Diffusion Models for Tissues and Tumor Growth

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1 Introduction

Researchers have been studying cancer and the patterns behind tumor growth for thousands of years. Hippocrates was accredited with possibly being the first to describe a tumor, which were mainly described by their color and their response to touch. However, ancient physicians did not separate benign and malignant tumors, but they acknowledged the tumor's ability to infect nearby tissue. The application of mathematical models to tumor growth did not start to gain traction until much later, however. In the early 20th century, one of the most famous uses of the diffusion model was first developed: Hill released a paper discussing how the movement of lactic acid and oyxgen throughout the body could be shaped into a diffusion problem (Hill, 1928). This paper eventually led to Greenspan's paper which modeled the growth of tumors using diffusion, applying many of the mathematical tools employed by Hill some years before (Greenspan, 1972). This paper will present an overview of the diffusion model in mathematical biology and will discuss the mathematics and biology behind two of the most influential diffusion papers.

2 Hill's Paper on Diffusion

Hill's paper, titled 'Diffusion of Oxygen and Lactic Acid through Tissues', set the scene for most of the diffusion models developed in the late 20th century to present. In the introduction of this paper, Hill states that the 'diffusion of dissolved substances through cells and tissues is a determining factor in many vital processes'. The diffusion constant, k, is introduced, along with its usages. It is representative of the number of unit quantities of a substance that diffuse throughout an area of 1 cm^2 in a minute. The diffusion constant is usually a small value when related to systems that are outside of the body; for example, the diffusion constant would be very small when studying the diffusion of a gas within a large room. However, when studying systems within the body, the diffusion constant can be quite large. Hill gives the following example when explaining this:

Object	Diameter	Time to 90% Saturation
Cylinder	1 cm	185 minutes
Actual Nerve	0.7 mm	54 seconds
Single Nerve Fiber	7 μ (0.0007 cm)	0.0054 seconds

As seen by this example, many processes of diffusion throughout the body are extremely rapid. However, at the time of Hill's paper, another problem was evident: not many problems in diffusion could be completely solved using mathematical methods. Even when evaluating these equations, the existence of a unique solution was only guaranteed with certain inital conditions. The steady state also needed to have specific parameters in order for the result to be of any interest.

2.1 Diffusion of Oxygen Within a Steady State

The first problem that Hill dealt with was the case where oxygen was being diffused from a gaseous or liquid phase. It was assumed that the oxygen was being used up by metabolic processes at some rate a and that the concentration of oxygen, y_0, is maintained constant at $x = 0$.

Let x be the distance from the constant source of oxygen to any point within the tissue. Given the assumptions above, the rate of diffusion across any unit area will be $J = -k\frac{dy}{dx}$, where J is the rate of diffusion, k is the diffusion rate and the (-) represents that the diffusion is occuring in the opposite direction from the source. This is more commonly known as Fick's first law of diffusion. To find the measure of this rate of accumulation, Fick's second law can be applied:

$$\frac{dJ}{dx} = k\frac{d^2y}{dx^2} \tag{1}$$

Hill then combined these equations along with a, the rate of usage by the metabolic process, to come up with the first diffusion equation for this model:

$$\frac{dy}{dt} + a = k\frac{d^2y}{dx^2} \tag{2}$$

This equation states that the rate of change of the concentration of oxygen plus the rate of usage of the oxygen is equal to the diffusion equation. Note that from the assumptions above, the concentration is held constant, so the equation can be further simplified to:

$$a = k\frac{d^2y}{dx^2} \tag{3}$$

The solution of the equation is

$$y = \frac{ax^2}{2k} + bx + y_0 \tag{4}$$

where b is a constant. This can be verified by taking the derivative of this equation twice:

$\frac{dy}{dx} = \frac{a}{k}x + b,$

$\frac{d^2y}{dx^2} = \frac{a}{k}$

To find the value of b that satisfies these equations, we assume that there must be some point very far away from the source where the concentration is zero and the diffusion of oxygen is not occuring, so $\frac{dy}{dx}$ is also equal to zero.

We define x' as the minimum distance where the concentration is equal to zero and then set these two equations equal to zero and solve:

$0 = \frac{ax'^2}{2k} + bx' + y_0$

$0 = \frac{ax'}{k} + b \Leftrightarrow b = -\frac{ax'}{k}$

Substituting back into the first equation:

$0 = \frac{ax'^2}{2k} - \frac{ax'^2}{k} + y_0 \Leftrightarrow y_0 = \frac{ax'^2}{2k}$

So

$$x' = \sqrt{\frac{2ky_0}{a}} \tag{5}$$

(the maximum permeation distance of the oxygen from the source)

and

$$b = \sqrt{\frac{-2ay_0}{k}} \tag{6}$$

We can now solve to find how much oxygen has been absorbed by the tissue: $\int_0^{x'} ydx$, where y is found in equation (3).

We get the integral:

$$Y = \int_0^{\sqrt{\frac{2ky_0}{a}}} \frac{ax^2}{2k} + bx + y_0 dx \tag{7}$$

To solve (7), we integrate and then simplify:

$Y = \frac{ax^3}{6k} - \frac{x^2}{2}\sqrt{\frac{2ay_0}{k}} + y_0 x \Big|_0^{\sqrt{\frac{2ky_0}{a}}}$

$= \sqrt{2ky_0}\frac{y_0}{3\sqrt{a}} - \frac{ky_0\sqrt{\frac{2ay_0}{k}}}{a} + y_0\sqrt{\frac{2ky_0}{a}}$

$$= y_0\frac{x'}{3} \tag{8}$$

This result (which Hill also derived) shows that the maximum absorption of oxygen in a tissue that is x' thick is one-third the full amount of oxygen that is diffused.

2.2 Diffusion of Lactic Acid Within a Steady State

This case is the exact opposite of the case studied above. As the tissue uses up the oxygen, lactic acid is built up at a rate of $-\alpha$, the opposite sign as seen in equation (3) above. So our equation then becomes

$$-\alpha = k' \frac{d^2 y'}{dx^2} \tag{9}$$

where k' is the new diffusion constant of lactic acid and y' is the concentration of lactic acid at any point x. Using the same processes as above, we can find a solution to this equation:

$$y' = \frac{-\alpha x^2}{2k'} - \beta x + y'_0 \tag{10}$$

and can find that the total amount of lactic acid dissolved is

$$Y = \frac{y'_0 \beta}{3} \tag{11}$$

These equations all assume that there exists some point in the tissue where the concentration of lactic acid or oxygen is equal to zero. If this is not the case, Hill showed in his paper that the amount of oxygen dissolved would be

$$y_0 b - \frac{ab^3}{3k} \tag{12}$$

and the total amount of lactic acid dissolved would be

$$y'_0 b + \frac{\alpha b^3}{3k'} \tag{13}$$

2.3 Combining Oxygen and Lactic Acid Diffusion

Hill then combined both equations to come to a conclusion on how lactic acid and oxygen would interact in a muscle.

The conclusions made from this section of the paper were essential for future models of diffusion. First, it was assumed that the thickness $b > x'$ so none of the oxygen was able to penetrate through the entire system. From above, the concentrations of oxygen and lactic acid are y and y' respectively. The plane sheet of tissue will have oxygen at a partial pressure of y_0 from the left and an impenetrable wall on the right. Also let a be the rate of usage (in cubic centimeters of tissue) of oxygen by the tissue. Then the following graphic describes the system:

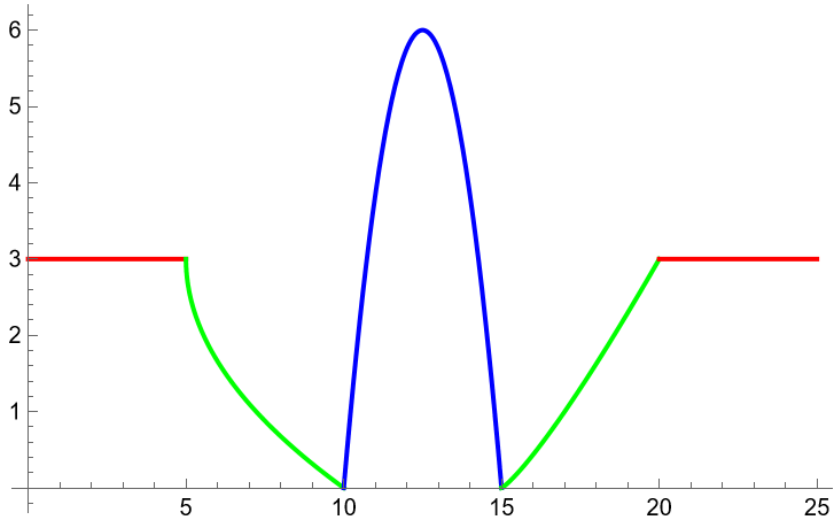

Figure 1: From 0 to 5 and 20 to 25, the concentration y is equal to the steady state y_0. From 5 to 10, the concentration y is decreasing until it reaches 0 at 10 (in green). From 10 to 15, the lactic acid concentration y' (in blue) is increasing to its maximum and then decreases to 0 at 15. From 15 to 20, the oxygen concentration y_0 increases until reaching the steady state (red) at x = 20. Note that the x and y values for this graphic are arbitrary.

The diffusion equations that satisfy this model are easily seen from the graphic and discussion above:

$-\alpha = k' \frac{d^2 y'}{dx^2}$(the source of lactic acid on the right)

$a = k \frac{d^2 y}{dx^2}$ (the oxygen from the left.)

The boundary conditions for these PDEs are:

(a) $y = y_0$ when x is to the left of the source of oxygen diffusion.

(b) $\frac{dy'}{dx} = 0$ for $x = b$ since no diffusion of oxygen occurs here.

(c) The concentration of lactic acid must become zero at the same point as the concentration of oxygen becomes zero.

At the point where (c) occurs, the diffusion of oxygen from the left must be equal to the diffusion of lactic acid from the right. Mathematically, this can be expressed as the equation

$$-k \frac{dy}{dx} = k' \frac{dy}{dx} \tag{14}$$

Expressed as a ratio and simplified, this means that:

$$\frac{-k\frac{dy}{dx}}{k'\frac{dy}{dx}} = \frac{-k\frac{ax}{k}}{k'\frac{-\alpha x}{k'}} = \frac{a}{\alpha} \tag{15}$$

This equation states that in this steady state, it takes $\frac{a}{\alpha} cm^3$ of oxgyen to remove 1 gram of lactic acid. Hill continues the paper by discussing other possible steady states that could be used to investigate this model. However, they are not of interest for this paper.

3 Greenspan's Paper: Models for the Growth of a Solid Tumor by Diffusion

Greenspan's paper was released almost 50 years after the inital paper by Hill was authored. Since then, many mathematical models had been employed to try to model processes within the body. A few years prior to the release of Greenspan's paper, Burton (1966) authored one of the most famous papers on the growth of tumors as a problem of diffusion. Greenspan expanded on many of the models developed by Burton.

The primary goal of Greenspan was to 'infer the chemical source of growth inhibition from the most easily obtained data...the outer radius of the nodule as a function of time.' The conclusions were also described 'with as little mathematics as possible' to try to attract a more general audience, unlike the previous papers of the time.

3.1 Overview of the Biology

A tumor is any abnormal group of cells, which can either be benign or malignant. Benign tumors are defined by being confined to their original location and do not infect surrounding tissue or body sites. Malignant tumors, however, are capable of invading nearby tissue and can spread throughout the body via metastasis. For a tumor to be classified as cancer, it must be a malignant tumor; cancers are so dangerous because of their ability to spread to various sites in the body, making localized treatments very hard to administer.

Tumor growth is usually backed by the tumor receiving nutrients and wastes from nearby cells via a diffusion process similar to one discussed in section 2 of the paper. When the tumor is small, most cells nearby still are receiving most of the necessary nourishment from the source of the diffusion. In terms discussed before, the cells are absorbing γa times the normal rate of absorption, where $\gamma \in [0, 1]$ represents the proportion of nutrients that go to the healthy cell. As the size of the tumor increases, $\gamma \to 0$; however, the growth rate of the tumor begins to decrease as it becomes harder for it to absorb resources from the healthy cells. A necrotic core - the collection of dead and dying cells that allow for metastasis - is formed at the center of the tumor. The steady state configuration for this tumor is typically modeled to be a sphere with multiple layers. This leads into the variation of this model that is utilized by Greenspan.

3.2 The Model

The typical model used to represent a tumor is as follows:

(a) The outermost layer: A layer several cells thick where cell activity proceeds as normal with exponential growth.

(b) The middle layer: Cells are alive but do not perform mitosis.

(c) The inner layer: This is the necrotic core. The cells here are dead or dying.

A better illustration of this is shown in Figure 2:

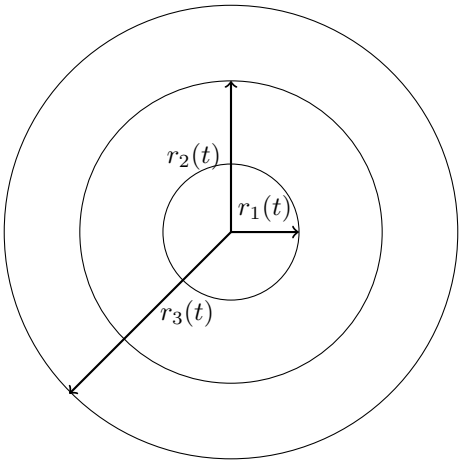

Figure 2: A cross-section of the sphere that represents the tumor. The necrotic core is situated between $0 < r < r_1$, the middle layer is situated between $r_1 < r < r_2$, and the healthy outer layer is located between $r_2 < r < r_3$.

Typically, the few tumor cells can expand quite rapidly depending on several parameters, such as the cell types and nutrient levels of the body. They can multiply in number to around a million in a growth period of days. The nodule (Figure 2) can expand from being microscopic to having a radius of over 1 millimeter. Greenspan wished to apply this model to understand how $r_3(t)$ - the outer radius of the nodule - changes with respect to time by analyzing the steady state. To do this, several assumptions were adopted by the model:

(i) The tumor is a sphere with perfect symmetry at all times, leaving the experiment to have 2 independent variables: time, t, and r, the radial distance.

(ii) Cancer cells die when the nutrient levels, $\sigma(r, t)$ drop below a critical minimum of σ_{min}. Oxygen is the most essential nutrient and is modeled using the methods described in the paper by Hill (1928).

(iii) Oxygen is used by living cells only and depends on the nutrient concentration.

The model also assumes that living cancer cells maintain a compact solid mass and that any mass lost from the diffusion of permeable substances coming from disintegrated necrotic cells is replaced by cells pushing towards the center of the compact mass. Because of this, we arrive at the conclusion in equilibrium that, if the rate of cell production exceeds the losses from necrotic disintegration, then the tumor must be growing in size. The reverse of this statement also holds.

Recall from above that the middle layer of the tumor has some substance that inhibits the mitosis of cancer cells. We define $\beta(r,t)$ to be the concentration of this substance in cubic centimeters.

3.3 Compartments and Conservation of Mass

We need a few additional approximations before establishing the model:

(i) All living tumor cells are the same and do not fluctuate in size.

(ii) Mitosis occurs instantaneously and all new cells are the same size as existing cells.

(iii) The growth rate via mitosis is a distribution $S(\sigma,\beta)$ with $S(\sigma,\beta)=0$ for $\beta > \beta_{max}$ or $\sigma < \sigma_{min}$.

(iv) The core loses cell volume proportional to its volume with the proportionality constant defined as 3λ.

Now we can discuss the conservation of mass law:

$$c_{total}(t) = c_0 + c_{prod}(t) - n(t) - n_{lost}(t) \tag{16}$$

where

$c_{total}(t)$ is the total number of cells produced at time t,

c_0 is the inital population,

$c_{prod}(t)$ is the total amount of cells produced during the interval $[0,t)$,

$n(t)$ is the total volume of necrotic cells at t,

and $n_{lost}(t)$ is the volume lost to the necrotic core during the interval $[0,t)$.

Let $r_3(0)$ be the inital outer radius of the tumor. Recall that cell death occurs when the nutrient level σ falls below its minimum value σ_{min}, the edge of the inner radius, $r_1(t)$, must satisfy

$$\sigma(r_1(t),t) = \sigma_{min}, t \geq 0 \tag{17}$$

Let $r_2(t)$ be the radius where the chemical inhibitor reaches the critical level. Then by definition

$$\beta(r_2(t),t) = \beta_{max} \tag{18}$$

We can now replace the formulas described above with mathematical expressions:

$$c_{total}(t) = \frac{4\pi}{3}(r_3^3(t) - r_1^3(t)) \tag{19}$$

by subtracting the areas of the two spheres.

It is quite obvious to see that

$$c_{init}(t) = \frac{4\pi}{3}r_3^3(0) \tag{20}$$

and that

$$n(t) = \frac{4\pi}{3}r_1^3(t) \tag{21}$$

Using our assumption that the necrotic core loses volume at a constant rate, we can derive the integral

$$n_{lost}(t) = \frac{4\pi}{3}\int_0^t 3\lambda r_1^3(t)dt \tag{22}$$

where 3λ is the proportionality constant.

Our final equation requires more rigorous mathematics. We know that the proliferation rate is parameterized by both σ and β. Since we need to accumulate the total amount of cells produced over a continuous time period, we must integrate. However, there are some values of t where $r_1(t) > r_2(t)$, so we must include another integral to account for this. Mathematically, this is:

$$c_{prod}(t) = 4\pi\int_0^t dt\int_{max(r_1(t),r_2(t))}^{r_3(t)} S(\sigma,\beta)r^2dr \tag{23}$$

where the factor of $1/3$ seen in the other equations comes from the integration of the r^2 term.

We must now plug these formulas into the conservation of mass equation (16) seen above.

$r_3^3(t) - r_1^3(t) = r_3^3(0) + 3\int_0^t dt\int_{max(r_1(t),r_2(t))}^{r_3(t)} S(\sigma,\beta)r^2dr - r_1^3(t) - \int_0^t 3\lambda r_1^3(t)dt$ (removing the factors of 4π)

$$r_3^3(t) = r_3^3(0) + 3\int_0^t dt\int_{max(r_1(t),r_2(t))}^{r_3(t)} S(\sigma,\beta)r^2dr - \int_0^t 3\lambda r_1^3(t)dt \tag{24}$$

This is equation (3.1) in Greenspan's paper. It is described as the 'conservation of volume' equation and is what governs the growth of the tumor. To see how the tumor changes with time, the time partial derivative of this equation would be useful. This is equation (3.2) in the paper and will be verified below:

Recall that taking the derivative of an integral with a constant lower bound and t as the upper bound removes the integral, simplifying the second and third terms on the right hand side of the equation. So we get:

$$3r_3^2\frac{dr_3}{dt} = 3\int_{max(r_1(t),r_2(t))}^{r_3(t)} S(\sigma,\beta)r^2dr - 3\lambda r_1^3(t) \tag{25}$$

Removing the factor of 3 from each term simplifies the equation to (3.2).

3.4 The Inward Movement of Live Tumor Cells

Using the same concepts, it is also possible to model the movement of cells towards the inside of the necrotic center. This rate is equal to the rate of production minus the volume rate of death of live cells at the center. If v is the velocity of a cell towards the center, the relative velocity of this cell with respect to the necrotic core can be written as $r_1'(t) - v$. See the following figure for clarification:

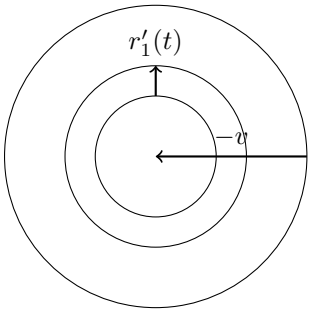

Figure 3: A cross-section of the sphere that represents the inner layer of the tumor. If the tumor is growing outward (the positive direction) and the velocity of the tumor is towards the inside, then the magnitude of the relative velocity of the cell volume is smaller than the rate v.

The rate of change of the outer volume of cells moving into the necrotic core will then be $-4\pi r_1^2(r_1'(t) - v)$.

So the rate of change of the total cell volume, $c_{total}(t)$ is then

$$\frac{4\pi}{3}\frac{d}{dt}(r_3^3(t) - r_1^3(t)) = \int_{max(r_1,r_2)}^{r_3} S(\sigma,\beta)r^2dt - 4\pi r_1^2(r_1'(t) - v) \tag{26}$$

To find the value of v, we need to compare this equation with equation (25). Taking the derivative of the left hand side of (26) yields:

$4\pi(r_3^2\frac{dr_3}{dt} - r_1^2\frac{dr_1}{dt})$.

Moving the term $-4\pi r_1^2\frac{dr_1}{dt}$ to the right-hand side cancels it out. The first term on the left and right hand sides of both equations will be the same. So the

only term not identical to equation (25) can be set equal to the respective one in equation (26):

$$4\pi r_1^2 v = -\lambda r_1^3 \tag{27}$$

with solution

$$v = -\lambda r_1 \tag{28}$$

3.5 Overview of Diffusion Model

Greenspan (1972) proposed that the steady state of the tumor was caused by the combination of two factors: the lack of nutrients and the forces caused by necrosis (as described above.) In that model, the inhibitor β was assumed to be a product of necrosis. Following that, we need to make a few approximations before describing the model:

(i) $\beta(r,t)$ is produced in the core ($r < r_1(t)$) at some constant rate per unit volume P.

(ii) The rates of diffusion of any of the chemicals are uniformly constant throughout all three regions of the tumor. As seen in Hill (1928), we will use k and k' to denote the diffusion constants for σ and β respectively.

(iii) As also seen in Hill's model, cells consume nutrients at a constant rate per volume a.

(iv) The rate of growth of cells per unit volume is some constant s. Greenspan (1972) uses an approximation for the distribution of new cells via mitosis:

$$S(\sigma,\beta) = sH(\sigma - \sigma_{min})H(\beta_{max} - \beta) \tag{29}$$

where $H(x) = 1, x \geq 0; H(x) = 0, x < 0$.

(v) The composition of the tumor medium is kept constant and the compositions outside the tumor (at the outer surface) are constants as well.

Using the nice simplification given by assumption (iv), we can simplify our previous equation further:

$$r_3^2 \frac{dr_3}{dt} = \int_{max(r_1(t),r_2(t))}^{r_3(t)} sr^2 dr - \lambda r_1^3(t) \tag{30}$$

Evaluating the integral:

$$r_3^2 \frac{dr_3}{dt} = \frac{s}{3}(r_3^3(t) - max(r_1^3(t), r_2^3(t))) - \lambda r_1^3(t) \tag{31}$$

Now we will derive the diffusion equations for β and σ. Since we are assuming to be in diffusive equilibrium, we can greatly simplify the expressions.

Recall Fick's second law:

$$\frac{\partial J}{\partial t} = k\nabla^2 J + S(r,t) \tag{32}$$

where the $S(r,t)$ term represents the source rate. We can then formulate our diffusion equations by simplifying this equation. Since we are in the steady state, we know that the rate of change of concentration is equal to zero (or otherwise we would still have diffusion occuring). So we plug in for the $\nabla^2 J$ Laplacian term:

$$\nabla^2 J = \frac{-S(r,t)}{k} \tag{33}$$

By assuming spherical symmetry, we can simplify this Laplacian into spherical coordinates:

$$\nabla^2 J = \frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r} J \tag{34}$$

First, solve for the diffusion equation for β. As long as we are in the core, by assumption (i), $-S(r,t)$ will be equal to P.

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\beta(r,t) = \frac{-P}{k'} \tag{35}$$

Then use the step function to make sure that the necrotic core assumption is held:

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\beta(r,t) = \frac{-P}{k'} H(r_1(t) - r) \tag{36}$$

This makes the right-hand side of the equation equal to zero when $r_1(t) < r$. This equation now takes the form of (4.3) from Greenspan (1972).

Doing the same process for σ: First, use assumption (iii) to replace the rate $S(r,t)$ with a:

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\sigma(r,t) = \frac{a}{k} \tag{37}$$

Then add the appropriate step function conditions:

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\sigma(r,t) = \frac{a}{k} H(r - r_1(t)) H(r_3(t) - r) \tag{38}$$

This is equivalent to equation (4.4).

3.6 Solving the Diffusion Equations

To solve these partial differential equations, boundary equations need to be established. The boundary conditions have been briefly mentioned at the beginning of this section. First, σ and its partial derivatives need to be continuous, along with β and its partial derivatives. It is also necessary for equations (17) and (18) to be satisfied to guarantee a unique solution. Only one initial condition is necessary to solve the diffusion equation: the inital size of the outer tumor, $r_3(0)$. It is assumed that at $t = 0$, the tumor is small enough such that $r_1(t) = r_2(t) = 0$.

The equations (4.6) - (4.9) will be verified by checking the solutions. The equations given in Greenspan (1972) are as follows:

If $r_1(t) < r < r_3(t)$:

$$\sigma = \sigma_\infty - \frac{a}{6k}(r_3^2 - r^2) + \frac{ar_1^3}{3k}(\frac{1}{r} - \frac{1}{r_3}) \tag{39}$$

and

$$\beta = \frac{Pr_1^3}{3k'}(\frac{1}{r} - \frac{1}{r_3}) \tag{40}$$

From the boundaries of the step functions found above, in this region, evaluating the left-hand side of β should yield zero, since $r > r_1(t)$.

First checking β:

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}(\frac{Pr_1^3}{3k'}(\frac{1}{r} - \frac{1}{r_3}))$$

$$= \frac{1}{r^2}\frac{\partial}{\partial r}r^2(-\frac{Pr_1^3}{3kr^2})$$

$$= \frac{1}{r^2}(0) = 0$$

Next, checking σ:

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}[\sigma_\infty - \frac{a}{6k}(r_3^2 - r^2) + \frac{ar_1^3}{3k}(\frac{1}{r} - \frac{1}{r_3})]$$

σ_∞ does not depend on the value of r, so it is a constant. We get

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2(\frac{ar}{3k} - \frac{ar_1^3}{3kr^2})$$

$$= \frac{1}{r^2}(\frac{ar^2}{k})$$

$$= \frac{a}{k}$$

So we have successfully shown that the first two equations hold according to the parameters provided via the assumptions. Now doing the same process for equations (4.8) and (4.9):

If $r \leq r_1(t)$:

$$\sigma = \sigma_{min} \tag{41}$$

and

$$\beta = \frac{Pr_1^3}{3k'}(\frac{3}{2r_1} - \frac{r^2}{2r_1^3} - \frac{1}{r_3}) \tag{42}$$

The verification of σ can be done directly. If $r < r_1(t)$, the only solution that exists must be $\sigma = \sigma_{min}$. This is because of being inside of the necrotic core and has been shown in equation (17).

To verify β, the same method as before will be used. We start with the equation

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}[\frac{Pr_1^3}{3k'}(\frac{3}{2r_1} - \frac{r^2}{2r_1^3} - \frac{1}{r_3})]$$

$$= \frac{1}{r^2}\frac{\partial}{\partial r}r^2(-\frac{Pr}{3k'})$$

$$= \frac{1}{r^2}(-\frac{Pr^2}{k'})$$

$$= -\frac{P}{k'}$$

All of the differential equations have now been verified. We can solve for σ_{min} and β_{max}:

First, solving for σ_{min} requires using equation (17):

$$\sigma(r_1(t), t) = \sigma_{min}$$

We now have solutions to the differential equations and directly plug in to them. Since $r = r_1(t)$, the first equation is used.

$$\sigma(r_1(t), t) = \sigma_\infty - \frac{a}{6k}(r_3^2 - r_1^2) + \frac{ar_1^3}{3k}(\frac{1}{r_1} - \frac{1}{r_3})$$

After simplification, this is

$$\sigma_\infty - \sigma_{min} = \frac{a}{3k}[\frac{r_3^2 - r_1^2}{2} - r_1^2 + \frac{r_1^3}{r_3}] \tag{43}$$

For β, equation (16) is used:

$$\beta(r_2(t), t) = \beta_{max}$$

Then the same process for finding the max value is used:

$$\beta_{max} = \frac{P}{3k'} r_1^3 (\frac{1}{r_2} - \frac{1}{r_3}) \tag{44}$$

which represents the condition for which the slowing of mitosis for cells in the middle layer occurs.

4 Conclusion

Hill (1928) and Greenspan (1972) both proposed diffusion models to solve their specific modeling situation. Many modern diffusion models now follow the patterns shown in these two papers and expand on them by adding additional terms to the diffusion PDE. For example, a recent paper by Stepien et al. (2015) included a diffusion model for in vitro glioblastoma growth which included the following diffusion equation:

$$\frac{\partial u_i(r,t)}{\partial t} = \underbrace{k\nabla^2 u_i}_{\text{Diffusion}} + \underbrace{g u_i \left(1 - \frac{u_i}{u_{\max}}\right)}_{\text{Logistic growth}} - \underbrace{\nu_i \nabla_r \cdot u_i}_{\text{Taxis}} + \underbrace{s\delta(r - R(t))}_{\text{Shed cells from core}} \tag{45}$$

Many additional papers also exists which discuss how to modify Fick's second law equation in order to better model biological processes. Possible improvments to the two models above could be adding a logistic growth term into the diffusion equation; however, both authors were limited by the lack of computing power and availability of past models. Both authors utilized similar methods for completely different biological topics, demonstrating the versatility of the diffusion model. Overall, the diffusion model is a relatively simple and flexible model to apply to various biological circumstances.

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