Coupled agent-based and finite element modelling of cancer cell behaviour

Miljan Milosevic[1,2*], Vladimir Simic[1], Ziko Milanovic[1], Ana Rilak Simovic[1], Milos Kojic[3]

[1] Institute for Information Technologies, University of Kragujevac, Kragujevac, Serbia (Jovana Cvijića bb 34000 Kragujevac); e-mail: miljan.m@kg.ac.rs, vsimic@kg.ac.rs, ziko.milanovic@uni.kg.ac.rs, anarilak@kg.ac.rs

[2] Belgrade Metropolitan University, Faculty of Information Tehnology, Serbia (Tadeuša Košćuška 63, Beograd 11158);

[3] Bioengineering Research and Development Center, BioIRC, Kragujevac Serbia (Andre Marinkovica 26, 34000, Kragujevac); e-mail: mkojic42@gmail.com

* *Corresponding author*

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Abstract: In order to study the anti-cancer properties of new drugs, it is possible to create in silico models of cells or tissues, incorporating cell growth phenomena. Here we present the model that combines the finite element (FE) method for the diffusion transport of signaling molecules and an agent-based approach for the cancer cell simulation. In this approach, each cell is treated as a discrete entity with an internal state that depends on the concentration of apoptotic factors, while the diffusion of signaling molecules is solved using the FE method. The simulation follows individual cells as they respond to chemical signals and make decisions about survival or death. By defining appropriate material properties, boundary conditions, and interaction parameters, such models can simulate the diffusion and efficacy of anticancer agents within biological tissues. This computational approach allows for a detailed analysis of drug-tissue interactions, potentially reducing the need for extensive in vitro or in vivo experiments.

Keywords: finite element model, agent-based model, cancer cell, apoptosis

1. Introduction

Advances in bioengineering increasingly rely on computational modeling to accelerate the discovery and optimization of new therapeutic agents. In particular, numerical simulations can complement or reduce the need for extensive in vitro and in vivo experiments by providing quantitative insight into cellular responses to drug treatments. While in vitro assays remain a standard approach for evaluating cytotoxicity and apoptotic potential, the parameter values they yield—such as reaction rates or transport coefficients—are often limited in scope. Computational models can bridge this gap by integrating chemical, biological, and physical processes into predictive, multiscale frameworks.

Recently synthesized ruthenium(III)-Schiff base complexes [1] of the general formula [Ru(L)Cl(H_2O)], where L is given in [1], have been investigated for their anticancer potential, with in vitro assays performed on human and murine lung adenocarcinoma (A549, LLC1) and colorectal cancer (HCT116, CT26) cell lines, and in vivo evaluation of selected complexes (compounds 2 and 5) on a heterotopic murine Lewis lung carcinoma model. Their apoptotic potential has also been assessed, highlighting the need for mechanistic modeling to better understand their action at both the molecular and tissue scales.

In this work, we present a coupled finite element (FE) and agent-based (ABM) modeling approach for simulating multiphysics phenomena relevant to anticancer drug action. The FE model is used to describe the spatiotemporal transport of key biomolecules and nutrients within a tissue domain, while the ABM framework simulates the discrete behavior of individual cells. The multiscale nature of this approach allows the cell-level decisions in the ABM to be driven by local concentrations from the FE solution, while cell death and proliferation patterns influence tissue-level nutrient consumption and drug distribution. This framework is aimed to be applied to simulate the effect of ruthenium(III) complexes of the general formula [Ru(L)Cl(H_2O)] on apoptosis, providing an example of how computational modeling can enhance the evaluation and optimization of novel chemotherapeutic agents. In this paper, we focus on presenting the novel modeling framework, while detailed simulation results for ruthenium(III) complexes will be reported in future work.

2. Methodology

In order to simulate behavior of individual cells using the coupled ABM-FE model, it is necessary to formulate the appropriate differential equations that describe the key biological processes. For the 2D cell-based model of apoptosis, we will use two main groups of equations: reaction-diffusion model for the transport of signaling molecules, and equations for cell dynamics and apoptosis (ABM). This methodology is implemented in FE code PAK-KTM (https://github.com/BogdanM1/PAK-KTM).

To simulate the transport of molecules like TNF-α, FasL, caspases, Bcl-2, etc., we will use diffusion and reactions within the 2D domain. The basic equation that describes this phenomenon is the reaction-diffusion law. For each biomolecule C_i, diffusion is described by the equation:

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C_i + R_i(C_1, C_2, \ldots, C_n) \tag{1}$$

where C_i is the signal molecule concentration (mol/L), D_i is the diffusion coefficient (cm²/s), $R_i(C)$ is the reaction term (mol/L/s), which describes the production and degradation of molecules (ie. binding to the cancer cells). The behavior of each cancer cell depends on the local concentration of nutrients in that particular lattice node that the cell occupies. AMB is using following reaction equations [2] for:

- Production and degradation of TNF and FasL:

$$\frac{\partial C_i}{\partial t} = k_p - k_d C_i, \qquad C_i = C_{TNF} \; ili \; C_{FasL} \tag{2}$$

where k_p is the production rate and k_d is the degradation rate.

• Activation of caspases:

$$\frac{\partial C_{caspase}}{\partial t} = k_a(TNF + FasL) - k_i(Bcl2 + Mcl1) \quad (3)$$

where k_a is the rate of activation and k_i is the rate of inhibition of caspases.

• Regulation of apoptosis inhibitors (Bcl2 and Mcl1):

$$\frac{\partial C_{Bcl2}}{\partial t} = k_p - k_d Bcl2 - k_i C_{caspase} C_{Bcl2} \quad (4)$$

Stochastic model of cell survival. Apoptosis can be modeled as a stochastic process with the probability of cell death $P_{apoptosis}$, which depends on the concentration of key proteins. In our case, the main factors that will govern apoptosis at the cellular level include:

1) Dynamics of cell state (survival, apoptotic). Cell i is modeled using a discrete state system: 0 - Healthy cell, 1 - Apoptotic cell, and 2 - Removed cell. The dynamics of the transition between states (live → apoptosis) is based on the concentrations of signaling molecules, such as TNF-α and FasL. To inhibit apoptosis using proteins like Bcl-2 and Mcl-1, we can add an additional factor to the formula:

$$P_{apoptosis} = 1/(1 + e^{-(C_{TNF} + C_{FasL} - \theta - C_{Bcl2} - C_{Mcl1})}) \quad (5)$$

where: $P_{apoptosis}$ is the probability that the cell goes into apoptosis, C_{TNF} and C_{FasL} are the concentrations of signaling molecules in the cell environment, θ is concentration trashhold, while C_{Bcl2} and C_{Mcl1} are the concentrations of inhibiting proteins that reduce the probability of apoptosis. For example, if $P_{apoptosis} > 0.5$, the cell enters the apoptotic state. Additionally, we can have a different condition, ie. if $P_{apoptosis}$>rand(0,1) the cell is marked as apoptotic and stops dividing.

2) Removal of apoptotic cells (phagocytosis). Apoptotic cells are removed from the domain according to a certain rate of phagocytosis:

$$dN_{Apoptosis}/dt = -k_{phagocytosis} N_{Apoptosis} \quad (6)$$

where: $N_{Apoptosis}$ represents the number of apoptotic cells, $K_{phagocytosis}$ is the rate of removal of apoptotic cells. If the cell is apoptotic for 50 iterations, it goes into the "removed" state.

3. Results and Discussion

To simulate the coupled ABM-FE model of the following input data is used: geometry of the domain and number of cells, concentrations of key biomolecules (mol/L) in the intercellular space: (a: TNF-α, FasL (inducers of apoptosis)., b) Caspases (activators of cell death), c) Bcl-2, Mcl-1 (inhibitors of apoptosis), parameters of cellular dynamics: apoptosis activation threshold for each cell, speed of removal of apoptotic cells, and diffusion coefficients of molecules in the intercellular space (D = 10^{-6} to 10^{-9} cm^2/s). The model is capable to present the: percentage of apoptotic cells in a domain over time, spatial distribution of apoptotic cells in the tissue, concentration of signaling molecules in different nodes of the network, the time required for the spread of

apoptosis through the domain, or Influence of inhibition of key molecules. Parameters used in the model are presented in Table 1:

Table 1. Parameters used in the study (Diffusion coefficients and reaction parameters)

Diffusion Coefficients cm²/s	Value	Reaction parameters	Value
D_{TNF}	0.1	Biomolecule production rate	0.05
D_{FasL}	0.08	Biomolecule degradation rate	0.02
$D_{Caspase}$	0.05	Caspase activation rate	0.03
D_{Bcl2}	0.03	Caspase inhibition rate	0.02
D_{Mcl1}	0.03	Apoptotic cell clearance factor	0.01

4. Conclusions

The presented coupled finite element (FE) and agent-based (ABM) modeling framework provides a powerful in-silico platform for evaluating the anticancer potential of selected Ru compounds. By integrating experimental data from chemists on how complexes alter the concentrations of key biomolecules involved in apoptosis pathways, the model has a potential to enable quantitative prediction of cell fate dynamics under drug treatment. Detailed simulation results for ruthenium(III) complexes will be reported in future work.

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