

# INTRODUCTION

A computational model is a mathematical model in computational science which studies the behavior of a complex system by computer simulation. The system under study is often a complex nonlinear system for which simple, intuitive analytical solutions are not readily available. Rather than deriving a mathematical analytical solution to the problem, experimentation with the model is done by adjusting the parameters of the system in the computer, and studying the differences in the outcome of the experiments. Operation theories of the model can be derived/deduced from these computational experiments [5].

Examples of common computational models are weather forecasting models, earth simulator models, flight simulator models, molecular protein folding models, and neural network models [5].

Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can divide through mitosis to produce more stem cells. They are found in multicellular organisms [6]. Mitosis is the cell cycle process which divides into two new cells containing roughly equal shares of cellular components [8].

Cancer stem cells (CSCs) are cancer cells found within tumors or that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. CSCs are therefore tumor-forming, perhaps in contrast to other non- tumor-forming cancer cells. CSCs are special type of cells which have been shown to associate with different aggressive cancer phenotypes including drug resistance. CSCs are transformed cancer cells possessing the properties similar to stem cells. A phenotype is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, phenology, behavior, and products of behavior. A phenotype results from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two. CSCs if unheeded, can, in theory, cause continual relapses of a tumor, and are capable of metastasis – the migration cancerous cells including CSCs to other organs or tissues in the body to create new tumors (carcinogenesis).

Further, new information suggesting a dependence of tumour composition and growth on the microenvironment has yet to be studied theoretically [1]. The theoretical model is a computational model which is a hybrid, discrete/continuous computational cellular automaton model of a generalised stem-cell driven tissue with a simple microenvironment.

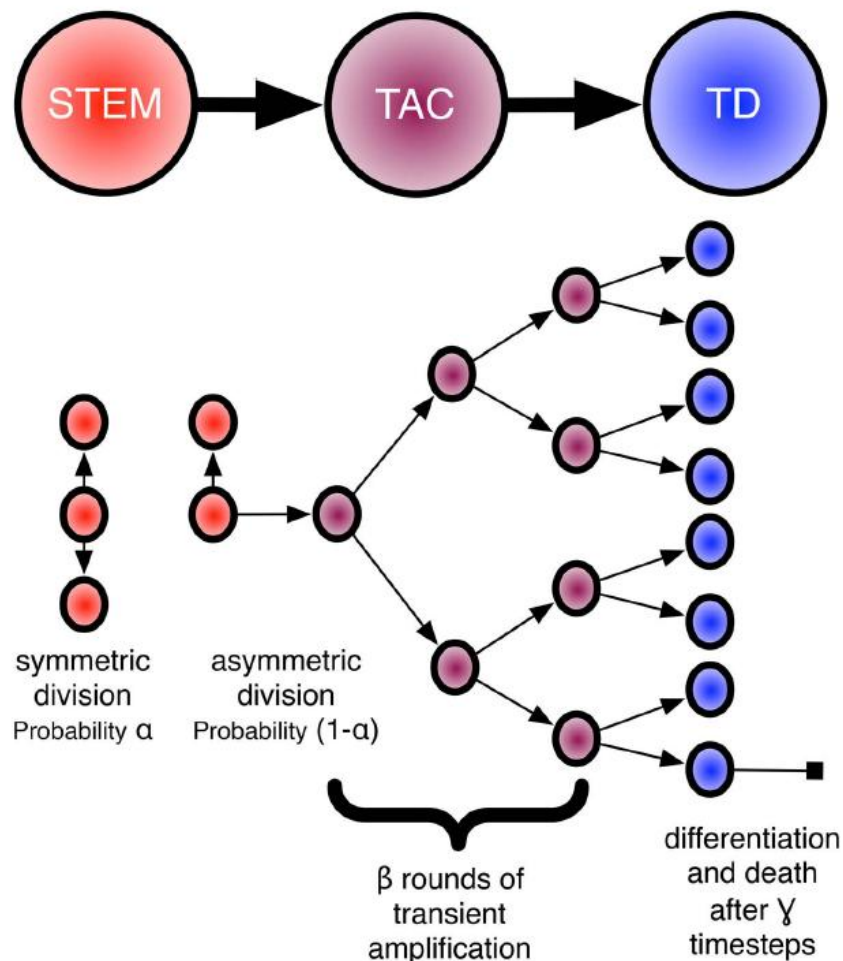
A cellular automaton consists of a regular grid of cells, each in one of a finite number of states, such as on and off. The grid can be in any finite number of dimensions. For each cell, a set of cells called its neighborhood is defined relative to the specified cell [3].

Using the phenotypic traits inherent to the tumour initiating cells, and the effect of the microenvironment on tissue growth can be explored [1].

Since the discovery of TICs in solid tumours, studies focussing on their role in cancer initiation and progression have abounded. The biological interrogation of these cells continues to yield volumes of information on their pro-tumourigenic behaviour, but actionable generalised conclusions have been scarce. Further, new information suggesting a dependence of tumour composition and growth on the microenvironment has yet to be studied theoretically [1], where a cellular automaton is helpful.

A subpopulation of tumour cells, called TICs, produce non-TIC cancer cells or self-renew to promote tumor maintenance. As TICs have been demonstrated to be resistant to a wide variety of therapies including radiation and chemotherapy, the TIC hypothesis has important implications for patient treatments. Specifically, the effect of current strategies on the tumor cell hierarchy should be defined, and TIC specific therapies are likely to provide strong benefit for cancer patients.

In a simplified view of the tumour cell hierarchy, TICs can divide symmetrically or asymmetrically to produce two TIC daughters or a TIC daughter and a more differentiated progeny [17,18], respectively. More differentiated TIC progeny which still have the capability of cell division and are similar to transient amplifying cells (TACs) in the standard stem-cell model and are capable of several rounds of their own symmetric division before the amplified population then differentiates into terminally differentiated cells (TDs) which are incapable of further division. This mode of division and differentiation, termed as Hierarchical Model (HM) is schematized in Figure 1.



**Figure 1 [1]. Cartoon representing the hierarchical model of stem-cell driven tissues.** In this formulation, each stem can undergo two types of division, either symmetric (with probability  $\alpha$ ) or asymmetric (with probability  $1-\alpha$ ). Each subsequently generated transient

amplifying cell (TAC) can then undergo a certain number ( $\beta$ ) of round of amplification before differentiating into a terminally differentiated cell (TD) which will live for a certain amount of time before dying ( $\gamma$  timesteps). It is these three parameters, which we assume are intrinsic to a given stem cell.

## **PROBLEM STATEMENT**

To develop a computational model based on the available experimental data to gain further insights about the origin of CSCs and their role in promoting cancer. The computational model will be developed by combining discrete and continuous modeling approaches. By applying discrete models, automata theory, and cellular automaton programming to create more accurate models of population growth and a better understanding of population dynamics. A simple two dimensional computational model of the HM of a TIC-driven tissue. And to generalise the intrinsic alterations which a TIC could undergo much in the same way that the hallmarks of cancer have generalised non TIC-specific alterations.

The model will integrate the cell evolution cycle related to CSC and effects of microenvironmental parameters on this cycle. Computational predictions will be experimentally tested by PhD students in the lab.

## MOTIVATION

One of the main problems of CSCs in cancer treatment is that they are generally unaffected by chemotherapy used to kill most differentiated cancer cells (which make up most of the tumor). CSCs generally make up about 1-3% of a tumor [14]. Thus, following chemotherapy, CSCs left behind would be able to replenish a tumor and cause a relapse of the cancer [15]. In addition, tumor modeling and understanding relapse due to CSCs are currently ill understood because most organisms with relapse cancers *in vitro* die before they can be further studied.

CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. Such cells are proposed to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors.

Therefore, development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease [7].

## OBJECTIVES AND SCOPES

A simulation is seeded with one TIC with a given set of intrinsic parameters ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) governing its and its progenys behaviour, which is placed in the centre of the computational domain.

Successful completion of the problem will contribute to our understanding of how CSCs contribute to cancer invasiveness. Considering the parameters in the model as non-specific, they could apply to any tissue TIC and do not assume specific genetic mutations.

The most relevant parameters for the addressing are the following:

1. Symmetric/asymmetric division rate of stem cells ( $\alpha$ )
2. Number of allowed divisions of TACs ( $\beta$ )
3. Lifespan of TDs ( $\gamma$ )

## DESCRIPTION OF THE WORK

Object oriented concept of abstraction, encapsulation very well serve the purpose to create a grid, array of cells as array of object of classes. Cellular automaton, where an initial state (time  $t = 0$ ) is selected by assigning a state for each cell. A new generation is created advancing  $t$  by 1, according to some fixed rule generally, a mathematical function that determines the new state of each cell in terms of the current state of the cell and the states of the cells in its neighborhood. Typically, the rule for updating the state of cells is the same for each cell and does not change over time, and is applied to the whole grid simultaneously [3].

Cancer Stem cells abbreviated as CSCs are cancerous cells that exhibit properties similar to normal stem cells. This means that CSCs are multipotent and are able to differentiate into cancer cells and can undergo self-renewal. CSCs essentially are tumorigenic, meaning they are capable of creating tumors, a quality other cancerous cells do not possess. Another quality of CSCs is immortality; whereas other cells have a limited number of times they can divide CSCs are able to divide indefinitely [13].

Procedure to be followed would be create:

1. class with cell properties as member variables
2. constructors to set properties
3. getters and setters for each property
4. update function for each type of cell to simulate automata
5. after each time instant save the state into a file
6. use the state values to plot properties of cell against time
7. use the cell type and properties to get graphical representation

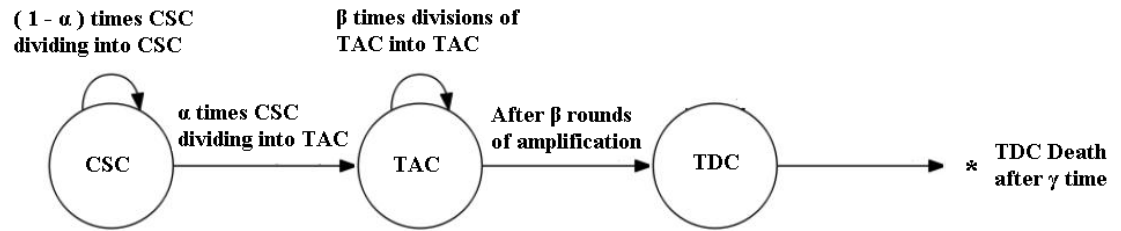
Types to simulate:

1. CSC
2. TAC
3. TDC
4. Extra Cellular Matrix Site ( ES , where E stands for ECM Extra Cellular Matrix )

The rules to update the state of cells are based on parameters:

1.  $\alpha$  : P( CSC dividing into TAC )
2.  $1 - \alpha$  : P( CSC dividing into CSC )
3.  $\beta$  : Number of divisions of TAC ( after which they transform into TDC )
4.  $\gamma$  : Life time of TDC

Figure 2 gives the brief overview of cellular automata to simulate and the conditions for transition in states.



**Figure 2 : Cellular Automata to Simulate**

Tools and programming to be used:

1. Using C++ in Dev C ++ IDE [10].
2. Doxygen [20] to generate documentation out of program
3. Octave [11] to generate images and graphs
4. GitHub [21] for version control

Other aspects:

1. Start with a simple prototype, use incremental development
2. Use meaningful call, variable, function names
3. Include documentation informing what and why of code
4. Test all functions, corner case



## **CONCLUSION**

Learning outcomes on successful completion will be to understanding to develop computational models for getting insights into biological problems and create a computational model which is a hybrid, discrete/continuous computational cellular automaton model of a generalised stem-cell driven tissue with a simple microenvironment.

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