Glioblastoma Tumour Model

# Project overview

The goal of the project is to create a single cell-based model of human brain tumour glioblastoma. The behaviour of the model should agree with clinical data, i.e. magnetic resonance imaging (MRI) datasets.

The current state of the art in the field of glioblastoma modelling adopts one of the two main approaches existing approaches: a reaction-diffusion model [1, 2] and a shape-based model [G. Gerig]. While these approaches have been used successfully to model the response of tumours to chemotherapy and surgical resection, they do not recapitulate the different morphological compartments of the tumour – the proliferating rim of tumour cells, the necrotic center of the tumour, and the infiltrative zone around the tumour core. Therefore we create a new single cell-based executable model of the tumour to encode the clinical and experimental knowledge regarding tumour development.

# The mathematical model

The model consists of 2 parts:

* An automata describing the stages of the lifecycle of a cell (i.e. proliferation, functioning and death)
* Molecular Dynamics methods to calculate the spatial characteristics of a cell (the location, the velocity and forces)

Both parts of the model are calculated with a discrete time step.

## Automata describing the stages of a cell lifecycle

The model differs 2 types of cells: stem and non-stem.

Stem cells can divide symmetrically (to produce two stem cells) and asymmetrically (to produce a stem and a non-stem cells). The probability of division of a cell (both stem and non-stem) depends on the level of oxygen and cell packing density. The assumption of the model is that stem cells can not die. Stem cells can transit into a non-stem cell “with memory”. Non-stem cells “with memory” can take only one action - transit back into a stem cell.

Non-stem cells can divide symmetrically (to produce two non-stem cells). Non-stem cells can die via two mechanisms: apoptosis (depends on the age of the cell) or necrosis (caused by low level of oxygen).

Initially the model has a single cell which is a stem cell.

The states of the automata correspond to different stages of the lifecycle, and the arcs correspond to the transitions between them. Division is currently modelled as an instant transition to the same state and shown in the automata diagram below as a label on the arc. (In principle division can be modelled as a separate state if necessary).

We model the automata as a probabilistic discrete-time automata automata. Every transition in the automata is modelled as a function of the external state and the state of the system. When provided with concrete values of the state, the function yields the probability p of transition. The outcome (whether the transition is taken or not) is calculated as follows. A pseudo-random real number n uniformly distributed in the range from 0 to 1 is generated, and if n < p, then the transition is taken.



### Probability functions

The probability functions are modelled with a (generalised) logistic function and exponent function.

Logistic function: , where , , ,  are calibration parameters

Exponent function: , where , , are calibration parameters

The probability of cell division is calculated with an ad-hoc formula:



where  and are generalised logistic functions ranging from 0 to 1

is the concentration of oxygen in point of the cell location

is the cell packing density in point of the cell location

### The concentration of oxygen

The oxygen is calculated with diffusion-consumption equation [3] as follows:



where is the concentration of oxygen at the point  at the time 

is the time step

is the oxygen diffusion coefficient

is the Laplace operator, 

is the rate of oxygen supply per time unit. equals to zero if the point is inside the tumour mass and to a positive constant otherwise

is the rate of oxygen consumption, 

where and is the number of dividing and non-dividing resp. live cells in a unit square embracing the point 

and are the consumption rates of one dividing and non-dividing resp. cell per time unit

The concentration of oxygen is calculated in the vertices of a two-dimensional grid and interpolated in between the vertices with two-dimensional splines.

The Laplace operator is calculated using finite difference method as described in <http://www.rsmas.miami.edu/personal/miskandarani/Courses/MSC321/lectfiniteDifference.pdf>

### Cell packing density

The cell packing density is calculated as follows:



where  is the number of live and necrotic cells in the unit square embracing the point . A cell is considered to be in the square is at least some part of it is inside the square.

is the weighting coefficient, which shows the ratio of the grid size  and the cell diameter .

## Molecular Dynamics model

Molecular dynamics is a collection of methods to model physical movements of interacting particles. In our model a cell is modelled as a sphere (however, the current implementation is two-dimensional).

A cell can experience two types of forces:

* Repulsive force which occurs when two or more cells overlap. When a cell divides, the daughter cells need more space and apply pressure on the surrounding cells.
* Friction force which is needed to stop the movement caused by repulsive forces.

The forces are calculated as follows:

, 

where and are calibration parameters,

is the vector from the center of the overlapping cell to the center of the cell which experiences Frepulsive,  is the length of this vector

and is the sum of the radiuses of the two cells.



where  is the velocity of the cell

and  is the coefficient of viscosity.

# Simulation of the model

## The main window

## 3.1.1. Encoding cell type and state with colour

The colours used to render the cells have the following meaning:

* Green is used for stem cells
* Blue is used for non-stem cells
* Light green is used for “non-stem with memory” cells
* Red-brown is used for cells in the pre-necrotic state
* Black is used for cells in the necrotic state

### 3.1.2. Running the simulation

The following events are processed in the main window:

* Pressing the key ‘p’ stops/resumes the simulation
* Pressing the key ‘s’ runs one step of the simulation

### 3.1.3. Getting the summary of the system state

Pressing the left key of the mouse shows a tooltip with summary of the system state at the location of the cursor. Pressing the right key of the mouse hides the tooltip. The tooltip is automatically hiden after 20 seconds.

## The statistics of the number of cells

### Overview of the statistics

The statistics of the number of the cells shows for each time step the number of

* cells of different types:
  + Stem, non-stem, “non-stem with memory”
* cells in different states
  + Live – cells in the Functioning or Pre-necrotic state
  + Dying – cells which transit to the Apoptosis or Necrosis state in the current time step
  + Dividing – cells (both stem and non-stem) which divide in the current time step

### GUI features

As in the main window, clicking on the left/right button of the mouse shows/hides the summary of the plot in the point of the cursor location.

The plot can be scaled by pressing plus/minus buttons on the axes. A part of the plot can be zoomed in/out by selecting a region with cursor.

## The concentration of oxygen

The concentration of oxygen is plotted as a grid (two-dimensional array of dots), and the colour of each point is calculated based on the concentration of oxygen in this point. The lower concentration corresponds to darker colour.

The region where the tumour is located, is shown in blue.

## Visualisation of the model

<video.mp4>

# Building the project

The solution consists of two projects:

* alglib is a numeric open-source library written in C#. The library is used for numerical computations, namely two-dimensional interpolation with splines.
* CancerCellModel is the main project

Alglib project should be built before the CancerCellModel project.

# 5. References

[1] Menze BH, Van Leemput K, Honkela A, Konukoglu E, Weber MA, Ayache N, Golland P. A generative approacj for image-based modeling of tumor growth. Inf Process Med Imaging. 2011, 22:735-47.

[2] Durrleman S, Pennec X, Trouve A, Braga J, Gerig G, Ayache N. Towards a comprehensive framework for the spatiotemporal statistical analysis of longitudinal shape data. International Journal of Computer Vision 2013, 103(1): 22-59.

[3] Jiang, Yi, et al. "A multiscale model for avascular tumor growth." *Biophysical journal* 89.6 (2005): 3884-3894.