energy terms,

$$E = E_{adhesive} + E_{cell\_size} + E_{chemotaxis} + \ldots$$

The CPM will repeat the same process used before. However there will be a slight difference in what we see happening biologically. Because of chemotaxis, there will be a general movement of the cells; in our case we considered a movement of left to right due to chemo-repulsion.

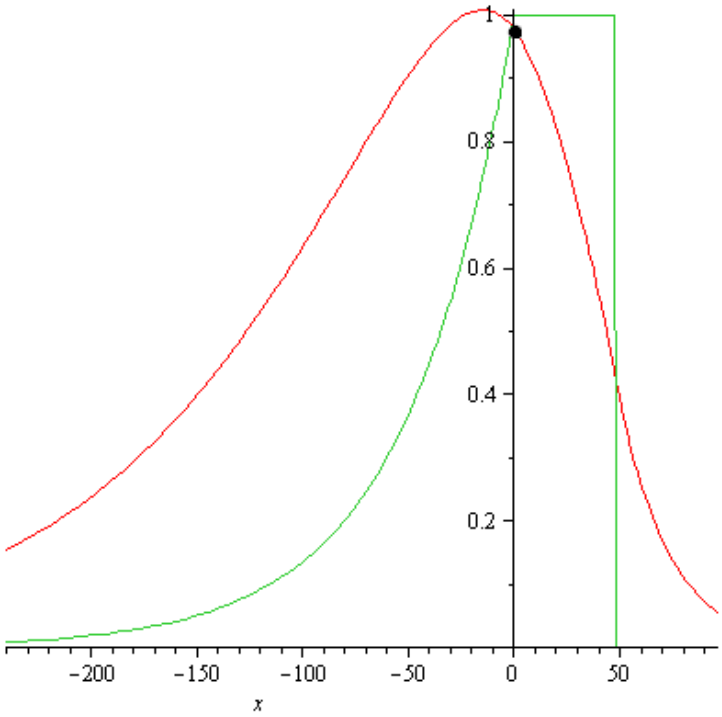


Fig 2.8 shows the concentration plots of gene FGF8 and Protein A as before; the black dot represents the point where gene FGF8 is no longer produced

If we consider the concentrations of the gene FGF8 and the protein FGF8 that we found before, we can see that there will come a point at $x < 0$ where the gene FGF8 is no longer produced (shown in Fig 2.8). At this point, protein FGF8 reaches its threshold value, as it is only produced wherever FGF8 is produced. As the stem zone moves from left to right, the stem cells are constantly proliferating; however, at this point where the gene FGF8 is no longer produced, any cells behind this point will stop moving and turn into neurons- they differentiate from cells in front as they no longer express the gene FGF8. The stem zone continues to move and reproduce cells in this fashion. As the neurons left behind are now stationary, graphically we will see a trail of neurons dragging behind the stem cells that are still expressing the gene FGF8. This is a feasible explanation of how the primitive streak forms, with the group of cells known as Hensen's node at the forefront differentiating from the rest of the cells on the primitive streak. In Fig 2.9, the cells coloured red represent the stem cells, and the cells coloured green represent the cells that no longer express the gene FGF8 (the neurons), trailing behind the stem zone.

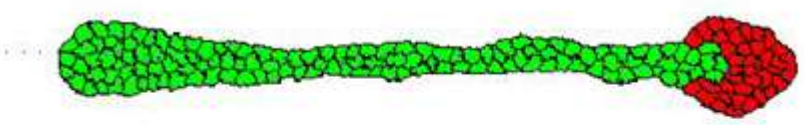


Fig 2.9 shows Hensen's node (red coloured cells) formed at the forefront of the primitive streak (green coloured cells)

The CPM model is much slower than the 1-D model, so to solve we use different parameters to cause dimensional diffusion and kinetic constants to be slightly smaller than used in the 1-D model.

3.Bibliography

Websites

Wikipedia articles on:
Ferromagnetism
Cellular Potts Model
Gastrulation

Papers

"A cell-centered approach to developmental biology"- Merks and Glazier 2005
"An Investigation Of Epithelial Cell Alignment Using A Modified Cellular Potts Model."- Nigel C Harrison 2008
"Coordination of cell differentiation and migration in mathematical models of caudal embryonic axis extension"- Nigel C Harrison, Ruth Diez del Coral, Bakhtier N Vasiev

Books

Principles of Development- Wolpert

Images from:
http://ghr.nlm.nih.gov
http://www.phschool.com
http://www.geochembio.com