Multi-Scale Modeling for Image Analysis of Brain Tumor Studies

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***Abstract*—Image-based modeling of tumor growth combines methods from cancer simulation and medical imaging. In this context, we present a novel approach to adapt a healthy brain atlas to MR images of tumor patients. In order to establish correspondence between a healthy atlas and a pathologic patient image, tumor growth modeling in combination with registration algorithms is employed. In a first step, the tumor is grown in the atlas based on a new multi-scale, multi-physics model including growth simulation from the cellular level up to the biomechanical level, accounting for cell proliferation and tissue deformations. Large-scale deformations are handled with an Eulerian approach for finite element computations, which can operate directly on the image voxel mesh. Subsequently, dense correspondence between the modified atlas and patient image is established using non-rigid registration. The method offers opportunities in atlas-based segmentation of tumor-bearing brain images as well as for improved patient-specific simulation and prognosis of tumor progression.**

***Index Terms*—Brain Tumor, Glioma, Image Analysis, Tumor Growth Modeling, Tumor Biomechanics**

I. Introduction

COMPUTATIONAL ONCOLOGY is recently gaining increased attention among the research community. This field aims to investigate computational models for tumor progression, which can help to better understand the phenomenon of cancer and finally provide better diagnosis and treatment plans for patients. Current approaches range from the molecular, to the cellular, up to the macroscopic level including biomechanics. In Stamatakos et al. [1] an "Oncosimulator" has been proposed, which aims to model cancer progression on a biological level, taking into account cell proliferation. Konukoglu et al. [2] used physical models to better understand the progression of gliomas by adapting reaction-diffusion dynamics. As gliomas also exhibit a significant mass-effect on the surrounding tissues, biomechanics should be considered as presented by Hogea et al. [3].

Brain tumor image analysis is a more established field than computational oncology, however active research is being conducted to handle the varying appearance of brain tumors, which makes generic tumor-bearing brain segmentation and registration a challenging task. While the majority of methods are mostly concerned with tumor segmentation, e.g. Verma et al. [4], fewer work has been done on aligning brain tumor images with a standard template using registration. One of the latest efforts to adapt a registration and segmentation method for brain tumor images was done by Zacharaki et al. [5]. In this work, a purely macroscopic biomechanical tumor growth model is used to simulate tumor growth in a healthy atlas, which is subsequently registered to the patient image using deformable registration algorithms.

The aim of this paper is to present a novel multi-scale method for patient-specific adaptation of a healthy brain atlas to tumor patient images, which also offers implicit segmentation of the brain tissues. A major problem is to establish correspondence between a healthy atlas and a tumor-bearing patient image in a generic way. To this end, we combine patient-specific tumor growth simulation with medical image analysis. The approach comprises a multi-scale, multi-physics model of tumor growth and progression, from the cellular, up to the biomechanical level, and state-of-the art methods for non-rigid registration of brain images.

II. Methods

In a first step, we simulate tumor growth in a healthy brain atlas. We use the publicly available SRI24 atlas provided by Rohlfing et al. [6], which is an average of 24 normal adult subjects. This atlas provides different modalities, including label maps. It exhibits increased sharpness, making it suitable for atlas-based segmentation purposes.

After applying a preprocessing pipeline to the patient image, including intensity normalization, customized skull-stripping[1], edge-preserving smoothing and bias-field correction, initial correspondence between the atlas and the patient image is established using an affine registration method. Next, the tumor area in the patient can either be delineated manually or using classification methods on multi-modal magnetic resonance (MR) images as shown in [4]. A physically realistic seed for tumor growth is automatically chosen in the vicinity of the center of mass of the patient tumor, with the patient tumor outline also delimiting the growth process later.

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[1] software tool available at www.istb.unibe.ch/content/surgical_technologies/medical_image_analysis/software

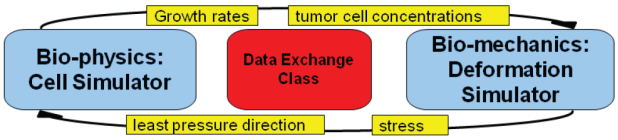

Fig. 1. Illustration of the coupling between the bio-cellular simulator and the bio-mechanical simulator. Both modules are iteratively called to simulate the growth process.

A. Simulating Tumor Growth with a coupled Bio-Physical-Bio-Mechanical Model

In order to provide a comprehensive perspective on tumor growth, two models focusing on both different length and time scales as well as different physics have been coupled to constitute a self-consistent multi-scale approach. The first model is a discrete entity - discrete event cellular level based oncosimulator focusing on biological phenomena like cell cycling and apoptosis. Due to the macroscopic view, the effect of probabilistic rules of this model on the final result is negligible. A detailed description of the method and the relevant parameters (which are all obtained from literature data) can be found in [1]. This cellular level model, while providing a detailed description of the cellular evolution of the imageable component of the tumor, assumes a conformal expansion or shrinkage of the tumor due to a lack of information on preferred growth directions. This motivates the coupling with a biomechanical stress/strain simulation, which can provide pressure gradient information [7]. The latter solves a linear elastic model on a brain atlas using values for the Young's modulus E and Poisson ratio ν for different constituent brain materials from established publications [8]. Since the limit of applicability of the standard Lagrangian formulation of structural mechanics can easily be reached under large deformations as occurring in rapid tumor growth, an Eulerian approach has been implemented. In the latter formulation, the calculation is performed on a fixed geometrical mesh and material properties are advected to neighboring elements upon deformation. This offers the additional advantage that the simulation can operate directly on the voxel mesh obtained from the image, without the need for complex and time-consuming automatic meshing methods.

The coupling of the two aforementioned models is outlined in the following: On the one hand, the cell simulator requires information on the direction to which new tumor cells will spread, which can be decided based on the pressure of the surrounding tissue. On the other hand, the mechanical simulation needs information on the amount by which individual geometrical cells will expand, which in turn can be extracted from the cell concentrations calculated by the cellular simulator. This is illustrated in figure 1.

As far as the direction decision is concerned, newly produced biological cells follow the direction $\mathbf{d}$ of least pressure p, i.e. the negative gradient

$$\mathbf{d} = -\frac{\nabla p}{||\nabla p||}. \tag{1}$$

In the discrete formulation of the code, each geometrical element e is attributed a pressure $p(e)$ given in terms of the trace of the stress tensor $\boldsymbol{\sigma}$ by

$$p = \frac{1}{3}\mathrm{Tr}(\boldsymbol{\sigma}). \tag{2}$$

The corresponding direction of least pressure $\mathbf{d}(e)$ is then found as the vector pointing to the center of element $e_{\min}$, defined as

$$e_{\min} = \mathrm{argmin}\{p(f)|dist(f,e) < R\}. \tag{3}$$

R here denotes the distance to the nearest neighbors and must be increased to next-nearest neighbors upon full occupancy. Note that the minimum pressure only has to be determined when a direction is requested, i.e. it is not necessary to keep a full map of least pressures as cell proliferation is generally only taking place in small regions of the computational domain.

Due to the space-dependent mechanical properties arising from the segmentation into gray matter, white matter and ventricles, a growing tumor generates a non-uniform stress distribution. A linear elastic model with Young's modulus E and Poisson ratio ν serves as governing physical law for the deformation and arising stress. This stress distribution, along with the boundary conditions of zero displacement imposed by the fixed skull, provides a non-uniform pressure environment. From this information, a pressure gradient force can be derived, which allows us to determine the most likely proliferation direction.

In order to address the volume change of elements, the volume of a geometrical element $V(c)$, computed as a function of the biological cell concentration c is assumed to follow the relation

$$V(c) = V_0\frac{c}{c_0}, \tag{4}$$

where V_0 represents the volume at the reference concentration c_0 (here set to 3×10^6 cells mm^{-3}). The obtained volume change subsequently serves as input for the material law used in the biomechanical stress/strain calculation.

The tumor is grown in the atlas according to this approach until the approximate tumor volume in the patient is reached. Based on experience, growth iterations are stopped once the simulated tumor reaches 90% of the volume of the tumor in the patient image, while the final deformation is handled by the non-rigid registration algorithm.

Due to restrictions imposed by the computational complexity of the multi-scale growth model, tumor growth is performed on a coarser version of the atlas only. Therefore, the image is subsampled by a factor of two, to obtain a resolution of 2 mm in each dimension.

B. Adapting the Modified Atlas to the Patient Image

After tumor growth modeling, the modified atlas is warped to the patient image using a non-rigid, intensity-based registration technique. We use the Diffeomorphic Demons registration method introduced by Vercauteren et al. [9]. This algorithm offers fast non-parametric registration and yields a dense deformation field which can be used to warp the atlas label map or any other atlas map available.

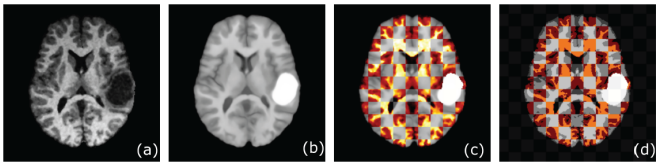

Fig. 2. Results shown on one axial slice of the simulated dataset Case-1S. From left to right: the patient image (a), the atlas image after tumor growth simulation and registration (b), a checkerboard of patient and atlas tissue image after tumor growth simulation & registration (c), and finally a checkerboard of patient and atlas label image after tumor growth simulation & registration (d). A hot-metal and a gray-level colormap have been used for generating the checkerboard images.

The idea of this registration method is to treat registration as an optimization problem and minimize an energy function E, which corresponds to the similarity between both images, where similarity is based on image intensities. We perform the optimization using a cascade of three resolution levels in order to increase robustness and speed. The Diffeomorphic Demons method has the advantage of being fast and producing physically justifiable and realistic deformations by ensuring the invertibility of the deformation field.

III. Results

It has been demonstrated recently that applying a tumor growth-model before non-rigid registration improves the outcome compared to using a standard registration technique [10]. For the current study, the proposed method was evaluated on volumetric T1-weighted MR images of 4 simulated glioma datasets with 1x1x1 mm resolution, provided by Prastawa et al. [11], and volumetric T1-weighted MR images with 1x1x2 mm resolution of 4 real glioma patient datasets from the ContraCancrum database [12]. For the datasets from [11] a ground-truth segmentation exists, while the datasets from [12] have been semi-manually segmented in order to provide a "ground-truth" for quantitative evaluation.

Figure 2 shows the results for one simulated case. From left to right one can see the patient image, the registered atlas image after tumor-growth simulation and a checkerboard of the tissue and of the label images. The checkerboard images demonstrate a good match after adapting the atlas to the patient image.

In terms of quantitative analysis, table I summarizes the Dice similarity coefficients we obtained for the four synthetic cases and for the four real patient cases. The Dice coefficient measures the mean overlap between two regions, it can range from 0 (indicating no overlap) to 1 (indicating perfect overlap). Dice similarity for the relevant tissues cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM) ranged between 0.56 and 0.8. When compared to a recently published simpler, purely biomechanical tumor growth model [10], Dice results were similar, but sometimes slightly inferior on the same data (at maximum 4% less overlap). Further tests showed that the final result is not sensitive to small variations in seed point location or tumor growth stop condition.

In figure 3 several steps of the algorithm are depicted for one of the four real patient cases from the ContraCancrum database. In the top row, the patient image, the atlas image with the tumor seed and an intermediate growth iteration step in the atlas are shown from left to right. In the bottom row one can see the deformed atlas after the final growth iteration, the adapted atlas after tumor growth and non-rigid registration and a checkerboard of the atlas and patient tissue images. It can be observed how the ventricles and other surrounding tissues are deformed by the tumor mass-effect during the growth process. However, the final deformation of individual tissues can only be achieved by the non-rigid registration process. From the checkerboard images it is obvious that the atlas is apparently well adapted to the patient image after tumor-growth simulation and non-rigid registration.

TABLE I
Dice similarity coefficients using the proposed method for the synthetic datasets (Case-xS) and the real patient datasets (Case-xP). We show Dice similarity coefficients for cerebrospinal fluid (CSF), gray matter (GM), white matter (WM) and the tumor region.

	CSF	GM	WM	Tumor
Case-1S	0.66	0.75	0.78	0.94
Case-2S	0.62	0.76	0.77	0.94
Case-3S	0.65	0.75	0.78	0.95
Case-4S	0.65	0.76	0.8	0.97
Case-1P	0.56	0.72	0.77	0.92
Case-2P	0.60	0.75	0.78	0.93
Case-3P	0.58	0.67	0.73	0.92
Case-4P	0.57	0.69	0.71	0.76

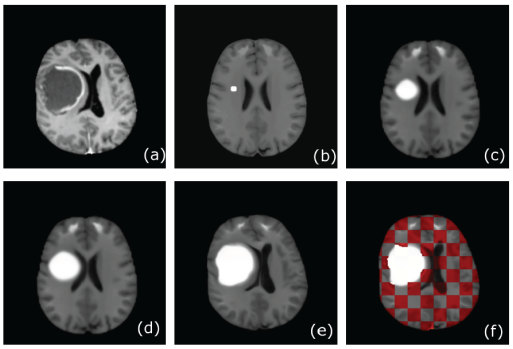

Fig. 3. Evolution of results shown on one axial slice of ContraCancrum real patient Case-1P. Top row, left to right: Patient image (a), seeded atlas after affine registration (b), deformed atlas during intermediate step of tumor growth (c). Bottom row, left to right: Deformed atlas after final step of tumor growth (d), non-rigidly registered modified atlas (e), checkerboard of patient and atlas tissue image after tumor growth simulation & registration (f).

Figure 4 shows an axial, coronal and sagittal view of the atlas adapted to the same real patient dataset Case-1P. In the first row, the deformed atlas label map after the final growth step is depicted. The second row illustrates the magnitude of the displacement field after the final step of tumor growth. The displacement field determines how much each individual voxel is pushed due to the biomechanical mass-effect of the tumor, which is determined by the increase in number of cells computed from the oncosimulator. As expected, we can observe a strong displacement in areas directly affected by the tumor and a smaller displacement for areas further away. Additionally, it is obvious from the displacement field how the cell simulator accounts for the necrotic core of the tumor. No

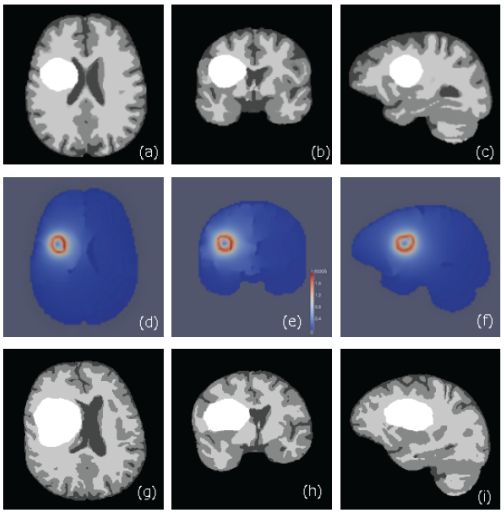

Fig. 4. ContraCancrum real patient Case-1P. First row: Deformed atlas label map after the final step of tumor growth in axial (a), coronal (b) and sagittal (c) view, Second row: Magnitude of the displacement field after the final step of tumor growth in axial (d), coronal (e) and sagittal (f) view, Third Row: Atlas label image after tumor growth and non-rigid registration in axial (g), coronal (h) and sagittal (i) view.

new cells are produced in the center, which ensures that the biomechanical deformation only takes place at the rim of the tumor, not in the center. The third row shows the atlas label map after the tumor-growth and non-rigid registration step.

Depending on the size of the tumor, total computation time was between 10 hours and 36 hours on a single CPU running at 2.67 GHz. Computation time was almost completely determined by the iteratively coupled tumor-growth model, which involves the repetitive solution of large systems of equations.

IV. Discussion and Conclusion

We presented a new method which makes use of sophisticated models of bio-physio-mechanical tumor growth to adapt a general brain atlas to an individual tumor patient image. It can be applied for solid tumors and gliomas with distinct boundaries to capture the important tumor mass-effect, while the less pronounced infiltration effect is not considered in this case. The method essentially comprises two steps: patient-specific tumor growth modeling in combination with non-rigid registration techniques, where the proposed method for tumor growth modeling integrates discrete and continuous approaches for simulation.

The results show that it is possible to adapt a healthy atlas to a tumor-bearing patient image using the proposed approach. Quantitative overlap measures indicate that this sophisticated method achieves reasonable results in a similar range as other models [10] without being very sensitive to the initial and stopping conditions of the growth model. The accuracy of Dice coefficients is also comparable to values reported for a different approach in [5], however different data was used in this case. We expect better results when using the full image resolution for the tumor growth model. Computation times are significantly longer compared to the approach in [10] because several bio-physical and biomechanical layers are taken into account.

The proposed method offers the possibility to implicitly segment tumor-bearing brain images by atlas-based registration. This is not only important for brain tissue segmentation, but it also allows us to easily delineate subcortical structures by label-map propagation, which can be useful for surgical planning of brain tumor resection or for radiotherapy planning.

A. Outlook

The deformation vector field obtained after non-rigid registration can be used to simultaneously warp other atlas maps, e.g. diffusion tensor images, to the patient. We plan to investigate if a patient-specific diffusion map then allows for more precise predictions of tumor progression. A significant potential for speed-up by parallelization of the algorithm was observed in initial trials. We plan to exploit this, so that the method can be used in a clinical scenario.

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