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A Hybrid Model of Tumor Growth Under Chemotherapy Medicine

Mohammed BENMIR^{*1,2}, Salma CHABBAR¹, Rajae ABOULAICH¹, Nabil ISMAILI²

¹Mohammadia School of Engineering, Mohammed V University in Rabat, LERMA,

¹ Avenue Ibn Sina B.P 765 Agdal, Rabat, 10090, Morocco

²Mohammed VI University of Health Sciences, Anfa City : Bld Mohammed Taïeb Naciri,

¹Commune Hay Hassani 82403 Casablanca, Morocco

*E-mail : med.benmir@gmail.com

Abstract

In this work we propose a hybrid model to simulate the evolution of a solid tumor. We consider a tumor under treatment and we use agent-based modeling to simulate the cells behavior while the diffusion of nutrients and drugs in the tumor environment is described using partial differential equations. The proposed model is implemented using NetLogo software and the partial differential equations are solved using a finite difference method and implemented using Python. The tests carried out give encouraging results and show that the number of tumor cells decreases under the effect of the chemotherapy and the size of the tumor decreases as well. This study offers an easy-to-use decision support tool for oncologists and clinicians.

Keywords

Hybrid tumor model ; PDE model ; Multi-agents simulation ; Chemotherapy medicine

I INTRODUCTION

Cancer is a major public health problem and one of the leading causes of death in the world. It is imperative to find promising clinical approaches to fight cancer based on new or existing therapies such as surgery, radiation therapy, hormone therapy, immunotherapy, cytotoxic chemotherapy and targeted therapy. These treatments depend on the type, location and grade of cancer, as well as the person's health and wishes. Chemotherapy is the use of drugs to treat a disease. Specifically, chemotherapy generally refers to the destruction of cancer cells using powerful chemicals.

The division and death of cells is regulated in an orderly way in the human body. However, in cancer, cell division and growth are out of control. As a result, damaged cells begin to occupy more and more space in a part of the body and push out useful healthy cells. This is how a tumor develops in that part of the body. The fight against these cancerous cells and the modification of their mode of production and accumulation is therefore a crucial question for medical science. Scientists have developed different methods for the treatment of cancer. The use of less invasive methods has always played an essential role in the treatment of patients. Chemotherapy, as a method of treating cancer, involves applying drugs that affect the ability of cancer cells to divide and reproduce. The drug weakens cancer cells and destroys them by applying it directly to the cancer site or by passing it through the bloodstream [1, 18, 19]. Mathematical modeling is a powerful tool for testing hypotheses, confirming experiments and simulating the

dynamics of complex systems. As well as helping to understand the mechanistic foundations of dynamic and complex systems. In the field of oncology in particular, these models can be calibrated using experimental or clinical data. Competing hypotheses of tumor progression can be combined and treatment options thoroughly analyzed before clinical intervention [5, 7, 8, 13]. Quantitative modeling techniques are numerous, and an increasing number of theoretical approaches are successfully applied to cancer biology.

Tumor growth models can be categorized into continuous models, discrete models, and hybrid models, which combine the strengths of discrete and continuous approaches. Continuous models are based on ordinary differential equations (ODE) or partial differential equations (PDE) to describe the tumor growth phenomenon [4, 17]. PDE models account for greater complexity than ODE models. By using cell densities and nutrient concentrations as state variables, PDE models can be used to analyze various spatio-temporal phenomena. However, in some situations, individual and agent-based modeling (ABM) approaches, which treat the cells as discrete objects with predefined interaction rules, may offer an improvement over differential equation methods. The ABM approach provides a natural description of a system as a form of computational science. ABM agents interact and influence each other, make individual decisions, learn from their experiences and adapt their behaviors. They are therefore better adapted to their environment. A number of ABM simulation packages have been developed and applied to cancer research, among them [9, 10, 16]. These packages have facilitated the overall process of developing an agent-based cancer model and also enabled computational oncologists to focus their time and energy on the specific cancer problems that interest them. The solid tumors develop in two distinct phases: the avascular phase and the vascular phase. Modeling the avascular phase of tumor growth and the vasculature of tumor angiogenesis has been covered widely in literature see [3, 6, 11, 12, 14, 15]. This work follows the work in [2], using an analogous approach, we propose a more complete model by considering a treatment by chemotherapy in the multi-agent environment.

This paper is organized as follows. In section 2, we present the diffusion-reaction equations for the oxygen and chemotherapeutic drug concentrations. Section 3 provides an overview of the hybrid tumor growth model under chemotherapy medicine using ABM and PDEs. The cell behavior is described using a multi-agent model in NetLogo where the oxygen and the drug treatment is diffused through the agent environment using the continuous diffusion equations to determine whether the environment is conducive to tumor cell survival and proliferation. In section 4, we present the results of the simulations that illustrate the impact of chemotherapy on tumor growth. Finally, in Section 5, we discuss our results and future research directions.

II DIFFUSION-REACTION MODEL FOR TEMPORAL-SPATIAL EVOLUTION OF OXYGEN AND CHEMOTHERAPEUTIC DRUG CONCENTRATIONS

To simulate the temporal-spatial evolution of oxygen and drug concentrations in tumor systems, we employ the following diffusion-reaction models.

2.1 Oxygen diffusion equation

To survive and multiply, the cells need nutrients and especially oxygen. Hypoxia occurs when a cell is deprived of oxygen. Severe hypoxia can lead to cell death [2, 20]. When faced with an unfavorable environment, a cell can transition to a quiescent resting phase where it stops multiplying and reduces its nutrients needs to survive waiting for the environmental conditions to become favorable again [2, 21]. Oxygen is therefore an important parameter in the dynamics

of cells. The equation for the diffusion of the oxygen concentration is based on the one proposed in [2].

$$\begin{cases} \partial_t C - \Delta C = \alpha(C_B - C) - \alpha_{cons}C \\ \partial_n C = 0 \\ C(t = 0, x, y) = C_0(x, y). \end{cases}$$

where C_B is the oxygen concentration in the vascular system, $\alpha(C_B - C)$ is the rate of oxygen concentration supplied by the vascular system and α_{cons} is the consumption rate of oxygen by the cells, which depends on the cell type such that quiescent cells have a lower oxygen consumption than other cells.

2.2 Chemotherapeutic drug diffusion equation

Chemotherapy drugs do not distinguish between healthy and cancerous cells. They can be divided into three classes. Class I drugs are non-phase specific and affect both quiescent and proliferating cells; class II drugs are phase specific and target only cells in a given phase; and class III drugs kill only proliferating cells [18]. In our work we treat the third class of drugs that kill only proliferating cells. The diffusion equation of the drugs in the cell environment is considered similar to that of oxygen as proposed in [1].

$$\begin{cases} \partial_t \phi - \Delta \phi = \beta(\phi_B - \phi) - \beta_{cons}\phi \\ \partial_n \phi = 0 \\ \phi(t = 0, x, y) = \phi_0(x, y). \end{cases}$$

where ϕ_B is the drug concentration in the vascular system, $\beta(\phi_B - \phi)$ is the rate of drug concentration supplied by the vascular system and β_{cons} is the consumption rate of drug by the cells, which also depends on the cell type such that quiescent cells have a lower drug consumption than other cells [1].

III HYBRID AGENT-BASED / PDE MODEL

In this section, a discrete cell population model based on the one in [2] where the cell behavior is described using ABM and combined with PDEs to describe the operating environment of the cells is presented. A schematic overview of the resulting hybrid tumor model is given in Figure 1.

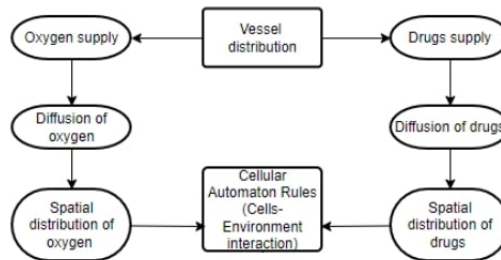


Figure 1: Schematic diagram of the hybrid model.

The governing rules for cell behavior are modeled using NetLogo software: a programming language and modeling environment for agent-based systems. The oxygen and chemotherapeutic drug equations are solved using a finite difference method in Python. The interaction between Python and NetLogo is ensured by an extension implemented in NetLogo which allows the exchange of data between the two programs.

The biological rules governing the cell behavior in Netlogo according to their environmental conditions are presented below.

3.1 Agent-based model

The tumor environment Ω in NetLogo is modeled as a square grid divided into patches where the agents move freely: $\Omega = \bigcup_k Patch_k$. The evolution of the tumor is followed in a time interval $[0, T]$. Each agent represents a cell. Three different cellular states are defined: the healthy state (S), the proliferative cancer state (P) and the quiescent state (Q). Necrotic dead cells are discarded. Oxygen and chemotherapeutic drug are diffused through Ω , each $Patch_k$ has its own level of oxygen and drug concentrations. The cells move freely within the patches and meet the biological criteria listed in the paragraph below.

3.2 Cellular automata rules

At each time iteration, two random numbers p_1 and p_2 in $[0, 1]$ are generated and the following rules are applied to each cell:

- A normal healthy cell S can divide at a rate λ_S if: $p_1 < \lambda_S$ and if, in the patch where it is located, there is sufficient oxygen and there is not a lethal concentration of drug.
- Healthy cells mitosis spawns a new healthy cell.
- S cell can mutate into P cell with a probability p_{mut} if $p_2 < p_{mut}$. Its mitosis rate is then multiplied by 10 to emphasize the uncontrolled proliferation of tumor cells.
- The conditions for the mitosis of a P cell are the same as for the S cell.
- P cells mitosis spawns a new P cell.
- Each of S and P cells need a level of oxygen $C_{S,P}$ in order to survive and proliferate. When it is in hypoxia:
 1. If it is a S cell: the cell dies and it will be destroyed.
 2. If it is a P cell: to model the uncontrollable nature of cancer cells, the P cell attempts to survive the unfavorable environment by transitioning to the quiescent state Q. It therefore stops dividing and its oxygen requirement is then reduced to C_Q to enable it to survive.
- Q cell can revert to being P cell if the environment becomes favorable in oxygen.
- A cell that remains quiescent for more than T_{max} iterations in a row will die of necrosis and will be destroyed.
- The class III drugs used only target multiplying cells and only have an effect on the proliferating cells when the lethal dose is reached. Therefore, they do not affect Q cells.
- If the concentration of drug in the patch reaches the drug's threshold ϕ^* : if it is a S or P cell, the cell dies while a Q cell is not affected.

3.3 Hybrid model implementation

The hybrid model makes use of the results of the oxygen and the chemotherapeutic drug diffusion equations in the agent-based model defined through the cellular automata rules. The model is similar to the one used in [2], but under chemotherapy and runs as follows :

- The first step is the initialization of the model on NetLogo:
 1. N healthy cells are created in the environment.
 2. Each $Patch_k$ is supplied with its initial oxygen concentration C_k^0 and initial drug concentration ϕ_k^0 .
 3. A specific $Patch_B$ is selected to hold the blood vessel supplying oxygen and drug to the environment
- At each time iteration t :
 1. The oxygen and the drug concentrations C_k^t and ϕ_k^t respectively, are collected from the patches and sent to Python as the initial conditions.
 2. $\partial_t C - \Delta C = 0$ and $\partial_t \phi - \Delta \phi = 0$ are solved in Python using a finite difference method.
 3. The new oxygen and the new drug concentration levels C_k^{t+1} and ϕ_k^{t+1} respectively, are sent back to NetLogo and redistributed to the patches.
 4. The environment is supplied with oxygen C_B from the vascular system through $Patch_B$.
 5. If the drug is administered, the environment is supplied with ϕ_B from the vascular system through $Patch_B$.
 6. The cells interact with their environment according to the cellular automata rules.
 7. The oxygen and the drug levels in each patch are reduced by the amounts consumed by the cells.

IV SIMULATIONS

For the simulations, we assign different colors to each cell depending on its type and to the background of the patches depending on their oxygen and drug levels. The S cells are blue, the P cells red and the Q cells brown. Patches have a gray shade proportional to their oxygen and drug concentration. A patch filled with oxygen or medication is white, while a patch with insufficient oxygen or a low level of medication is black.

We investigate how the dynamics of the normal and cancer cells change when a chemotherapeutic drug is introduced. We assume that the drug is continuously administered into the blood vessel. It diffuses through the tissue and is absorbed by all types of cells.

The initial setup used to test the response of our virtual tumor to different drugs is shown in Figure 2 and the numerical values of the parameters used are given in Table 1.

Symbol	Value	Unit
ϕ^*	0.20	$\mu M/iteration/cell$
$[C_S, C_P, C_Q]$	[0.0157, 0.057, 0.0032]	$\mu M/iteration/cell$
$[\phi_S, \phi_P, \phi_Q]$	[0.034, 0.034, 0.007]	$\mu M/iteration/cell$
T_{max}	20	iterations

Table 1: Summary of the parameters used in the tumor growth process

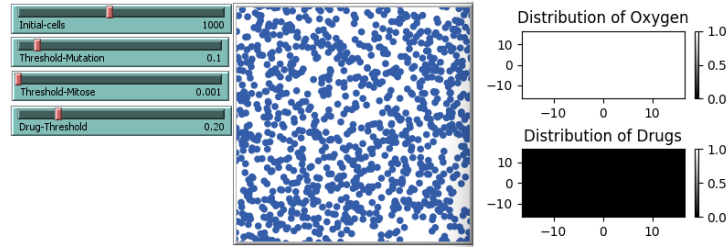


Figure 2: (Left) Initialization using NetLogo: $S = 1000$, $p_{mut} = 0.01$ and $\lambda_S = 0.001$. (Right) The distribution of the oxygen concentration (upper panel), and of the drug concentration (lower panel).

The simulation results presented in Figure 3 show that the drug class used is not very effective on the tumor modeled. The drug fails to completely treat the tumor. The proliferating cancer cells were eliminated but the quiescent cells survived the treatment. The patch that contains the vasculature is clearly visible in the middle of the environment with a white color. Before the drug level in the patches reaches the critical threshold, the cells furthest from the center and thus from the oxygen source have either died of hypoxia or gone into quiescence. The healthy and cancerous cells close to the center managed to survive. Once the drug levels increased and reached the critical threshold, the S and P cells close to the center, therefore close to the source of the diffusion of the drug, whether they are healthy or cancerous, were killed. As for the quiescent cells, they have survived the treatment.

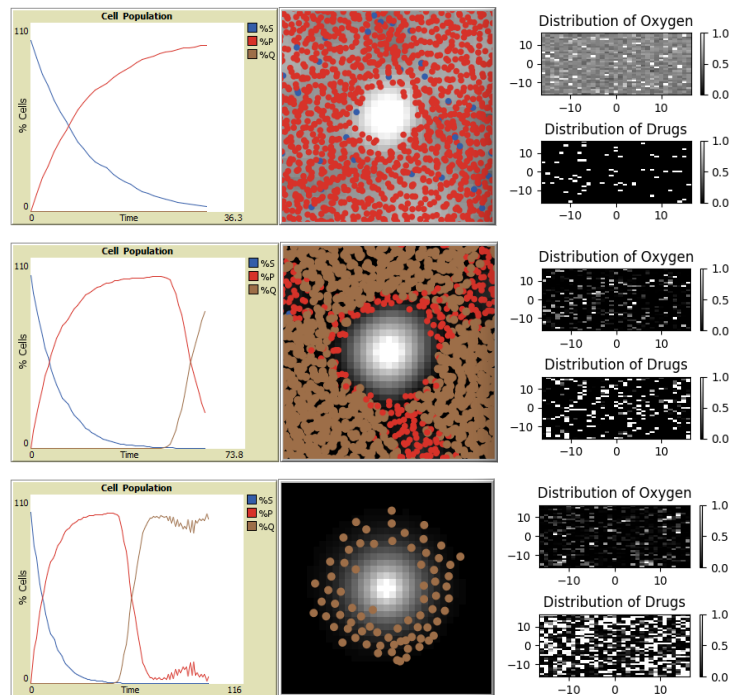


Figure 3: Evolution of the cells, oxygen and drugs distributions at different iterations with $\phi_B = 10\mu M/iteration$ (From the top to the low at iterations suivantes: $t = 30, 60$ and 97 iterations).

We tested different scenarios by changing the concentration of drug administered ϕ_B and we noticed that the effectiveness of the treatment does not increase much. The quiescent

cells are still present at the end of the simulations although the higher the dose, the further they are from the center. This is explained by the fact that the modeled tumor is still in the avascular stage. The vascularization present is not sufficient to supply the tissue with oxygen, which results in a large number of quiescent cells that are not affected by the class of drugs used.

V CONCLUSION AND REFERENCES

5.1 Conclusion

The aim of this work was to present a hybrid method to model tumor growth under chemotherapy medicine. We used agent-based modeling to simulate the behavior of cells, while the diffusion of oxygen and chemotherapeutic drug in the tumor environment is described using diffusion-reaction equations. The simulations show that the tumor cell population generally grows exponentially when not exposed to anti-cancer drug or low drug dose, while tumor cell growth is contained with high drug dose. However, to effectively treat the tumor, a drug that is appropriate to its stage of development must be used. In our case, to improve the effectiveness of the treatment we can either change the type of drug used or include in, our model, the phenomenon of angiogenesis which allows the tumor to create its own vasculature and enter the vascular stage. The hybrid model developed can also be extended to take into account some important constraints like the effect of glucose consumption and hydrogen ion production on tumor growth. The extracellular matrix, cell-cell adhesion and cell movement can also be included in the model as additional environmental parameters to predict the survival probability of the abnormal cells.

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