

ANALYSIS OF CELL PROLIFERATION AND APOPTOSIS IN VIRTUAL MODEL

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Abstract

Breast cancer is the second leading cause of cancer among women globally. Several treatments are involved in breast cancer like surgery, chemotherapy, radiotherapy, and hormone therapy; chemotherapy being used most often. Multicellular systems complications can be deeply understood by analyzing and studying how cells grow, move, divide, die and interact. To examine these factors, we use PhysiCell as our modelling platform. Virtual cell growth analysis is essential to view the cancer cell growth daily. PhysiCell physics-based multicellular simulator is an open-source agent-based simulator used to design a virtual model to analyze the changing cell cycle progression, volume, death, motility, mechanics and processes. Analysis was made on the cancer cell death rate, cell damage rate, and cell repair rate. Data were taken for every 6 hours of simulation and the result confirms that the chemotherapeutic agent kills 45% of cancer cells.

Key words: apoptosis, breast cancer, cancer cell death rate, cancer cell repair rate, cell proliferation, chemotherapeutic agent

1. Introduction. Breast cancer is the most widespread cancer among other types of cancer in women, ranking as the second-largest cause of female mortality worldwide [1]. The data conveys that women with breast cancer can have cognitive and physical decline at an increased rate, which corresponds to vulnerabilities of cellular senescence, epigenetic changes, and genome instability [2].

Chemotherapy is majorly used for breast cancer. Chemo refers to drugs and it is also called drug therapy. Cytotoxic drugs used for treatment are often followed by loss of appetite, vomiting, dry mouth, changes in smell or taste perception, and nausea [3]. The selection of the most accurate process for the chemotherapy treatment is based on many details, such as cancer stage, localization, type and molecular subtype [1]. Different agents' efficiency comparatively in chemotherapy yields a median overall survival in registration studies of two years [4]. Chemotherapy is used in the advanced cancer stage and after or before surgery. Chemotherapy is limited for clinical use due to its high toxicity [5]. Chemotherapy produces heart disease, chronic obstructive pulmonary disease, (osteo)arthritis, obesity and diabetes mellitus [6]. Natural compounds combined with chemotherapeutic agents have adverse effects on cancer cells and reduce the side effects [7]. The agent-based or virtual approach merged with brace learning aims to optimize and simulate typical biological issues such as radiotherapy. Merge the optimization and simulation compartments using the R-NetLogo package. Tuning the specification of the learning algorithm attained aims to overcome tumours with fewer side effects [8]. The simulation models mainly concentrate on immune cells and the interactions between stromal cells and cancer cells. The aspects of digital pathology are important in parameterizing and potential applications to therapeutics [9].

Modelling individual cells allows straightly translating biological observations into simulation rules. Respective cell agents have molecular-scale models. Models also simulate the growth factors, oxygen transport, and drugs that associate cancer development with microenvironmental conditions [10]. The researchers developed a 3D, lattice-free multiscale agent-based model of DCIS (Ductal carcinoma in situ) to compute ductal invasion rates. The clinicians are allowed best to evaluate the extent of invasion and disease age and estimate surgical margins due to features taken from non-invasive testing [11]. The differential equation-based, multiscale, agent-based, image-driven and lattice-based modelling has elucidated the new role of breast cancer dynamics. The abovementioned models contribute to the aspect mathematical modelling may play in realizing breast cancer treatment therapies, development and invasion [12]. Monte Carlo-based quantitative structure-activity relationship was analyzed on a dataset having 102 phenylindoles. It is used to investigate the best cytotoxic phenylindoles across MCF7 cell lines. A combination of HSG with ^0ECk connectivity and SMILES was used to classify and find the structural facet as promoters and hinderers of cytotoxicity [13].

Behavioural rules can be calibrated and provided by in vitro assays, and rising population-level dynamics can be examined by in vivo and in vitro experiments. The implementation and design of a lattice-based agent-based model of cancer stem cell-induced tumour growth [14]. The technical challenges and benefits associated with the agent-based model as a utensil for validating morphogenetic events. This displays incomparable flexibility for gathering differential morpho-

genetic aspects at multiple levels [15]. An agent-based model is a multicellular system. Every cell is considered a software agent with its state and rules to modify its characteristics based on surrounding communication and environmental condition.

PhysiCell simulates millions of cells; from that, tissue scale behaviour emerges. PhysiCell physics-based multicellular simulator is nothing but an open-source agent-based simulator that gives the players the stage to examine more collaborating cells in dynamic tissue. Their modelling techniques and features are also discussed here [16]. The PhysiCell based research revealed that the computational models for the multicellular systems need solving systems of partial differential equations for diffusion release, decay and uptake of multiple substrates in three dimensions. It is needed when consolidating the signalling factors, growth substrates and impact of drugs on subcellular systems biology and cell receptors [17]. The researchers described PhysiCell as a definite agent-based model with cell death, volume changes, cell cycling, and cell motion. This model has been enforcement tested on systems of differential cells on computers [18]. Combining two methods, one to aid the building of multiscale agent-based model, and the other to expand model optimization and exploration, can give a computational method for high-throughput hypothesis optimization and testing [19]. This paper proposed the virtual model for breast cancer treatment with a chemotherapeutic agent. After simulation, we calculated the overall death rate, cancer cell repair rate, and cancer cell damage rate.

2. Materials and methods. 2.1. Agent-based modelling. The tumour morphology has been influenced by angiogenesis, micro-environment adaptation, extracellular matrix influence, changing phenotype mutations, etc. The above said has been investigated and consolidated in ABMs (agent-based models) and the effects of nutrient availability and oxygen effects. The most novel agent-based models have been introduced which have brought observation into the better understanding of tumour invasion and growth, spanning more biological scales in space and time [20].

2.2. Types of cells. Cancer cells. While consuming oxygen, the cancer cells divide rapidly. Hypoxia reduces the chances of survival of cancer cells. Sufficient oxygen drives faster cancer cell growth, while insufficient oxygen could trigger necrotic death, forming a necrotic core (brown cells) at the central portion of the tumour. In our model, cancer cells appear in green colour.

Cargo cells. The cargo cell carries chemotherapeutic agent. While it reaches the cancer cell, it releases the chemotherapeutic agent to kill it. These cells do not divide and are non-motile. The cargo cell attaches to the worker cell by spring-like focal adhesions. It also consumes oxygen at a minimum rate, i.e., 10% of the speed of cancer cells. In our model cargo cell appears in blue.

Worker cells. Worker cells do not divide and are motile. The worker cell attaches to the cargo cell by spring-like focal adhesion. It brings the cargo cell to the

oxygen-depleted region in the cancer cells. It leaves the cargo cell to secrete the chemotherapeutic agent to kill the cancer cell. After secretion of the chemotherapeutic agent, cargo cells will be permanently deactivated. The unattached worker cell searches for another cargo cell that carries a chemotherapeutic agent. In our model worker cell appears in red.

2.3. Methodology. In the proposed methodology, a virtual model is created to view the cancer cell growth because there was more restriction in research cancer cells directly, so we have gone for a virtual model. By studying cell movement, growth, division, interaction, and death the multicellular systems problems can only be identified. Tissue-scale dynamics emerge from systems of many interacting cells as they respond to and influence their micro-environment. The multicellular systems can be simulated with the virtual laboratory for such biochemical micro-environment. The models also simulate many mechanically and biochemically interacting cells. PhysiCell was developed to work with the Finite volume method for biological problems to fill this role as a virtual laboratory.

When treated with a chemotherapeutic agent, the various parameters of breast cancer cells are collected. Then, the parameter values are incorporated into the PhysiCell software. PhysiCell aims to provide a robust, scalable code for simulating large systems of cells in 3-D tissues on standard desktop computers. In PhysiCell, we have the option to include additional parameters we want. Using C++ coding, we can add different parameters. After adding the parameters and their values, we run the coding to view the process that takes place in the cancer cell every second.

3. Results and discussion. The cancer cell has a radius of 200 μm and it divides fast when the oxygen rate is high; after oxygen reduces its dividing rate and repair rate are also reduced. Due to the lack of oxygen in cancer cells, its multiplication tendency reduces. The cancer cell appears green (Fig. 1) and the necrotic core appears due to the lack of oxygen in the proposed model. The cell which has insufficient oxygen was the trigger to necrotic death. This lack of oxygen in cells was denoted by brown colour. In that time, cargo cells and worker cells were injected. Cargo cells contain a chemotherapeutic agent used to kill cancer cells. The blue colour represents the cargo cell and the red colour represents the worker cell. Worker cells attach with cargo cells through spring-like focal adhesion. Worker cells search for cargo cells, form focal adhesion, and haul their cargo towards the tissue's hypoxic (oxygen-depleted) region. Once they reach the low oxygen region, they release their cargo and resume their initial search for more cargo. Worker cells carry the cargo cells towards the cancer cells and release the chemotherapeutic agent, as illustrated in Fig. 1.

Once worker cells reach the hypoxic region, they release their cargo and resume their initial search for more cargo. When cargo cells reach the sufficiently low oxygen region they release the chemotherapeutic agent. This chemotherapeutic agent kills the cancer cells to decrease the cancer cell count and radius.

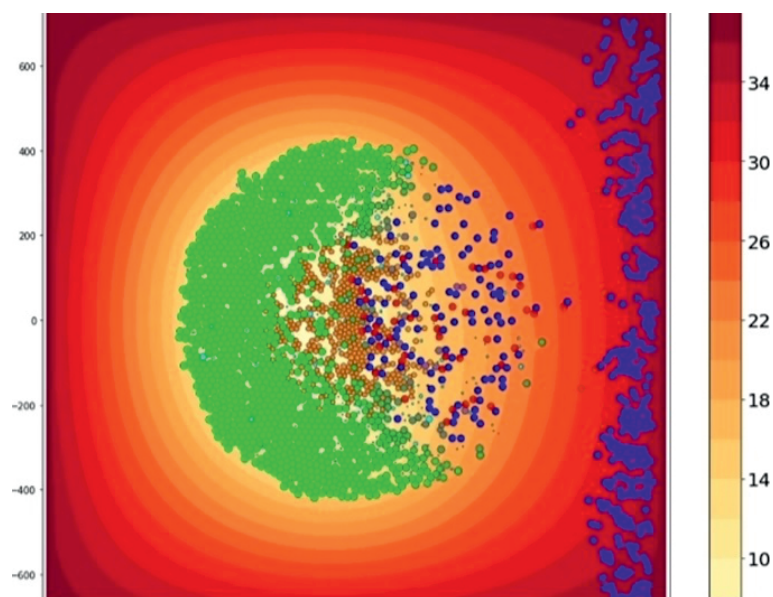


Fig. 1. Worker cells carry the cargo cells and release the chemotherapeutic agent

3.1. Analysis. Analysis was made on the cancer cell death rate, cell damage rate, and cell repair rate. The data were taken every 6 h after starting the simulation on the eighth day. With this information, graphs were plotted to get more precise information and these data are used for future work.

3.1.1. Overall cancer cells death rate. When the time increases, cell count decreases due to the release of the chemotherapeutic agent. At the start of the simulation, the cancer cells were about 1648 cells and after 138 h, they reduced to 748 cells. Due to chemotherapeutic action, 45% of cells are dead.

3.1.2. Cancer cells damage rate. The graph in Fig. 2 denotes the damage rate of cancer cells at a rate of 1 cell as 0.033333/min for every 6 h. When the cell death count decreases, the damage rate also decreases accordingly. Based on the cell count every 6 h, it shows the damage rate of cells.

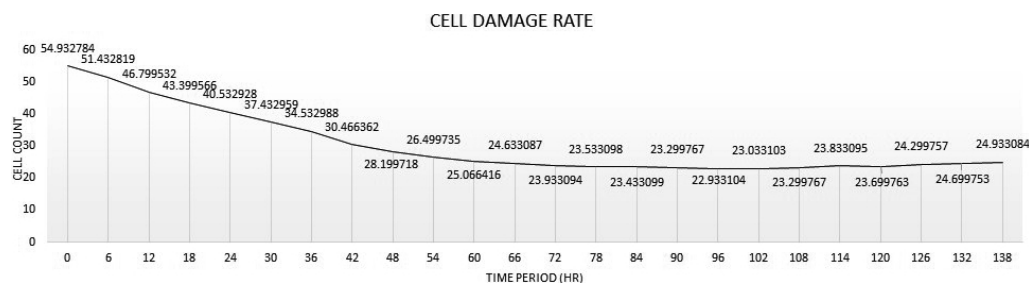


Fig. 2. Cancer cells damage rate graph

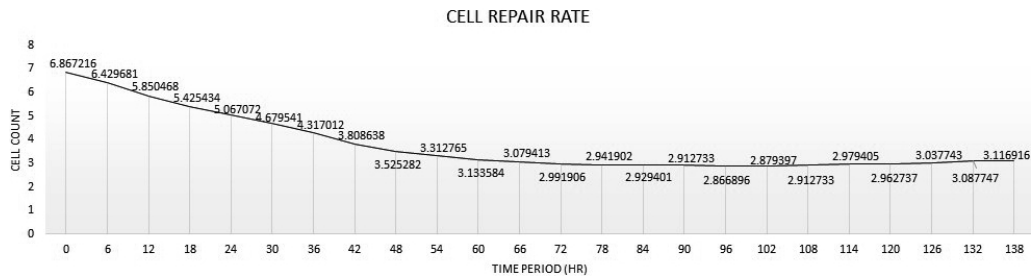


Fig. 3. Cancer cells repair rate graph

3.1.3. Cancer cells repair rate. The graph in Fig. 3 denotes the repair rate of cancer cells every 6 h. The repair rate of 1 cancer cell is 0.004167/min. Due to lack of oxygen, the repair rate decreases and decreases accordingly by reducing cell count. Based on the cell count every 6 h, it shows the repair rate of cells.

Different parameters of cancer cells, worker cells, and cargo cells are defined and their values are identified. They are incorporated to run the designed model. Parameters play an essential role; they contain many features. Table 1 shows the various parameters and their values in the developed model.

4. Conclusion. There are restrictions to analyze the cancer cells directly since clinical trials are not possible due to the limitations in the engineering discipline, so agent-based modelling is necessary to implement the new research and analysis on the cancer cells. This virtual model brings a clear idea about cell proliferation and cell apoptosis. Chemotherapeutic agents kill 45% of cancer cells. The death count of cancer cells was plotted every 6 hours for 138 h. It is possible to take cell death count and survival count every second by viewing this virtual model simulation.

T a b l e 1

Parameters of cells treated with curcumin and doxorubicin

Si. No	Parameters	Quantity
1.	Oxygen	38 mmHg (initially)
2.	Chemotherapeutic agent death rate	0.004167/min
3.	Tumour cells proliferation	Doubles in 120 h
4.	Tumour radius	200 μ m
5.	Tumour cells death rate	0.033333/min
6.	Tumour cells repair rate	0.004167/min
7.	Cargo cells death rate	0.00004065/min
8.	Worker cells death rate	0
9.	Worker cells migration rate	2 μ m/min
10.	Overall process time	14400 min

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