S4 Text – Gradients for Atlas Informed Model The minimization of the energy E_v of (12) in terms of the vector field is the LDDMM gradient of Beg [25]:

$$\nabla_v E_v(x,y) = \sum_i \int_{\mathbb{R}^2} K(x-x', y-y', z-z_i)|D\varphi_{t,1}| \left(I \circ \varphi_{t1} - I_0 \circ \varphi_t^{-1}\right) \nabla(I_0 \circ \varphi_t^{-1})(x', y', z_i)\big)\, dx'dy' \ . \quad (1)$$

Variation of the Image Matching Term: The variation of $\int (I - I_0 \circ \varphi^{-1})^2 dx$ via perturbation $\varphi \to \varphi^\varepsilon = \varphi + \varepsilon\delta\varphi$ requires the inverse perturbation $\delta\varphi^{-1} = -(d\varphi)^{-1}_{\varphi^{-1}}\delta\varphi|_{\varphi^{-1}}$, derived in (2) above. Then we have

$$\begin{aligned} \frac{d}{d\varepsilon}\int_{\mathbb{R}^3} (I - I_0 \circ \varphi^{\varepsilon-1})^2 dx|_{\varepsilon=0} &= 2\int_X (I - I_0 \circ \varphi^{-1})\nabla(I_0)|\varphi^{-1} \cdot (d\varphi)^{-1}_{|\varphi^{-1}}\delta\varphi_{|\varphi^{-1}})dx \\ &= 2\int_X (I \circ \varphi - I_0)(d\varphi)^{-1T}\nabla I_0|d\varphi| \cdot \delta\varphi dx \ . \end{aligned}$$

Rigid motion variations: Rigid motion minimization is standard for rigid registration in 2D and 3D images. Denoting $\|f_{\theta,t,z_i}\|^2 = \|J^R(\cdot, z_i) - I_0 \circ \varphi^{v^*-1}(\cdot, z_i)\|_2^2$ to represent each rigid registration norm-square minimization within each histological plane, then

$$\nabla_\theta \|f_{\theta,t,z_i}\|^2 = \int_{\mathbb{R}^2} 2 f_{\theta,t,z_i}(\cdot)\frac{\partial_\theta f_{\theta,t,z_i}}{\partial\theta} dxdy \ ;$$
$$\nabla_t \|f_{\theta,t,z_i}\|^2 = \int_{\mathbb{R}^2} 2 f_{\theta,t,z_i}(\cdot)\nabla_t f dxdy \ .$$

$$\nabla_{R,t}\ell(v,R;J) = \Big\langle \frac{1}{\sigma_{JI}^2}(I_{\varphi^{-1}}(x) - J(r(\theta,z)x + t(z))) - \frac{1}{\sigma_{JJ}^2}\frac{d^2}{dz^2}\left(J(r(\theta,z)x + t(z))\right) r(\theta,z), \nabla_X J(r(\theta,z)x + t(z))\Big\rangle + \frac{t(z)}{\sigma_{reg_t}^2} \quad (2)$$

$$\nabla_{R,r}\ell(v,R;J) = \Big\langle \frac{1}{\sigma_{JI}^2}(I_{\varphi^{-1}}(x) - J(r(\theta,z)x + t(z))) - \frac{1}{\sigma_{JJ}^2}\frac{d^2}{dz^2}\left(J(r(\theta,z)x + t(z))\right), \nabla_X J(r(\theta,z)x + t(z))R\begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} x\Big\rangle + \frac{\theta}{\sigma_{reg_r}^2} \quad (3)$$

where σ_{JI} is a weighting factor on the matching term between atlas and target.