VariationalRegistration – A Flexible Open-Source ITK Toolbox for Nonrigid Image Registration

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Abstract. In this article, we present the flexible open-source toolbox *VariationalRegistration* for non-parametric variational image registration, realized as a module in the *Insight Segmentation and Registration Toolkit* (ITK). The toolbox is designed to test, evaluate and systematically compare the effects of different building blocks of variational registration approaches, i.e. the distance/similarity measure, the regularization method and the transformation model. In its current state, the framework includes implementations of different similarity measures and regularization methods, as well as displacement-based and diffeomorphic transformation models. The implementation of further components is possible and encouraged.
The implemented algorithms were applied to different registration problems and extensively tested using publicly accessible image data bases. This paper presents a quantitative evaluation for inter-patient registration using 3D brain MR images of the LONI image data base. The results demonstrate that the implemented variational registration scheme is competitive with other state-of-the-art approaches for non-rigid image registration.

1 Introduction

Image registration is a crucial aspect of many applications in medical image computing. During the past years, a wide variety of approaches for non-linear registration has been proposed and successfully applied for diverse registration tasks. Examples for applications of non-linear registration algorithms are the estimation of organ deformations due to respiratory or cardiac motion [1], the co-registration of images acquired from different subjects for atlas construction or statistical analyses [2], or atlas-based segmentation methods [3].

Due to the diversity and number of existing registration approaches, it is a bewildering task to choose an appropriate registration method for a given application. A number of multi-institutional studies and challenges have taken place to give an overview of the field and to evaluate and compare different algorithms for specific registration tasks, for example in respiratory motion estimation [4,5] or inter-patient registration for neurological applications [2]. These studies have a competitive design and each registration algorithm is treated as a complete pipeline. In this setting, a systematical investigation of the effects of separate building blocks of the registration problem (distance measure, regularization, transformation space, etc.) is not possible and the influence of these components is hardly to divide from the impact of implementation details (discretization details, stop criterion, pre- and post-processing).

In this paper, we present a flexible open-source toolbox for non-parametric variational image registration named *VariationalRegistration*. The toolbox is implemented as a module in the *Insight Segmentation and Registration Toolkit* (ITK) and freely available with ITK version 4.6 and higher. The aim of this toolbox is to provide a framework to systematically investigate and compare the building blocks of registration algorithms in a variational setting. The implementation design allows to combine and modify different components like distance measure, regularization, stop criterion or transformation model, and new components can easily be implemented.

The initial motivation for the development of the toolbox was a comparison and evaluation study for lung motion estimation in thoracic 4D CT images [1]. Therefore, state-of-the-art algorithms for variational registration were implemented in the toolbox and extensively tested using publicly accessible image data bases[1]. The results of this study show that the implemented algorithms perform similar to other state-of-the-art methods. In contrast to [1], this paper describes implementation concepts of the toolbox, and we present results for *inter*-patient registration of 40 brain 3D MR images used to construct the LONI Probabilistic Brain Atlas (LPBA40) [6]. We evaluate different distance measures, regularization methods and transformation models and compare our results to other state-of-the-art registration algorithms.

2 Methods and materials

2.1 Variational formulation of the image registration problem

Without going into detail, this section is to shortly summarize the variational registration setting. Given a fixed image $F : \Omega \to \mathbb{R}$ ($\Omega \subset \mathbb{R}^d$) and a moving image $M : \Omega \to \mathbb{R}$, registration is the process of finding a (plausible) spatial transformation $\boldsymbol{\varphi} : \Omega \to \Omega$ that maps points from F to corresponding points in M. We compute $\boldsymbol{\varphi}$ by minimizing an energy functional

$$\mathcal{J}[\boldsymbol{\varphi}] = \mathcal{D}[F, M \circ \boldsymbol{\varphi}] + \alpha \mathcal{S}[\boldsymbol{\varphi}] \to \min . \tag{1}$$

Thus, the main building blocks of the functional $\mathcal{J}$ can be summarized as being the distance measure $\mathcal{D}$, the regularization term $\mathcal{S}$, and the transformation model of $\boldsymbol{\varphi}$. In our non-parametric variational setting, $\boldsymbol{\varphi}$ is represented by a dense vector

[1] www.dir-lab.com and www.creatis.insa-lyon.fr/rio/popi-model

Algorithm 1 Diffeomorphic variational registration

Set $\boldsymbol{v}^{(0)} = 0$ or to an initial field, $\boldsymbol{\varphi}^{(0)} = \exp(\boldsymbol{v}^{(0)})$ and $k = 0$
repeat
  Compute the force field $\boldsymbol{f}[F, M \circ \boldsymbol{\varphi}^{(k)}]$
  Let $\boldsymbol{v}^{(k)} \leftarrow \boldsymbol{v}^{(k)} + \tau \boldsymbol{f}$
  Regularize the velocity field using $\boldsymbol{v}^{(k+1)} = (Id - \tau\mathcal{A})^{-1}\, \boldsymbol{v}^{(k)}$
  Calculate the corresponding transformation $\boldsymbol{\varphi}^{(k+1)} = \exp(\boldsymbol{v}^{(k+1)})$
  Let $k \leftarrow k + 1$
until $k \geq K_{max}$ or another stop criterion is fulfilled

field, i.e. by a *displacement* field $\boldsymbol{u}$, with $\boldsymbol{\varphi}(\boldsymbol{x}) = \boldsymbol{x} + \boldsymbol{u}(\boldsymbol{x})$, in the small deformation setting or by a (static) *velocity* field $\boldsymbol{v}$, with $\boldsymbol{\varphi}(\boldsymbol{x}) = \exp(\boldsymbol{v})(\boldsymbol{x})$, to represent diffeomorphic transformations. To minimize Eq. (1), the Euler-Lagrange equations are analytically derived, resulting in partial differential equations that are solved by gradient descent. This optimize-than-discretize approach results in an iterative scheme (here for the small displacement setting):

$$\boldsymbol{u}^{(k+1)} = (Id - \tau\mathcal{A})^{-1} \left(\boldsymbol{u}^{(k)} + \tau \boldsymbol{f}[F, M \circ \boldsymbol{\varphi}^{(k)}]\right), \qquad (2)$$

where $\boldsymbol{f}$ denotes a force field that is related to the derivative of the distance measure $\mathcal{D}[F, M \circ \boldsymbol{\varphi}]$ and $\mathcal{A}$ is a linear partial differential operator, which can be deduced from the derivative of $\mathcal{S}$ (cf. [7]). The resulting registration algorithm for the diffeomorphic setting is summarized in Alg. 1.

2.2 Implementation

The toolbox *VariationalRegistration* is implemented in C++ and realized as part of ITK's finite difference solver hierarchy. A part of the class diagram is shown in Fig. 1. Further classes provide different stop criteria or handle multi-resolution schemes, for example. Within this framework, force term and regularizer remain exchangeable and additional terms can be easily integrated.

The following distance measures (i.e. its derivatives) are implemented in the current version of the toolbox: *sum of squared differences (SSD)*, *demons-based or normalized SSD (NSSD)*, and *normalized cross correlation (NCC)*. The implementation of further force terms like NMI or NGF is subject of future work.

The regularization step as shown in Eq. (2) requires to solve a linear equation system with a very large number of unknowns. We provide efficient FFT-based solving strategies for *curvature* and *elastic regularization* and a *diffusive regularization* based on additive operator splitting. Further, a *Gaussian regularization* is implemented that smooths a dense vector field with a Gaussian kernel similar to the demons registration approach. All regularizers and distance measures are multi-threaded; however, efficiency was not the main design goal of this toolbox but generalization and clarity of the source code. More implementation details can be found in [8].

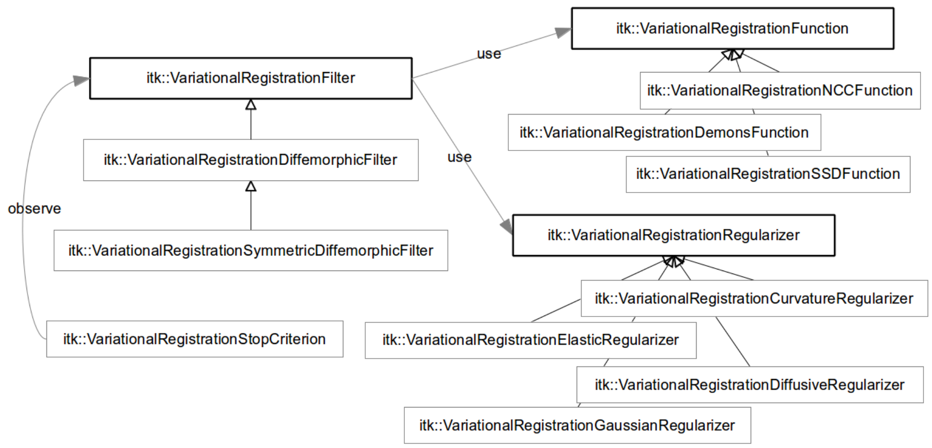

Fig. 1. Extraction from the class diagram of the toolbox *VariationalRegistration*. The overall registration algorithm is implemented in the class `VariationalRegistrationFilter` and its child classes for (symmetric) diffeomorphic registration. The force field (related to the distance measure) is computed in child classes of `VariationalRegistrationFunction` and the regularization step is done in classes derived from `VariationalRegistrationRegularizer`.

2.3 Comparison and evaluation based on public data sets

We evaluate the implemented algorithms for inter-patient registration using 40 brain 3D MR images of the LPBA40 data set [6]. For each of the 3D MR images a label image containing 56 segmented structures is available. The data set is publicly available and the results therefore reproducible. Further, we can directly compare our results to 14 image registration algorithms that were investigated in a previous study performed by Klein et al. [2]. According to this study, we perform pairwise registration and compute Jaccard overlap coefficients between the labeled structures for the quantitative evaluation. We also compute the standard deviation of the Jacobian to quantify the smoothness of the computed transformations. Before non-linear registration, a skull stripping and intensity bias correction was applied and all images were rigidly registered to the MNI152 atlas space [6]. Fig. 2 shows an example image and the associated labels. To analyze the influence of the building blocks of the registration algorithm each of the image pairs (in total 780) was registered with each combination of distance measure, regularizer and transformation space ($3 \times 4 \times 3 = 36$ combinations).

3 Results

Five randomly selected patient images were used to determine suitable registration parameters. We used 3 multi-resolution levels and a maximum of 300 iterations per level, other parameters are given in Table 1 (see [1] for explana-

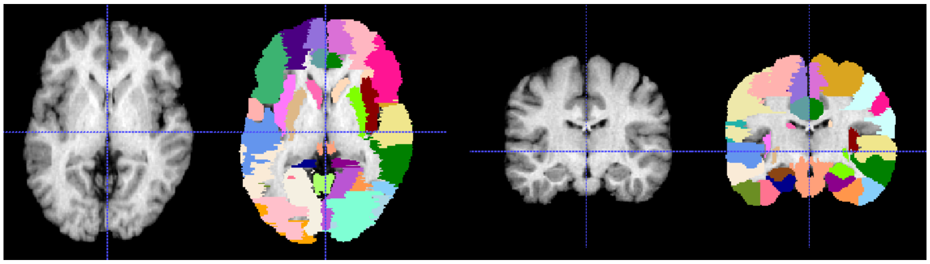

Fig. 2. An example image of the LPBA40 data set with labels used for the evaluation.

tions). Computation times largely depended on the exact algorithm configuration and vary between 5 and 40 minutes on a Quad Core PC.

Table 1 shows the Jaccard overlap coefficients and standard deviations of the Jacobian averaged over all labels and image pairs for the twelve combinations of regularizers and distance measures. Only results of the non-diffeomorphic transformation model are presented here due to space limitations. NCC-based registration has significant higher Jaccard values compared to SSD- and NSSD-based registration (paired t-test, $p < 0.0001$). Fig. 3 shows a comparison of the best performing algorithm for each of the three distance measures together with the 14 registration algorithms analyzed in [2].

4 Discussion and Conclusion

We presented a flexible open-source toolbox for non-parametric variational image registration that is publicly available with ITK. The code design of the toolbox allows to easily combine and systematically investigate the building blocks of

	NCC		***SSD***		***NSSD***	
	Jaccard	$\sigma_{Jacobian}$	*Jaccard*	$\sigma_{Jacobian}$	*Jaccard*	$\sigma_{Jacobian}$
Curvature	55.9	0.55	53.6	0.44	50.8	0.58
	$(\tau = 40, \alpha = 1.0)$		$(\tau = 2.5e^{-6}, \alpha = 1.0)$		$(\tau = 1.0, \alpha = 5.0)$	
Elastic	55.4	0.39	55.3	0.27	54.2	0.30
	$(\tau = 30, \lambda = \mu = 0.1)$		$(\tau = 2.5e^{-6}, \lambda = \mu = 0.1)$		$(\tau = 1.0, \lambda = \mu = 0.5)$	
Diffusive	56.1	0.58	54.2	0.37	53.5	0.47
	$(\tau = 30, \alpha = 0.1)$		$(\tau = 2.5e^{-6}, \alpha = 0.2)$		$(\tau = 1.0, \alpha = 1.0)$	
Gaussian	55.3	0.57	53.6	0.44	53.4	0.52
	$(\tau = 40, \sigma^2 = 0.5)$		$(\tau = 1.0e^{-5}, \sigma^2 = 1.25)$		$(\tau = 1.0, \sigma^2 = 1.5)$	

Table 1. Jaccard coefficents and standard deviations of the jacobian ($\sigma_{Jacobian}$) for twelve combinations of distance measure and regularization approach. The values are averaged over all image pairs (Jaccard coefficents and $\sigma_{Jacobian}$) and all labels (Jaccard coefficents). Registration parameters are shown in brackets.

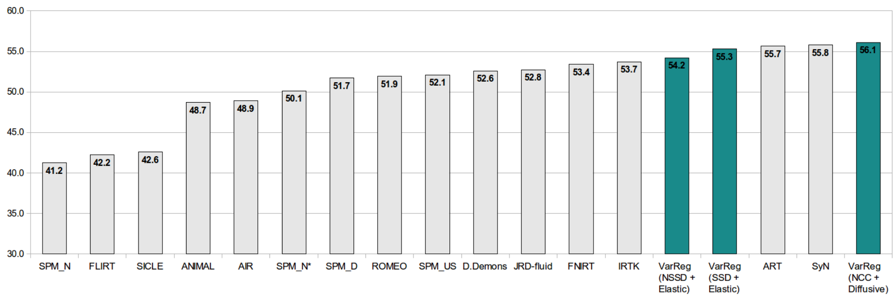

Fig. 3. Jaccard overlap (over 56 regions) for 17 registration algorithms for the LPBA40 data set. VarReg denotes algorithms from the *VariationalRegistration* toolbox, the 14 remaining algorithms were tested in [2].

variational registration algorithms, as well as to implement new components. Based on publicly available data sets, the toolbox was applied for intra-patient (see [1]) and inter-patient registration and an accuracy comparable to state-of-the-art algorithms has been proven.

Analyzing the results of the inter-patient registration of MR images shows that the NCC distance measure provides the best results, however, SSD and NSSD perform surprisingly well. The elastic regularizer generates smooth displacement fields while preserving a high registration accuracy. NSSD does not perform well with curvature regularization, whereas NCC with curvature regularization combines high accuracy and smooth transformations.

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