# Tumor Growth Modeling in Oncological Image Analysis

## 1 Introduction

Tumor growth modeling is the study of explaining complex dynamics of cancer progression using mathematical descriptions. Internal dynamics of tumor cells, their interactions with each other and with their surrounding tissue, transfer of chemical substances and many phenomena are encoded in formulae by mathematical abstractions. These abstractions rely on biological and clinical observations coming from different sources.

Mathematical growth models offer important tools for both clinical and research communities in oncology. They give us the opportunity to interpret and integrate experimental results made in diverse fields of cancer research by providing a common mathematical ground to combine them in. Models, which can be adapted to patient-specific cases, could be used for quantification of apparent growth by extracting invasion speed, therapy planning by suggesting irradiation regions adapted to growth dynamics or optimal dose/temporal planning of chemotherapy. The role of image analysis is to serve this purpose by building the link between theoretical growth models and medical images in order to quantify factors that cannot be observed directly (e.g. extent of the tumor, deformation of the brain, effect of therapy,...).

There has been vast amount research conducted on tumor growth modeling during the last 20 years. These works can be coarsely classified into two different groups, microscopic and macroscopic models, based on the scale of observations they try to explain. Microscopic models, forming the major class, concentrate on the microscopic observations such as *in-vitro* and *in-vivo* experiments. They formulate growth dynamics at the cellular level using the observables at that scale like, internal dynamics of cells, vascularization, acidity,... Macroscopic models on the other hand, concentrate on the macro scale like medical images and histological slices, where the type of observations are different. Average behaviour of large number of tumor cells, invasion of white matter and grey matter, the mass effect of tumor growth

and growth at patient specific geometry are types of phenomena formulated by such models.

Despite the large amount of research conducted on growth models at microscopic scale, macroscopic models using medical images and image analysis tools based on such models are still in their dormancies. In this chapter, we would like to provide an overview of recent works in this field for the case of brain tumors. In Section 2 we review recently proposed macroscopic growth models and explain different approaches. Different tools proposed for therapy planning based on these models will be presented in Section 3. Section 4 gives details about application of tumor growth modeling on registration and segmentation problems. Finally, Section 5 concludes with awaiting challenges and perspectives.

# 2 Mathematical Models

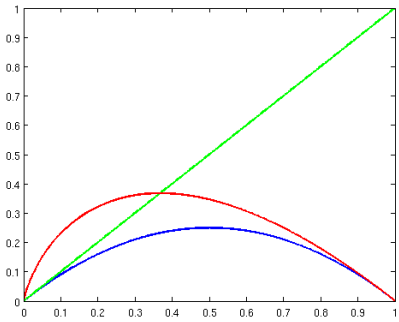
Observations at the macroscopic scale consist of medical images such as computed tomography scans (CT) and magnetic resonance images (MRI) as the most common ones. Since resolutions of these observations are limited, typically around $1mm \times 1mm \times 1mm$ in the best case, observable factors are limited as well. Macroscopic models try to combine knowledge coming from experimental research and biology with these observables, such as boundaries of the brain, grey-white matter segmentation or water diffusion tensors, to formulate tumor growth.

Macroscopic tumor growth models can be classified in two different classes: mechanical models, which concentrate on the mass-effect of the tumor on the brain tissue, and diffusive models, which concentrates on the invasion of surrounding tissue by tumor cells. In terms of mathematical formulations, the major part of macroscopic models use continuum, where tumor cells are assumed to form a continuous distribution. As a result, formulations contain several ordinary and/or partial differential equations to describe the growth process. Recently, there have also been some discrete macroscopic models proposed, using similar ideas to cellular automata. These result in certain set of probabilistic rules for individual or group of cells explaining their behaviour.

## 2.1 Diffusive Models

Almost all macroscopic models, which formulate the growth process concentrating on the diffusive nature of the tumor, use the reaction-diffusion formalism, [1]. The 'building block' equation of this formalism is the reaction-

Table 1: Commonly used population growth terms



| Exponential (green) | Gompertz (red) | Logistic (blue) |
|---|---|---|
| $\partial u/\partial t = \rho u$ | $\partial u/\partial t = \rho u \ln(1/u)$ | $\partial u/\partial t = \rho u(1-u)$ |

diffusion type PDE given as:

$$\frac{\partial u}{\partial t} = \nabla \cdot (D\nabla u) + R(u,t) \tag{1}$$

$$(\eta \cdot \nabla)u = 0 \tag{2}$$

where in equation 1 $u$ is the tumor cell density, $\partial/\partial t$ is the differentiation operator with respect to time, $D$ is the diffusion tensor for tumor cells and $R(u,t)$ is the so-called reaction term. This equation isolates two different characteristics of the tumor growth in two terms: diffusion and proliferation. The first term on the right hand side, $\nabla \cdot (D\nabla u)$ describes the invasion of tumor cells by means of a brownian motion, which is characterized by the diffusion tensor $D$. The second term in the equation, $R(u,t)$, describes the proliferation of tumor cells. Population growth equations are commonly used for the proliferation rate as summarized in Table 1. Equation 2 represents the no-flux boundary condition which is applied at the brain boundary and ventricles with normal directions $\eta$, formulating the fact that tumor cells do not diffuse towards these structures.

One of the first models using the reaction-diffusion formalism for the tumor growth was proposed by Cruywagen *et al.* in [2]. They argue that, a growth model using equation 1 consisting of a single population was not able to capture the growth dynamics seen in CT images. Hence, they proposed to use a model with two populations of tumor cells, which is formulated by coupling two equations such as Equation 1, each one describing a different population. Through coupling terms they were able to describe the competition between populations for nutrients and growth factors. The second population of tumor cells, were assumed to be a mutation of the first type. The

occurrence of these cells was attributed to the use of chemotherapy and/or radiotherapy, causing cells to mutate into a more resistant type. They also included the effect of treatment in their model as a constant cell loss mechanism, which is basically another reaction term. Their final formulation had the form:

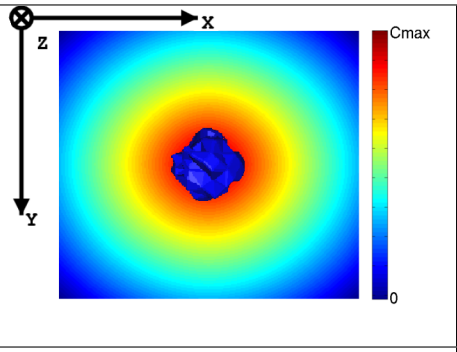
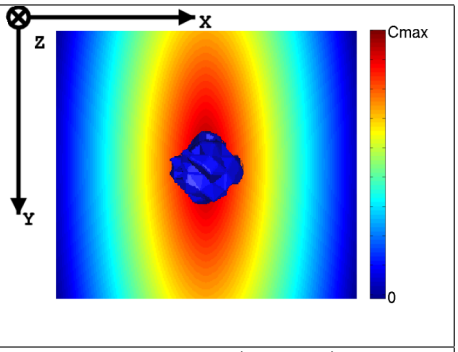
$$\frac{\partial u_1}{\partial t} = D_{u_1}\nabla^2 u_1 + f(u_1, u_2) - C_1(u_1, t)$$
$$\frac{\partial u_2}{\partial t} = D_{u_2}\nabla^2 u_2 + g(u_1, u_2) - C_2(u_2, t)$$

where reaction terms $f$ and $g$ describe the coupling between tumor populations given by $u_1$ and $u_2$, while $C_1$ and $C_2$ formulate effects of theraphy. In their model, Cruywagen *et al.* formulated the invasion of tumor cells as an isotropic-homogeneous diffusion where speed of diffusion was given by coefficients $D_{u_1}$ and $D_{u_2}$.

In [3], Swanson *et al.* revised the isotropic diffusion assumption made in previous works. Under the influence of experimental results of Giese *et al.* regarding the differential motility of tumor cells on grey and white matters [4], they formulated the invasion of tumor cells by isotropic-nonhomogeneous diffusion. In this formulation the diffusion tensor $D$ of Equation 1 was assumed to be isotropic and nonhomogeneous (spatially dependent), in other words its form was given as: $D = d(\mathbf{x})\mathbf{I}$, where $\mathbf{I}$ is an identity matrix and $d(\mathbf{x})$ is the diffusion coefficient. $d(\mathbf{x})$ took two different values in the white matter,$d_w$, and in the grey matter, $d_g$, where $d_w >> d_g$ corresponding to the observation that tumor cells move faster on myelin. In this work, only one population was used and the no-flux boundary conditions were applied. For the reaction term, authors used exponential growth, taking into account only the proliferation of tumor cells (see Table 1). Later on, Swanson *et al.* in [5] included the effect of chemotherapy through a negative reaction term. Instead of modelling the effect of therapy via a constant cell loss, they took into account the temporal effectiveness of drugs used and also the possible spatial heterogeneity of drug efficacy. In both works CT and MR images were used and attention for validating the model was given to predicting survival times after diagnosis.

Extending the idea of Swanson *et al.* regarding the differential motility of tumor cells on different tissues, Clatz *et al.* and later Jbabdi *et al.* included anisotropy to the invasion mechanism of tumor cells, [6] and [7]. They modelled the diffusivity of tumor cells through an anisotropic-nonhomogeneous diffusion. The assumption they have made is that tumor cells not only move faster on myelin, but also follow the white matter fiber tracts in the brain. They have constructed the tumor diffusion tensor (TDT) from the water dif-

Table 2: Differential motility between white and grey matter. The fiber tract is along the y-axis in the second image. (Images taken from [6])

|  |  |
|---|---|
| $D_g = d\mathbf{I}$ | $D_w = \alpha d\mathbf{f}(D_{water})$ |



fusion tensor using magnetic resonant diffusion tensor images (MR-DTI). Although methods of construction of the TDT were different in these works, the main idea was to assign isotropic diffusion in the grey matter and anisotropic diffusion in the white matter having greater diffusion along the fiber direction as given in table 2. where $\alpha$ is the multiplicative constant between grey and white matter motility and $f$ is the relation between water diffusion and tumor diffusion. By including the anisotropy of tumor diffusion in the formulation, these models were able to capture the "spiky" and fingering patterns of tumors observed in the images, see figure 1. Both of the works proposed an evaluation of their models by comparing visible tumors in the MR images with the ones simulated with the model.

Besides the continuum formulations explained above, recently Stamatakos *et al.* proposed to use a cellular automata based algorithm to model tumor growth in medical images [8] and [9]. Their model discretizes the visible tumor volume in the T1-weighted MR image into mesh cells containing groups of tumor cells. They explain growth by assigning certain probabilistic set of rules to every mesh cell, which define cell cycle dynamics for the group of cells inside that mesh cell. These rules take into account nutrition distribution throughout the tumor, effect of abnormal p53 gene expression and type of metabolic activity of the cell in assigning transition probabilities between different phases of the cell cycle, mitosis, apoptosis (controlled death of cells) and necrosis (infected death of cells). As a result, the growth phenomena is explained by the cell cycle, governed by probabilistic transition rules. Although some of these features are not well observable in medical images they model them based on assumptions coming from biological experiments. As

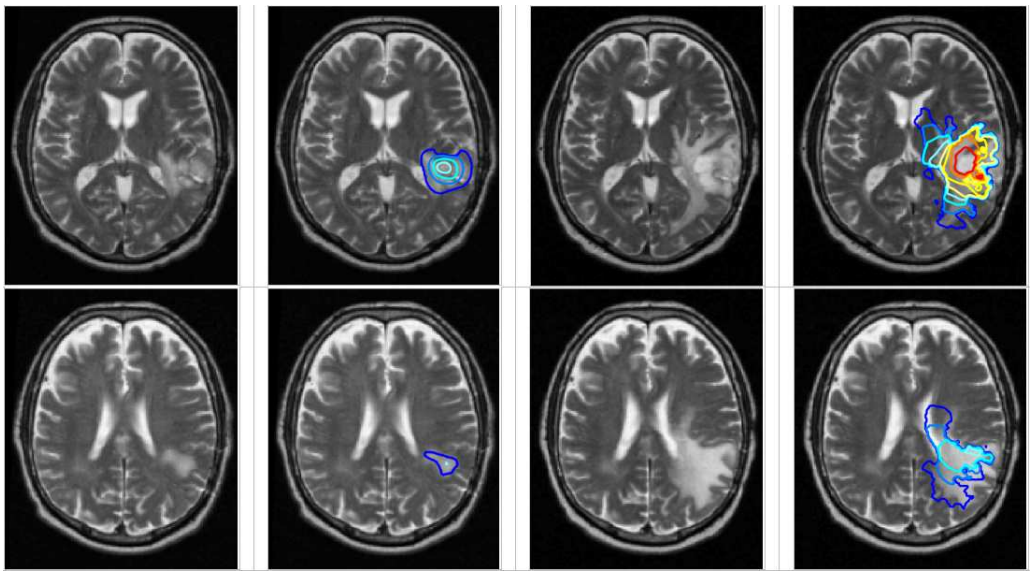


Figure 1: Diffusive models including anisotropy in the tumor diffusion are able to capture spiky nature of tumor growth. Figures show evolution of the tumor in two different slices. First two columns show the initial image and initial state of the model respectively, while the third column shows the tumor after 6 months and the fourth column shows the evolved tumor using the model given in [6].

an example, the nutrition distribution is taken to be decreasing homogeneously from the periphery of the tumor to the center. Their model does not take into account the infiltration of tumor cells, but rather only the growth through mitosis. Through the probabilistic nature of their model they were able to obtain realistic looking differentiated tumor growth.

## 2.2 Mechanical Models

Mechanical models, which concentrated on the mass-effect of the tumor, contain two distinct formulations, one for the tumor growth and one for the mechanical characteristics of the brain tissue. These models combine these formulations through coupling of equations, to describe the mechanical interactions between tumor growth and brain tissue leading to deformations. There have been many different works on characterizing the mechanical properties of the brain tissue, which is deformable but not elastic. In [10] it is said that the brain tissue is a sponge like material, possessing instantaneous properties of elastic materials and time-dependent properties of the viscoelastic ones. Moreover, there is a great variation between elastic parameters of brain

tissue within similar tissues as well as between differing tissues. Instead of formulating these complex mechanical characteristics, almost all models use assumptions to simplify brain tissue's characteristics.

Wasserman *et al.* proposed one of the first mechanical models in [10]. In this 2D model they assume the brain tissue is a linear elastic material for which stress-strain relations can be given by generalized Hooke's law. Moreover the amount of strain caused on a given volume, by a specific amount of stress (Young's modulus), was proportional to the density of brain tissue in that volume. For the tumor growth part, they assumed a very simple formulation including only the proliferation of cells, in which the rate of mitosis was set to be constant. The coupling between the growth and constitutive equation of the tissue was established by assigning a homogeneous pressure proportional to the number of tumor cells per volume. Through this coupling they were able to model the growth of the tumor under mechanical constraints and the interactions in CT images.

In [13], Kyriacou *et al.* assumed that brain tissue can be better characterized by a nonlinear elastic material than a linear one. They modelled white, grey and tumor tissue as nonlinear elastic solids obeying equations of an incompressible nonlinearly elastic neo-Hookean model. With the introduction of nonlinear elasticity into the model and the use of nonlinear geometry, they were able to describe large deformations through their formulation. Tumor growth was kept as a pure proliferation process with uniform growth causing uniform outward strain. They have applied this model in registering images of patients with tumor induced deformations to brain atlases. Their 2D model was applied on individual cross-sectional images obtain by CT or MR.

Mohamed and Davatzikos extended this model by modelling the brain tissue as an isotropic and homogeneous hyperelastic material, [11]. With this they relaxed the incompressibility assumption made in [13] and ignored the viscous effect, keeping in mind that times related to deformations was very large compared to viscosity time constants. In addition to modeling the mass effect due to bulk tumor growth they have also taken into account the expansion caused by the edema and the fact that part of the mass effect should be attributed to edema. They have also assumed a proliferation model for the tumor growth, which had a constant mitosis rate. Coupling of tumor growth and mechanical interactions was done the same way as in Wasserman's model. As in the work of Kyriacou *et al.*, this model was also able to describe large deformations. In [12], Hogea et al. reformulated the model within a general Eulerian framework, with a level-set based approach for the evolving tumor aiming at a more efficient method, see figure 2. They have also mentioned that for patient specific models, parameters should be found via solving an inverse problem. However this work was aiming to generate

large number of brain anatomies deformed by simulated tumors, hence they did not concentrate on the patient specific modelling. In order to validate their model they have compared deformations seen in MR images with the ones simulated with their models.

Tumor growth process has been kept very simple and has been associated with only proliferation of tumor cells in all previous macroscopic models, which concentrate on the mass-effect of the tumor. Clatz *et. al* combined two approaches of the macroscopic modelling in [6] in creating a formulation for glioblastoma multiforme (GBM). They have formulated the invasive nature of the tumor growth, besides proliferation, and the deformation this causes on the brain tissue. They assumed that brain tissue is a linear viscoelastic material, which can be modeled using a static equilibrium equation, since the

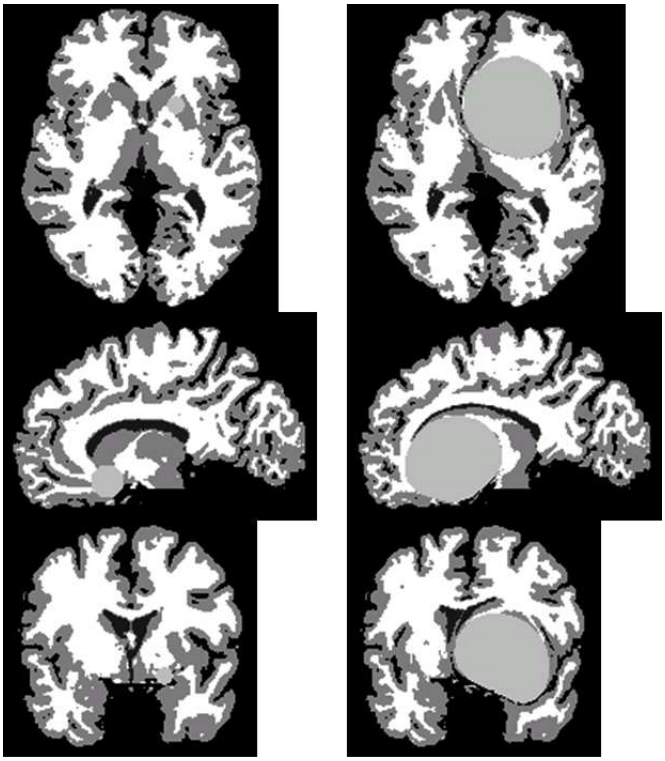


Figure 2: Models can model large deformations due to tumor growth and edema. Simulated tumor growth in a normal brain template, starting from a small initial seed, orbital-frontal left, using the modeling framework in [11] and [12]. Left: original healthy segmented brain template (axial, sagittal, coronal) with a small tumor seed; Right: corresponding deformed template with the grown tumor at the end of the simulation. Large deformations can be clearly observed.

time scale of tumor growth is very large. The coupling of the growth with the mechanical deformation on brain tissue was established using two different mass-effects: one for the bulk tumor and the other for the tumor infiltrated edema. The effect of bulk tumor was set as a homogeneous pressure caused by the volume increase as a result of cell proliferation. The mass-effect of the tumor infiltrated edema included the effect of invasion through a stress term which contained tumor cell density as given in Equation 3.

$$\nabla \cdot (\sigma - \lambda \mathbf{I}_3 c) + f_{ext} = 0 \tag{3}$$

where $\nabla\cdot$ is the divergence operator, $\sigma$ is the strain tensor, $c$ is the tumor cell density at a location and $f_{ext}$ is the external force. Using their model they were able to simulate both the invasion and the mass effect simultaneously.

# 3 Image Guided Tools for Therapy Planning

The tumor growth models explained in the previous section have formed the basis for several recently proposed therapy tools. Using the dynamics of the tumor growth, they can provide realistic simulations of the therapy or predict the extent of the tumor. Such tools aim at helping the doctor in planning the therapy course by quantifying and predicting the efficacy of a given scheme. As noted above, several authors have included the effect of therapy in their models, specifically chemotherapy. Cruywagen *et al.* modeled the effect of drugs through a constant cell loss mechanism using a negative reaction term. Swanson *et al.*, improving this idea, formulated temporal effectiveness of the drug and spatial heterogeneity of its efficacy.

Recently in [8] Stamatakos *et al.* have modeled the effect of chemotherapy based on their cellular automata growth model, which was explained in the previous section. The effect of the drug is included as a damage to each cell, which if large enough drives the cell to apoptosis. The relation between drug dose administered orally ($D$) and the plasma concentration ($C_p$) the tumor encounters is given by the relation

$$C_p = \frac{FDk_a}{V_d(k_a - k_{el})}(e^{-k_{el}t} - e^{-k_a t}) \tag{4}$$

where $F$ is the fraction of drug reaching the circulation, $V_d$ total volume the drug will distribute in, $t$ time elapsed since drug administration, $k_a$ and $k_el$ are the absorption and elimination rate respectively. For those parameters that are not observable through clinical situations and medical images, like $k_a$, population mean values proposed in the literature are used. The damage

given to a cell is computed through survival fraction

$$SF = e^{-K_{SF}T_{SF}C_p}, \tag{5}$$

which depends on $K_{SF}$ survival fraction constant and $T_{SF}$ exposure of tumor cells to the drug. Equation 5 depends on the type of drug used and the given form is for the drug called TMZ, which the authors used in their simulations. Using this model they simulated two different oral administration schemes with 3 different doses and compared the outcomes in terms of the number of proliferating tumor cells. Using probabilities for cell cycle and drug damage they captured the stochastic nature of the therapy and tumor growth. In their simulations they use the drug TMZ and a patient data with a high grade glioma. They start using the real tumor delineation and demonstrate a virtual realistic evolution, see Figure 3.

In another work of the same group [9], Stamatakos *et al.* have used their cellular automata based model in modeling the effect of radiotherapy and simulating therapy. They have included in the model the damage caused in a tumor cells (group of cells in their case) due to irradiation. This is explained by survival probabilities given by the linear-quadratic model

$$S(D) = exp[-(\alpha D + \beta D^2)]. \tag{6}$$

$S(D)$ is the survivial probability of a cell given that it takes $D$ dose of irradiation (in Gy). The $\alpha$ and $\beta$ parameters define the radiosensitivity of the cell and they are varying according to the phase of the cell-cycle, p53 gene expression and the metabolic activity type of the cell (oxic or hypoxic). Parameters not observed from medical images are set by assumptions and mean values coming from experiments in biology. Their model was able to demonstrate conformal shrinkage of the tumor due to irradiation, which is observed in real cases. Using their model, they simulated standard and hyper fractionation of irradiation and compared these two strategies through simulation. Although they obtained realistic results several phenomena are not taken into account in their model such as infiltration of tumor cells and the effect of irradiation on the surrounding healthy tissue. As in the case of the chemotherapy modeling, simulations start from the real tumor delineation and demonstrates a virtual evolution.

Konukoglu *et al.* proposed a different kind of tool for radiotherapy in [14], which extrapolates the extents of the tumor invasion not visible in MR images from the visible part. Their formulation aims in creating irradiation regions that takes into account tumor growth dynamics rather than the conventional 1.5-2.0 cm constant margin around the visible tumor. Based on the reaction-

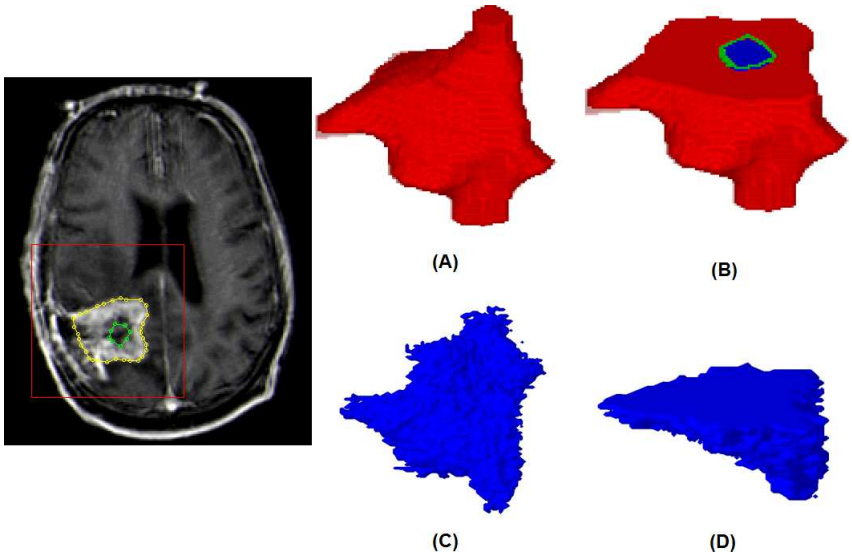



Figure 3: Left: An MRI slice depicting a glioblastoma multiforme tumour. Both the gross volume of the tumour and its central necrotic area have been delineated. The same procedure has been applied to all MRI slices. Right: 3D visualization of the simulated response of a clinical glioblastoma multiforme tumor to one cycle of chemotherapeutic scheme (150 mg/m orally once daily for 5 consecutive days/28-day treatment cycle, [fractionation scheme A)]. (A) External surface of the tumor before the start of chemotherapy, (B) internal structure of the tumor before the start of chemotherapy, (C) external surface of the tumor 20 days after the start of chemotherapy, and (D) internal structure of the tumor 20 days after the start of chemotherapy. Pseudocolor Code: red: proliferating cell layer, green: dormant cell layer (G0), blue: dead cell layer. The following 99.8 %criterion has been applied: If the percentage of dead cells within a geometrical cell of the discritizing mesh is lower than 99.8 % then [if percentage of proliferating cells ¿ percentage of G0 cells, then paint the geometrical cell red (proliferating cell layer), else paint the geometrical cell green (G0 cell layer)] else paint the geometrical cell blue (dead cell layer) [8].

diffusion formalism they deduced the anisotropic eikonal equation

$$\frac{\sqrt{\nabla u \cdot (D \nabla u)}}{\sqrt{\rho} u} = 1,\ u(\Gamma) = u_0 \tag{7}$$

describing the extents of the tumor starting from the visible tumor contour in the MR image. In the equation $u$ is the tumor cell density (or probability of

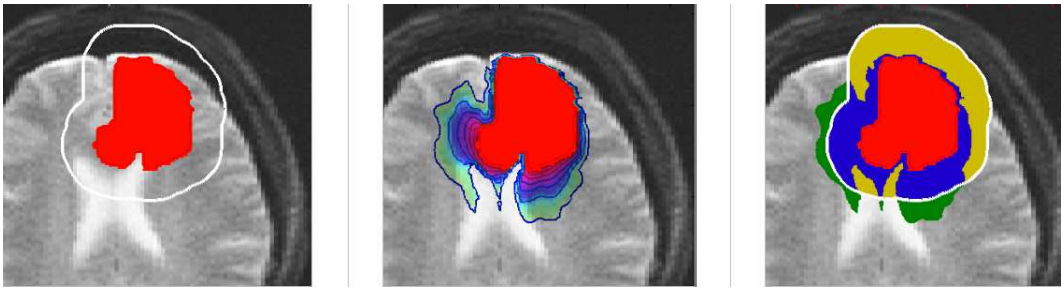


Figure 4: Left: In red we see the tumor delineation with the constant margin irradiation region in white. The visible tumor contour corresponds to the extents of this region. Middle: Extent of tumor infiltration computed by the model given in [14]. Probability of finding tumor cells decrease from red to blue. Right the computed invasion region is drawn with the constant margin region.Blue part shows tumor infiltrated regions effected by the irradiation, green parts shows infiltrated regions not irradiated and brown parts show regions not infiltrated according to the model but irradiated with constant margin approach.

finding a tumor cell), $D$ is the diffusion tensor constructed in the same spirit as the works proposed by Clatz *et al.* and Jbabdi *et al.*, $\rho$ is the proliferation rate, $\Gamma$ is the visible tumor contour in the image and $u_0$ is the density of tumor cells assumed to be constant on $\Gamma$. By including the different tissue structures and the fiber directions in their formulation, they quantify the effect of these factors on the tumor extent. They have used artificial tumors grown in the images of a healthy subject using reaction-diffusion formalism. In order to show the discrepency between constant margin irradiation region and the tumor extent computed using Equation 7 they compared both with the real distribution of the artificial tumor, see Figure 3.

# 4 Applications to Registration and Segmentation

Tumor growth models, besides being used to create therapy planning tools, have been used to aid registration and segmentation tools as well. Problems of brain tissue segmentation and atlas to patient registration in the presence of a pathology have received attention from the medical imaging community for a long time. Lately there have been several works proposed for these purposes using the tumor growth dynamics. These works can be classified

into two related groups: atlas to patient registration and synthetic brain image creation consisting of a tumor.

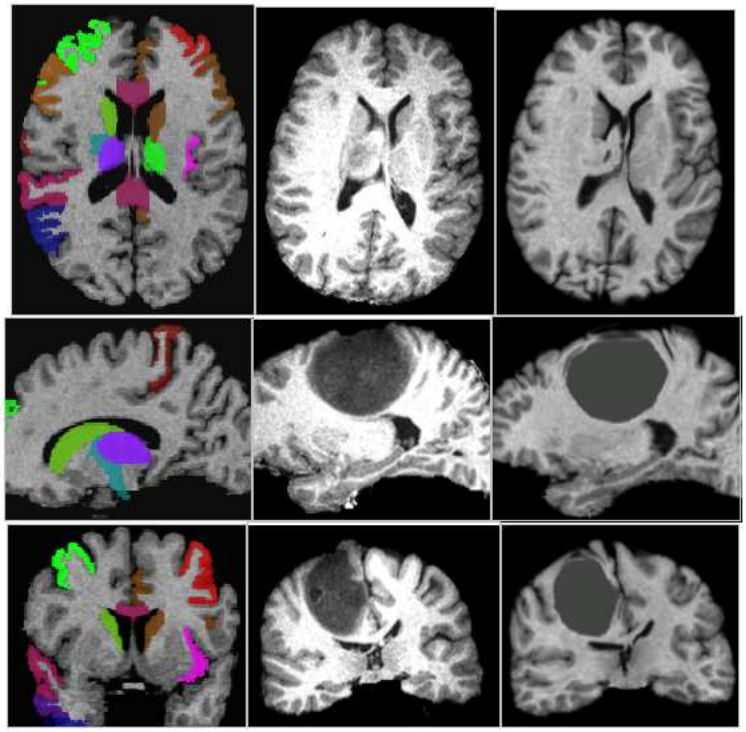
## 4.1 Registration

The registration of an anatomical atlas to a patient with a brain tumor is a difficult task due to the deformation caused by the tumor. Registration algorithms proposed for normal to normal registration fail due to this reason. Recently, several authors proposed to include the tumor growth models in their registration algorithms to tackle this diffucult task. The important ingredient growth models can add is the quantification of the tumor-induced deformation on the brain structures through model parameters. Proposed algorithms use these model parameters in separating the deformation field between the atlas and the patient into inter-subject variation and tumor-induced parts during the registration process.

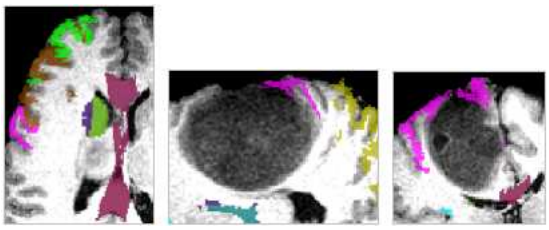
Kyriacou *et al.* proposed one of the first atlas to patient registration algorithms based on the tumor growth dynamics [13]. Starting from the patient image, their algorithm first simulates the biomechanical contraction in the case of the removal of the tumor to estimate patient anatomy prior to the tumor. A normal to normal registration between the atlas and the tumor-free patient brain follows the contraction. At this point instead of deforming the registered atlas with the inverse of the deformation field obtained during the contraction, they perform a nonlinear regression in order to estimate the tumor growth parameters that would best fit the observed tumor-induced deformation. These parameters consist the center and the amount of expansion of the tumor. Once the parameters are estimated they perform the biomechanical tumor growth inside the registered atlas to obtain the final atlas to patient registration, which was in 2D.

In contrast to separating the deformation caused by the tumor and the deformation explaining inter-subject variability, in [15], Cuadra *et al.* proposed to combine these two in a nonlinear *demons* based registration algorithm [16] for the atlas to patient registration. The algorithm starts by placing the two brains on the same frame and scale using a global affine registration. An expert manually places the tumor *seed* on the affinely registered atlas, which corresponds to the place of it in the patient image. The seeding is followed by a nonlinear registration algorithm with adaptive regularization. The tumor growth is modeled as an outward pressure causing radial displacement of the surrounding structures. Authors included this displacement field in their registration algorithm to take into account the tumor-induced deformation.

Mohamed *et al.* took a statistical approach for the atlas to patient registration problem in [17]. They propose a statistical model on the deformation



(a)



(b)

Figure 5: Left to right: the atlas image with manually labeled regions, the patient image, the atlas to patient registration result using the algorithm explained in [17], which includes tumor growth modeling. (b) The selected labels in the atlas are warped and correspondingly superimposed on the patients image

map created by applying a nonlinear elastic registration to match an atlas with the patient image. This model is based on the fact that although normal registration techniques would fail in the vicinity of the tumor, they will provide the right deformation field for the other parts. Their statistical model uses the space of displacement fields and decomposes any deformation field

on two orthogonal hyperplanes, one describing the tumor-induced deformations and other inter-subject variability. The formulation of the hyperplanes is done by principal component analysis (PCA) assuming linearity of the governing space and that displacement fields are realizations of two independent Gaussian random vectors. The training of the PCA for the inter-subject variability is done by samples coming from registering the atlas to a dataset of healthy subjects. On the same dataset they grow artificial tumors using their growth model explained in Section 2.2 for different sets of growth parameters, including center of the tumor, expansion of the tumor and the edema extent. These instances serve as the training samples of the PCA for the tumor-induced deformation. When a new patient image is encountered, they decompose the deformation field and find the tumor growth parameters specific for the patient as

$$U_f \approx \mu_c + \mathbf{V}_c\mathbf{a} + \mu_d + \mathbf{V}_d\mathbf{b} \tag{8}$$

where $U_f$ is the total displacement field, $\mu_c$ and $\mathbf{V}_c$ are the mean and covariance matrix displacement fields for inter-subject registration, and $\mu_d$ and $\mathbf{V}_d$ are the same identities corresponding to tumor-induced deformation. Once the deformation field linking atlas to subject and tumor growth parameters are found, the atlas is registered and the tumor is grown in it. Zacharaki *et al.* in [18] proposed to improve the registration algorithm used in this work by a more flexible one, based on HAMMER algorithm [19], taking into account the fact that around the tumor region the deformation field is distorted when the tumor model parameters are not optimal. To tackle this, they introduced a patient-specific optimization framework based on similarity matching and smoothness properties of the deformation around the tumor, see Figure 4.1.

## 4.2 Segmentation

Another application of tumor growth modeling is the synthetic dataset creation for validating segmentation algorithms. Presence of a tumor is a big challenge for the segmentation algorithms. Algorithms are compared with expert manual segmentations for validation and performance analysis. Manual segmentations however, show high inter-expert variability and contains human error due to fatigue and other reasons. In order to tackle this problem, several works proposed to generate synthetic realistic MR images cotaining tumors, for which ground truths are known and can be used for validation and analysis. There are two different subproblems for the generation. One of them is to simulate the tumor growth realistically. The other one is to mathematically describe the effect of tumor growth on MR signal intensities.

In other words, how the image intensities change in different parts of the image (e.g. edema, actively proliferating tumor region, tumor free part,...).

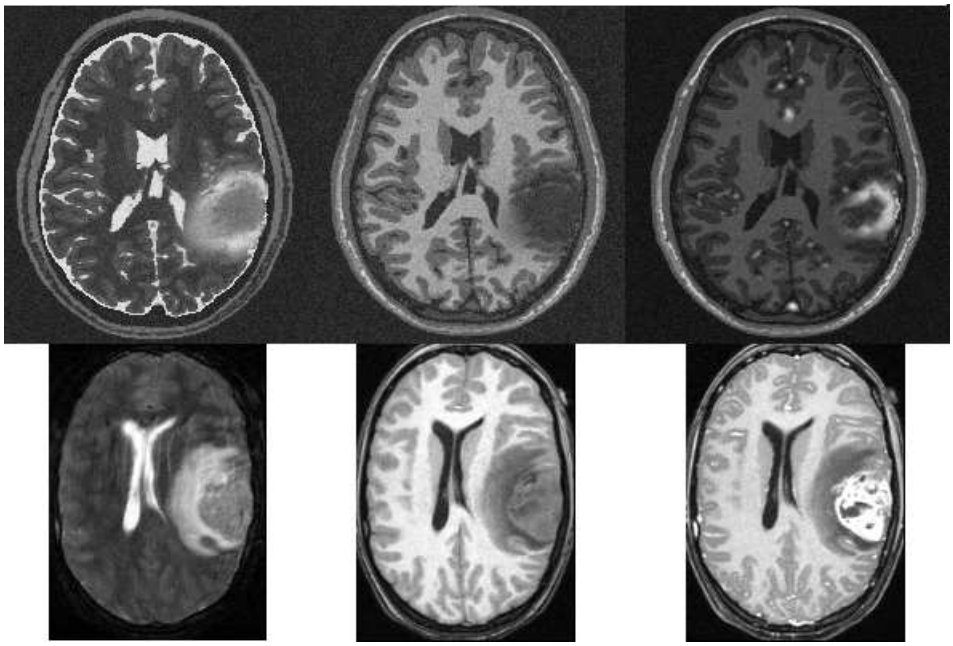


Figure 6: Upper row shows the syntetic images generated of a patient with meningioma using the algorithm proposed in [20]. T2w, contrast enhanced T1w and T1w images from left to right. Bottom row shows the same images coming from a real patient.

Rexilius *et al.* proposed one of the first models for this problem in [21]. They have modeled the tumor with three compartments: the active tumor tissue, the necrotic (dead) tumor core and the edema. The active tissue and the necrotic part are drawn in the desired location with the desired size. Later on reasonable grey values are assigned to these regions including Gaussian noise to make the intensities realistic. As an example, in the case of contrast enhanced T1w image the realistic values included contrast accumulation in the active tumor part. The mass effect of the drawn tumor is applied to the underlying healthy subject MR image assuming linear elastic material properties for tissues. The growth is simulated by a radial displacement applied to surrounding tissues using finite element methods. Lastly for the edema, they use the distance transform of the tumor on the white matter mask of the underlying image and deform it with the same mass effect applied to the brain. Based on the resulting distance transform values they assign intensity values corresponding to edema infiltration.

In order to create more realistic MR images, Prastawa *et al.* have tackled the same problem using a more sophisticated tumor growth model and adding contrast accumulation properties of different tissues. They have adopted the growth model proposed by Clatz *et al.* [6]. In addition to this model, in their formulation they took into account the displacement and destruction of white matter fibers using image warping and nonlinear interpolation, based on the observations of Lu *et al.* [22]. For the image generation part, they have modeled the contrast agent diffusion inside the brain using the reaction-diffusion formalism. Using such a formulation they were able to simulate the high contrast accumulation in csf and in active tumor regions. As a result they obtained realistic looking synthetic data with contrast irregularities as in Figure 4.2.

# 5 Perspectives and Challenges

In this chapter, we have tried to review some works on mathematical tumor growth modeling and its applications proposed by the medical image analysis community. Away being from a complete review on this subject, this chapter is an attempt to highlight the main approaches and applications.

In terms of realistically modeling the growth phenomena, some solid attempts have been taken however, there are very exciting challenges awaiting to be solved. Tumor growth is a very complex phenomena, including different scales of ingredients from genetic to macroscopic. The biggest lacking point at the moment is the link between these scales. Observations that can be obtained from medical images are limited and obtaining microscopic observations for a large view-area is not possible at the moment. One approach that can be taken to tackle this problem would be to included information coming from different modalities of images in growth models. Including techniques like positron emission tomography (PET), magnetic resonance spectroscopy (MRS) and functional-MRI (fMRI) would yield information about nutrient, oxygen and metabolite levels in the tumor giving an opportunity to integrate microscopic phenomena in macroscopic models and for patient specific models.

Personalization of the tumor growth models and therapy models summarized in this chapter is an important missing link between mathematical methods and clinical applications. Inter-patient variation of parameters can be large, hence obtaining the necessary parameters automatically through inverse problems is a required step in adapting general growth models to individual patients. Such inverse problems also serve as quantification tools that can asses the efficacy of a therapy or understanding the amount of de-

formation caused as we have seen in Section 4.1. Moreover, intra-patient variation of these parameters has not been studied yet. Variation within the same tumor would yield different growth patterns than a specific set of parameters. On the other hand, the heterogeneity in a single tumor can be very high as well strengthening the need for stochastic approaches for tumor growth models.

One other big challenge for creating more accurate models, is the lack of a proper quantitative validation technique. For macroscopic models the comparison is done with observed medical images, which are not able to visualize the whole tumor. Although some quantitative validation methods was proposed by some authors, [6, 11], the field still lacks a golden standard in validation methodology.

Improving imaging techniques and more accurate models will yield valuable tools for clinical oncology in the future. Patient-specific models combining information from different scales will enable us to perform patient-specific simulations. Such simulations, either for therapy or simple growth will aid in patient treatment and hopefully improve prognosis.

# References


[1] Murray, J.: Mathematical Biology. Springer-Verlag (2002)

[2] Cruywagen, G., Woodward, D., Tracqui, P., Bartoo, G., Murray, J., Alvord, E.: The modelling of diffusive tumours. J. Biol. Systems **3** (1995)

[3] Swanson, K., Alvord, E., Murray, J.: A quantitative model for differential motility of gliomas in grey and white matter. Cell Prolif. **33** (2000)

[4] Giese, A., Kluwe, L., Laube, B., Meissner, H., Berens, M., Westphal, M.: Migration of human glioma cells on myelin. Neurosurgery **38** (1996)

[5] Swanson, K., Alvord, E., Murray, J.: Quantifying efficacy of chemotherapy of brain tumors with homogeneous and heteregeneous drug delivery. Acta Biotheoretica **50** (2002)

[6] Clatz, O., Sermesant, M., Bondiau, P., Delingette, H., Warfield, S., Malandain, G., Ayache, N.: Realistic simulation of the 3d growth of brain tumors in mr images coupling diffusion with biomechanical deformation. IEEE T.M.I. **24**(10) (2005)

[7] Jbabdi, S., Mandonnet, E., Duffau, H., Capelle, L., Swanson, K., Pélégrini-Issac, M., Guillevin, R., Benali, H.: Simulation of anisotropic growth of low-grade gliomas using diffusion tensor imaging. Magnetic Reson. in Med. **54** (2005)

[8] Stamatakos, G., Antipas, V., Uzunoglu, N.: A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy in vivo: The paradigm of glioblastoma multiforme treated by temozolomide. IEEE Tran. Bio. Med. Eng. (2006)

[9] Stamatakos, G., Antipas, V., Uzunoglu, N., Dale, R.: A four-dimensional compute simulation model of the in-vivo response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density. Brit. J. Rad. (2006)

[10] Wasserman, R., Acharya, R.: A patient-specific in-vivo tumor model. Math. Biosci. **136** (1996)

[11] Mohamed, A., Davatzikos, C.: Finite element modeling of brain tumor mass-effect from 3d medical images. In: Lec. Notes Comp. Sci 3749, MICCAI (2005)

[12] Hogea, C., Abraham, F., Biros, G., Davatzikos, C.: A framework for soft tissue simulations with applications to modeling brain tumor mass-effect in 3d images. In: Workshop on Computational Biomechanics for Medicine, MICCAI (2006)

[13] Kyriacou, S., Davatzikos, C., Zinreich, S., Bryan, R.: Nonlinear elastic registration of brian images with tumor pathology using a biomechanical model. IEEE TMI **18** (1999)

[14] Konukoglu, E., Clatz, O., Bondiau, P., Delingette, H., Ayache, N.: Extrapolating tumor invasion margins for physiologically determined radiotherapy regions. In: Lec. Notes Comp. Sci. 4190, MICCAI (2006)

[15] Cuadra, M., Pollo, C., Bardera, A., Cuisenaire, O., Villemure, J.G., Thiran, J.P.: Atlas-based segmentation of pathological mr brain images using a model of lesion growth. IEEE Tran. Med. Imag. **23** (2004)

[16] Thirion, J.P.: Image matching as a diffusion process: An analogy with maxwell's demons. Med. Im. Anal. **2** (1998)

[17] Mohamed, A., Zacharaki, E., Shen, D., Davatzikos, C.: Deformable registration of brain tumor images via a statistical model of tumor-induced deformation. Med. Im. Anal. **10** (2006)

[18] Zacharaki, E., Shen, D., Mohamed, A., Davatzikos, C.: Registration of brain images with tumors: Towards the construction of statistical atlases for therapy planning. In: Proceedings of 3rd IEEE International Symposium on Biomedical Imaging, ISBI (2006)

[19] Shen, D., Davatzikos, C.: Hammer: Hierarchical attribute matching mechanism for elastic registration. IEEE Tran. Med. Imag. **21** (2002)

[20] Prastawa, M., Bullitt, E., Gerig, G.: Synthetic ground truth for validation of brain tumor mri segmentation. In: Lec. Notes Comp. Sci. 3749, MICCAI (2005)

[21] Rexilius, J., Hahn, H., Schlüter, M., Kohle, S., Bourquain, H., Böttcher, J., Peitgen, H.O.: A framework for the generation of realistic brain tumor phantoms and applications. In: Lec. Notes Comp. Sci. 3217, MICCAI (2004)

[22] Lu, S., Ahn, D., Johnson, G., Cha, S.: Peritumoral diffusion tensor imaging of high-grade gliomas and metastatic brain tumors. Am. J. Neuroradiology (2003)