Registration of 3D MR Images of the Mouse Embryos

M. Zamyadi[1,2], R. M. Henkelman[1,2], S. Bhattacharya[3], J. E. Schneider[3], and J. G. Sled[1,2]

[1]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada, [2]Mouse Imaging Centre, Hospital for Sick Children, Toronto, ON, Canada, [3]Department of Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetic, Oxford, United Kingdom

Introduction

Birth defects such as congenital heart disease result in a major global disease burden, and understanding the mechanisms requires genetic studies in appropriate model organisms such as the mouse. One strategy to understand genetic function is to selectively inactivate, or "knock out", each gene in the mouse genome, and an international consortium has been assembled to knock out each of the approximately 25,000 genes one at a time. Studying these knock out embryos should provide insight into genetic factors in normal development and disease. High resolution, high-throughput 3D magnetic resonance (MR) embryo imaging provides a cost effective and rapid approach to analyzing late gestational embryonic malformations and gives a comprehensive view of the anatomical phenotype. However, there is too much data to be analyzed simply by visual inspection considering that thousands of such data sets will be generated each year. Thus, imaging of the embryos must be accompanied by an automated computer analysis able of identifying significant anatomical differences based on 3D images of mutant and normal embryos. We are developing an image registration technique to detect subtle anatomical shape differences between mouse embryos. In order to assess feasibility, we have used non-linear registration to align a group of genetically identical embryos. Specifically, we tested the assumption that embryo anatomy is highly conserved among specimens.

Materials and Methods

Sample preparation and MRI: Image acquisition was carried out in Oxford as previously described in [1]. Briefly, a multi-embryo MRI technique at high spatial resolution was employed to image 32 embryos that were arranged in 8 layers of 4 (see Fig. 1). An 11.7 T vertical magnet was used for imaging of the embryos that were embedded in agarose gel in a 28 mm MR tube. A 3D spoiled gradient echo sequence (TE=10 ms) with a short repetition time (TR=30 ms) was used to obtain strong T1 contrast. The resolution of the dataset in hand is 25.4 x 25.4 x 24.4 μm^3.

Preprocessing of data: Before starting the registration process, the individual embryos were manually segmented from the surrounding gel using the Image Segmentation Editor of the Amira 4.1 software package (see Fig. 1). Furthermore, a region of the embryos which did not include the limbs and the tail was selected to facilitate the registration process.

Registration method: We have used an automated intensity-based group-wise registration approach [2] to register 6 genetically identical embryos. In the first step of the registration algorithm, a linear 12-parameter affine transformation model was used to normalize the embryos with respect to the orientation, location, scale, and overall MR intensity. For the remaining steps a multi-resolution, multi-scale nonlinear registration methodology was used to match subtle anatomical features of the embryos. The nonlinear step begins by nonlinear registration of the individual embryos to the voxel-wise average of the linearly registered images. The new set of images is then used to create an improved average image and this process is repeated iteratively to obtain the final average image that contains data from a group of (in this case 6) individual embryos.

Results and Conclusion

Six 3D embryos have been registered together using the outlined registration technique. The final average image obtained (Fig. 2) demonstrates enhanced structural and anatomical definition compared to individual images. This can be attributed to the high degree of correspondence among the individual embryos and the improvement in SNR that comes with averaging. We noted for instance an exact correspondence among somites following alignment. In addition to the average image, we have also calculated the root mean squared (RMS) displacement image (Fig. 2) which gives a visual representation of the variability between the final average and individual images. In other words, the RMS displacement image is a representation of the anatomical variation among the genetically identical embryos. We found that the average RMS displacement is 105 microns which indicates low variability. These initial findings suggest that embryo anatomy is highly conserved among specimens and that image registration of 3D MRI data is a feasible approach for subsequently detecting abnormal phenotypes.

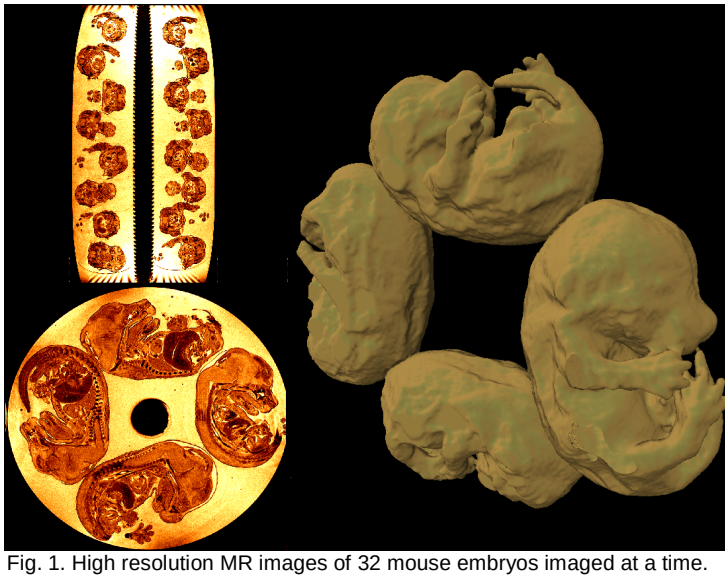

Fig. 1. High resolution MR images of 32 mouse embryos imaged at a time. Embryos are stacked into 8 layers (upper left) of 4 embryos (lower left). Surface rendered segmented embryos (right).

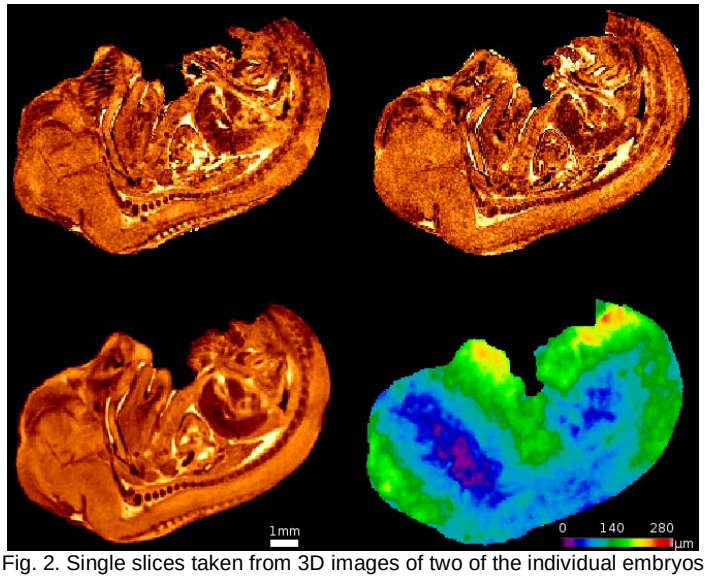

Fig. 2. Single slices taken from 3D images of two of the individual embryos (top). Average image consisting of data from 6 individuals (lower left). Root mean squared displacement image (lower right).

References:

1. J. E. Schneider, et al., Identification of cardiac malformations in mice lacking *Ptdsr* using a novel high-throughput magnetic resonance imaging technique, *BMC Developmental Biology* 2004, 4:16.
2. N. Kovacevic, et al., A Three-dimensional MRI Atlas of the Mouse Brain with Estimates of the Average and Variability, *Cerebral Cortex* 2005, 15: 639.