Symmetric image normalization for mouse brain magnetic resonance microscopy

Zhenrong FU[1,a], Lan LIN[1,b]*, and Cong Jin[1,c]

[1]College of Life Science and Bio-engineering, Beijing University of Technology, Beijing 100124, China

[a]email: fuzhenrongbest@126.com, [b]email: lanlin@bjut.edu.cn,

[c]email: jc15210371024@163.com

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Abstract. Various genetic mouse models have been used to understand aspects of the biology of the neurodegenerative disease. A rapid growth of data collection from the mouse brain has put image registration, a key prerequisite step for brain image analysis in great focus. SyN (symmetric image normalization method) is one of the most performed diffeomorphic strategies which has been widely used in human brain mapping. In this study, we optimized the SyN strategy for tiny mouse brain. The optimized protocol is able to accurately remove the anatomical variability between mouse brain MR microscopy (MRM) and offers superior performance over the SyN protocol for human.

Introduction

A rapid growth of brain image collection from the mice has taken place recently, strengthened by the extensive use of genetic mice for various types of brain research [1]. Inter-subject image registration technique is one of the most significant prerequisite steps that establishes a one-to-one correspondence between two brains. It is well established that linear registration is inadequate for inter-subject registration, especially between normal and lesioned or diseased mice. Various automated nonlinear algorithms have been proposed for human study, such as HAMMER [2], SPM5 [3], SPM-DARTEL [4], SPM-Shooting [5], Demons [6], FFD [7], SyN [8], et al. The performance of those methods have also been evaluated [9,10]. However, most of those methods are specially designed or optimized for human brain, and special tuning is necessary to make them work for tiny mouse brain.

The animal experiment plays an irreplaceable role in medical research, because of it maneuverability, easier usability, et al. At present, the MRI has been widely used in clinical. As the technology innovation, MR microscopy (MRM) which can be used for studying mouse brain has “borned”. Because of its 3D characteristic and high resolution, it is possible to analysis the mechanism of the structures and functions of mouse brain.

SyN is a kind of registration algorithms based on ANTs(Advanced Neuroimaging Tools) [11], which have showed great performance on human brain mapping(http://stnava.github.io/ANTs/). SyN has showed some advantages compared with the other algorithms mentioned above. The Exponential Mapping approach as SPM-DARTEL is achieved by controlling the velocity field time-invariant. The algorithms based on elastic or related such as HAMMER, Demons, FFD,SPM5 can’t keep topology persevering. SyN is a symmetric diffeomorphic normalization, which is more robust than SPM-Shooting that is only symmetric in theory.

In this paper, we first briefly introduced the SyN registration approach; then discussed how we optimized it for mouse brain; and finally, we evaluated the performance of the optimized protocol.

Data acquisition

The mouse MRM (five in vivo male C57BL/6 mice) used in this study is shared by the computational functional anatomy lab, National University of Singapore (http://www.bioeng.nus.edu.sg/cfa/mouse_atlas.html). The brain images have been manually

labeled to 39 neuroanatomical structures based on Franklin–Paxinos atlas [12]. The 3D T_2-weighted images were acquired [13] on a Bruker 7-T/20-cm ClinScan MRI. Turbo spin echo TR=2000 ms, TE=46ms, FOV=9mm*13mm*25mm, matrix size=88*140*256, echo train length=13. The intensity-inhomogeneity was corrected and the image intensity was normalized to the range of 0~255. The research based on the data has published.

SyN Registration algorithm

The transformation based on vector field may change the brain topology, a advantage of the transformation based on velocity field is the preservation the topology. Here, ϕ is assumed as the diffeomorphism,Ω is the image domain. Through Eq. 1, integration a time varying and smooth velocity field $v : \Omega \times t \rightarrow \mathbb{R}^d$, obtained a series of diffeomorphisms $\phi(x,t) : \Omega \times t \rightarrow \Omega$

$$\frac{d\phi(x,t)}{dt} = v(\phi(x,t),t), \phi(x,0) = x. \quad (1)$$

The deformation created depend on ϕ is $u(x) = \phi(x,1) - x$.

LDDMM(large deformation diffeomorphic metric matching) [14] is the primary widely used diffeomorphic registration for brain, it used Eq. 2 to take it gradient descent optimization strategy, v^* is used to indicate the optimization of the time-dependent velocity field.

$$v^* = \text{argmin}_v \left\{ \int_0^1 \|Lv\|^2 \, dt + \lambda \int_\Omega \Pi(I, \phi(x,1), \Gamma) d\Omega \right\} \quad (2)$$

Π is a similarity metric, which is depend on the image properties and the mapping. Then λ is used for control the matching accuracy. Γ and I are the different instance of anatomicals. L is an appropriate norm.

Here, the diffeomorphism ϕ is capable of disassembled in two components, $\phi_1$and ϕ_2. Therefore, generating the Eq. 3, a symmetric variant of Eq. 2

$$\{v_1^*, v_2^*\} = \text{argmin}_{v_1, v_2} \left\{ \int_0^{0.5} (\|Lv_1(x,t)\|^2 + \|Lv_2(x,t)\|^2) dt + \lambda \int_\Omega \Pi\left(I(\phi_1(x,0.5)), \Gamma(\phi_2(x,0.5))\right) d\Omega \right\} \quad (3)$$

There are two kinds of SyN algorithms in ANTs tookit, the time-varying SyN which is theoretical close to the optimal Eq. 3. The greedy SyN is a fast approach of time-varying SyN, the gradient is calculated only at the mid-point of the global diffeomorphism.

As it defines, the time-varying SyN computes the gradient all the time in $t \in [0,1]$ of the global diffeomorphism, which the optimization Eq. 4 is:

$$\text{gradient}: \quad \nabla E(x,t) = \partial_{\phi_i} \Pi\left(I\left(\phi_1^{-1}(x,t)\right), \Gamma\left(\phi_2^{-1}(x,1-t)\right)\right)$$

$$\text{update}: \quad v(x,t) = v(x,t) + G_\sigma \star \nabla E(x,t) \quad (4)$$

Where, σ represent the Gaussian of variance, smoothness the gradient step. $i \in \{1,2\}$.

Because the intensive time gradient, time-varying SyN is more computational expensive, while it generates more accurate registration than greedy SyN. In human study, the greedy SyN is accurate enough for most analysis.

Optimizing strategy

The mouse brain MRM is different from human brain MRI. The signal to noise ratio (SNR) is poor, morphological change is more subtle, and brain anatomy is quite different [15], which raise the question to existing registration algorithms. The performance of SyN registration is subject to several adjustable parameters(regularization, similarity measures in transformation, transformation model, iterations and window radius). The speed/accuracy trade-off is the balance among most of those parameters. We chose those factors to value accuracy over speed, but allowing the computational time not to be prohibitively expensive.

Keliven, et al [10] have optimized the SyN (regularization [2, 0], similarity measures in

transformation [MI PR], transformation model [0.5], iterations [30, 99, 11], window radius 2) for human brain MRI registration and achieved good performance. Regularization is an important component in transformation model. The default value is [3, 0.5], which means that a Gaussian filter with variance of 3 voxel size smoothes the similarity gradient and a Gaussian filter with variance of half voxel size smoothes the deformation field. Increasing the first parameter(σ in Eq. 4) will increase the smoothness of the gradient, on the contrary , decreasing it will reduce the smoothness. The second value works on deformation field for smoothness. According to Avants et al.'s study [16], using MI(Mutual Information) for affine registration and CC(Cross Correlation) for SyN offer the best performance. So we chose [MI CC] as similarity measures for transformation. For time-varying SyN, the first parameter (∇E in Eq. 4) is ranged from 0.1 to 1, which depends on the property of the issue, the regularization parameters and the data we choose. The second parameter time step is fixed at 2. The third parameter the integration time discretization step, lower is more accurate. If we need to increase the second parameter of the regularization, we must increase the corresponding gradient step size. After a great deal of experiments, we set the parameters of SyN at [1, 2, 0.05]. The window radius value in the CC option was set to 4, which is balanced between computation time and accuracy. The iteration parameters is the multi-resolution optimization parameters, the first parameter indicates the max iterations at coarsest resolution (here, reduce by power of 2); the second parameter means the middle resolution iterations (here, reduce by power of 2); the third parameter represents the fine resolution iterations (here, full resolution), this level takes much more time per iteration. The affine transform we use the default value 10000*10000*10000 and the nonlinear transform we use the optimized parameters as 100*100*30. These values can ensure the quality of the registration.

Quantitative assessment of registration

Each mouse was used as the reference image, the other four mice were used as moving images. SyN was first used to transform moving images to the reference image, then inversed deformation is used to map 39 segmented brain regions from reference space to moving image space. There are total 10 registrations. The nearest neighbor interpolation is used to preserve the intensity of ROIs.

IS(Index Similarity) [17] was used to calculate the overlap values between the transformed ROIs and the ROIs in the original space, The computed formula is:

$$\mathrm{IS}(\mathrm{L_A}, \mathrm{L_M}) = \frac{2\mathrm{V}(\mathrm{L_A} \cap \mathrm{L_M})}{\mathrm{V}(\mathrm{L_A}) + \mathrm{V}(\mathrm{L_M})} \times 100\% \quad (5)$$

$\mathrm{V}(\mathrm{L})$ is the volumes for one of the ROIs.

The two-tailed paired t test was used for comparing the mean values of VOP among affine algorithm, SyN with optimized setting for human, SyN with optimized setting for mouse.

Results

Fig.1 showed the of brain 39 structures. The mean IS for affine registration is 62.78%, the mean IS for SyN with optimized setting for human is 64.89%, and SyN with optimized setting for mouse is 76.63%. The SyN optimized protocol for mice has a 22.06% improvement compared with affine registration and 18.09% improvement compared with SyN optimized protocol for human. The standard deviations of for three approaches are 9.41%, 2.79%, 9.07%, the optimized protocol for human, the optimized protocol for mice and the affine registration. Compared with the optimized for human and the affine registration, the optimized for mouse has a decline of 70.35% and 69.23%. The optimized protocol for SyN has big improvements, especially for those small brain structures. The two-tailed paired t test indicated that there is a significantly different of IS between our optimized mouse protocol and the optimized protocol for human ($P<0.001$). A word of clarification here, the optimization for human brain use the greedy SyN as the transformation model, a fast approach of time-varying SyN as we elaborate before. The IS over 80% of the optimized for human, the affine registration and the optimized for mice are 20.51%, 10.25%, 46.15%.

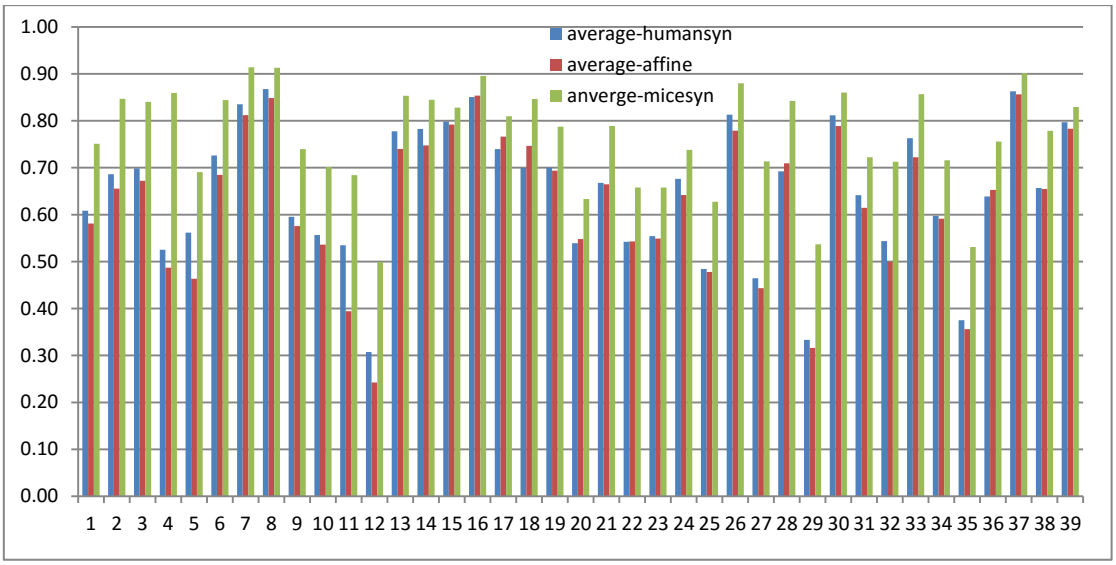

Figure 1 Segmentation accuracy comparison of different registration algorithm optimization strategy for SyN algorithm and the affine transformation. The region 1 to 39 represents the structures as: Corpus Callosum, Lateral Ventricle, Third Ventricle, Cerebral Aqueduct, Fourth Ventricle, Periaqueductal Gray, Medulla, Pons, Cerebellar Lobules, Cerebellar Cortex, Anterior Commissure, Lateral OlfactoryTract, Olfactory System, Frontal Cortex, Visual, Auditory, Somatosensory, Motor Cortex, General Region of the Cortex, Perirhinal Cortex, Entorhinal Cortex, Hippocampus-CA1 Region, Hippocampus-CA3 Region, Dentate Gyrus, General Region of Hippocampus, Superior and Inferior Colliculus, Pituitary, Hypothalamus, Optic Nerve, Caudoputamen, General Basal Ganglia, The Fornix System, Septum, Internal Capsule, Cerebral peduncle, SubstantiaNigra, Thalamus, Amygdala, General region of the midbrain.

Conclusion

In mouse brain MRM analysis, registration technique is essential and very important. It has a great relationship with the segmentation accuracy. In this study, we introduce the SyN diffeomorphic transformation model into mouse brain registration and achieve a good performance. Finally, our work has make significant contribution to the mouse brain registration which it is a fundamental for the mouse neuroimage analysis, whatever the research on neuropathology or brain network et al.

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