Combining Homogenization and Registration

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Abstract. We present a novel approach for a combined homogenization and registration technique. Medical image data is often disturbed by inhomogeneities from staining, illumination or attenuation. State-of-the-art approaches tackle homogenization and registration separately. Our new method attacks both troublemakers simultaneously. It is modeled as a minimization problem of a functional consisting of a distance measure and regularizers for the displacement field and the grayscale correction term. The simultaneous homogenization and registration enables an automatic correction of gray values and improves the local contrast. The combined approach takes slightly more computing time for an optimization step as compared to the non-combined scheme and so is much faster than sequential methods. We tested the performance both on academic and real life data. It turned out, that the combined approach enhances image quality, especially the visibility of slightly differentiable structures.

1 Introduction

A generic task in modern image processing is the integration and/or comparison of data obtained from different images. Particularly in a medical environment, there is a huge demand for comparing pre- and post-intervention images, integrating modalities like anatomy (obtained, e.g., from computer tomography) and functionality (obtained, e.g., from positron emission tomography), or reconstruction of two-dimensional projections to a three-dimensional volume (applies to all tomography techniques and histology).

This task is often disturbed by two sources. The first source is related to a geometrical change of the displayed objects. This change might be introduced, e.g., by motion and/or positioning of objects, distortions and/or changes of imaging devices etc. A well-known technique to compensate these types of distortion is the so-called *image registration*, see, e.g., [5, 7] and references therein. The second source is related to a different appearance of the displayed objects. In histology, e.g., the section typically shows inhomogeneities that are completely related to staining. As a consequence, even after a perfect registration one still observes differences of the displayed objects. While for some applications, e.g., the integration of different modalities, these differences are more or less the goal of the image processing, for other applications, like histology or ultra-sound, these differences are artificial. Typically, *homogenization* is used to compensate these disturbances.

The state-of-the-art approach to the problem is to separate homogenization and registration and to tackle them independently. The homogenization, for example, might be treated based on morphological operations, illumination models, and/or statistical approaches (Markov random fields). For the registration part, there exists a variety of different and well-understood similarity measures in image registration like, for example the sum of squared differences, cross-correlation, or mutual information [2, 11, 9, 7]. All these measures focus on the maintenance of grayvalues and hence none of these measures allow for a correction of grayvalues. There are also some heuristic based schemes for a combined approach. However, these are based one a limited parametric model. A typical example is a straightforward globally linear model, which allows for a mean adaption and a contrast correction [8].

In this paper, we present a novel approach for a combined homogenization and registration technique. Our new approach is based on a sound mathematical formulation that attacks both troublemakers simultaneously. The new method is attractive for grayvalue correction in a variety of applications, including histological serial sectioning (staining), optical flow (illumination), digital radiography (attenuation), and magnetic resonance images (device/user dependency).

The paper is organized as follows. In Section 2 we introduce our notation and give a mathematical foundation of the new combined approach. In Section 3, we describe particular homogenization approaches. Some implementation issues are discussed in Section 4, results for academical as well as real life examples are given in Section 5, and a discussion is given in Section 6.

2 The theoretical setup

For convenience, we prefer a continuous formulation of the problem. Therefore, our reference R and template T images are mappings from $\Omega \subset \mathbb{R}^d$ to the real numbers $\mathbb{R}$. The mathematical framework covers all image dimensionalities d. However, since our main interest is in histology, we focus on $d = 2$.

A standard distance measure in image registration is the L_2-norm of the difference image, also called *sum of square differences*, which is basically the energy of the difference image,

$$D(R,T) := \|T - R\|^2 := \int_\Omega \big(T(x) - R(x)\big)^2 \, dx, \tag{1}$$

cf., e.g., [1, 7]. Introducing the deformation u and the deformed template

$$T[u], \quad \text{where} \quad T[u](x) := T(x + u(x)), \tag{2}$$

the basic registration goal is to minimize $D(R, T[u])$ with respect to the geometry u. Note that this problem is ill-posed [3, 7] and thus needs to be regularized. Since this regularizer is not central to this paper, for the sake of simplicity, we only focus on the elastic potential S, see [7] for details and further regularization. However, our approach has no limitations to this particular regularization.

In order to compensate inhomogeneities, we introduce a correction function c which in addition enables a multiplicative gray value change of the deformed template

$$cT[u], \quad \text{where} \quad (cT[u])(x) := c(x) \cdot T(x + u(x)) \tag{3}$$

and our final distance measure $\|cT[u] - R\|^2$ is to be minimized with respect to the geometry u and the homogeneity correction c. For the particular choice $c \equiv 1$, we get the "standard" registration problem back. Setting $c(x) := 1$ for all x where $T(x) = 0$ and $c(x) := R(x)/T(x)$ otherwise, we obtain a trivial minimizer without any geometrical correction. It is obvious that this solution is not helpful. Thus, an additional regularizer H for c has to be introduced. We discuss choices in the next section. The final formulation of the registration problem reads

$$J(u, c) := \|cT[u] - R\|^2 + \alpha S[u] + \beta H[c] \overset{!}{=} \min, \tag{4}$$

where α and β are regularization parameters and the minimization is with respect to u and c simultaneously. It is very important, that this formulation already combines the minimization of geometry and homogeneity.

3 Homogeneity correction

The central and remaining question is, how to regularize the homogeneity correction c? The answer to this question is related to the variation of c. If c varies to much (e.g., $c = R/T$), the solution of (4) is meaningless. If on the other hand c does no vary (e.g., $c = 1$) it will not compensate inhomogeneities. We therefore propose a gradient based regularizer,

$$H_p[c] := \int_{\Omega} \|\nabla c\|^p dx.$$

Obvious choices for p are $p = 2$ (diffusivity) or $p = 1$ (total variation). Simple tests show that the first choice leads to blurred images $cT[u]$. We thus prefer the total variation approach, since it leads to piecewise continuous corrections.

Alternatively, one could also use an explicit regularized version. For example, in histology we might change mean gray value and contrast by a parametric model

$$(cT)(x) = \begin{cases} \gamma_1 T(x) + \gamma_2, & T(x) \neq 0 \\ 0, \text{else} \end{cases} .$$

Here, c is parameterized by γ_1 and γ_2 and varies basically over linear maps. Due to this limitations, no additional regularization is needed and we may set $\beta = 0$ in (4).

4 Implementation

The new approach is based on a variational formulation of the combined registration problem. From this mathematically sound approach, we derive Euler-Lagrange equations as a system of necessary conditions for a minimizer. The efficient solution of these partial differential equations is the backbone of our algorithm. However, any adequate numerical scheme can be used.

The Euler-Lagrange equations for (4) are given by

$$J_u = 2c(cT - R)\nabla T - 2\alpha(\mu \Delta u + (\mu + \lambda)\nabla\nabla \cdot u) = 0, \tag{5a}$$

$$J_c = (cT - R)T - \nabla \cdot \tfrac{\nabla c}{\|\nabla c\|} = 0. \tag{5b}$$

This system of non-linear partial differential equations is discretized using standard finite differences. In principle, a fast multigrid solver has to be used in order to solve these equations efficiently. However, a proper multigrid treatment of total variation - particularly if combined with the elastic operator - is non-trivial and topic of current research and a forthcoming paper. Here, the particular solution scheme is minor and we thus take the solution scheme based on [4] and a straightforward solve for the total variation. Note that our limitation to periodic boundary conditions for the displacement is only due to this particular solution scheme but not part of our method. For a solution of the discrete version we use a non-linear Gauss-Seidel approach. The implementation is coded under MATLAB [6] and executed on an AMD Athlon XP 2700+ with 2 GB RAM. The overall computation time is about one minute for the academical and about three minutes for the real life data. Note that this code runs completely under MATLAB and is far away from being optimized or tuned. We basically aim to show the ability of the new method rather than to focus on a smart implementation.

5 Results

We implemented our new scheme and tested the performance on a variety of different examples ranging from academical to real life data. For the academical examples, it is obvious, that the new method benefits from the combined approach. This manifests not only in a much faster execution time, but most importantly in significantly improved registration results. It is easy to construct examples where inhomogeneous regions lead to miss-registration of non-simultaneous schemes. Particularly, we present detailed results for an academical and a real life example.

We tuned our academical example in order to emphasize the power of the simultaneous approach. Our reference image displays a disk, our template image a smaller disk with a grayscale ramp in its interior. Without a simultaneous approach, the inner ramp immediately leads to displacements within these regions; see Figure 1c. With the simultaneous approach, we are not only able to compute a reasonable displacement field (Figure 1g) but also a grayscale correction (Figure 1e and 1f). Only due to this correction we are enabled to display the final $cT[u]$, which in this example happens to be a perfect copy of the reference image. Parameter used: $\alpha = 2e5$, $\beta = 1e3$, $\lambda = 0$, $\mu = 1$, ten iterations (for the simultaneous approach, the minimizer was already obtained after 4 iterations).

Examples for a real life application are also presented. Here we show the results of a registration of two images from consecutive sections within a serial sectioning of about 800 sections; see [10] for an overview on the overall procedure. As expected, the grayscale correction is not as important as in the academical example. This can be observed from the two deformed grids (Figure 2e and 2h) which more or less look the same. However, a staining trend in this data (visible in the difference image Figure 2f) has been resolved with our combined approach. In contrast to the plain scheme, the combined registration approach results in a visually more pleasing and anatomically superior three-dimensional reconstruction. Parameter used: $\alpha = 5e5$, $\beta = 5e4$, $\lambda = 0$, $\mu = 1$, 40 iterations.

6 Discussion

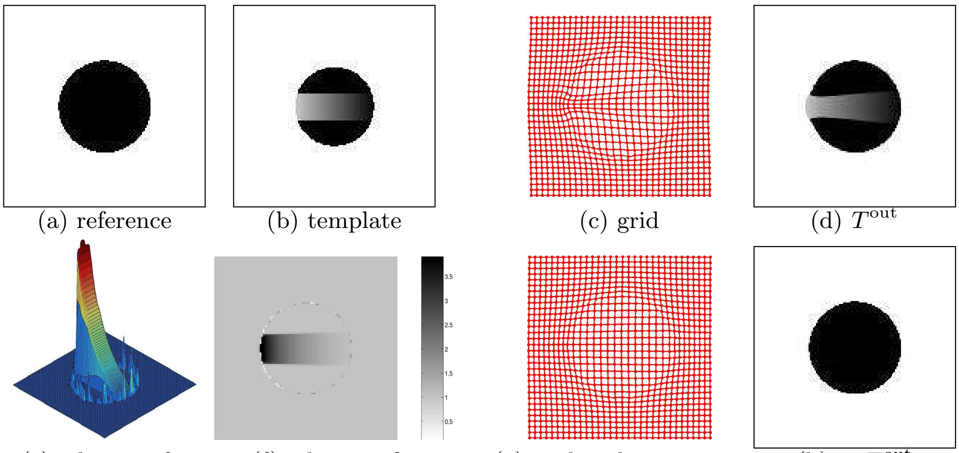
We present a novel registration scheme which enables an unified and simultaneous treatment of the combined registration problem. Our numerical experiments indicate, that the new approach outperforms the uncombined scheme. Our academical examples indicate that the results obtained from the combined scheme are much more reliable. This also applied for the histological serial sectioning, however, the phenomena are less pronounced. Still and most importantly, the automatic homogenization enables an automatic correction of gray values and improves the local contrast. Thus, it leads to a much better visualization of otherwise non-differentiable structures.

Based on an additional solution step for the grayscale correction, the combined scheme takes slightly more computing time for an optimization step as compared to the non-combined scheme. However, this disadvantage is compensated by the fact, that the registration and grayscale correction results are obtained simultaneously. A faster and more efficient implementation of the combined approach is topic of further research. In addition, we like to adapt the combined approach to other areas of applications.

References

1. Lisa Gottesfeld Brown, *A survey of image registration techniques*, ACM Computing Surveys **24** (1992), no. 4, 325–376.
2. A. Collignon, A. Vandermeulen, P. Suetens, and G. Marchal, *3d multi-modality medical image registration based on information theory*, Kluwer Academic Publishers: Computational Imaging and Vision **3** (1995), 263–274.
3. M. Droske and M. Rumpf, *A variational approach to non-rigid morphological registration*, SIAM Appl. Math. **64** (2004), no. 2, 668–687.
4. B. Fischer and J. Modersitzki, *Fast inversion of matrices arising in image processing*, Num. Algo. **22** (1999), 1–11.
5. J Hajnal, D Hawkes, and D Hill, *Medical image registration*, CRC Press, 2001.
6. MathWorks, Natick, Mass., *Matlab user's guide*, 1992.
7. J. Modersitzki, *Numerical methods for image registration*, Oxford University Press, 2004.
8. J. Modersitzki and O. Schmitt, *Image registration of histological sections*, Preprint A-02-06, Institute of Mathematics, University of Lübeck, Germany, 2002.

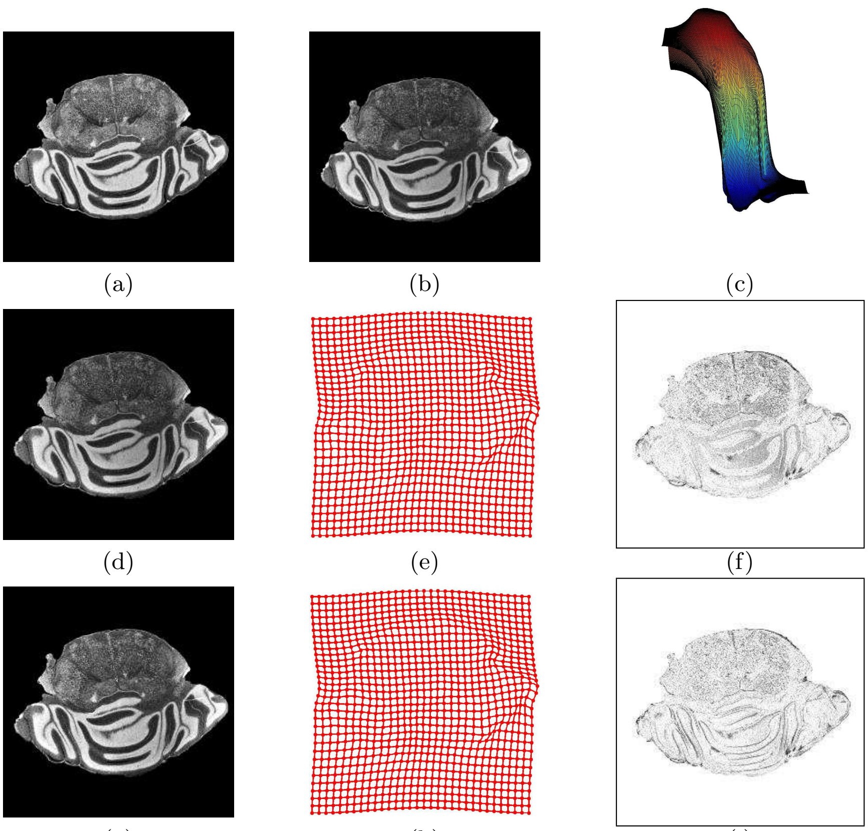
9. A. Roche, *Recalage d'images médicales par inférence statistique*, Ph.D. thesis, Université de Nice, Sophia-Antipolis, France, 2001.
10. O. Schmitt and J. Modersitzki, *Registrierung einer hochaufgelösten histologischen Schnittserie eines Rattenhirns*, Bildverarbeitung für die Medizin 2001 (H Handels, A Horsch, TM Lehmann, and HPH Meinzer, eds.), Springer, 2001, pp. 174–178.
11. Paul A. Viola, *Alignment by maximization of mutual information*, Ph.D. thesis, Massachusetts Institute of Technology, 1995, pp. 1–155.



(a) reference (b) template (c) grid (d) T^{out}

(e) 3d view of c (f) 2d view of c (g) grid with correction (h) $c \cdot T^{\text{out}}$

Fig. 1. Academic example: (a) disk as reference, (b) smaller disk with ramp as template, (c) deformed grid (no grayscale correction), (d) deformed template (no grayscale correction), (e) 3d and (f) 2d visualizations of the homogenization correction, (f) deformed grid (with grayscale correction), (g) deformed and corrected template.



(a) (b) (c)

(d) (e) (f)

(g) (h) (i)

Fig. 2. Histological serial section: (a) reference, (b) template: consecutive section, (c) 3d visualization of the homogenization, (d) deformed template (no grayscale correction), (e) deformed grid (no grayscale correction), (f) difference image (no grayscale correction) (g) deformed template (with grayscale correction), (h) deformed grid (with grayscale correction), (i) difference image (with grayscale correction).