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Review Article

A Survey of Mathematical Models of Cancer Growth and Therapies

Worrawimol Chareontummasathit

Department of Mathematics, Faculty of Science, Burapha University, Chonburi, Thailand.

Corresponding Author : ankana@go.buu.ac.th

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Abstract *- Mathematical modeling is a well-known powerful tool for testing hypotheses in deep mechanisms to understand chemistry, physics, and biology research areas. Over the past decades, the number of mathematical models in cancer research has increased development because of the high – performance of computers with high technologies. However, clinical data from cancer laboratories and cancer treatments are still a golden key for cancer modeling. This review article will show compositions from some of the various mathematical models both discrete and continuous dynamical systems to predict cancer growth and therapies.*

Keywords *- Mathematical model, Cancer growth and treatment model, Ordinary differential equations.*

1. Introduction

As known, cancer is one of the major causes of death in our world. Many biological mechanisms of cancer growth are still not fully understood. Researchers in medical and computational sciences have been playing a crucial role in investigating these mechanisms. In 1972, mathematical models of tumor growth with immune response have been proposed by Greenspan [1] with diffusion equations. Till et al. [2] proposed a discrete stochastic model of stem cell proliferation of the spleen colony-forming cells in 1963. Till and coworkers [2] established the Birth-and-Death Process, a single cell may either give rise to progeny like itself so-called “birth” or be removed so-called “death”, and especially, birth and death events occur with randomness. In 1993, Qi et al. [3] presented a cellular automaton model or agent-based model, which is a discrete model using a stochastic process with von Neumann neighborhood on a two-dimensional square lattice. In 2009, Boondirek and Triampo [4] and recently, Srisuk and Boondirek [5] proposed a cellular automaton model on a three-dimensional cubic lattice, which was inspired by the previous work of Qi et al.’s model [3]. In 2003, Ferreira et al. [6] and [7] proposed the two nutrient species with diffusion equations using partial differential equations (PDEs). The PDEs of [6] and [7], the first and the second nutrients equations are essential for cell division processes and the cell division processes, respectively. A mathematical model hybrid a cellular automata model created by Mallet and Pillis [8] was inspired by Ferreira et al. [6], [7]. Mallet and Pillis [8] presented the hybrid cellular automata model of oncolytic virotherapy employing the ODE system will be concerned.

Kim et al. [9] developed a system of ordinary differential equations (ODEs) as a mathematical model to predict the dynamics of virotherapy cancer treatment. In 2020, Abernathy and co-researchers [10] employed the work done by Kim and coworkers [8] to propose a mathematical model for tumor growth using virotherapy treatment.

In 2005, Belostotski and Freedman [11] established a mathematical model of cancer treatment by radiotherapy. Belostotski and Freedman [11] used the Lotka-Volterra competition system. Liu and Yang [12] also proposed two – species Lotka-Volterra competition system of ODEs for describing the dynamics between the concentration of healthy and cancer cells in both cancer radiation treatment and no-treatment stages, respectively.

In the present study, we illustrate several mathematical model approaches to cancer treatments, such as chemotherapy, radiotherapy, chemo-immunotherapy, and immunological therapy, respectively.

2. Mathematical Model of Cancer Growth and Treatments

2.1. Differential Equations

2.1.1. The System of Ordinary Differential Equation Models for Tumor Growth and Virus Therapeutics

Kim et al [9] presented the model of tumor-virus dynamics as shown in Figure 1. We can see the details of biological mechanisms modelling from [9].

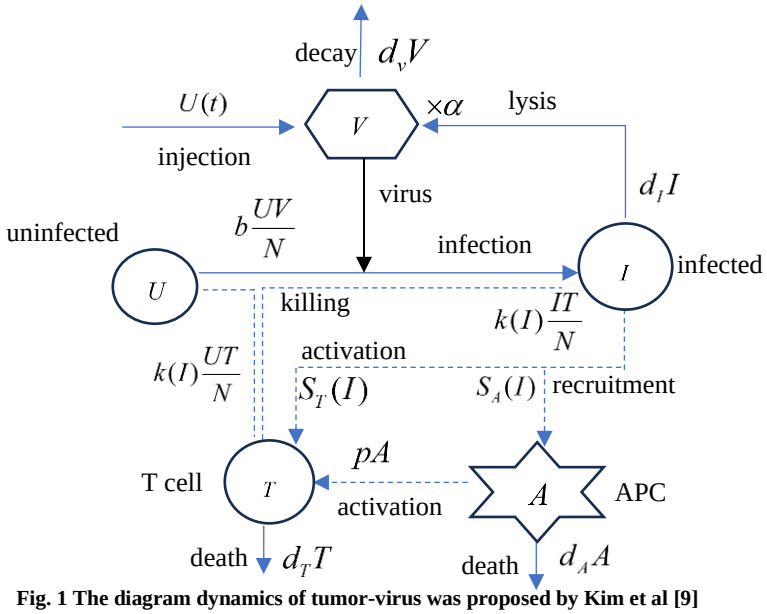

Fig. 1 The diagram dynamics of tumor-virus was proposed by Kim et al [9]

Kim and co-researchers [9] employed the population dynamical model in Figure 1 to present the mathematical model for predicting the tumor size in response to treatment with four adenoviruses by the system of ordinary differential equations (ODEs):

$$\frac{dU}{dt} = rU - \beta\frac{UV}{N} - k(I)\frac{UT}{N},$$
$$\frac{dI}{dt} = \beta\frac{UV}{N}\delta_I I - k(I)\frac{IT}{N},$$
$$\frac{dV}{dt} = u(t) + \alpha\delta_I I - \delta_V V,$$
$$\frac{dT}{dt} = S_T(I) + pA - \delta_T T,$$
$$\frac{dA}{dt} = S_A(I) - \delta_A A.$$

Where $\boldsymbol{U}$is the number of uninfected tumor cells, $\boldsymbol{I}$is the number of infected tumor cells, $\boldsymbol{V}$is the number of virions, $\boldsymbol{T}$is the number of T cells at the tumor site, and $\boldsymbol{A}$is the number $\boldsymbol{APCs}$at the tumor site. Here$\boldsymbol{N = U + I + T + A}$ is the number of the total cell population at the time $\boldsymbol{t}$. The biological mechanisms of parameters in ODEs with the major assumptions and conditions were described by Kim et al. [9].

Recently, Nave [13] proposed a mathematical model for cancer treatment by chemoimmunotherapy for brain cancer. Nave [13] proposed a system of first-order nonlinear ordinary differential equations to investigate the interaction of immune system cells with cancer cells and chemotherapy medicine. Nave [13] investigated the as a combination of chemotherapy and immunotherapy for cancer treatment in terms of the time intervals and dosages.

2.1.2. Lotka-Volterra Dynamics for Radiotherapy

Belostotski and Freedman [11] using Lotka-Volterra model of competition between healthy and cancer cells, by ODEs:

$$\dot{x}_1 = \alpha_1 x_1\left(1 - \frac{x_1}{K_1}\right) - \beta_1 x_1 x_2, x_1(0) = x_{10} \geq 0,$$
$$\dot{x}_2 = \alpha_2 x_2\left(1 - \frac{x_2}{K_2}\right) - \beta_2 x_1 x_2 - \eta(t,x,x), x_2(0) = x_{20} \geq 0,$$

where $x_1$and $x_2$are the concentrations of healthy and cancer cells, respectively. $\alpha_1, K_1$and $\beta_1$are the growth rates, carrying capacities, and death rates of healthy cells, α_2, K_2 and $\beta_2$are the growth rates, carrying capacities, and death rates of cancer cells, respectively.

The radiation control on the cancer cells is defined by the non-negative$\boldsymbol{\eta}$. The research of Belostotski and Freedman [11] discusses the treatment of cancer with radiotherapy with four types of relevant of $\boldsymbol{\eta}$.

2.1.3. The Reaction-Diffusion Partial Differential Equations for the Nutrient's Species

The nutrient species model of Ferreira and co-workers [6] and [7] is presented by PDEs:

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N - k_1 HN - k_2 TN - k_3 IN,$$
$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - k_4 HM - k_5 TM - k_6 IM,$$

where N and Massume the proliferation nutrient and survival nutrient, respectively. H for host cells (normal tissue), T for tumor cells, and $I$for immune cells are cell species defined.

D_N and are the diffusion coefficients for the two nutrients, k_1, k_2 and $k_3$are the rates of consumption of proliferation nutrients by host cells, tumor cells, and immune cells, respectively. k_4, k_5 and $k_6$are the rates of survival nutrients of host cells, tumor cells, and immune cells, respectively. See details of the model formulations and biological assumptions in Ferreira et al. [6] and [7].

2.2. Discrete Model

2.2.1. The Monte Carlo of Birth and Death Process

In 1963, Till and co-workers [2] proposed the Monte Carlo model of the proliferation cells during the growth of spleen colonies with birth and death processes, as shown in Fig. 2, and the two case histories in six generations were illustrated in Fig. 3.

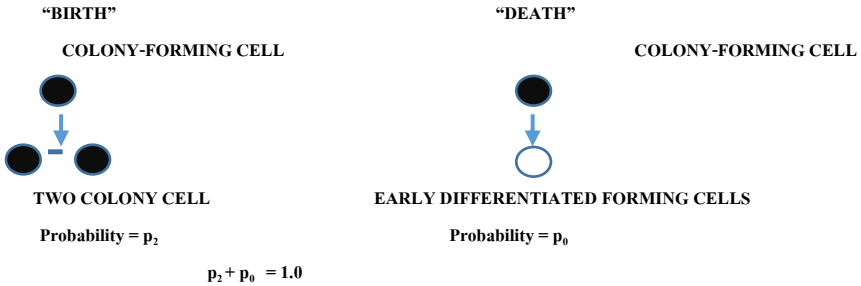

Fig. 2 This Figure was taken by the research paper 's Tim and co-workers [2]

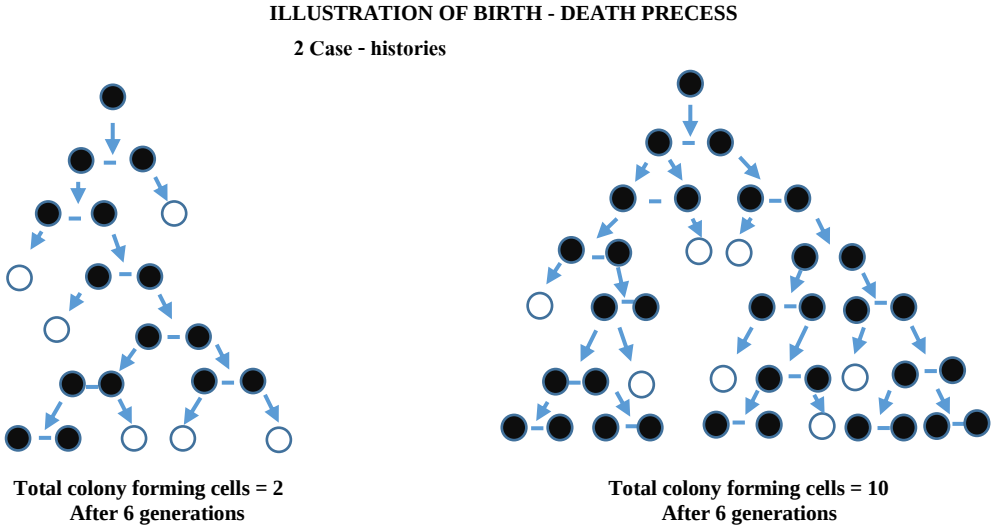

Fig. 3 The two typical diagram for six generations carried out by monte carlo processes [2]

2.2.2. The Cellular Automata Model for Tumor Growth Under the Effect of Therapy

In, 1993, Qi et al. [3] proposed the dynamical kinetics model with three discrete states representing cancer cells or proliferating cells, quiescent cells, and necrotic cells with local transition rules using von Neumann's Neighborhoods in their stochastic cellular automaton model. The research of Qi et al. [3] and Boondirek and Triampo [4] inspired Srisuk and Boondirek [5] to publish a stochastic cellular automaton model on a three-dimensional cubic lattice. The simulation results of [5] will be shown in Figure 4.

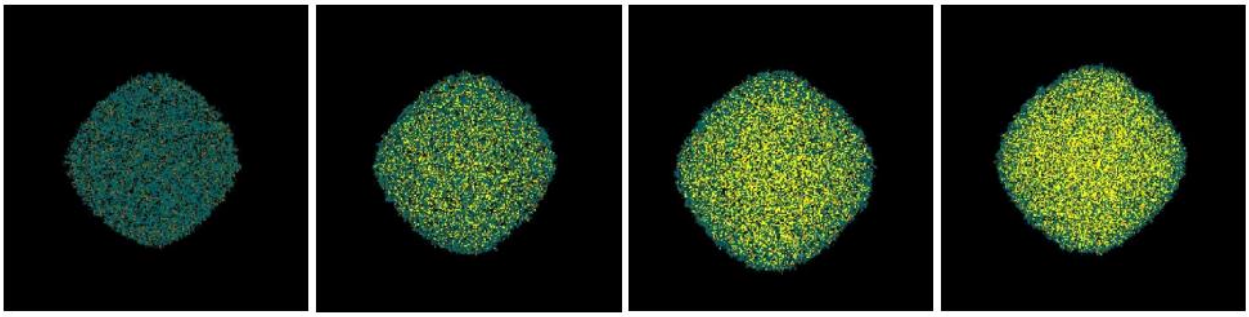

Fig. 4a. Snapshots from cross-section from simulated tumor growth of Srisuk and Boondirek 's model [5], with four cancerous cell types are proliferative tumor cell, tumor-immune complex cell, dead tumor cell, and dormant cell, which are represented with green, brown, red, and yellow, respectively

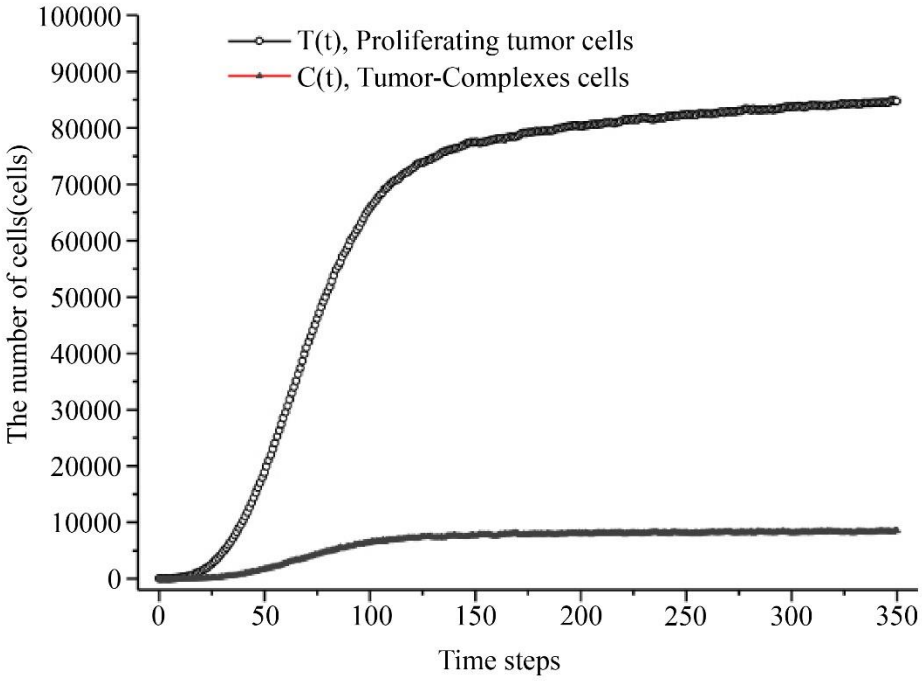

Fig. 4(b) Simulated growth curve of the simulated tumor, which is taken from Srisuk and Boondirek 's research [5]

The simulated tumour growth curves from many researchers, such as [2], [3], [4], [5], and [8] were able to capture the nonlinear dynamics of Gompertzian behaviours, which were observed in experimental tumour growth data.

Reis and coworkers [14] proposed the SCA model for avascular solid tumor growth under the effect of therapy. The CA's model of [14] created a cellular automaton's rule on two-dimensional square lattice with four discrete states with a block diagram and the dynamics of cell states, as depicted in Figure 5. The snapshots of simulated growing tumor of Reis et al. 's results will be depicted and shown in Figure 6. Reis et al. [14] analyzed two classes of behavior, not treatment and treatment as detailed in their research's paper.

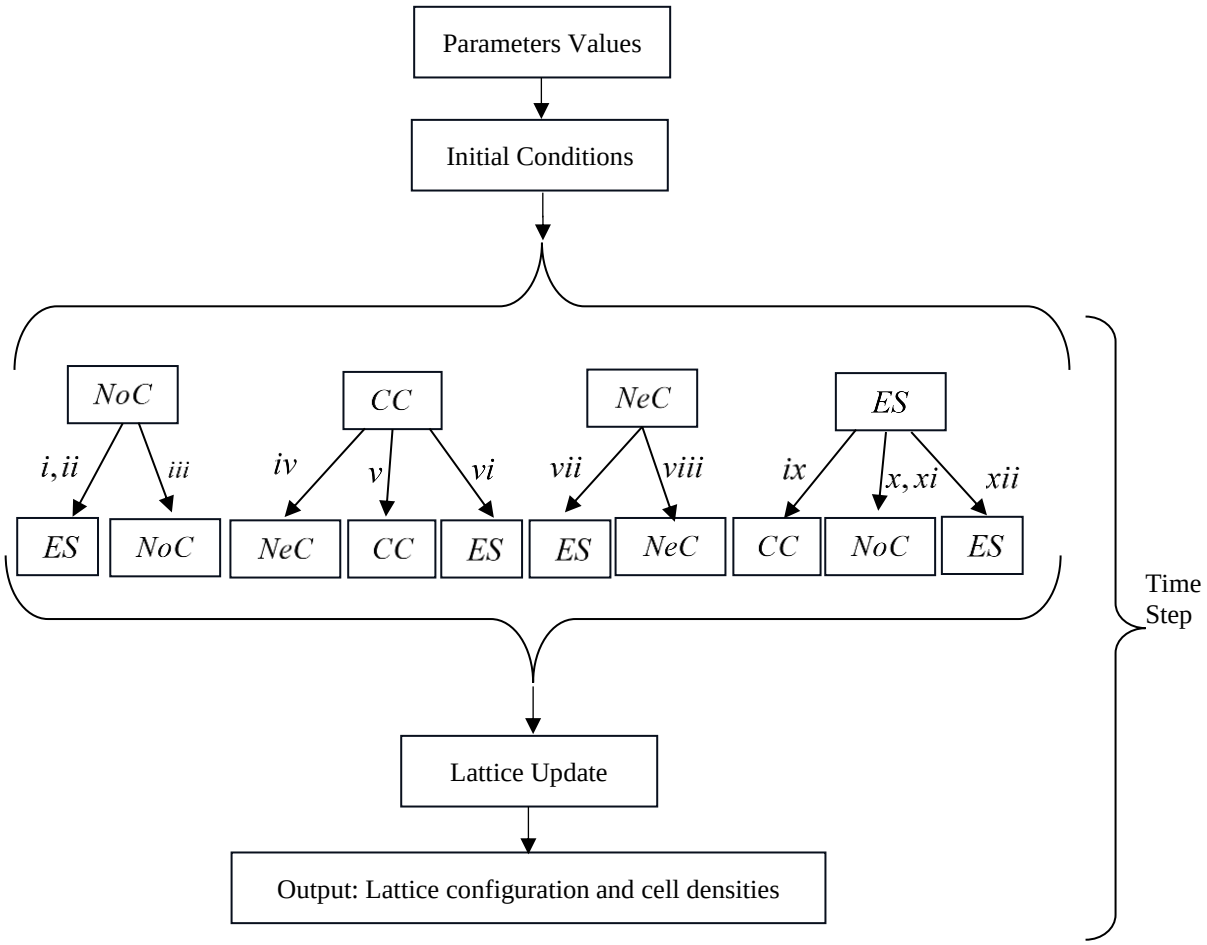

Fig. 5 Subroutines for each state of cell: normal cell (NoC), cancer cell (CC), necrotic cell (NeC) and empty site (ES) in a time step. This diagram is taken from Reis et al. [8]

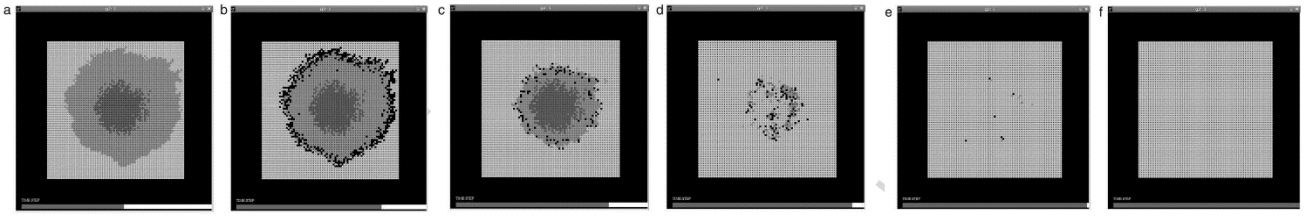

Fig. 6 Two-dimensional snapshots of simulated destroying tumor. Light grey, grey, dark grey, and black represent normal, cancer, necrotic cells, and empty sites, respectively. This figure is taken from Reis et al. [8]

In 2019, Pourhasanzade and Sabzpoushan [15] proposed the SCA model of tumor growth under the effects of chemotherapy on two-dimensional square lattice. The SCA model of [15] proposed six states of cell, i.e., normal cell, proliferating tumor cell, quiescent cell, necrotic cell, unstable state of cell, immune cell and dead cell, respectively. The initial condition of a simulation starts with one cell in the center of a squared lattice. [15] established cancer stem cells and non-stem cells in their model.

2.3. Hybrid Model

A few researchers have modelled hybrid continuum-discrete models over the past 20 years. The CA model was hybridized with the PDEs approach and has been used to investigate tumor growth development, such as by Mallet and Pillis [8] and Xie et al. [16]. In 2005, Mallet and Pillis [8] proposed a stochastic two-dimensional cellular automata model for tumor growth under therapy with periodic boundary conditions, and recently, Xie and co-researchers [16] modelled a three-dimensional invasive tumor growth under chemotherapy in 2018. The work done by [8] employed reaction-diffusion equations for describing growth nutrients and CA to track tumors and two species of immune cells, and the research of Xie and co-workers developed a hybrid

CA model coupled with diffusion–reaction model for temporal–spatial evolution of drug concentration in tumor growth dynamics under periodic dosing conditions. Xie et al. [16] investigated the effects of different chemotherapy on the growth dynamics based on the pharmacokinetically model, see clinical evidence and simulation results in [16]. Fig. 7, shows the model of capillaries and different cell types in the grid of the two-dimensional patch of tissue, which was proposed by Reis et al. [8].

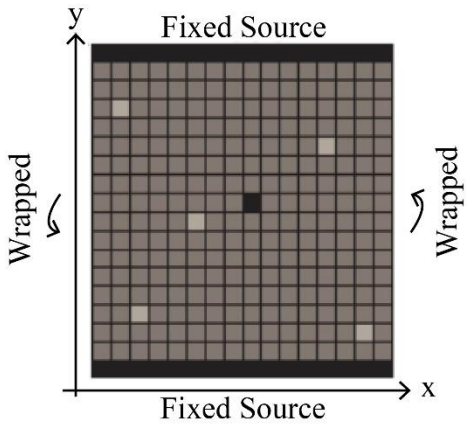

Fig. 7(a) A two-dimensional patch of tissue, blood vessels that occupy at fixed source, see details in [8], and this figure is taken from [8]

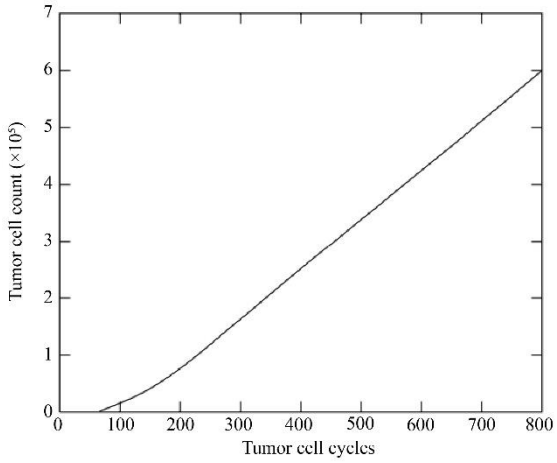

Fig. 7(b) This graph shows the tumor cell population over time which generated by Mallet and De Pillis [8] and this figure is taken from [8]

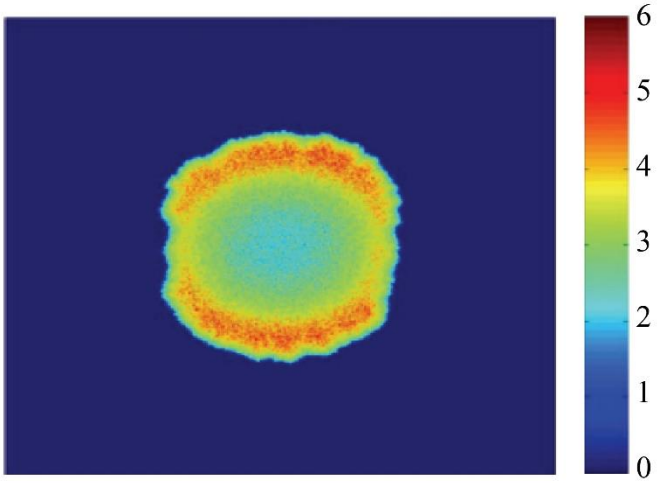

Fig. 7(c) Snapshot of simulated tumor cell distribution after 800 cell division cycle, and this figure is taken from Mallet and De Pillis [8]

3. Conclusion

The kinetics of tumor growth in biological relevant have been interesting to researchers for creating many mathematical models in various ways. This article characterized mathematical models into three types, that is discrete, continuum, or hybrid models. The study of both tumor growth and the effect the tumor growth in the different types of therapies has been shown in these referred papers. The mathematical models of tumor growth with therapies have still been challenged by modelers to develop much more complexity in their model, caused by cancer is a group of highly harmful diseases in the world.

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