Anatomically Guided Registration Of Whole Body Mouse MR Images

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Abstract. A new methodology for three-dimensional (3D) non-linear registration of articulate objects is presented. This approach is described in the context of a program to screen for mutant mouse phenotypes based on high resolution MR images of whole animals. This automatic screening process requires statistical definition of the normal (non-mutant) mouse anatomy and its variation. The registration algorithm is designed to remove postural differences between mice and thus enable meaningful comparisons between images. The main focus of our approach is anatomical content and its preservation under deformations. Prior knowledge guides the registration through an evolutionary process based on a hierarchical tree of mouse anatomy.

1 Introduction

The comprehensive study of the biological functions of genes has lead a number of centers around the world to start large scale mouse mutagenesis projects (Jackson Laboratory, Mouse Genome Centre at Harwell, RIKEN Genomics Sciences Center, to name the few). At CMHD, The Centre For Modeling Human Disease at Mount Sinai Hospital in Toronto, a genome-wide random mutagenesis is used for discovering new genes and creating new mouse models of human diseases. A set of primary physiological and behavioral screens is designed to parse the high throughput of mice and identify those with unusual phenotypes. Most of the primary test are designed to screen for human-like diseases and are tissue or organ specific (for example, heart rate, blood chemistry, glucose tolerance test, vision and hearing). High resolution, whole body MR imaging is being added to the screening process to help identify outliers in gross morphology. MR images enable a thorough search for unusual phenomena regarding sizes, shapes and textures of organs and tissues. The difficulties in assessing images lies in: a) large image size (about 512x512x2048 isotropic voxels at 60 microns) and b) inter and intra subject postural differences hindering comparative image navigation. When these difficulties are combined with a high throughput, having radiologists with expertise in mouse anatomy perform image assessment becomes impractical. Instead, there is a clear need for the development of computer aided procedures that can help in phenotyping mice. This area of research is quite new and unexplored.

By contrast, medical images in humans have a long history. Current computerized medical image analysis is largely driven by clinical applications and can be described as a collection of mostly disjoint knowledge bases: typically, medical images capture a *specific* part of the human body and image processing techniques are focused in the same way. In particular, registration comes in many different flavors: registration of human brains into single coordinate space, elastic intrasubject registration of pre and post contrast breast images, rigid or non-rigid template driven registration for surgical planning, surface based atlas matching etc. With the use of whole body imaging systems comes a need for whole body algorithms. In this sense, efforts in developing whole mouse body algorithms will have wider impact.

Numerous automatic and semi-automatic methods for non-rigid registration have been developed and successfully applied to medical images. Non-rigid registration of human brain images, for example, has been in a focus of many studies. An excellent review of brain warping algorithms is given in [1]. Another excellent review of various registration techniques is given in [4]. Existing registration methods typically require a considerable number of image specific preprocessing steps. For example, intensity-based algorithms require precise masks outlining structures of interest, while model-based algorithms require feature extraction (e.g., curves or polygons are often used for modeling important anatomical structures). The preprocessing steps are often performed using manual or semi-automatic procedures.

In the context of MRI based mouse phenotyping we need to formulate a knowledge of normal (non-mutant), strain specific mouse anatomy and its modes of variation. As a first step toward this goal we propose a method for 3D non-rigid registration which enables uniformly approximate correspondence between the same anatomical structures in inter subject comparisons. In the most general setting this could be an intractable problem. In our case, however, we work with a strictly controlled experiment that cannot be done in humans: all subjects are taken from the same inbred strain, same sex and same age. Uniform genetic background guarantees small phenotypical variations (for example, see The Jackson Laboratory Genome database).

The underlying physical deformation model for the whole mouse body is remarkably complex and cannot be treated in a uniform way. For example, head position is reasonably well modeled by affine transformations, while inner, somewhat amorphous organs like the liver require elastic or free-form deformations. Using elastic or spline based matching algorithm on the entire body would lead to physically implausible results. An additional complication comes from intestines with their complicated, highly variable geometry, even across a single strain. They are also susceptible to many extrinsic factors due to digestion and metabolism. Registering intestines themselves is not only impractical, but their richness with features can be misleading to any registration algorithm.

Drawing the line between extrinsic (insignificant) and intrinsic (significant) differences has been addressed in the context of human brain atlases [1]. Most widely accepted rules state that any higher order deformations, following the

initial linear alignment, are anatomically significant. In the context of the entire mouse body, it is much harder to define a similar rule. On one hand, removal of extrinsic (postural) differences clearly requires non-linear deformations. On the other hand, highly-nonlinear transformations are likely to erase anatomically significant variations. Therefore deformations must be constrained. The challenge is in finding the right balance between these opposing requirements.

In view of the above considerations, we propose an organ or a region of interest (ROI) based approach to mouse anatomy. In other words, we consider mouse body as a collection of ROI's so that a class of piecewise affine transformations provides means for the removal of extrinsic differences. In this work, we introduce a fully automatic, hierarchical, anatomically guided, piecewise affine method for 3D registration of mouse images. The main focus of our approach is anatomical content and its preservation under deformations. Prior anatomical knowledge, which is necessary for this goal, is encoded in a single image as a reference resource. Deformation fields produced by the algorithm enable transfer of anatomical knowledge to all other images. This type of registration has many possible applications. Registration based segmentation, though somewhat inaccurate due to the limitations of locally affine transformations, can provide a starting point for more sophisticated segmentations of specific organs. Another application will be in enabling quick ROI browsing of images. For example, if a researcher is interested in mouse heart, then its approximate location and segmentation will be available from the database which records images together with their corresponding deformation fields produced by the algorithm. Furthermore, all mouse hearts form the database could be resampled so that they live in the same coordinate space, which in turn enables easy simultaneous viewing and comparison.

2 Registration Method

2.1 Standard Coordinate Space And Labeling

We select an image of a representative member of the population, and we refer to it as the *reference* image. The reference image is considered as the target for all registrations, i.e., images of all other members of population are registered into the coordinate space of the reference image.

Given an arbitrary image from the mouse population, which we refer to as a *sample* image, we must describe a transformation which brings it into alignment with the reference image. The alignment must ensure correspondence between anatomical structures, e.g., the 5-th vertebra of the sample mouse must be aligned with the 5-th vertebra of the reference mouse. This is an important point: simple evaluation of some similarity function based on image intensities and/or features without awareness of the underlying anatomy is not sufficient. For this reason prior anatomical knowledge about the reference image is obtained first and subsequently used for guiding the registration process. Anatomical knowledge about the sample image gradually emerges and improves as the registration process evolves.

Prior anatomical knowledge is encoded via manual or semi-automatic labeling of the entire reference image. More precisely, each voxel in the reference image is assigned to one of a finite number of anatomical labels or to the background. The labels are defined so that they represent distinct structures of similar volume (e.g, one label for each vertebra). In cases when neighboring structures can assume independent positions (e.g., femur and pelvis) particular care is taken in the delineation along their boundary. As mentioned earlier, intestines are best avoided in the registration, so all voxels in this region are assigned to the background. The parcelation of the reference mouse thus obtained is considered to be on the finest scale, with the largest number of labels. The next subsection explains how other, coarser parcelations are derived in a hierarchical manner.

2.2 Hierarchical Anatomical Tree

Starting from the finest scale labeling we build a hierarchical tree based on a "part-of" concept. The tree consists of labelings L_0, L_1,..., L_N which increase in discriminatory power. The finest scale labeling, L_N, is the manual one, described above. Its parent labeling, L_{N-1}, is obtained by simply merging together labels of L_N. For example, if L_N has separate labels for each of the heart chambers (total of 4 labels), then L_{N-1} may have only two labels: the two ventricles are merged into one label and the two atriums are merged into another. As a result, L_{N-1} is a coarser labeling i.e., it has fewer labels but they encompass larger volumes. The "part-of" hierarchy is clear: labels from L_N are children of their parent labels from L_{N-1}. The next coarser labeling L_{N-2} is obtained by merging together labels of L_{N-1} and so on, until we arrive at the coarsest labeling L_0 which consists of a single label encompassing the whole reference mouse body. Fig. 1 illustrates the concept of hierarchy. The tree enables a hierarchical piecewise affine approach to the registration, as we explain next.

2.3 Hierarchical Registration

The registration is designed as an evolutionary process following the descent down the hierarchical tree. It starts with the alignment of the single label of L_0 and it ends with the piecewise alignment corresponding to the finest labeling L_N. The transformations produced in the process are piecewise affine in nature (where pieces correspond to labels) and are expressed as vector fields.

We begin with the affine alignment of the single label (the whole mouse body) of L_0 to the sample image. This step accounts for global rotations, translations, shears and scalings. Next, we descend to the next hierarchical level, L_1. The labels of L_1 are independently aligned with the sample image, again using an affine transformation model. The transformation of the single parent label of L_0 obtained in the previous step is used to initialize all L_1 label alignments. Once labels of L_1 have been aligned, we proceed to the next level, L_2, in a similar fashion: the initial transformations for L_2 labels are set from the transformations of their L_1 parent labels. The process continues until the finest labeling L_N is reached.

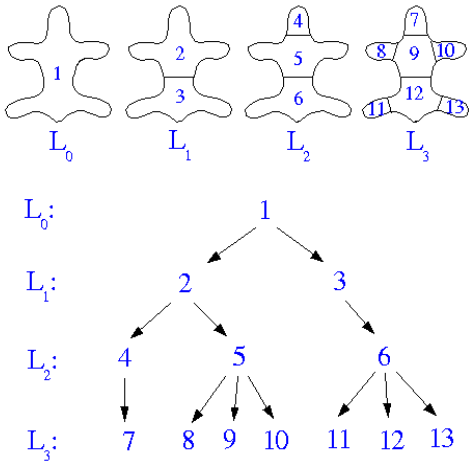

Fig. 1. Hierarchy of labelings L_0, L_1,..., L_N. Arrows represent parent $\rightarrow$ child relationship based on a "part-of" concept.

Label specific transformations of L_N are gathered to form a vector field, V_N: for each voxel in the reference image, we apply the transformation of its L_N label to calculate the corresponding point in the sample image. The difference between the two spatial coordinates is encoded as a 3D displacement vector (see fig:vectorfield).

Having in mind that the purpose is to establish a general anatomical correspondence for ROI' based comparisons, we measure the success of the registration accordingly: for each label of L_N, we compare the corresponding ROI's in the reference image and the V_N-transformed sample image respectively; if visual inspection confirms that the two ROI's encompass the same anatomical structure, then the registration is considered a success. Regularization of the final transform is subject of our future work.

3 Implementation

We have implemented the registration algorithm in view of its future applications in atlas development and phenotypical screening. The implementation is guided by the following assumptions: (i) all images are acquired with the same MR sequence, (ii) the phenotypical variation between subjects is small and (iii) postural differences are moderate (mice are positioned on platforms defining the general position of the head and limbs).

We have chosen the affine alignment of AIR5.2.2 ([5]) as our core alignment algorithm for its computational efficiency and robustness. With the same imaging modality assumption, we have chosen the scaled least square difference as the similarity function.

Given label X at level L_i, implied is a corresponding ROI in the reference

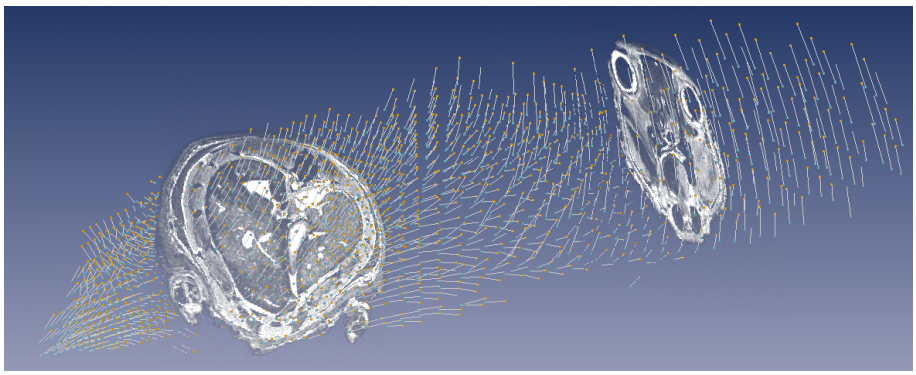

Fig. 2. Final displacement field V_N depicted with two cross-sections for reference. Shown is regular grid of points in the reference space (blue dots) with displacement vectors connecting them with their corresponding points in the sample space (yellow dots)

image. In order to align this ROI with the corresponding region in the sample image, we set up an alignment protocol in a fashion similar to [3]. Assume that label Y of L_{i-1} is the parent label of X and that T_Y is the transformation corresponding to label Y, found previously. In order to find T_X, we use T_Y in two ways: (i) as an initialization for T_X and (ii) to define an ROI (via a mask) in the sample image which approximately corresponds to the X-defined ROI of the reference image. Because of the postural differences, this mask may not include all of the required anatomy. Therefore, we dilate this approximate mask by number of voxels appropriate for the level of confidence at this stage (Fig. 3). Effectively, this puts us in a standard registration framework: target image and target mask vs. source image and source mask. To find an alignment, we follow a protocol (similar to [3]) which specifies successive use of smoothed and/or edge detected versions of images. The protocol also specifies details of pyramidal sampling and the number of iterations used in each succession.

The independence of individual label alignments on the same hierarchical level enables parallelized implementation. We also have gained additional speed through the use of downsampled images in the first 3 levels.

4 Results

We have evaluated the performance of the algorithm in a synthetic experiment. As a reference image we selected a full mouse body MR image (1.5T Signa, magnevist profused, 3d spin-echo TR/TE = 100ms/6.552 ms, 90 flip, 1024x256x256 acquisition matrix, 102.4 x 25.6 x 25.6 mm fov). From this image we created a second, synthetic image to be used as the sample image. We picked 14 landmarks in the reference image and displaced them arbitrarily in 3D space. The average magnitude of the landmark displacement vectors was 1.8mm (approx. 16 voxels).

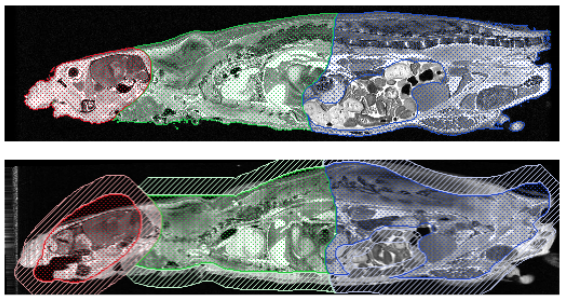

Fig. 3. Example: labeling L_1 consists of 3 labels. Corresponding approximate masks in the sample image are dilated by a fixed, level specific amount

Based on the landmark displacements, we next transformed the entire reference image using thin-plate splines as in [2]. To create a more realistic scenario, we added 9% gaussian noise (standard deviation of noise = 9% of mean signal intensity) to the deformed image and the result was used as a sample image. We manualy created 66 labels on the reference image as the finest scale labeling, and from it a hierarchical tree with 5 levels. On each of the registration levels, we used the same protocol for all labels. For different levels, however, the protocols were different. For example, L_1 was composed of 3 labels: head, upper body and lower body. For this level we first downsampled both images by a factor of 3 in each dimension. These images were then filtered in 3 different ways to enable a multi-scale/multi-resolution registration. Further details of the protocol are given in Table 1.

Table 1. Details of L_1 registration protocol. Sampling schedule refers to subsampling of images using a regular grid with nodal distance given in mm's. If two sampling distances are given, then registration was done in two steps, first using the coarser sampling, followed by the finer one

Filter (kernel width)	Sampling (mm)	Dilation (mm)
17.25mm gaussian blur	10.35, 6.9	69
6.9mm gaussian blur	10.35, 6.9	51
6.9mm gaussian blur on edge-detected images	6.9	51
none	6.9	51

To asses the accuracy of the registration we created a regular grid of points within the labeled region, totaling to 24042 points. The true displacements of the grid points, produced by the thin plate transformation, were compared to the displacements prescribed by the final deformation field V_5. Average error,

measured by the distance between true and recovered grid point displacements was 0.08mm ($\leq$ 1 voxel), maximal error was 0.7mm (approx. 6 voxels) and standard deviation of the error was 0.0005mm. With exclusion of a tiny region near the edge of the mouse body, agreement was of subvoxel quality. The quality of agreement is illustrated in Fig. 4.

The algorithm executed in less than 1 hour using 16 800MHz processors. Given that the images were 256x256x1204 voxels in size, the achieved speed was satisfactory.

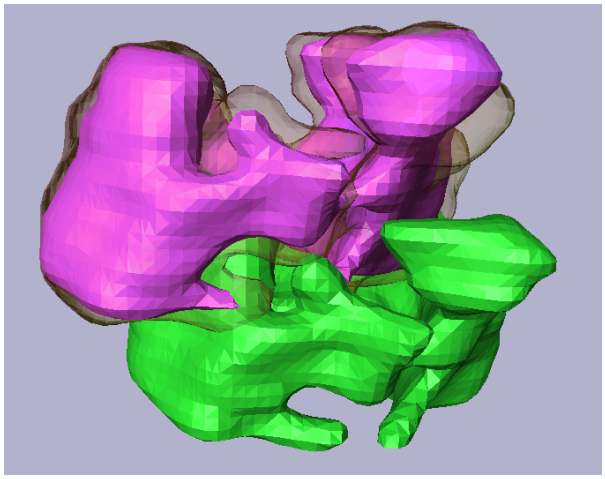

Fig. 4. Registration effect on a single vertebra. Green surface shows the reference vertebra. Purple surface represents the same vertebra deformed by the synthetic transformation while the transparent surface represents its deformation under the recovered transformation (the transparent surface is dilated by one voxel to enhance visual perception of the agreement)

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