OSTI Phase 1: A Cellular Automaton Model of Early Tumor Growth and Invasion

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Systems Biology DTC 2012

Name 1, 2, 3, 4, 5 (no particular order)

January 2013

Systems Biology DTC
University of Oxford

Contents

1 Introduction **1**

2 Methods **2**

2.1 Setup of Cellular Automaton 2
2.2 Rules of Cellular Automaton 3
2.3 Running the Simulation 3
2.4 Glucose Inversion Problem 4
2.5 Vessel Boundary Conditions 5
2.6 Numerical Approach 5

1 Introduction

by Jackie Ang

Cancer is a major cause of death worldwide and is defined as unregulated cell growth within a structure known as a tumour. Tumour growth can be classified into a few distinct stages, which are hyperplasia, dysplasia, in situ carcinoma and finally invasive cancer. As tumours are made up of rapidly dividing cells, they require high amounts of oxygen and glucose for survival and cell division. This rapidly overwhelms the ability of normal blood vessels to provide these nutrients and leads to angiogenesis within the tumours as well as the death of both normal cells as well as cells in the interior of the tumour. Also, as a consequence of hypoxia within the tumour, cells switch to using anaerobic respiration and release lactic acid into the extracellular environment. This causes a decrease in the pH in the environment within and around the tumour and also leads to necrosis.

Cellular automata has a long history of usage to model the growth and development of tumours. In this investigation by A.A. Patel et al, a hybrid cellular automaton was used to model an early stage of tumour growth. The cellular automaton assumes tumour avascularity and a random distribution of blood vessels in a tissue, which is true for pre-angiogenic tumours. The model includes variables for glucose and lactic acid concentration. It however, does not include a variable for oxygen concentration as the author is focusing on the effects of acidification of the microenvironment rather than hypoxia. It was shown[1] that anaerobic respiration in tumour cells persists even in high levels of oxygen and tumour cell viability is independent of oxygen levels[2].

2 Methods

by Jackie Ang et al.

2.1 Setup of Cellular Automaton

A two-dimensional cellular automaton was set up to model this tumour growth. This was made up of a N by N array of elements with a value corresponding to the state of each point. This state describes the occupation status of each point, with values corresponding to dividing normal cell, quiescent normal cell, dividing tumour cell, quiescent tumour cell, blood vessel and unoccupied element. Two other N by N arrays of elements with positional conservation to the first array were also created to represent the glucose and lactic acid concentrations of each individual automaton element. This differs from the authors in that they created a matrix of state-vectors each containing four components which correspond to the same variables, but leads to the similar results.

The author also mentioned one of the four above components as ghost values used only on elements occupied by vessels to enforce gradient boundary conditions at the four walls of the vessels. However, this has been covered In our program by fixing the glucose and lactic acid concentrations in elements occupied by vessels and not allowing them to change during the process of running the cellular automaton.

The cellular automaton was populated with a user defined microvessel density ϕ_v where

$$\phi_v = \frac{N_v}{N^2} \tag{2.1}$$

where N_v is the number of vessel elements inside the automaton.

The program situates the vessel elements randomly, subject to the condition that any given tumour cell or normal cell element can only border zero or one vessel element. This is because if a cell element borders two or more vessels, the value of the glucose and lactic concentrations would be too strongly affected by the multiple boundary conditions imposed by the vessels.

All other elements within the cellular automaton were then populated with dividing normal cells. Following this, a disc shaped group of dividing tumour cells with a user defined diameter is introduced in the centre of the automaton grid, replacing any normal cells or vessels previously there.

The other two N by N arrays are then populated with starting values for glucose and lactic acid concentrations. For glucose concentrations, a glucose profile is generated based on the diffusion equations and the position of the vessels before the insertion of any non-vessel cells. The glucose concentration at vessels however, is kept constant at $G_s = 5.0mM$. The lactic acid concentration is initialised at all elements at $H_s = 3.98 \cdot 10^{-5}mM$. This lactic acid concentration corresponds to a pH of 7.4 in the extracellular environment. Within

the simulation, assumptions are made that lactic acid is the sole acid responsible for pH changes in the model, none of the lactic acid is neutralised and the pKa of lactic acid is constant.

2.2 Rules of Cellular Automaton

There are several rules for this cellular automaton as described below

1. Elements occupied by microvessels do not change in status, glucose and lactic acid concentrations in the entire simulation.
2. Normal cells and tumour cells cannot evolve into other forms of cells. They can only change status from dividing to quiescent or vice versa. They may also die and this results in a vacant element.
3. If the occupancy of an automaton element is with a normal cell or tumour cell, after each updating of glucose and lactic acid concentrations of elements, if the local glucose concentration is below G_N^D or G_T^D, which were both defined to be 2.5mM, the cell dies and the occupancy becomes vacant.
4. If there is enough glucose, the local lactic acid concentration of the individual elements is then checked. For normal cells, if the local lactic acid concentration exceeds H_N^D, defined as $1.58 \cdot 10^{-4} mM$ (pH 6.8), it dies. Otherwise if the concentration of lactic acid is between H_N^Q, defined as $7.94X10 - 5mM$ (pH 7.1) and HDN, the cell survives but becomes quiescent. For tumour cells, if the local lactic acid concentration is above H_D^T, defined as $1 \cdot 10^{-3} mM$ (pH 6.0), it dies. Otherwise if the concentration of lactic acid is between H_T^Q, defined as $3.98 \cdot 10^{-4}$ (pH 6.4) and H_T^D, it survives but becomes quiescent.
5. If the cell survives and is still actively dividing, it will be allowed to reproduce. This can only occur if there is a vacant element adjacent to the cell and can only occur once per cell even if there is more than one vacant element adjacent to the cell. If there is more than one vacant neighbour, the neighbouring element with the highest glucose concentration will receive the daughter cell.

2.3 Running the Simulation

While there is a large disparity in the timescales of cell division(10^2 hours) and diffusion of glucose and lactic acid(10^{-2} hours) between cells, the author has attempted to reconcile this difference by stating that the cellular distributions of nutrients and by products do not change after reaching a steady state quickly and changes in cell status can be treated as perturbations on the chemical distributions. He has also addressed the problem of all cells responding simultaneously to changes in chemical distributions by advancing the automaton in a series of sub-generations. A generation is defined as the time taken for all the elements within the automaton to be updated. For the purpose of the simulations, a generation consists of 10 sub-generations.

Within each sub generation, a random subset (a tenth) of non-vessel automaton elements are selected for updating. The update follows the following order:

1. The glucose and lactic acid concentrations within the element are updated according to the solution of the equilibrium boundary value problems.
2. The resultant concentrations are checked against threshold values to determine if the status of elements containing normal or tumour cells changes.
3. Normal and Tumour cells are checked for potential of cell division and cell division occurs if applicable.

2.4 Glucose Inversion Problem

EDIT, EDIT, EDIT! pH should probably be added in the gluc section. Adapt variable names to code, etc.

The problem is to obtain a spatial solution of a steady state diffusion equation

$$D_G \nabla^2 G(\mathbf{r}) - k(\mathbf{r}) G(\mathbf{r}) = 0 \tag{2.2}$$

for G. Here, D_G is a scalar and G, K are an $N \times N$ matrices. We want to solve this equation for the glucose concentration $G(\mathbf{r})$, i.e. on an $N \times N$ domain, with periodic boundary conditions.

I don't know about the level of rigor but maybe define G in V^2 and in an orthonormal basis $\{\mathbf{e}_k\}$

$$G = G_{i,j} \mathbf{e}_i \otimes \mathbf{e}_j \tag{2.3}$$

so you can properly talk about indices. The periodic boundary condtions for the first index are

$$\begin{aligned} G_{0j} &\longrightarrow G_{Nj} \\ G_{N+1,\,j} &\longrightarrow G_{1,\,j} \end{aligned}$$

and the same for index. The cell distribution is expressed through the matrix $k(\mathbf{r})$ in terms of scalar values as

$$k(\mathbf{r}) = \begin{cases} k_N & \forall \mathbf{r} = \text{Normal Cells} \qquad 1 \cdot 10^{-6}/s < k_N < 5 \cdot 10^{-4}/s \\ k_T & \forall \mathbf{r} = \text{Tumor Cells} \qquad 1 \cdot 10^{-5}/s < k_T < 1 \cdot 10^{-3}/s \\ 0 & \forall \mathbf{r} = \text{Vacant Cells} \qquad \text{no vacant cells at simulation startup} \\ 0 & \forall \mathbf{r} = \text{Vessel Cells} \end{cases} \tag{2.4}$$

The discretisation of (2.2) in terms of finite differences can be written as

$$\frac{G_{i+1,j} + G_{i-1,j} + G_{i,j+1} + G_{i,j-1} - 4G_{i,j}}{\Delta^2} - \frac{k_{i,j} G_{i,j}}{D_G} = 0 \tag{2.5}$$

where $D_G = 9.1 \cdot 10^{-5} cm^2/s$ where $\Delta^2 \approx (20\mu)^2$ is a rough approximation for cell size, i.e. an automaton element. At this point, we have set up the system fully except for the vessel boundary conditions.

2.5 Vessel Boundary Conditions

The reason why 2.5 unfortunately cannot be written as a linear system $DG = K. * G$[1] is the vessel boundary conditions. If a vessel is placed at i, j (corresponding to $k_{ij} = 0$ since no vacant at startup, see 2.4) then G_{ij} cannot be accessed and therefore 2.5 must be modified.

If, for instance, a cell (i, j) has a vessel to its right $(i, j-1)$, the latter cannot be accessed.

$$\frac{G_{i+1,j} + G_{i-1,j} + G_{i,j+1} - 4G_{i,j}}{\Delta^2} - \left(3 + \frac{\Delta^2 k_{i,j} + q_G \Delta}{D_G}\right) G_{i,j} = -\frac{q_G \Delta}{D_G} G_S \tag{2.6}$$

where G_S is the serum glucose value $G_S \approx 5.0mM$ and the permeability of the vessel wall is $q_G \approx 3.0 \cdot 10^{-5} cm/s$.

2.6 Numerical Approach

In order to be able to manipulate elements corresponding to G_{ij} individually, we construct an $N^2 \times N^2$ matrix D and reformulate the $N \times N$ matrix G into a column vector $\mathbf{g}$ with N^2 elements. More precisely, if

$$G^T = (\mathbf{G}_1 \quad \mathbf{G}_2 \quad \cdots \quad \mathbf{G}_N) \qquad G^T \text{ is } N \times N \tag{2.7}$$

we choose

$$\mathbf{g} = \begin{pmatrix} \mathbf{G}_1 \\ \mathbf{G}_2 \\ \vdots \\ \mathbf{G}_N \end{pmatrix} \qquad \mathbf{g} \text{ has } N^2 \tag{2.8}$$

$$\begin{pmatrix} \\ \\ \\ \end{pmatrix} \begin{pmatrix} G_{11} \\ \vdots \\ G_{1N} \\ G_{21} \\ \vdots \\ \\ \end{pmatrix} = \begin{pmatrix} \mathbf{G}_1 \\ \\ \\ \end{pmatrix} \tag{2.9}$$

[1] meaning $(DG)_{ij} = D_{im} G_{mj}$ and $(K. * G)_{ij} = K_{ij} G_{ij}$, not sure how to express that mathematically, I am just using Matlab element wise notation ;-)