Modelling the spread of brain tumours

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The study of mathematical biology attempts to use
mathematical models to draw useful conclusions
about biological systems. Here, we consider the mod-
elling of brain tumour spread with the ultimate goal
of improving treatment outcomes.

1 Introduction

Brain tumours, or gliomas, are among the most difficult forms of cancer to treat.
Because the human brain is such an important and complex organ, doctors
must take special care not to damage brain tissue while killing cancer cells.
This is a very difficult task, as brain cancer cells are very diffuse, infiltrating
the brain far beyond the visible tumour mass. This means that if we wish to
effectively treat a brain tumour, we must treat not only what we can see, but
also what we cannot see.

Usually, the first step in treatment is surgery to remove the bulk of the
tumour; but with brain tumours, surgery is sometimes not possible. The
proximity of the tumour to critical brain structures that may be nearby makes
surgical intervention too dangerous. Even when surgery is possible, many cancer
cells are left behind because of their microscopic spread. As such, whether a
patient receives surgery or not, radiation treatment is typically prescribed. To
have an effective treatment we need to determine the location of the invisible
cancer cells. Usually, the region over which the radiation is administered is
determined to be a uniform extension of the visible tumour mass. In other
words, radiation treatment usually extends 2 cm beyond the mass that is visible

using MRI[1]. This extension of the visible region is chosen in an attempt to kill the cancer cells that are distributed throughout the healthy brain tissue and are hard to detect.

To summarize, the problem we face is this: Cancer cells invade the brain beyond the main mass of the tumour in quantities that are undetected by imaging methods. We need to figure out where these cells are, as they should be treated also. In this snapshot, we will describe how we use a mathematical model to predict where the most invasion has really occurred beyond what is visible, in the hopes of determining a more beneficial treatment region.

2 A mathematical model

In sciences, we often use mathematical models to try to predict or explain observations in the real world. These models can be very simple, or quite complicated. To explain how mathematical models work, we will use the example of a ball being thrown in the air. The equation for this instance is given by

$$h(t) = -\frac{1}{2}9.8t^2 + v_0 t + h_0,$$

where $h(t)$ gives the height of the ball in meters (m) at time t seconds (s), v_0 meters per second gives the initial velocity of the ball when it is thrown upwards, and h_0 meters is the height from which the ball is released. The constant -9.8 describes the acceleration due to the gravity of the earth[2]. We call v_0 and h_0 *parameters* of our model, which means we can vary them to change the result. For example, if we throw the ball from a higher starting point (larger h_0), we would expect a different trajectory. We call $h(t)$ the *dependent variable*, which depends on t – the *independent variable*. The real world has far too many parameters and subtleties to fully include in a model, so we expect this model to give us a good *approximation* for what the height of the ball would be at time t. For example, the above equation neglects the effects of air resistance, focusing instead on the effects of gravity. This is something we commonly do in mathematical modelling: try to pick out the most important things to model, to prevent our models from becoming too complicated.

To model the spread of glioma (brain tumour) cells, we will use an idea called diffusion. Diffusion is the process by which substances spread out. A simple example to think about is a drop of blue food-colouring in a glass of

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[1] Magnetic Rosonance Imaging (MRI) is a technique utilizing oscillations in magnetic fields to create images of the interior of the body.
[2] The earth accelerates the ball *downwards* (so we get the $-$ sign) at a rate of $9.8m/s^2$, which translates (via motion equations) to $4.9m$ times the square of seconds passed.

water. The concentrated colour droplet will slowly spread out until the whole glass of water is a uniform pale blue colour. This process is very slow, and will take a long time to arrive at the uniform colour. This final state is something we refer to in mathematics as a *steady state*, which means the state of a system when it is no longer changing without external interference.

We can describe this process mathematically, taking as our dependent variable the colour concentration, and taking time and space to be our independent variables. This means that we are trying to model the concentration of colour at some spatial location after a certain amount of time has passed. The results of such a model are shown in Figure 1. The different colours correspond to different concentrations, with **red** being a high concentration, and **blue** being a low concentration. This figure does not show the steady state, as this would just be a constant uniform colour, and not very interesting. Instead, the picture shows what the concentrations would look like while the colour particles still spread out. The highest concentration is seen in the middle, where the colour droplet began, with the lowest concentration at the edges as it spreads out.
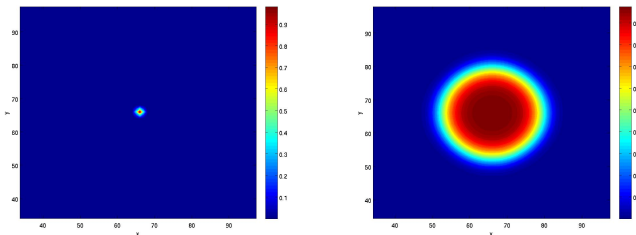
Figure 1: Figure showing colour concentration both initially, and after 100 iterations. Note that the highest concentration (**red**) is seen at the centre, where the colour drop began. The lowest concentration is seen farthest from the centre, in a circular shape.

It turns out that cancer cells follow a similar process: spreading through the brain just as the food-colouring spreads through the glass of water. We can use mathematical equations to describe this process and to predict the distribution of cancer cells after some time has passed. We want to predict the cancer cell concentration at each point in space, and how it changes with time. A parameter of this model is the rate at which the cells spread. This can depend on a lot of things, such as the medium they are in, the type of cells, and the local environment. We call this the *diffusion coefficient*, and must find the

appropriate value in order to have an accurate model[3]. In Figure 1, a higher diffusion coefficient would result in a larger circular distribution after the same amount of time has passed, as the colour would spread out faster.

In reality, the situation is more complicated. The brain is non-uniform, and is made up of two main types of tissue: grey matter, and white matter. White matter contains the myelinated axons (the long projections of the nerve cells), arranged in bundles called *tracts*, along which electric signals are sent. The grey matter is the surrounding tissue, composed mainly of the nerve cell bodies, where the signals are processed. The first model for brain tumour spread was developed by Swanson in 2000 [1], where the assumption was made that cancer cells diffused five times faster in white matter than in grey. This is based on the idea that cancer cells use the white matter tracts as sort of "highways" for their spread. This would mean that the diffusion coefficient should be five times higher in the white matter regions than in the grey matter regions, and so it would be different depending on where the cancer cells are within the brain.

2.1 Anisotropic Diffusion

Cancer cells seem to actually crawl along the fibers of white matter [2], meaning that the rate of spread is higher along the white matter tract than along the perpendicular direction. An illustration of this can be found in [2, Figure 2].

Within the grey matter, cancer cells will travel at approximately equal rates in all directions, resulting in the circular cell distribution seen in Figure 1. However, when cancer cells travel in the white matter, they spread out more quickly along the direction of the white matter tract, and more slowly in the perpendicular directions. This results in an oblong, ellipsoidal cell distribution that is aligned with the white matter tract. We refer to this type of diffusion as *anisotropic diffusion.* An example of such a distribution is seen in Figure 2. So now we need to take into account that the diffusion coefficient will depend not only on where a cell is within the brain (higher in white matter regions), but also on the different directions (higher in the direction of the tracts).

A technique known as diffusion tensor imaging[4] can measure the rates of diffusion in each direction, at each spatial location within the brain. We can then use this information to adjust our calculation of the diffusion coefficient to make our model more realistic. A full description of the model can be found in [3] and [4]. A similar model can be found in [5]. An excellent description of all of the models that are being used for this type of problem can be found

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[3] As in the thrown ball model in the beginning of this section, where we had to know the initial speed v_0 and height h_0, and the acceleration of the earth's gravity, in order to predict the ball's height at any given second.

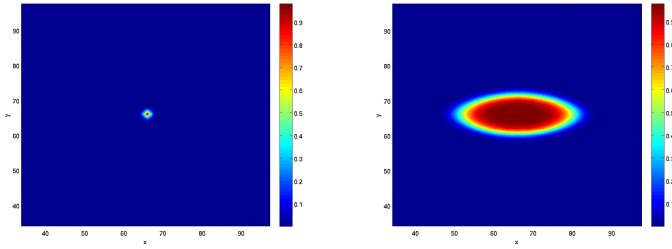[4] A special type of MRI, also known as *Diffusion MRI.*

Figure 2: Figure showing distribution of cells both initially, and after 100 iterations. Notice that because the diffusion rate is higher in the direction of the horizontal axis, the cells spread out further along this direction than along the direction of the vertical axis.

in [6]. We can then compute what we call the *fractional anisotropy*, which is a measure of "how anisotropic" a particular spot in the brain is. This value varies between 1 – fully anisotropic, very elongated ellipsoidal (actually a line) cell distribution, and 0 – fully isotropic, circular cell distribution. An example of what these values look like within the brain is shown in Figure 3. Notice that regions containing grey matter appear **blue** (very isotropic), whereas regions where we find white matter appear **red** (very anisotropic).
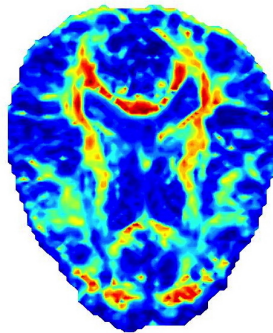

Figure 3: Figure showing a sample fractional anisotropy plot. The **red** regions represent regions of the brain that are very anisotropic (the white matter), while the **blue** regions represent areas of the brain that tend to be more isotropic (grey matter). The data processing was provided by our colleagues from the group of Dr. Russ Greiner.

Now that we have gained an understanding of the important parameters and variables, and the tools to measure them, we want to combine all these into a model. We would like to construct an equation like the one describing the height of the thrown ball, that will tell us where we can expect cancer cells in the brain. In order to do so we use a *partial differential equation* (PDE). This equation relates a function, describing the concentration of cancer cells in the brain, and its partial derivatives, encoding the rates of change of the function along different directions. The equation itself is:

$$c_t = \nabla\nabla(D(x)c). \tag{1}$$

This equation involves the function $c(t, x)$ (c, for short) which describes the cancer cell concentration at a point x in the brain, at time t. This is the function we want to find, telling us where in the brain cancer cells will be, so we could apply treatment to these areas. On the left-hand side we have the time-derivative c_t – describing how c changes with time. Since we are dealing with anisotropic diffusion, the rate of spread of cancer cells has different values in different directions. This is encoded by the matrix $D(x)$[5] on the right-hand side of the equation. The notation $\nabla\nabla$ involves second order spatial derivatives of c (with the information in D) – that is, the rates of change in the speed by which cancer-cells spread along the various directions – effectively describing the diffusion process.

So now to solve equation (1), that is, to find c, we need to find the aforementioned derivatives of c. This is an interesting characteristic of PDEs: they have functions we want to find on one side and derivatives (which are therefore unknown also) on the other. This makes such equations seem impossible to solve. It is, indeed, very hard to solve such equations (and many times impossible), but in the case of equation (1), adding *initial conditions* – information about the concentration of cancer cells at some point of time – can yield a solution[6].

3 Model Simulations

Once we have developed our model and measured the diffusion rates in the brain of a sample patient, we can use this information to predict the spatial distribution of cancer cells in the brain. Figure 4 shows the cell distribution as predicted by the diffusion model for a sample patient. The black line shows the outline of the actual tumour, and the white line shows the 0.8 contour

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[5] A matrix is an array of values. Matrices are often used to describe quantities in multidimensional circumstances.

[6] For more discussion and examples of PDEs, see Snapshot 7/2015 "Darcy's law and groundwater flow modelling" by Ben Schweizer.

of the cell density distribution. Note that the mathematical model provides more information about the density of cancer-cells in different directions, and so enables a more beneficial application of treatment. It has been suggested that this is the density that shows up on an MRI scan [7].
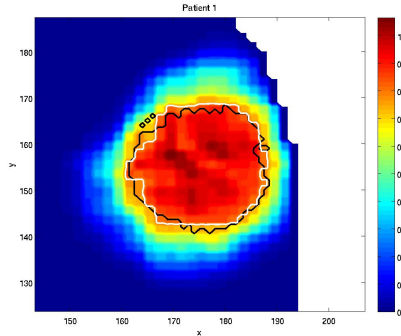

Figure 4: Figure showing the predicted cancer cell distribution. **Red** corresponds to high density, while **blue** corresponds to low density. The black line represents the actual tumour boundary as determined from imaging, and the white line represents the predicted tumour boundary based on our model.

4 Conclusions

Based on the anisotropic diffusion model, it appears that the distribution beyond what is seen on an MRI image is not uniform, and in fact extends further beyond the visible boundary in some areas than others. This is seen in Figure 4. Based on this, a uniform treatment region may not be the best choice to ensure the best treatment possible. We believe that a three-dimensional version of our model will describe the cell distribution beyond what is visible, helping clinicians to determine where to treat. This should improve the outcome for glioma patients. We will also work to improve our model by including a *mass effect*, which involves incorporating the deformation that the growing tumour will cause in the brain. There are many challenges involved in this, and we will need to draw ideas from continuum mechanics (a branch of physics dealing with motion of substances as if they are not made of clearly distinguishable particles), as well as sophisticated numerical techniques (methods to find solutions for equations by approximation).

In the end, the fight against cancer is difficult, and our best chance is to work together with many scientists from many different disciplines. Cancer is an interdisciplinary problem, and we must work to find an interdisciplinary solution.

Acknowledgements

Image credits

All images by Amanda Swan.

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