Extending the Quadratic Taxonomy of Regularizers for Nonparametric Registration

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ABSTRACT

Quadratic regularizers are used in nonparametric registration to ensure that the registration problem is well posed and to yield solutions that exhibit certain types of smoothness. Examples of popular quadratic regularizers include the diffusion, elastic, fluid, and curvature regularizers.\textsuperscript{1} Two important features of these regularizers are whether they account for coupling of the spatial components of the deformation (elastic/fluid do; diffusion/curvature do not) and whether they are robust to initial affine misregistrations (curvature is; diffusion/elastic/fluid are not). In this article, we show how to extend this list of quadratic regularizers to include a second-order regularizer that exhibits the best of both features: it accounts for coupling of the spatial components of the deformation and contains affine transformations in its kernel. We then show how this extended taxonomy of quadratic regularizers is related to other families of regularizers, including Cachier and Ayache’s differential quadratic forms\textsuperscript{2} and Arigovindan’s family of rotationally invariant regularizers.\textsuperscript{3,4} Next, we describe two computationally efficient paradigms for performing nonparametric registration with the proposed regularizer, based on Fourier methods\textsuperscript{5} and on successive Gaussian convolution.\textsuperscript{6,7} Finally, we illustrate the performance of the quadratic regularizers on the task of registering serial 3-D CT exams of patients with lung nodules.

Keywords: Image registration, regularization

1. INTRODUCTION

In the mathematical sense, nonrigid image registration algorithms are procedures for optimizing a functional over a specified class of deformable transformations. The functional typically contains two terms: an image similarity term, which is used to gauge the degree of similarity between the two images, and a regularizer, which is used to guarantee a unique solution to the optimization problem. The class of transformations can be parameterized in terms of basis functions (such as B-splines\textsuperscript{8,9} or thin-plate splines\textsuperscript{10}), or it can be nonparametric,\textsuperscript{1,11,12} containing any deformation field that satisfies prescribed boundary conditions.

In nonparametric (or variational) registration, the set of vector-valued functions \( \{ \Phi : \mathbb{R}^n \rightarrow \mathbb{R}^n \} \) forms the allowable space of transformations. A regularization term must be incorporated to guarantee that the resulting functional minimization problem is well-posed and has a smooth solution. In medical image registration, the regularization term is typically based on penalizing some differential quadratic form\textsuperscript{2} (DQF) of the displacement or velocity fields of the deformation. Penalties can be applied in a homogeneous manner, as in the quadratic taxonomy of elastic, diffusion, and curvature regularizers,\textsuperscript{1} or in a nonhomogeneous manner, as in the taxonomy of diffusion-based regularizers used in optical flow\textsuperscript{13} or the multiple-material regularizers used in elastic registration.\textsuperscript{14} The Euler-Lagrange equations resulting from functional minimization with the homogeneous quadratic regularizers have partial differential operators that are identical to those developed in the field of computational anatomy\textsuperscript{15,16} to induce priors for Bayesian estimation of large deformations.

This article focuses on the quadratic taxonomy of regularizers and presents a new regularizer, the second-order elastic regularizer, to extend the quadratic taxonomy. The second-order elastic regularizer combines the benefits of the elastic, diffusion, and curvature regularizers, of accounting for coupling of the spatial components

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of the deformation field and of containing affine transformations in its kernel. The new regularizer is shown to fit directly into other families of regularizers that have been developed in other contexts; namely, Cachier and Ayache’s vector field filters and Arigovindan’s rotationally invariant regularizers for image reconstruction. Computationally efficient algorithms for nonparametric registration based on Fourier methods and successive Gaussian convolution are extended for use with the second-order elastic regularizer, and these algorithms are used to compare and contrast the behavior of various quadratic regularizers on the task of nonrigid registration of serial CT examinations of patients with lung nodules.

The remainder of this article is organized in the following manner: Section 2 provides some preliminaries on nonparametric registration and describes some of the quadratic regularizers commonly in use. Section 3 presents the second-order elastic regularizer, illustrates some of its properties, and shows how it fits in with other families of regularizers. Section 4 describes how computationally efficient algorithms can be designed for second-order elastic registration. Finally, Section 5 illustrates the behavior of the various regularizers on the task of nonrigid registration of serial CT examinations of patients with lung nodules.

2. PRELIMINARIES

Consider two images, a reference image $R$ and a floating image $F$, both as functions on $\Omega \subseteq \mathbb{R}^n$. Define a deformation $\Phi : \Omega \mapsto \Omega$ by $\Phi(x) = x - u(x)$, and call $u$ the displacement. The general form of the registration problem is given by:

$$\min_u \mathcal{E}(R, F, u) := S(u) + \alpha \mathcal{J}(R, F, u),$$

where $\mathcal{J}$ is an image similarity measure, such as sum of squared differences, cross correlation, mutual information, etc., $S$ is a regularizer, and $\alpha$ is a positive regularizing parameter.

A number of quadratic regularizers have been used for image registration. Using the terminology of Mehrizi et al., the diffusion, elastic, and curvature regularizers are shown in Table 1. These regularizers have been used in both parametric (B-spline and thin-plate spline) and nonparametric approaches to registration. In the parametric approaches, Eq. 1 is typically minimized directly using standard optimization techniques. In nonparametric approaches, Eq. 1 can be minimized directly, or the minimization problem can be transformed into the process of finding a solution of the Euler-Lagrange equations:

$$\mathcal{A}(u) = \alpha f(x, R, F, u),$$

with suitable conditions on the boundary $\partial\Omega$. The partial differential operator $\mathcal{A}$ and force vector $f$ arise from the Gâteaux derivatives of the regularizer and dissimilarity measure, respectively. The partial differential operator corresponding to each standard quadratic regularizer is shown in Table 1.

<table>
<thead>
<tr>
<th>Regularizer $S(u)$</th>
<th>Partial Differential Operator $\mathcal{A}(u)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion</td>
<td>$\frac{1}{2} \sum_{j=1}^{n} \int_{\Omega} \langle \nabla u_j, \nabla u_j \rangle dx$</td>
</tr>
<tr>
<td>Elastic</td>
<td>$\frac{1}{2} \int_{\Omega} \left( \frac{\mu}{2} \sum_{j,k=1}^{n} (\partial_{x_j} u_k + \partial_{x_k} u_j)^2 + \lambda (\text{div } u)^2 \right) dx$</td>
</tr>
<tr>
<td>Curvature</td>
<td>$\frac{1}{2} \sum_{j=1}^{n} \int_{\Omega} (\Delta u_j)^2 dx$</td>
</tr>
</tbody>
</table>

Table 1. Standard regularizers with corresponding partial differential operators

2.1 Steepest Descent

At first glance, one can approximate the solution to the Euler-Lagrange equations by performing a fixed-point iteration. This can be problematic, as the partial differential operators may have nontrivial kernels. To overcome this problem, we introduce an artificial time variable $t$ and embed Eq. 2 in the parabolic PDE system:

$$\partial_t u(x, t) + \mathcal{A}(u(x, t)) = \alpha f(x, t, u(x, t)), \quad x \in \Omega, \ t > 0,$$

$$u(x, 0) = u(0),$$

$$u(x, t) = u(0).$$

(3)
and the same boundary conditions as chosen in Eq. 2. This parabolic system also arises from applying the steepest descent algorithm to solve the Euler-Lagrange Equations. The stationary solution of Eq. 3 is given by:

\[ u^*(x) = \lim_{t \to \infty} u(x, t), \tag{4} \]

and it satisfies \( \partial_t u^*(x) = 0 \), making it a solution to Eq. 2.

### 2.2 Large Deformations

Early work in computational anatomy\(^{15,16}\) tackled the large deformation registration problem in a Bayesian estimation framework by inducing priors via partial differential equations. The same partial differential operators in our Table 1 emerged in this work, although they were applied to the velocity field \( v(x, t) \) of the deformation, which is related to the displacement field by the material derivative:

\[ v(x, t) = \partial_t u(x, t) + (\nabla u(x, t))^T v(x, t). \tag{5} \]

If the parabolic system in Eq. 3 is applied to the velocity field; i.e.,

\[ \partial_t v(x, t) + A(v(x, t)) = \alpha f(x, t, u(x, t)), \quad x \in \Omega, \ t > 0, \]

and the elastic operator is chosen for \( A \), then the coupled system in Eq.’s 5–6 is essentially the well known fluid registration problem formulated by Christensen.\(^{15,17}\) Since large deformation registration can be achieved by applying any of the quadratic regularizers to the velocity field, we do not include the fluid regularizer in the same class of quadratic regularizers as the elastic, diffusion, and curvature regularizers. (This is a departure from Modersitzki.\(^1\))

### 2.3 Comparing Quadratic Regularizers

Each regularizer has advantages and disadvantages for nonparametric registration. The diffusion regularizer enables a fast solution via Additive Operator Splitting (AOS),\(^{1,13}\) although it does not couple the spatial directions of the deformation field, which would be physically appropriate. Furthermore, diffusion-based registration is not immune to any initial affine misregistration of the images. The curvature regularizer, on the other hand, contains affine transformations in its kernel, making curvature-based registration more robust to initial affine misregistrations. However, the curvature regularizer still does not couple the spatial directions of the deformation field. The elastic regularizer models linear elasticity, and hence appropriately handle coupling of the spatial directions. However, it suffers the disadvantage of the diffusion regularizer in not being immune to any initial affine misregistration.

### 3. THE SECOND-ORDER ELASTIC REGULARIZER

Fortunately, a regularizer can be constructed that combines the advantages of the standard regularizers. One such regularizer is presented by Amodei \textit{et al.}\(^{18}\) in the context of vector splines, and later appears for use in image reconstruction problems\(^3,4\) and B-Spline based image registration:\(^9\)

\[ R_{Amodei}(u) = \int_{\Omega} \left( \alpha_1 \| \nabla \text{div} u \|^2 + \alpha_2 \| \nabla \text{rot} u \|^2 \right) \, dx, \tag{7} \]

where \( \text{rot} u \) refers to the rotational component of a vector field, which is defined by:

\[ \text{rot} u = \begin{cases} -\partial_{x_2} u_1 + \partial_{x_1} u_2, & n = 2 \\ \text{curl} u, & n = 3 \end{cases}, \tag{8} \]

where \( n \) is the number of dimensions.
We define the second-order elastic regularizer, which is a second-order differential quadratic form, by:

$$R_{\text{elastic-2}}(u) = \frac{1}{2} \int_{\Omega} \left( \frac{\mu}{3} \sum_{j,k,l=1}^{n} \left( \partial_{x_j x_k}^2 u_l + \partial_{x_j x_l}^2 u_k + \partial_{x_l x_j}^2 u_l \right) + \lambda \| \nabla \text{div} u \|^2 \right) d\mathbf{x}. \quad (9)$$

This regularizer is slightly different than $R_{\text{Amodei}}$; however, the second-order elastic and Amodei regularizers have the same Gâteaux derivative up to boundary conditions. (This can be established by referring to the results of Cachier and Ayache on second-order differential quadratic forms.) The reason, therefore, that we choose the second-order elastic regularizer over the Amodei regularizer to extend the quadratic taxonomy is that Eq. 9 reveals a direct generalization of the elastic regularizer in terms of the Lamé parameters $\mu$ and $\lambda$.

The second-order elastic regularizer has a corresponding differential operator that is simply the composition of the elastic and diffusion partial differential operators:

$$A(u) = \mu \Delta^2 u + (\lambda + 2\mu)\Delta \nabla \text{div} u. \quad (10)$$

As can be verified mathematically, any affine transformation is in the kernel of $A_{\text{elastic-2}}$. (That is, $u = C\mathbf{x} + \mathbf{b} \Rightarrow \Delta u = 0 \Rightarrow A_{\text{elastic-2}}(u) = 0$). Therefore, the second-order elastic regularizer has the same advantage as the curvature regularizer. Furthermore, the inclusion of the $\Delta \nabla \text{div}$ term enforces spatial coupling of the components of the deformation, giving the second-order elastic regularizer the same advantage as the elastic and fluid regularizers.

### 3.1 Visual Analysis

To place the second-order elastic regularizer in the context of the other quadratic regularizers we consider the behavior of each regularizer on two separate examples. In the first example, shown in Fig. 1(a), the force vector field is an impulse function in the $x$ direction and zero in the $y$ direction. In the second example, shown in Fig. 1(c), the force vector field arises from the mean squared differences similarity measure applied to axial slices from two CT volumes of the same patient. (The CT slices are shown later in Fig. 2.) In Figs. 1(b) and 1(d), we see the magnitudes and angles of the solutions at an iteration of the fixed-point algorithm for solving the Euler-Lagrange equations with various regularizers. For every case, $\alpha$ has been chosen so that the maximum magnitude of the solution is scaled to be one.

Figure 1(b) shows the magnitudes and angles of the solutions of the Euler-Lagrange equations with each homogeneous regularizer for the impulse vector field in Fig. 1(a). It is clear that the diffusion and elastic regularizers propagate the information from the impulse to a much lesser extent than the curvature and second-order elastic regularizers. It is also clear that the diffusion and curvature regularizers yield solutions with no coupling in the spatial components, whereas the elastic and second-order elastic regularizers do exhibit spatial coupling. Figure 1(d) illustrates the magnitudes and angles of the solutions of the Euler-Lagrange equations for the CT slice example. It is apparent that the regularizers propagate information from the force vector field in different ways. The diffusion and elastic regularizers propagate information to a lesser extent than the curvature and second-order elastic regularizers.

### 3.2 Families of Quadratic Regularizers

The diffusion, elastic, curvature, and second-order elastic regularizers are not the only homogeneous regularizers that can be used for nonparametric registration. However, we can establish an interesting link between these regularizers and the space of all rotationally invariant regularizers of second order or less. Arigovindan developed a family of regularizers given by the linear combination of four terms:

$$S_{\gamma_1,\gamma_2,\gamma_3,\gamma_4}(u) = \gamma_1 S_1(u) + \gamma_2 S_2(u) + \gamma_3 S_3(u) + \gamma_4 S_4(u), \quad (11)$$
Figure 1. Examples of responses to impulse and CT force vector fields for quadratic regularizers.
where

\[ S_1(u) = \frac{1}{2} \int_{\Omega} (\text{div } u)^2 \, dx, \quad (12) \]

\[ S_2(u) = \frac{1}{2} \int_{\Omega} \| \text{rot } u \|^2 \, dx, \quad (13) \]

\[ S_3(u) = \frac{1}{2} \int_{\Omega} \| \nabla \text{div } u \|^2 \, dx, \quad \text{and} \]

\[ S_4(u) = \frac{1}{2} \int_{\Omega} \| \nabla \text{rot } u \|^2 \, dx. \quad (15) \]

Note that if \( \gamma_1 = \gamma_2 = 0 \), the Arigovindan regularizer reduces to the Amodei regularizer in Eq. 7. As explained by Arigovindan,\(^4\), \( S_1 \) quantifies the compression rate of the displacement field, \( S_2 \) quantifies the squared angular velocity, \( S_3 \) quantifies the spatial roughness of the compression rate, and \( S_4 \) quantifies the variation in angular velocity. Arigovindan proved that \( S_{1;2;3;4} \) generates all possible rotationally invariant regularizers of second order or less.

By referring to the results of Cachier and Ayache\(^2\) on first and second order differential quadratic forms, we can see that the space spanned by the Gâteaux derivatives of the diffusion, elastic, curvature, and second-order elastic regularizers is equivalent, up to boundary conditions, of the space spanned by the Gâteaux derivative of the Arigovindan regularizer. This link to the Arigovindan regularizer family suggests that if boundary conditions are ignored, the Gâteaux derivative of any rotationally invariant regularizer up to second order is in the span of the Gâteaux derivatives of the diffusion, elastic, curvature, and second-order elastic regularizers.

4. COMPUTATIONALLY EFFICIENT REGISTRATION ALGORITHMS

This section shows how two different algorithms can be constructed for solving the second-order elastic registration problem. The first algorithm uses Fourier methods\(^5\) to solve a succession of linear systems, and the second uses successive Gaussian filtering\(^6,7\) to approximate a Green’s function approach to resolving the partial differential equation. Both algorithms focus on the large deformation case and rely on approximating the stationary solution of Eq. 6 with \( \mathcal{A} \) chosen as the second-order elastic regularizer.

4.1 Fourier Methods

To approximate the stationary solution of Eq. 6, we discretize forwards in time and centered in space. This yields a semi-implicit discretization that can be written as:

\[ \left[ I + \tau \mathcal{A} \right] \hat{v}^{(k+1)}(x) = \hat{v}^{(k)}(x) + \tau \alpha f(x, u^{(k)}(x)) , \quad (16) \]

where \( \tau \) is a time step, and where \( \mathcal{A} \) is the discretized version of \( \mathcal{A} \).

Now, if we define the linear operator \( \mathcal{L} \) by:

\[ \mathcal{L} = - (\lambda + 3 \mu) \Delta I + (\lambda + 2 \mu) \nabla \text{div } , \quad (17) \]

it can be shown\(^9\) that the linear PDE system \( [I + \tau A_{\text{elastic-2}}] \mathbf{v} = \mathbf{w} \) is equivalent to the system:

\[ [I + \tau (\lambda + 4 \mu) \Delta^2 + \tau^2 \mu (\lambda + 3 \mu) \Delta^4] \mathbf{v} = [I - \tau \Delta \circ \mathcal{L}] \mathbf{w} . \quad (18) \]

Hence, Eq. 16 can be solved rapidly if there is a way to exploit the structure of the discretized version of the operator on the left hand side of Eq. 18.

Luckily, there is such a way that the structure can be exploited, and it is based on the eigenstructure of the discrete Laplacian. If certain boundary conditions are considered, the eigenfunctions and eigenvalues of the discrete Laplacian are given in Table 2. Using this eigenstructure, we can state the following equivalence:

\[ \hat{v}_\ell^{(k+1)} = \frac{\hat{r}_\ell}{1 + \tau (\lambda + 4 \mu) \omega_\ell^2 + \tau^2 \mu (\lambda + 3 \mu) \omega_\ell^4} \forall \ell , \quad (19) \]
where \( \mathbf{r} = [I - \tau \Delta \circ \mathcal{L}] (\mathbf{v}(k) + \tau \mathbf{f}(k)) \), and where \( \tilde{\cdot} \) indicates the coefficient of the expansion of \( \cdot \) corresponding to the eigenfunction \( \Theta_{j}^{\ell} \). For homogeneous Dirichlet boundary conditions, the expansion can be computed using the discrete sine transform (DCT); for homogeneous Neumann boundary conditions, the expansion can be computed using the discrete cosine transform (DCT); and, for periodic boundary conditions, the expansion can be computed using the discrete Fourier transform (DFT).

These operations are summarized in the listing of Algorithm 1. Note that the eigenvalues and use of the DST / DCT / DFT depends on the choice of boundary conditions.

Algorithm 1 Fourier Methods for Large Deformation Second-Order Elastic Registration

Set \( \mathbf{v}^{(0)} = \mathbf{u}^{(0)} = 0 \), \( k = 0 \); Select \( \tau_{1}, \tau_{2} \) such that \( 0 < \tau_{1}, \tau_{2} << 1 \).

repeat

Compute \( \mathbf{w}^{(k)}(\mathbf{x}) = \mathbf{v}^{(k)}(\mathbf{x}) + \tau \mathbf{f}(\mathbf{x}, \mathbf{u}^{(k)}(\mathbf{x})) \).

Compute the DST / DCT / DFT of \( [I - \tau \Delta \circ \mathcal{L}] \mathbf{w}^{(k)} \).

For all \( \ell \), divide the \( \ell \)th component of the result by \( (1 + \tau (\lambda + 4\mu) \omega_{\ell}^{2} + \tau^{2} \mu (\lambda + 3\mu) \omega_{\ell}^{4}) \).

Compute the inverse DST / DCT / DFT of the result, yielding \( \mathbf{v}^{(k+1)} \).

Solve for \( \mathbf{u}^{(k+1)} \) by Euler integration.

If \( \min |I - \nabla \mathbf{u}^{(k+1)}| < \tau_{1} \), regrid.

Increment \( k \).

until \( d(\mathbf{u}^{(k)}, \mathbf{u}^{(k-1)}) < \tau_{2} \).

4.2 Successive Gaussian Convolution

A different algorithm based on successive Gaussian convolution can be used to perform registration in a computationally efficient manner. This algorithm is based on one of the variants of Thirion’s Demons algorithm,\(^6\) which essentially solves the diffusion registration problem. Previously,\(^7\) we showed that successive Gaussian convolution can be used to rapidly solve elastic and curvature registration problems; here, we show how the same idea can be applied for second-order elastic registration.

To design an algorithm based on successive Gaussian convolution, we exploit the relationship between \( \mathcal{A}_{\text{elastic}-2} \) and the triple Laplacian by using the linear operator \( \mathcal{L} \) from Eq. 17; i.e.,

\[
\mu \Delta^{2} \mathbf{v} + (\lambda + 2\mu) \Delta \nabla \text{div} \mathbf{v} = \alpha \mathbf{f} \quad \Rightarrow \quad (-\Delta)^{3} \mathbf{v} = \frac{\alpha \mathbf{f}}{\mu (\lambda + 3\mu)} . \tag{20}
\]

This relationship does not necessarily hold in the opposite direction, although we will ignore this problem for the sake of constructing a rapid registration algorithm. Furthermore, it can be shown\(^{19}\) that the stationary solution of the coupled diffusion equations:

\[
\begin{align*}
\partial_{t} \mathbf{w}(\mathbf{x}, t) - \Delta \mathbf{w}(\mathbf{x}, t) &= \sqrt{\alpha} \mathbf{f}(\mathbf{x}, R, F, \mathbf{u}) \tag{21} \\
\partial_{t} \mathbf{z}(\mathbf{x}, t) - \Delta \mathbf{z}(\mathbf{x}, t) &= \sqrt{\alpha} \mathbf{w}(\mathbf{x}, t) \tag{22} \\
\partial_{t} \mathbf{v}(\mathbf{x}, t) - \Delta \mathbf{v}(\mathbf{x}, t) &= \sqrt{\alpha} \mathbf{z}(\mathbf{x}, t) \tag{23} \\
\mathbf{w}(\mathbf{x}, 0) &= \mathbf{z}(\mathbf{x}, 0) = \mathbf{v}(\mathbf{x}, 0) = \mathbf{u}(\mathbf{x}, 0) = 0 , \tag{24}
\end{align*}
\]
is equivalent to the solution of the equation \((-\Delta)^3 v = \alpha f(x, R, F, u)\).

By using the property that the Green’s function of an inhomogeneous diffusion equation (over infinite space) is a Gaussian, we can approach the stationary solution of Eq.'s 21–23 by successive Gaussian convolution. An algorithm for registration using this approach is listed in Algorithm 2. The notation \(K(x, \sigma)\) denotes a Gaussian with standard deviation \(\sigma\) centered at \(x\), and \(*\) denotes convolution.

**Algorithm 2** Successive Gaussian Convolution for Large Deformation Second-Order Elastic Registration

Set \(h^{(0)} = w^{(0)} = z^{(0)} = v^{(0)} = u^{(0)} = 0\), \(k = 0\); Select \(\tau_1, \tau_2\) such that \(0 < \tau_1, \tau_2 << 1\).

Select time step \(\tau\).

repeat

Compute \(h^{(k+1)}(x) = \mathcal{L} f(x, u^{(k)}(x)) / (\mu(\lambda + 3\mu))\).

Compute \(w^{(k+1)}(x) = K(x, \sqrt{2}\tau) * \left[ \sqrt{3\alpha} h^{(k+1)}(x) + w^{(k)}(x) \right]\).

Compute \(z^{(k+1)}(x) = K(x, \sqrt{2}\tau) * \left[ \sqrt{3\alpha} w^{(k+1)}(x) + z^{(k)}(x) \right]\).

Compute \(v^{(k+1)}(x) = K(x, \sqrt{2}\tau) * \left[ \sqrt{3\alpha} z^{(k+1)}(x) + v^{(k)}(x) \right]\).

Solve for \(u^{(k+1)}\) by Euler integration.

If \(\min |I - \nabla u^{(k+1)}| < \tau_1\), regrid.

Increment \(k\).

until \(d(u^{(k)}, u^{(k-1)}) < \tau_2\).

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5. CT REGISTRATION EXPERIMENT

In this section, we describe an experiment that focuses on the practical problem of registering serial chest CT studies. Registration is performed via Fourier methods and successive Gaussian convolution using all of the quadratic regularizers. The algorithms are tested and compared according to how well they predict the positions of manually identified lung nodules as well as the amount of computation required.

The data we use comprises a set of serial chest CT examinations of 18 patients with lung nodules. Each serial examination included a prior image and a current image. Axial slices of the one of the patient examinations are shown in Fig. 2.

5.1 Experimental Setup

For each patient, we resampled the CT volumes to approximately \(6 \times 6 \times 6\text{mm}^3\) isotropic resolution and performed a rigid preregistration step. We then performed nonparametric registration for all of the quadratic regularizers, and with the squared correlation coefficient (SCC) similarity measure. Registration was performed in a multiresolution pyramid at three resolution levels; at each level, the registration process was terminated if there was no significant change in SCC or if a maximum number of 50 iterations have been performed.

![Figure 2. Axial slices from 3D CT chest scans.](image-url)
Values for $\alpha$ were chosen from the set $\{0.001, 0.01, 0.1\}$. (Other values of $\alpha$ were tried; however, larger values tended to cause the registration to diverge, whereas smaller values caused a very large number of iterations.) The time step $\tau$ was chosen to be identical to one voxel, and the Gaussian kernels were discretized and truncated to $5 \times 5 \times 5$ voxels. Registration was performed in a multiresolution pyramid at four resolution levels; at each level, the registration process was terminated if there was no significant change in SCC or if a maximum number of 50 iterations have been performed.

To establish a set of ground truth points that can be used to measure target registration error (TRE), we manually identified the centers of lung nodules less than 6mm in diameter that are observable in both the prior and current images of a patient. This yielded from 4-20 ground truth points for each patient. After each nonrigid registration algorithm was performed, the manually identified locations of nodules in the prior image were mapped through the resulting deformation field to predict their positions in the current image. The TRE is then defined as the Euclidean distance between the predicted positions and the manually identified positions of the nodules in the current image.

Computational requirements of each algorithm are measured in terms of effective convolution steps (ECS). A unit of ECS is defined as the amount of computation required to convolve a vector field at the finest resolution level with a Gaussian kernel. Hence, 50 iterations of Algorithm 2 at each of the two finest resolution levels would require $3 \times 50 + 3 \times (1/8) \times 50 = 168.75$ ECS. For the Fourier-based methods of Algorithm 1, we note that in our implementation, solution of one linear system at the finest resolution level requires approximately twice the computation as convolution with a $5 \times 5 \times 5$ kernel; hence, we compute ECS for Fourier-based methods by multiplying the number of iterations at each resolution level by 2 and weighting according to the resolution level. Therefore, 50 iterations of any Fourier-based registration algorithm at each of the two finest resolution levels would require 112.5 ECS.

5.2 Results

Tables 3 and 4 list various statistics that allow a direct comparison of the speed and accuracy of the various registration procedures. Target registration error (TRE) is computed for each nodule as the distance between predicted location and actual location of the nodule in the current image. Aggregate TRE (ATRE) is computed for each case as the median TRE of all the nodules for a case; the ATRE allows a TRE-based measure that is normalized for the different numbers of nodules in each case. Finally, effective convolution steps (ECS) are computed for each algorithm and roughly allow algorithms to be compared in terms of their relative efficiency.

Based on the results reported in Tables 3 and 4, we see that all of the variations of nonrigid registration appear to predict nodule locations to within voxel accuracy. In terms of TRE and ATRE, there does not appear to be one variation that stands out as significantly better than the rest. However, when ECS is taken into account, we see that with one exception, the second-order regularizers (curvature and second-order elastic) outperform their first order counterparts (diffusion and elastic, respectively). With respect to the second-order elastic regularizer, we can state that it appears to yield errors that are similar to those yielded by the elastic regularizer; however, it does so with a much lower computational requirement.

6. CONCLUSIONS

In this article, we have presented the second-order elastic regularizer for nonparametric registration. This regularizer combines advantages of other quadratic regularizers, enabling coupling of the spatial components of the deformation field while containing affine transformations in its kernel. We then presented two computationally efficient algorithms for registration with the second-order elastic regularizer; one based on Fourier methods, and the other based on successive Gaussian convolution. An experiment on the registration of serial CT images of patients with lung nodules indicates that the second-order elastic regularizer, like the curvature regularizer, enables registration to be performed with much less computational effort than is possible with the diffusion and elastic regularizers.
<table>
<thead>
<tr>
<th>Registration Type</th>
<th>Mean TRE (mm)</th>
<th>Median TRE (mm)</th>
<th>Std. dev. TRE (mm)</th>
<th>Mean ATRE (mm)</th>
<th>Median ATRE (mm)</th>
<th>Std. dev. ATRE (mm)</th>
<th>25th Percentile ECS</th>
<th>50th Percentile ECS</th>
<th>75th Percentile ECS</th>
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<td>Rigid Only</td>
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<td>4.9</td>
<td>7.7</td>
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<td>3.3</td>
<td>–</td>
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Table 3. Statistics of TRE across all nodules, ATRE across all cases, and ECS for rigid registration and nonrigid registration via large deformation registration by successive Gaussian convolution with each quadratic regularizer and various values of \( \alpha \).
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Table 4. Statistics of TRE across all nodules, ATRE across all cases, and ECS for rigid registration and nonrigid registration via large deformation Fourier solvers with each quadratic regularizer, homogeneous Dirichlet boundary conditions on the displacement and velocity fields, and various values of $\alpha$. 
REFERENCES