Image Fusion and Registration – a Variational Approach

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Summary. Image fusion or registration is central to many challenges in medical imaging today and has a vast range of applications. The purpose of this paper is to give an introduction to intensity based non-linear registration and fusion problems from a variational point of view. To do so, we review some of the most promising non-linear registration strategies currently used in medical imaging and show that all these techniques may be phrased in terms of a variational problem and allow for a unified treatment.

A generic registration or fusion method depends on an appropriate chosen distance measure, a regularization, and some additional constraints. The idea of constraints is to incorporate higher level information about the expected deformation. We examine the most common constraints and show again that they may be conveniently phrased in a variational setting. As a consequence, all of discussed modules allow for fast implementations and may be combined in any favorable order. We discuss individual methods for various applications, including the registration of magnetic resonance images of a female breast subject to some volume preserving constraints.

Key words: image processing, image fusion, image registration, matching, variational approach, partial differential equation

1 Introduction

Registration is the determination of a geometrical transformation that aligns points in one view of an object with corresponding points in another view of the same object or a similar object. There exist many instances in a medical environment which demand for a registration, including the treatment verification of pre- and post-intervention images, study of temporal series of cardiac images, and the monitoring of the time evolution of an agent injection subject to patient motion. Another important area is the need for combining information from multiple images, acquired using different modalities, like for example computer tomography (CT) and magnetic resonance imaging (MRI).

This problem is also called fusion. The problem of fusion and registration arises whenever images acquired from different subjects, at different times, or from different scanners need to be combined for analysis or visualization. In the last two decades, computerized non-rigid image registration has played an increasingly important role in medical imaging, see, e.g., [21], [11], [28], [22] and references therein.

An optimal registration requires to incorporate characteristics of the underlying application. Thus, each individual application should be treated by a specific registration technique. Due to the wide range of applications a variety of techniques has been developed and is used. We present a flexible variational setting for intensity driven registration schemes, which may be adapted to a particular application. The building blocks of our variational framework resemble user demands and may be assembled in a consistent and intuitive fashion.

The idea is to phrase each individual block in terms of a variational formulation. This not only allows for a unified treatment but also for fast and reliable implementation. The various building blocks comprises five categories: image model, distances and external forces, smoother and internal forces, "hard" or "soft" constraints, and optimization procedures. The *external forces* are computed from the image data and are defined to drive the *displacement field* in order to arrive at the desired registration result. In contrast, the *internal forces* are defined for the wanted displacement field itself and are designed to keep the displacement field smooth during deformation. Whereas the internal forces implicitly constrain the displacement to obey a smoothness criterion, the additional *constraints* force the displacement to satisfy explicit criteria, like for example landmark or volume preserving imposed constraints.

In Sec. 2 we summarize the most popular choices for the outlined building blocks. Furthermore, we set up a general and unified framework for automatic non-rigid registration. In Sec. 3 we show in more detail, how these building blocks can be translated into a variational setting. It is this formulation, which allows for a fast and reliable numerical treatment. In Sec. 3.4 we indicate on how to actually implement the registration schemes. An example in Sec. 4 highlights the importance of adding constraints.

2 The variational framework

Given the two images, a reference R and a template T, the aim of image registration is to find a global and/or local transformation from T onto R such that the transformed template matches the reference. Ideally there exists a coordinate transformation u such that the reference R equals the transformed template $T[u]$, where $T[u](x) = T(x + u(x))$. Given such a displacement u, the registration problem reduces to an interpolation task. However, in general it is impossible to come up with a perfect u, and the registration problem is to compute an application conformal transformation u, given the reference and template image. Apart from the fact that a solution may not exist, it is not necessarily unique. In other words, intensity based image registration is inherently an ill-posed problem; see, e.g., [22].

A displacement u which does produce a perfect or nearly perfect alignment of the given images is not necessarily a "good" displacement. For example, a computed displacement which interchanges the eyes of one patient when registered to a probabilistic atlas in order to produce a nearly perfect alignment, has obviously to be discarded. Also, folding and cracks introduced by the displacement are typically not wanted. Therefore it is essential to have a possibility to incorporate features into the registration model, such that the computed displacement u does resemble the properties of the acquisition, like for example the elastic behavior of a human brain. To mimic the elastic properties of an objects under consideration is a striking example for internal forces. These forces constrain the displacement to be physically meaningful.

In contrast, the external forces are designed to push the deformable template into the direction of the reference. These forces are based upon the intensities of the images. The idea is to design a similarity measure, which is ideally calculated from all voxel values. An intuitive measure is the sum of squares of intensity differences (SSD). This is a reasonable measure for some applications like the serial registration of histological sections. If the intensities of corresponding voxels are no longer identical, the SSD measure may perform poorly. However, if the intensities are still linearly related, a correlation (CC) based measure is the measure of choice for monomodal situations. In contrast, the mutual information (MI) related measure is based on the cooccurrence of intensities in both images as reflected by their joint intensity histogram. It appears to be the most successful similarity measure for multimodal imaginary, like MR-PET. For a discussion or comparison see, e.g., [3], [4], [27], [23], [19]. As compared to MI, the normalized gradient field (NGF) [13] measure is more restrictive. Here, the basic idea is to reduce the image contents to edges or contours and to ignore the underlying intensity information completely. In contrast to MI, where some kind of probability enters into play, the NGF approach is completely deterministic, easy to implement and to interpret.

Finally, one may want to guide the registration process by incorporating additional information which may be known beforehand. Among these are landmarks and fiducial markers; cf., e.g., [20] or [7]. Sometimes it is also desirable to impose a local volume-preserving (incompressibility) constraint which may, for example, compensate for registration artifacts frequently observed by processing pre- and post-contrast images; cf., e.g., [24] or [16]. Depending on the application and the reliability of the specific information, one may want to insist on a perfect fulfilment of these constraints or on a relaxed treatment. For examples, in practise, it is a tricky (and time consuming) problem to determine landmarks to subvoxel precision. Here, it does not make sense to compute a displacement which produces a perfect one to one match between the landmarks.

Summarizing, the general registration problem may be phrased as follows.

(IR) image registration problem:

$$\mathcal{J}[u] = \mathcal{D}[R, T; u] + \alpha\mathcal{S}[u] + \beta\mathcal{C}^{\text{soft}}[u] = \min,$$
$$\text{subject to} \quad \mathcal{C}[u] = 0 \quad \text{for all} \quad x.$$

Here, $\mathcal{D}$ models the distance measure (external force, e.g., SSD or MI), $\mathcal{S}$ the smoother (internal force, e.g., elasticity), $\mathcal{C}^{\text{soft}}$ a penalization (soft constraints), and $\mathcal{C}$ hard or explicit constraints. The penalization and constraints could be empty (unconstrained) or based on landmarks, volume preservation, or anything else. The regularization parameter α may be used to control the strength of the smoothness of the displacement versus the similarity of the images and the parameter β controls the impact of the penalization. In the following we will discuss these building blocks in more detail.

3 Building blocks

Our approach is valid for images of any spatial dimension d (e.g., $d = 2, 3, 4$). The reference and template images are represented by the compactly supported smooth mappings $R, T : \Omega \to \mathbb{R}$, where without loss of generality, $\Omega =]0, 1[^d$. Hence, $T(x)$ denotes the intensity of the template at the spatial position x. For ease of discussion we set $R(x) = b_R$ and $T(x) = b_T$ for all $x \notin \Omega$, where, b_R and b_T are appropriately chosen background intensities. The overall goal is to find a *displacement* u, such that ideally $T[u]$ is similar to R.

In this paper we use a continuous image model which is advantageous for three reasons. Firstly, it allows the proper computation of the deformed image at any spatial position. Secondly, it enables the usage of continuation, scale space, or pyramidal techniques. However, the discussion of these techniques is beyond the scope of this paper. Thirdly, and most importantly, it enables the usage of efficient and fast optimization techniques, which typically rely on smoothness. If the images are given in terms of discrete d-dimensional arrays $\boldsymbol{R}$ and $\boldsymbol{T}$, one typically uses interpolations or approximations R and T which are based on localized functions like splines or wavelets.

3.1 Smoother and Internal Forces

The nature of the deformation depends strongly on the application under consideration. For example, a slice of a paraffin embedded histological tissue does deform elastically, whereas the deformation between the brains of two different individuals is most likely not elastically. Therefore, it is necessary to supply a model for the nature of the expected deformation.

We now present some of the most prominent smoothers $\mathcal{S}$ and discuss exemplarily the Gâteaux-derivatives for two of them. An important point is, that we are not restricted to a particular smoother $\mathcal{S}$. Any smoother can be incorporated into this framework, as long as it possesses a Gâteaux-derivative.

In an abstract setting, the Gâteaux-derivative looks like

$$d\mathcal{S}[u;v] := \lim_{h\to 0} \frac{1}{h}(\mathcal{S}[u+hv] - \mathcal{S}[u]) = \int_\Omega \langle \mathcal{B}[u], \mathcal{B}[v]\rangle_{\mathbb{R}^d} \; dx,$$

where $\mathcal{B}$ denotes the associated linear partial differential operator. Note that for a complete derivation one also has to consider appropriate boundary conditions. However, these details are omitted here for presentation purposes; see [22] for details.

Typically, the operator $\mathcal{B}$ is based on first order derivatives. Therefore, also affine linear deformation are penalized which unfavorable for many application. There are two remedies: choose a higher order operator (like the curvature regularizer below) or split the deformation space into a coarse (or linear) and a disjoint fine part and regularize only with respect to the fine space; see [12] for details.

Example 1 (Elastic registration). This particular smoother measures the elastic potential of the deformation. In connection with image registration it has been introduced by [2] and discussed by various image registration groups; see, e.g., [1] or [10]. The partial differential operator is the well-known Navier-Lamé operator. For this smoother, two natural parameters, the so-called Lamé-constants can be used in order to capture features of the underlying elastic body. A striking example, where the underlying physics suggests to look for deformations satisfying elasticity constraints, is the three-dimensional reconstruction of the human brain from a histological sectioning; details are given in [25] and [22].

Example 2 (Curvature registration). As a second example, we present the curvature smoother

$$\mathcal{S}^{\text{curv}}[u] := \frac{1}{2} \sum_{\ell=1}^{d} \int_\Omega (\Delta u_\ell)^2 \; dx, \tag{1}$$

introduced by [8]. The design principle behind this choice was the idea to make the non-linear registration phase more robust against a poor (affine linear) preregistration. Since the smoother is based on second order derivatives, affine linear maps do not contribute to its costs, i.e.,

$$\mathcal{S}^{\text{curv}}[Cx+b] = 0, \quad \text{for all} \quad C \in \mathbb{R}^{d\times d},\; b \in \mathbb{R}^d.$$

In contrast to other non-linear registration techniques, affine linear deformations are corrected naturally by the curvature approach. Again the Gâteaux-derivative is explicitly known and leads to the so-called bi-harmonic operator $\mathcal{A}^{\text{curv}}[u] = \Delta^2 u$.

3.2 Distances and External Forces

Another important building block is the similarity criterion. As for the smoothing operators, we concentrate on those measures $\mathcal{D}$ which allow for differentiation. Moreover, we assume that there exists a function $f : \mathbb{R}^d \times \mathbb{R}^d \to$

$\mathbb{R}^d$, the so-called *force field*, such that

$$d\mathcal{D}[u;v] = \lim_{h\to 0} \tfrac{1}{h}(\mathcal{D}[R,T;u+hv] - \mathcal{D}[R,T;u]) = \int_\Omega f^\top v \; dx.$$

Again, we are not restricted to a particular distance measure. Any measure can be incorporated into our framework, as long as it permits a Gâteaux-derivative.

The most common choices for distance measures in image registration are the *sum of squared differences*, *cross correlation*, *cross validation*, and *mutual information*. We give explicit formulae for only two of them; for more information see, e.g., [23], [19] or [22]. We close this section by commenting on a relatively new measure, the so-called *normalized gradient field*; see [13, 17].

Example 3 (Sum of squared differences). The measure is based on a point-wise comparison of image intensities,

$$\mathcal{D}^{\mathrm{SSD}}[R,T;u] := \tfrac{1}{2}\int_\Omega (R - T[u])^2 \; dx,$$

and the force-field is given by $f^{\mathrm{SSD}}(x,y) = \nabla T(x-y)^\top (T(x-y) - R(x))$. This measure is often used when images of the same modality have to be registered.

Example 4 (Mutual information). Another popular choice is mutual information. It basically measures the entropy of the joint density $\rho(R,T)$, where $\rho(R,T)(r,t)$ counts the number of voxels with intensity r in R and t in T. The precise formula is

$$\mathcal{D}^{\mathrm{MI}}[R,T;u] := -\int_{\mathbb{R}^2} \; \rho(R,T[u]) \log \tfrac{\rho(R,T[u])}{\rho(R)\rho(T[u])} \; d(r,t),$$

where $\rho(R)$ and $\rho(T[u])$ denote the marginal densities. Typically, the density is replaced by a Parzen-window estimator; see, e.g. [26]. The associated force-field is given by

$$f^{\mathrm{MI}}(x,y) = (\Psi_\sigma * \partial_t L)(R(x), T(x+y)) \cdot (\nabla T(x+y)^\top v(x),$$

where $L := 1 + \rho(R,T[u]) \log \frac{\rho(R,T[u])}{\rho(R)\rho(T[u])}$ and Ψ is the Parzen-window function; see, e.g., [19] or [5]. This measure is useful when images of a different modality have to be registered.

Example 5 (Normalized Gradient Field). Any reasonable distance measure depends on the deformed image and can thus be written as $\mathcal{D}[R,T[u]]$. Therefore, the associated force-field contains the factor ∇T and edges enter inter play naturally. A distance measure directly based on edges has been proposed by [13, 17]. The basic idea is to use a directly accessible stable edge detector

$$n_e(I,x) = \nabla I / \sqrt{\|\nabla I(x)\|_2^2 + e^2},$$

where the parameter e is related to the noise level and distinguishes between important and unimportant structures within the images. The distance measure is based on the pointwise alignment of the regularized gradient fields,

$$\mathcal{D}^{\mathrm{NGF}}[R,T;u] := -\int_{\Omega} \left((n_e(R,x))^\top n_e(T[u],x) \right)^2 \, dx,$$

see [13] for details.

3.3 Additional Constraints

Often it is desirable to guide the registration process by incorporating additional information which may be known beforehand, like for example markers or characteristics of the deformation process. To incorporate such information, the idea is to add additional constraints or penalization to the minimization problem.

Example 6 (Landmarks). One may want to incorporate information about landmarks or fiducial markers. Let r^j be a landmark in the reference image and t^j be the corresponding landmark in the template image. Our setting allows for either adding hard or explicit constraints

$$\mathcal{C}_j[u] := u(t^j) - t^j + r^j, \quad j = 1, 2, \ldots, m,$$

which have to be precisely fulfilled $\mathcal{C}_j[u] = 0$ ("hard" constraints), or by adding an additional cost term

$$\mathcal{C}^{\mathrm{soft}}[u] := \textstyle\sum_{j=1}^{m} \|\mathcal{C}_j[u]\|^2_{\mathbb{R}^d}$$

("soft" constraints, since we allow for deviations). For a more detailed discussion of landmark constraints, we refer to [7].

Example 7 (Volume preservation). In some applications, like, for example, the monitoring of tumor growth, a change of volume due to registration is critical. Therefore one may restrict the deformation to be volume preserving, using the point wise constraints

$$\mathcal{C}[u](x) := \det \nabla u(x) - 1.$$

[24] presented a penalized approach based on

$$\mathcal{C}^{\mathrm{soft}}[u](x) := \int_{\Omega} |\log(\mathcal{C}[u] + 1)| \, dx.$$

An extended discussion and the treatment of the constrained approach can be found in [16], see also [15] for numerical issues.

3.4 Numerical Treatment of the constrained problem

There essentially are two approaches for the minimization of (IR). The first approach is to first discretize the continuous problem and to treat the discrete problem by some optimization techniques; see, e.g. [15]. The second approach which we discussed is this paper is to deal with a discretization of the so-called Euler-Lagrange equations, i.e. the necessary conditions for a minimizer of the continuous problem; see [9] for an extended discussion. It remains to efficiently solve this system of non-linear partial differential equations. After invoking a time-stepping approach and after an appropriate space discretization, we finally end up with a system of linear equations. As it turns out, these linear systems have a very rich structure, which allows one to come up with very fast and robust solution schemes for all of the above mentioned building blocks. It is important to note that the system matrix does not depend on the force field and the constraints. Thus, changing the similarity measure or adding additional constraints does not change the favorable computational complexity. Moreover, fast and parallel solution schemes can be applied to even more reduce the computation time; see also [18], [6], or [14].

4 An example: MRI mammography

In order to demonstrate the flexibility of the variational approach, we present numerical results for the registration of magnetic resonance images (MRI). In this application, MRI's of a female breast are taken at different times (images from Bruce Daniel, Lucas Center for Magnetic Resonance Spectroscopy and Imaging, Stanford University). Fig. 1 shows an MRI section taken during the so-called wash-in phase of a marker (c) and an analogous section during the so-called wash-out phase (a). A comparison of these two images indicates a suspicious region in the upper part of the images (b). A quantitative analysis is a delicate matter since observable differences are not only related to contrast uptake but also due to motion of the patient, like breathing or heart beat.

Fig. 1 shows the results of an elastic/SSD registration for the unconstrained (non) and volume preserving (VP) constrained approaches. Though it is almost impossible to distinguish the two deformed image (d) and (g) and even the difference images (e) and (h) are very much alike, there is a tremendous difference in the deformations as can be see from (f) and (i), where a region of interest is superimposed with the deformed grids. A further analysis shows that the unconstrained solution u^{non} does change tissue volume by a factor of 2.36 ($\max|\mathcal{C}[u^{\text{non}}]| \approx 1.36$), whereas the VP solution u^{VP} satisfies the constraints up to a numerical tolerance ($\max|\mathcal{C}[u^{\text{VP}}]| \leq 10^{-8}$).

Note that a comparison or discussion of the results from an application point of view is beyond the scope of this paper. More generally, a general setting does not answer the question, which particular combination of building blocks leads to best results. However, the framework enables the computation of results for different choices and can thus be used to optimize the building blocks.

5 Conclusions

In this note we presented a general approach to image fusion and registration and thereby giving an overview of state-of-the-art medical image registration schemes. The flexibility of the presented framework enables one to integrate and to combine in a consistent way various different registration modules. We discussed the use of different smoothers, distance measures, and additional constraints. The numerical treatment is based on the solution of a partial differential equation related to the Euler-Lagrange equations. These equations are well studied and allow for fast, stable, and efficient schemes. In addition, we reported on one example, showing the effect of constraints.
Part of the software is available via `http://www.math.uni-luebeck.de/SAFIR`.

References

1. R. Bajcsy and S. Kovačič, *Toward an individualized brain atlas elastic matching*, Tech. Report MS-CIS-86-71 Grasp Lap 76, Dept. of Computer and Information Science, Moore School, University of Philadelphia, 1986.
2. C. Broit, *Optimal Registration of Deformed Images*, PhD thesis, Computer and Information Science, University of Pensylvania, 1981.
3. L. G. Brown, *A survey of image registration techniques*, ACM Computing Surveys, 24 (1992), pp. 325–376.
4. A. Collignon, A. Vandermeulen, P. Suetens, and G. Marchal, *3d multimodality medical image registration based on information theory*, Kluwer Academic Publishers: Computational Imaging and Vision, 3 (1995), pp. 263–274.
5. E. D'Agostino, J. Modersitzki, F. Maes, D. Vandermeulen, B. Fischer, and P. Suetens, *Free-form registration using mutual information and curvature regularization*, in 2nd International Workshop on Biomedical Image Registration 2003, J. Gee, J. Maintz, and M. Vannier, eds., LNCS 2717, Springer, 2003, pp. 11–20.
6. M. Droske, M. Rumpf, and C. Schaller, *Non-rigid morphological registration and its practical issues*, in Proc. ICIP '03, IEEE International Conference on Image Processing, Sep. 2003, Barcelona, Spain, 2003.
7. B. Fischer and J. Modersitzki, *Combining landmark and intensity driven registrations*, PAMM, 3 (2003), pp. 32–35.
8. ———, *Curvature based image registration*, J. of Mathematical Imaging and Vision, 18 (2003), pp. 81–85.
9. ———, *Large scale problems arising from image registration*, Technical Report TR-2004-027-A, Institute of Mathematics, University of Lübeck, Dec 2004. To appear in GAMM Mitteilungen 2005.
10. ———, *A unified approach to fast image registration and a new curvature based registration technique*, Linear Algebra and its Applications, 380 (2004), pp. 107–124.

11. J. M. Fitzpatrick, D. L. G. Hill, and C. R. M. Jr., *Image registration*, in Handbook of Medical Imaging, Volume 2: Medical Image Processing and Analysis, M. Sonka and J. M. Fitzpatrick, eds., SPIE, 2000, pp. 447–513.
12. E. Haber and J. Modersitzki, Cofir*: Coarse and fine image registration*, Technical Report TR-2004-006-A, Department of Mathematics and Computer Science, Emory University, Atlanta GA 30322, Jun 2004.
13. ———, *Intensity gradient based registration and fusion of multi-modal images*, Technical Report TR-2004-027-A, Department of Mathematics and Computer Science, Emory University, Atlanta GA 30322, Jun 2004. Submitted to IEEE TMI.
14. ———, *A multilevel method for image registration*, Technical Report TR-2004-005-A, Department of Mathematics and Computer Science, Emory University, Atlanta GA 30322, May 2004. Accepted for publication in SIAM J. of Scientific Computing.
15. ———, *Numerical methods for volume preserving image registration*, Inverse Problems, Institute of Physics Publishing, 20 (2004), pp. 1621–1638.
16. ———, *Volume preserving image registration*, in Medical Image Computing and Computer-Assisted Intervention – MICCAI 2004, C. Barillot, D. Haynor, and P. Hellier, eds., vol. 3216, Springer LNCS, 2004, pp. 591–598.
17. ———, *Beyond mutual information: A simple and robust alternative*, in Bildverarbeitung für die Medizin 2005, A. H. et al, ed., Springer, 2005, pp. 1–5. Accepted for publication.
18. S. Henn and K. Witsch, *Iterative multigrid regularization techniques for image matching*, SIAM J. on Scientific Comp., 23 (2001), pp. 1077–1093.
19. G. Hermosillo, *Variational methods for multimodal image matching*, PhD thesis, Université de Nice, France, 2002.
20. H. J. Johnson and G. E. Christensen, *Consistent landmark and intensity-based image registration*, IEEE Transactions on Medical Imaging, 21 (2002), pp. 450–461.
21. J. B. A. Maintz and M. A. Viergever, *A survey of medical image registration*, Medical Image Analysis, 2 (1998), pp. 1–36.
22. J. Modersitzki, *Numerical Methods for Image Registration*, Oxford University Press, 2004.
23. A. Roche, *Recalage d'images médicales par inférence statistique*, PhD thesis, Université de Nice, Sophia-Antipolis, France, 2001.
24. T. Rohlfing, C. R. Maurer, Jr., D. A. Bluemke, and M. A. Jacobs, *Volume-preserving nonrigid registration of MR breast images using free-form deformation with an incompressibility constraint*, IEEE Transactions on Medical Imaging, 22 (2003), pp. 730–741.
25. O. Schmitt, *Die multimodale Architektonik des menschlichen Gehirns*, habilitation, Insitute of Anatomy, Medical University of Lübeck, Germany, 2001.
26. P. Viola and W. M. Wells III, *Alignment by maximization of mutual information*, (1995), pp. 16–23. IEEE 1995.
27. P. A. Viola, *Alignment by Maximization of Mutual Information*, PhD thesis, Massachusetts Institute of Technology, june 1995.
28. B. Zitová and J. Flusser, *Image registration methods: a survey*, Image and Vision Computing, 21 (2003), pp. 977–1000.

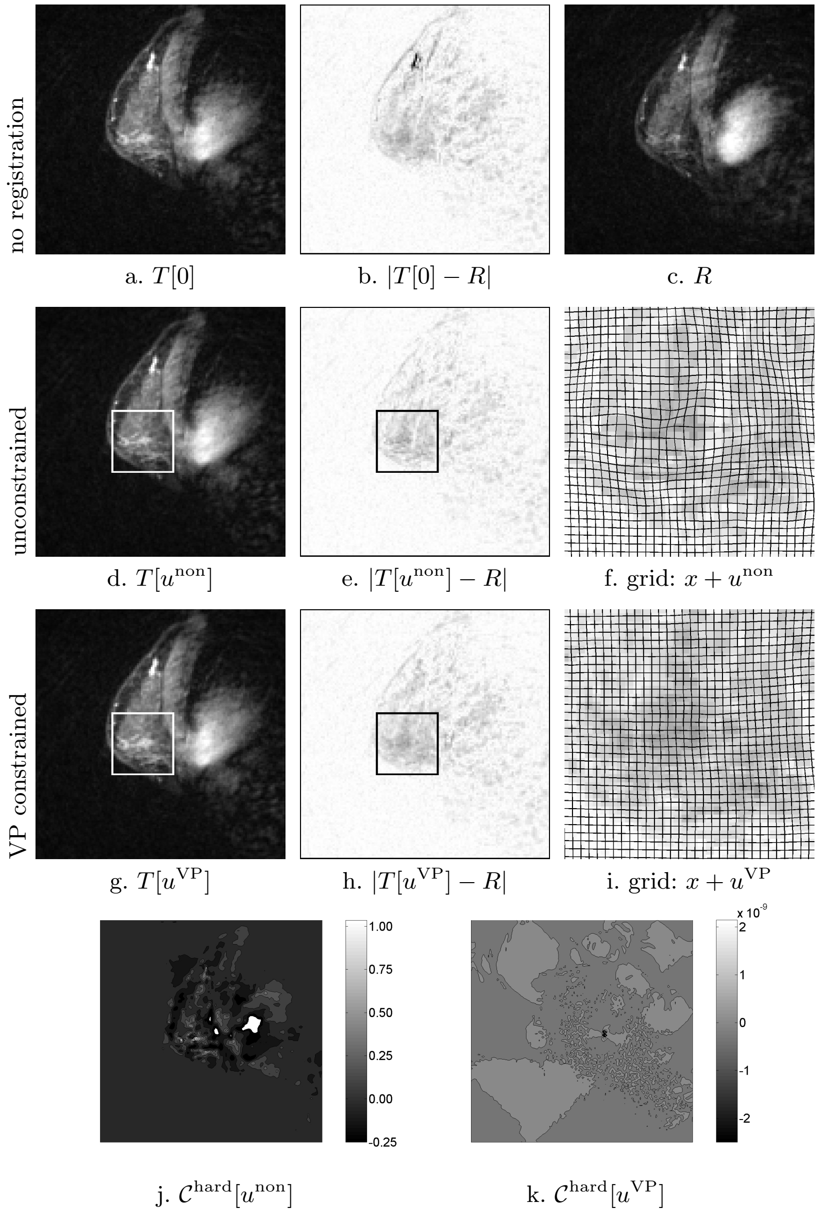

Fig. 1. Results for the unconstrained (non) and volume preserving (VP) elastic/SSD registrations of a reference (a) and template (c) image; registered templates $T[u^{\mathrm{non}}]$ (d) and $T[u^{\mathrm{VP}}]$ (g); difference $|T[0] - R|$ (b), $|T[u^{\mathrm{non}}] - R|$ (e), and $|T[u^{\mathrm{VP}}] - R|$ (h); deformed grid on a region of interest $x + u^{\mathrm{non}}$ (f) and $x + u^{\mathrm{VP}}$ (i); image of volume preservation of the unconstrained (j) and VP constrained (k) solutions.