In: Proc. of Medical Image Computing and Computer-Assisted Intervention (MICCAI'01), pp. 734 – 742
LNCS 2208. Utrecht, The Netherlands – October 2001

Multisubject Non-Rigid Registration of Brain MRI using Intensity and Geometric Features

Pascal Cachier[1], Jean-François Mangin[2], Xavier Pennec[1], Denis Rivire[2], Dimitri Papadopoulos-Orfanos[2], Jean Rgis[3], and Nicholas Ayache[1]

[1] Projet Epidaure, INRIA, Sophia-Antipolis, France
{Pascal.Cachier, Xavier.Pennec, Nicholas.Ayache}@inria.fr
[2] Service Hospitalier Frdric Joliot, CEA, Orsay, France
mangin@shfj.cea.fr
[3] Service de Neurochirurgie Fonctionnelle, CHU La Timone, Marseille, France

Abstract. In this article we merge point feature and intensity-based registration in a single algorithm to tackle the problem of multiple brain registration. Because of the high variability of the shape of the cortex across individuals, there exist geometrical ambiguities in the registration process that an intensity measure alone is unable to solve. This problem can be tackled using anatomical knowledge. First, we automatically segment and label the whole set of the cortical sulci, with a non-parametric approach that enables the capture of their highly variable shape and topology. Then, we develop a registration energy that merges intensity and feature point matching. Its minimization leads to a linear combination of a dense smooth vector field and radial basis functions. We use and process differently the bottom line of the sulci from its upper border, whose localization is even more variable across individuals. We show that the additional sulcal energy improves the registration of the cortical sulci, while still keeping the transformation smooth and one-to-one.

1 Introduction

While the goal of monosubject registration is somewhat clear and corresponds intuitively to the retrieval of motion, multisubject brain registration is an ill-posed problem because the topology of the brain, and especially the cortex, varies strongly from one individual to another. Geometrically, there is an ambiguity on which feature should be matched to a given feature. Therefore, intensity-based registration algorithms are expected to fail at least on some pathological cases.

These geometrical ambiguities can be partially resolved when using higher-level, anatomical knowledge. Indeed, the sulci of the cortex can be labelled, and for a number of labels (e.g. the central sulcus) we know that the associated sulcus has roughly the same position and topology for all brains, and are therefore landmarks that should be registered in any cases. Collins [3] extracts 2×16 (16 for each hemisphere) parametric sulcal ribbons, and adds a chamfer matching step in his intensity registration algorithm. Hellier [4] extracts 2×6 parametric sulcal ribbons, and adds the distance between homologous control points of these active surfaces to his registration energy, which underlies a strong assumption about the segmentation. Vaillant [13] inflates each cortex into a sphere, and then matches both spheres using the trace of a few sulci on the spheres as a constraint. Thompson [12] segments the cortex using balloon surfaces and 2×7 interactively outlined sulcal ribbons which are then matched together with the cortical surface. Chui [2] semi-automatically extracts 2×5 sulci of both hemispheres before matching them with a piecewise affine robust point-matching algorithm.

While the role of some major sulci as anatomical and even functional landmarks can be admitted [14, 15], some research still has to be done on the role of other minor sulci. Moreover, even the reliable manual or automatic identification of standard sulci for any brain is still an open issue, because of the variability of sulcus interruptions.

In this article, we present a new non-rigid matching algorithm using both intensity and sulcus matching. The whole set of the cortical sulci is first automatically extracted with a non-parametric approach, which enables the capture of the complex and variable topology of the sulci. They are then automatically labelled by a neural network using a set of 45 labels per hemisphere. We construct a registration energy made up of an intensity similarity measure, a geometric distance between sulcal points of the same label, and a regularization energy. The minimization of this energy leads to a transformation that is a combination of a dense smooth vector field and radial basis functions. We show that the introduction of the sulcal energy helps to better match the sulci, especially when the initial affine registration cannot match them well in the first place: this may happens because of the variability of the topology and the position of the sulci across individuals. Furthermore, we show that this improvement of matching does not deteriorate the smoothness and the bijectivity of the transformation.

2 Methodology

Intensity-based non-rigid registration algorithms have proven to be a fast and accurate way to achieve registration of volumetric images, at least in the case where the organs to be registered have approximately the same geometry. Our intensity-based algorithm uses the following generic registration energy:

$$E(C,T) = E_{sim}(I,J,C) + \sigma ||C - T||^2 + \sigma \lambda E_{reg}(T) \qquad (1)$$

where I and J are two images to register, C and T are non-parametric transformations (C pairs homologous points according to the similarity measure, T is the smooth estimate of the non-rigid transformation), E_{sim} is an intensity similarity energy and E_{reg} a regularization energy or physical model. The attractive behavior and properties of this form of registration energy is extensively discussed in [1].

In the case of the registration of two different brains, the intensity constraint is not sufficient anymore, especially if we are interested in the cortex, because there is an ambiguity on which sulci should be matched to a given sulcus. These anatomical decisions are far beyond the capacity of an intensity similarity measure.

To resolve these ambiguities, we introduce geometric features in the images and mix geometric and intensity matching. The geometric features are labelled segmentations of the bottom and border lines of sulci, which contain a strong anatomical *a priori* knowledge.

2.1 Sulci extraction

The sulci are first automatically extracted from an MRI. The main steps of the process segmenting the sulci are [8]: ① Non-uniform bias correction; ② Segmentation of grey matter/CSF; ③ Homotopic skeletonization; ④ Splitting into simple surfaces.

These surfaces are then automatically labelled with the algorithm of Rivire [10], using a set of 90 labels. This algorithm uses a neural network trained on a manually-labelled set. The informations used by the neural network to label a sulcus is both intrinsic (size, depth, localization, etc. of the sulcus) and relational (number of neighbors, minimal distance, etc. with neighboring sulci).

The computed error rate of the algorithm is about 24%. However, errors are partly due to an actual ambiguity of the labelization on some areas of the cortex, and to errors of the manual labelization done by the expert to build the training data set. Sometimes, the result found by the neural network actually seems more coherent than the labels found manually by the expert.

From these surfaces, we then extract two one-dimensional features (fig. 1), defined from discrete topology [6]:

- The sulcal bottom, which is the edge of the sulcus deep in the brain;
- The sulcal border, which is the outside edge of the sulcus and correspond to its junction with the hull of the brain.

Note that because we use non-parametric sulci, and also because several cortical folds may have the same label, a sulcus may have a very complex topology.

The use of the sulcal bottom lines as a geometrical feature for registration is driven by anatomical and computational considerations.

On an anatomical point of view, a theory has risen that the sulcal bottom lines are more stable anatomical landmarks than the sulci themselves. These lines, indeed, correspond to the shallow creases that appear on the foetal brain during the beginning of the cortical folding process. These lines are very stable across individuals because they delimit the main functional areas of the human brain [15, 9]. The rest of the sulci, however, is more difficult to match across individuals, because the sulcus border localization on the cortical surface depends on the local extent of the folding process, which varies with the subjects. This interpretation also explains the presence or absence of secondary folds or branches around the main sulcus.

On a computational point of view, the use of one-dimensional features drastically reduces the number of points to be processed and hence improves the speed of the algorithm.

The use of the sulcal borders helps the intensity-based algorithm to match the entire sulcus, not only its bottom. However, to follow the anatomical understanding of the folding process mentioned above, we want them to help the registration only if they are distant. Hence, the matching of sulcal borders is looser than for sulcal bottoms.

Given a label ℓ, $1 \leq \ell \leq 90$, we note $\mathcal{S}_\ell(I)$ the set of points of the image I classified as belonging to the sulcus ℓ. We note $\mathcal{S}_\ell^\downarrow(I)$ the subset of points of $\mathcal{S}_\ell(I)$ making up its sulcal bottom, and $\mathcal{S}_\ell^\uparrow(I)$ those belonging to the sulcal border. Finally, we note $\mathcal{S}(I) = \bigcup_\ell \mathcal{S}_\ell^\downarrow(I) \cup \mathcal{S}_\ell^\uparrow(I)$.

2.2 Registration using intensity and geometric features

Given two brain MR images I and J, we do not want to perfectly register the sulci $\mathcal{S}_\ell^\downarrow(I)$ and $\mathcal{S}_\ell^\downarrow(J)$ (or sulcal borders $\mathcal{S}_\ell^\uparrow(I)$ and $\mathcal{S}_\ell^\uparrow(J)$) because:

1. $\mathcal{S}_\ell^\downarrow(I)$ and $\mathcal{S}_\ell^\downarrow(J)$ may have very different topologies, e.g. the number of creases or branches. Sometimes, the same sulcus can even be made of one part in one brain, and two parts in the other: an exact matching would require the creation of an additional fold, which implies discontinuities in the deformation field on the cortex. Therefore, we want to get them as close as possible without actually totally map one onto the other. A partial matching is often the intuitive solution, as if one of the sulcus has grown further than the other.
2. The neighbors of a given sulci are not always the same for all brains. Matching two sulci that do not have the same neighboring relation in both brains would also lead to discontinuities in the deformation field on the cortex. Look at labelled brains in [10] for an illustration of these two first points.
3. On top of that, there exits a problem of robustness due to the errors in the automatic labelization. Therefore $\mathcal{S}_\ell^\downarrow(J)$ might not be the corresponding feature of $\mathcal{S}_\ell^\downarrow(I)$.

To integrate sulcus matching in our algorithm, we generalize the registration energy (1) by introducing a second set of correspondences C_2 between points of both images located on a landmark with the same label ℓ, i.e. $\forall \mathbf{x} \in \mathcal{S}_\ell^\downarrow(I)$, $C_2(\mathbf{x}) \in \mathcal{S}_\ell^\downarrow(J)$ (and similarly for $\mathbf{x} \in \mathcal{S}_\ell^\uparrow(I)$). We now set

$$E(C_1, C_2, T) = E_{sim}(I, J, C_1) + \sigma||C_1 - T||^2 + \sigma\gamma||C_2 - T||^2 + \sigma\lambda E_{reg}(T) \quad (2)$$

where in the following $E_{sim}(I, J, C_1) = \int(I - J \circ C_1)^2$, $E_{reg}(T)$ is a quadratic energy whose impulse response is a Gaussian, and γ is a trade-off coefficient between intensity matching and sulcal matching. The minimization of this energy with respect to C_1, C_2 and T leads to a 3-step algorithm:

1. Minimize $E_{sim}(I, J, C_1) + \sigma.||C_1 - T||^2$ w.r. to C_1, i.e. find dense correspondences C_1 between voxels according to the intensity information.
2. Minimize $||C_2 - T||^2$ w.r. to C_2, i.e. find corresponding points C_2 between sulci with the same label ℓ closest to T with a closest point algorithm.

3. Fit T to C_1 and C_2 by minimizing $||C_1 - T||^2 + \gamma.||C_2 - T||^2 + \lambda.E_{reg}(T)$ w.r. to T. T is thus of the form
$$T(\mathbf{x}) = \alpha G * C_1(\mathbf{x}) + \sum\nolimits_{\mathbf{x}_i \in \mathcal{S}(I)} \boldsymbol{\alpha}_i G(\mathbf{x} - \mathbf{x}_i)$$
where G is the impulse response of the filter associated to E_{reg}, in our case a Gaussian, $\alpha \in \mathbb{R}$ and $\boldsymbol{\alpha}_i \in \mathbb{R}^3$, $\forall i$. (See [1] for technical details).
4. Go back to the first step until convergence.

We will however slightly modify this third step, as it would need the fitting of radial basis functions (RBF) at typically 2000 points at each iteration, which implies the inversion of a consequently huge matrix, and also because the errors of labelization and the topology variability, as previously discussed, imply the use of a robust fitting. A sulcal point $\mathbf{x}_i \in \mathcal{S}_\ell^{\{\downarrow,\uparrow\}}(I)$ being associated to another sulcal point $C_2(\mathbf{x}_i) \in \mathcal{S}_\ell^{\{\downarrow,\uparrow\}}(J)$, we associate to $\mathbf{x}_i$ the RBF $\alpha_i[C_2(\mathbf{x}_i) - T(\mathbf{x}_i)]G(\mathbf{x} - \mathbf{x}_i)$, where $\alpha_i \in \mathbb{R}$ a multiplicative coefficient which is equal to

- 1 if $\mathbf{x}_i$ belongs to a small set of 30 sulci for which we have a confident labelization for all brains,
- $\exp(-||C_2(\mathbf{x}_i) - T(\mathbf{x}_i)||^2/\beta)$ otherwise, β being a cut-off distance above which we decide that two points cannot be homologous, which may help both for labelization and topological problems.

We furthermore multiply α_i by $1 - \exp(-||C_2(\mathbf{x}_i) - T(\mathbf{x}_i)||^2/\beta_2)$, $\beta_2 < \beta$, if $\mathbf{x}_i$ belongs to a sulcal border, because the localization of these features on the cortical surface are not as accurate as for the sulcal bottom.

The final estimate transformation is then a weighted average of the fitting of intensity and feature points:
$$T(\mathbf{x}) = \lambda G * C_1(\mathbf{x}) + (1 - \lambda).\frac{\sum_i \alpha_i.[C_2(\mathbf{x}_i) - T(\mathbf{x}_i)].G(\mathbf{x} - \mathbf{x}_i)^2}{\sum_i G(\mathbf{x} - \mathbf{x}_i)}$$
where λ is a trade-off coefficient between intensity and feature matching. All the parameters λ, β, β_2 are chosen *a priori*. Before registration, we applied an anisotropic diffusion to the images, and carefully removed their bias [7] to use the SSD. The whole registration process is also set in a multiresolution scheme which helps preventing from local minima.

3 Experiments

We have run our multisubject registration on a set of 5 labelled brains. One of the brains have been arbitrarily chosen as the reference brain, and we have registered the other brains on it, using a robust affine registration [11] (also used as an initial alignment for non-rigid registration), and our non-rigid algorithm without and with the sulcus matching.

The results of the registrations, for a manually-chosen set of registration parameters, is given in fig. 2. The intensity-based method is able to match the sulci

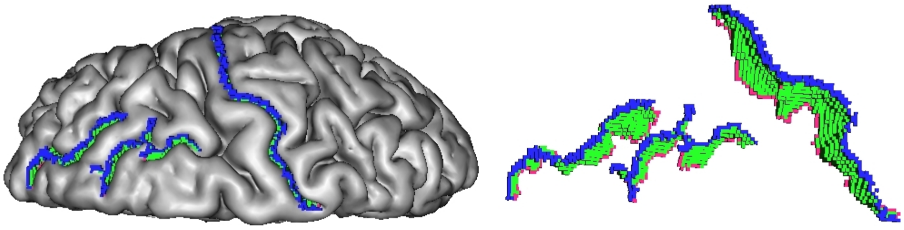

Fig. 1. *Three segmented sulci $\mathcal{S}$ in green, and their associated sulcal bottom $\mathcal{S}^{\downarrow}$ in red and sulcal border $\mathcal{S}^{\uparrow}$ in blue.*

when their topology is simple (i.e. mostly linear) and the initial affine registration is good. For example, the central sulci in red are generally matched; however, for one the brain, the central sulcus is relatively backwards, and a part of the precentral sulcus initially matches the central sulcus of the reference brain after

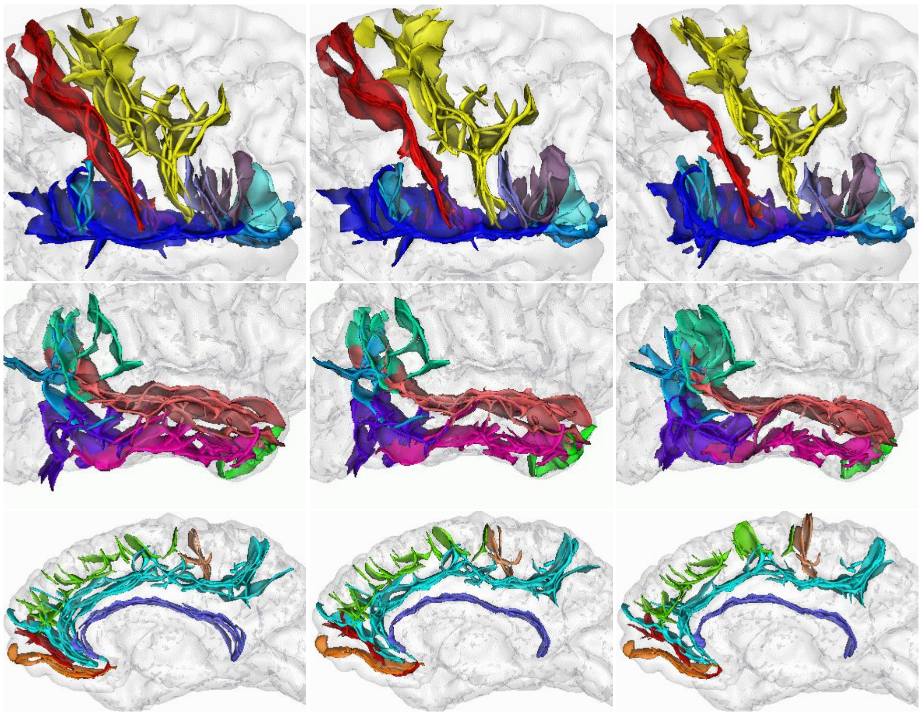

Fig. 2. *Position of the sulci after affine registration (left column), and after non-rigid registration without (middle column) and with (right column) sulcus matching. The sulcus matching helps to pair homologous sulci when they are initially far apart, and also improves the precision of the matching especially when the topology of the sulci is complex.*

affine registration: in this case the precentral sulcus stays at its original position if we register them using intensities only, but they are correctly registered using the additional sulcus matching. Sulcus matching also helps to more efficiently register sulci with complex topology such as the precentral sulcus, and generally improves the accuracy of the matching of all sulci.

Authors working on multisubject registration often omit to present the transformation itself. However, it is very important to make sure that the registration is smooth and bijective, especially in multisubject registration where the topology preservation is more than ever in competition with the matching of sulci. Presenting the position of the registered sulci is only one aspect of the non-rigid registration; the other is the smoothness of the transformation, and it is always possible to have a better sulci registration by deteriorating the smoothness and the topology. Here, the sulcal matching is done without deteriorating the smoothness and the bijectivity of the transformation: the Jacobian of the transformation is always positive, except for some points outside of the brain where there are boundary effects or occlusion problems due to the initial affine registration. Fig. 3 gives an idea of the quality of the estimated transformation for the four multisubject registrations.

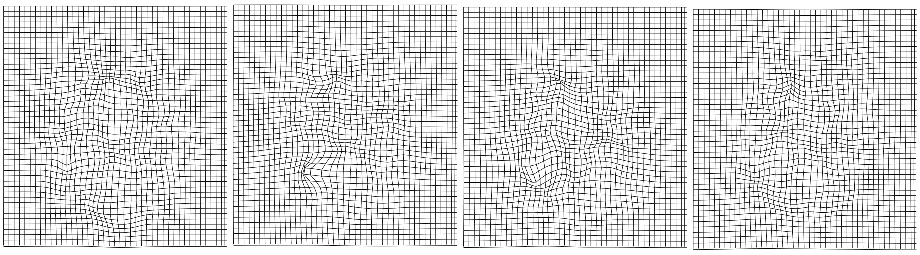

Fig. 3. *Estimate of the transformation at an arbitrary axial slice, for the 4 multisubject brain registration. Despite the additional sulcus matching, the recovered transformation is still smooth and one-to-one.*

4 Conclusion

In this work, we presented a registration energy that merges intensity and point feature registration. Its minimization leads to a linear combination of a dense smooth vector field and radial basis functions. We have adapted this energy to the robust matching of sulcal bottoms and borders of the brain, which are automatically extracted in a non parametric way and labelled, for all the creases of the cortex. We show that this additional information helps the algorithm to register homologous sulci while keeping the estimated transformation very smooth and one-to-one.

An extension of this work will consist in using a more detailed labelling of the sulcal patterns using the sulcal root model [9, 5]. Sulcal roots correspond to elementary creases always appearing on the foetal brain as only one connected component. Several studies tend to prove that sulcal roots may be identified in adult brains using variations of depth or curvature properties along sulcus bottoms. The simpler topology of these roots relative to standard sulci could allow us to use more stringent sulcal constraints in order to achieve a perfect matching of the folding patterns.

Another application of this work is the study of secondary folds after registration in order to discover stable patterns across individuals that could improve the description of the human cortex.

References

1. P. Cachier and N. Ayache. Regularization in Image Non-Rigid Registration: I. Trade-Off between Smoothness and Similarity. Technical Report RR-4188, INRIA, 2001.
   `http://www.inria.fr/rrrt/`.
2. H. Chui, J. Rambo, J. Duncan, R. Schultz, and A. Rangarajan. Registration of Cortical Anatomical Structures via Robust 3D Point Matching. In *Proc. of IPMI'99*, number 1613 in LNCS, pages 168 – 181, Visegrd, Hungary, June 1999.
3. D. L. Collins, G. Le Goualher, and A. C. Evans. Non-Linear Cerebral Registration with Sulcal Constraints. In *Proc. of MICCAI'98*, volume 1496 of *LNCS*, pages 974 – 984, Cambridge, USA, October 1998. Springer.
4. P. Hellier and C. Barillot. Coupling Dense and Landmark-Based approaches for Non Rigid Registration. Technical Report 1368, IRISA, November 2000.
5. G. Lohmann and D. Y. von Cramon. Automatic Labelling of the Human Cortical Surface using Sulcal Basins. *Medical Image Analysis*, 4(3):179 – 188, 2000.
6. G. Malandain, G. Bertrand, and N. Ayache. Topological Segmentation of Discrete Surfaces. *Int. J. of Comp. Vision*, 10(2):158 – 183, 1993.
7. J.-F. Mangin. Entropy minimization for automatic correction of intensity nonuniformity. In *Proc. of MMBIA'00*, pages 162 – 169, 2000.
8. J.-F. Mangin, V. Frouin, I. Bloch, J. Regis, and J. López-Krahe. From 3D MR images to structural representations of the cortex topography using topology preserving deformations. *J. of Math. Imaging and Vision*, 5(4):297 – 318, 1995.
9. J. Rgis, J.-F. Mangin, V. Frouin, F. Sastre, J. C. Peragut, and Y. Samson. Generic Model for the Localization of the Cerebral Cortex and Preoperative Multimodal Integration in Epilepsy Surgery. *Stereotactic Functional Neurosurgery*, 65:72 – 80, 1995.
10. D. Rivire, J.-F. Mangin, D. Papadopoulos, J.-M. Martinez, V. Frouin, and J. Rgis. Automatic Recognition of Cortical Sulci using a Congregation of Neural Networks. In *Proc. of MICCAI'00*, volume 1935 of *LNCS*, pages 40 – 49, Pittsburgh, USA, October 2000. Springer.
11. A. Roche, G. Malandain, and N. Ayache. Unifying Maximum Likelihood Approaches in Medical Image Registration. *Int. J. of Imaging Systems and Technology*, 11:71–80, 2000.
12. P. Thompson and A. W. Toga. A Surface-Based Technique for Warping 3-Dimensional Images of the Brain. *IEEE Trans. on Medical Imaging*, 15(4):402–417, 1996.
13. M. Vaillant and C. Davatzikos. Hierarchical Matching of Cortical Features for Deformable Brain Image Registration. In *Proc. of IPMI'99*, volume 1613 of *LNCS*, pages 182 – 195, Visegrd, Hungary, June/July 1999. Springer.
14. J. D. G. Watson, R. Myers, and R. Frackowiak *et al.* Area (V5) of the human cortex: evidence from a combined study using positron emission tomography and magnetic resonnance imaging. *Cerebral Cortex*, 3:79–94, 1993.

15. W. Welker. Why does the cerebral cortex fissure and fold. *Cerebral Cortex*, 8B:3 – 135, 1989.