DTC-OSTI-MatlabCancerModelling-A

**Main reference:**

[K. Smallbone, R.A. Gatenby, R.J. Gillies, P.K. Maini, D.J. Gavaghan. Metabolic changes during carcinogenesis: potential impact on invasiveness. *J. Theor. Biol.* **244**, 703-713 (**2007**)](http://eprints.maths.ox.ac.uk/566/1/223.pdf)

**Abstract**

Based upon the work of Smallbone et al. we have developed a hybrid cellular automaton to model the adaptation of cancer cells to its microenvironment. Our aim is to replicate Smallbone’s results with our own MatLab code. The code is a mathematical model of a theoretical model proposed by Gatenby and Gillies (2004). Gatenby and Gillies hypothesised that cancerous growth starts with hyper-plasticity (increased proliferation) in cells. Initially, cell survival and proliferation is limited by oxygen levels, as dictated by the oxygen diffusion limit away from blood vessels. Any adaptations by cells that reduce the reliance on oxygen for ATP production are promoted and result in cell proliferation towards the glucose diffusion limit. Reduced oxygen reliance is associated with an up-regulation in glycolysis and an increase in anaerobic metabolism. As a by-product of glycolysis, acidification of the local environment is observed (increased levels in lactic acid), that now acts as the proliferation limit by inducing cell death (both necrotic and apoptotic). Low pH promotes the next stage in cellular evolution with the emergence of acid-resistance (i.e. resistance to acid-induced toxicity). The cellular phenotype has a significant proliferation advantage because it will acidify the surroundings in a way that is toxic to its competitors but harmless to itself. By using mathematical methods to examine cellular evolution of premalignant cells within anatomical constraints, Smallbone suggests Gatenby and Gillies’ sequence is integral in the formation of invasive cancer tissue. He goes on to predict that the transition from self-limited premalignant growth to invasive cancer could be delayed or prevented by interrupting the hypoxia-glycolysis-acidosis cycle.

**Introduction**

Cancer-related diseases cause 7 million deaths worldwide every year (The World Health Report 2006) despite significant improvements in understanding, diagnosing and treatment of the disease. The use of mathematical and computation models may be central to the next step in understanding cancer progression and dynamics in patients (L. Preziosi et al. & E. Y. Rodin et al.).

Cancerous cells often show increased rates in glycolysis (glucose consumption) as a result of persistent increases in anaerobic metabolism. Importantly the phenomenon is not observed solely around hypoxic tissue where there is irregular and disordered vascular coverage. Glycolytic cells are observed even in the presence of oxygen where aerobic metabolism would be expected to dominate. Anaerobic metabolism is very inefficient at extracting energy from glucose, and to compensate a several-fold increase in cellular glucose consumption is observed (Di Chiro et al., 1987).

Numerous studies have demonstrated that linear, intuitive word-models cannot explain the complex dynamics in multi-scale systems (such as carcinogenesis) (Gatenby et al. 2002; Gatenby and Maini, 2003; Komarova, 2005). Instead a detailed mathematical model is required. In Smallbone’s study, he uses evolutionary models of carcinogenesis with explicit spatial parameters to accommodate the geometry of early tumour development. The method uses a hybrid cellular automaton (Anderson, 2005; Patel et al, 2001). The advantage of an automaton model is that each cell can be treated as discrete individuals such that cellular processes (proliferation, death, adaptation and metabolite consumption/production) can be modelled for each cell individually. The automaton is described as hybrid because metabolite distribution (oxygen, glucose and H+ concentrations) are allowed to form a continuous field across the cells.

**Materials and Methods**

Our hybrid automaton was designed using the guidelines and parameters outlined by Smallbone et al. The conditions of the automaton is stored in 5 matrices of size height x width. Each one holds information on one of the five variables: cell state, ATP, glucose, hydrogen (pH) or oxygen. The first matrix contains information of the state of the cell in each element. An element can be empty, contain healthy cell, or contain a tumour cell in one of seven states. A tumour cell can be hyperplastic, glycolic, acid-resistant or any combination of the three.

The automaton is initialised and updated according to the following structure:

**A – Initialise conditions**

Set up 5 matrices of size height x weight:

1. State: all elements ‘empty’ except the bottom row, which are marked as 1 (or normal cells).
2. ATP: All elements with state > 0 marked as a=1. Otherwise a=0.
3. Glucose: All elements with state > 0 marked as g=1. Otherwise g=0.
4. Oxygen: All elements with state > 0 marked as c=1. Otherwise c=0.
5. Hydrogen: All elements marked as h=0.

*Input:* params.

*Output:* Matrices(state,ATP,glucose,oxygen,hydrogen).

**B – Cellular Automata**

Implement changes in cell state (cell division, metabolism, death and evolution).

*Inputs:* ATP, hydrogen, state, oxygen, params.

*Outputs:* state.

**C – Update ATP matrix**

Calculate new ATP levels for each element depending on the new states of each element.

*Inputs:* glucose, oxygen, state.

*Outputs:* ATP.

**D – Update X matrix, where X = glucose, oxygen or hydrogen**

Calculate new X levels for each elements depending upon the new state of each element and the diffusion boundary conditions.

*Inputs:* state, boundary conditions

*Outputs:* X

**E – Plot results**

Graphical display of each matrix to represent the distribution of cells and metabolites.

The input parameters (params) were selected such that they could be changed upon each running of the model. They can be checked and edited in the file setParams.m. Below are all important variables listed in alphabetical order for reference:

a0 : Minimum ATP for a cell to survive.

ATP : Matrix containing cellular ATP levels.

c : Oxygen level.

dc : Diffusion coefficient for oxygen.

vec\_delta : Used to describe eq.(16), used in the paper by Smallbone et al.

dg : Diffusion coefficient for glucose.

Glucose : Matrix containing cellular glucose levels.

height : Height of the grid.

hypl : Cells in hyperplastic state.

hyplgly : Cells in hyperplastic and glycolytic state.

hyplglyar : Cells in hyperplastic, glycolytic and acid-resistant state.

hn : Normal cell acidity threshold.

ht : Tumour (acid-resistant) cell acidity threshold.

Hydrogen : Matrix containing cellular acidity levels.

k : Glycolytic rate constant.

na : Number of ATP molecules produced during complete oxidation.

Niter : Number of iterations.

Oxygen : Matrix containing cellular oxygen levels.

pa : Adaptation rate.

phiOxygen : Rate of oxygen uptake by cells.

phiGlucose : Rate of glucose uptake by cells.

u : Random number generated to determine any probabilistic change of state (cell division or cell death).

width : Width of the grid.

y : Matrix of 0s and 1s to describe any changes of state (cell division or cell death).

Our code utilises the equations outlined by Smallbone et al. to determine changes to cell state and metabolite levels. During each time-step, a cell may divide or die. The probability of dividing, *p*div, is proportional to a0, or a0. The probability of cell death due to acidity levels, *p*dea, is proportional to hn, or *h*n, in normal cells and ht, or *h*t, in acid-resistant cells. The probabilities are defined below:

Hydrogeni,j/*h*n in a normal cell, if Hydrogen<*h*n,

*p*dea = Hydrogeni,j/*h*t in an acid-resistant cell, if Hydrogen<*h*t,

1 otherwise.

(ATPi,j – a0)/(1 – a0) a0<ATP<1,

*p*div=

1. ATP≥1.

These are equivalent to equations (3) and (4) in Smallbone et al.’s paper.

If division is to occur, the new cell will appear in an empty neighbouring element. If there are no empty neighbouring elements then no division occurs. If there is more than one empty space the new cell goes to the element with the largest oxygen concentration. The two daughter cells have a probability of inheriting a one of the three mutations (hyperplasmia, glycolysis or acid-resistance) as defined by pa.

ATP is updated each time-step according to glucose and oxygen levels. In our model *n*a = 36 because 36 molecules of ATP are generated per glucose molecule during aerobic respiration (see equation (1) in the Smallbone et al. paper). We used an equivalent to equation (11) from the Smallbone et al. paper to determine cellular ATP levels:

ATP = Oxygeni,j + (2/*n*a)(phiGlucosei,j – Oxygeni,j).

The levels of oxygen, glucose and hydrogen are updated each time-step using a non-dimensionalised diffusion equation. The equation is based upon the steady-state approximation such that glucose levels can be assumed to be in diffusive equilibrium at all times. The equation uses the diffusion coefficient of the relevant metabolite, dg (or *d*g) for glucose and dc (or *d*c) for oxygen:

(*d*g2 ∇ξ2)\*x – phiX = 0, where x = Glucose or Oxygen,

and phiX = phiGlucose or phiOxygen.

Note that:

phiGlucose = Glucose i,j for normal cells.

phiGlucose = k \* Glucose i,j for glycolytic cells.

phiOxygen = c = Oxygen i,j. for all cells.

Equation () can be solved for Glucosei,j using a finite difference approximation:

Glucosei+1,j + Glucosei-1,j + Glucosei,j+1 + Glucosei,j-1 – (4 + δi,j)\*Glucosei,j = 0.

Where,

0 in a vacant cell,

δi,j  = 1/ *d*g2  in a normal cell,

k/ *d*g2 in a glycolytic cell.

Further details of these equations can be seen with equantions (16) and (17)

[A nice descriptive figure](http://www.nature.com/nrc/journal/v4/n11/fig_tab/nrc1478_F6.html)