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Gene Expression Data to Mouse Atlas Registration Using a Nonlinear Elasticity Smoother and Landmark Points Constraints

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Abstract

This paper proposes a numerical algorithm for image registration using energy minimization and nonlinear elasticity regularization. Application to the registration of gene expression data to a neuroanatomical mouse atlas in two dimensions is shown. We apply a nonlinear elasticity regularization to allow larger and smoother deformations, and further enforce optimality constraints on the landmark points distance for better feature matching. To overcome the difficulty of minimizing the nonlinear elasticity functional due to the nonlinearity in the derivatives of the displacement vector field, we introduce a matrix variable to approximate the Jacobian matrix and solve for the simplified Euler-Lagrange equations. By comparison with image registration using linear regularization, experimental results show that the proposed nonlinear elasticity model also needs fewer numerical corrections such as regridding steps for binary image registration, it renders better ground truth, and produces larger mutual information; most importantly, the landmark points distance and L^2 dissimilarity measure between the gene expression data and corresponding mouse atlas are smaller compared with the registration model with biharmonic regularization.

Keywords

Mouse atlas; Gene expression data; Image registration; Nonlinear elasticity; Landmark-based; Multi-modal; Saint Venant-Kirchhoff material; Calculus of variations

1 Introduction

Medical image registration is important for clinical studies of disease and for atlas-based identification and segmentation of anatomical structures. The registration process is to

deform a template image T to match an unbiased, reference image R through a smooth, invertible transformation. The transformation may further provide information, such as the changes of location and degree of deformation, to help with diagnostics. For images of the same modality, a well-registered template has geometric features and intensity distribution matched with the reference; for images produced by different mechanism and possessing distinct modalities, the goal of registration is to correlate the images while maintaining the modality of the template. In the case of mapping gene expression data to atlas, we want to match anatomically or geometrically significant points for the template with those corresponding ones for the reference.

An extensive overview of registration models is given in two book manuscripts by Modersitzki [7, 8], including parametric model such as landmark-based spline registration, and nonparametric models employing linear diffusion, linear elasticity, biharmonic and fluid regularization.

In general, it is assumed that there are given two images T (template) and R (reference), both defined on the open and bounded domain Ω in the plane (a rectangle in general), and taking real values. There are forward and backward registrations. The former is done in the Lagrangian framework where a forward transformation Φ is sought and grid points $\mathbf{x}$ with intensity values $T(\mathbf{x})$ are moved and arrive at non-grid points $\mathbf{y}$ with intensity values $T(\Phi^{-1}(\mathbf{y})) = T(\mathbf{x})$, $\mathbf{x} = \Phi^{-1}(\mathbf{y})$ or $\mathbf{y} = \Phi(\mathbf{x})$. In the Eulerian framework (considered here) we find a backward transformation $\Phi = \Phi^{-1}$ such that grid points $\mathbf{y}$ in the deformed image arrive from non-grid points $\mathbf{x} = \Phi^{-1}(\mathbf{y})$ and are assigned intensity values $T(\mathbf{x}) = T(\Phi^{-1}(\mathbf{y}))$. For more detailed description of the two frameworks, readers may refer to [7]. It is common to search for a smooth displacement vector field $\mathbf{u} = (u_1, u_2)$, instead of directly searching for the transformation $\Phi(\mathbf{x}) = \mathbf{x} + \mathbf{u}(\mathbf{x})$, $\mathbf{x} = (x_1, x_2)$.

In variational framework, the registration problem can be solved by finding a smooth displacement vector field $\mathbf{u}(\mathbf{x})$, $\mathbf{x} = (x_1, x_2)$ that minimizes an energy functional consisting of data fidelity, landmark constraints, and regularization. The general form of the minimization problem is,

$$\inf_{\mathbf{u}} \left\{ J(\mathbf{u}) = \text{Fid}_{T,R}(\mathbf{u}) + \gamma D^{LM}(\mathbf{u}) + \alpha \text{Reg}(\mathbf{u}) \right\}, \quad (1)$$

where γ and α are weighting parameters. In the gradient descent framework, the time-dependent Euler-Lagrange equations in the displacement vector field $\mathbf{u} = (u_1, u_2)$ are,

$$\frac{\partial u_l}{\partial t} = - \frac{\partial \text{Fid}(\mathbf{u})}{\partial u_l} - \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial u_l} - \alpha \frac{\partial \text{Reg}(\mathbf{u})}{\partial u_l}, \quad l=1, 2.$$

where it is assumed that all terms of energy J are Gâteaux differentiable.

We first review the most standard choices for each of the terms in the general energy functional J from (1). In what follows, h denotes the space discretization step in our numerical schemes. Also, we will use the notation $T_l(\mathbf{x})$ for the transformed template $T(\mathbf{x} +$

$\frac{\partial T_l}{\partial x_l}(\mathbf{x})$, and $\frac{\partial T_l}{\partial x_l}$ for $T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x}))$. This last expression $T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x}))$ is obtained by applying Matlab interpolation function to the discrete partial derivative of T , T_{x_l}

1.1 Data Fidelity in Eulerian Framework

The simplest data matching term, most commonly used for images T and R of the same modality, is the standard L^2 distance as dissimilarity measure between T and R , defined by

$$Fid(\mathbf{u}) = \frac{1}{2} \int_{\Omega} |T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})|^2 d\mathbf{x},$$

using $\mathbf{x} = \mathbf{x} + \mathbf{u}(\mathbf{x})$, $\mathbf{x} = (x_1, x_2)$. Its Gâteaux derivative is given by

$$\frac{\partial Fid(\mathbf{u})}{\partial u_l} = (T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})) T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x})), \quad l=1, 2,$$

where T_{x_l} denotes the gradient of the intensity field of the template in the x_l -direction, $l=1, 2$.

1.2 Landmark Constraints

Let $\mathbf{x}^{R,k}$ be manually-selected landmark points for the reference R , and $\mathbf{x}^{T,k}$ those for the template T . We want to map $\mathbf{x}^{R,k}$ to $\mathbf{x}^{T,k}$ via a smooth deformation such that $\mathbf{x}^{R,k} \sim \mathbf{x}^{T,k}$ by minimizing the following landmark distance function:

$$D^{LM}(\mathbf{u}) = \frac{1}{2} \sum_{k=1}^m \|\mathbf{x}^{T,k} - \Phi(\mathbf{x}^{R,k})\|^2 = \frac{1}{2} \sum_{k=1}^m \|\mathbf{x}^{T,k} - \mathbf{x}^{R,k} - \mathbf{u}(\mathbf{x}^{R,k})\|^2,$$

using $\mathbf{x}^{R,k} = \mathbf{x}^{R,k} + \mathbf{u}(\mathbf{x}^{R,k})$. Here $\|\cdot\|$ denotes the Euclidean norm and m is the number of landmarks. Its Gâteaux derivative is given by:

$$\partial D^{LM}(\mathbf{u})(\mathbf{x}) = \begin{cases} \mathbf{x}^{T,k} - \mathbf{x} - \mathbf{u}(\mathbf{x}) & \text{if } \mathbf{x} = \mathbf{x}^{R,k} \\ 0 & \text{otherwise,} \end{cases}$$

for $k = 1, \dots, m$.

1.3 Regularization

For comparison purposes, we review here the most common and simplest regularization terms that lead to linear terms with respect to derivatives in the Euler-Lagrange equations. Such regularizations can be most used for small deformations. We refer the reader again to the instructive textbooks [7, 8]. These standard regularizations are combined with the above L^2 similarity measure and landmark distance function, to form the energy J from (1) to be minimized. We also give the discretization of the corresponding Euler-Lagrange equations using finite differences.

1.3.1 Image Registration Using Diffusion Regularization—The diffusion H^1 regularization, defined as

$$Reg(\mathbf{u}) = \frac{1}{2} \sum_{l=1}^2 \int_{\Omega} \|\nabla u_l\|^2 d\mathbf{x},$$

is motivated by its smoothing properties and also by its small number of operations required [2, 7]. Combined with the above L^2 similarity measure and landmark distance function, minimizing the energy J from (1) in this case leads to the time-dependent Euler-Lagrange equations:

$$\frac{\partial u_l}{\partial t} = -(T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})) T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x})) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) + \alpha \Delta u_l, \quad l=1, 2.$$

These time-dependent Euler-Lagrange equations can be discretized by the following semi-implicit finite differences scheme:

$$\begin{aligned} \frac{u_{i,j}^{n+1} - u_{i,j}^n}{\Delta t} = & - \left(\frac{\partial T_1}{\partial x_l} \right)_{i,j} (T_{1,i,j} - R_{i,j}) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) \\ & + \alpha \left(\frac{u_{i+1,j}^n - 2u_{i,j}^{n+1} + u_{i-1,j}^n}{h^2} + \frac{u_{i,j+1}^n - 2u_{i,j}^{n+1} + u_{i,j-1}^n}{h^2} \right), \end{aligned}$$

where $l = 1, 2$.

1.3.2 Image Registration Using Biharmonic Regularization—The biharmonic $\dot{H}^2$ regularization is defined as

$$Reg(\mathbf{u}) = \frac{1}{2} \sum_{l=1}^2 \int_{\Omega} (\Delta u_l)^2 d\mathbf{x}.$$

The integrand $(\Delta u_l)^2$ approximates the curvature and thus this regularizer minimizes the curvature of the displacement vectors [3, 7]. According to [7], the biharmonic registration is less dependent on the initial alignment of the two images to be registered and thus it is more suitable when an affine linear pre-registration is not available. Combined with the above L^2 similarity measure and landmark distance function, minimizing the energy J from (1) in this case leads to the time-dependent Euler-Lagrange equations

$$\frac{\partial \mathbf{u}}{\partial t} = -(T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})) T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x})) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) - \alpha \Delta^2 \mathbf{u}, \quad l=1, 2.$$

These time-dependent Euler-Lagrange equations can be discretized by the following semi-implicit finite differences scheme:

$$\begin{aligned} \frac{u_{i,j}^{n+1} - u_{i,j}^n}{\Delta t} = & - \left(\frac{\partial T_1}{\partial x_l} \right)_{i,j} (T_{1,i,j} - R_{i,j}) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) \\ & - \alpha \frac{1}{h^4} \left(16u_{i,j}^{n+1} + u_{i+2,j}^n - 6u_{i+1,j}^n - 6u_{i-1,j}^n + u_{i-2,j}^n \right. \\ & \left. + u_{i,j+2}^n - 6u_{i,j+1}^n - 6u_{i,j-1}^n + u_{i,j-2}^n \right. \\ & \left. + u_{i+1,j+1}^n + u_{i+1,j-1}^n + u_{i-1,j+1}^n + u_{i-1,j-1}^n \right), \quad l=1, 2. \end{aligned}$$

1.3.3 Image Registration Using Linear Elasticity Regularization—It is physically motivated to view the displacement of vector fields as the deformation of some elastic material under force. Viewing the shape change of the image after transformation as the deformation of an elastic material under external force was first adopted in [14] in

developing linear elastic registration method, allowing for small smooth deformations. We recall its formulation here.

Using the strain-displacement relations

$$\epsilon(\mathbf{u}) = \frac{1}{2} (\nabla \mathbf{u}^t + \nabla \mathbf{u}),$$

and the stored energy

$$W(\epsilon) = \frac{\lambda}{2} (\text{trace}(\epsilon))^2 + \mu \text{trace}(\epsilon^2)$$

(where λ and μ are the Lamé coefficients of the material), the strain energy given by

$$Reg(\mathbf{u}) = \int_{\Omega} W(\epsilon) d\mathbf{x}$$

defines the regularization term in the registration problem. Combined with the above L^2 similarity measure and landmark distance function, minimizing the energy J from (1) in this case leads to the time-dependent Euler-Lagrange equations

$$\begin{aligned} \frac{\partial \mathbf{u}}{\partial t} = & - (T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})) T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x})) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) \\ & + 2\alpha [\mu \Delta \mathbf{u} + (\lambda + \mu) \nabla (\text{div} \mathbf{u})], \quad l=1, 2. \end{aligned}$$

These time-dependent Euler-Lagrange equations can be discretized by the following semi-implicit finite differences scheme:

$$\begin{aligned} \frac{u_{p,i,j}^{n+1} - u_{p,i,j}^n}{\Delta t} = & - \left(\frac{\partial T_1}{\partial x_l} \right)_{i,j} (T_{1,i,j} - R_{i,j}) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) \\ & + 2\alpha \left[(\lambda + \mu) A_p + \mu \left(\frac{u_{p,i+1,j}^n - 2u_{p,i,j}^{n+1} + u_{p,i-1,j}^n}{h^2} \right. \right. \\ & \quad \left. \left. + \frac{u_{p,i,j+1}^n - 2u_{p,i,j}^{n+1} + u_{p,i,j-1}^n}{h^2} \right) \right] \\ & + (\lambda + \mu) \left(\frac{u_{q,i+1,j+1}^n - u_{q,i+1,j-1}^n - u_{q,i-1,j+1}^n + u_{q,i-1,j-1}^n}{4h^2} \right), \end{aligned}$$

where $p, q = 1, 2$, $p \neq q$, and

$$A_1 = \frac{u_{2,i+1,j}^n - 2u_{2,i,j}^{n+1} + u_{2,i-1,j}^n}{h^2}, \quad A_2 = \frac{u_{2,i,j+1}^n - 2u_{2,i,j}^{n+1} + u_{2,i,j-1}^n}{h^2}.$$

1.4 Prior Related Work

We refer the reader again to the textbook manuscripts [7, 8].

Variational methods for regularization of the deformation, by linear elasticity or by diffusion tensor, using mutual information and other information-theoretic approaches, are presented in [23] in a theoretical framework.

For models that deal with larger deformations, we refer to [27] for a well-known large deformation fluid registration method (not in variational form), and to a variational registration for large deformations (Large Deformation Diffeomorphic Metric Mapping, LDDMM) [4, 5]. The log-unbiased fluid registration method [21, 22] developed more recently also handles large deformations. Besides fluid models, nonlinear elasticity regularization is implemented using the finite element method in [10] and [25]. Non-linear elasticity principles have also been used with the regularized gradient flow in [24].

As for landmark-based registration methods, we refer to [26], where a consistent landmark and intensity-based registration method is presented using thin-plate spline regularization (or biharmonic regularization). Another related reference is [19] where data fidelity, spline regularization and soft landmark constraints are combined, as in the present work.

Preliminary results of this work have been published in conference proceedings [11, 28].

2 Proposed Image Registration Algorithm Using Nonlinear Elasticity Regularization

For the proposed variational registration model, we have chosen to use the standard L^2 distance as dissimilarity measure between T and R for simplicity of calculation, even if the real application that we consider here deals with template and reference images of different modalities. The L^2 measure is complemented by the use of additional landmarks as geometric constraints and it is the simplest one by comparison to information theoretic matching measures such as the mutual information (appropriate for different modalities). We will see that even if we use such a simple similarity measure, the mutual information between the transformed template and the reference also increases within iterations.

The mapping of landmark points is done simply by minimizing the sum of the squared distances between the points without incorporating a spline model.

Since the linear elastic model works better for small smooth deformations, we propose to use a nonlinear elastic model to allow larger deformations. Among the various nonlinear elastic models, we have chosen the St. Venant-Kirchhoff material for its simplicity [15]. As we mentioned, the finite element method has been used in prior work based on nonlinear elasticity principles. To have a simpler numerical algorithm, we hereby introduce an auxiliary variable for the Jacobian matrix of the displacement in order to remove the nonlinearity in the derivatives. This idea has been inspired by a more theoretical work [20] (see also [17, 18] for a joint segmentation and registration model).

Compared with the experimental results on characteristic images using models with linear diffusion, linear elasticity and biharmonic regularization, the proposed nonlinear elasticity algorithm allows larger and smoother deformations without numerical correction such as regriding [27] in most of our experiments.

We would like to refer the reader to [17, 18], where this regularization method and its implementation have been applied to a joint segmentation and registration model for binary-like images; in that work, a region-based segmentation method is solved via registration with a different data term. The model in [17, 18] can be applied to segmentation of images with topology preservation, or to matching of binary-like images. The present work does not treat the segmentation problem, but focuses on matching more general images, and not only binary-like ones. In our section of numerical results, we discuss a comparison between the two models.

The strain energy corresponding to Saint Venant-Kirchhoff hyperelastic materials [6] is given by

$$Reg(\mathbf{u}) = \int_{\Omega} W(\epsilon) d\mathbf{x},$$

with tensor

$$\epsilon(\mathbf{u}) = \frac{1}{2} (\nabla \mathbf{u}^t + \nabla \mathbf{u} + \nabla \mathbf{u}^t \nabla \mathbf{u})$$

and the stored energy

$$W(\epsilon) = \frac{\lambda}{2} (\text{trace}(\epsilon))^2 + \mu \text{trace}(\epsilon^2),$$

where λ and μ are the Lamé coefficients of the material (to allow larger smooth deformations, we keep the nonlinear term in $(\mathbf{u})$). The regularization can be expressed as

$$Reg(\mathbf{u}) = \int_{\Omega} \left\{ \frac{\lambda}{8} \left[2(\text{div} \mathbf{u}) + \sum_{k=1}^2 |\nabla u_k|^2 \right]^2 + \frac{\mu}{4} \left\{ \sum_{i=1}^2 \left[2 \frac{\partial u_i}{\partial x_i} + \sum_{k=1}^2 \left(\frac{\partial u_k}{\partial x_i} \right)^2 \right] \right. \right. \\ \left. \left. + \sum_{i,j=1, i \neq j}^2 \left[\frac{\partial u_j}{\partial x_i} + \frac{\partial x_i}{\partial x_j} + \sum_{k=1}^2 \frac{\partial u_k}{\partial x_i} \frac{\partial u_k}{\partial x_j} \right]^2 \right\} \right\} d\mathbf{x}.$$

It is cumbersome to directly compute and discretize the associated Euler-Lagrange equation

in $\mathbf{u}$. To avoid this difficulty, we introduce a matrix variable $\mathbf{v} = \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix}$ for $\mathbf{u}$, and we substitute $\nabla \mathbf{u}$ by $\mathbf{v}$ in the above term $Reg(\mathbf{u})$. To deal with the hard constraint $\nabla \mathbf{u} = \mathbf{v}$, we employ the quadratic penalty method [9] and we redefine the regularization for large enough as $Reg(\mathbf{u}, \mathbf{v})$:

$$Reg_{\beta}(\mathbf{u}, \mathbf{v}) = \int_{\Omega} \left[W \left(\frac{1}{2} (\mathbf{v}^t + \mathbf{v} + \mathbf{v}^t \mathbf{v}) \right) + \beta |\mathbf{v} - \nabla \mathbf{u}|^2 \right] d\mathbf{x} \\ = \int_{\Omega} \left\{ \frac{\lambda}{8} [2(v_{11} + v_{22}) + (v_{11}^2 + v_{12}^2 + v_{21}^2 + v_{22}^2)]^2 \right. \\ \left. + \frac{\mu}{4} [(2v_{11} + v_{11}^2 + v_{21}^2)^2 + (2v_{22} + v_{12}^2 + v_{22}^2)^2 \right. \\ \left. + 2(v_{12} + v_{21} + v_{11}v_{12} + v_{21}v_{22})^2] \right\} d\mathbf{x} \\ + \beta \int_{\Omega} \left(\left| v_{11} - \frac{\partial u_1}{\partial x_1} \right|^2 + \left| v_{12} - \frac{\partial u_1}{\partial x_2} \right|^2 + \left| v_{21} - \frac{\partial u_2}{\partial x_1} \right|^2 + \left| v_{22} - \frac{\partial u_2}{\partial x_2} \right|^2 \right) d\mathbf{x}.$$

Thus, the proposed registration method in the presence of landmarks can be expressed as the minimization

$$\inf_{\mathbf{u}, \mathbf{v}} \left\{ J(\mathbf{u}, \mathbf{v}) = \frac{1}{2} \int_{\Omega} |T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})|^2 d\mathbf{x} \right. \\ \left. + \gamma \frac{1}{2} \sum_{k=1}^m \|\mathbf{x}^{T,k} - \mathbf{x}^{R,k} - \mathbf{u}(\mathbf{x}^{R,k})\|^2 + \alpha Reg_{\beta}(\mathbf{u}, \mathbf{v}) \right\}.$$

Now, we solve by gradient descent the Euler-Lagrange equations in u_l , $l = 1, 2$,

$$\frac{\partial u_l}{\partial t} = - (T(\mathbf{x} + \mathbf{u}(\mathbf{x})) - R(\mathbf{x})) T_{x_l}(\mathbf{x} + \mathbf{u}(\mathbf{x})) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) + 2\alpha\beta \left(\Delta u_l - \frac{\partial v_{l1}}{\partial x_1} - \frac{\partial v_{l2}}{\partial x_2} \right), \quad l=1, 2,$$

and then update the approximation matrix $\mathbf{v}$ by solving the four (nonlinear) Euler-Lagrange equations in $\mathbf{v}$:

$$\begin{aligned} \frac{\partial v_{11}}{\partial t} &= \alpha \left\{ 2\beta \left(\frac{\partial u_1}{\partial x_1} - v_{11} \right) - \lambda \mathcal{J} (1+v_{11}) - \mu \left[(2v_{11}+v_{11}^2+v_{21}^2) (1+v_{11}) + \mathcal{J} v_{12} \right] \right\}, \\ \frac{\partial v_{12}}{\partial t} &= \alpha \left\{ 2\beta \left(\frac{\partial u_1}{\partial x_2} - v_{12} \right) - \lambda \mathcal{J} v_{12} - \mu \left[(2v_{22}+v_{12}^2+v_{22}^2) v_{12} + \mathcal{J} (1+v_{11}) \right] \right\}, \\ \frac{\partial v_{21}}{\partial t} &= \alpha \left\{ 2\beta \left(\frac{\partial u_2}{\partial x_1} - v_{21} \right) - \lambda \mathcal{J} v_{21} - \mu \left[(2v_{11}+v_{11}^2+v_{21}^2) v_{21} + \mathcal{J} (1+v_{22}) \right] \right\}, \\ \frac{\partial v_{22}}{\partial t} &= \alpha \left\{ 2\beta \left(\frac{\partial u_2}{\partial x_2} - v_{22} \right) - \lambda \mathcal{J} (1+v_{22}) - \mu \left[(2v_{22}+v_{12}^2+v_{22}^2) (1+v_{22}) + \mathcal{J} v_{21} \right] \right\}, \end{aligned}$$

where $\mathcal{J} = v_{11} + v_{22} + \frac{1}{2}v_{11}^2 + \frac{1}{2}v_{21}^2 + \frac{1}{2}v_{12}^2 + \frac{1}{2}v_{22}^2$ and $\mathcal{J} = v_{12} + v_{21} + v_{11}v_{12} + v_{21}v_{22}$. The following are the semi-implicit finite difference schemes for the time-dependent Euler-Lagrange equations for the regularization term in $\mathbf{u}$ and in $\mathbf{v}$:

$$\begin{aligned} \frac{u_{i,j}^{n+1} - u_{i,j}^n}{\Delta t} &= - \left(\frac{\partial T_1}{\partial x_l} \right)_{i,j} (T_{1,i,j} - R_{i,j}) + \gamma \frac{\partial D^{LM}(\mathbf{u})}{\partial t}(\mathbf{x}) \\ &\quad + 2\alpha\beta \left(\frac{u_{i+1,j}^n - 2u_{i,j}^{n+1} + u_{i-1,j}^n}{h^2} + \frac{u_{i,j+1}^n - 2u_{i,j}^{n+1} + u_{i,j-1}^n}{h^2} \right. \\ &\quad \left. - \frac{v_{l1,i+1,j}^n - v_{l1,i-1,j}^n + v_{l2,i,j+1}^n - v_{l2,i,j-1}^n}{2h} \right), \end{aligned}$$

and

$$\begin{aligned} \frac{v_{11}^{n+1} - v_{11}^n}{\Delta t} &= \alpha \left[2\beta \left(\frac{2u_1^n}{\partial x_1} - v_{11}^{n+1} \right) - \lambda E_1 E_5 - \mu (E_2 E_5 + E_3 v_{12}) \right], \\ \frac{v_{12}^{n+1} - v_{12}^n}{\Delta t} &= \alpha \left[2\beta \left(\frac{2u_1^n}{\partial x_2} - v_{12}^{n+1} \right) - \lambda E_1 v_{12} - \mu (E_4 v_{12} + E_3 E_5) \right], \\ \frac{v_{21}^{n+1} - v_{21}^n}{\Delta t} &= \alpha \left[2\beta \left(\frac{\partial u_2^n}{\partial x_1} - v_{21}^{n+1} \right) - \lambda E_1 v_{21} - \mu (E_2 v_{21} + E_3 E_6) \right], \\ \frac{v_{22}^{n+1} - v_{22}^n}{\Delta t} &= \alpha \left[2\beta \left(\frac{\partial u_2^n}{\partial x_2} - v_{22}^{n+1} \right) - \lambda E_1 E_6 - \mu (E_4 E_6 + E_3 v_{21}) \right], \end{aligned}$$

where

$$\begin{aligned} E_1 &= v_{11} + \frac{1}{2}v_{11}^2 + \frac{1}{2}v_{21}^2 + v_{22} + \frac{1}{2}v_{12}^2 + \frac{1}{2}v_{22}^2, \\ E_2 &= 2v_{11} + v_{11}^2 + v_{21}^2, & E_3 &= 2v_{22} + v_{12}^2 + v_{22}^2, \\ E_4 &= v_{12} + v_{21} + v_{11}v_{12} + v_{21}v_{22}, & E_5 &= 1 + v_{11}, & E_6 &= 1 + v_{22}. \end{aligned}$$

3 Experimental Results

We present here numerical results for image registration using the proposed nonlinear elasticity algorithm, and comparisons with the diffusion, biharmonic and linear elasticity models on synthetic and real data. As a real application, we consider the problem of mapping gene expression data to the mouse atlas, motivated by research in neuroscience.

3.1 Numerical Correction: Regridding

An admissible deformation field $\Phi: \bar{\Omega} \rightarrow \bar{\Omega}$, $\Phi(\mathbf{x}) = \mathbf{x} + \mathbf{u}(\mathbf{x})$, should satisfy $\det(\nabla \Phi) > 0$ in $\bar{\Omega}$, $\Phi(\mathbf{x}) = \mathbf{x}$ on $\partial\bar{\Omega}$, and Φ is one-to-one and onto on $\bar{\Omega}$. To enforce such a constraint, some numerical corrections such as regridding are introduced [27]. In the present work, if $\det(\nabla \Phi)^{n+1} < 0.025$ ($= tol$), we set the displacement field $\mathbf{u}^{n+1} = \mathbf{0}$, the template $T(\mathbf{x}) = T(\mathbf{x} + \mathbf{u}^n)$, and the landmarks, if any, $\mathbf{x}^{R,k} = \mathbf{x}^{T,k} - \mathbf{u}^n(\mathbf{x}^{R,k})$. After the iteration is done, we calculate the composite displacement field by interpolating each of the intermediate displacement fields, which are saved during the regridding process.

The main algorithm is as follows:

1. formulate identity matrices S_1 and S_2 so that $S_1(x, y) = x$, $S_2(x, y) = y$, $x, y \in \mathbb{R}$;
initialize $\mathbf{u}^0 = (u_1^0, u_2^0)$;
2. iteration starts: compute $\mathbf{u}^{n+1}$, $n = 0, 1, 2, \dots$; update displacement matrices S_{11} and S_{22} so that $S_{11}^{n+1} = S_1 + u_1^{n+1}$, $S_{22}^{n+1} = S_2 + u_2^{n+1}$;
3. if $\det(\text{Jacobian}(\Phi)) < tol$,
then $regrid.count = regrid.count + 1$;
if $regrid.count < regrid.number.limit$,
then $T = T_1$;
save $\mathbf{u}^n$ as data files $u_k(regrid.count)$, $k = 1, 2$; $\mathbf{u}^{n+1} = \mathbf{0}$;
else iteration ends;
4. if landmark points distance converges, iteration ends; go to (5); otherwise, go to (2);
5. if $regrid.count > 0$
then $composite.S_{kk} = S_k^{final.iteration}$,
 $composite.u_k = u_k^{final.iteration}$, $k = 1, 2$, $k = 1, 2$;
for $i = regrid.count : -1 : 1$
read and load data files $u_k(regrid.count)$;
 $UO_k = u_k(regrid.count)$, $k = 1, 2$;
 $composite.u_k(regrid.count) = composite.u_k(regrid.count) + interpolation(UO_k, composite.S_{22}, composite.S_{11})$;
 $composite.S_{kk}(regrid.count) = S_k + composite.u_k(regrid.count)$;
end
 $u_k = composite.u_k(1)$;
 $S_{kk} = composite.S_{kk}$.

One of the many criteria in evaluating non-rigid registration models could be the number of regridding steps (fewer regridding steps may be preferable). The following results are done mostly without regridding.

3.2 Synthetic Images

We compare the four models presented on synthetic data, without using the landmark distance.

3.2.1 Disk to Letter C—We first compare the linear elasticity, linear diffusion, biharmonic, and nonlinear elasticity models for registration from disk to letter C (Fig. 1), which is the “academic” example used in [7]. No special treatment of corners has to be made.

From the registration results shown in Fig. 2, we can see that linear elasticity regularization is only suitable for small deformations. The linear diffusion regularization works better but introduces a lot of artifacts. The biharmonic model produces a more satisfactory result (even though a darker background is observed) together with the nonlinear elasticity model. In terms of the regridding numbers, the biharmonic model and the nonlinear elasticity model require three regridding steps while the linear diffusion model requires four.

3.2.2 Other Binary Images—We further compare the four models for the registration of other binary images (Fig. 3) artificially obtained from the real data used later. We found from the registration results (Fig. 4) that the nonlinear elasticity model does not introduce artifacts (e.g. under the right ear where we expect the largest deformation) like other models do. In terms of regridding numbers, the nonlinear elasticity model is the only one which does not require any regridding step, and the biharmonic model requires fewer regridding steps than the other two linear models.

Since the biharmonic model is more comparable to the nonlinear elasticity model, we want to further examine the two models on real data. The nonlinear elastic model requires longer computational time than the biharmonic model (13–16 minutes versus 5–7 minutes per 4000 iterations using Intel(R) Core(TM)2 Duo CPU t7500 @2.20 GHz processor with code in Matlab).

3.3 Real Data

3.3.1 Ground Truth Test—In this experiment (without landmark distance), we start with two images T and R , such that T has been obtained from R via a known artificial deformation. We have a magneto-resonance image R (Fig. 5 left) and its artificially deformed version T (Fig. 5 right) using a known distortion map from R to T shown in Fig. 6 left (data test kindly provided by H. Tagare [16]). We want to see if the distortion maps rendered by the nonlinear elasticity and biharmonic models are similar to the true map. The true distortion map plots the vector fields from R to T , and the error between the true map and the maps after registration by the two models is measured by the Euclidean norm. The difference from the ground truth is smaller for the nonlinear elasticity model (Fig. 6 right) than for the biharmonic model (Fig. 6 middle) after the same number of iterations. Therefore, the nonlinear elasticity model results in closer match to the true map than by the biharmonic model. Thus, we expect that the nonlinear elasticity model will produce better results for our gene expression data to atlas registration.

3.3.2 Mapping Gene Expression Data to Mouse Atlas—The C57BL/6J mouse digital brain atlas [12, 13] is a comprehensive framework for storing and accessing information, and serves as a canonical representation of the mouse brain. We use the mouse brain atlas as a common and unbiased framework and map gene expression data to the atlas in order to facilitate the integration of anatomic, genetic, and physiologic observations from multiple subjects in a common space. Since genetic mutations and knockout strains of mice provide critical models for a variety of human diseases, such linkage between genetic

information and anatomical structure would allow neuroscientists to further advance their research.

We now show some experimental results obtained by the two methods presented in the previous sections (the biharmonic and nonlinear elasticity models) for mapping one 2D slice of mouse brain gene expression data (template T) to its corresponding 2D slice of the mouse brain atlas (reference R), in the presence of landmarks. The data is provided by the Center for Computational Biology, UCLA [1]. The mouse atlas acquired from the LONI database was pre-segmented. The gene expression data was segmented manually to facilitate data processing in other applications. Some studies have developed algorithms for automatically segmenting the brain area of gene expression data. Moreover, since the intensity range and intensity values of the gene expression data are so small that the images almost resemble to characteristic images, we also match the histogram of the gene expression data to that of the atlas in order to facilitate better registration for area away from the edges. The two models have been independently tested on 8 pairs, all of size 200×200 pixels. The non-brain regions have been removed, to produce better matching. The number of iterations for both methods depends on how small we wish the landmark distance and the similarity measure to be. The landmarks are marked by an experienced neuroanatomist based on the anatomical structures present in the images. This is based on prior knowledge in neuroanatomy.

Energy: Figure 7 shows the numerical energies J decreasing with time for both models applied to the image pair labeled number 5. Any other pair of images could have been considered.

Landmark Convergence: Figure 8 shows the landmark distance with iterations with and without the enforcement of landmark constraints. We see that the convergence is much faster with the enforcement of the constraints.

Visualization of Registration Results: Now we show the registration results of the eight pairs of images studied in this work. The number of iterations is the same for both models; the time step $dt = 1$ and the space discretization $h = 1$ for both models. For the biharmonic model, we vary the regularization weighting parameter and the landmark constraint coefficient; for the nonlinear elasticity model, we vary the coefficient of the approximation matrix $\mathbf{v}$ and while fixing $\alpha = 1$, $\beta = 1$, and $\mu = 1e-2$. The choice of and does not vary too much among the tested pairs of images; $5e+4$ and $75e+3$ will give satisfactory results. The choice of more or less depends on the total landmark distance before registration; the larger the landmark distance is, the smaller should be. Note that an almost constant (or slightly increasing) ratio, α/β or β/α , for each image pair can be found; increasing in accordance with or by the ratio may result in smoother transformation, faster landmark convergence, but slower similarity convergence.

For each pair of images we show three sets of figures: one contains the mouse atlas as the reference, the original mouse gene expression data, and the gene expression data after histogram equalization as the template with landmark points marked (Figs. 9, 12, 15, 18, 21, 24, 25, 27 and 30); the second one contains the deformed template, distortion map with landmark points marked, and inverse of the determinant of Jacobian of with deformed grid using the biharmonic registration model (Figs. 10, 13, 16, 19, 22, 25, 28, 31); the third one contains the deformed template, distortion map with landmark points marked, and inverse of the determinant of Jacobian of with deformed grid using the nonlinear elasticity registration model (Figs. 11, 14, 17, 20, 23, 26, 29, 32).

Tables 1 and 2 list the landmark points' averaged distances after registration (LD, Sect. 1.2), L^2 dissimilarity measures (DM, Sect. 1.1), and ranges of determinant of Jacobian matrix $\mathbf{v}$

(RJ) for the biharmonic model (BH) and the nonlinear elasticity model (NE), respectively. We can see that the nonlinear elasticity model renders better landmark matching and larger deformation. The range of determinant of Jacobian is also larger corresponding to larger deformation. Since the lower bound of the range of determinant of Jacobian remains positive and no regridding step is triggered, the transformation is well defined and desirable.

The distortion maps draw the vectors from the grid points of the reference image to the non-grid points after registration; the original reference/template landmarks are marked in red/green, the reference landmarks after registration are marked in blue. We can see that the landmarks converge (moving from red spots to blue spots to approach the green spots) in accordance with the distortion field. As for the deformed grids, where the grid area expands/shrinks, we observe lighter/darker gray levels corresponding to larger/smaller value of the inverse of determinant of Jacobian which indicates areal expansion/shrinkage.

We refer the reader again to [18] for comparison of numerical results that appear in Figs. 9, 10, 11, 21, 22, 23, and 24, 25, 26, 27, 28, 29. As we can see in [18], Figs. 5–9 (results obtained in two steps), the deformation is mainly present near the boundary of the brain region, while in the present work, the deformation is present both near the boundary and inside the brain region.

Mutual Information: Furthermore, we want to evaluate the registration results in a different way. We compute another cost functional measuring image alignment, called the mutual information between two random variables, and defined as follows:

$$MI_{\mathbf{X}, \mathbf{Y}} = \int_{\mathbf{Y}} \int_{\mathbf{X}} p(\mathbf{x}, \mathbf{y}) \log \frac{p(\mathbf{x}, \mathbf{y})}{p(\mathbf{x}) p(\mathbf{y})} d\mathbf{x} d\mathbf{y},$$

where $\mathbf{X}$ and $\mathbf{Y}$ are random variables; $p(\mathbf{x}, \mathbf{y})$ is the joint probability density function of $\mathbf{X}$ and $\mathbf{Y}$; $p(\mathbf{x})$ and $p(\mathbf{y})$ are the marginal probability density functions of $\mathbf{X}$ and $\mathbf{Y}$ respectively.

Mutual information quantifies the dependence between $\mathbf{X}$ and $\mathbf{Y}$, which in our case are the intensity maps of R and T . Considering that larger mutual information indicates better registration, we see in Figs. 33 and 34 that the nonlinear elasticity model, indicating by black line, is more desirable in this respect.

4 Conclusion and Future Work

We presented variational registration models for obtaining smooth deformations between two dimensional slices of mouse atlas and gene expression data. We proposed a nonlinear elastic regularization with an implementation that removes the nonlinearity in the derivatives and compared it with the biharmonic model. Experimental results showed that the biharmonic model and the nonlinear elasticity model both render large deformation with no regridding step. Moreover, the nonlinear elasticity model renders higher mutual information and better landmark points matching. A better parameter selection and extension to three dimensions will be made.

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Fig. 1.
Reference (*left*) and template (*right*)

Fig. 2.

Transformed images by (from left to right) linear elasticity, linear diffusion, biharmonic, and nonlinear elasticity regularizations. The dissimilarity values between the transformed template $T1$ and the reference image R are: 2201.8619 (linear elasticity), 196.7257 (linear diffusion), 43.1154 (biharmonic regularization), and 29.0903 (nonlinear elasticity)

Fig. 3.
Reference (*left*), template (*right*)

Fig. 4.
From left to right: transformed images by linear elasticity, linear diffusion, biharmonic, and nonlinear elasticity regularizations

Fig. 5.
Reference (*left*) and template (*right*)

Fig. 6.

From left to right: true distortion map; distortion map by biharmonic model (error = 0.12692); distortion map by the nonlinear elasticity model (error = 0.12413)

Fig. 7. Energy decreasing with time using the biharmonic model (*left*) and the nonlinear elasticity model (*right*)

Fig. 8. Discrete landmarks distance with iterations using the biharmonic model (*left*) and the nonlinear elasticity model (*right*); without/with enforcement of landmark constraints

Fig. 9.
Image pair 1: mouse atlas as the reference R (*left*), mouse gene expression data T (*middle*),
gene expression after histogram equalization with specified landmarks as the template
(*right*)

Fig. 10.

Image pair 1: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 11.

Image pair 1: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 12.

Image pair 2: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 13.

Image pair 2: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 14. Image pair 2: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 15.

Image pair 3: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 16.

Image pair 3: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 17.

Image pair 3: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 18.
Image pair 4: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 19.

Image pair 4: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 20.

Image pair 4: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 21.

Image pair 5: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 22.

Image pair 5: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 23.

Image pair 5: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 24.

Image pair 6: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 25.

Image pair 6: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 26.

Image pair 6: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 27.

Image pair 7: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 28.

Image pair 7: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 29.

Image pair 7: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 30.

Image pair 8: mouse atlas as reference R (*left*), mouse gene expression data as template T (*middle*), gene expression after histogram equalization with specified landmarks (*right*)

Fig. 31.

Image pair 8: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using biharmonic regularization

Fig. 32.

Image pair 8: deformed template (*left*), deformation field plus the landmarks transformation (*middle*), $1/\det(\nabla\Phi)$ plus the deformed grid (*right*) using nonlinear elasticity regularization

Fig. 33.

(Color online) Mutual information increasing with time using biharmonic regularization (*red line*), and nonlinear elasticity regularization (*black line*) for image pairs 1 to 4

Fig. 34.

(Color online) Mutual information increasing with time using biharmonic regularization (*red line*), and nonlinear elasticity regularization (*black line*) for image pairs 5 to 8

Table 1

Biharmonic regularization

	LD	DM	RJ
Pair 1	0.49519	1,942	(0.34, 3.38)
Pair 2	0.42388	1,806	(0.15, 2.11)
Pair 3	0.26758	1,168	(0.28, 1.99)
Pair 4	0.90027	4,130	(0.25, 2.05)
Pair 5	0.70846	3,723	(0.04, 1.87)
Pair 6	0.11232	1,255	(0.23, 2.30)
Pair 7	0.46912	1,266	(0.31, 2.30)
Pair 8	0.71972	3,073	(0.37, 2.12)

Table 2

Nonlinear elastic regularization

	LD	DM	RJ
Pair 1	0.49282	1,938	(0.32, 3.55)
Pair 2	0.41299	1,790	(0.01, 3.16)
Pair 3	0.26593	1,151	(0.10, 2.15)
Pair 4	0.74304	4,101	(0.08, 2.57)
Pair 5	0.60741	3,693	(0.10, 2.82)
Pair 6	0.10712	1,177	(0.15, 2.40)
Pair 7	0.34660	1,173	(0.18, 3.23)
Pair 8	0.55106	3,058	(0.03, 2.35)