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CANCER GROWTH MODELS AND ITS TREATMENT

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ABSTRACT. The success of radiotherapy treatment relies in accurately localizing the target region close to tumor as well as avoiding damage to the nearby healthy organ. In order to control the tumor growth and minimize side effects to the patient, it is crucial to make some substantial modifications on the patient's anatomy due to the reduction of the patient's weight; shrinkage of the tumor; and the edema of the tissue before the treatment. For surgery consideration, an efficient registration method to delineate the clinically critical objects in computed tomography images obtained from the radiation treatment process is needed. Over the last decades, the Deformable Image Registration Model has undergone intensive investigation from researchers in the fields of computer vision, remote sensing, and etc. Despite the significant progress that has been made, deformable registration remains a challenging problem in the field of radiotherapy. In this paper, we discuss several Cancer Growth Models, as well as the Deformable Image Registration techniques used in Radiotherapy treatment and finally, the model of Quenching-induced deactivation of photosensitizer to improve phototherapy of cancer will be introduced.

AMS (MOS) Subject Classification. 39A10.

1. INTRODUCTION

Cancer is the leading cause of death in Hong Kong over the last decade. Approximately 60% of cancer patients are treated with external beam radiotherapy treatment in which the localization of killing the target region (tumor) as well as avoiding damage to the healthy organ (organ at risk) is crucial to control the tumor growth and minimize the side effects to the patient.

Radiotherapy is one of the essential treatments on cancer diseases, which works by destroying the genetic material of cancer cells with ionizing radiation. The radiation can be administered as external beam radiotherapy (EBRT) where a planned radiation dose is delivered from an external device. This radiotherapy planning is based on the information from the Computed Tomography (CT) scan. In surgery operation, the geometric changes due to digestive process and growth or shrinkage of the tumor of the target and healthy organ over the process of radiation therapy may lead

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to severe treatment uncertainties. The integration of different image sources (CT and Magnetic Resonance (MR)) helps to reduce the geometric difference but the patient's weight loss; tumor shrinkage; and tissue edema will induce substantial modification of his anatomy during radiotherapy (RT) or chemo-radiotherapy. These modifications may have impact on the dose distribution to both target volumes (TVs) and organs at risk (OARs). Adaptive radiotherapy (ART), in which patients are re-imaged and re-planned several times during the treatment, is a common strategy to improve treatment delivery that requires a proper validation of some specific deformable registration (DR) algorithms on a clinical material. Nowadays, Photodynamic therapy (PDT) is also a treatment that uses a photosensitizer or photosensitizing agent, and a particular type of light that come from a laser. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. In this paper, we present several Cancer Growth Models, as well as the Deformable Image Registration techniques used in Radiotherapy treatment and introduce the model of Quenching-induced deactivation of photosensitizer to improve phototherapy of cancer.

2. MATHEMATICAL MODELS OF TUMOR GROWTH

Due to its internal complexity, tumor growth kinetics follow relatively simple laws that can be expressed as mathematical models. For all the models given below, the descriptive variable is the total tumor volume, denoted by V, as a function of time t. It is assumed to be proportional to the total number of cells in the tumor c.

2.1. Model 1: Exponential-linear models.

Let c be the population of cancer cell, $\lambda(c)$ be the cell proliferation function, giving the growth rate

$$\frac{\partial c}{\partial t} = \lambda(c)c \tag{2.1}$$

$$c(0) = c_0, \tag{2.2}$$

the coefficient c_0 denotes the initial population of cancer cell. The particular solution to the differential equation is

$$c = c_0 \exp(\lambda(c)t), \quad \lim_{t\to\infty} c \to \infty. \tag{2.3}$$

2.2. Model 2: Logistic and Gompertz models.

A general class of models used for quantification of tumor growth kinetics have a sigmoid shape, i.e., an increasing curve with one inflection point that asymptotically converges to a maximum volume, the carrying capacity of cancer cell, denoted by K. The Gompertz model suggests

$$\frac{\partial c}{\partial t} = \lambda(c) \ln \frac{K}{c} c \tag{2.4}$$

$$c(0) = c_0. \tag{2.5}$$

The particular solution to the differential equation is

$$c = K \exp\left(\ln \frac{c_0}{K} \exp(-\lambda(c)t)\right), \quad \lim_{t\to\infty} c \to K. \tag{2.6}$$

Limitation of Gompertz Model: Single set of growth parameter $\lambda(c)$ is insufficient to model the clinical data. Tumor cells have different growth characteristics in different patient. Micrometastases within a single patient may have different growth parameter. Readers may refer to the paper of Bloor and Wilson [12].

2.3. **Model 3: A General Tumor Growth Models.** The rate of change of the particular cell population in terms of growth and death, cell-cell kill, cell recruitment, and cell inactivation. In particular, rate of change of cancerous cell population = net proliferation of the cancerous cells + diffusion (random motility) of the cancerous cells − tumor invasion (taxis) due to chemical and molecular species. That is

$$\frac{\partial c}{\partial t} = \underbrace{\lambda(c)c}_{\text{cell proliferation}} - \underbrace{\delta(c)c}_{\text{cell death}} + \underbrace{\phi(c)\nabla^2 c}_{\text{random motility}} - \underbrace{\psi\nabla\cdot(c\nabla f)}_{\text{taxis}}, \tag{2.7}$$

where $\delta(c)$, $\phi(c)$, ψ and f represents the cell death function, tumor specific random motility, taxis coefficients and host. [13] and [14].

2.4. **Model 4: Presence of Radiotherapy.** In the presence of radiotherapy, model 3 can be modified as

$$\frac{\partial c}{\partial t} = \underbrace{\lambda(c)c}_{\text{cell proliferation}} - \underbrace{\delta(c)c}_{\text{cell death}} + \underbrace{\phi(c)\nabla^2 c}_{\text{random motility}} - \underbrace{\psi\nabla\cdot(c\nabla f)}_{\text{taxis}} - R(\alpha,\beta,d,t)c, \tag{2.8}$$

where

$$R = \begin{cases} 0, & \text{radiotherapy does not exist} \\ 1-S, & \text{radiotherapy exist,} \end{cases} \tag{2.9}$$

represents the proportion of cell loss due to radiation with dose d at time t for cells with radiosensitivity parameters α and β, in which S is the cell surival function.

3. CANCER IMAGING

Radiotherapy is one of the essential treatments on cancer diseases, which works by destroying the genetic material of cancer cells with ionizing radiation. The radiation can be administered as external beam radiotherapy (EBRT) where a planned radiation dose is delivered from an external device. This radiotherapy planning is based on the information from the Computed Tomography (CT) scan. In surgery operation, the geometric changes due to digestive process and growth or shrinkage of the tumor of the target and healthy organ over the process of radiation therapy may lead to severe treatment uncertainties. The integration of different image sources (CT and Magnetic Resonance (MR)) helps to reduce the geometric difference but

the patient's weight loss; tumor shrinkage; and tissue edema will induce substantial modification of his anatomy during radiotherapy (RT) or chemo-radiotherapy. These modifications may have impact on the dose distribution to both target volumes (TVs) and organs at risk (OARs). Adaptive radiotherapy (ART), in which patients are re-imaged and re-planned several times during the treatment, is a common strategy to improve treatment delivery that requires a proper validation of some specific deformable registration (DR) algorithms on a clinical material.

Aligning images rigidly allows some changes in images to be easily detected. Such an alignment, however, does not model the changes from organ deformation; patient's weight loss; or tumor shrinkage. It is possible to take such changes into account using deformable image registration (DIR) which gives the mapping between points in one image and the corresponding points in another image. DIR has the perspective of being widely integrated into many different steps of the radiotherapy process. The tasks of planning, delivery and evaluation of radiotherapy can also be improved by taking organ deformation into account. Use of deformable image registration in image guided radiotherapy (IGRT) can be split into intra- and inter-patient registrations. Some related methods have been reported in [1], [2], [3] and [4].

Deformable image registration technique is a clinical tool to restore the displacement and deformation of organs in a series of medical images. The volumetric analysis and the positional changes in TVs and OARs can be observed efficiently and accurately in the patient during the concomitant chemo-radiotherapy so that adaptive strategies can be adopted to improve the treatment delivery.

3.1. **Deformable Image Registration.** The mathematical formulation of deformable image registration is an ill-posed problem because there is in general no unique solution to the model of a registration problem. In order to overcome the unstable computation due to the ill-posedness, the image registration models are commonly formulated as the following optimization problem.

Image registration is defined as finding the functions h and g in the following mapping between two images I_1 and I_2:

$$I_2(x, y) = g(I_1 h(x, y)), \tag{3.1}$$

where I_1 is the source image and I_2 is the reference image. The images I_1 and I_2 can be thought of a $\mathbb{R}^2 \to \mathbb{R}^2$ mappings from two dimensional coordinates to image intensities.

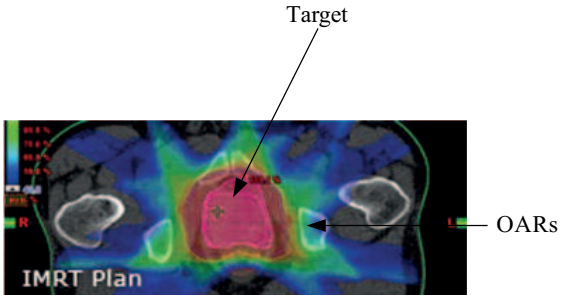

FIGURE 1. IMRT plan for patient with prostate cancer, adopted from Varian Medical Systems, Palo Alto, CA.

The main feature of deformable image registration is to resolve the differences in geometry whereas the modality-specific differences in information content of corresponding structures across image data sets are maintained. The solution of deformable registration allows the transfer of geometrically corrected dose of target volumes (TVs) and organs at risk (OARs) among images (Figure 1).

The quantitative description of physiological motion patterns, measurement of image-based surrogates of treatment response, and the reconfiguration of dose patterns and determination of their effect in deforming anatomy on a patient-specific basis can then be achieved. Details can be found in [5].

Based on a core component of deformable registration model developed by Pennec et al [6], the Diffusion or Demon's algorithm is described as follows:

The deformation field is defined as

$$\mathbf{u} = \frac{(\mathbf{m}-\mathbf{s})\nabla\mathbf{s}}{|\nabla\mathbf{s}|^2 + (\mathbf{m}-\mathbf{s})^2} = \frac{\mathbf{F}\nabla\mathbf{s}}{|\nabla\mathbf{s}|^2 + \mathbf{F}^2}, \tag{3.2}$$

where $\mathbf{F} = \mathbf{m} - \mathbf{s}$ is the external force, or the differential force between the static and moving images. Rearranging equation (3.2) gives

$$\mathbf{u}\left(|\nabla\mathbf{s}|^2 + \mathbf{F}^2\right) - \mathbf{F}\nabla\mathbf{s} = \mathbf{0}, \tag{3.3}$$

where $\mathbf{u} = (u_x, u_y)^T$ is the displacement from the deformed image to the static image, $\nabla = (\partial/\partial x, \partial/\partial y)$ is the spatial derivatives and $\nabla\mathbf{s}$ is the gradient of the static image. To obtain numerical solution to the partial differential equation given by equation (3.3), the common discretization techniques included variational approximations, boundary integral equations method, finite difference method and finite element method. In these discretization methods, the computational framework is based on a set of grids/elements generated over the concerned domain. The common type of finite elements includes triangular, quadrilateral, or unstructured elements. The strict requirements on proper distributions of these grids/elements for stable numerical approximation pose an intrinsic difficulty on the development of interactive deformation image registration package for surgery use because these grids/elements

generation are extremely difficult and troublesome for problems with complex domains.

4. MATHEMATICAL MODEL OF PHOTOTHERAPY

Suppose a tumor was inscribed by 3-dimensional ball B centered at the origin with a radius R $\{\mathbf{x} \in \mathbb{R}^3 : |\mathbf{x}| < R\}$, $\bar{B}$ be its closure, and ∂B be its boundary. Let $v(\mathbf{x})$ be the unit inward normal at $\mathbf{x} \in \partial B$, and $\chi_B(\mathbf{x})$ be the characteristic function such that

$$\chi_B(\mathbf{x}) = \begin{cases} 1, & \mathbf{x} \in B, \\ 0, & \mathbf{x} \in \mathbb{R}^3 \backslash B. \end{cases}$$

Consider the following 3-dimensional semilinear parabolic first initial-boundary value problem on a semi-infinite interval with a concentrated nonlinear source on ∂B

$$Lu = \alpha \frac{\partial \chi_B(\mathbf{x})}{\partial v} f(u(\mathbf{x}, t)) \quad \text{in } \Omega = \mathbb{R}^3 \times [0, T], \tag{4.1}$$

$$u(\mathbf{x}, 0) = 0 \quad \text{for } \mathbf{x} \in \mathbb{R}^3 \tag{4.2}$$

$$u(\mathbf{x}, t) \to 0 \quad \text{as } |\mathbf{x}| \to \infty \quad \text{for } 0 < t \leq T, \tag{4.3}$$

where $L = \partial/\partial t - \Delta$, α and T be positive real number, there is a nonlinear heat source of strength $\alpha f(u)$, where f is a given function such that

$$f(u) \to \infty \text{ as } u \to c^- \quad \text{for some positive constant } c, \tag{4.4}$$

and $f(u)$ and its first and second derivative $f'(u)$ and $f''(u)$ are positive for $0 \leq u < c$. A solution u is said to quench in a finite time if there exists a real number $t_q \in (0, \infty)$ such that

$$\sup\{u(\mathbf{x}, t) : \mathbf{x} \in \mathbb{R}^3\} \to c^- \quad \text{as } t \to t_q. \tag{4.5}$$

Chan and Tragoonsirisak [7] showed that the nonlinear equation in (4.1) has a unique nonnegative continuous solution u, which is a strictly increasing function of t. u quenches everywhere on ∂B and there exists a number α^* such that u exists globally for $\alpha \leq \alpha^*$ and quenches in a finite time t_q for $\alpha > \alpha^*$, where α^* is given as

$$\alpha^* = \frac{1}{R\Gamma(1)} \max_{0 \leq U(b) \leq c} \frac{U(b)}{f(U(b))}, \quad \text{where } U(\mathbf{x}) = \lim_{t \to \infty} u(\mathbf{x}, t). \tag{4.6}$$

The solution of u that quenches on the boundary of B can apply into the Photodyamic therapy (PDT), PDT uses toxic free light-sensitive compounds that are exposed selectively light, immediately after which they become toxic to the diseased cells or other malignant cancers. It is widely used clinically to deal with a wide range of medical conditions, such as malignant cancer. The treatment of PDT is recognised as a treatment technique which offers both minimally invasive and minimally toxic to the OARs.

The Chinese have been developing specialist clinical expertise with PDT using their own locally produced photosensitizers, derived from Haematoporphyrin, and light sources for more than 25 years [8]. PDT in Asian countries, such as China is especially distinguished for the technical skill of specialists in effecting resolution of difficult to reach cancer cells [9].

5. CONCLUSION AND FUTURE WORK

In this paper, we review some model of tumor growth and present the model of Quenching-induced deactivation of photosensitizer, which improve phototherapy of cancer because it offer minimal invasive and toxic to the OARs.

The modelling of deformable image registration algorithm in the radiotherapy treatment. The pre-treatment planning and post-treatment evaluation of radiotherapy are tasks that run over hours or days. A short registration time is crucial in the development of interactive deformation image registration package suitable for surgery use.

Meshless computational methods have been recognized to be more suitable for solving problems with complex domains and hence are favorable in solving medical image registration problems. Among these meshless methods, the radial basis functions as a special kind of kernels is found to have advantages over the traditional mesh-dependent finite element or finite difference methods. Based on our recent meshless computational method using radial basis functions as a special kind of kernels [10-11], we will devise a computational package for the deformable image registration model given in equations (3.2) and (3.3).

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