The Use of Hybrid Cellular Automaton Models for Improving Cancer Therapy

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Abstract. The Hybrid Cellular Automata (HCA) modelling framework can be an efficient approach to a number of biological problems, particularly those which involve the integration of multiple spatial and temporal scales. As such, HCA may become a key modelling tool in the development of the so-called integrative biology. In this paper, we first discuss HCA on a general level and then present results obtained when this approach was implemented in cancer research.

1 Introduction

Traditionally, mathematical modelling of biological problems has focused on the integration of the most crucial properties of the phenomenon under study into a model formulated in terms of continuum ordinary differential equations (ODEs) and/or partial differential equations (PDEs) [23]. However, these methods impose a significant restriction on the modelled system's time-scales.

Physiologically-structured models [11,6] are one of the many approaches proposed to cope with this problem. In this paper we will focus on the hybrid cellular automata (HCA), a multiple scale individual-based framework for modelling biological processes.

The paper is structured as follows. In Section 2, biological complexity and complexity in cancer are introduced as limitations to the traditional modelling approach. In Section 3, we give a general introduction to the HCA framework and its uses in biology, focusing on its integrative capabilities. In Section 4, we focus on a particular application of the HCA framework, namely evaluation of the efficiency of CHOP chemotherapy on non-Hodgkin's lymphoma.

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2 Biological Complexity and Complexity in Cancer

Biological complexity has been recognized as a limitation to the current mathematical research approach, particularly in areas such as physiology, molecular biology and genetics [29]. Complexity in pathophysiology and therapeutics may be due in part to the diversity of the levels of our knowledge: gene, molecular, cellular, tissue, organ, body and population. All entities of a living organism interact through quantitative functional relations with time scales varying from nanoseconds to the organism's lifespan. This observation has led to the development of so-called systemic or integrative biology [16] and to the exploration of new methodologies [21], which might be more appropriate for studying complex and heterogeneous diseases such as cancer.

It is necessary to understand the many intricacies of cancer in order to design efficient treatment. Many approaches to anticancer treatment have had limited success. Certain biological properties of cancer render it even more problematic than other complex diseases. One fundamental obstacle to cancer therapy is acquired tumor "robustness", i.e. a self-organizing system which builds resistance to treatment [17]. Another feature is the multitude of intricate pathways for signal transduction. Though intermediates of multiple signalling pathways have been identified, understanding their function has proved to be an extremely difficult task [18]. The increasing evidence of cross-talk between pathways via signal transactivation adds an additional degree of complexity which is difficult to incorporate into traditional modelling approaches. Only fully integrative descriptive methods, capable of dealing with multiple scales, may assess disease and afford reliable treatment prediction. In this context, HCA models possess such capabilities.

3 HCA Modelling of Biological Processes

Cellular automata (CA) models have been applied to many areas of biology (see [14,22,1,4] for an overview). In recent years, a modification to the classic definition of CA has been introduced, yielding the so-called HCA.

The classic definition of CA involves only local rules for the evolution of the state of a given element: the transition rules that define the site dynamics depend only on the configuration of its spatial neighborhood. However, many biological processes depend upon non-local signalling cues or nutrients. Chemical cues and nutrients are usually diffusive substances, smaller than the typical cell.

Nutrient spatial distribution and various signalling processes play a fundamental role in tumor growth [12,24,5], as well as in developmental processes [20]. Therefore, in order to obtain an appropriate description of these processes in CA modelling, it is necessary to expand the original setup to incorporate these non-local effects. This expansion is the essence of the HCA framework, which constitutes a first step towards an integrative (multiple scale) approach to biology.

Given that molecules such as chemical cues and nutrients are usually small when compared to the size of a cell, they can be described in terms of continuous

fields that evolve according to appropriate reaction-diffusion equations (RDEs). Signalling cues are secreted by the cell's internal machinery in response to either internal or external stimuli and feed back at the population level, altering the observed macroscopic pattern. The macroscopic structure of the vascular system affects the nutrient supply to the cells. In turn, nutrient levels modulate internal cellular processes such as cell division [6]. The HCA concept has recently been expanded to take into account such intra-cellular processes [6,25].

The HCA approach has been adopted to study various aspects of tumor growth. The model proposed in [12] is formulated as a two-dimensional HCA (or, more precisely a lattice-gas model) and reproduces many of the features of avascular tumors *in vitro*, e.g. their layer structure. In [24], a hybrid CA model of tumor growth in the presence of native vasculature is proposed to analyze the role of host vascular density and tumor metabolism on tumor growth. It seems that unlike normal cells, which use aerobic metabolism, tumor cell metabolism is glycolytic. One by-product of glycolysis is increased acidity. Since tumor cells are more resistant to acidity than their normal counterparts, it appears that cancer uses the glycolytic phenotype (which produces H^+ ions) in order to increase its invasiveness. Several results regarding the interplay between vessel density, increased acidity, and tumor progression were obtained in this study. One of the most significant conclusions is the existence of a sharp transition between states of initial tumor confinement and efficient invasiveness when H^+ production passes through a critical value. This phenomenon has been observed in the clinic [15]. Finally, studies proposed in [7,8] use HCA in order to obtain realistic models for blood flow dynamics.

Recently, HCA has been applied to study the effect of blood flow heterogeneity on tumor growth [5]. Oxygen reaches the tissues via the vascular system. Due to the highly complex nature of blood flow and its interaction with the structure of the vascular system, which is also affected by the metabolic needs of the surrounding tissue, blood flow appears to be highly heterogeneous. Consequently, the spatial distribution of blood-borne nutrients and drugs is also heterogeneous. This heterogeneity has significant implications on tumor growth [5] and therapy, as we will observe in the following sections.

In the next section, we will discuss a particular example of the application of HCA in order to evaluate the efficiency of current clinical protocols for CHOP therapy of non-Hodgkin's lymphoma.

4 CHOP Therapy for Non-Hodgkin's Lymphoma: Insights from an HCA Model

In this section, we present an application of HCA for assessing chemotherapy treatment for non-Hodgkin's lymphoma (NHL) [25].

NHL patients are currently treated with CHOP chemotherapy
(Cyclophosphamide, Doxorubicin, Oncovin, Prednisone) in which Doxorubicin

and Cyclophosphamide are the more active drugs [19]. CHOP is usually administered over a total of 6 to 8 cycles separated by 21-day intervals [10]. The relationship between this dosing interval and the efficiency of NHL CHOP treatment has not been systematically analyzed. However, theory suggests that the success of cancer chemotherapy is primarily determined by the frequency of drug administration [2,3].

4.1 Methods

A two-dimensional HCA-based mathematical model aimed at simulating the effect of Doxorubicin on NHL was developed. The model takes into account two key factors which influence the efficiency of drug delivery:

- coupling of NHL growth to the vascular network [31], which affects the structure of the blood vessels;
- blood flow heterogeneity which results from this diverse construction.

The domain corresponds to a 2 mm square tissue initially filled with NHL cells forming a random pattern, and composed of 110 vessels whose radii are subject to adaptation through vessel structural modification processes [5].

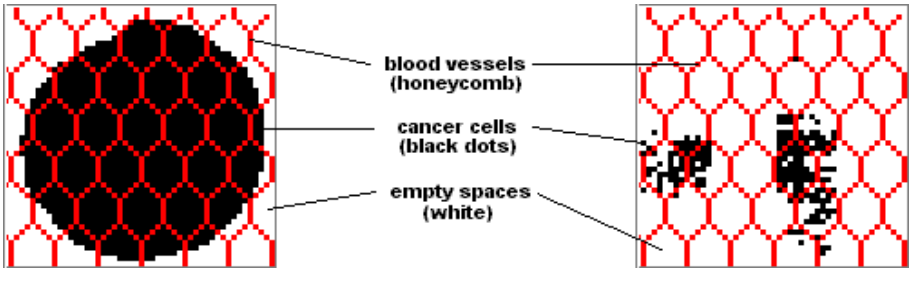

Fig. 1. Representation of NHL cells and the honeycomb-like vascular network on the computational domain (see [5]).
Left: a fully populated domain; Right: the domain following significant cell depletion.

The blood flow in each vessel is assumed to be laminar steady Poiseuille flow. For the dynamics of nutrient and drugs, the adiabatic approximation is applied, according to which chemicals (nutrient and drug) can be considered instantaneously in steady state. For drug pharmocokinetics (PK), i.e. decay of the blood-borne drug, a one-compartment model, in which the drug concentration in plasma over time declines exponentially, is considered. For drug pharmacodynamics (PD), i.e. effect of the extracellular concentration of drug on NHL cells, a simple logit relation is used for determining the probability for a cell to survive the drug. See the Appendix for the continuous model equations and [25] for further details.

The initial cell colony is composed of NHL cells divided into two categories: proliferative and quiescent cells.

To model cell division, a simple cell-cycle model is considered in which the duration of each phase of the cell-cycle was set according to various NHL-kinetic studies [9,13,27]. Each cell is assigned an age, which increases at each iteration. Thus, the cells progress through the different stages of the cell-cycle. Normal progression through the cell-cycle may be disrupted by lack of nutrient, leading to quiescence or cell death, or cells may be killed by the drug. A significant attribute of this model is the ability of the cell colony to influence vascular morphology. Normal vasculature is known to be well organized and endowed with smooth muscle cells and pericytes. This allows the vessels to adapt their structure to various mechanochemical stimuli [28]. Due to neovascularisation, cancer vessels are immature and therefore lack this structure. Consequently they are not able to undergo structural adaptation. Furthermore, cancer cells can destabilize established, mature vasculature, rendering it immature [31]. Therefore, in the model presented in [25] whenever a vessel is engulfed by cancer cells it is assumed that it loses its ability for adaptation and its radius is fixed at random. Vessels not surrounded by lymphoma cells retain the structural adaptation mechanism [5]. The status of all vessels (mature and immature) is updated at each time step.

The following CA rules hold for each cell and at each time step of the model.

- The probability of cell death is determined by the drug concentration and PD;
- If the cell is not killed by the drug, it advances one time step in its cycle phase;
- Between G1 and S-phase, the cell can either die, be arrested, or continue progressing through the cell cycle according to its local environment, i.e, local concentration of nutrient and over-crowdedness.
- If the environmental conditions are appropriate, the cell enters into G2 and divides, daughter cells moving towards higher nutrient concentrations.

4.2 Results

When the dynamics of a simulated NHL cell colony under CHOP chemotherapy were examined [25], a significant phenomenon was observed. After the initial effect of a drug application, the tumor begins to regrow at a steady and rapid rate. However, beyond a certain point, the cell colony's growth ceases to be stable and begins to display unpredictable oscillations of significant amplitude (see Figure 2). Blood flow heterogeneity appears to be a key factor in this result and its effect is illustrated in Figure 3, which compares cell recovery from a chemotherapy cycle when the vessel maturation/destabilization process is taken into account, compared to a case in which this assumption is relaxed [25]. Consequently, one of the conclusions from this study is that in order for treatment to be efficient, additional drug cycles must be administered before the tumor can enter the unstable stage of its regrowth. Note that we have considered a

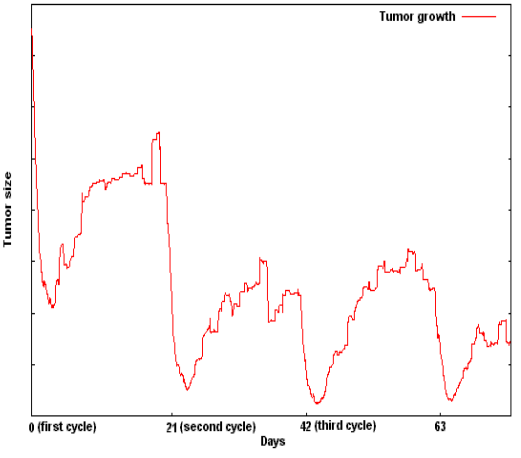

Fig. 2. Model prediction of tumor growth with Doxorubicin chemotherapy treatment cycles separated by 21 days.

regular hexagonal array of blood vessels which is unrealistic, in actual tumors the vasculature is very heterogeneous so we would expect the effects of blood flow heterogeneity to be even more pronounced.

The HCA framework has also been used to describe tumor structures in two pathophysiological settings in a study of which the purpose was to predict the efficacy of two different conventional strategies for chemotherapy intensification [26]. Results suggest the existence of a critical drug regimen intensity (CI) value, i.e. the ratio between the total dose administered and the duration of the treatment. If the regimen intensity is lower than CI, the tumor succeeds in recovering to its initial size over the duration of the dosing interval.

5 Conclusion

HCA can be viewed as an effective means of dealing with some of the problems raised by biological complexity. Through its ability to integrate different temporal and spatial scales, it constitutes a promising investigative tool for analyzing complex biological systems such as cancer and cancer therapy. In the example we presented, an HCA model has been used for investigating the efficacy of current and potential therapies of non-Hodgkin's lymphoma. Within the context of certain model assumptions, our results have raised relevant and interesting conclusions on the issue of treatment efficacy.

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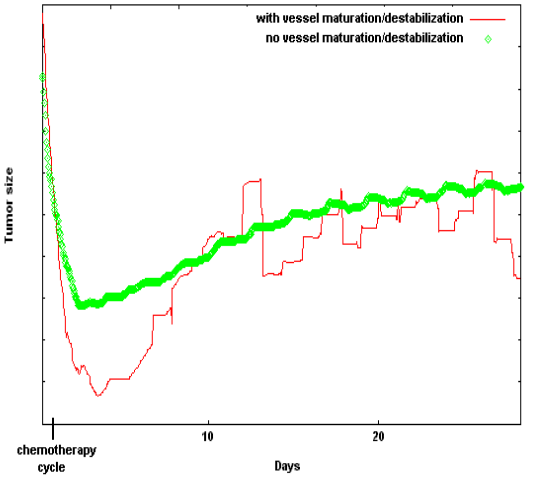

Fig. 3. Model prediction on the effect of vessel maturation/destabilization process on cell population recovery following a 10 mg/m^2 Doxorubicin administration.
Thin line: with vessel maturation/destabilization; Empty circles (thick line): no vessel maturation/destabilization is assumed.

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A HCA Model Equations

A.1 Blood Flow

Assuming Poiseuille flow, the flow rate ($\dot{Q}$) and resistance (Z) in each vessel are given respectively by:

$$\dot{Q} = \frac{\Delta P}{Z} \tag{1}$$

$$Z = \frac{8\mu(r,H)L}{\pi r^4} \tag{2}$$

where ΔP is the pressure drop between two points of the network, L, r, and H are respectively the resistance, length, radius, and hematocrit. μ is the radius and hematocrit dependent viscosity [5].

A.2 Vessel Structural Modification

We assume that the radius of each immature vessel (r_{im}) is modified at each time step according to the equation:

$$r_{im} = r_{mat} \cdot (1 + \epsilon) \tag{3}$$

where r_{mat} is the initial radius of the mature vessels, and ϵ is a random number uniformly distributed in the interval $(0, 3)$ according to [30].

A.3 Nutrient and Drug Diffusion

Assuming adiabatic conditions, the diffusion equation for the concentration ($C(x, y, t)$) of nutrient or drugs is given by:

$$K\nabla^2 C(x, y, t) - q(x, y) \cdot C(x, y, t) = 0 \tag{4}$$

where K is a diffusion coefficient and $q(x, y)$ the uptake coefficient at position (x, y).
On the vessel walls, we impose the boundary conditions:

$$-K\mathbf{n_w} \cdot \nabla C(x, y, t) = P \cdot (C_b - C) \tag{5}$$

where $\mathbf{n_w}$ is the unit vector, orthogonal to the vessel wall, C_b is the drug or nutrient concentration in the blood, and P the permeability of the vessel.
On the edges of the computational domain we impose no-flux boundary conditions:

$$n|_{\partial\Omega} \cdot \nabla C(x, y, t) = 0 \tag{6}$$

where $n|_{\partial\Omega}$ is the unit outward vector, orthogonal to the boundary of the domain.

A.4 Doxorubicin PK/PD

The decline of drug concentration in plasma (C_b) is given by:

$$\frac{\partial C_b}{\partial t} = -k \cdot C_b(t) \tag{7}$$

with initial condition:

$$C_b(0) = \frac{dose}{V_d} \tag{8}$$

where V_d is the volume of distribution of the drug, and k the fraction of drug which is eliminated from the compartment per unit time, inversely related to the half-life $t_{1/2}$:

$$k = \frac{ln(2)}{t_{1/2}} \tag{9}$$

The survival fraction SF (percentage of cells that survives the drug at each time step) is given by:

$$SF = \frac{a \cdot C_b(t)}{C_b(t) + Ec_{1/2}} \tag{10}$$

where $C_b(t)$ is the relevant drug concentration and a, $Ec_{1/2}$ are constants.
See [25] for model parameters and further details.