Medical Image Analysis 18 (2014) 555–566

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

# Patient specific tumor growth prediction using multimodal images

Yixun Liu [a], Samira M. Sadowski [b], Allison B. Weisbrod [b], Electron Kebebew [b], Ronald M. Summers [a], Jianhua Yao [a,*]

[a] Clinical Image Processing Service, Radiology and Imaging Sciences, NIH, United States
[b] Endocrine Oncology Branch, National Cancer Institute, NIH, United States

ARTICLE INFO

*Article history:*
Received 31 May 2013
Received in revised form 2 December 2013
Accepted 11 February 2014
Available online 20 February 2014

*Keywords:*
Tumor growth modeling
Multimodal images
Intracellular Volume Fraction
Metabolic rate

ABSTRACT

Personalized tumor growth model is valuable in tumor staging and therapy planning. In this paper, we present a patient specific tumor growth model based on longitudinal multimodal imaging data including dual-phase CT and FDG-PET. The proposed Reaction–Advection–Diffusion model is capable of integrating cancerous cell proliferation, infiltration, metabolic rate and extracellular matrix biomechanical response. To bridge the model with multimodal imaging data, we introduce Intracellular Volume Fraction (ICVF) measured from dual-phase CT and Standardized Uptake Value (SUV) measured from FDG-PET into the model. The patient specific model parameters are estimated by fitting the model to the observation, which leads to an inverse problem formalized as a coupled Partial Differential Equations (PDE)-constrained optimization problem. The optimality system is derived and solved by the Finite Difference Method. The model was evaluated by comparing the predicted tumors with the observed tumors in terms of average surface distance (ASD), root mean square difference (RMSD) of the ICVF map, average ICVF difference (AICVFD) of tumor surface and tumor relative volume difference (RVD) on six patients with pathologically confirmed pancreatic neuroendocrine tumors. The ASD between the predicted tumor and the reference tumor was 2.4 ± 0.5 mm, the RMSD was 4.3 ± 0.4%, the AICVFD was 2.6 ± 0.6%, and the RVD was 7.7 ± 1.3%.

Published by Elsevier B.V.

## 1. Introduction

Quantitatively characterizing the tumor spatial–temporal progression is valuable in staging tumor and designing optimal treatment strategies. In clinical practice, due to the lack of the characterization of the spatially heterogeneous pattern of the cancer progression, a conservative therapy is usually adopted by treating a margin of normal-appearing tissue surrounding the tumor as part of the tumor. This conservative approach necessities a better understanding of the spatial–temporal progression of the tumor.

Tumor growth not only relies on the properties of cancer cells, but also depends on dynamic interactions among cancer cells, and between cells and their constantly changing microenvironment. The complexity of the cancer system motivates the study of the tumor growth using mathematical models (Swanson et al., 2000; Clatz et al., 2005; Hogea et al., 2008).

Cancer modeling can be classified into four scales: atomic, molecular, microscopic, and macroscopic (Deisboeck et al., 2011). Atomic scale modeling studies the structure and dynamic properties of proteins, peptides, and lipids, as well as their dependency on the features of the environment using molecular dynamics. Molecular scale modeling studies average properties of a population of proteins, peptides, and lipids. Microscopic scale, i.e. tissue or multicell, studies cell–cell and cell–microenvironment interactions. Macroscopic scale studies dynamics of the gross tumor behavior including morphology, shape, extent of vascularization, and invasion, which are observable by clinical imaging data. Tumor modeling requires the knowledge of the underlying tumor physiological parameters. Clinical imaging data offers the benefit of non-invasive, in vivo and timely measurement of these parameters. In this paper, we focus on the image-driven tumor modeling on the macroscopic scale.

In the image-driven tumor modeling field, Swanson et al. (2000) assumed an infiltrative growth of the tumor cells, while considering differences in cell diffusion in white and gray matter. Clatz et al. (2005) modeled locally anisotropic migration patterns by integrating information from diffusion tensor images (DTI). Hogea et al. (2008) included the mechanical properties of the lesion on surrounding structures to model mass effect.

* Corresponding author. Address: Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, 10 Center Drive, Building 10, Rm 1C515, Bethesda, MD 20892-1182, United States. Tel.: +1 301 402 3225.
*E-mail address:* JYao@cc.nih.gov (J. Yao).

http://dx.doi.org/10.1016/j.media.2014.02.005
1361-8415/Published by Elsevier B.V.

In this paper, we not only consider mass effect, but also the cell metabolic rate. To incorporate cell metabolism into the tumor growth modeling, we combine the energy conservation law presented in West et al. (2001) with cell proliferation law (Swanson et al., 2000). As pointed by West et al. (2001), ontogenetic development is fuelled by metabolism and occurs primarily by cell division. The incoming metabolic energy is allocated to two parts: one part for the maintenance of the existing cells and the other part for the creation of new cells. This work was further extended by Herman et al. to study the relationship between tumor vascularization and growth (Herman et al., 2011). FDG-PET (2-[18F] Fluoro-2-deoxyglucose positron emission tomography) is widely used in oncology to find regions in the body which are more active and need more energy, which motivates us to use FDG-PET to measure metabolic rate and incorporate it into the tumor growth modeling. Tracer kinetic modeling is a formal way to calculate glucose metabolic rate (Huang et al., 1980); however, this modeling approach usually requires taking series of blood samples from the studied subject to give the time course of the tracer delivery and requires measuring the dynamics of the radiolabel in local tissues. Standardized Uptake Value (SUV) is a semi-quantitative measurement of the metabolic rate and does not need dynamic blood sampling and PET scanning, therefore is suitable for routine clinical use. In this paper, we present the quantitative relation between both glucose metabolic rate and SUV, and the proliferation rate of the model.

Anatomical modality imaging data such as CT and MRI can be used to monitor the progress of the tumor boundary, which motivates the studies (Swanson et al., 2000; Clatz et al., 2005; Hogea et al., 2008) on using tumor boundary as the biomarker to estimate model parameters by comparing the predicted tumor boundary with the measured boundary. However, tumor boundary only provides quite limited tumor physiological information and in some cases cannot really reflect the growth of the tumor. For instance, the cancerous cell proliferation might not be reflected in the tumor boundary progression, which motivates us to find a way to extract the underlying physiological parameter related to the cell number. In this paper, we introduce Intracellular Volume Fraction (ICVF) into tumor growth modeling and present the principle and method to estimate ICVF using dual-phase CT.

In this paper, we focus on integrating FDG-PET and CT into tumor modeling. Our work is based on the extension of a Reaction–Diffusion model (Swanson et al., 2000). The Reaction–Diffusion model plays a fundamental role in modeling spatial–temporal dynamics in system biology. The Reaction–Diffusion model describes the change of the cell density or population. However, (1) the Reaction–Diffusion model does not incorporate cell metabolic rate and (2) due to the difficulty to calculate the cell number, the prediction of the Reaction–Diffusion model, i.e., the cell number has to be converted to the front progression in order to connect the model with the clinical observation (tumor boundary). In this paper, we (1) develop a Reaction–Diffusion model enabling the incorporation of the cell metabolic rate and (2) present a method to calculate ICVF using dual-phase CT. As a result, the model prediction can be directly related to clinical imaging data.

The proposed model is formalized as a coupled PDE system (forward problem). The patient specific parameters (control variables) are estimated by fitting the model prediction to the observed tumor leading to a coupled PDE-constrained optimization problem (an inverse problem). To obtain realistic solution, Tikhonov regularization was introduced to regularize the solution. The optimality system was derived and solved by the Finite Difference Method (FDM).

The proposed model was evaluated on pancreatic neuroendocrine tumors. A dedicated protocol was developed to accumulate longitudinal CT and FDG-PET of untreated pancreatic tumors. The only work on the pancreatic tumor modeling that we are aware of is (Haeno et al., 2012), in which the authors used a compartment model to divide the cell population into three subpopulations: primary tumor cells, metastasis-enabled cells and metastasized cells. The migration rate between subpopulations and the growth rate and death rate within each subpopulation were estimated based on autopsy data. In this paper, we focus on the way to combine routine clinical multimodal images to study the growth of the primary solid tumor.

## 2. Material and methods

In this section, we first present the whole framework of the modeling and evaluation; second, derive a Reaction–Advection–Diffusion model incorporated with cell metabolic rate and mass effect; third, describe how to adapt the model to associate it with routine dual-phase CT and FDG-PET; finally, describe the process for parameter estimation using longitudinal imaging data.

The flow chart of the proposed method is illustrated in Fig. 1. The flow chart includes two parts: parameter estimation and evaluation. We introduce ICVF as the biomarker for both model parameter estimation and evaluation. In the parameter estimation part, ICVF calculation takes longitudinal dual-phase CT images as inputs. At each time point, ICVF is measured based on pre- and post-contrast CT images (see Section 2.2 for details). The measured ICVF at the 1st follow-up is compared with the predicted ICVF growing from the base line to find the optimal parameters $\boldsymbol{g}$ by minimizing the deviation between the two ICVF maps. Once the model parameter $\boldsymbol{g}$ is estimated, the tumor grows from the 1st follow-up with estimated model parameter. The predicted ICVF and the extracted tumor surface are compared with the measured ICVF and tumor surface at the 2nd follow-up for evaluation.

To use dual-phase CT to calculate ICVF, the non-rigid registration for the imaging data at one time point, i.e., between pre- and post-contrast CT, needs to be performed. To incorporate PET into the model, we also need to non-rigidly align the post-contrast CT and PETCT, and then apply the transform to the PET. The non-rigid registration method we used was the Free-Form Deformation (FFD) based method in Rueckert et al. (1999). To align the longitudinal data, we performed the rigid registration between longitudinal post-contrast CT using an ITK implementation of an affine transform-based registration (Yoo et al., 2002). For the tumor segmentation, we used a Level Set segmentation implemented in Malladi et al. (1995).

### 2.1. Derive the tumor growth model

According to the tumor logistical growth model presented in Swanson et al. (2000), the number of the newly created cells within unit time can be described by,

$$\frac{dN}{dt} = \rho N\left(1 - \frac{N}{K}\right) \tag{1}$$

where $N$ is the number of cells, a function of time $t$. $\rho$ is spatial–temporal invariant proliferation rate. This model describes that the tumor grows exponentially at the beginning and then gradually slows down as approaching the carrying capacity $K$.

As a tumor progresses, the parts with sufficient nutrients and oxygen grow faster, and those suffering vascular inefficiencies will develop into necrosis, suggesting a heterogeneous or spatial–temporal varying proliferation function $\rho(\boldsymbol{x}, t)$. The metabolic energy conservation law presented by West et al. (2001) quantitatively describes the relationship between the metabolic energy and the ontogenetic growth, providing the theoretical foundation to explore the heterogeneity of the proliferation rate. The energy

Download English Version:

https://daneshyari.com/en/article/444064

Download Persian Version:

https://daneshyari.com/article/444064

Daneshyari.com