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Tumor growth prediction with reaction-diffusion and hyperelastic biomechanical model by physiological data fusion

Ken C.L. Wong [a], Ronald M. Summers [a], Electron Kebebew [b], Jianhua Yao [a,*]

[a] Clinical Image Processing Service, Radiology and Imaging Sciences, Clinical Center, NIH, Bethesda, MD, USA
[b] Endocrine Oncology Branch, National Cancer Institute, NIH, Bethesda, MD, USA

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ABSTRACT

The goal of tumor growth prediction is to model the tumor growth process, which can be achieved by physiological modeling and model personalization from clinical measurements. Although image-driven frameworks have been proposed with promising results, several issues such as infinitesimal strain assumptions, complicated personalization procedures, and the lack of functional information, may limit their prediction accuracy. In view of these issues, we propose a framework for pancreatic neuroendocrine tumor growth prediction, which comprises a FEM-based tumor growth model with coupled reaction-diffusion equation and nonlinear biomechanics. Physiological data fusion of structural and functional images is used to improve the subject-specificity of model personalization, and a derivative-free global optimization algorithm is adopted to facilitate the complicated model and accommodate flexible choices of objective functions. With this flexibility, we propose an objective function accounting for both the tumor volume difference and the root-mean-squared error of intracellular volume fractions. Experiments were performed on synthetic and clinical data to verify the parameter estimation capability and the prediction performance. Comparisons of using different biomechanical models and objective functions were also performed. From the experimental results of eight patient data sets, the average recall, precision, Dice coefficient, and relative volume difference between predicted and measured tumor volumes were 84.5 ± 6.9%, 85.8 ± 8.2%, 84.6 ± 1.7%, and 14.2 ± 8.4%, respectively.

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1. Introduction

The goal of tumor growth prediction is to accurately model the tumor growth process, which is mainly achieved by physiological modeling and model personalization from clinical measurements. If accurate prediction can be achieved from noninvasive measurements, better treatment planning and patient prioritization can be determined, allowing more efficient use of resources. For example, if tumor doubling times of pancreatic neuroendocrine tumors can be estimated, the risk of metastatic disease, operative resection, and unnecessary testing can be better managed (Blansfield et al., 2007). Furthermore, if phenotype or genotype information can be revealed from the personalized growth model, outcomes of drug treatments can be improved with reduced toxicity (Clayton et al., 2006; Schilsky, 2010).

Tumor growth modeling is particularly pertinent for tumors that are either unresectable, or that are not removed until they reach a certain size threshold (Ehehalt et al., 2009; Kazanjian et al., 2006). Therefore, image-based tumor growth modeling has been actively researched. Image-based tumor growth personalization requires three key components: a tumor growth model, medical images, and a parameter estimation algorithm. The tumor growth model accounts for the general physiological properties derived from ex vivo or in vitro experiments, or in vivo animal tests, providing a powerful tool for tumor growth prediction. On the other hand, medical images provide the in vivo measurements of the patient, revealing the structural or functional information of the underlying physiological status. Through computational or mathematical algorithms, the complementary information from the model and images can be combined together to provide patient-specific tumor growth prediction.

Tumor growth is the abnormal growth of tissue, which usually involves cell invasion and mass effect (Friedl et al., 2012). In collective cell invasion, tumor cells migrate as a cohesive and multicellular group with retained cell-cell junctions and penetrate to the surrounding normal tissues. Mass effect is caused by expansive growth, for which the increase in tumor volume leads to multicellular outward pushing with intact cell-cell junctions, and tumor cells may be displaced by the volume expansion and pushing. If coupled with migration, mass effect contributes to and enhances collective invasion. To model invasion and mass effect, most image-based

* Corresponding author.
E-mail addresses: ken.wong@nih.gov (K.C.L. Wong), rsummers@cc.nih.gov (R.M. Summers), kebebewe@mail.nih.gov (E. Kebebew), jyao@cc.nih.gov (J. Yao).

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frameworks use macroscopic models to trade-off between realism and computationally efficiency. Cell invasion has mostly been modeled through reaction-diffusion equations which describe cell migrations and proliferations (Chen et al., 2013; Clatz et al., 2005; Hogea et al., 2008; Konukoglu et al., 2010; Liu et al., 2014; Menze et al., 2011). Cell migrations have been modeled as diffusion of cell densities, which can be anisotropic or inhomogeneous when the corresponding tissue structure information is available (Clatz et al., 2005; Hogea et al., 2008; Konukoglu et al., 2010; Menze et al., 2011). Cell proliferations have been modeled as the increase of local cell densities, which can be described by the logistic function (Hogea et al., 2008; Konukoglu et al., 2010; Liu et al., 2014; Menze et al., 2011) or the Gompertz function (Chen et al., 2013; Clatz et al., 2005). Mass effect has usually been modeled using biomechanics. Although nonlinear mechanics should be used for soft tissue modeling (Fung, 1993) and is the mainstream in the tissue growth modeling society (Menzel and Kuhl, 2012), for simplicity, most image-based tumor growth modeling frameworks use the less realistic linear stress–strain relation with infinitesimal strain assumption (Chen et al., 2013; Clatz et al., 2005; Hogea et al., 2008; Liu et al., 2014) with few exceptions (Kyriacou et al., 1999). Different approaches have been used to incorporate the mechanical models, such as using the traditional solid mechanics approaches with finite element methods (FEM; Clatz et al., 2005; Chen et al., 2013), or approximating the mechanical effects as an extra advection term in the reaction-diffusion equation (Hogea et al., 2008; Liu et al., 2014).

For subject-specific tumor growth prediction, different personalization frameworks have been proposed to incorporate different image modalities to personalize different tumor growth models. In Hogea et al. (2008), a reaction-advection-diffusion equation describing both the invasion and mass effect of brain gliomas growth was solved using a fictitious domain method. Using a Lagrangian functional with manually identified landmarks from brain magnetic resonance images (MRI) as measurements, the model was personalized using adjoint-based partial-differential-equation-constrained (PDE-constrained) optimization. In Konukoglu et al. (2010), a reaction-diffusion-based brain gliomas growth model was personalized using structural information from MRI and diffusion tensor images. The evolution of the tumor delineation was approximated by a modified anisotropic eikonal model, which could be efficiently solved by a recursive anisotropic fast marching approach. By fixing the proliferation rates, the diffusion coefficients were estimated by comparing between the simulated and measured tumor delineations using the UOBYQA (Unconstrained Optimization BY Quadratic Approximation) optimization algorithm. In Chen et al. (2013), kidney tumor growth was modeled by a coupled reaction-diffusion and linear mechanical model, which was solved using FEM. Using the segmented tumor volumes from contrast-enhanced computed tomographic (CT) images at multiple time points, the model parameters were estimated by the hybrid optimization parallel search package (HOPSPACK). The estimated proliferation rates at different time points were combined together by exponential curve fitting to obtain the proliferation rate at the current time point for the growth prediction. In Liu et al. (2014), using a similar model and optimization approach in Hogea et al. (2008), a multimodal framework was proposed for pancreatic tumor growth prediction. With the intracellular volume fractions (ICVF) obtained from contrast-enhanced CT images, and the standardized uptake values (SUV) obtained from 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), the model was personalized with fused functional and structural information.

Although these frameworks are promising, several issues may limit their prediction performances. For simplicity, most frameworks use linear stress–strain relation with infinitesimal strain assumption. In continuum mechanics, linear strain–displacement approximation should only be used when deformation is less than 5% (Bathe, 1996; Holzapfel, 2000), which is usually not the case for tumor growth. Furthermore, most biological tissues should be modeled as hyper-viscoelastic materials (Fung, 1993). For parameter estimation, Hogea et al. (2008) and Liu et al. (2014) formulated the problem as adjoint-based PDE-constrained optimization, whose formulations are very complicated and the analytical derivatives of the model and objective function are required. Such an approach is not suitable for more complex models, and may limit the choices of more realistic models and better objective functions. Moreover, except Liu et al. (2014), only structural but not functional information was utilized, which may limit the patient-specificity of the personalized model and thus its prediction capability.

In view of these issues, we propose here a framework for pancreatic neuroendocrine tumor growth prediction (Fig. 1). Pancreatic neuroendocrine tumors are abnormal growths of hormone-producing cells in the pancreas (Ehehalt et al., 2009; Ries et al., 2007). They are very rare, with only about 1000 new cases in the United States per year. They are also slow growing, and usually not treated until reaching a certain size threshold. Our framework includes:

- A FEM-based tumor growth model with coupled reaction-diffusion equation and hyperelastic biomechanical model to improve physiological plausibility.
- A derivative-free global optimization algorithm for model parameter estimation to facilitate the complicated model and accommodate flexible choices of the objective function.
- Physiological data fusion of contrast-enhanced CT and FDG-PET images to improve subject-specificity.

Using this framework, more complicated objective functions can be studied, and we propose an objective function which accounts for both the volume difference and the root-mean-squared error of ICVF between simulations and measurements. Sensitivity analysis was performed to understand the impacts of different model parameters. Experiments were performed on synthetic data to verify the parameter estimation capability of the framework under different growth rates, and on clinical data for the prediction performance in reality. Comparisons of using different biomechanical models and objective functions are also presented.

Although this work is partially based on the work of Liu et al. (2014) in terms of computing ICVF from contrast-enhanced CT images and computing proliferation rates from FDG-PET images, there are fundamental differences between these two works:

(i) **Biomechanical model**. In this paper, a hyperelastic biomechanical model is used instead of a linear model. Furthermore, in Liu et al. (2014), the mechanical response was approximated as advection in a reaction-advection-diffusion equation solved by the finite difference method, which is simple but physically less accurate. In contrast, in this paper, the total-Lagrangian formulation is used with FEM for more accurate mechanical response but increased computational complexity.

(ii) **Objective function**. In Liu et al. (2014), only the ICVF differences between the simulations and measurements were used. In this paper, apart from the ICVF differences, the differences between the simulated and segmented tumor volumes are also considered.

(iii) **Optimization method**. In Liu et al. (2014), the adjoint-based PDE-constrained optimization was used to estimate the model parameters, which requires the analytical derivatives of the objective function and model. In this paper, as the objective function and model are more complicated, it is difficult to derive the analytical derivatives and thus a more flexible gradient-free optimization method is used.

In this paper, the macroscopic tumor growth model is described in Section 2, followed by the image-derived information in Section 3, and the model personalization in Section 4. Results of the sensitivity analysis are presented in Section 5, and the experimental results on synthetic and clinical data are presented in Section 6. The discussion is provided in Section 7.