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AN IMPROVED MODEL OF TUMOUR-IMMUNE SYSTEM INTERACTIONS

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Abstract. The immune system plays an important role in defending the body against tumours and other threats. Currently, mechanisms involved in immune system interactions with tumour cells are not fully understood. Here we develop a mathematical tool that can be used in aiding to address this shortfall in understanding. This paper describes a hybrid cellular automata model of the interaction between a growing tumour and cells of the innate and specific immune system including the effects of chemokines that builds on previous models of tumour-immune system interactions. In particular, the model is focused on the response of immune cells to tumour cells and how the dynamics of the tumour cells change due to the immune system of the host. We present results and predictions of *in silico* experiments including simulations of Kaplan-Meier survival-like curves.

Keywords and Phrases: hybrid cellular automata, tumour, chemokine, immune, dendritic cell, cytotoxic T lymphocyte.

1. INTRODUCTION

Cancer is one of the leading causes of death worldwide, with 7.9 million people dying as a result of cancer in 2007 alone. This is projected to rise to 12 million by 2030 (see `http://www.who.int/cancer/en`, [13]). A similar report (see `http://www.aihw.gov.au/`, [1]) states that in Australia in 2007, cancer was the second most common cause of death and that $108,368$ new cases of cancer were diagnosed. For those diagnosed, the relative survival between 1998 and 2004 for all cancers combined was 61%. Clearly, cancer is a major concern for public health officials around the world and a greater understanding of cancer has potential to save many lives.

There is strong evidence in the literature for the hypothesis that tumour growth is directly influenced by the cellular immune system of the human host. For example, Sandel *et al.* [12] discuss the influence of dendritic cells in controlling prostate cancer. Furthermore, tumour infiltrating dendritic cells (DCs) are a key factor at the interface between the innate and adaptive immune responses in malignant diseases. While the interactions of a tumour and the host immune system have been modelled previously by, for example, Mallet and de Pillis [9] and de Pillis *et al.* [4], here we present the first multidimensional, hybrid cellular automata model of the process that incorporates important signalling molecules.

Hart [7] states that dendritic cells (DCs), found in many types of tumours, are the dominant antigen presenting cells for initiating and maintaining the host immune response. They are critical in activating, stimulating and recruiting T lymphocytes: cells with the ability to lyse tumour cells. DCs have numerous states of activation, maturation and differentiation. Natural killer (NK) cells and cytotoxic T lymphocyte (CTL) cells also play important roles in the response of the immune system against the tumour as described in Kindt *et al.* [8].

The dynamics of tumour growth and the interactions of growing tumours with the host immune system have been studied using mathematical models over the past four decades. Most of these models are presented using ordinary differential equations (ODEs) or partial differential equations (PDEs) that impose restrictions on the modelled system's time-scales, as described in Ribba *et al.* [11]. However, a cellular automata (CA) model can describe more complex mechanisms in the biological system without such restrictions by detailing phenomena at the individual cell or particle level. The classic definition of a CA model holds that they involve only local rules that depend on the configuration of the spatial neighbourhood of each CA element. Hybrid cellular automata (HCA), on the other hand, extend the CA to incorporate non-local effects, often via coupling the CA with PDEs.

The purpose of the model developed in the present research is to investigate the growth of a small solid tumour, when the growth is affected by the immune system. In this preliminary study, we present a hybrid cellular automata model of the interaction between a growing tumour and cells of the innate and specific immune system that also includes generic signalling molecules known as chemokines. Chemokines are a family of small cytokines, or proteins secreted by many different cell types, including tumour cells. They can affect cell-cell interactions and play a fundamental role in the recruiting or attracting cells of the immune system to sites of infection or tumour growth.

To include the effect of a chemokine in this model, we recognise the significantly smaller size of such molecules compared with biological cells and introduce a partial differential equation to describe the concentration of chemokine secreted by the tumour. We combine the analytic solution of the partial differential equation model with a number of biologically motivated automata rules to form the HCA model. We use the hybrid cellular automata model to simulate the growth of a tumour in a number of computational 'cancer patients'. Each computational patient is distinguished from others by altering model parameters. We define 'death' of a

patient as the situation where the cells of the tumour reach the boundary of our model domain; effectively this represents tumour metastasis.

In the sections to follow, we present the development of the HCA model before analysing numerical simulations. We conclude with a discussion of the results and conclusion.

2. MATHEMATICAL MODEL

We investigate the growth of a solid tumour and its interaction with the host immune system and a tumour-secreted chemokine. The model is comprised of a partial differential equation to describe the chemokine secreted by the tumour, coupled with a discrete, stochastic cellular automata describing individual cells. We employ a square-shaped computational domain of length L, which is partitioned into a regular square grid. Each square element in the grid represents a location that may contain a healthy cell, tumour cell or immune cell.

We consider a number of biological cell types including normal healthy cells, tumour cells (necrotic, dividing and migrating), DCs (mature and immature), NK cells and CTL cells. To build the CA model, we define 'rules' that draw upon the biological literature to describe cell-cell interactions, cell effects on the environment, and effects of the environment on cells.

Initially, non-cancerous healthy cells cover the whole of the model domain, then the tumour mass is allowed to grow from one cancer cell placed at the centre cell of the grid. Cells of the host immune system are spread randomly over the domain throughout the other healthy cells. Three separate immune cell populations are considered here – the CTL cells of the specific immune response and cells of the innnate immune system, represented by the NK cells and DCs.

The model solutions are progressed via discrete time steps, at which each spatial location is investigated to determine its contents and whether or not actions will occur. This is summarised in Algorithm 1.

Algorithm 1 Brief pseudocode for the overall algorithm.

    Draw parameters for current computational patient
    Initialise domain
    for each time step **do**
        for each CA element **do**
            Determine cell type in element
            Characterise neighbourhood of element
            Test whether event will occur and update state
        end for
    end for
    Export data

2.1. **Cellular Automata Rules.** Each particular cell-level action is associated with a probability of success, P_{event}, that is compared with a pseudo-random number, r, drawn from the uniform distribution on the interval $[0, 1]$ to determine whether or not it is carried out. To describe the evolution of the cell population, we introduce the general algorithm of cellular automata rules as presented below.

Algorithm 2 Pseudocode for testing occurrence of individual events.

Draw $r \sim U[0, 1]$
Calculate P_{event} using current state of CA
if $r < P_{\text{event}}$ **then**
    update state (the event occurs)
end if

2.1.1. *Host cells.* As described in the work of Ferreira *et al.* [5] and of Mallet and de Pillis [9], we assume that the healthy host cells are effectively passive bystanders in the interaction. They do not hinder the growth of the tumour cells or the movement of any cell type.

2.1.2. *Tumour cells.* In this model, we consider tumour growth to be influenced by the immune system via NK cells, CTL cells and DCs. The tumour cells undergo the processes of division, migration and lysis resulting from interaction with the immune system. We assume that NK cells, CTL cells and mature dendritic cells can directly kill the tumour cells. At each time step, the neighbourhood of each tumour cell is surveyed to determine whether the cells of the immune system are present or not. If they are, the tumour cell will be killed by the immune system whereas if there are no immune system cells in the neighbourhood then the tumour cell is marked for potential division or migration. Following this, a stochastic rule is checked to determine whether or not the action will be carried out. The probability of tumour division that depends on the density of tumour cells in the neighbourhood of the dividing cell has the form as follows

$$P_{\text{div}}^{\text{tmr}} = \exp\left(-\left(\theta_{\text{div}} T_{\text{sum}}\right)^2\right),$$

where θ_{div} controls the shape of the curve allowing it to capture qualitative understanding of the biology and T_{sum} is the number of tumour cells in a one cell radius of the cell of interest. From Figure 1(a), it can be seen that tumour cell division is more likely when there is space in the neighbourhood for the resulting daughter cell.

The probability of tumour lysis depends on the strength of the immune system in the neighbourhood of the tumour cell (see Figure 1(b)), and is given by

$$P_{\text{lysis}}^{\text{tmr}} = 1 - \exp\left(-\left(\theta_{\text{lysis}} I_{\text{sum}}\right)^2\right),$$
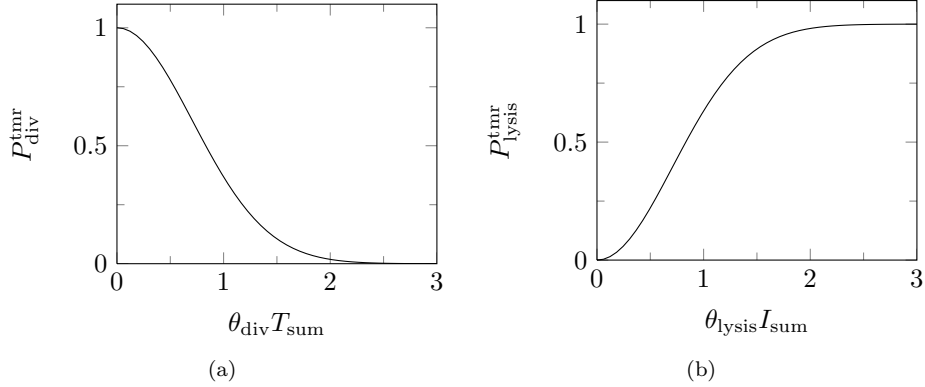
FIGURE 1. The form of the curves used to determine the probability of (a) tumour cell division and (b) tumour cell lysis, given different neighbourhood conditions.

where again θ_{lysis} controls the shape of the curve allowing it to capture qualitative understanding of the biology and I_{sum} is the number of immune cells in a one cell radius of the cell of interest.

2.1.3. *Immune System.* At each time step, the neighbourhood of each immune cell is surveyed to determine whether the tumour cells are present. If tumour cells are present, the immune system will kill the tumour cells in the manner described above. If there are no tumour cells in the neighbourhood of the CTL cells, then the CTL cells move towards areas of higher chemokine concentration.

To control the normal background level of CTL cells, at each time step there is a chance that healthy cells are replaced (from outside the computational domain) by new immune cells. This is carried out by imposing a probability of healthy cell replacement with a CTL, given by

$$P_{\text{rep}}^{\text{CTL}} = \text{CTL}_0 - \frac{1}{n^2} \sum_{\text{domain}} \text{CTL}_{i,j}, \tag{1}$$

where CTL_0 is the 'normal' density of CTL cells and n^2 is the total number of CA elements.

NK cell and dendritic cell have similar rules to CTL cells, except that NK cells and mature dendritic cells can lyse the tumour cell only once. When immature dendritic cells come in contact with tumour cell it becomes a mature dendritic cell that has the ability to kill the tumour cell.

2.2. **Chemokine Equation.** To include the effect of a chemokine in this model, we use a partial differential equation to describe the evolution of the concentration of chemokine throughout the model domain. We combine the analytic solution of the partial differential equation with a number of biologically motivated automata

rules as described above. The equation for the concentration of chemokine is given by

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right), \tag{2}$$

where $C(x, y, t)$ represents the chemokine concentration, D is the diffusion coefficient of the chemokine, x and y represent the spatial variables along the horizontal and vertical axes, and t represents time. The initial condition is given by

$$C(x, y, 0) = f(x, y), \quad 0 < x < b, \quad 0 < y < c,$$

where $b = c = 1\,\text{mm}$. For all four boundaries of the domain, we set $C = 0$.

Using the boundary conditions as presented above along with an unspecified initial condition, equation (2) is exactly solvable using separation of variables, with a solution given by

$$C(x, y, t) = A_{m,n} \exp\left(-D\left(\frac{m^2\pi^2}{b^2} + \frac{n^2\pi^2}{c^2}\right)t\right) \sin\left(\frac{m\pi x}{b}\right)\sin\left(\frac{n\pi y}{c}\right),$$

where

$$A_{m,n} = \frac{4}{bc}\int_0^c \int_0^b f(x, y)\sin\left(\frac{m\pi x}{b}\right)\sin\left(\frac{n\pi y}{c}\right)\,\mathrm{d}x\,\mathrm{d}y.$$

For the present study, initially, a tumour cell placed in the middle of the grid and is assumed to secrete a chemokine. The initial value of the chemokine concentration is therefore a function of the form

$$f(x, y) = \exp(-0.5((x - b/2)^2 + (y - c/2)^2)). \tag{3}$$

Chemokines then start to diffuse from the centre to the whole domain and attract the immune system to the site of tumour. This represents the behaviour of chemokines, such as is described by Allavena *et al.* [2] and Murooka *et al.* [10]. For the initial condition given in equation (3) we have numerically integrated using MATLAB's in-built adaptive Simpson quadrature to obtain $A_{m,n}$.

3. RESULTS

We combine the solution of the PDE with the CA as described in Section 2 to simulate the evolution of the growing tumour. A two-dimensional regular 100×100 square domain is used with 100 cell cycles and a Moore neighbourhood is considered for the cellular automata rules. In this simulation, an estimated value of diffusion coefficient for chemokine, D, is $10^{-4}\,\mu\text{m}^2\text{s}^{-1}$. The distribution of the growing tumour after 50 and 100 cell cyces is shown in Figure 2(a), with results qualitatively matching those of Mallet and de Pillis [9].

Figure 3(a) shows the evolution of the tumour cell and necrotic cell densities over 100 cell cycles. This plot shows the characteristic exponential and linear growth phases of solid, avascular tumours (see for example, Folkman and Hochberg [6]), as well as a slower growing population of necrotic cells. In 3(b) we see that initially,
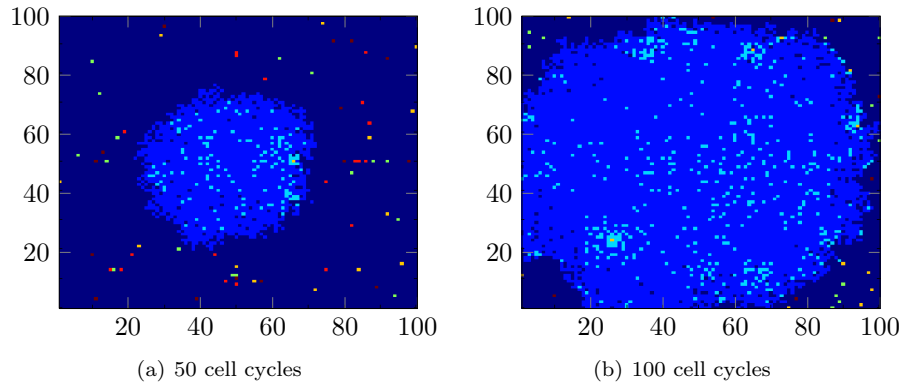
(a) 50 cell cycles   (b) 100 cell cycles

FIGURE 2. The growing tumour and host immune system.

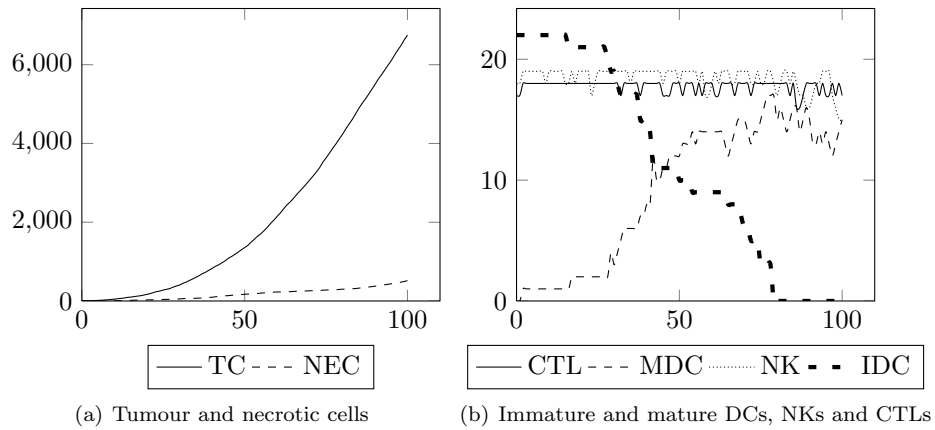(a) Tumour and necrotic cells   (b) Immature and mature DCs, NKs and CTLs

FIGURE 3. Total cell counts after 100 cell cycles.

the number of mature dendritic cell is zero until immature dendritic cells come in contact with tumour cells, at which point the matured dendritic cells commence killing the tumour cells. After around 80 cycles, all immature dendritic cells have matured and the number of mature dendritic cells stabilises. As expected, due to the nature of equation (1), the populations of NK cells and CTL cells remain approximation steady over the extent of the tumour growth.

We also use the hybrid cellular automata model to investigate the growth of a tumour in a number of computational 'cancer patients'. Each computational patient is distinguished from others by altering model parameters. We define 'death' of a patient as occurring when the tumour is able to metastasise. Effectively, this is when the cells of the tumour reach the boundary of our model domain. We present the results of these simulations using a simulated Kaplan-Meier survival curve,
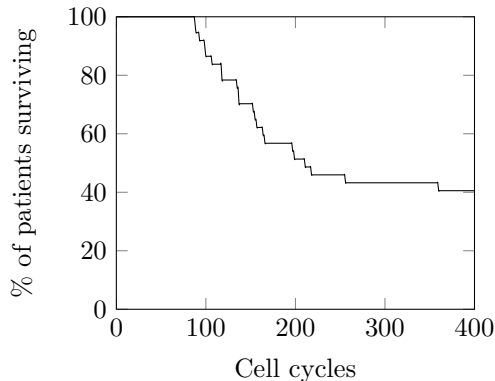
FIGURE 4. Simulated Kaplan-Meier curve.

shown in Figure 4. The figure shows that metastasis sets in for the first patients after 80 cycles. Metastasis of the simulated tumours occurred in approximately 60% of simulated patients after 250 cycles after which time most surviving patients exhibited dormant tumours being controlled by the immune system.

4. **CONCLUSION**

Duchting and Vogelsaenger [3] pioneered the use of discrete cellular automata for modelling cancer, investigating the effects of radio-therapy. Ferreira *et al.* [5] modelled avascular cancer growth with a CA model based on the fundamental biological process of proliferation, motility, and death, including competition for diffusing nutrients among normal and cancer cells. Mallet and de Pillis [9] constructed a hybrid cellular automata cancer model that built on the work of Ferreira *et al.* to include NK cells as the innate immune system and CTL cells as the specific immune system. The Mallet and de Pillis model lacked sufficient detail of the immune system and in this present research, we attempt to improve on their work by explicitly describing more of the host immune system. While direct comparison of the models is difficult, the results as described in Figure 3(a) qualitatively reflect the findings of Mallet and de Pillis and of Ferreira *et al.*.

While models based on differential equations allow for analytical investigations such as stability and parameter sensitivity analyses, and ease of fitting the model to experimental data, these types of models cannot capture the detailed cellular and sub-cellular level complexity of the biological system. On the other hand, HCA models can describe greater complexity of the biological process such as the interaction between every single cell. In current work complementary to the present research of this paper, we have included greater realism in the modelling of tumour-secreted chemokines by allowing secretion due to cell-cell interaction.

Currently, chemokines and their receptors in the tumour microenvironment are being extensively investigated to produce therapeutic interventions to combat cancer, (see for example, Allavena *et al.* [2] and Murooka *et al.* [10]). Our models currently under development will allow for simulation-based and theoretical investigations of such interventions.

We have developed a useful model that can be employed as a preliminary investigative tool for experimentalists who conduct expensive *in vitro* and *in vivo* experiments to test and refine hypotheses prior to entering the lab. With further cross disciplinary collaboration, this type of model can be refined to provide a more accurate description of the underlying cancer biology and hence yield more relevant predictions and tests of hypotheses. Future developments based upon this model will be related to the specific context of colorectal cancer, and the effect of chemokines on the cell-cell interactions will be deeply investigated. More complex partial differential equations related to chemokines secretion resulting from cell-cell interactions will be introduced in future work.

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