CLAIMS

What is claimed is:

1. A computer-implemented method, comprising:

receiving a reference image of biological tissue;

receiving a displaced image of the biological tissue;

applying a normalization process to the reference image, resulting in a normalized reference image;

applying the normalization process to the displaced image, resulting in a normalized displaced image;

performing a first registration of the normalized displaced image relative to the normalized reference image, resulting in a group of parameters defining a coarse transformation and further resulting in a second displaced image;

supplying the normalized reference image to a machine-learning alignment model;

supplying the second displaced image to the machine-learning alignment model;

performing a second registration of the second displaced image relative to the reference image by applying the machine-learning alignment model to the reference image and the second displaced image, wherein the applying yields a deformation vector field representative of a registration transformation between the reference image and the second displaced image.

2. The computer-implemented method of claim 1, further comprising:

receiving reference spatial coordinates of spots within a first transcriptome profile of the biological tissue, the first transcriptome profile corresponding to the reference image, wherein each spot comprises one or more cells;

receiving displaced spatial coordinates of spots within a second transcriptome profile of the biological tissue, the second transcriptome profile corresponding to the displaced image;

performing, based on the coarse transformation, a first registration of the displaced spatial coordinates relative to the reference spatial coordinates, resulting in second displaced spatial coordinates of the spots within the second transcriptome profile; and

performing, based on the registration transformation, a second registration of the second displaced spatial coordinates of the spots within the second transcriptome profile.

3. The computer-implemented method of any one of claims 1 or 2, wherein the supplying the normalized reference image comprises:

generating a tiling of the normalized reference image, wherein the tiling of the normalized reference image consists of a first defined number of tile images; and

supplying, in sequence, each tile image of the tiling of the normalized reference image to the machine-learning alignment model.

4. The computer-implemented method of claim 3, wherein the supplying the second displaced image comprises:

generating a tiling of the second displaced image, wherein the tiling of the second displaced image consists of a second defined number of tile images, the second defined number being equal to the first defined number; and

supplying, in sequence, each tile image of the tiling of the second displaced image to the machine-learning alignment model, wherein a first tile image of the tiling of the second displaced image is supplied concurrently with a first tile image of the tiling of the normalized reference image;

wherein the first tile image of the tiling of the second displaced image spans a section of the second displaced image, and wherein the first tile image of the tiling of the normalized reference image spans a section of the tiling of the normalized reference image, and

wherein the section of the second displaced image and the section of the normalized reference image are identical to one another in terms of placement and size.

5. The computer-implemented method of claim 4, wherein the applying the machine-learning alignment model comprises applying the machine-learning alignment model to the first tile image of the tiling of the normalized reference image and the first tile image of the tiling of the second displaced image, and optionally

wherein the applying the machine-learning alignment model yields a first tile deformation vector field and a second tile deformation vector field, the method further comprising joining the first tile deformation vector field and the tile second deformation vector field to form, at least partially, the deformation vector field.

6. The computer-implemented method of claim 5, wherein each one of the first tile deformation vector field and the second tile deformation vector field and respective adjacent tile deformation vector fields have a defined region in common, the joining comprising:

determining, for each pixel within the defined region in common, a weighted average of one of the first tile deformation vector field or the second tile deformation vector field and one of the respective adjacent tile deformation vector fields overlapping at the pixel; and

assigning, for each pixel within the defined region in common, the weighted average to the deformation vector field.

7. The computer-implemented method of any one of the preceding claims:

wherein the coarse transformation is an affine transformation, and wherein the performing the first registration comprises determining the affine transformation between the normalized displaced image and the normalized reference image; and/or

wherein the machine-learning alignment model comprises a convolutional neural network (CNN) having an encoder module, a decoder module, and a field composition module configured to output the deformation vector field.

8. The computer-implemented method of any one of the preceding claims, wherein the normalization process comprises at least one of:

a first set of steps comprising:

receiving an input image of the biological tissue;

generating a tissue mask image for the input image; and

configuring non-tissue pixels in the tissue mask image as black pixels;

wherein the tissue mask image having black pixels constitutes a normalized input image; or

a second set of steps comprising:

receiving transcriptome profiling data corresponding to the input image;

generating, based on the transcriptome profiling data, a label map comprising a first label associated with multiple first pixels and a second label associated with multiple second pixels;

generating a contour map based on the label map, wherein a first contour in the contour map defines a boundary separating a subset of the multiple first pixels and a subset of the multiple second pixels;

identifying, within the normalized input image, particular pixels corresponding to the first contour;

updating the normalized input image by modifying respective values of the particular pixels, each value of the respective values arising from a linear combination of a first value from the normalized input image and a second value based on the transcriptome profiling data.

9. The computer-implemented method of any one of the preceding claims, wherein the machine-learning alignment model comprises a neural network comprising:

one or more first layers configured to extract features from the normalized reference image and the second displaced image, the one or more first layers being of a first type; and

one or more second layers configured to output the deformation vector field, the one or more second layers being of a second type.

10. A computer-implemented method, comprising:

generating, based on multiple pairs of training label maps, multiple pairs of training images, wherein each pair of the multiple pairs of training images comprises a training reference image and a training displaced image;

determining a solution to an optimization problem with respect to a loss function based on a similarity metric of a pair of training label maps and a deformation vector field representative of a registration transformation between a first training reference image and a first training displaced image in a pair of the multiple pairs of training images, wherein the solution defines an alignment model for registration of an evaluation displaced image of biological tissue relative to an evaluation reference image of the biological tissue.

11. The computer-implemented method of claim 10, wherein the determining the solution to the optimization problem comprises:

generating a current deformation field vector by applying a current alignment model to a first pair of training images, wherein the current alignment model is configured at a current iteration of the determining the solution to the optimization problem;

applying the current deformation field vector to a displaced label map of a first pair of training label maps, resulting in a registered displaced label map;

determining, based on (i) a reference label map of the first pair of training label maps, (ii) the registered displaced label map, and (iii) the current deformation field vector, a value of the loss function; and

generating, based on the value of the loss function, a next deformation field vector.

12. The computer-implemented method of claim 11, wherein the loss function comprises a Dice similarity coefficient and the gradient of the deformation vector field, wherein the gradient is weighted by a regularization factor.

13. The computer-implemented method of any one of claims 10-12, wherein the machine-learning alignment model comprises a neural network comprising:

one or more first layers configured to extract features from the normalized reference image and the second displaced image, the one or more first layers being of a first type; and

one or more second layers configured to output the deformation vector field, the one or more second layers being of a second type.

14. The computer-implemented method of any one of claims 10-13, wherein the generating the multiple pairs of training images comprises:

configuring labels for respective pixels spanning an area of a defined size; and

generating a base label map based on the configured labels, the base label map spanning the area of the defined size.

15. The computer-implemented method of claim 14, wherein the configuring comprises:

configuring multiple sets of simplex noise distributions within respective layers, each one of the layers corresponding to the area of the defined size, wherein a first set of the multiple sets comprises a first simplex noise distribution centered at respective positions within a first layer of the respective layers, and wherein a second set of the multiple sets comprises a second simplex noise distribution centered at respective positions within the second layer;

configuring multiple defined labels for each pixel within the area, each one of the multiple defined labels corresponds to a particular layer of the respective layers;

determining, using the multiple sets of simplex noise distributions, respective numerical weights for the multiple defined labels at a particular pixel within the area; and

assigning, to the particular pixel, a first label corresponding to a first numerical weight having the greatest magnitude among the respective numerical weights; and optionally

wherein the generating the base label map comprises merging the respective layers having labeled pixels into a single define layer defining the base label map; and optionally:

wherein the generating the multiple pairs of training images further comprises:

generating a reference label map by warping, using a first simplex noise field, the base label map; and

generating, based on the reference label map, a particular training reference image by:

configuring, at random, colors for respective labels in the reference label map, resulting in a colored image;

blurring the colored image, resulting in a blurred image; and

applying a bias field to the blurred image, the bias intensity field spanning the area of the defined size.

16. The computer-implemented method of claim 15, wherein the generating the multiple pairs of training images further comprises:

generating a displaced label map by warping, using a second simplex noise field, the base label map;

generating, based on the displaced label map, a particular training displaced image by:

configuring, at random, colors for respective labels in the second label map, resulting in a second colored image;

blurring the second colored image, resulting in a second blurred image; and

applying the bias intensity field to the second blurred image; and optionally

wherein the generating the multiple pairs of training images further comprises

configuring the particular training reference image and the particular training displaced image as pertaining to a particular pair of the multiple pairs of images.

17. The computer-implemented method of claim 16, further comprising configuring the reference label map and the displaced label map as pertaining to a particular pair of multiple pairs of training label maps.

18. A computer-implemented method, comprising:

generating, based on multiple pairs of training label maps, multiple pairs of training images, wherein each pair of the multiple pairs of training images comprises a training reference image and a training displaced image;

training, based on multiple pairs of label maps and the multiple pairs of training images, a machine-learning alignment model for registration of an evaluation displaced image of biological tissue relative to an evaluation reference image of the biological tissue, wherein the alignment model yields a deformation vector field representative of a registration transformation between the evaluation reference image and the evaluation displaced image;

receiving a particular reference image of the biological tissue and a particular displaced image of the biological tissue;

applying a normalization process to the particular reference image and the particular displaced image;

performing coarse registration of the normalized particular displaced image relative to the normalized particular reference image, resulting in a group of parameters defining a coarse transformation and further resulting in a second particular displaced image;

supplying the particular reference image and the second particular displaced image to the trained machine-learning alignment model;

performing fine registration of the second particular displaced image relative to the particular reference image by applying the machine-learning alignment model to the particular reference image and the second particular displaced image.

19. The computer-implemented method of claim 18, further comprising:

receiving particular reference spatial coordinates of spots within a first transcriptome profile of the biological tissue, the first transcriptome profile corresponding to the reference image, wherein each spot comprises one or more cells;

receiving particular displaced spatial coordinates of spots within a second transcriptome profile of the biological tissue, the second transcriptome profile corresponding to the displacement image;

performing, based on the coarse transformation, coarse registration of the particular displaced spatial coordinates relative to the particular reference spatial coordinates, resulting in second particular displaced spatial coordinates of the spots within the second transcriptome profile; and

performing, based on the registration transformation, fine registration of the second particular displaced spatial coordinates of the spots within the second transcriptome profile.

20. The computer-implemented method of any one of claims 18 or 19, wherein the training comprises determining a solution to an optimization problem with respect to a loss

function based on a similarity metric of a first pair of training label maps of multiple pairs of training label maps and a deformation vector field associated with a first training reference image and a first training displaced image in a pair of the multiple pairs of training images, wherein the solution defines the trained machine-learning alignment model.