

## S2 Appendix

### Registration Algorithm

Image registration is the process of estimating the transformation between two images in order to align them in a single coordinate system. The algorithm is called deformable image registration (DIR) when the images need to be transformed in a deformable manner, typically with a deformation field. This is the case of images with internal organs of the human body acquired during breathing motion.

DIR is expressed as computing the diffeomorphic mapping  $\varphi(x)$  of the moving image  $I_1$  into the reference image  $I_0$ . The registration problem can be posed as a cost- or

energy optimization problem involving a similarity metric  $E_M$  and a regularization term  $E_R$ , such as:

$$\varphi^*(x) \equiv \arg \min_{\varphi(x)} \underbrace{E_M(I_0, I_1 \circ \varphi(x)) + E_R(\varphi(x))}_{\equiv E(\varphi(x))} \quad (3)$$

Where:

$$\varphi(x) : \Omega_0 \rightarrow \Omega_1, x \in \Omega, \Omega \subset \mathbb{R}^d,$$

$$I_j : \Omega_j \rightarrow \mathbb{R}, \forall j \in \{0, 1\}.$$

Avants et al. [1] introduce Symmetric Image Normalization (SyN) a DIR algorithm. The algorithm is available with ANTs toolbox [2] and supported by ITK toolbox [3].

SyN algorithm uses cross correlation as the similarity metric  $E_M$  defined as:

$$E_M(I_0, I_1 \circ \varphi(x)) = CC(I_0, I_1, \varphi(x)) \equiv \frac{\left( \sum_{x \in \Omega_0}^n (I_0(x) - \bar{I}_0) \cdot (I_1 \circ \varphi(x) - \bar{I}_1) \right)^2}{\sum_{x \in \Omega_0}^n (I_0(x) - \bar{I}_0)^2 \cdot \sum_{x \in \Omega_0}^n (I_1 \circ \varphi(x) - \bar{I}_1)^2} \quad (4)$$

The regularization  $E_R$  is defined as the Sobolev norm of the velocity field  $v_t$ , similar to the term proposed by Beg et al. [4]. The velocity field is related to the deformation field  $\varphi(x)$  with the ordinary differential equation  $\frac{d\phi_t(x)}{dt} = v_t(\phi_t(x), t)$ , with solution  $\varphi(x) = \phi_0 + \int_0^1 v_t(\phi_t(x))dt$ . In order to address consistency and reduce computation time, SyN algorithm divide the deformation field in two, such as:  $\varphi(x) = \phi_1 \circ \phi_2^{-1}(x, t)$ . Consequently, the regularization term involves two velocity fields. The mathematical setup is expressed as follows:

$$E_R(\varphi(x)) = \int_0^1 \|v_t\|_L^2 dt = \int_{t=0}^{0.5} (\|v_1(x, t)\|_L^2 + \|v_2(x, t)\|_L^2) dt \quad (5)$$

Where:

$L = a\nabla + bId$ , is a linear differential operator that induces regularity.

The optimization in SyN is described by the minimization of the energy equation:

$$\varphi^*(x) \equiv \arg \min_{\varphi(x)} \underbrace{\int_{t=0}^{0.5} (\|v_1(x, t)\|_L^2 + \|v_2(x, t)\|_L^2) dt + \int_{\Omega} CC(I_0, I_1, \varphi(x))d\Omega}_{\equiv E(\varphi(x))} \quad (6)$$

## References

1. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Medical image analysis. 2008;12(1):26–41.

2. ANTs. Advanced Normalization Tools; 2021. Web Page:  
<http://stnava.github.io/ANTs/>.
3. ITK. Insight Segmentation and Registration Toolkit; 2021. Web Page:  
<https://itk.org/>.
4. Beg MF, Miller MI, Trouvé A, Younes L. Computing large deformation metric mappings via geodesic flows of diffeomorphisms. *International journal of computer vision*. 2005;61(2):139–157.