Framework for Visualisation of Cancer Tumours

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Abstract. This paper discusses the use of Fister-Panetta model in the visualisation of cancerous growths. Cancer evolution and the associated proper medication strategy is an example of such a complex problem that requires an interdisciplinary approach in order to be properly addressed. The paper addresses some basic aspects regarding how cancer research could benefit from the cooperation between mathematics and biology, describes how to model and visualize cancer tumor with recursive algorithms and Fister and Panetta pattern.

Keywords: Cancer modeling, cancer visualization, computer graphics, Fister-Panetta upper bound.

1 Introduction

Cancer is a class of diseases or disorders characterized by uncontrolled division of cells, and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis. Metastasis is defined as the stage in which cancer cells are transported through the bloodstream or lymphatic system. Cancer may affect people at all ages, but risk tends to increase with age. It is one of the leading causes of death in developed countries [1].

Mathematical modeling can be a powerful tool for understanding biologically observed phenomena which cannot be understood by verbal reasoning alone. One such example is that of homeostasis in the colonic crypt. The single layer of epithelial cells that line the crypt is renewed every two to three days by a number of long-living stem cells that remain at the bottom of the crypt [2]. As the stem cells divide, their progeny migrate up the crypt wall, and once at the top they are shed into the lumen or undergo apoptosis. This general structure of stem, transit and differentiated cells is also found in many other biological systems, for example the hematopoietic system.

In recent years there has been a great deal of interest concerning three catchphrases: nonlinear dynamics, chaos, and complexity. This interest has led to a large number of popular-science articles relating to the visualization of cells, many of these feature very high end graphical simulations [3].

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carcinogenesis [5]. Models and Simulations are being widely used, for example Mathematical models have been used to describe ontogenetic growth [6]. Two-dimensional modelling has been used in the area of tumour growth and morphology [7], while simulations have been used in the area of benign avascular tumour growth [8].

Recent studies of cancer visualisations focus on fractal geometry. The irregular shapes, can be used to describe the pathological architecture of tumours and for yielding insights into the mechanisms of tumour growth and angiogenesis that complement those obtained by modern molecular methods [9]. Until now the emphases of fractal based cancer research was to determine cancer cell growth patterns at cell level but not the geometrical shape of tumour itself.

The process of understanding the underlying pathophysiology of cancer, its progression, mechanisms of drug resistance at various scales, as well as the optimization of drug dosing protocols is a quite difficult one as it is the subject of a vast amount of research, directed towards the development of effective treatment and prevention strategies. Because of the high complexity of this disease, it has always been difficult to assign quantitative measurements to each of its components [10]. This may be, in part, because of the nature of the experimental investigation, where the mechanisms are often studied and analyzed in an isolated context. It has often been suggested that a conceptual framework is highly required in order to better understand the quantitative data produced by tumor biologists and clinical oncologists. In this quite complex context, cancer research may consistently benefit from mathematical modeling and biocomputation. Of course, this approach can be fully integrated with biological research and clinical experiments and trials. Traditional biological and clinical experiments require costly investments in both time and materials, and are sensibly limited by the equipment precision, human error and the inability to distinguish between various underlying mechanisms that govern the tumor growth dynamics. Meantime, a critical weakness of the theoretical models is their plasticity in uncritically recapitulating training data, without impeding on the model's actual validity and predictive capacity. Nevertheless, models can provide researchers with tools likely to allow them to run computational experiments that would be otherwise very difficult to recreate in an experimental environment [11]. The modeling techniques could be particularly useful for analyzing phenomena like the varying adhesion forces between cells or the varying membrane permeability of a particular cell line. Also, modeling can provide valuable quantitative and even qualitative data, particularly useful for planning biological experiments, used to test the theoretical hypotheses [12]. Data produced by the biological experiments defines necessary constraints in order to choose the appropriate model parameters. Therefore, although theoretical-only and experimental-only approaches have inherent flaws and limitations, an ideal synergy between the two can be approached by using a circular and recursive-like methodology.

Mathematical models are popping up everywhere in cancer research. The approaches are as diverse as the disease they are grappling with. Fister, a mathematician at Murray State University in Kentucky, studies optimalcontrol models

that promise to provide physicians the best timetables for drug treatments. Her colleague Carl Panetta, of the St. Jude Children's Research Hospital in Tennessee, uses systems of elementary differential equations, typically 30 or 40 at a time, to predict a patient's response to a given drug regimen. At the University of Washington, applied mathematicians James Murray and Kristin Swanson have developed a brain tumor model that is simple by comparison but uses complex three-dimensional brain anatomy to improve on the predictions of physicians about the spread of the tumors. Meanwhile, in Israel, Zvia Agur from the Institute for Medical Biomathematics is working on the ultimate biomathematical model: a "virtual cancer patient" for non-Hodgkin's lymphoma, which will take into account all the stages of a cancer cell's life cycle. If these mathematical descriptions of cancer have any common denominator, it is a scrupulous attention to biological correctness. They are moving past the vague qualitative conclusions of older mathematical models in biology and making quantitative, testable predictions about real patients (or at least laboratory animals). "I have worked in applications of mathematics to biology for nearly 30 years," says Murray, who was the founding director (in 1983) of the Centre for Mathematical Biology at Oxford University [13]. "The whole tenor has changed in the last 10 years. At the Dundee meeting of the Society for Mathematical Biology, one could have been delighted to see that almost all of the talks were biologically oriented. The speakers were solving their equations quantitatively and saying what the answers predicted biologically. Having been brought up in Scotland, under the gloom of Calvinism, one shouldn't be optimistic about anything, but I am particularly optimistic about the future of mathematical biology."

To combine 3D visualisation with mathematical modeling is significant for cancer research. It not only visually quantises data, but also scientifically support data for visualisation. This combination gives an approach to visualise and simulate functionally for cancer tumour. It will truly help cancer research in both educational academic and practical area.

2 Review of Similar Works

Modelling the complex development and growth of tumour angiogenesis using mathematics and biological data is a rapidly increasing area of cancer research. Architectural complexity is the main feature of every anatomical system, including organs, tissues, cells and sub-cellular entities. The vascular system is a complex network whose geometrical characteristics cannot be properly defined using the principles of Euclidean geometry. However, fractal geometry is a more powerful means of quantifying the spatial complexity of real objects [14].

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carcinogenesis [5]. Models and Simulations are being widely used, for example Mathematical models have been used to describe ontogenetic growth [6]. Two-dimensional modelling has been used in the area of tumour growth and morphology [7], while simulations have been used in the area of benign avascular tumour growth [8].

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3 Mathematical Modeling

Mathematical models can provide for both biologists and medical personnel the necessary tools for guiding their efforts to elucidate fundamental mechanisms of cancer progression and either improve current treatment strategies or stimulate the creation of new ones. Many already proposed cancer models focus on one or more of the cancer progression phases, more specific avascular, angiogenesis or vascular, and can typically be considered a discreet, continuum or hybrid approach [13]. Continuum models are inspired by principles from fluid and continuum mechanics, and generally describe cancer-related variables, such as cell population, oxygen concentration, nutrient distribution or growth factor as continuous fields by means of differential equations. By contrast, cellular automaton (CA) models describe the dynamics of discrete elements, for example tumor cells, whose states are governed by a set of probabilistic and/or deterministic rules [15]. The state evolution of these elements can and usually must be tracked through space and time. Hybrid cancer modeling approaches generally combine continuous fields with CA descriptions. In particular, substances, such as oxygen, nutrient, drug and growth factors can be as a continuum in the tumor microenvironment, while individual CA elements dynamically evolve in response to local substance concentration [16].

3.1 General Considerations

Optimal control techniques are used to develop optimal strategies for chemotherapy. In particular, the article [17] investigates the qualitative differences between three different cell-kill models: log kill hypothesis (cell-kill is proportional to mass); Norton-Simon hypothesis (cell-kill is proportional to growth rate); and, Emax hypothesis (cell-kill is proportional to a saturable function of mass). For each hypothesis, an optimal drug strategy is characterized that minimizes the cancer mass and the cost (in terms of total amount of drug). The cost of the drug is nonlinearly defined in one objective functional and linearly defined in the other. Existence and uniqueness for the optimal control problems are analyzed [18]. Each of the optimality systems, which consists of the state system

coupled with the ad joint system, is characterized. Finally, numerical results show that there are qualitatively different treatment schemes for each model studied. In particular, the log-kill hypothesis requires less drug compared to the Norton-CSimon hypothesis to reduce the cancer an equivalent amount over the treatment interval [19]. Therefore, understanding the dynamics of cell-kill for specific treatments is of great importance when developing optimal treatment strategies. When developing effective treatment strategies, understanding the effects of chemotherapeutic drugs on tumors is of primary importance. Several approaches to modeling chemotherapeutic induced cell-kill (killing of tumor cells) have been developed. One of the early approaches was by Schabel, Skipper, and Wilcox who proposed that cell-kill due to a chemotherapeutic drug was proportional to the tumor population. This hypothesis is based on in vitro studies in the murine leukemia cell-line L1210. It states that for a fixed dose, the reduction of large tumors occurred more rapidly than for smaller tumors. Skipper's concept is referred to as the log-kill mechanism.

Norton and Simon find this model to be inconsistent with clinical observations of Hodgkin's disease and acute lymphoblastic leukemia which showed that, in some cases, reduction in large tumors was slower than in histologically similar smaller tumors. Therefore, Norton and Simon hypothesize that the cell-kill is proportional to the growth rate (e.g., exponential, logistic, or Gompertz) of the tumor. A third hypothesis notes that some chemotherapeutic drugs must be metabolized by an enzyme before being activated. This reaction is saturable due to the fixed amount of enzyme. Thus, Holford and Sheiner [20] develop the Emax model which describes cell-kill in terms of a saturable function of Michaelis-CMenton form. Fister and Panetta have previously developed a treatment strategy using optimal control techniques for the use of cellcycle specific drugs such as Taxol for the reduction of breast and ovarian cancers [19]. The model included a resting phase which made it more realistic in the clinical setting. Among other things, the model showed that treating with repeated shorter periods allows more drug to be given without excess damage to the bone marrow. Several other models where optimal control methods have been utilized in analyzing effective chemotherapeutic treatments include Swan and Murray. Swan obtained feedback treatment control drug characterizations for cancer models under a quadratic performance criterion. Murray has considered systems of normal and tumor cells under the hypotheses of Gompertzian and logistic growth in which he controls the rate of administration of drugs. Murray has minimized the tumor burden at the end of treatment and, in another application, the toxicity level, defined as the area under the drug concentration curve.

4 Application for Cancer

The 3D visualization system is a Java based application that uses the Swing package for User Interface design and the Java3D package for rendering the 3D scene. There are three distinct sections to the interface (Figure 1). The main display window (1), which displays the 3D tumour rendering. It provides zoom

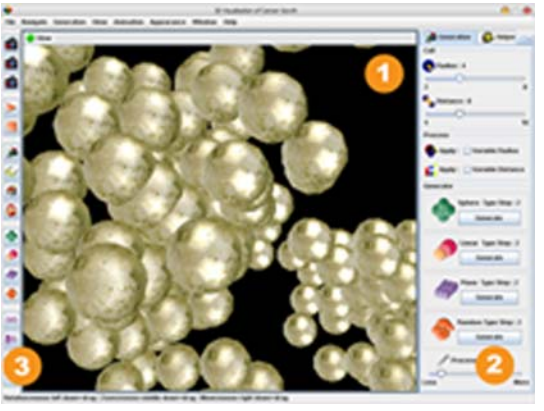

Fig. 1. Interface of application

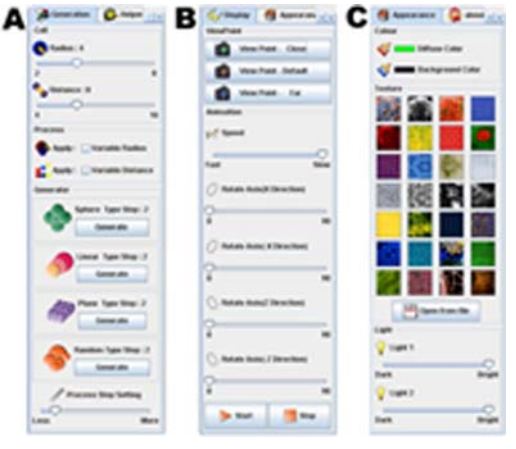

Fig. 2. Control Panel Group

and rotational, user interaction modalities. The Control Panel (2) situated to the right of the main visualisation window, allows for the modification of input parameters to the visualisation engine. It contains a group of tabs for various controlling functions. The tool bar (3), features options to quickly change settings such as camera views, animation, saving of images to disk, and so forth.

4.1 Recursive Routing

The visualisation engine provides for four differing methods of scene generation: Sphere, Linear, Plain and Random. The Sphere mode allows tumour growth to extend out from a central mass in a spherical fashion. Linear growth extends the tumour mass in one direction only. The Plane type allows for growth across an axial plain. Random tumour growth produces a mass that extends from the nodal point in an irregular pattern.

A rendering class specifies all the nuances of how a tumour may be described, details include type, age, cell details and so on. Each type of tumour visualisation has its own generation procedures and includes recursive method calls to generate new cells.

Two of the most notable parameters that influence the behaviour of the recursive methods ability to generate new cells are: sphere radius(R) and the step (level).

Within a 3D coordinate system, the initial construct is a sphere, the central point of the sphere is mapped to the origin of 3D space (0, 0, 0) , the radius is R. Therefore there are 6 directional vectors by which the tumour can grow outward from the central point.

Tumour volume is related by radius. Recursive functions get level parameter to generate surface of tumour with different radius that calculated by volume result of mathematical functions.

The code shows how to generate a tumour with specified volume(Listing 1.1). To generate tumour for specified volume, first gets radius with tumour type. Then calculate the level that recursive functions needed by voxel radius. Finally call recursive functions to generate tumour.

```
function generateVolume(volume){
    var radius = getRadius(volume, tumourType);
    var level = getRecursiveLevel(radius, voxelRadius);
    processDivid(level, vectora, vextorb);
    ...
}
```

Listing 1.1. Generate tumour with specified volume

Tumour growth is determined by the inclusion of additional cancerous cells. Given any two neighbouring voxels (v_1, v_2) a new central voxel can be added(v_3). With the inclusion of the new voxel (v_3), examination of the relation between it and its outlying neighbours, voxels (v_1, v_2) will allow for the addition of another two voxels (v_4, v_5). This operation is carried out recursively until the desired level of detail is reached (Listing 1.2).

```
public void processDivid(int level, Vector3d v1,
                                 Vector3d v2){
  if (level<=0) return;

  Vector3d vc=getCenterVector(v1,v2);
  rootBG.addChild(
  new Cell(appc,vc,getRRnum()));
  //get center voxel

  processDivid(level-1,v1,vc);
  // recursion
  processDivid(level-1,v2,vc);
  // recursion
}
```

Listing 1.2. Recursive Cell Insertion between two neighbouring Voxels

Insertion of additional voxels between three neighbouring voxels (v_1, v_2, v_3) requires the insertion of a central voxel (v_4). Between this new voxel (v_4) and the three initial voxels (v_1, v_2, v_3) insert voxels (v_5, v_6, v_7). For two of the new voxels (v_5, v_6, v_7) and one of the original voxels (v_1, v_2, v_3) carry out the same operations as for voxels (v_1, v_2, v_3). The recursion parameter (level) (Listing 1.3) is the step of the insert processing.

```
public void processDivide(int level, Vector3d v1,
          Vector3d v2,Vector3d v3){
  if (level<=0) return;

  Vector3d vc=getCenterVector(v1,v2,v3);
  rootBG.addChild(new Cell(appc,vc,getRRnum()));
  // and center cell into three voxels
  Vector3d newvc1=getCenterVector(v1,v2,vc);
  rootBG.addChild(new Cell(appc,newvc1,getRRnum()));
  Vector3d newvc2=getCenterVector(v1,v3,vc);
  rootBG.addChild(new Cell(appc,newvc2,getRRnum()));
  Vector3d newvc3=getCenterVector(v2,v3,vc);
  rootBG.addChild(new Cell(appc,newvc3,getRRnum()));
  // get three new cells
  processDivide(level-1,v1,newvc1,newvc2);
  processDivide(level-1,v2,newvc3,newvc1);
  processDivide(level-1,v3,newvc2,newvc3);
}
```

Listing 1.3. Recursive Cell Insertion between three neighbouring Voxels

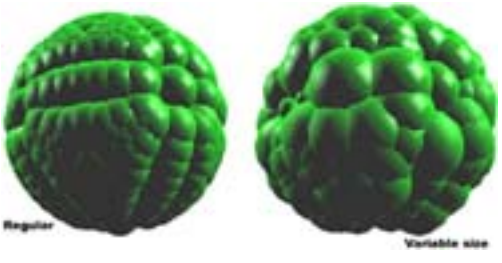

Fig. 3. Example of sphere geometry

An example of the spherical geometry shape (Figure 3) gives an example of the output produced from the algorithms above. In this case the step of the processing is two. It shows spherical geometry with uniform cell size (left) and random cell size (right).

4.2 Critiques of the Application

The visualisation algroithms are based only on visual. The cancer cell simply presented by sphere and the quantity of cancer is reduced. This application is not

based on mathematical modeling. This might limit the practical of application only on education. It can't be use for most of research propose that need precise calculation or mathematical framework.

Sphere presentation for voxel spends too much system resource. Only small part of surface be presented in final image, rest of surface increases data and occupation of memory space. It will decrease calculation speed and rendering performance.

The application generates tumour without exact volume. The overlapped sphere voxels are hard to calculation. Mensuration of research is not rely on this presentation algorithms.

5 Framework for Cancer Visualisation

The Fister-Panetta growth provides a very realistic approach for the cancer control, considering a significant amount for the dose magnitude and control.

Some simple simulation was carried out with a dose magnitude of 0.1 units and a response to the treatment of 1 for several values of the cancer grow rate. As we can see, $N_0(t)$ (represented by the red line) is an upper bound for the cancer growth. The third problem $N_3(t)$ is closely related to the upper bound, its graph being represented by the orange line. The first and the second problems $N_1(t)$ and $N_2(t)$, represented by the blue and the green lines respectively, prove to have a sensibly less abrupt growth rate. In other words, these mathematical models of the drug administration therapy configure the best options for designing a drug administration strategy and, therefore, they are more likely to be used for the real medical activity calibration. The numerical values for $r = 0.05$, $r = 0.1$ and $r = 0.2$ are represented in the next 2 figures. Figures (Figure 5) and (Figure 7) show the output of the simulation when using $N_1(t)$.

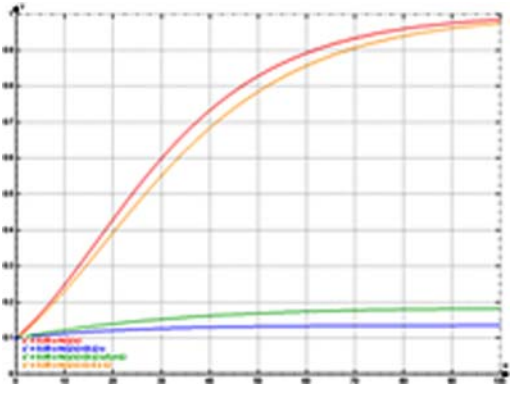

Fig. 4. Fister-Panetta growth functions for $r = 0.05$

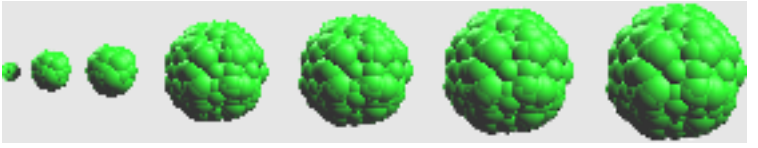

Fig. 5. Tumour simuliation growth functions for $r = 0.05$

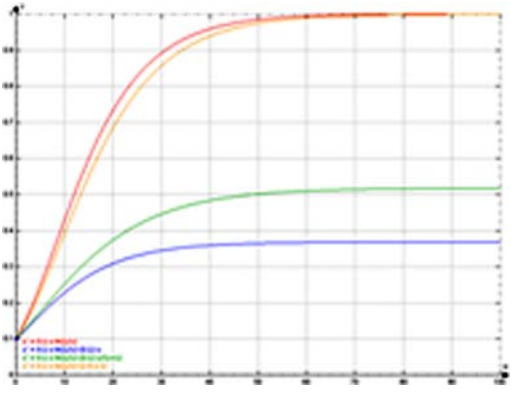

Fig. 6. Fister-Panetta growth functions for $r = 0.1$

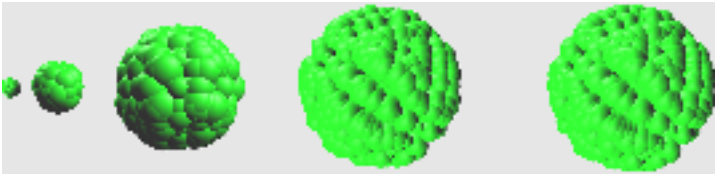

Fig. 7. Tumour simuliation growth functions for $r = 0.1$

6 Conclusion

The article specifies a general framework to simulate growth of cancer tumour. The mathematical model generates cancer tumour volume by time; volume value could be used for 3D visualisation of cancer tumour that could be simulation cancer tumour growth under different situations. Thus, this framework could be useful for similar medical simulation work with different mathematical models and visualisation tools.

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