A Generic Framework for Modeling Brain Deformation as a Constrained Parametric Optimization Problem to Aid Non-diffeomorphic Image Registration in Brain Tumor Imaging

A. Mang1; A. Toma1,2; T. A. Schuetz1,3; S. Becker1,2; T. M. Buzug1

1Institute of Medical Engineering, University of Luebeck, Germany;
2Centre of Excellence for Technology and Engineering in Medicine (TANDEM), Luebeck, Germany;
3Graduate School for Computing in Medicine and Life Sciences, University of Luebeck, Luebeck, Germany

1. Introduction and Motivation

Glioma is a common primary brain tumor with heterogeneous presentation and poor prognosis [1]. Despite all efforts in a multidisciplinary area of research the outcome for patients diagnosed with high grade manifestations of glioma (glioblastoma (WHO grade IV)) remains fatal. A fundamental problem for a successful treatment is the complexity of the associated biophysical phenomena. That is, the precise manifestation of the tumor in an individual is determined by a complicated interplay within an intricate system (i.e. the human body) ranging from molecular signaling pathways, cellular and micro-environmental interactions to macroscopic phenomena. As a consequence, strong variations of cancer profiles are to be observed across and in individual patients. This results in the fact that the progression of primary brain tumors is not well understood until the present day. A powerful tool to systematically analyze hypotheses on molecular or cellular interactions and by that aid the understanding of individual processes of cancer development and progression is mathematical modeling. That is, mathematical models of cancer progression enable systematic analysis and identification of key bio-physiological phenomena that determine the precise appearance of glioma (glioblastoma (WHO grade IV)) remains fatal. A fundamental problem for a successful treatment is the complexity of the associated biophysical phenomena. That is, the precise manifestation of the tumor in an individual is determined by a complicated interplay within an intricate system (i.e. the human body) ranging from molecular signaling pathways, cellular and micro-environmental interactions to macroscopic phenomena. As a consequence, strong variations of cancer profiles are to be observed across and in individual patients. 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contrast, macroscopic models (cf. e.g. [3–6, 52]) are in general less complex aiming at reducing the problem dimensionality to enable model personalization [3, 4, 52]. Once adequate strategies for model individualization are established and validity of such type of models has been proven, they could become a key tool to support decision making for clinical interventions. That is, it is clinical practice to target a typically over-conservative and highly empirical margin of normal appearing tissue in the proximity of the primary tumor site for preventive reasons. This is due to the fact that cancerous cells have the ability to infiltrate healthy brain tissue well beyond the visible extent of the solid tumor inside modern magnetic resonance (MR) imaging devices. Consequently, there is a strong uncertainty in planning therapeutic interventions. Reliable, individualized models of tumor progression could help to reveal areas that are with high probability infiltrated by cancerous cells. They could become a valuable tool for decision support during planning clinical intervention by drawing attention to particular areas distal to the primary tumor site that might have not been considered when solely examining intensity patterns in MR imaging data. Accordingly, recent work on modeling cancer progression on a tissue level is aimed at model personalization [3, 4, 52]. The computed probability maps for the spread of cancer inside brain parenchyma should be considered as an additional source of information that might (due to the simplifications, noise in the data and sparseness of the available information) contain uncertainties. However, it might in combination with other available medical and biological sources potentially add valuable dynamic information on the current state of the pathology and, most importantly, allow for a systematic analysis of the pathology.

These models have not only been used to recover patterns of cancer progression seen in individual patients, but also serve as a fundamental ingredient for hybrid, model-based image computing strategies [7–11]. The present work is exclusively devoted to this particular area of research: Multi-modal MR imaging is commonly used to acquire information about the spread, the localization and the morphological and functional state of the tumor and its surroundings [12, 13] to e.g. aid diagnosis and planning of treatment. However, it only provides a stationary snapshot that is quite restricted in terms of forecasting the progression of a particular disease in an individual patient.

A potentially more powerful tool for learning about the course of a disease is to study temporal changes and identify biophysical markers from imaging patterns in a series of images of an individual patient [14–17] or, likewise, to conduct population studies. Due to the large amount of data, medical image computing [18, 19] has become a key technology to extract quantitative image parameters that characterize the functional and morphological state of a considered anatomical structure of interest. In recent years, population-based statistical analysis of imaging patterns has evolved to a promising approach for studying the development of normal brains [20, 21], or the progression of neurodegenerative diseases [22–24]. Non-rigid image registration [25–28] is at the core of such medical image analysis studies.

The application of image registration in brain tumor imaging studies is a delicate matter [15–17]. Large changes over time result in severe irregularities that in general violate the basic assumptions on diffeomorphism that any state-of-the-art non rigid image registration algorithm is funded on. That is, when it e.g. comes to registering serial tumor imaging data [15–17], or, in particular, when performing atlas based segmentation [7–9, 29, 30] or likewise, when considering generating statistical atlases of brain tumor disease, the emergence and death of tissue during tumor progression results in ill-defined correspondences. That is, if we consider corresponding anatomical structures in a set of medical images as level-sets of similar topology, the presence of pathology introduces a new iso-surface so that the topology between the considered data-sets differs. Another fundamental problem is the presence of tumor induced deformation of anatomical structures in vicinity to the primary tumor site. These deformations are in addition difficult to recover by standard non-rigid image registration technologies. Due to all of the contemplated problems, standard non-rigid image registration approaches are per definition not suited for registering tumor bearing images. This in turn demands the introduction of novel strategies that have been specifically tailored towards this very application.

A straight-forward approach to overcome the problem of ill-defined correspondence is to simply fade out the area affected by the pathology during optimization [31–33]. However, this approach results in an inaccurate alignment of anatomical structures in the close vicinity of the primary tumor site. Another strategy, which recently has been proposed [34–36], is to embed the three-dimensional images into a four-dimensional Riemannian space: Here, pathology-induced changes are handled by explicitly recovering associated intensity-drifts. Even though these approaches are applicable in a general setting, a much more elegant and powerful approach is to resolve the inherent irregularities contemplated above by explicitly modeling the pathology under consideration during the process of registration [7–11]. Such approaches in general share an accepted and well-established model for the population dynamics of cancerous cells formulated on a tissue level.

In the present work, an extension of a model that has originally been proposed in [37] is described. The search for an adequate deformation pattern is phrased as a constrained optimization problem that has a strong connection to the problem formulation typically seen in medical image registration. This in turn renders this scheme a generic tool that can potentially be introduced into any type of medical image registration algorithm. Therefore, this approach is particularly suited for being integrated into a hybrid framework for model based image registration [7–11]. To reduce the dimensionality of the search space for the deformation pattern a parametric deformation model is considered. Prior knowledge is introduced by adding a soft constraint to the proposed objective function.

The fundamental aim of this work is to provide a heuristic approximation of a model of tumor induced brain de-
formation that serves as a bio-physical prior to aid non-rigid image registration in order to resolve irregularities when it comes to registering images of varying topology. The heuristics on plausible deformation patterns are introduced in terms of soft constraints. The primary intention is to bridge the gap between sophisticated bio-physical models [10, 11, 38] and registration models that are completely independent of the underlying pathology [34–36]. The key concept is to exploit mathematical and numerical tools that are readily available in the non-rigid image registration community and by that reduce model complexity. The heuristic character in turn implicates that the model is neither targeted to precisely recover patterns in medical imaging data nor does it serve as a predictive tool. It rather is a general building block to make the considered images more similar (i.e. topologically equivalent) and by that aid the registration problem. The ultimate goal is the design of a novel hybrid, registration framework that jointly estimates model parameters and deformation patterns by exploiting numerical tools readily available in non-rigid image registration so that both building blocks mutually benefit from each other.

The area of application is to provide tools for the analysis of brain tumor imaging data in clinical research and not to establish a tool that can be used in order to plan and guide clinical interventions. More precisely, we aim at atlas based image segmentation or the generation of probabilistic atlases of brain tumor disease. The latter is of particular interest to enable the possibility to analyze brain tumor profiles in terms of e.g. voxel based morphometry across a large cohort of patients. As already stated above, this is to date not possible on the basis of standard non-rigid image registration approaches. Such atlases are a generic tool for increasing the understanding of the progression and systematically analyzing imaging patterns of a particular pathology across a cohort of patients. They in turn offer great potential for identifying imaging markers for a particular disease. The obtained information does not only serve as an additional source of information for improving the understanding of cancer progression but also could become valuable for identifying potential markers for model personalization.

The fundamental contribution of the present paper is the introduction of a novel computational framework for modeling tumor induced brain deformation on the basis of a constrained optimization problem. An elementary ingredient for this model is a cell-density map obtained via the solution of an initial boundary value problem (see Modeling Brain Cancer Dynamics) that describes the spatio-temporal spread of cancerous cells inside brain parenchyma. In the original work [37] a log-barrier approach has been considered to constrain the search space of the deformation pattern. In the present work the general applicability of the overall idea of modeling tumor induced brain deformation as constrained optimization problem is demonstrated by introducing a multi-constrained optimization framework that allows for accounting for a variety of different soft constraints (see Modeling Tumor Induced Brain Deformation). The actual implementation exploits the parametric nature of the mapping function. That is, analytical derivatives of the objective function with respect to a given set of parameters are used during the optimization of the considered problem. Due to the fact that the optimization of the log-barrier approach is numerically delicate, a limited-memory Broyden-Fletcher-Goldfarb-Shanno (LBFGS) method that uses a backtracking line search is considered instead of the initially proposed gradient descent optimization. We additionally introduce a novel numerical time integration method for the solution of the forward model for computing the spatio-temporal spread of cancerous cells inside brain parenchyma (see Numerical Implementation).

2. Methods

The implemented model consists of two fundamental building blocks: A model for the spatio-temporal spread of a population density of cancerous cells inside the brain parenchyma (denoted by $\Omega_B \subset \Omega$; see Modeling Brain Cancer Dynamics) and a heuristic approximation for a model of tumor induced brain deformation (see Modeling Tumor Induced Brain Deformation) that phrases the search for a deformation pattern as a constrained optimization problem.
2.1 Modeling Brain Cancer Dynamics

A widely used model for the dynamics of cancerous cells inside brain parenchyma is to phrase the spatio-temporal spread of a population density as an initial boundary value problem. The basic and well accepted (see e.g. [6] and references therein) assumption here is that tumor progression on a tissue level is governed by two principle phenomena: the migration of cancerous cells into surrounding healthy tissue and proliferation:

Problem 1: Let the \(d\)-dimensional interval \(\Omega = ([0, 1] \times \ldots 	imes [0, 1]) \times \mathbb{R}^d \subset \mathbb{R}^d\) and the domain \(\Omega_0 \subset \Omega\) with boundary \(\Gamma_{\Omega_0}\) and closure \(\overline{\Omega}_0\) be given. Further, let the complement \(\overline{\Omega}_0^c = \Omega \setminus \overline{\Omega}_0\), the function \(D \in \mathcal{D}_d \subset \overline{\Omega}_0^c \rightarrow \mathbb{R}^{d \times d}\) parameters \(\gamma > 0, \sigma_\nu > 0, \nu > 0\) as well as the seed point \(x_0 \in \overline{\Omega}_0\) be given. Find a suitable \(\nu \in \mathcal{D}_d \subset \overline{\Omega}_0^c \rightarrow \mathbb{R}^{d \times d}\) such that \(\partial_\nu \nu(x, t) = \dot{\nu}(D)\dot{\nu}(x, t) + \gamma \nu(x, t)(1 - \nu(x, t))\), in \(\overline{\Omega}_0^c \times \mathbb{R}_t^+\) with boundary and initial condition \(\partial_\nu \nu(x, 0) = 0\) on \(\partial_\nu \nu_0 \times \mathbb{R}_t^+\) and \(\nu(x, 0) = \nu_0\exp(-\|x - x_0\|_2^2/\sigma^2)\), for all \(x \in \overline{\Omega}_0\) respectively. Here, \(\partial_\nu \nu_0\) and \(\|\|_2\) is the normal derivative of \(\nu\) pointing from \(\overline{\Omega}_0^c\) to \(\overline{\Omega}_0\).

The function \(D\) is a diffusion tensor map and the parameter \(\gamma\) represents the net growth rate. The model for the increase in net cell density is modeled as a self-limiting logistic function (see Eq. 1). Its trend is illustrated in Figure 2. The migration is modeled as passive diffusion controlled by the tensor field \(D\). In the present work we limit ourselves to an inhomogeneous, isotropic diffusion model such that \(D(x) = r(x)E\), where \(r: \Omega \rightarrow \mathbb{R}\) is a coefficient map that exploits fuzzy labels for the tissue classes \(\Omega_\nu \subset \Omega_\nu\) (white matter) and \(\Omega_\nu \subset \Omega_\nu\) (gray matter). That is, \(r(x) = \alpha_\nu \gamma_\nu + \alpha_\nu \gamma_\nu\), with the fuzzy label maps \(\gamma_\nu: \Omega \rightarrow [0, 1]\) (for gray matter) and \(\gamma_\nu: \Omega \rightarrow [0, 1]\) (for white matter) and the parameters \(\alpha_\nu > 0, \alpha_\nu > 0\). The tissue labels are at this obtained from a digital brain phantom [39].

2.2 Modeling Tumor Induced Brain Deformation

This section is devoted to describe the proposed model of tumor induced brain deformation. We start with the employed parametric deformation model (see section Overall Setting and Parametric Deformation Model) and subsequently introduce the proposed model of brain deformation (see section Constrained Optimization Problem).

2.2.1 Overall Setting and Parametric Deformation Model

The deformation pattern is computed for a set \(Q = \{t^\prime \geq 0\}: t^\prime = \tau/q, q = \tau/n, j = 0, 1, 2, \ldots, n\) of discrete simulation time points \(t^\prime\), where \(\tau \in \mathbb{R}^+\) represents the total simulation time. For the sake of a clear representation we will use time-discrete (i.e. semi-discrete) functions below. For the computed net cell density we exemplarily define \(\nu(x, t^\prime) = \nu(x, t^\prime)\) under the assumption \(\nu^i \in C^2(\Omega, \mathbb{R}_0^+)^d\). Accordingly, we denote all time-dependent functions and variables with a super-script \(j\). To deform a given brain template a parametric mapping function \(y(x; \nu) = y(x, t^\prime, \nu), y^\prime \in C^2(\Omega)^d\) is used [40]. The mapping is represented as a linear combination of a set of parameters (control points) \(\psi = \{\nu^j \in \mathbb{R}_0^+: l = (l^1, \ldots, l^d) \in \mathbb{Z}_l, -l \leq l^i \leq m^i + 1, m^i \in \mathbb{N}, i = 1, \ldots, d\} \) and some b-spline basis functions \(\beta_l \in C^2(\mathbb{R}_0^+), l \in \{1, 2, 3\}, i = 1, \ldots, d\) of order 3. This approach in turn allows for reducing the search space to a finite dimensional set of mappings. The mapping \(y(x; \nu) = x + u^i(x; \nu)\) reads

\[
y^i(x; \nu) = x + \sum_{l^i=0}^{\tau} \sum_{l^i=1}^{\tau} \prod_{k^i=0}^{\tau} \beta_l^i(\mu^i)\nu_{l^i+1,l^i+1,l^i+1}^i + \tau^i + k^i
\]

At this \(\mu^i = x/l^i - [x/l^i]\) represents the relative position of a grid node, which corresponds to the parameter \(\nu^j \in \mathbb{R}_0^+\) at index \(l = (l^1, \ldots, l^d) \in \mathbb{Z}_l, l = (x/l^i)\) inside a nodal grid \(G = [h^1 \mathbb{N}^d \times \ldots \times h^d \mathbb{N}^d \in \mathbb{R}^{m_1+1} \times \ldots \times \mathbb{R}^{m_d+1}]\) with cell width \(h = (h^1, \ldots, h^d) \in \mathbb{R}_{>0}^d\).

Fig. 2 Logistic proliferation model for the growth rates \(\gamma \in (1.0E-2, 1.5E-2, 2.0E-2, 2.5E-2)/d\) (left) and weighting functional w for different parameters \(p \in \{2.0E-1, 1.0E-1, 2.0E-2\}\) (right).
2.2.2 Constrained Optimization Problem

The model of tumor induced brain deformation proposed in this manuscript is based on a constrained optimization problem. It reads

**Problem 2:** Find a mapping \( y^j \in C^2(\Omega)^d, \) which fulfills \( J : C^2(\Omega)^d \times C^2(\Omega \mathbb{R}^n) \to \mathbb{R}, \)

\[
J[y^j] = f(y^j, v^j)
\]

where \( P : C^2(\Omega)^d \times C^2(\Omega \mathbb{R}^n) \to \mathbb{R}, \)

\[
P[y^j] = P(y^j, v^j)
\]

is a data term that drives the deformation, \( C : C^2(\Omega)^d \to \mathbb{R}, \) is a so-called soft constraint and \( \alpha > 0 \) is a weighting parameter to control the influence of the soft constraint.

Let us have a closer look at the individual building blocks of Problem 2. The data term is defined by

\[
P[y^j] = -\int_{\Omega} w(v^j(x))v^j(x)\,dx.
\]

The weighting functional \( w : C^2(\Omega \mathbb{R}^n) \to \mathbb{R}^n \) is used to locally control the deformation pattern with respect to the given net cell density \( v^j. \) It is defined by (modified from [10])

\[
w(v^j(x)) = \exp \left(-\frac{p}{(v^j(x)/\kappa)^2} - \frac{p}{2 - (v^j(x)/\kappa)^2}\right)
\]

where \( \kappa > 0 \) and \( p \geq 0 \) controls the non-linearity of \( w. \) As can readily be observed in Figure 2 (right) this functional is monotonically increasing for densities \( 0 \leq v^j \leq \kappa \) and approaches its maximum at \( v^j = \kappa. \) Increasing \( p \) allows for limiting the computed deformation pattern to the close vicinity of the tumor (Figure 3).

In a variational optimize-then-discretize approach, which is traditionally used for a numerical treatment of the non-rigid image registration problem [26, 27], it can be shown via calculus of variation that the Gâteaux derivative of the data term \( P \) yields a force that is in accordance with the force field of bio-physical models [10].

The constraint \( C \) in Equation 3 is a fundamental building block for the present approach. It not only allows for e.g. ensuring the regularity of the computed deformation pattern but also to limit the magnitude of the displacement vectors. The latter is of fundamental concern since minimizing solely Equation 4, i.e. setting \( \alpha \) in Equation 3 to zero, would ultimately result in a displacement field \( v^j : \mathbb{R}^d \to \mathbb{R}^d \) that consists of vectors of infinite length, i.e. the optimum is at infinity. The general setting for the constraints implemented in this work is

\[
C[y^j] = \int_{\Omega} \phi_i(y^j(x; \psi))\,dx,
\]

where \( \phi_i : C^2(\Omega)^d \to \mathbb{R} \cup [\infty], i \in [I, SC], \)

\( f \) represents some penalty function that judges on the properties (regularity, smoothness, …) of the mapping \( y^j \) in some sense. We have made available three soft constraints, the first of which penalizes large displacements in terms of the \( L^2 \)-norm. The weighting functional is accordingly given by

\[
\phi_i : \mathbb{R}^d \to \mathbb{R} \cup [\infty], \quad i \in [I, SC],
\]

\[
f(y^j(x; \psi)) = \frac{1}{2} |H(y^j(x; \psi))|^2_F.
\]

**2.2.3 Numerical Implementation**

The numerical scheme for the solution of Problem 1 is an unconditionally stable, explicit time marching regime that originally has been proposed in the field of image computing [42]. The fundamental idea of this regime is to overcome the stability restriction on the maximal admissible time step size for a standard explicit scheme by introducing a time step sub-division (the interested reader is referred to [42] for a detailed discussion). We have

\[
u^{n+1} = \left( \sum_{l=0}^{n} (E + q_l^2 \mathbf{A}) \right) u^n + q^n w^{n+1}_0,
\]

where \( q^n \in \mathbb{R}^n \) is a vector representation (lexicographical ordering) of the numerical solution at iteration \( i, f \in \mathbb{R}^{n \times n} \) denotes a vector representation of the logistic growth model, \( E = \text{diag}(1, \ldots, 1) \in \mathbb{R}^{n \times n} \) is the identity matrix and \( \mathbf{A} \in \mathbb{R}^{n \times n} \) is a sparse, positive semi-definite matrix that arises from the discretization of the linear diffusion differential operator. Further, \( n = \prod_{i=1}^m m_i \) denotes the total number of grid nodes and \( w^* \in \mathbb{N} \) is the number of substeps with step size \( q^*_l, l = 0, \ldots, w^* - 1. \)

The derivatives are approximated via finite difference operators. The particular choice

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We omit any further technical details on the actual numerical implementation of this scheme, since the central aspect here is the model of tumor induced brain deformation. For a detailed discussion of this numerical scheme against the background of diffusion based image filtering the interested reader is referred to [42].
for the time steps $q_i$ renders this scheme unconditionally stable. The rule for their computation is given by [42]

$$q_i = \nu \left( 2 \cos^2 \left( \frac{2i + 1}{4} \right) \right)^{-1}.$$  

Here, $\nu > 0$ represents a problem specific scaling parameter, which depends on the spectral properties of the coefficient matrix $A$.

The implementation of the deformation model is in accordance with the overall framework described in [43], which thus makes it generally applicable for being integrated into such a registration framework. That is, we exploit the availability of analytical expressions for the derivative of the mapping function. The analytical derivative for the data term is given by

$$\partial_{\phi_k} P_o[y^j] =$$

where $\partial_{\phi_k}$ is the derivative with respect to the j-th component of the k-th parameter. As for the derivatives of the smoothness constraint as well as the constraint on the magnitude of the displacements $u(x, \psi)$, we obtain $\partial_{\phi_k} \phi_{C_j}(u(x, \psi)) = 2(y(x, \psi) - x)$, where $\partial_{\phi_k} \phi_{C_j}(y(x, \psi)) = 2\partial_{x_k} y(x, \psi)$, respectively. For the derivative of the volume constraint we obtain $\partial_{\phi_k} C_v[y^j] = \int \text{tr}(J(y(x, \psi))) \partial_{\phi_k} J(y(x, \psi)) \, dx$.

A limited memory Broyden-Fletcher-Goldfarb-Shanno (LBFGS) method with either, a More and Thuente’s line search [44] or a backtracking line search, is used to search for a (local) minimizer of Equation 3. To test for convergence the strong Wolfe conditions [45] are used. The backtracking line search is particularly suited in case a log-barrier strategy is used to constrain volume change. This is due to the fact that the optimization can become a quite delicate matter when approaching a local singularity since the constraint tends to infinity (Fig. 4). Further, so to say “Dirichlet boundary conditions” are stipulated on the control points outside of the brain not only to reduce the computational burden, but also to ensure that there are less spurious deformations of rigid structures (e.g. the skull).

4. Results

In the present section we provide a variety of numerical experiments for the above contemplated model. We start with a simu-

![Fig. 4](image-url)  
Constraining volume change: Left: constraint on the magnitude of the displacement. Right: Log-barrier approach to constrain the determinant of the Jacobian of the mapping for different choices of the weighting function. Both weighting functions penalize deviations of the determinant of the Jacobian matrix from unity and thus local tissue compression and expansion.

![Fig. 5](image-url)  
Simulation results. On the left the coronal view of the computed cancer profile together with an illustration of the corresponding color coding scheme used to visualize the density map is given. The arrows indicate estimates for detection thresholds in MR imaging devices (T2w: green arrow; T1w (contrast enhanced): orange arrow) [46]. The surface representations illustrate the folding pattern of the white matter and by that the complexity of the considered computational domain as well as iso-surfaces of the computed tumor profiles for the given detection thresholds (visualized in the corresponding color) viewed from left (central two views) and superior (leftmost two views).
lation that solely is based on the solution of Problem 1. From this we continue with a variety of numerical experiments for the devised model of tumor induced brain deformation.

### 4.1 Modeling Brain Cancer Dynamics

In the first set of numerical experiment the tumor induced deformation is neglected. Solely results for the solution of Problem 1 are provided to explain the visualization of the computed density map (Fig. 5, left). The model parameters are as follows: \( \alpha_c = 0.005 \text{ mm}^2/\text{d}, \alpha_w = 0.05 \text{ mm}^2/\text{d}, \gamma = 0.016/\text{d}, x_S = (115, 120, 92)^T \). Figure 5 provides an illustration of the computed density map as well as surface renderings of the white matter together with level-sets for the given tumor profile. The computation time to obtain these results is 1 m 14 s on a standard desktop PC (Intel Core i5 760, 2.8 GHz, 8GB DDR3 RAM) with a step size of \( q = 2.0 \text{ d} \).

### 4.2 Modeling Tumor Induced Brain Deformation

In this section, we present a numerical study for the proposed model of tumor induced brain deformation. The first experiments in Figure 6 analyze the effect of the control parameter \( p \) in Equation 5 on the computed deformation pattern. We use the Jacobian constraint as penalty. The step length for the back-tracking line search is 1.0. The reduction rate for the step size is 0.5. This factor is used to reduce the step size once a degenerate mapping is detected as judged by computing the determinant of the Jacobian matrix of the mapping function \( y \) in case the constraint on volume change is used as a penalty. The parameters for the optimizer will remain fixed throughout all experiments.

The simulation is initialized at \( x_S = (45, 100, 60)^T \) with \( \sigma = 2.0 \). The remaining parameters for the model of brain cancer progression are \( \alpha_c = 0.005 \text{ mm}^2/\text{d}, \alpha_w = 0.05 \text{ mm}^2/\text{d} \) and \( \gamma = 0.005/\text{d} \). The number of grid points (coefficients) for the deformation model are 14 along each spatial direction. The weighting for the Jacobian constraint is \( \alpha = 0.001 \) and the simulation time is 400 days. As can readily be seen from the images in Figure 6, the smaller the parameter \( p \) the larger the area affected by the computed deformation.

Further, we provide an illustration of the trend of the computed deformation pattern. The parameters are essentially those from the former experiment, apart from the fact that the initial point is set to \( x_S = (120, 140, 90)^T, p \) is fixed to \( 10^{-4} \) and we use a soft constraint that penalizes the \( L_2 \)-norm of the displacement with a weighting parameter \( \alpha = 10^{-5} \). The results are illustrated in Figure 7. With the same setting, but initialized at \( x_S = (110, 155, 80)^T \), an illustration of the influence of the weighting parameter that controls the contribution of the penalty on the \( L_2 \)-norm of the displacement field is provided in Figure 8 (left).

Figure 8 (right) additionally features a comparison of the computed deformation pattern for the implemented set of soft constraints. The parameters are again like those in the former experiment apart from the initial point, which is given by \( x_S = (75, 150, 60)^T \) and the weighting for the constraint, which is set to \( \alpha = 10^{-4} \).

In the last set of experiments we exemplarily compare the computed cancer profiles to patterns of a brain tumor (glioblastoma) in a T2 weighted (T2w) MR image of an individual patient. The results are displayed in Figure 9. A constraint on the Jacobian of the mapping function with a weighting of \( \alpha = 10^{-4} \) and \( p = 0 \) has been used. The parameters for modeling the cancer progression are \( \alpha_c = 0.065 \text{ mm}^2/\text{d}, \alpha_w = 0.013 \text{ mm}^2/\text{d} \) and \( \gamma = 0.05/\text{d} \). The top row in Figure 9 provides the simulation results in axial, coronal and sagittal view, respectively. The corresponding view of the T2w MR image of the associated patient is given below. The bottom row provides the computed profile overlayed on top of the T2w MR image with a detection threshold (based on a hypothesis [46] on the minimal density of cancerous cells visible in T2w MR images) being applied on the computed tumor profile as illustrated in Figure 5. The qualitative comparison demonstrates that the computed tumor profile is in good agreement with the observation inside the MR images. In order to qualitatively rate the

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**Fig. 7** Trend of the deformation pattern for a penalty on the \( L_2 \)-norm of the displacement field. The time points are from left to right 40 d, 200 d, 400 d and 480 d after tumor emergence.
agreement between the patterns in the T2w image and the computed density map, different distance measures for binary labels, which are widely used in the segmentation and registration community, are considered (cf. e.g. [47]). More precisely, the average Hausdorff distance, the volume similarity, the total overlap and the mean overlap are computed. The hyperintense area of the tumor inside the T2w image is manually delineated by an expert observer. Since the expert segmentations have to be transformed to the atlas space, the employed interpolation model results in a set of fuzzy labels. To remap these to a binary label map, a threshold of 0.5 is applied. The associated binary label for the cell density map is obtained by applying the detection threshold hypothesized in [46]. The results for the average Hausdorff distance, the volume similarity, the total overlap and the mean overlap are 0.691 mm, −0.031, 0.748 and 0.759.

5. Discussion and Conclusion

We have introduced a novel, generic optimization problem for modeling tumor induced brain deformation as a bio-physical prior for non-rigid image registration. The present work is an extension of [37]. More precisely, we have extended the modeling framework by introducing additional strategies to constrain the parametric search space for the deformation pattern, which demonstrates the generality of the contemplated model.

The intension of this work is to provide a prior for non-rigid image registration that allows for resolving the inherent problem (change in topology) posed in non-differeomorphic brain tumor image registration scenarios. Registration of such data is per definition not possible on the basis of available, state-of-the-art non-rigid image registration techniques. The area of application is the generation of statistical pathology atlases. Such a type of atlas yields a powerful tool for summarizing data across a population, analyzing the spatial relation between the primary tumor site and anatomic structures and to learn about glioma progression across a population of patients [11].

The quantitative analysis yields a value for the overlap that is in accordance to results obtained for standard non-rigid image registration techniques in multi-subject registration [47]. The volume between the computed and the segmented tumor is in a very good agreement. These are indeed promising findings, since the computation did not yet include any optimization for matching the profiles to the observables in the data (i.e. the result is obtained via plain forward simulation with parameters identified by experience for which the time point that is visually in best accordance with the displayed image is chosen). There are anatomical variations between the considered patient individual data and the data in the model space (atlas image) that inevitably result in residual differences between the computed profiles and the observations in the data that cannot fully be corrected for. In addition, the data to which the model is compared (i.e. the manual segmentation) has a very low cross-plane resolution (spacing: approx. 0.5 mm × 0.5 mm × 5.5 mm) as compared to the grid the PDE is solved on (spacing: 1 mm × 1 mm × 1 mm). The computed average Hausdorff distance is well below the diagonal of a voxel in the patient space and the simulation space demonstrating good agreement between the manually delineated contour and the contour of the computed tumor profile.

As for the constraints analytical derivatives have been developed to speed up the optimization. To constrain volume change in terms of the determinant of the Jacobian matrix adds a prior that not only is biophysically motivated (it is assumed that tissue is in general incompressible) but also allows for enforcing regularity during deformation. However, it must be noted that even though point-wise regularity is guaranteed by computing the determinant of the Jacobian on the basis of analytical derivatives of the parametric mapping function $y$, the mapping is not necessarily regular throughout the entire domain. In order to rigorously ensure regularity, one should embed the devised model into a non-parametric setting (see e.g. [48]) that particularly has been designed to yield non-degenerate mappings. This is something we will investigate in future. As for the remaining constraints it must be noted that the computed deformation pattern, yet restricted to be smooth, does not necessarily have to be regular, i.e. one-to-one, which is why we currently favor the bio-physically motivated constraint on the determinant of the Jacobian. On the other hand, the computed deformation patterns are more flexible and the implementation is less delicate as compared to the log-barrier approach. Further, this demonstrates the generalizability of the proposed constrained optimization

![Fig. 8](image_url) Influence of the weighting parameter for the $L^2$-penalty (left) and comparison of the results for the three different penalties introduced into the proposed framework. Left figures: The weighting is reduced from left to right and given by $10^{-2}$, $10^{-3}$ and $10^{-4}$, respectively. Right figures: incompressibility constraint, constraint on the $L^2$-norm of the displacement field and smoothness constraint.
framework for modeling tumor induced brain deformation. Clearly, further investigation on the particular choice of the penalty (or regularizer if non-parametric approaches are considered) as well as the best choice of the precise registration framework is an important question. In this work we have limited ourselves to a parametric framework. The log barrier on volume change seems from a bio-physical perspective a sensible choice. In future work, we will address if it indeed is necessary to actually introduce this bio-physical prior in terms of restricting change in volume or if simple constraints are adequate for the purpose of image registration. At this, the translation to non-parametric, state-of-the-art non-rigid image registration frameworks (cf. e.g. [26]) is something that we are currently investigating. In particular, spatially adaptive, elastic regularization [49] or integration into a hyperelastic framework for mass preserving image registration [50] seems a natural choice, as already indicated above. This also includes the question on if it is necessary to introduce bio-physical deformation models [10] or if the approximate formalisms in this work suffice to improve on the registration accuracy.

We have suggested using a back-tracking line search strategy for an LBFGS optimization scheme instead of our initial gradient descent based optimization [37]. This in turn allows for a numerically sound handling of the log-barrier approach, i.e. to handle the case when the constraint on the Jacobian of the mapping function tends towards infinity.

As for the model of the population density of cancerous cells we have replaced the commonly used binary, tissue-dependent weighting that is generally used to model isotropic diffusion by a fuzzy coefficient map (see section Modeling Brain Cancer Dynamics). Further, we have introduced a novel fast, explicit numerical scheme to compute the solution of the associated initial-boundary value problem, which has recently been proposed in the field of image computing [42] to our modeling problem. This very scheme is – likewise to implicit numerical schemes – unconditionally stable with the additional features of being straightforward to implement and intrinsically matrix free. The latter is especially attractive since it renders this scheme efficient in terms of memory requirements as compared to standard implicit numerical schemes. This in turn makes it particularly suited for being integrated into computational demanding frameworks for parameter estimation from medical imaging data [3] or likewise – as suggested in the present work – modeling approaches that serve as a prior for medical image computing. The present work features a parallel, multi-threaded implementation of this scheme. The simulation time is – in a two-dimensional setting – at the order of about 30 s and in a three-dimensional setting at the order of two hours for the given image (the simulation time point from tumor emergence is 730 d; standard desktop PC (Intel Core i5 760, 2.8 GHz, 8GB DDR3 RAM)). These timings also include the solution of the optimization problem for modeling tumor induced brain deformation. Even though the framework features a local evaluation of the objective, the use of analytical derivatives and an L-BFGS optimization strategy there clearly is still much room for improving on the computational speed. Due to the fact that the discussed methodology is novel, an optimization of computational time has not been considered thoroughly. As a matter of fact, changing to computational more efficient registration frameworks is something to be investigated in future. Due to the concept of constrained optimization, the computation time in general can be estimated by considering the time it takes to solve a registration problem on the data of the considered size times the number of optimization steps performed (i.e. how often the optimization problem is to be solved).

In the current work, the optimization problem is solved every 20th time integration step of the initial boundary value problem.

Considering the model parameters, there is no advice to be given on how to set them in unseen data. The ultimate goal is to provide a hybrid formalism that allows for optimizing for these parameters during the process of registration. That is, instead of solely optimizing for a dense displacement field (non-parametric registration) or like-

![Fig. 9](image-url) Comparison of the computed tumor profile to the pattern seen in an exemplary T2-weighted MR image.
wise for a set of parameters (parametric registration, which is considered here) that parameterize the computed deformation pattern, one extends the search space to the parameters of the model of tumor induced brain deformation or cancer progression. Currently, a set of model parameters is used that is based on standard values typically found in literature (cf. e.g. [6] and references therein). Our current perspective on establishing a hybrid framework for model based non-rigid image registration is to find a most likely set of model parameters in the sense that the altered atlas image “best matches” the patient individual image. The idea of jointly estimating model parameters and the deformation pattern is motivated from the fact that both processes (registration and simulation) are likely to mutually benefit from each other. At this, match is considered as the residual distance between the two images in the area distal to the primary tumor site. Thus, the problem of parameter estimation is not considered in terms of model individualization (i.e. to relate the model to patterns of the pathology in the patient individual data), but in terms of identifying a set of model parameters that allows for generating the “best” registration result. Another idea could be to translate the computed tumor profile into an MR intensity map and also evaluate the registration cost function inside the area affected by the brain tumor pathology. How the computed cell density map relates to intensity patterns in MR imaging is an open question.

It is necessary to have some idea on the initial values as well as the bounds for the model parameters (i.e. it is necessary to have some idea for a bio-physiologically sensible range). These initial values and parameter bounds are in general unknown and have to be determined by experiments from forward simulations supported by results obtained for model individualization available in the literature (cf. e.g. [3, 4, 52]). In order to demonstrate the flexible control of the deformation pattern with the proposed optimization framework numerical experiments have been performed. This in turn provides strong evidence that it is indeed possible to adapt the resulting deformation pattern to patient individual patterns of tumor induced brain deformation. To confirm this statement, we have in addition provided a qualitative comparison of the modeled results to medical imaging patterns in patient individual imaging data as well as a quantitative analysis. At this it must be noted, that the model parameters have been identified by performing several forward simulations and then choosing the images that visually best match the patterns observed in the data. The above suggested hybrid framework for model based image registration is expected to strongly reduce these residual differences.

In a next step, we will carry forward this scheme by introducing it to non-rigid image registration algorithms and by that design a hybrid, model based registration framework for medical image registration in brain tumor imaging data (likewise to e.g. hybrid registration frameworks that combine variational models of non-rigid image registration with level set image segmentation [51]).

Such a hybrid framework will also enable the possibility to come up with a quantitative analysis of the devised model and by that to relate the registration performance to available approaches [34–36]. This in turn yields a framework for validating the pursued idea of a hybrid, model-based registration algorithm on the basis of established methodology to judge the performance of image registration techniques (cf. e.g. [47]). More precisely, possible strategies include exploiting the model in atlas based image segmentation (registering an atlas to an image of a patient that displays brain tumor pathology) and rating the overlap for a given set of anatomical labels. Likewise, the distance between anatomical landmarks identified in both images or the residual dissimilarity after registration on the basis of different distance measures employed in image registration can serve as a criteria to rate the performance of the proposed approach. Clearly, it will be essential to relate these findings to approaches that exploit sophisticated bio-physical models [10, 11, 38] and registration algorithms that are completely independent of the underlying pathology [34–36].

Further comparison to more realistic bio-physical models of tumor induced brain deformation [38] as well as the design of strategies for automated model personalization [3, 4, 52] will be essential for our future work. Comparison to bio-physical models of tumor induced brain deformation will in turn allow for further ranking the computed deformation patterns obtained with the proposed optimization framework. The design of tools for automated model calibration is of particular interest to not only provide individualized probability maps of cancer progression but also to systematically analyze confidence and uncertainty in model predictions. Comparison to such tools could in turn also allow to further rank the proposed framework. This in turn permits testing if the employed heuristics are sufficient for generating plausible deformation patterns or if additional bio-physical knowledge is to be incorporated.

Rating registration performance serves as a surrogate for a preliminary validation of the described framework. At this it must be noted that an explicit validation of models of brain tumor progression is in general a delicate matter. It demands the availability of a ground truth data inside the medical images to which the model can be related (in the current work manual segmentation is considered as such gold standard). A detailed model validation is especially of interest when it comes to prediction of cancer progression and model individualization [3, 4, 52]. However, since the primary intention of this work is to provide a novel concept for registration of images of varying topology and not to precisely recover the patterns seen in patient individual data, a detailed model validation remains subject to future work. Further, as stated above, within the framework presented in this work the validity of the model is to be verified by analyzing the capabilities when it comes to integration into non-rigid image registration, something that forms the basis of our current work.

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