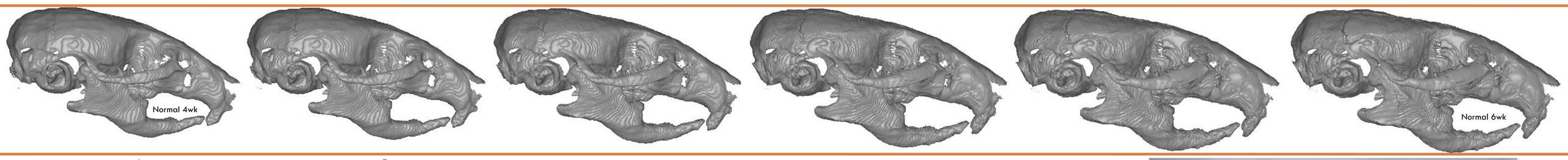

Average growth in mice – comparison between wild-type mice and Crouzon mice

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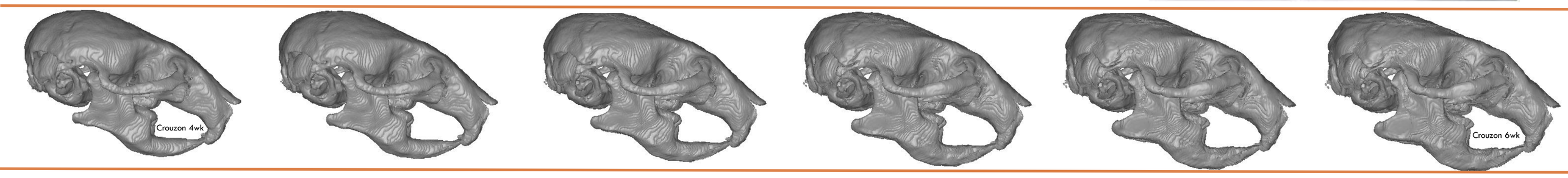

Introduction

Crouzon syndrome is a genetic disease causing premature fusion of the cranial sutures leading to growth disturbances. The syndrome has an incidence of 1:64.500 [Rice, 2008].
In 1994 the gene causing Crouzon syndrome was discovered, and a mouse model was introduced in 2004 [Eswarakumar, 2004].
Micro CT scans of mouse skulls may be used in order to carry out a detailed analysis of the morphology and growth of the Crouzon mice as well as their deviation from normality. The analysis contributes to the understanding of the syndrome and the craniofacial deformities as well as it might help improve diagnosis and surgery planning for children in the future.
Previous studies have validated the mouse model as a suitable model for studying the syndrome [Ólafsdóttir, 2007].

Material

The data material consists of 3-dimensional micro CT scans of 30 mouse skulls – 10 four week and 20 six week old mice. Each age group consists of 50% wild-type (normal) mice and 50% Crouzon mice. The material is cross-sectional: the mice were euthanised before they were CT scanned.

Aim

The aim of the study was to build craniofacial atlases (intensity and shape averages of the CT scans) for the 4 groups, see figure 1. Furthermore, to determine, characterise and visualise average growth for wild-type and Crouzon mice, respectively, from 4 to 6 weeks of age.

Method

Average growth in any spatial point is defined as the displacement vector from one point in an average 4 weeks old mouse to the corresponding point in an average 6 weeks old mouse.

1) A craniofacial atlas was constructed for each age (4 and 6 weeks) and group (wild-type and Crouzon) using non-rigid image registration applying a B-spline deformation model and a normalised mutual information similarity metric, [Ólafsdóttir, 2007]. An atlas is an average of all mice in a particular group, see figure 1. First an intensity average atlas (intensity atlas) was constructed by registering all mice in each group to a chosen suitable reference mouse. However, the intensity atlas preserves the shape of the reference mouse. To reduce the shape bias from the reference mouse, all mice in each group were registered to the group intensity atlas and the deformations from this registration were averaged.
2) Detailed point correspondence was constructed (by non-rigid image registration) between the 4 and 6 week atlases in each group. The resulting deformation fields represent the average growth. To get the deformation vectors (growth vectors) the 4 week atlas was registered to the 6 week atlas within each group. Using the deformation vectors a detailed point correspondence was achieved.
3) Visualisation of results was created by
   a) Animations by linear interpolation between 4 week and 6 week atlases.
   b) Drawing of growth vectors on top of the surface representations.

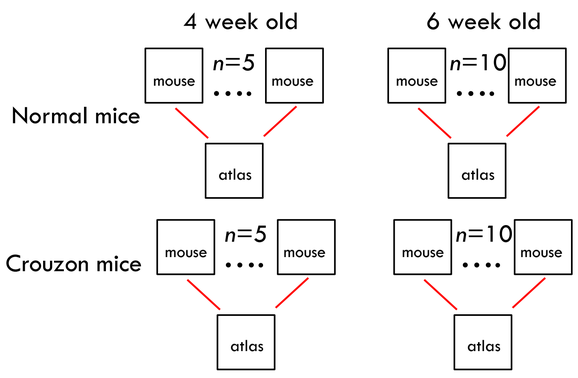

Figure 1: Schematic drawing of the construction of a computational atlas. The figurative description of atlas construction is to sum all mice in a group and average by the number *n*.

Results

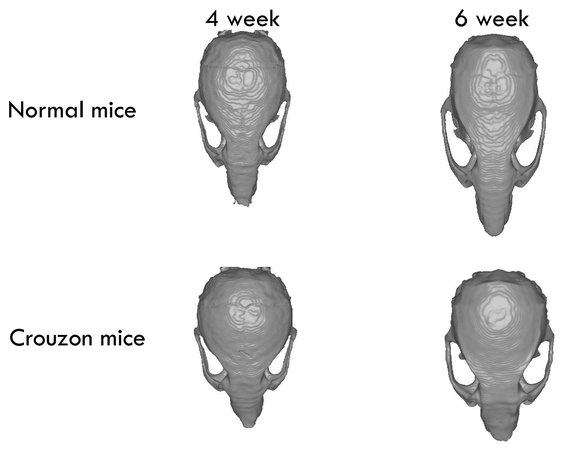

Figure 2: Surface representations of the 4 atlases (intensity atlases with reduced shape bias) grouped as in figure 1: The asymmetry is much more apparent in the Crouzon case.

Results continued…

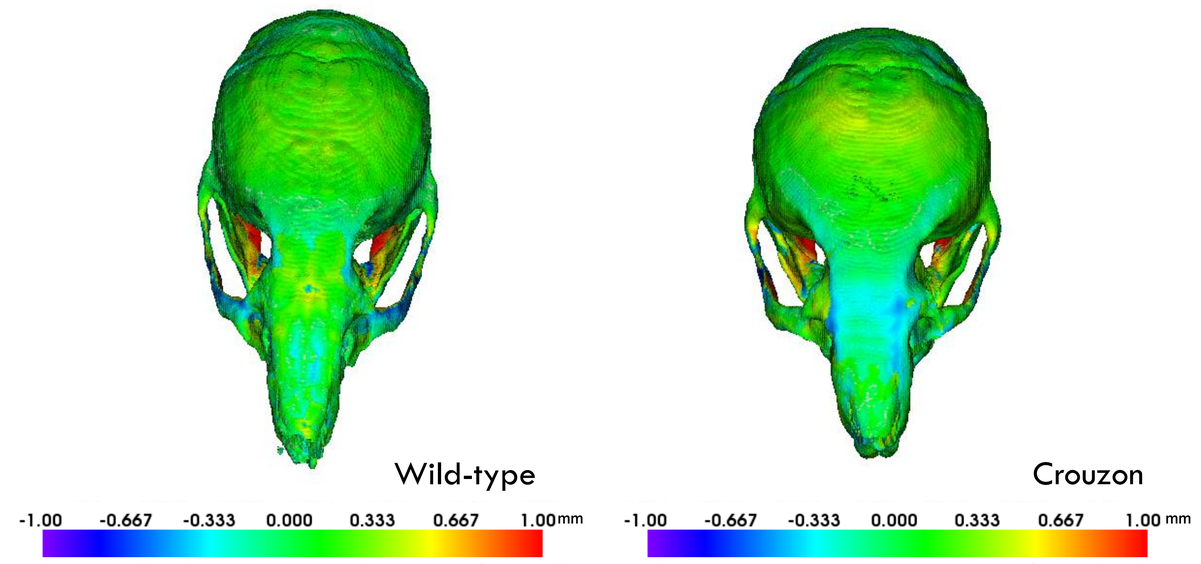

Figure 3: The 6 week atlases: wild type (left) and Crouzon (right). Colours represent the results of a validation experiment using the closest point algorithm: The difference between the 4 week atlas deformed ("grown") according to the growth vectors, and the 6 week atlas is shown. The green colour indicates small differences.

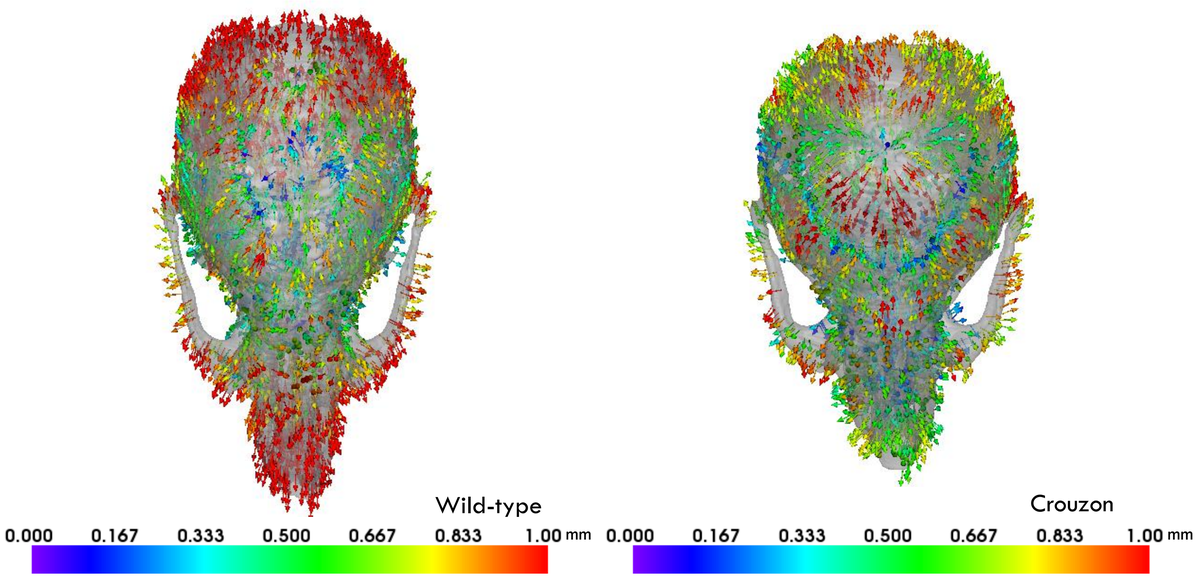

Figure 4: Growth vectors displayed on 4 week atlases. Red indicates large displacements and violet/blue indicates no or little displacements . The occurrence of more red growth vectors on the wild-type mouse indicates that the average wild-type mouse grows more in the nasal region and at the back of the head during 2 weeks on average compared to the average Crouzon mouse.

Discussion and conclusion

The growth analysis demonstrated that the average growth in Crouzon mice is smaller than in wild-type mice (figure 4), as expected. Premature suture fusion over time in each Crouzon mouse could explain an increased variability in size, shape and the asymmetry across mouse-type and age.
Furthermore, the growth was more asymmetric in the Crouzon mice, especially in the nose region (figure 4, right and figure 1). This fits well with previous work. [Ólafsdóttir, 2007] shows that shape variation within the Crouzon group is larger than for wild-type mice. For instance, Crouzon mice have a shorter skull and are in general more asymmetric.

A methodology for growth analysis using non-rigid image registration was developed and applied to two groups of mice: wild type and Crouzon mice. The method allowed detailed growth patterns to be studied in both groups.

Further investigation is needed to see whether the growth differences between Crouzon and wild-type are significant.

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