AN EFFICIENT, VARIATIONAL NON-PARAMETRIC MODEL OF TUMOUR INDUCED BRAIN DEFORMATION TO AID NON-DIFFEOMORPHIC IMAGE REGISTRATION

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ABSTRACT

In the present work we propose a novel, efficient strategy for modelling tumour induced brain deformation as a prior for non-rigid image registration in non-diffeomorphic registration problems seen in serial or cross-population brain tumour imaging studies. Here, the presence of pathology dramatically alters the morphological and textural appearance of the anatomical structures under consideration and by that induces changes in topology in the considered images rendering the registration problem non-diffeomorphic.

In the present work we extend on a model of tumour induced brain deformation that has been formulated as a parametric optimisation problem and translate it to a non-parametric model, for which efficient solution strategies are available. More precisely, we exploit the fact that diffusive regularisation can efficiently be approximated via successive Gaussian convolution. To generate diffeomorphic deformation patterns, a regridding strategy is employed. The resulting (point-wise) regularity of the mapping allows for accounting for mass preservation during deformation.

Numerical experiments demonstrate the flexible control of the deformation pattern. A qualitative comparison to imaging data substantiates the potential of the proposed model. The generic variational framework makes this model generally applicable for an integration into any non-parametric image registration algorithm. The discussed implementation makes it particularly suited for demons-type registration approaches.

Index Terms— tumour induced brain deformation, brain tumour imaging, non-diffeomorphic image registration

1. INTRODUCTION AND MOTIVATION

Non-rigid image registration [1] is a versatile and powerful tool with a variety of different applications in medical image computing. However, its application becomes a delicate matter in case the pathology dramatically alters the morphological and textural appearance of the anatomical structures under consideration inside the given image data.

A straightforward approach is to treat the areas affected by the pathology as unreliable and fade them out during evaluation of the distance measure. This approach, however, does not guarantee for an accurate registration in the vicinity of the pathology. Recently, it has been suggested to account for changes in topology by embedding the d-dimensional images in a $d+1$-dimensional Riemannian manifold [2]. This approach yields not only a displacement field that relates the template image, T, to the reference image, R, but also a mapping that acts on the intensity to recover pathology induced intensity drifts between T and R. This strategy is (in theory) generally applicable for any given set of images that vary in topology, but does not include pathology specific priors. In [3, 4] it has been demonstrated that mathematical models of brain cancer progression [5, 6] serve as a powerful tool to resolve the contemplated irregularities posed to non-rigid image registration approaches when it comes to registering images in brain tumour imaging studies. Possible areas of application include atlas based segmentation or the generation of pathology atlases.

In the present manuscript we redesign the approach described in [7] in order to (i) translate it to state-of-the-art non-rigid image registration approaches, (ii) reduce algorithmic complexity and (iii) improve on its efficiency. In [7] the problem of modelling tumour induced brain deformation has been phrased as a parametric optimisation problem with a strong relation to the problem formulation seen in non-rigid image registration [1]. This approach represents an approximate shortcut to biophysical models [5, 6] and is based on mathematical tools widely used in image registration. It by that does not depend on the solution of a coupled non-linear system of partial differential equations [5, 6] and can easily be integrated into available techniques for constrained optimisation. This approach essentially lives in-between the work described in [2] and [4, 5, 6]. In [7] we have suggested to use a mapping that is expanded in terms of a set of parameters and

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some basis functions. Further, to introduce a problem specific prior, a soft constraint based on a log-barrier approach on the Jacobian of the mapping is used. In this work we suggest to translate this approach from a parametric model [7] to a non-parametric strategy and by that exploit efficient optimisation regimes originally proposed for demons type image registration [8, 9, 10]. To enforce diffeomorphic deformation patterns a regridding strategy is introduced (similar to the approach typically seen in fluid registration [11]), in case one approaches singular deformation patterns. Further, we propose a modification of the objective for enforcing mass preservation of the density during optimisation.

2. MATERIAL AND METHODS

In the following sections we will provide a concise description of the mathematical model of cancer progression[1] (§2.1) and discuss the model of brain deformation (§2.2).

2.1. Model of Brain Cancer Progression

The model for the description of the spatio-temporal spread of a density, w, of cancerous cells inside brain parenchyma, Ω_B, is based on an initial boundary value problem (IBVP). At this, we assume that the domain occupied by brain parenchyma forms an open set, $\Omega_B \subset \Omega$, with boundary, $\partial\Omega_B$, and closure, $\bar{\Omega}_B$, defined on $\Omega := (0,1)^d \subset \mathbb{R}^d$, $d \in \{2,3\}$. The partial differential equation that describes the spread of cancerous cells, $w \in C^2(\Omega_B, \mathbb{R}_0^+) \times C^1(\bar{\Omega}_B, \mathbb{R}_0^+) =: \mathcal{W}$, reads

$$\partial_t w(\boldsymbol{x},t) = \nabla \cdot (\boldsymbol{D}(\boldsymbol{x}) \nabla w(\boldsymbol{x},t)) + f(w(\boldsymbol{x},t)), \quad (1)$$

in $\Omega_B \times \mathbb{R}_0^+$ with homogeneous Neumann boundary condition $\partial_{\boldsymbol{n}} w(\boldsymbol{x},t) = 0$ on $\partial\Omega_B \times \mathbb{R}_0^+$ and initial conditions $w(\boldsymbol{x},0) = w_S \exp(-\|\boldsymbol{x} - \boldsymbol{x}_S\|_2^2 / 2\sigma^2)$, $\forall \boldsymbol{x} \in \Omega_B$. The migration of cancerous cells is modelled as passive diffusion and controlled via the tensor field $\boldsymbol{D} \in C^1(\Omega, \mathbb{R}^{d\times d})$. The proliferation is modelled on the basis of a logistic function, $f\colon \mathcal{W} \to \mathbb{R}_0^+$ (i.e. $f(w(\boldsymbol{x},t)) = \gamma w(\boldsymbol{x},t)(w_L - w(\boldsymbol{x},t))$ with growth rate $\gamma > 0$ and upper limit $w_L > 0$). The diffusion tensor, $\boldsymbol{D}$, is modelled to be isotropic so that $\boldsymbol{D}(\boldsymbol{x}) = \phi(\boldsymbol{x})\boldsymbol{E}$, where we suggest to use a fuzzy coefficient map, $\phi(\boldsymbol{x}) = \chi_W \phi_W(\boldsymbol{x}) + \chi_G \phi_G(\boldsymbol{x})$, with the user defined diffusion coefficients, $\chi_l > 0$, $l \in \{W, G\}$ for **w**hite and **g**rey matter, respectively, and the fuzzy tissue label map, $\phi_l : \Omega \to [0,1]$, $l \in \{W, G\}$, for these very tissues, obtained from an anatomical brain atlas [13].

2.2. Model of Tumour Induced Brain Deformation

We consider a semi-discrete representation $w^j(\boldsymbol{x}) := w(\boldsymbol{x}, t^j)$, $w^j \in C^2(\Omega, \mathbb{R}_0^+)$ at a given point in time $t^j = jq$, $q > 0$, $j = 1, \ldots, m$. For ease of presentation a super-script j is introduced for every function that is evaluated at t^j. Note that this also indicates that we have to solve the discussed optimisation problem m times on the basis of the solution of the forward problem[2] given at a time point t^j (see §2.1).

Algorithm 1

$k = 0$; $\tau = \tilde{\sigma}^2/2$; $t^k := \tau k$; $r = \varepsilon + 1$
$\hat{\boldsymbol{u}}^j(\boldsymbol{x},0) = \boldsymbol{u}^j(\boldsymbol{x})$; $\hat{w}^j(\boldsymbol{x},0) = w^j(\boldsymbol{x})$; $\hat{\boldsymbol{v}}^j(\boldsymbol{x},0) = 0$
while $k \leq \hat{m}$ & $r > \varepsilon$ **do**
  IF $J_y < \varepsilon_J$ **regrid**
  $\boldsymbol{b}^k \leftarrow \boldsymbol{b}^j(\boldsymbol{x}, \hat{w}^j(\boldsymbol{x},t^k), \hat{\boldsymbol{u}}^j(\boldsymbol{x},t^k), J_y)$; $r \leftarrow \|\boldsymbol{b}^k\|_2$
  $\hat{\boldsymbol{v}}^j(\boldsymbol{x},t^k) \leftarrow \mathcal{K}(\boldsymbol{x},\tilde{\sigma}) * \left[\hat{\boldsymbol{v}}^j(\boldsymbol{x},t^k) + \alpha \boldsymbol{b}^k\right]$
  $\hat{\boldsymbol{u}}^j(\boldsymbol{x},t^{k+1}) \leftarrow \hat{\boldsymbol{u}}^j(\boldsymbol{x},t^k) + \tau \left(\boldsymbol{E} - \nabla \hat{\boldsymbol{u}}(\boldsymbol{x},t^k)\right)^{\mathsf{T}} \hat{\boldsymbol{v}}^j(\boldsymbol{x},t^k)$
  $k \leftarrow k+1$
end while
$\boldsymbol{u}^j(\boldsymbol{x}) \leftarrow \hat{\boldsymbol{u}}^j(\boldsymbol{x},t^k)$, $w^j(\boldsymbol{x}) \leftarrow \hat{w}^j(\boldsymbol{x},t^k)$

The model of tumour induced brain deformation is in accordance with [7] phrased in terms of a variational problem and reads

$$\min_{\boldsymbol{u}^j} \mathcal{J}(w^j, \boldsymbol{u}^j) := \mathcal{S}(\boldsymbol{u}^j) + \alpha \mathcal{D}(w^j, \boldsymbol{u}^j). \quad (2)$$

Here, $\alpha \geq 0$ is a weighting parameter and $\boldsymbol{u}^j : \mathbb{R}^d \supset \Omega \to \mathbb{R}^d$, $\boldsymbol{u}^j(\boldsymbol{x}) = (u^{j,1}(\boldsymbol{x}), \ldots, u^{j,d}(\boldsymbol{x}))^{\mathsf{T}}$ a displacement field that models the sought deformation pattern. The functional $\mathcal{D} : C^2(\Omega, \mathbb{R}_0^+) \times C^k(\Omega, \mathbb{R}^d) \to \mathbb{R}_0^+$, $k \in \mathbb{N}$, drives the deformation and $\mathcal{S} : C^k(\Omega, \mathbb{R}^d) \to \mathbb{R}_0^+$ is a regulariser that ensures well-posedness of the minimisation problem and typically stipulates smoothness of the solution in some sense (i.e. it decides on k). Necessary conditions for a minimiser of (2) are—in accordance with calculus of variation—given by the Euler-Lagrange equations

$$\mathcal{A}[\boldsymbol{u}^j](\boldsymbol{x}) = \boldsymbol{b}^j(\boldsymbol{x}, w^j(\boldsymbol{x}), \boldsymbol{u}^j(\boldsymbol{x})), \quad \text{for all } \boldsymbol{x} \in \Omega. \quad (3)$$

Thus, in an *optimise-then-discretise* approach the task of modelling tumour induced brain deformation translates into finding the solution of (3). Here, the force vector $\boldsymbol{b}^j : \mathbb{R}^d \supset \Omega \to \mathbb{R}^d$ as well as the differential operator, $\mathcal{A}\colon C^k(\Omega, \mathbb{R}^d) \to C^{k-n}(\Omega, \mathbb{R}^d)$, of order $n \in \{0, 1, \ldots, k\}$ are obtained from computing the Gâteaux derivatives of the functional $\mathcal{D}$ and $\mathcal{S}$, respectively. Motivated from [7] we have

$$\mathcal{D}(w^j, \boldsymbol{u}^j) = -\int_\Omega s(w^j(\boldsymbol{x}))\, w^j(\boldsymbol{u}^j(\boldsymbol{x}))\, \mathrm{d}\boldsymbol{x} \quad (4)$$

for which the Gâteaux derivative yields a force vector, $\boldsymbol{b}^j$, that is in accordance with biophysical models [6] and reads

$$\boldsymbol{b}(\boldsymbol{x}, w^j(\boldsymbol{x}), \boldsymbol{u}^j(\boldsymbol{x})) = -s(w^j(\boldsymbol{x})) \nabla w^j(\boldsymbol{u}^j(\boldsymbol{x})). \quad (5)$$

The weighting, $s \in C^\infty(\Omega, \mathbb{R}_0^+)$, is motivated from [6] and given by $s(w^j(\boldsymbol{x})) = \exp(-p/(w^j(\boldsymbol{x})/w_L)^2 + p/(2 -$

[1] We only provide a brief description since this type of model is well accepted (cf. [12, pp. 536 ff] for a discussion of the pioneering work).

[2] It is accordingly also necessary to feed back the deformed atlas image to the IBVP (i.e. to update the anatomical labels).

$w^j(\boldsymbol{x})/w_L)^2)$, with $w_L > 0$ (limit for f (see §2.1)). The parameter, $p > 0$, controls the non-linearity of s and allows for limiting the deformation to the close vicinity of the primary tumour site. For the regulariser, $\mathcal{S}$, there exists a variety of options [1, 10]. In the present work a diffusive regularisation [14] is chosen so that $\mathcal{S}$ in (2) reads

$$\mathcal{S}(\boldsymbol{u}^j) = \frac{1}{2}\int_\Omega \sum_{i=1}^{d} \|\nabla u^{j,i}\|_2^2 \,\mathrm{d}\boldsymbol{x}, \tag{6}$$

for which the partial differential operator, $\mathcal{A}$, is given by $\mathcal{A}[\boldsymbol{u}^j](\boldsymbol{x}) = -\Delta\boldsymbol{u}^j(\boldsymbol{x})$ so that $\boldsymbol{u}^j \in C^2(\Omega, \mathbb{R}^d)$ (i.e. $k = 2$). This choice for $\mathcal{S}$ is not only motivated from the fact that we intend to demonstrate the generalizability of the proposed approach but also that we aim at integrating the proposed algorithm into available, demons type registration approaches [8, 9]. In accordance with [8] we therefore rephrase (3) into the problem of computing a stationary solution[3] to $\partial_t\hat{\boldsymbol{v}}^j(\boldsymbol{x},t) - \Delta\hat{\boldsymbol{v}}^j(\boldsymbol{x},t) = \hat{\boldsymbol{b}}^j(\boldsymbol{x}, \hat{w}^j(\boldsymbol{x},t), \hat{\boldsymbol{u}}^j(\boldsymbol{x},t))$ on $\mathbb{R}^d \times \mathbb{R}_0^+$ with initial condition $\hat{\boldsymbol{v}}^j(\boldsymbol{x},0) = 0$ for all $\boldsymbol{x} \in \mathbb{R}^d$. This is equivalent to applying $\mathcal{S}$ from (6) to the velocity field, $\hat{\boldsymbol{v}}^j$, which can be related to the displacement field, $\hat{\boldsymbol{u}}^j$, via the *material derivative*. Herewith, it is possible to exploit the fact that the Green's function of the above given inhomogeneous diffusion equation (over an infinite space) is given by a Gaussian kernel $\mathcal{K}$. Accordingly, it is possible to approximate the stationary solution via successive convolution with $\mathcal{K}$ of standard deviation $\tilde{\sigma}$. This yields an algorithm that is straight forward to implement and is, likewise to multi-grid or Fourier techniques typically used to solve (3), of linear complexity. Thus, the search over a non-parametric space of displacements essentially translates into iteratively alternating between (i) the computation of an unconstrained update $\boldsymbol{b}^j$ and (ii) successive convolution of $\boldsymbol{b}^j$ with a Gaussian kernel $\mathcal{K}$. Due to the fact that we optimise across the entire space of non-parametric mappings, regularity of the deformation pattern is not guaranteed. In accordance with [10, 11] a regridding step is introduced every time the point-wise Jacobian of the mapping (see also below) drops below a user defined threshold, ε_J.

A problem not addressed in [7] is preservation of mass of the density map subject to a mapping $\boldsymbol{y}^j(\boldsymbol{x}) = \boldsymbol{x} - \boldsymbol{u}^j(\boldsymbol{x})$. From integration by substitution it follows that

$$\int_{\boldsymbol{y}^j(\Omega)} w^j(\boldsymbol{x})\,d\boldsymbol{x} = \int_\Omega w^j(\boldsymbol{y}^j(\boldsymbol{x}))|\det(\nabla\boldsymbol{y}^j(\boldsymbol{x}))|\,d\boldsymbol{x}, \tag{7}$$

where the deformed density w^j is weighted by the Jacobian operator $J_y := \det(\nabla\boldsymbol{y}^j(\boldsymbol{x})) = \det(\boldsymbol{E} - \nabla\boldsymbol{u}^j(\boldsymbol{x}))$ (cf. e.g. [15]). Thus, to enable the possibility to guarantee the preservation of mass after applying the mapping $\boldsymbol{y}^j$ we have to modify (7) by inserting the Jacobian operator (cf. [15]). The resulting algorithm is summarised in Alg. 1.

[3] In order to clearly indicate the resulting dependence on time of the considered functions, an accent $\hat{\cdot}$ is introduced into our notation.

3. RESULTS

In this section the numerical experiments are described[4]. The model parameters are $\gamma = 0.012/\mathrm{d}$, $\chi_W = 0.065\,\mathrm{mm}^2/\mathrm{d}$, $\chi_G = 0.1\chi_W$, $w_S = 1.0$, $\sigma = 2.0$, $\alpha = 2.0$, $\varepsilon = 10^{-6}$, $\varepsilon_J = 0.5$ and $\tilde{\sigma} = 1.0$ pixels with a maximum number of iterations of $\hat{m} = 50$. Fig. 1 (left) shows the results for the temporal trend of the computed deformation pattern (top row) and for varying the control parameter, p (bottom row; $t^j = 800$ d). A comparison to patient data (T1w and T2w MR imaging data) is given in Fig. 1 (right). The colour bar illustrates the colour coding of the density profiles as well as estimates for detection thresholds in T1w (orange arrow) and T2w MR images (green arrow). We note, that we did obtain this match to imaging patterns, similar to [16] though not yet accounting for the registration component, via optimisation[5] (i.e. by minimising the mismatch between the predicted state of the model and the observed state in the data) instead of a greedy search [7]. The computed deformation patterns are (point-wise) diffeomorphic, as also suggested by the displayed grids.

4. DISCUSSION AND CONCLUSION

In the present work we have translated a novel model of tumour induced brain deformation from a constrained, parametric optimisation problem [7] to an efficient optimisation on the entire space of non-parametric displacement fields. This not only is an improvement on the efficiency but also on the ease of implementation as compared to [7]. The log-barrier in [7] renders this model numerically delicate due to the fact that the objective rapidly tends towards infinity. This in turn poses the demand for sound numerical schemes. Further, even though the log-barrier on the determinant of the Jacobian matrix is targeted to enforce regularity, the parametric nature of the model does not necessarily guarantee diffeomorphism. To enforce (point-wise) regularity of the deformation pattern a regridding strategy is introduced. Under the assumption of a diffeomorphic mapping it is possible to account for the preservation of mass during deformation. Another option for mass-preservation is to eliminate the Jacobian operator (see (7)) by introducing an advection operator in (1). As demonstrated (see Fig. 1), local control of the deformation pattern is enabled via the parameter p. Further, it is demonstrated that the patterns match observations in clinical data.

The aim of this work is to provide fundamental tools to aid non-diffeomorphic image registration problems in tumour imaging that fill the gap between sophisticated, biophysical

[4] We limit the experimental part to $d = 2$ for ease of interpretation of the results but note that the described model is actually implemented in a d-dimensional setting (C++ implementation templated over d)

[5] Due to space restrictions we omit a description of this preliminary parameter estimation approach in the present manuscript and leave it for future work in connexion with integrating the present model into hybrid image registration approaches.

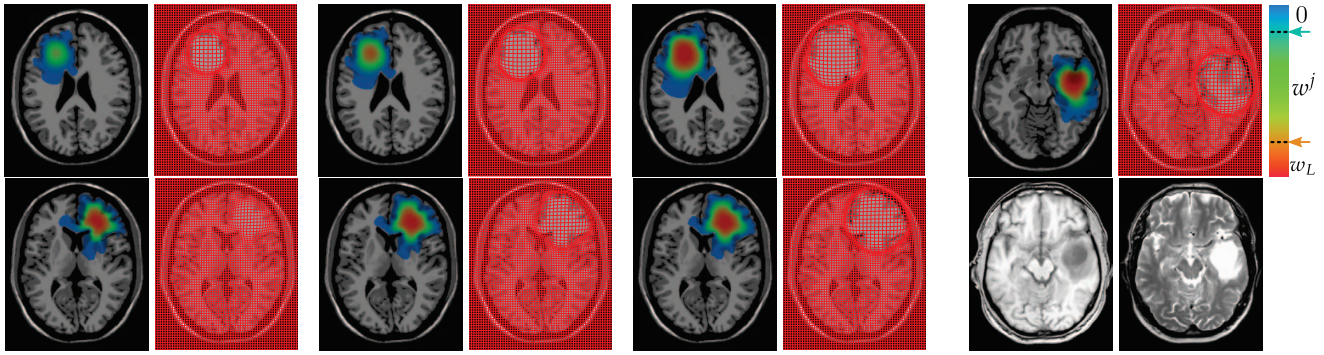


Fig. 1. Computed deformation patterns: Trend of the deformation pattern over time ($t^j \in \{480\,\mathrm{d}, 600\,\mathrm{d}, 800\,\mathrm{d}\}$, top row (left)) and for varying p, where $p \in \{10^{-1}, 10^{-4}, 0.0\}$ (bottom row (left)) and comparison to patient data (right).

models [5, 6] and approaches based on a Riemannian embedding [2] that are completely disconnected from the underlying pathology. The proposed approach further disconnects from biophysical models [5, 6] in comparison to [7] not only for the sake of translating the framework to efficient and popular state-of-the-art strategies for non-rigid image registration [8, 9, 10, 14], but also to demonstrate the generalisability of the overall idea. In particular, this generalisability strongly suggests that the proposed approach is not limited to brain tumour imaging. Further, from (2) and (3) it is apparent that the described framework can account for any type of regularisation. In particular, an extension to (hyper-)elastic [1, 10, 15, 17] regularisers $\mathcal{S}$ seems natural. We conclude that the overall formalism makes this approach particularly suited for an integration into state-of-the-art image registration approaches [8, 9, 10], something we are investigating at the moment in connexion with approaches for image-driven parameter estimation [16]. First preliminary results for a framework that enables the possibility to match the model to data have already been included into the present manuscript. A complete integration into image registration algorithms will allow for quantifying the performance of the discussed model by assessing registration accuracy.

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