Group 5

Modelling of tumours

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Abstract

The aim of this project has been to model the growth of glioma cells and determine which factors characterize the growth and speed of the tumour. In order to try to imitate the real evolution of glioma cells, a reaction-diffusion PDE with Neumann boundary conditions is used. The results gained showed that the growth of the tumour radius is actually linear, after a stabilization period. The velocity of the moving boundary of the tumour is shown to be constant. After adding a treatment function to the model, representing chemotherapy, it was observed that the treatment was only effective for a limited period of time. Due to the diffuse nature of glioma cells surgery is typically not efficient to completely remove the tumour. Since the movement and proliferation of cells in general is stochastic we also modelled the tumour growth with a stochastic model. For this specific problem of a pure birth process the stochastic effect was shown to be negligible.

Problem presentation.

The aim of this project is to study glioma cells and their growth in the human brain. Simulations will be made to see which parameters affect the growth rate the most and if there is a dependence between the parameters. Net proliferation ρ and diffusion D will be two important features in the model. Hopefully this model could be useful for a doctor treating a cancer patient.

The glioma cells are studied at an individual level as a concentration and not as the volume of the actual tumour. It is of interest to compare the tumour model in 1D with the same one in 3D, and see if there could be a change in events. For simplicity, the model is not taking into account where in the brain the tumour initially occurs.

Finally, the original model will be modified to also analyze the impact of a chemotherapy treatment function as well as surgery. The treatment function should simply decrease the number of infected glioma cells and by that matter decrease the volume of the tumour. Surgery should remove a certain quantity of cells.

The same modelling problem will also be solved using a stochastic approach were spatial effects are ignored. At the end of the report the results from both models will be discussed and analysed.

Introduction.

Cancer is one of the major factors of death and a better understanding of it is necessary in order to increase the survival rate for the patients suffering from this condition. There are a number of common features of tumours, which can form as the starting point to build mathematical models describing the growth of tumours.

Cancer.

When the body is not infected cells grow and divide in a very controlled way. Usually mutation in the DNA does occur but the reparation system in the body can obviate the damage. Sometimes the damage or change in the genetic material caused by these factors cannot be repaired though. In most cases the mutated cells do not cause cancer, but rarely it can occur. In these rare cases cells continue to multiply instead of dying. The mass of multiplying cells forms a cancer tumour which can interfere with the whole human system.

Unlike regular cells, cancer cells can experience uncontrolled growth, and therefore, cause damage to the genes involved in the cell division. Cellular division is called proliferation and in the case of cancer it occurs in a rapid and excessive way.

Cell migration is a process which allows development and maintenance of multicellular organism, for instance when tissue is created and wound healing. On the other hand, cell invasion is the ability for a cell to actively invade tissue, this is in fact an extension of the cell migration. Invasion is the property of tumour cells. The invasive grade of the cell depends on the location of the tumour. Some tumours grow in a limited way and stay in one spot while others move to other locations in the body through the blood and lymph systems.

Glioma.

Glioma are a common type of tumour cells which are diffusive and highly invasive. The gliomas form from glial cells, which are non-neuronal cells mainly located in the brain. During the lifetime of a glioma it can enter four different grades under which they have different probabilities of growth and spreading.

The grade of malignancy of a glioma mainly depends on two factors known as net proliferation rate and invasiveness [4]. A low -grade glioma cell, also called a benign tumour, is relatively slow growing and less likely to spread in the brain. It is therefore profitable to use surgery for removal of the tumour since it is less likely to come back after the procedure. The prognosis nowadays for patients with low -grade gliomas are rather optimistic. In a 10-year period the relative survival rate is 47 % [3].

Malignant cells, or high -grade gliomas, are fast growing and high likely to spread in the brain, but also to the spinal cord. These cells are associated with high probability of causing death for the patient. Surgery and removal of the visible tumour is not likely to be enough to cure the cancer since malignant tumours have high tendency of coming back. Radio- or chemotherapy are often used as complementary treatment. However, glioma patients have a median survival time of 12 to 14 months [2].

First Mathematical Model: PDE.

As mentioned above, gliomas are diffuse and invasive brain tumours. This makes it difficult to model the growth rate of the tumour. Therefore the concentration $c(\mathbf{x}, t)$ of the tumour cells, is going to be modelled as a function of t. The concentration $\mathbf{x}$ designates the location of the tumour cell and t

the time. In order to model the rate of tumour population two factors are considered:

1. The creation of new tumour cells, i.e, the net proliferation.

2. The diffusion of the tumour cells in the brain.

The first factor depends on the proliferation rate, denoted by ρ. Therefore, the effect of proliferation on the concentration $c(\mathbf{x}, t)$ can be written as

$$\frac{\partial c}{\partial t} = \rho c. \tag{5.1}$$

The above equation, however, does not model the reality properly since it implies that the density of the tumour would grow infinitely. This is physically impossible since the capacity of the brain matter is not infinite. As a consequence of this, (5.1) is rewritten as,

$$\frac{\partial c}{\partial t} = \rho c \left(1 - \frac{c}{c_m}\right). \tag{5.2}$$

where c_m denotes the maximum capacity of infected cells in the brain. An approximation of the value of c_m can easily be found considering that we assume a cell to be spherical.

$$c_m = \frac{\text{max.\#cells}}{V_{\text{cell}}} \approx 2 \cdot 10^6 \ \frac{\text{cells}}{mm^3}.$$

where the radius of the cell has been approximated to be $5\mu m$.

Since the tumour cells are moving in a random way in the brain we can use the diffusion term to model this behaviour. To predict how diffusion causes the concentration to change, second Fick's law is used

$$\frac{\partial c}{\partial t} = D\nabla^2 c. \tag{5.3}$$

where D is the diffusion coefficient representing the active motility of glioma cells.

Combining (5.2) and (5.3), the rate of change of the tumour concentration is

$$\frac{\partial c}{\partial t} = \rho c \left(1 - \frac{c}{c_m}\right) + D\nabla^2 c. \tag{5.4}$$

This model was first proposed by James Dickson Murray [1] and in this section some results derived from this report will be discussed.

Implementation.

To illustrate the impact of proliferation and diffusion on the concentration and growth of the tumour all simulations are done in Matlab. For simplicity a 1D model is used to initially describe the tumour growth. When this is working as expected the model is modified to fit the 3D case.

In order to implement the model an equidistant finite difference discretization is used.

$$c_i^{n+1} = D\frac{\Delta t}{\Delta x^2}(c_{i-1}^n - 2c_i^n + c_{i+1}^n) + c_i^n(\Delta t\rho + 1)$$

is obtained in the 1D case, where n is the discrete time and i represents space. To get a realistic model of tumour growth, the grid points of time and space have to be small enough.

Let Ω be defined as the interval $[0,L]$, where L is arbitrary. Boundary conditions are chosen to be homogeneous Neumann

$$\frac{\partial c}{\partial x}\Big|_{\partial\Omega} = 0$$

and initial conditions

$$c_0(x) = \begin{cases} c_m, & |x - \frac{L}{2}| \leq a \\ 0, & \text{otherwise} \end{cases}$$

where $a \in [0, \frac{1}{2}]$.

In the 3D model, spherical coordinates are assumed and the Laplacian operator is obtained on the following form

$$\Delta c = \frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r}$$

. This expression does not depend on θ and ϕ because of the assumed the spherical symmetry of the tumour. Similarly to the 1D case, the tumour is set into the center of the sphere and boundary conditions are Neumann conditions.

Having established the model, the values of ρ and D are varied to observe how the combination of these two parameters affect the tumour growth. The velocity of the tumour boundary, v, can be calculated for each combination of ρ and D separately. Therefore, the first equation (5.4) can be modified to the non-dimensional one, without dependence ρ and D.

Non-dimensionalization.

As we know, concentration can be measured in different units. Dividing each term in the first equation by c_m we get

$$\frac{\partial \tilde{c}}{\partial t} = \rho \tilde{c}(1 - \tilde{c}) + D\Delta \tilde{c} \tag{5.5}$$

$$\text{where} \qquad \tilde{c} = \frac{c}{c_m}$$

Further on, the goal is to remove the parameters ρ and D from the original model. Each term in the equation is divided by ρ,

$$\frac{\partial \tilde{c}}{\rho \partial t} = \tilde{c}(1 - \tilde{c}) + \frac{D}{\rho}\Delta \tilde{c}$$

. Then, a new variable τ is introduced in order to get a non-dimensional time parameter,

$$t = \frac{\tau}{\rho}$$

Similarly, the variable in space is modified to be

$$r = \sqrt{\frac{D}{\rho}}\tilde{r}$$

by introducing new variable $\tilde{r}$. This will in turn lead to

$$dt = \frac{d\tau}{\rho}; \qquad dr^2 = \frac{D}{\rho}d\tilde{r}^2$$

and finally the non-dimensional equation is obtained

$$\frac{\partial \tilde{c}}{\partial \tau} = \tilde{\Delta}\tilde{c} + \tilde{c}(1 - \tilde{c}) \tag{5.6}$$

Since we have now fixed the values of the ρ and D, the results of our model can instead be modified by changing the time and space scale.

Results

The following pictures show the distribution of c along the space for different periods of time, where t is measured in days in all plots.

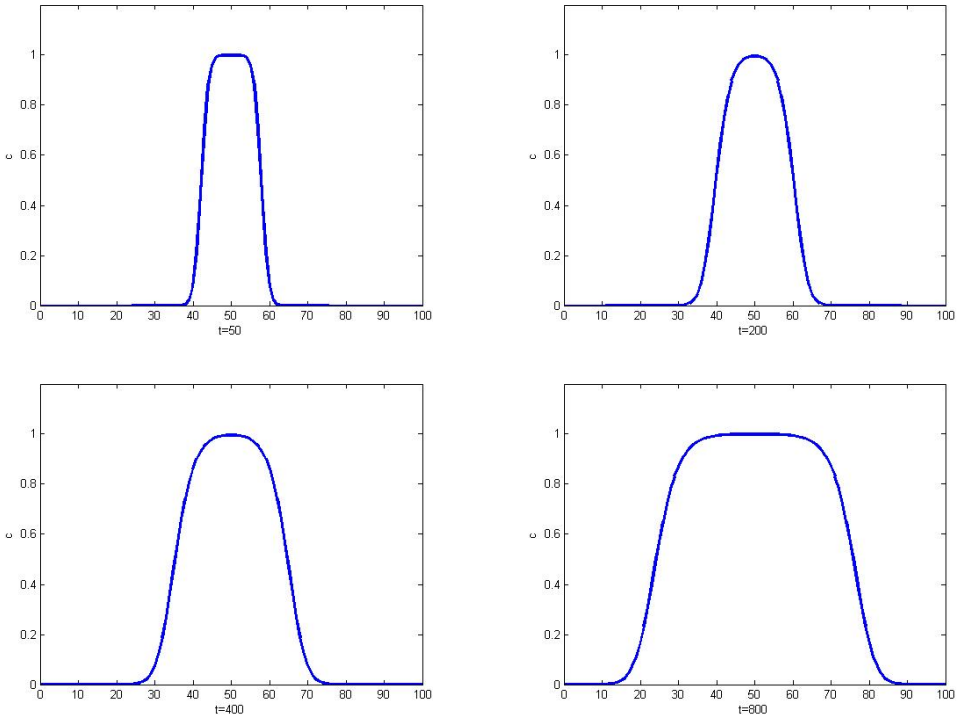


Table 5.1: $\rho_1 = 0.107\text{days}^{-1}$, $D_1 = 0.255\frac{mm^2}{days}$

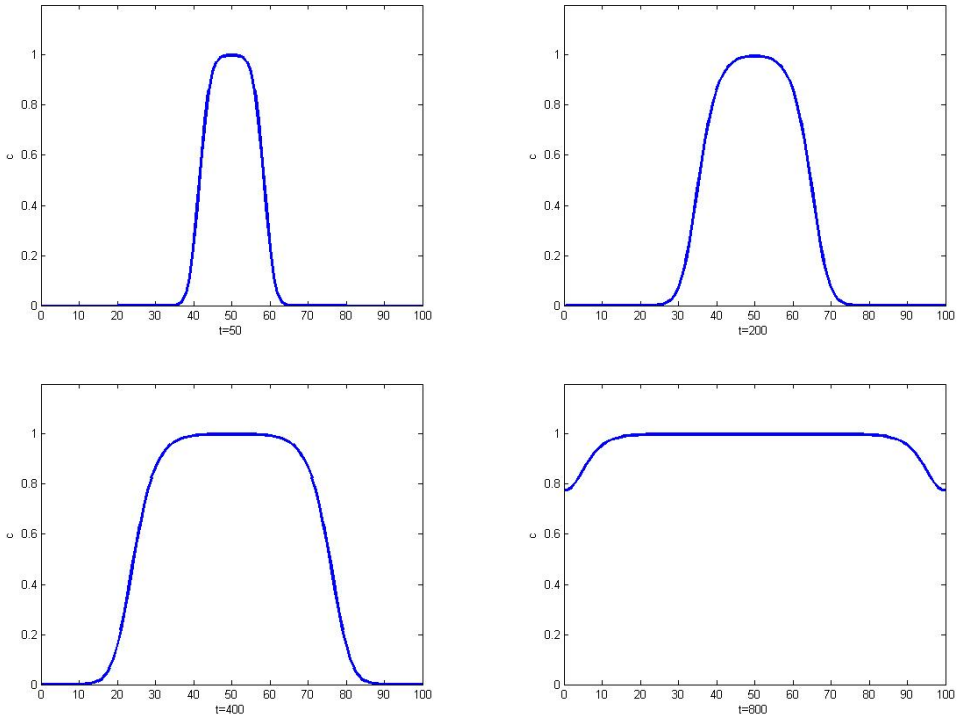
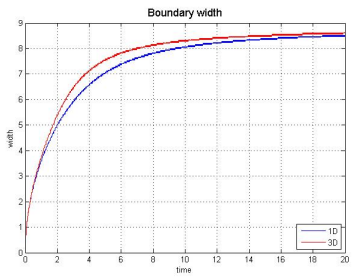
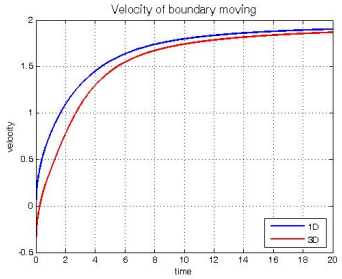


Table 5.2: $\rho_2 = 0.214\text{days}^{-1}$,$D_2 = 0.510\frac{mm^2}{days}$

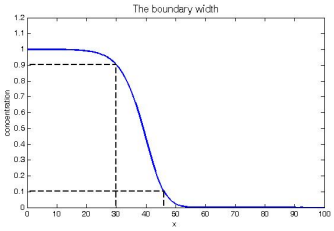
The below plots describe the boundary width and velocity of boundary moving, which are the main results in this paper. Blue color presents result for the 1D model and red is for the 3D model.
This graphs are made in Matlab using the fixed values for the diffusion $D = 1$, net proliferation $\rho = 1$ and initial diameter of tumour $L = 10$.



(a) Width as a function of time.



(b) Velocity as a function of time.



(c) Definition of the boundary width.

Figure 5.1: Width and velocity of the moving tumour boundary.

Second Mathematical Model: Effect of Chemotherapy.

Until now, it has been considered that the patient has not been subjected to any treatment. This section aims to consider the effect of a chemotherapy treatment on the evolution of the tumour growth. With this purpose, a term needs to be added to (5.7) which takes into account the effect of the treatment.

Let $b(t)$ be a function which models the percentage of killed cells per day due to the chemotherapy at time t. Then (5.7) becomes

$$\frac{\partial c}{\partial t} = \rho c \left(1 - \frac{c}{c_m}\right) + D\nabla^2 c - b(t)c. \tag{5.7}$$

For simplicity, it has been considered that the effect of chemotherapy is independent on the location of the tumour and that its effect just depends on which time the treatment is applied. The treatment starts at the time T_1 which is related to the time the tumour is detected on the MRI scan and treatment can be started.

Approximately, a tumour can be detected when it weights 1 g. Therefore information about how the mass of the tumour evolves in time is needed before applying chemotherapy to the model. Considering the expression for speed of growth of the tumour found in the model below, one obtains

$$\begin{aligned} m(t) &= d_C V_T(t) = \frac{m_C}{V_C} V_T(t) = \frac{10^{-9}}{4/3\pi r_C^3} \frac{4}{3}\pi r(t)^3 = 2 \cdot 10^6 \ \frac{4}{3}\pi r(t)^3 \\ &= 2 \cdot 10^6 \ \frac{4}{3}\pi 8 \cdot (\rho D)^{3/2} t^3 \approx 6.7 \cdot 10^7 (\rho D)^{3/2} t^3. \end{aligned}$$

where the index C stands for "cell" and T for "tumor".

Therefore,

$$T_1 = \left(\frac{1}{6.7 \cdot 10^7}\right)^{1/3} \frac{1}{(\rho D)^{1/2}} \approx 0.0023 \frac{1}{(\rho D)^{1/2}}.$$

The following plot shows how the chemotherapy function has be considered:

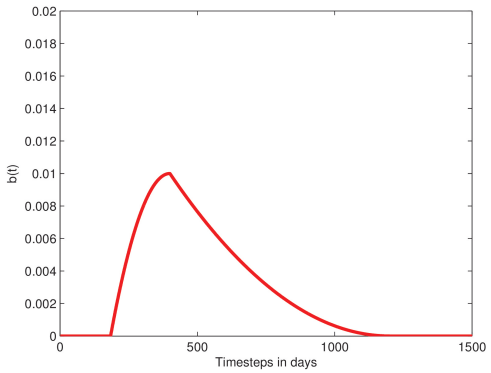


Figure 5.2: chemotherapy function

This treatment corresponds to a three steps of therapy:

1. For $t \in [0, T_1]$, the tumour has not been detected and then there is any applied treatment.
2. For $t \in (T_1, T_2]$, the treatment is efficient and each day the percentage of killed cells is higher.
3. For $t \in (T_2, \infty)$ the tumour becomes resistant to chemotherapy and therefore the treatment is progressively less efficient.

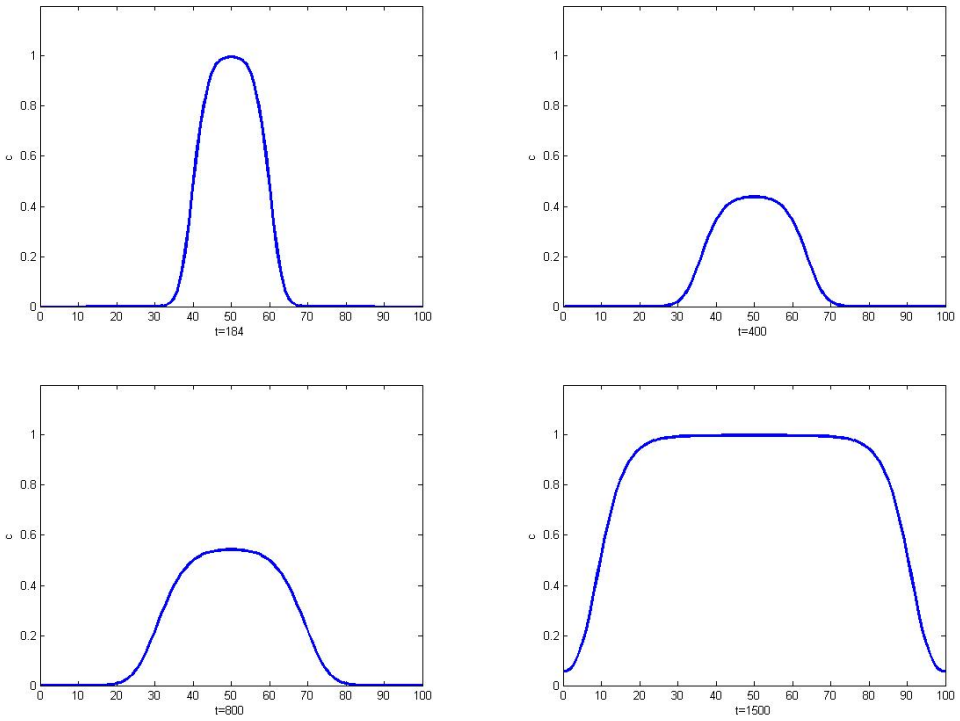
The therapy function will look like

$$b(t) = \delta \begin{bmatrix} 0 & \text{if} \quad t \in [0, T_1] \\ \frac{-t^2 + 2T_2 t + T_1(T_1 - 2T_2)}{(T_1 - T_2)^2} & \text{if} \quad t \in (T_1, T2] \\ \frac{t^2}{4T_2^2} - \frac{3t}{2T_2} + \frac{9}{4} & \text{if} \quad t \in (T_2, 3T_2] \\ 0 & \text{if} \quad t \in (3T_2, \infty) \end{bmatrix} \tag{5.8}$$

where δ can be interpreted as the strength of the chemotherapy. This value must be optimized in order to maximize the effect of chemotherapy but it should be low enough to not kill the patient since chemotherapy affects either tumour cells or healthy cells.

Results.

The following pictures show the distribution of c along the space for different moments of time. The first picture corresponds to $t = T_1$, i.e, the time when the tumor is detected. The second picture corresponds to $t = T_2$, i.e, the time when the effectiveness of the treatment is maximum. Third and fourth picture correspond to more advanced times.



Third Mathematical Model: Effect of Surgery.

An extension of the above treatment function is after a time T, surgery is carried out on the patient with the purpose of removing the tumour. Due to the fact the glioma is a diffusive tumour and surely malignant, a surgery that completely removes it is in general not possible. The surgery can just remove the part of the brain in which the concentration of tumour is higher than a given concentration, c_0. The value of c_0 will depend on how diffusive the tumour is. The biological constraints such that an essential part of

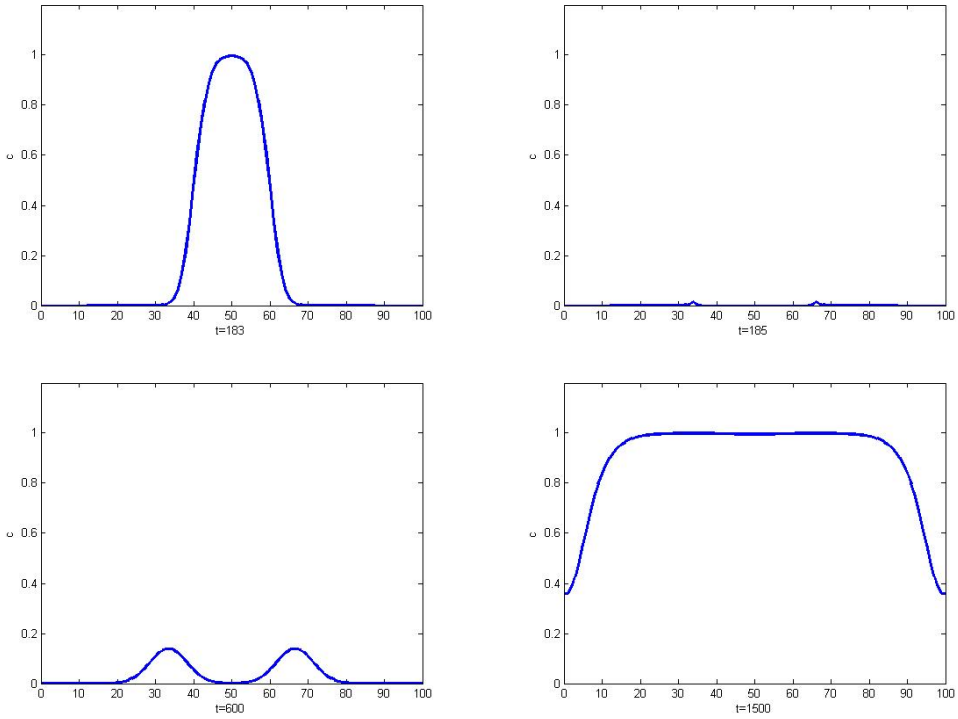
the brain can not be removed must also be taken into account. Under this assumptions, the model becomes

$$\left[\begin{array}{l} \dfrac{\partial c}{\partial t} = \rho c\left(1 - \dfrac{c}{c_m}\right) + D\nabla^2 c. \\ c(\mathbf{x}, T) = 0, \quad \forall \mathbf{x} \in B(\hat{\mathbf{x}}, d) \end{array}\right] \tag{5.9}$$

where d is the distance corresponding to a concentration of $c = c_0$.

Results.

The following pictures show the distribution of c along the space for different moments of time. The first picture corresponds to the time when the tumor is detected. The second picture corresponds to the day after the sugery. Third and fourth picture correspond to more advanced times.



Fourth Mathematical Model: A Stochastic Approach.

In this section we want to study the following equation

$$\frac{\partial c}{\partial t} = \rho c \tag{5.10}$$

from a stochastic point of view.
We note that

$$c = \frac{\mathbb{E}\left[N(t)\right]}{K}, \tag{5.11}$$

where $N(t)$ is equal to the number of infected cells at time t and K is the total number of cells in the brain. We assume that $(N(t))_{t\in\mathbb{R}^+}$ is a pure birth process subject to a birth rate λ and we know, from the definition of the expected value of a discrete random variable, that

$$\mathbb{E}\left[N(t)\right] = \sum_{n=1}^{+\infty} n\,\mathbb{P}(N(t)=n).$$

Before computing $\mathbb{E}\left[N(t)\right]$, we want to specify the value of the probability involved:

$$\begin{aligned}
\mathbb{P}(N(t)=n) &= \overbrace{\mathbb{P}(N(t)-N(t-\Delta t)=1, N(t-\Delta t)=n-1)}^{\text{number of births in a previous time: } n-1} \\
&\quad + \underbrace{\mathbb{P}(N(t)-N(t-\Delta t)=0, N(t-\Delta t)=n)}_{\text{number of births in a previous time: } n} \\
&= \mathbb{P}(N(t)-N(t-\Delta t)=1 | N(t-\Delta t)=n-1)\cdot \\
&\quad \cdot \mathbb{P}(N(t-\Delta t)=n-1) \\
&\quad + \mathbb{P}(N(t)-N(t-\Delta t)=0 | N(t-\Delta t)=n)\cdot \\
&\quad \cdot \mathbb{P}(N(t-\Delta t)=n) \\
&= \mathbb{P}(N(t)=n | N(t-\Delta t)=n-1)\cdot \mathbb{P}(N(t-\Delta t)=n-1) \\
&\quad + \mathbb{P}(N(t)=n | N(t-\Delta t)=n)\cdot \mathbb{P}(N(t-\Delta t)=n)
\end{aligned}$$

Knowing that our $(N(t))_{t\in\mathbb{R}^+}$ is a pure birth process with a birth rate λ, we can define its conditional probability as

$$\mathbb{P}(N(t)=j | N(t-\Delta t)=i) = \begin{cases} \lambda\cdot i\cdot\Delta t + o(\Delta t) & \text{if } j=i+1 \\ 1-\lambda\cdot i\cdot\Delta t - o(\Delta t) & \text{if } j=i \end{cases}$$

Betaking this property of the pure bith processes, we arrive at the following equality,

$$\begin{aligned}
\mathbb{P}(N(t)=n) = [(n-1)\Delta t\lambda + o(\Delta t)]\,\mathbb{P}(N(t-\Delta t)=n-1) + \\
+ [1-n\Delta t\lambda - o(\Delta t)]\,\mathbb{P}(N(t-\Delta t)=n).
\end{aligned} \tag{5.12}$$

Now if we consider $\mathbb{P}(N(t+\Delta t)=n)$, we can write the Taylor series expansion like

$$\mathbb{P}(N(t+\Delta t)=n)=\mathbb{P}(N(t)=n)+\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)\Delta t+o((\Delta t)^2)$$

and we can rewrite (5.12) such as

$$\begin{aligned}\mathbb{P}(N(t+\Delta t)=n)=&\left[(n-1)\Delta t\lambda+o(\Delta t)\right]\mathbb{P}(N(t)=n-1)+\\&+\left[1-n\Delta t\lambda-o(\Delta t)\right]\mathbb{P}(N(t)=n)\end{aligned}\tag{5.13}$$

Then, taking both (5.12) and (5.13) we have

$$\begin{aligned}&\mathbb{P}(N(t)=n)+\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)\Delta t+o((\Delta t)^2)=\\&=\Delta t\left[(n-1)\lambda\mathbb{P}(N(t)=n-1)-n\lambda\mathbb{P}(N(t)=n)\right]+\\&\quad+o((\Delta t)^2)\left[\mathbb{P}(N(t)=n-1)-\mathbb{P}(N(t)=n)\right]+\mathbb{P}(N(t)=n)\\&\iff\\&\mathbb{P}(N(t)=n)+o((\Delta t)^2)=\\&=\Delta t\left[(n-1)\lambda\mathbb{P}(N(t)=n-1)-n\lambda\mathbb{P}(N(t)=n)-\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)\right]+\\&\quad+o((\Delta t)^2)\left[\mathbb{P}(N(t)=n-1)-\mathbb{P}(N(t)=n)\right]+\mathbb{P}(N(t)=n)\\&\implies\\&(n-1)\lambda\mathbb{P}(N(t)=n-1)-n\lambda\mathbb{P}(N(t)=n)-\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)=0\end{aligned}$$

Finally, we obtain

$$\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)=(n-1)\lambda\mathbb{P}(N(t)=n-1)-n\lambda\mathbb{P}(N(t)=n)\tag{5.14}$$

Now, we will rewrite (5.10) using (5.11) and we will compute $\mathbb{E}\left[N(t)\right]$.

$$\frac{\partial}{\partial t}\left(\frac{\mathbb{E}\left[N(t)\right]}{K}\right)=\rho\cdot\frac{\mathbb{E}\left[N(t)\right]}{K}\Leftrightarrow\frac{\partial}{\partial t}\left(\mathbb{E}\left[N(t)\right]\right)=\rho\cdot\mathbb{E}\left[N(t)\right]\tag{5.15}$$

We will first evaluate $\dfrac{\partial}{\partial t}\mathbb{E}\left[N(t)\right]$.

Resorting on the definitions of both a partial derivative and the expected

value of a discrete random variable we have that,

$$\begin{aligned}\frac{\partial}{\partial t}\mathbb{E}\left[N(t)\right] &= \lim_{h\to 0}\frac{\mathbb{E}\left[N(t+h)\right]-\mathbb{E}\left[N(t)\right]}{h} = \\ &= \lim_{h\to 0}\frac{\sum_{n=1}^{+\infty} n\,\mathbb{P}(N(t+h)=n)-\sum_{n=1}^{+\infty} n\,\mathbb{P}(N(t)=n)}{h} = \\ &= \lim_{h\to 0}\frac{\sum_{n=1}^{+\infty} n\,\left(\mathbb{P}(N(t+h)=n)-\mathbb{P}(N(t)=n)\right)}{h} = \\ &= \sum_{n=1}^{+\infty} n\,\left(\frac{\partial}{\partial t}\mathbb{P}(N(t)=n)\right)\end{aligned}$$

Using now the result we achieved in (5.14).

$$\begin{aligned}\frac{\partial}{\partial t}\mathbb{E}\left[N(t)\right] &= \sum_{n=1}^{+\infty} n\,\left((n-1)\lambda\mathbb{P}(N(t)=n-1)-n\lambda\mathbb{P}(N(t)=n)\right) = \\ &= \sum_{n=1}^{+\infty} n^2\,\lambda\mathbb{P}(N(t)=n-1)-\sum_{n=1}^{+\infty} n^2\,\lambda\mathbb{P}(N(t)=n)- \\ &\quad -\sum_{n=1}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n-1) = \\ &= \sum_{n=0}^{+\infty}(n+1)^2\,\lambda\mathbb{P}(N(t)=n)-\sum_{n=1}^{+\infty} n^2\,\lambda\mathbb{P}(N(t)=n)- \\ &\quad -\sum_{n=1}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n-1) = \\ &= \sum_{n=0}^{+\infty}\lambda\mathbb{P}(N(t)=n)+2\sum_{n=0}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n)- \\ &\quad -\sum_{n=1}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n-1) = \\ &= \sum_{n=0}^{+\infty}\lambda\mathbb{P}(N(t)=n)+2\sum_{n=0}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n)- \\ &\quad -\sum_{n=0}^{+\infty}(n+1)\,\lambda\mathbb{P}(N(t)=n) = \\ &= \sum_{n=0}^{+\infty} n\,\lambda\mathbb{P}(N(t)=n).\end{aligned}$$

So at last we have,

$$\frac{\partial}{\partial t}\mathbb{E}\left[N(t)\right] = \lambda\mathbb{E}\left[N(t)\right].$$

If we now use the following conditions

$$c = \frac{\mathbb{E}\left[N(t)\right]}{K}$$
$$\frac{\partial c}{\partial t} = \frac{\frac{\partial}{\partial t}\mathbb{E}\left[N(t)\right]}{K} = \lambda \mathbb{E}\left[N(t)\right]$$

into the equation (5.10), we obtain the equality

$$\lambda \frac{\mathbb{E}\left[N(t)\right]}{K} = \rho \frac{\mathbb{E}\left[N(t)\right]}{K},$$

that permits us to reach the relation

$$\lambda = \rho \tag{5.16}$$

between the birth rate and the proliferation.

Simulations of a Pure Birth Model.

After reaching the result (5.16) we decide to simulate the increase of the total number of infected cells in the brain as time went by.

The algorithm we used for one single simulation consists in the following steps:

1. Define the total time of study, as we can not go on with the simulation indefinitely.

2. Define the initial number of infected cells in the brain in the beginning of the study.

3. Generate the times at which a new infection occurs according to an exponential distribution.

4. Increase the total number of infected cells.

5. Register for each time the number of infected cells in the brain.

In practice, and as we also need to compute $\mathbb{E}\left[N(t)\right]$, we decided to run several simulations of each particular process.

Below, we can find the plots of several simulations and their expected values.

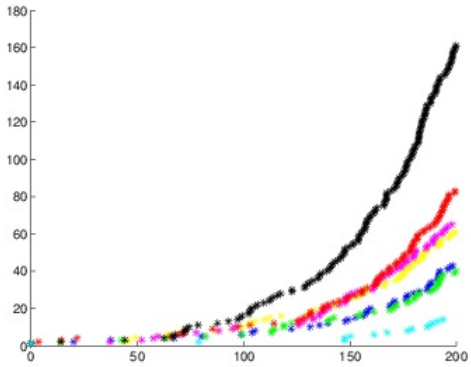


Figure 5.3: Simulations with 200 days and 1 initial infected cell

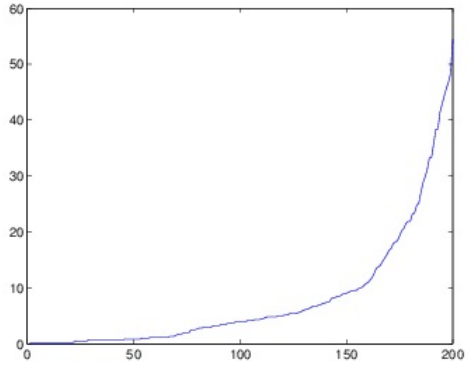


Figure 5.4: Expected value with 200 days and 1 initial infected cell

In this case, we have a simulation for 200 days and starting with one initial infected cell. As we can see in first 100 days, approximately, there is a very unstable and unpredictable behavior of our process but as time goes by, each simulation starts to have a very defined curve. However, even when we are already close to the 200^{th} day, we can clearly identify the several curves corresponding to each simulation. If we take a look at the plot of the expected value of these simulations, we can see that it is similar to an exponential function, as it was expected.

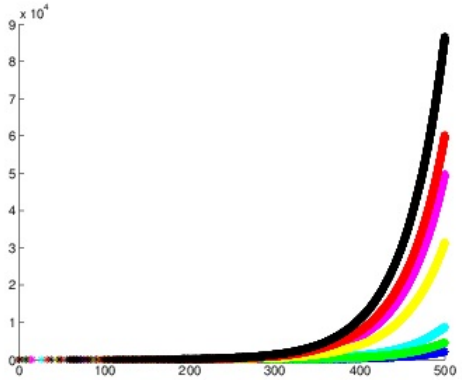


Figure 5.5: Simulations with 500 days and 1 initial infected cell

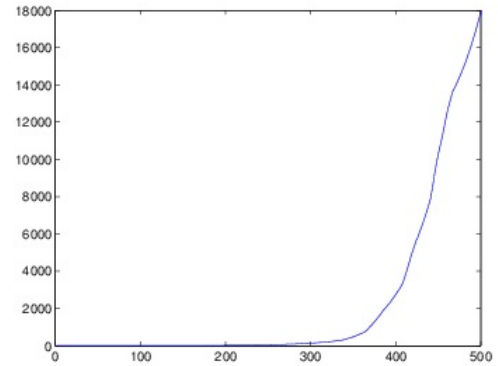


Figure 5.6: Expected value with 500 days and 1 initial infected cell

Here we have simulations for 500 days and also for one initial infected cell. In this case, the stochastic behavior in the beginning is smaller, although it

can still be spotted in the plot, and as time goes by the curves are now more defined than before. Nevertheless, they still present detectable differences between each other. The plot of the expected value, just like in the previous case, is still quite similar to an exponential distribution.

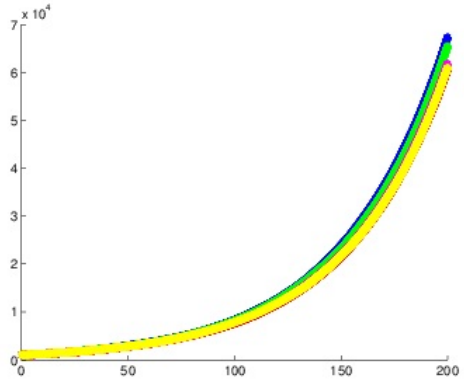


Figure 5.7: Simulations with 200 days and 1000 initial infected cell

At last, we have simulations for 200 days and 1000 initial infected cells. Here, we can clearly see several differences from the previous cases. Firstly, the initial random behavior has nearly disappeared and secondly, there is almost no difference between each simulation. This tells us that when my initial infection is already large, the tumor will grow roughly in the same way, exponentially. Thus, the stochastic effect in these cases can be negleted.

Discussion.

As it can be seen in figure (5.1b) the final stage of the process the tumour growth will be linear. If we instead observe the process at the beginning, the tumour growth will be different depending on the initial conditions. Velocity of the tumour boundary is found to be $v = 2\sqrt{\rho D}$ based on the received data from the simulations.

When presenting the project we wanted to observe how models in different dimensions differ. By using both a 1D and a 3D model we saw that the difference between the received results depends only on the initial conditions. The initial diameter of the tumour can be changed as well as the initial value of the concentration.

From a stochastic point of view, the study only makes sense when the initial infection is small. As we just have seen above, for a large infection the stochastic effect can be neglected. On the other hand, considering a

PDE model with the treatment effect would only make sense for a quite large infection, once there isn't going to be a treatment for a tumour that has not yet developed. So, it would make sense if one approach would be used for the first period of and the other one would be used for the second.

Conclusion.

In this paper the growth rate of the tumour was observed from two different approaches. Firstly, for simplicity, a PDE model was made in 1D. Observing simulation made in Matlab for that model, it was concluded how proliferation ρ and diffusion D affect the growth of the glioma cells. The next step was making a 3D model which is closer to reality. It was shown that those two models are similar for well-chosen initial values of concentration and diameter of tumour. The main results obtained from this model are the velocity of the moving boundary of the tumour and the boundary width. The velocity of the moving boundary showed to be constant after a certain time and the growth of the tumour radius showed to be linear. The boundary width is a helpful result if a doctor wants to apply surgery to remove the tumour. It depends on the smoothness of tumour boundary, which is actually described by the boundary width. Due to the diffuse nature of glioma cells surgery is not efficient to completely remove the tumour. Also, the treatment function was added to the model to represent a chemotherapy. It was observed that the treatment was only effective for a limited period of time. A stochastic approach was also observed, and mathematically, it gave us a result about the increasing number of glioma cells during the time. It was shown that when the initial infection is already large, the tumor will grow exponentially. However, this model does not provide useful information for the treatment of patients. An improvement to this project could be precisely to consider also a treatment effect on the stochastic approach.

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