A Mathematical Model for Tumor Growth and Angiogenesis

Wietse Boon

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1 Introduction

The growth of a tumor consists of several stages. Initially, a mutation in a cell or small group of cells causes an increase in cell division. As the tumor grows in size, it uses up a large amount of nutrients from the surrounding tissue. Eventually, this causes the growth rate to decrease as nutrients become less available. To receive a new supply, the tumor will need to get connected to blood vessels. At this point the tumor disperses a chemoattractant called TAF to start the formation of new blood vessels, also known as angiogenesis [4]. Once the blood vessels reach the mutated cells, they re-enable the tumor to grow.

Using this order of events, the initial tumor growth can be divided into three stages: the initial, prevascular mutation and growth, angiogenesis, and finally the continued growth. To model these phases, we will use numerical simulations based on individual models. However, these models were created independently from one other. Now the main goal of this paper is to combine these models so that they influence and depend on each other. These relationships between angiogenesis and tumor growth will be realised by using a new function for the oxygen concentration which will serve as a connection.

By making the combination, we can create an expansion on both models and bring the dynamic relationship between these two processes to light.

The most important outcome of the model is whether a tumor keeps growing or stops evolving when it reaches a certain size. Naturally, it will be very useful if we can predict this outcome. However, a lot more factors contribute to this process than the ones used in the mathematical models. Therefore, these predictions are not necessarily very accurate. As more dynamic relationships are added to the model, the accuracy of these predictions increases. By combining these two models, a small step is taken towards a model that takes all these factors into account.

Furthermore, we can change the parameters in the simulation and find out which parameters have the greatest influence in the tumor growth. This will then give a more complete insight into the growth and evolution of the tumor. Once we can resimulate the events close enough to reality, these parameters could reveal which course of action will be most effective to stop the growth of tumors [6].

For the first model, we consider the process of angiogenesis. Using a model made by H. M. Byrne and M. A. J. Chaplain [1], we focus on the underlying differential equations and reproduce the results. Secondly, a model for tumor growth is considered made by J. A. Sherratt and M. A. Nowak [2]. Again, we analyse the differential equations and explain what factors play an important role in this process. Next, we consider a few different types of tumor and resimulate the results from [2].

Thirdly, all differential equations have to be scaled to the same time and distance scale. Therefore, we redimensionalise the differential equations from the previously mentioned papers so that we are one step closer to making the combination. Afterwards, the actual combination is made using an equation for the oxygen concentration which links the angiogenesis to the tumor growth and vice versa. These results are then presented and analysed.

Finally, we will draw our conclusions and discuss possibilities for future research.
2 Angiogenesis

First, we will take a look at the formation of new blood vessels. This process, known as angiogenesis, is made possible by a few key components. The attractant TAF will be excreted from the tumor and cause endothelial cells to form and become mobile. These endothelial cells will serve as the tips of the blood vessels and as building blocks for the capillaries. Following close behind these tips will be the endothelial cells which make up the sides of the blood vessels [1, 4, 6].

The branching off of capillary tips from blood vessels will be referred to as primary angiogenesis. Furthermore, once the process has started a great increase in tip proliferation will take place. This is known as a second type of angiogenesis and is triggered by a certain threshold of TAF-concentration[3]. However, blood can only flow through this network of vessels once they form loops. Naturally, this happens once capillary cells merge into formed vessels.

All these events can be explained using underlying differential equations. The equations we use originate from a model made by Byrne and Chaplain [1]. It is important to note that the variables, as well as the time units and distance units, have been non-dimensionalised by using the proper scaling. The following notation is used for the different variables:

- \( q(x, t) \) is the capillary tip density,
- \( v(x, t) \) is the vessel density,
- \( c(x, t) \) is the concentration TAF.

Consequently, each of these variables will be subject to a differential equation. First, we consider the equation for the capillary tip density:

\[
\frac{\partial q}{\partial t} = \mu \left( \frac{\partial^2 q}{\partial x^2} \right) - \chi \frac{\partial}{\partial x} \left( q \frac{\partial c}{\partial x} \right) + \alpha_0 vc + \alpha_1 H(c - \hat{c})qc - \beta qv \tag{1}
\]

Considering the equation term by term, we start with the term \( \mu \left( \frac{\partial^2 q}{\partial x^2} \right) \) which describes a mobility of the capillary tips. The parameter \( \mu \) determines the rate of this mobility. The next term \( -\chi \frac{\partial}{\partial x} \left( q \frac{\partial c}{\partial x} \right) \) represents the influence of the TAF concentration on the mobility of the capillary tips. Due to this term, the capillary tips will grow towards an area with a higher concentration of the attractant.

Thirdly, the term \( \alpha_0 vc \) is responsible for the first type of angiogenesis. Due to this term, the number of capillary tips increases because they branch off from blood vessels as a reaction to TAF. The fourth term in the equation, \( \alpha_1 H(c - \hat{c})qc \), describes the second type of angiogenesis where a certain threshold of TAF causes capillary tips to branch very quickly. The function \( H \) is the Heaviside function which equals 1 if \( c \geq \hat{c} \) and 0 if \( c < \hat{c} \). Finally, the term \( -\beta qv \) represents the decrease in capillary tips when they start to form loops of blood vessels. This process is known as anastomoses[3].

The second equation represents the vessel density within a sprout:

\[
\frac{\partial v}{\partial t} = \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} - \gamma v \tag{2}
\]

The first two terms in this equation \( \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} \) represent the formation of blood vessels that follow a mobile capillary tip. Naturally, this is dependent on how the density of capillary tips and concentration of TAF in neighboring areas. The third and final term \( -\gamma v \) describes the decay of blood vessels.

The last equation, which completes the process of angiogenesis, represents the concentration of TAF:

\[
\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - \lambda_1 c \tag{3}
\]

First, the term \( \frac{\partial^2 c}{\partial x^2} \) is responsible for the diffusion of the attractant chemical. The diffusion rate factor that one would expect here is equal to 1 because the model has been non-dimensionalised with this diffusion rate. The second term in the equation represents the decay of TAF with parameter \( \lambda_1 \).
Now we need initial and boundary conditions for these equations. Because the distance has been scaled, the region is now defined between the tumor boundary at $x = 0$ and the closest blood vessels at $x = 1$. Initially, there will be no capillary or endothelial cells present in the region except for the right boundary at $x = 1$. Furthermore, the tumor will start excreting a certain amount of TAF. Then, for the boundary conditions, the model is based on the angiogenesis alone and not on what happens after the capillary tips reach the tumor. Therefore the excretion of TAF is at a constant maximum on the left and the capillary and vessel density are equal to zero at $x = 0$.

The right boundary conditions are based on experimental results in which is shown that the capillary tips decrease exponentially to zero with rate $r$. The vessel density decreases with the same rate to a minimum value $v_{min}$. Combining all these properties of the process, the following expressions define the initial and boundary conditions[1]:

$$
q(0, t) = 0, \quad q(1, t) = q_L e^{-rt}, \quad q(x, 0) = 0 \text{ for } 0 \leq x < 1, \quad q(1, 0) = q_L,
$$

$$
v(1, t) = v_{min} + (1 - v_{min}) e^{-rt}, \quad v(x, 0) = 0 \text{ for } 0 \leq x < 1, \quad v(1, 0) = 1,
$$

$$
c(0, t) = 1, \quad c(1, t) = 0, \quad c(x, 0) = 0 \text{ for } 0 < x \leq 1.
$$

2.1 Discretization

The next step is to approximate the solutions using numerical methods. First we split up the distance from the tumor to the healthy tissue at $x = 1$ into $M + 1$ points with a distance of $\Delta x$ between each pair of points. This creates a vector $x$ in which $x_i = (i - 1)\Delta x$ for $i = 1, 2, ..., M, M + 1$. Then the same is done for time in the vector $t$ with $T + 1$ elements and a distance of $\Delta t$ between each pair of points. Finally, matrices are created for each variable, where the first index represents the distance from the tumor and the second index represents a moment in time. Each one of these matrices has the property that column $k$ represents the values of the corresponding variable for the entire region at moment $t_k$.

For example, the TAF concentration is put into matrix $c$ so that $c_{i,k}$ represents the TAF concentration at position $x_i$ at time $t_k$. In other words:

$$
c_{i,k} = c(x_i, t_k)
$$

2.2 Concentration of TAF

We start the approximation of the different variables with the simplest differential equation, the concentration of TAF: $c$. To predict the values for the next moment in time, we use the implicit method Euler Backwards for the internal points. Because we look at a discretization in time of $c$, we define $c^k = c(x, t_k)$. The following lines show how the method is implemented:

$$
c^{k+1} = c^k + \Delta t \left( \frac{\partial c^{k+1}}{\partial t} \right)
$$

$$
c^{k+1} = c^k + \Delta t \left( \frac{\partial^2 c^{k+1}}{\partial x^2} - \lambda_1 c^{k+1} \right)
$$

Because $c$ is also discretized in space, we define the column vector $\mathbf{c}^k$ to represent all values of $c$ on the different grid nodes $x_i$ at time $t_k$. The equation then becomes

$$
\mathbf{c}^{k+1} = \mathbf{c}^k + \Delta t \left( \mathbf{k}_c \mathbf{c}^{k+1} - \lambda_1 \mathbf{c}^{k+1} \right)
$$

$$
[\mathbf{I} - \Delta t (\mathbf{A} - \lambda_1 \mathbf{I})] \mathbf{c}^{k+1} = \mathbf{c}^k
$$

5
Now the operator $A$ should be an approximation of the second derivative so that $\frac{\partial^2 c}{\partial x^2} \approx A_c$. To determine $A$, we need to look at the second derivative for internal grid nodes using finite differences:

$$\frac{\partial^2 c_i}{\partial x^2} \approx \frac{c_{i-1} - 2c_i + c_{i+1}}{\Delta x^2} \implies A = \frac{1}{\Delta x^2} \begin{bmatrix} -2 & 1 & & & 0 \\ 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \\ 0 & & & 1 & -2 \end{bmatrix}$$

So that:

$$\frac{\partial^2 c_i}{\partial x^2} \approx \frac{c_{i-1} - 2c_i + c_{i+1}}{\Delta x^2} = (A_c)_i$$

That concludes the equations for the internal nodes. The boundary conditions at $x = 0$ and at $x = 1$ are Dirichlet conditions. Therefore, the values of $c_{1}^{k+1}$ and $c_{M+1}^{k+1}$ are already known. Therefore, the first and last lines of the linear system become:

$$c_{1}^{k+1} = 1, \quad \text{for } i = 1$$
$$c_{M+1}^{k+1} = 0, \quad \text{for } i = M + 1.$$

The elements of $c_{i}^{k+1}$ can now be calculated by solving the linear system in which the rows for $i = 2, 3, ..., M$ are defined by the corresponding rows of the following system:

$$[I - \Delta t (A - \lambda_1 I)] c^{k+1} = c^k$$

### 2.3 Capillary tip density

The next variable is the density of capillary tips, $q$. This equation has a second order derivative in the second term. To simplify the equation, we split up this term to get:

$$\frac{\partial q}{\partial t} = \mu \left( \frac{\partial^2 q}{\partial x^2} \right) - \chi \frac{\partial}{\partial x} \left( q \frac{\partial c}{\partial x} \right) + \alpha_0 vc + \alpha_1 H(c - \hat{c})qc - \beta qv$$
$$\frac{\partial q}{\partial t} = \mu \left( \frac{\partial^2 q}{\partial x^2} \right) - \chi \left( \frac{\partial q}{\partial x} \frac{\partial c}{\partial x} + q \frac{\partial^2 c}{\partial x^2} \right) + \alpha_0 vc + \alpha_1 H(c - \hat{c})qc - \beta qv$$

By taking a small step $\Delta t$ in time, we approximate the solution using a forward Euler method for the integration in time:

$$q^{k+1} = q^k + \frac{\partial q^k}{\partial t}$$
$$q^{k+1} = q^k + \Delta t \left[ \mu \left( \frac{\partial^2 q^k}{\partial x^2} \right) - \chi \left( \frac{\partial q^k}{\partial x} \frac{\partial c^k}{\partial x} + q^k \frac{\partial^2 c^k}{\partial x^2} \right) + \alpha_0 vc^k + \alpha_1 H(c^k - \hat{c})q^k c^k - \beta q^k v^k \right]$$

Again, we create the column vector $q^k$ which contains the values of $q$ for all nodes $x_i$ at time $t_k$. For the second derivative, we can use the matrix $A$ which we created earlier. Now, to approximate the first derivative for internal grid points, we make the matrix $B$ using finite differences:

$$\frac{\partial q_i}{\partial x} \approx \frac{q_{i+1} - q_i}{\Delta x} \implies B = \frac{1}{\Delta x} \begin{bmatrix} -1 & 1 & & & 0 \\ -1 & 1 & & & \\ & \ddots & \ddots & \ddots & \\ & & -1 & 1 & \\ 0 & & & -1 & 1 \end{bmatrix}$$
So that for internal nodes:
\[
\frac{\partial q_i}{\partial x} \approx \frac{q_{i+1} - q_i}{\Delta x} = (Bq)_i
\]
The same discretisation is used for the first derivative of \(c\) in the internal nodes. Therefore:
\[
\frac{\partial c_i}{\partial x} \approx \frac{c_{i+1} - c_i}{\Delta x} = (Bc)_i
\]
However, a few minor problems arise when we substitute column vectors for all variables. First of all, we seem forced to multiply vectors with each other (for example: \(v^k*C^k\)). However, this simply means a multiplication of each value of \(v\) at the particular node with the value of \(c\) at that node. Therefore, we can multiply the vectors element-wisely, creating a new column vector in which element \(i\) equals \(v_i^k*c_i^k\). This element-wise multiplication will be noted with an asterisk (\(\ast\)). Using this, the equation for internal nodes becomes:
\[
q_i^{k+1} = q_i^k + \Delta t \left[ \mu k^k - \chi \left( (Bq_i^k) \ast (Bc_i^k) + q_i^k \ast (A_c^k) \right) + \alpha_0 v_i^k \ast c_i^k + \alpha_1 H(c_i^k - \hat{c}) \ast q_i^k \ast c_i^k - \beta q_i^k \ast v_i^k \right]
\]
The Heaviside function \(H\) is also used element-wisely and therefore returns a column vector with zeros and ones depending on the size of \(c_i^k\) for each \(i\). We now take a look at the boundary nodes which need to be implemented separately so that they fulfill the boundary conditions.

For \(x = 1\) we have the following boundary condition: \(q(1,t) = q_L e^{-rt}\). This is a known function for all values of \(t\), so this can very easily be implemented. Then for the first node, at \(x = 0\), we have a Dirichlet condition. All in all, the first and last elements of \(q_i^{k+1}\) become:
\[
q_i^{k+1} = q_L e^{-rtk+1}, \quad \text{for } i = M + 1
\]
\[
q_i^{k+1} = 0, \quad \text{for } i = 1.
\]

### 2.4 Vessel density within sprout

To conclude the model, we have the implementation of \(v\), the density of endothelial cells. Again, we use a small time step so that we can use a simple forward-in-time numerical method. We also create the vector \(v^k\) which represents the values of \(v\) at time \(t_k\). The method will then become the following:
\[
v_i^{k+1} = v_i^k + \frac{\partial v_i^k}{\partial t}
\]
\[
v_i^{k+1} = v_i^k + \Delta t \left[ \mu \frac{\partial n_i^k}{\partial x} - \chi n_i^k \frac{\partial v_i^k}{\partial x} - \gamma v_i^k \right]
\]
\[
v_i^{k+1} = v_i^k + \Delta t \left[ \mu Bn_i^k - \chi n_i^k \ast (Bc_i^k) - \gamma v_i^k \right]
\]

Similar to the previous variables, we can construct the first \(M\) elements of the discretization of \(dv\) using element-wise vector multiplication and the matrix \(B\). The Dirichlet boundary condition for \(x = 1\) is implemented by making the last element of \(v_i^{k+1}\) equal to \(v_{min} + (1 - v_{min})e^{-rtk+1}\)

### 2.5 Results

In order to apply the numerical method, we need to know the value of the different constants in the equations. The following values have been assigned:
<table>
<thead>
<tr>
<th>Name</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>$10^{-3}$</td>
<td>Mobility of capillaries</td>
</tr>
<tr>
<td>$\chi$</td>
<td>0.4</td>
<td>Attraction of TAF</td>
</tr>
<tr>
<td>$\alpha_0$</td>
<td>50</td>
<td>Factor of primary angiogenesis</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>10</td>
<td>Factor of secondary angiogenesis</td>
</tr>
<tr>
<td>$\hat{c}$</td>
<td>0.2</td>
<td>Threshold TAF concentration</td>
</tr>
<tr>
<td>$\beta$</td>
<td>50</td>
<td>Vessel loops closing</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.25</td>
<td>Decay of vessels</td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>1</td>
<td>Decay of TAF</td>
</tr>
<tr>
<td>$q_L$</td>
<td>1</td>
<td>Initial density of capillaries at $x = L$</td>
</tr>
<tr>
<td>$r$</td>
<td>5</td>
<td>Rate of decay at $x = L$</td>
</tr>
<tr>
<td>$v_{\text{min}}$</td>
<td>0.2</td>
<td>Minimum of vessel density at $x = L$</td>
</tr>
</tbody>
</table>

Using these values and the numerical method described above, we obtain the following result for the TAF concentration in which we use a dimensionless time interval of 0.2: As shown in figure 1,

![Figure 1: TAF concentration](image)

the tumor excretes a maximum amount of TAF which diffuses to the right border of the area. The concentration then takes on a stationary solution quite quickly within the region. Once this has been achieved, secondary angiogenesis is also possible wherever $c \geq \hat{c} = 0.2$. This happens on the left side of $x \approx 0.83$.

The most interesting of the three is the formation of capillary tips. As shown in figure 2, they diffuse from the right border into the area as expected. Then, once they reach the $x \approx 0.83$ border, secondary angiogenesis is started and capillary tips start branching off rapidly. The wave then reaches the tumor and, due to the boundary condition $q(0, t) = 0$, all capillaries and vessels return to zero. Therefore, the model is no longer applicable once the capillaries reach the tumor.
Finally, we have the vessel density shown in figure 3. According to the results, the vessels form a wave that follows the capillary front closely. Furthermore, the second type of angiogenesis has an influence here as well. Naturally, more capillary tips will result in more blood vessels so this is to be expected.

\[ \frac{\partial v}{\partial t} = \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} - \gamma v \]
\[ \frac{\partial v}{\partial t} = J - \gamma v \]

**Figure 2: Capillary density with time interval 0.2**

**Figure 3: Vessel density with time interval 0.2**

### 2.6 Boundary condition

As mentioned before, the boundary condition for the capillary tip density is \( q(0, t) = 0 \). This means that the model is valid as long as the tips do not reach the tumor at \( x = 0 \). However, since we are also interested in what happens afterwards, we need to change this boundary condition. For that purpose, we take a closer look at the differential equation for \( v \):

\[ \frac{\partial v}{\partial t} = \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} - \gamma v \]
\[ \frac{\partial v}{\partial t} = J - \gamma v \]
The variable $J$ represents a flux-term. Around $x = 0$, we would expect this flux to be zero. Therefore, our new boundary condition will be $J|_{x=0} = 0$. This is an example of a so-called “no-flux” boundary condition. This type of boundary conditions is implemented by making each first derivative equal to zero. However, as we can see in the differential equations for the TAF concentration and the capillary density, there is also an influence from the second derivative.

For the second derivative in the first node, we use a virtual node $c_0$. If we subject this second derivative to a no-flux boundary condition, the nodes on the left of $c_1$ would have to be the same as the nodes on the right. Therefore, this value of $c_0$ would equal $c_2$:

$$\frac{\partial^2 c_1}{\partial x^2} = \frac{c_0 - 2c_1 + c_2}{\Delta x^2} = \frac{-2c_1 + 2c_2}{\Delta x^2}$$

With a small adjustment in the matrix $A$ to implement this symmetry condition, we create the matrix $A_2$:

$$A_2 = \frac{1}{\Delta x^2} \begin{bmatrix} -2 & 2 & 0 \\ 1 & -2 & 1 \\ 1 & -2 & 1 \\ \vdots & \ddots & \ddots \\ 1 & -2 & 1 \\ 0 & \end{bmatrix}$$

However, if we apply the simple explicit way we have been using so far, the distance between two nodes would have to be small. The time step will then have to be even smaller, so the calculation will take quite a while. We therefore solve it using the method ImEx, which will be explained thoroughly in section 5.2.

### 2.6.1 Results

The concentration of TAF is not affected by this new boundary condition, because it only applies for the equations $q$ and $v$. If we look at the capillary wave, we only see a change once the capillaries reach the tumor. These no longer die out, but take on a stationary form as shown in figure 5. Again, the figures shown are the results with dimensionless time interval of 0.2.

![Figure 4: Capillary tips at various times](image-url)
The following result is the density of vessels with the no-flux boundary condition. Again, this new boundary condition only influences what happens after the tips reach the tumor. Similar to the capillary tips, the vessels take on a stationary form shown in figure 7.

Figure 5: Final state capillary tips

Figure 6: Vessel density at various times

Figure 7: Stationary density of vessels
3 Tumor Growth

The next step is to consider the growth and mobility of mutated cells. Cell growth is regulated by mitotic regulators which can act as an activator or inhibitor of cell division[2, 5]. These regulators are excreted by cells and therefore have their own concentration at each point in place and time. Moreover, cell division is limited by a certain upper bound for cell density, which gives a so-called logistic term. The cells will simply not be able to divide further due to crowding.

This phase in the evolution of the tumor will be based on a mathematical model by Sherratt[2]. Again, this model has been non-dimensionalized by means of scaling to simplify the equations. The following notation is used for the various variables:

- \( n(x,t) \) represents the density of healthy cells
- \( m(x,t) \) represents the mutated cell density and
- \( c_i(x,t) \) represents the \( i \)-th mitotic chemical out of a total of \( J \).

3.1 The Differential Equations

According to the model, an abnormal response to one of these regulators causes cell division to rapidly increase. To specify which regulator is responsible, it will be named \( c_1 \). It is important to note that the concentrations and densities are scaled to their equilibrium values. The density of healthy cells will progress according to the following differential equation:

\[
\frac{\partial n}{\partial t} = D \left( \frac{\partial^2 n}{\partial x^2} \right) + nr(n + m)s_1(c_1)\cdots s_J(c_J) - n
\]

(4)

Similar to the equations in the angiogenesis model, we will analyze the equation term by term. The first term \( D \left( \frac{\partial^2 n}{\partial x^2} \right) \) represents the mobility of the healthy cells in which the factor \( D \) determines the rate of this mobility. Secondly, the function \( r(n) \) is responsible for the crowding limitation. It is defined as follows:

\[
r(n) = \frac{N - n}{N - 1}
\]

Note that the function \( r(n) \) equals zero once \( n = N \) implying that there is no more growth once the cell density is at its maximum. Furthermore, its value is increasing as \( n \) decreases, meaning that cell growth will increase once there is room to grow.

The next function to consider is the implementation for the cell response to the various regulators defined by \( s_i(c_i) \):

\[
s_i(c) = \begin{cases} 
\alpha_i + (1 - \alpha_i)c & \text{if } c_i \text{ is a mitotic activator} \\
\frac{k_i}{1 + (k_i - 1)c} & \text{if } c_i \text{ is a mitotic inhibitor}
\end{cases}
\]

Depending on whether the regulator is a mitotic activator or inhibitor, the regulator will have an \( \alpha_i \) or a \( k_i \) which defines how cells react to its concentration. In both cases, a concentration of zero will result in a cell growth factor of this parameter. A concentration of 1 will make this a growth factor of 1. Note that these values are still scaled, so a concentration of 1 means that the concentration of the regulator is equal to its equilibrium concentration. A growth factor 1 means there will be just as much growth as decay, described in the last term \( -n \).

We choose each \( \alpha \) so that \( 0 < \alpha < 1 \). This way, the function \( s(c) \) is increasing which implies that cell division will increase once a higher concentration of this activator is present. The restriction for \( k \) will be that \( k > 1 \). Once this inequality is valid, the function \( s(c) \) for mitotic inhibitors becomes
decreasing. This is a desired property as well because it implies that cell growth will be slowed as the concentration of this mitotic inhibitor increases.

Looking back at the second term in the differential equation, it is clear to see that the growth of the healthy cells is determined by these functions, either representing a response to crowding or to a mitotic regulator. The product of all these reactions forms the growth factor for the amount of cells.

The second equation of the model defines the density of mutated cells over time in a similar way:

\[
\frac{\partial m}{\partial t} = D \left( \frac{\partial^2 m}{\partial x^2} \right) + mr(n + m)[s_0 + s_1(\xi c_1)s_2(c_2)...s_J(c_J)] - m - \delta m
\]  

(5)

Again, the first term represents the cell mobility and the second determines the growth. In the second term it is clear to see that the model can be used for two different types of mutations using the constants \( s_0 \) and \( \xi \). A positive value for \( s_0 \) can cause an extra growth in mutated cells without a mitotic activator. By giving \( \xi \) a positive value, the mutated cells will have an increased response to chemical \( c_1 \) which can be recognized in the equation.

The last two terms in the differential equation form the decay of the mutated tumor cells. Just like in the previous equation, the term \(-m\) represents natural cell death. The term \(-\delta m\) however, represents the body’s immune response to the mutated cells. A larger value for \( \delta \) obviously results in a stronger immune response.

\[
\frac{\partial c_i}{\partial t} = D_i \left( \frac{\partial^2 c_i}{\partial x^2} \right) + P_i + (n + m)p_i(n + m) - [P_i + p_i(1)] c_i
\]  

(6)

Similar to previous differential equations, the first term represents diffusion in which a chemical-specific value of \( D_i \) has the key role. Secondly, the term \( P_i \) represents the production of chemical \( c_i \) independent of cell density.

The next function that has to be defined is \( p_i(n) \) which is responsible for the excretion of the regulators. Again, this function needs to have a few crucial properties relative to whether it concerns a mitotic activator or inhibitor. Besides from the \( k \) or \( \alpha \), each regulator will have a second and third paramater noted as \( h_i \) and \( \beta_i \). The function \( p_i(c_i) \) will then become:

\[
p_i(n) = \begin{cases} 
  \frac{h_i(1 + \beta_i)}{1 + \beta_i n^2} & \text{if } c_i \text{ is a mitotic activator} \\
  \frac{h_i(1 + \beta_i)}{1 + \beta_i} & \text{if } c_i \text{ is a mitotic inhibitor}
\end{cases}
\]  

(7)

The first property both these functions share is that when the number of cells is at its equilibrium value, i.e. \( n = 1 \), they are equal to \( h_i \). Seperately, it is clear that the activator’s variant is a decreasing function, decreasing to zero, while the inhibitor’s variant is increasing. Basically, this means that as the number of cells increases, the excretion of activators will decline and more inhibitors will be excreted to stop the cell division.

The final term in the differential equation represents the decay of this regulator. In the equillibrium state, this will counteract the production.

As mentioned before, this model is based on an abnormality concerning the chemical \( c_1 \). Therefore, it behaves slightly differently than the rest of the mitotic regulators. We consider its differential equation separately:

\[
\frac{\partial c_1}{\partial t} = D_1 \left( \frac{\partial^2 c_1}{\partial x^2} \right) + P_1 + (n + m)p_1(n + m) + Hmp_1(n + m) - [P_1 + p_1(1)]c_1
\]  

(8)

The difference lies in the constant \( H \) which can cause an extra excretion of chemical \( c_1 \) by the mutated cells. If this chemical is an activator, this will also lead to an increase in cell growth. This can be seen as a third type of mutation.
3.2 Boundary and Initial Conditions

Naturally, these differential equations will need boundary and initial conditions as well. In the beginning, we have a mutation at \( x = 0 \) and the rest of the variables are in their equilibrium state. Intuitively, the tumor will start growing in all directions in the same way. It is therefore sufficient to look at what happens on one of these radial axes. Because the distance in the equations has been scaled with the radius of the tumor, the initial conditions become[2]:

\[
\begin{align*}
n(x, 0) &= \begin{cases} 
0, & x < 1 \\
1, & x > 1
\end{cases} \\
m(x, 0) &= \begin{cases} 
1, & x < 1 \\
0, & x > 1
\end{cases} \\
c_i(x, 0) &= 1
\end{align*}
\]

Due to the symmetry in \( x = 0 \), the boundary conditions become:

\[
\begin{align*}
n &= 1, \quad m = 0, \quad c_i = 1 \text{ at } x \pm \infty \quad \forall i, \\
\frac{\partial n}{\partial x} &= 0, \quad \frac{\partial m}{\partial x} = 0, \quad \text{and } \frac{\partial c_i}{\partial x} = 0 \text{ at } x = 0.
\end{align*}
\]

3.3 Discretization

Similar to the previous model for angiogenesis, space and time will be discretized into different nodes. The main difference is that this model does not have a right boundary. Therefore, we take a large distance \( L \) from the center of the tumor to function as a right boundary of the region. Now, we are able to create the familiar vectors \( \mathbf{t} \) and \( \mathbf{x} \) with \( T + 1 \) and \( M + 1 \) elements, respectively.

3.3.1 Healthy and Mutated Cells

The discretization and time integration of these differential equations is done in the same way as in the model for angiogenesis. We first create the column vectors \( \mathbf{n}^k \) and \( \mathbf{m}^k \) from the differential equations which represent the values for the corresponding variables at time \( t_k \). Then using a small time step \( \Delta t \), we can explicitly calculate the value for the elements 2, 3,.., \( M \) of the vectors \( \mathbf{n}^{k+1} \) and \( \mathbf{m}^{k+1} \) using the differential equations.

Some difficulty can arise when we encounter the product of the different \( s_i(c_i) \), but we will treat that in the following section.

Now for the boundary conditions, we have a Dirichlet condition at \( x = L \). This simply implies that the last element of each vector becomes 1. However, at \( x = 0 \), there is a symmetry condition. With the symmetry condition and using a virtual node, the second derivative becomes:

\[
\frac{\partial^2 n_i}{\partial x^2} = \begin{cases} 
n_{i-1} - 2n_i + n_{i+1} & \text{for internal nodes} \\
-2n_i + 2n_{i+1} & \text{for } i = 1
\end{cases}
\]

Using the matrix \( A_2 \) from the angiogenesis model as the discretization for the operator \( \frac{\partial^2}{\partial x^2} \) and the fact that the bottom entry is given, we can almost construct the vectors \( \mathbf{n}^{k+1} \) and \( \mathbf{m}^{k+1} \).
3.3.2 Mitotic Regulators

For the different regulators it is more useful to create a single 3-dimensional matrix rather than a matrix for each regulator. In this matrix, the first index represents a point in space, the second the index of the regulator and the third a moment in time. In other words:

\[ c_{i,j,k} = c_j(x_i, t_k) \]

Now \( c \) has the property that for each moment \( t_k \), the first 2 indices make a matrix in which each column \( j \) represents the values of \( c_j \) for each \( x_i \).

Next, we need to make a distinction between the activators and the inhibitors. We do this by making the row vector \( a_i \) which has the following property:

\[ a_i = \begin{cases} 1, & c_i \text{ is a mitotic activator,} \\ 0, & c_i \text{ is a mitotic inhibitor.} \end{cases} \]

This will prove to be useful when implementing the different functions for they differ significantly for activators as opposed to inhibitors. For example, \( s_i(c_i) \) will become:

\[ s(c^j) = [\alpha_i + (1 - \alpha_i)c]a_i + \frac{k_i}{1 + (k_i - 1)c}(1 - a_i). \]

Where the division is done separately for each element of \( c \). The resulting matrix \( s \) is of interest for the healthy and mutated cell equations because the row products define the reaction to the regulators.

Using the vector \( a_i \) in a similar way, we can create a single function \( p(c) \) as well. This will create a matrix where each element \( p_{i,j} \) represents \( p_j(c_j(x_i, t_k)) \) for each moment \( t_k \).

With these functions and the matrix \( A_2 \), we can now predict the values of \( c^{k+1} \) after a small time step explicitly.

3.4 Results

As mentioned before, this model can be used for a variety of mutations. In the following section, we will present the results for a few of these mutations as well as a few different activators and inhibitors. A total of 7 variations have been tested, and they all produce the same results as claimed in the article by J. A. Sherratt and M. A. Nowak. We will therefore limit this section to 3 of these variations.

Each of these variants has different parameters to show different aspects of the process. The only values that are the same for all variants are \( D \) which equals 0.01 and \( N \) which equals 10.

3.4.1 2 Regulators

The first variation we will look is the simple case with two mitotic regulators in which \( c_1 \) is an activator and \( c_2 \) is an inhibitor. Here, we have an increased response to the activator \( c_1 \) and an escape from mitotic control which we implement in \( s_0 \). Furthermore, there is no immune response and the constants will become:
<table>
<thead>
<tr>
<th>Name</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>0.01</td>
<td>Mobility of Cells</td>
</tr>
<tr>
<td>$N$</td>
<td>10</td>
<td>Upper bound for cell density</td>
</tr>
<tr>
<td>$s_0$</td>
<td>2</td>
<td>Abnormal growth</td>
</tr>
<tr>
<td>$\xi$</td>
<td>2.5</td>
<td>Abnormal response</td>
</tr>
<tr>
<td>$H$</td>
<td>0</td>
<td>Abnormal production</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.1</td>
<td>Activator’s response parameter</td>
</tr>
<tr>
<td>$h_1$</td>
<td>18</td>
<td>Normal excretion of activator by cells</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>10</td>
<td>Excretion parameter</td>
</tr>
<tr>
<td>$P_1$</td>
<td>0</td>
<td>Extra excretion independent of cell density</td>
</tr>
<tr>
<td>$D_1$</td>
<td>1.2</td>
<td>Diffusion rate of activator</td>
</tr>
<tr>
<td>$k_2$</td>
<td>15</td>
<td>Inhibitor’s response parameter</td>
</tr>
<tr>
<td>$h_2$</td>
<td>22</td>
<td>Normal excretion of inhibitor by cells</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.1</td>
<td>Excretion parameter</td>
</tr>
<tr>
<td>$P_2$</td>
<td>10</td>
<td>Extra excretion independent of cell density</td>
</tr>
<tr>
<td>$D_2$</td>
<td>2</td>
<td>Diffusion rate of inhibitor</td>
</tr>
</tbody>
</table>

The results show that the tumor will start growing as expected and will cause the density of healthy cells to decrease over time. In figure 8 the red lines represent the mutated cell density and the green lines represent the healthy cell density. Initially, the small mutation at $x = 0$ will cause the mutated cell density to increase to a certain maximum value. As seen in the figure, the group of mutated cells has a density of nearly 6 times the healthy cell density. The tumor will then expand to the right and due to this high density, healthy cells no longer have the ability to divide. The tumor then advances at a regular speed.

The results for the two different regulators are presented in figure 9. Here it is shown that the mitotic inhibitors (shown in green) are excreted in abnormally large amounts around the mutated cells. This is a reaction to the high density of cells there. Due to the abnormal response to the activator $c_1$, only small amounts of this regulator is needed to enable the tumor to grow.

Figure 8: Tumor growth from left to right with a dimensionless time interval of 3
3.4.2 Immune Response

As seen back in the differential equation for the mutated cell density $m$, the process can also be influenced by the immune system which has the parameter $\delta$. For this simulation, we take the same parameters as in the previous variant with an added $\delta = 0.01$.

For these parameters, the results show that a small immune response is sufficient to stop the tumor growth. As shown in figure 10, the mutation in the cells causes them to grow to a maximum of about 2 times the normal density. However, because of the immune response, the increase in size is stopped and the amount of mutated cells starts decreasing again. Naturally, this causes a type of “gap” in which the cell density is lower than normal. As shown in figure 11, this gap is filled in by healthy cells.
3.4.3 7 Regulators

Naturally, it is interesting to see what happens if we implement more regulators to influence the tumor growth. After all, this is physically a lot more realistic than merely one inhibitor and one activator. We therefore take 7 different regulators in the following edition of the model.

<table>
<thead>
<tr>
<th>Name</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>0.01</td>
<td>Mobility of Cells</td>
</tr>
<tr>
<td>$N$</td>
<td>10</td>
<td>Upper bound for cell density</td>
</tr>
<tr>
<td>$s_0$</td>
<td>3</td>
<td>Abnormal growth</td>
</tr>
<tr>
<td>$\xi$</td>
<td>5</td>
<td>Abnormal response</td>
</tr>
<tr>
<td>$\delta$</td>
<td>1.5</td>
<td>Immune response</td>
</tr>
<tr>
<td>$H$</td>
<td>0</td>
<td>Abnormal production</td>
</tr>
</tbody>
</table>

The seven regulators consist of 3 mitotic activators which are $c_1$, $c_3$, and $c_5$ while the other 4 are mitotic inhibitors. The following table shows the different parameters:

<table>
<thead>
<tr>
<th>$\alpha$</th>
<th>$k$</th>
<th>$h$</th>
<th>$\beta$</th>
<th>$P$</th>
<th>$D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>25</td>
<td>60</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15</td>
<td>60</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>20</td>
<td>50</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>20</td>
<td>40</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>18</td>
<td>100</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>25</td>
<td>4</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

The parameters show that the regulatory chemicals highly depend on the cell density. Therefore, the maximum mutated cell density shown in figure 12 is much lower and the tumor grows at a greater speed. The latter is true since we look at different time intervals of 3 instead of 15. Figure 13 shows the familiar tumor front. Again, we see that the mutated cells shown in red have a higher density and therefore suppress the healthy cells as the tumor grows.
In conclusion, we see that the different parameters can determine the tumor’s ability to grow. However, adding mitotic regulators has little effect on the way the mutated cells expand. The same suppressing of healthy cells is seen in both models as well as the increase in cell density within the tumor. For simplicity in our final model, we will therefore choose 2 mitotic regulators consisting of one activator and one inhibitor. Furthermore, we will choose to omit the immune response to the mutated cells. As we have seen in the last variant of the model, the effect of the immune system can easily be overcome by the tumor with the right choice of activator and inhibitor parameters.
4 Dimensionalisation

Before we can combine the two models, they have to be scaled to the same time and distance distribution. We therefore have to look back to how these models were made dimensionless. Using these scaling constants, we can scale the differential equations back to their original form.

4.1 Angiogenesis

For the angiogenesis model, the distance has been scaled by \( L = 0.3 \text{ cm} \), and time by \( \tau = \frac{L^2}{D_{taf}} \) which is the time it takes the TAF to diffuse to the border at \( x = L[1] \). The following nondimensionalisations were made in which the nondimensional variables are noted with an asterisk[3]:

\[
\begin{align*}
    x^* &= x/L, & t^* &= t/\tau \\
    v^* &= v/v_L, & q^* &= q/q_0, & q_L^* &= q_L/q_0, & c^* &= c/c_0, & \hat{c}^* &= \hat{c}/c_0 \\
    v_{min}^* &= v_{min}/v_L, & k^* &= k\tau, & \mu^* &= \mu_1/D_{taf}, & \chi^* &= \chi c_0/D_{taf}, & \gamma^* &= \gamma_1\tau, \\
    \alpha_0^* &= \alpha_0 c_0 L\tau, & \alpha_1^* &= \alpha_1 \tau c_0, & \beta^* &= \beta \tau v_L, & \lambda_1^* &= \lambda_1 \tau.
\end{align*}
\]

To give an example, we demonstrate how we redimensionalise the equation for TAF:

\[
\begin{align*}
    \frac{\partial c^*}{\partial t^*} &= \frac{\partial^2 c^*}{\partial x^*^2} - \lambda_1^* c^* \\
    \frac{\partial c^*}{\partial t^*} &= \frac{\partial}{\partial t^*} \left( \frac{\partial c^*}{\partial x^*} \right) - \frac{\lambda_1 \tau}{c_0} c \\
    \frac{\tau}{c_0} \frac{\partial c}{\partial t} &= \frac{L^2}{c_0} \frac{\partial^2 c}{\partial x^2} - \frac{\lambda_1 \tau}{c_0} c \\
    \frac{\partial c}{\partial t} &= D_{taf} \frac{\partial^2 c}{\partial x^2} - \lambda_1 c
\end{align*}
\]

The other two equations are treated similarly so that we get the following new system of differential equations:

\[
\begin{align*}
    \frac{\partial q}{\partial t} &= \mu \frac{\partial^2 q}{\partial x^2} - \chi \frac{\partial}{\partial x} \left( q \frac{\partial c}{\partial x} \right) + \frac{\alpha_0 Lq_0}{v_L} vc + \alpha_1 H(c - \hat{c})qc - \beta vq \\
    \frac{\partial v}{\partial t} &= \frac{v_L}{Lq_0} \left[ \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} \right] - \gamma v \\
    \frac{\partial c}{\partial t} &= D_{taf} \frac{\partial^2 c}{\partial x^2} - \lambda_1 c
\end{align*}
\]

Next, the redimensionalising of the initial and boundary conditions is carried out. In the dimensionalised model, we no longer look at a range from \( x^* = 0 \) to \( x^* = 1 \) but from \( x = 0 \) to \( x = L \). Using the same method as above, the boundary conditions become:

\[
\begin{align*}
    q(L,t) &= q_L e^{-kt}, & q(x,0) &= 0 \text{ for } 0 \leq x < L, & q(L,0) &= q_L, \\
    v(L,t) &= v_{min} + (v_L - v_{min}) e^{-kt}, & v(x,0) &= 0 \text{ for } 0 \leq x < L, & v(L,0) &= v_L, \\
    c(0, t) &= c_0, & c(L,t) &= 0, & c(x,0) &= 0 \text{ for } 0 < x \leq L.
\end{align*}
\]

We have changed the boundary condition for \( q(0,t) \) in Section 2.6 to a no-flux boundary condition. In this redimensionalised model, the analogous boundary condition becomes:

\[
\frac{\partial q}{\partial x}|_{x=0} = 0
\]

20
4.2 Tumor Growth

The model for tumor growth is applicable for a much smaller distance scale. As initial conditions for the nondimensionalised model we had:

\[
\begin{align*}
n(x,0) &= \begin{cases} 0, & x < 1 \\ 1, & x > 1 \end{cases} \\
m(x,0) &= \begin{cases} 1, & x < 1 \\ 0, & x > 1 \end{cases} \\
c_i(x,0) &= 1
\end{align*}
\]

The model was nondimensionalised using a factor \( Li \) equal to half a typical cell length. Because we use cm as the unit of distance, this means that \( Li = 5 \times 10^{-4} \). Now the diameter of the tumor will be a typical cell length \( t = 0 \). In other words, a very small group of cells are mutated initially which is the desired beginning phase of the model.

The following nondimensionalisations were made in which we denote the non-dimensional variables and constants with an asterisk:

\[
\begin{align*}
x^* &= x/Li, & t^* &= R_0 t, \\
n^* &= n/n^c, & m^* &= m/n^c, & c_i^* &= c_i/c_i^c, & D^* &= D/(R_0 Li^2), & D_i^* &= D_i/(R_0 Li^2), \\
P_i^* &= P_i/R_0, & r^*(n^*) &= r(n), & s_i^*(c_i^*) &= s_i(c_i), & p_i^*(n^* + m^*) &= p_i(n + m)n^c/(c_i^c R_0).
\end{align*}
\]

Again, we will give an example of the non-dimensionalisation. This time using the equation for the

\[
\frac{\partial n}{\partial t^*} = D^* \left( \frac{\partial^2 n^*}{\partial x^*} \right) + n^* r^*(n^* + m^*) s_i^*(c_i^*) ... s_j^*(c_j^*) - n^*
\]

In the next step, we split up the time derivative and substitute the scaled, dimensional variables for \( D^*, r^*, s^* \) and the two rightmost \( n^* \):

\[
\frac{\partial n^*}{\partial t} \frac{\partial t}{\partial t^*} = \frac{D}{R_0 Li^2} \left( \frac{\partial^2 n^*}{\partial x^*} \right) + \frac{n}{n^c} r(n + m)s_1(c_1)...s_J(c_J) - \frac{n}{n^c}
\]

Since \( \frac{\partial t}{\partial t^*} \) equals \( \frac{1}{R_0} \) and we can replace the first \( n^* \):

\[
\frac{1}{R_0 n^c} \frac{\partial n}{\partial t^*} = \frac{D}{R_0 Li^2} \left( \frac{\partial^2 n}{\partial x^2} \right) + \frac{n}{n^c} r(n + m)s_1(c_1)...s_J(c_J) - \frac{n}{n^c}
\]

Redimensionalisation of \( \frac{\partial^2 n}{\partial x^2} \) results in:

\[
\frac{1}{R_0 n^c} \frac{\partial n}{\partial t} = \frac{D Li^2}{R_0 Li^2 n^c} \left( \frac{\partial^2 n}{\partial x^2} \right) + \frac{n}{n^c} r(n + m)s_1(c_1)...s_J(c_J) - \frac{n}{n^c}
\]

Multiplying both sides with \( R_0 n^c \) concludes the redimensionalisation:

\[
\frac{\partial n}{\partial t} = D \left( \frac{\partial^2 n}{\partial x^2} \right) + R_0 n r(n + m)s_1(c_1)...s_J(c_J) - R_0 n
\]

Applying the same method on all differential equations in the model, the re-dimensionalised equations become:

\[
\begin{align*}
\frac{\partial n}{\partial t} &= D \left( \frac{\partial^2 n}{\partial x^2} \right) + R_0 n r(n + m)s_1(c_1)...s_J(c_J) - R_0 n \\
\frac{\partial m}{\partial t} &= D \left( \frac{\partial^2 m}{\partial x^2} \right) + R_0 m r(n + m) \left[ s_0 + s_1(\xi c_1) ... s_J(c_J) \right] - R_0 m \\
\frac{\partial c_i}{\partial t} &= D_i \frac{\partial^2 c_i}{\partial x^2} + c_i^c P_i + (n + m)p_i(n + m) - \left[ P_i + \frac{n}{c_i^c} p_i(1) \right] c_i
\end{align*}
\]
The scaling property of the functions $s(c)$ and $r(n)$ is given by:

\[
\begin{align*}
    r^*(n^*) &= r(n), & \quad s^*_i(c^*_i) &= s_i(c_i) \\
    r^*(\frac{n}{n^e}) &= r(n), & \quad s^*_i\left(\frac{c_i}{c^*_i}\right) &= s_i(c_i)
\end{align*}
\]

This will become useful in the implementation of these functions, since we can use the same functions from the nondimensionalised model with a scaled input.

However, the function $p_i(n)$ does not have this property. We therefore take a look at how this function is rescaled:

\[
\begin{align*}
    p^*_i(n^*) &= p_i(n)\frac{n^e}{(c^*_i R_0)} \\
    \frac{c^*_i R_0}{n^e} p^*_i(n^*) &= p_i(n)
\end{align*}
\]

Next, we look back at how the nondimensionalised function $p_i(n)$ was defined:

\[
\begin{align*}
    p_i(n) &= \frac{c^*_i R_0}{n^e} \begin{cases} 
        \frac{h_i^*(1 + \beta_i^*)}{1 + \beta_i^* n^e} & \text{if } c_i \text{ is a mitotic activator} \\
        \frac{h_i^*(1 + \beta_i^* n^e)}{1 + \beta_i^* n^e} & \text{if } c_i \text{ is a mitotic inhibitor}
    \end{cases} \\
    p_i(n) &= \frac{c^*_i R_0}{n^e} h_i^* \begin{cases} 
        \frac{1 + \beta_i^* n^e}{1 + \beta_i^* n^e} & \text{if } c_i \text{ is a mitotic activator} \\
        \frac{1 + \beta_i^*}{1 + \beta_i^*} & \text{if } c_i \text{ is a mitotic inhibitor}
    \end{cases}
\end{align*}
\]

As is shown, the constant $h_i$ can be placed in front of the brace. Recall that this constant represents the excretion rate of regulator $i$ when the number of cells is in its equilibrium state. When we redimensionalise this constant, we see that the function fulfills the scaling requirement:

\[
\begin{align*}
    h_i &= \frac{c^*_i R_0}{n^e} h_i^* \\
    \beta_i &= \beta_i^*
\end{align*}
\]

The function becomes:

\[
\begin{align*}
    p_i(n) &= \begin{cases} 
        \frac{h_i(1 + \beta_i)}{1 + \beta_i(\frac{n}{n^e})^e} & \text{if } c_i \text{ is a mitotic activator} \\
        \frac{h_i(1 + \beta_i(\frac{n}{n^e}))}{1 + \beta_i} & \text{if } c_i \text{ is a mitotic inhibitor}
    \end{cases}
\end{align*}
\]

To conclude the redimensionalisation, the initial and boundary conditions have to be rescaled. Since
they are Dirichlet conditions and a symmetry condition around \( x = 0 \), this is fairly simple to achieve:

\[
\begin{align*}
n(x, 0) &= \begin{cases} 0, & x < L_i \\ n^e, & x > L_i \end{cases} \\
m(x, 0) &= \begin{cases} n^e, & x < L_i \\ 0, & x > L_i \end{cases} \\
c_i(x, 0) &= c_i^e
\end{align*}
\]

The Boundary conditions now become:

\[
n = n^e, \quad m = 0, \quad c_i = c_i^e \text{ at } x \pm \infty \quad \forall i,
\]

\[
\frac{\partial n}{\partial x} = 0, \quad \frac{\partial m}{\partial x} = 0, \quad \text{and} \quad \frac{\partial c_i}{\partial x} = 0 \text{ at } x = 0.
\]

Again, we take a large distance from the tumor to act as a right boundary.
5 The Coupling of the two models

At this point, we have successfully re-dimensionalised the models for angiogenesis and tumor growth. These two models were created independently from one another which causes some unreliable results. First of all, the angiogenesis model has a constant excretion of TAF from the mutated cells, while these cells will only create these attractants once they are in need of nutrients\(^6\). Secondly, the tumor growth is not limited at all. According to the model, once the mutation is made, the tumor can continue growing indefinitely. Intuitively, there are some restrictions to the growth rate due to the size of the tumor and the amount of nutrients available around the mutated cells. Therefore, we are going to couple the models for angiogenesis and tumor growth.

To implement these restrictions and extra phenomena in the model, we introduce a new variable \(c_{ox}\) to represent the oxygen concentration. This concentration will decrease as cells use the oxygen needed for cell growth and will increase due to delivery by blood cells which are transported via the vascular system. The differential equation then becomes:

\[
\frac{\partial c_{ox}}{\partial t} = D_{ox} \left( \frac{\partial^2 c_{ox}}{\partial x^2} \right) + \psi_1 \frac{v}{v_L} - \psi_2 \frac{n + m}{n_e} c_{ox}
\]

In a short analysis of this differential equation, one can see that the first term represents the diffusion again. The second term with the constant \(\psi_1\) represents the delivery of oxygen which, of course, depends on the density of blood vessels \(v\). The third term represents the consumption of oxygen by the total amount of cells. Here, the constant \(\psi_2\) represents the consumption rate.

The oxygen concentration influences the mobility of all cells. Without oxygen, cell division is not possible and with enough oxygen, maximum mobility can be achieved. Therefore, the mobility constant \(D\) for both mutated and healthy cells will become dependent on the oxygen level. We need an increasing function equal to zero when there is no oxygen and a limit of the maximum cell mobility \(D_{cells}\) when oxygen is available in large amounts. With the proper rescaling with the equilibrium value to make the factor dimensionless, the following function satisfies the requirements.

\[
D(c_{ox}) = D_{cells} \frac{c_{ox}/c_{eox}}{c_{ox}/c_{eox} + K}
\]

Finally, the last influence from one model to the other is the excretion of TAF by the tumor cells. This has the property that it is zero as long as there is enough oxygen, but goes to the maximum excretion value once the oxygen is no longer available. Therefore, an extra term is added to the TAF equation:

\[
\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - \lambda_1 c + \lambda_2 \frac{m}{n_e} \left[ 1 - \frac{c_{ox}}{c_{eox}} \right] +
\]

The subscript + means that it is the maximum between \(1 - \frac{c_{ox}}{c_{eox}}\) and 0. This way, there is no excretion when the oxygen level exceeds the equilibrium value.
The total set of differential equations then becomes:

\[
\begin{align*}
\frac{\partial q}{\partial t} &= \mu \frac{\partial^2 q}{\partial x^2} - \chi \frac{\partial}{\partial x} \left( q \frac{\partial c}{\partial x} \right) + \frac{\alpha_0 L q_0}{v_L} - \alpha_1 H(c - \hat{c}) q c - \beta v q \\
\frac{\partial v}{\partial t} &= \frac{v_L}{Lq_0} \left[ \mu \frac{\partial q}{\partial x} - \chi q \frac{\partial c}{\partial x} \right] - \gamma v \\
\frac{\partial c}{\partial t} &= \frac{\partial^2 c}{\partial x^2} - \lambda_1 c + \lambda_2 m \left[ 1 - \frac{c_{ox}}{c^e} \right] + \\
\frac{\partial m}{\partial t} &= D(c_{ox}) \left( \frac{\partial^2 m}{\partial x^2} \right) + R_0 n r (n + m) s_1(c_1)...s_J(c_J) - R_0 n \\
\frac{\partial c_i}{\partial t} &= D_i \frac{\partial^2 c_i}{\partial x^2} + c^e_i P_i + (n + m) p_i (n + m) - \left[ P_i + \frac{n^e}{c^e_i} p_i (1) \right] c_i \\
\frac{\partial c_{ox}}{\partial t} &= D_{ox} \left( \frac{\partial^2 c_{ox}}{\partial x^2} \right) + \psi_1 \frac{v}{v_L} - \psi_2 n + m
\end{align*}
\]

5.1 Constants

In total, we have four new constants \([\psi_1, \psi_2, K, \lambda_2]\) that are yet to be approximated. We will try different values in the numerical simulations to see which produce the most realistic results. One of the most important constants will be \(K\), which determines the dependency of cell growth on the oxygen concentration. A lower value of \(K\) will result in a faster reaction to an increase in oxygen.

As we look through the rest of the constants, the redimensionalised mobility rate for capillary tips \(\mu\) is approximately equal to \(7.4 \cdot 10^{-11}\) cm\(^2\)/s. However, if we use the \(D\) from the redimensionalised model of Sherratt, we get a cell mobility rate of \(4.9 \cdot 10^{-15}\) cm\(^2\)/s for the healthy and mutated cells. The difference between these two values is too big to be realistic, so we go back to where the cell mobility rate was calculated. According to J. A. Sherratt and M. A. Nowak a typical order of magnitude for a cell diffusion coefficient is \(10^{-10}\) or \(10^{-11}\) cm\(^2\)/s. However, if we non-dimensionalise this by dividing it with \(R_0 L^2\), we get \(D^*\) between approximately 20 and 200. In the non-dimensional model, \(D^*\) was equal to 0.01. Apparently, some kind of mistake was made. Therefore, we do not use the rescaled \(D\) from the nondimensional model but \(D_{cells} = 10^{-10}\) which is a lot closer to the capillary cell’s mobility rate.

5.2 Numerical method

By now, the model has increased to a size of 8 different functions. Since we used an explicit method earlier, this would require a very small time step to ensure stability of the method. If we use a different method, which is partly implicit, this restriction would no longer be necessary. A larger time step can then be used resulting in fewer iterations.

Therefore, a numerical method called ImEx is used instead. This method is implicit for the linear terms of the differential equations and partially explicit for the non-linear terms. The following example for the healthy cells shows how this method is implemented. Again, we will use vectors like \(\mathbf{u}\) to represent
the values of the function at time $t_k$.

$$n^{k+1} = n^k + \Delta t \frac{\partial n^{k+1}}{\partial t}$$

$$n^{k+1} = n^k + \Delta t \left( D \frac{\partial^2 n^{k+1}}{\partial x^2} + n^{k+1}r(n^k + m^k)s_1(c_1^k)\ldots s_j(c_j^k) - n^{k+1} \right)$$

$$\frac{n^{k+1}}{n^k} = \frac{n^k}{n^{k+1}} \left[ I - \Delta t \left( D + r(n^k + m^k)s_1(c_1^k)\ldots s_j(c_j^k) - 1 \right) \right]$$

As is shown, the linear components are done implicitly, while the non-linear terms (like $r(n + m)$) are calculated for iteration $k$. However, not every derivative can be rewritten to form a matrix-vector multiplication. If we look at the vessel density $v$ the method works a little differently:

$$v^{k+1} = v^k + \Delta t \frac{\partial v^{k+1}}{\partial t}$$

$$v^{k+1} = v^k + \Delta t \left[ \frac{v^L}{L_0} \left[ \mu \frac{\partial q^k}{\partial x} - \chi q^k \frac{\partial c^{k+1}}{\partial x} - \gamma v^{k+1} \right] - \frac{v^L}{L_0} \left[ \mu \frac{\partial q^k}{\partial x} - \chi q^k \frac{\partial c^{k+1}}{\partial x} \right] \right]$$

Now it depends on which order we calculate the values for the next iteration, whether we can use $q^{k+1}$ or $q^k$. Since the equation for $c$ is relatively less complicated, it will prove useful to calculate the next values of this function first. We can then use $c^{k+1}$ for the rest of the method. It is interesting to note that $v^{k+1}$ will now be calculated by solving a linear system of equations with an added term on the right-hand side.

### 5.3 Initial Conditions

Naturally, some initial conditions need to be altered to make the combined model realistic. In the beginning of the model, we will look at a small group of mutated cells at $x = 0$ which have no connection to blood vessels or capillary cells. Then the interior of the area consists of healthy tissue with a small amount of blood vessels and a uniformly distributed oxygen concentration. Finally, on the right side of the region, there is an area of blood vessels, from $x = x_H$ to $x = L$. In this area, the concentration will increase linearly from zero to $v_L$ at the border. The first capillary tips will then branch off from these vessels.

For the entire area, the density of capillary tips and the concentration of TAF will be zero because there are no beginning formations for blood vessels yet. Then for the mitotic regulators, we maintain the same initial conditions as before: a constant equilibrium concentration.

In short, these are the new initial conditions:

$$q(x,0) = 0$$

$$v(x,0) = \begin{cases} 0, & \text{for } x < x_H \\ \frac{v^L}{L-x_H}(x-x_H), & \text{for } x \geq x_H \end{cases}$$

$$c(x,0) = 0$$

$$n(x,0) = \begin{cases} 0, & x < L_i \\ n^e, & x > L_i \end{cases}$$

$$m(x,0) = \begin{cases} n^e, & x < L_i \\ 0, & x > L_i \end{cases}$$

$$c_i(x,0) = c_i^e$$

$$c_{ox}(x,0) = c_{ox}^e$$
5.4 Boundary Conditions

We now take into consideration what happens on the boundaries of our region. For the angiogenesis equations, we no longer have the exponential function on the right border since we now have the region of vessels. Our choice for this boundary will be a no-flux condition for the capillary tips, vessels and TAF concentration. On the left hand side, at $x = 0$, we maintain the no-flux condition from the non-dimensional model.

In the tumor model, we no longer miss a right border. The new border at $x = 0.3$ cm is relatively far from the tumor center since the mutation occurs between $x = 0$ cm and $x = 5 \cdot 10^{-4}$ cm. Therefore, the tumor can grow through the region and we will have to stop the simulation before it reaches the right border. By that time, new factors will start playing a role because the tumor could start growing into different types of tissues or encounter other obstacles that will inhibit its growth. For the left border, we uphold the symmetry condition from the non-dimensional model.

The last equation in need of boundary condition is that of the oxygen concentration. Because this quantity acts in a similar way as the TAF-concentration, we will also use no-flux boundary conditions for this variable.
5.5 Results

As mentioned before, we will limit the model to two mitotic regulators. $c_1$ will be a mitotic activator and $c_1$ will be an inhibitor. The mutation that occurs will be a combination of extra cell growth and an abnormal response to the activator.

The constants after redimensionalisation are shown in the following table:

<table>
<thead>
<tr>
<th>Name</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L$</td>
<td>0.3</td>
<td>Distance to the right border</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$7.44 \cdot 10^{-7}$</td>
<td>Mobility of capillaries</td>
</tr>
<tr>
<td>$\chi$</td>
<td>2.5</td>
<td>Attraction of TAF</td>
</tr>
<tr>
<td>$\alpha_0$</td>
<td>$1.38 \cdot 10^{-4}$</td>
<td>Factor of primary angiogenesis</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>$8.27 \cdot 10^{-6}$</td>
<td>Factor of secondary angiogenesis</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$1.38 \cdot 10^{-4}$</td>
<td>Vessel loops closing</td>
</tr>
<tr>
<td>$v_L$</td>
<td>0.3</td>
<td>Initial value of vessels at the right border</td>
</tr>
<tr>
<td>$\hat{c}$</td>
<td>0.2</td>
<td>Threshold TAF concentration for secondary angiogenesis</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$1.38 \cdot 10^{-4}$</td>
<td>Decay rate of the capillary tips</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$2.07 \cdot 10^{-7}$</td>
<td>Decay rate of the vessels</td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>$8.27 \cdot 10^{-7}$</td>
<td>Decay rate of the TAF</td>
</tr>
<tr>
<td>$\lambda_2$</td>
<td>$8 \cdot 10^{-7}$</td>
<td>Production rate of TAF</td>
</tr>
<tr>
<td>$D_{cells}$</td>
<td>$10^{-10}$</td>
<td>Maximum cell mobility rate</td>
</tr>
<tr>
<td>$R_0$</td>
<td>$1.94 \cdot 10^{-6}$</td>
<td>Rate of cell growth</td>
</tr>
<tr>
<td>$\xi$</td>
<td>2.5</td>
<td>Abnormal response to $c_1$</td>
</tr>
<tr>
<td>$s_0$</td>
<td>2</td>
<td>Abnormal cell growth</td>
</tr>
<tr>
<td>$\psi_1$</td>
<td>$3 \cdot 10^{-5}$</td>
<td>Delivery of oxygen through blood vessels</td>
</tr>
<tr>
<td>$\psi_2$</td>
<td>$5 \cdot 10^{-6}$</td>
<td>Consumption of oxygen by cells</td>
</tr>
<tr>
<td>$N$</td>
<td>10</td>
<td>Crowding limitation</td>
</tr>
<tr>
<td>$\bar{\alpha}_1$</td>
<td>0.1</td>
<td>Cell response to the activator</td>
</tr>
<tr>
<td>$k_2$</td>
<td>15</td>
<td>Cell response to the inhibitor</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>10</td>
<td>Activator’s excretion parameter</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.1</td>
<td>Inhibitor’s excretion parameter</td>
</tr>
<tr>
<td>$h_1$</td>
<td>$3.5 \cdot 10^{-5}$</td>
<td>Normal activator excretion</td>
</tr>
<tr>
<td>$h_2$</td>
<td>$4.3 \cdot 10^{-5}$</td>
<td>Normal inhibitor excretion</td>
</tr>
<tr>
<td>$P_1$</td>
<td>0</td>
<td>Activator excretion independent of cell density</td>
</tr>
<tr>
<td>$P_2$</td>
<td>$1.94 \cdot 10^{-5}$</td>
<td>Inhibitor excretion independent of cell density</td>
</tr>
<tr>
<td>$K$</td>
<td>7</td>
<td>Parameter for cell mobility</td>
</tr>
</tbody>
</table>

In figure 14 is shown that the oxygen level decreases in the area of the tumor due to the consumption by the mutated cells. A small rise in TAF can already be seen excreted by the tumor to attract capillary tips. As the model progresses, angiogenesis occurs and the oxygen concentration rises again. This new state is shown in figure 15.
Figure 14: Blue represents TAF and green represents oxygen in the first phase of the process (t=20 days)

Figure 15: TAF in blue and oxygen concentration in green after angiogenesis has occurred (t=45 days)
However, with this boundary condition, the density of capillaries around \( x = 0 \) stops behaving realistically. Figure 16 shows that the number of tips in this area increases rapidly. The result is that the numerical integration no longer returns plausible values.

![Figure 16: Behavior of the capillary tips around \( x = 0 \) due to the numerical integration method](image1)

### 5.5.1 Alternative Boundary Condition

Since the no-flux boundary condition gave us limited results, we take a look at the original boundary condition for the angiogenesis model. According to [1], the density of capillary tips is equal to zero at \( x = 0 \). Using the same constants, the results show that the densities remain within a normal range.

Figure 17 shows the same capillary tip wave propagating towards the tumor. However, the density of capillaries on the left side of the region now remains in a relatively steady state. This state is shown in figure 18.

![Figure 17: Density of capillary tips with intervals of approximately 10 hours](image2)

When we take a look at the vessel density in figure 19, we clearly see an escape from the initial region after about 50 days.
Figure 18: Capillary tips final state

Figure 19: Vessels escaping after 50 days at various times
The most interesting result is the way the tumor grows. Figure 20 shows that the tumor front starts moving, but then slows down which is a result due to the lack of oxygen. Then, once the blood vessels have reached the tumor, they re-enable it to grow. This can be seen in the figure as the linear progression of the tumor front. This is exactly the relationship between the tumor growth and angiogenesis that we set out to simulate. To show the difference, figure 21 shows the tumor front for the original model.

Figure 20: Tumor front over time with the influence by angiogenesis

Figure 21: Tumor front over time in the original model
6 Conclusion

We have developed a mathematical model which combines the processes of angiogenesis and tumor growth. By analysing two independent models for angiogenesis and tumor growth, we have found a way to make a connection using a new variable. This new variable represents the oxygen concentration in the area. Naturally, both processes have an influence on the oxygen level but we have also restricted the cell mobility to this concentration. This way, the amount of blood vessels influences the growth of the tumor and on the other hand, the amount of blood vessels formed is influenced by the size of the tumor.

Using this model, we have shown that the relationship between these two processes plays a key role on the development of the tumor. Therefore, this model serves as an improvement towards the two initial separate models.

Further research can include adding more relationships to other processes that influence tumor growth to the model. One of these expansions can include the capability of malignant tumors to travel through the blood stream to spread into other parts of the body. This process is known as metastasizing. Accurate information about the rate of this process can be very valuable. Another example for further research is expanding the region so that adjacent organs or other types of tissue are added. The behavior of the tumor can then be analysed as it encounters such an obstacle.

These further investigations can lead to a better simulation of different types of tumor and therefore make more and more accurate predictions. On the other hand, the different parameters can be altered to find out which have the most influence on the outcome of the tumor. Using this information, new strategies could be used to effectively prevent tumor growth from succeeding.

On a final note, I would like to thank dr. ir. F. J. Vermolen for his guidance and assistance during this project.
References


[5] J. A. Adam *A Simplified Mathematical Model of Tumor Growth* Department of Mathematical Sciences, Old Dominion University, Norfolk, Virginia 1986