An optimal set of landmarks for metopic craniosynostosis diagnosis from shape analysis of pediatric CT scans of the head

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ABSTRACT

Craniosynostosis (premature fusion of skull sutures) is a severe condition present in one of every 2000 newborns. Metopic craniosynostosis, accounting for 20-27% of cases, is diagnosed qualitatively in terms of skull shape abnormality, a subjective call of the surgeon. In this paper we introduce a new quantitative diagnostic feature for metopic craniosynostosis derived optimally from shape analysis of CT scans of the skull. We built a robust shape analysis pipeline that is capable of obtaining local shape differences in comparison to normal anatomy. Spatial normalization using 7-degree-of-freedom registration of the base of the skull is followed by a novel bone labeling strategy based on graph-cuts according to labeling priors. The statistical shape model built from 94 normal subjects allows matching a patient’s anatomy to its most similar normal subject. Subsequently, the computation of local malformations from a normal subject allows characterization of the points of maximum malformation on each of the frontal bones adjacent to the metopic suture, and on the suture itself. Our results show that the malformations at these locations vary significantly ($p<0.001$) between abnormal/normal subjects and that an accurate diagnosis can be achieved using linear regression from these automatic measurements with an area under the curve for the receiver operating characteristic of 0.97.

Keywords: Head and Neck, Craniosynostosis, Computer-Aided Diagnosis, Decision support systems, Quantitative analysis

1. INTRODUCTION

Craniosynostosis is a congenital condition of young infants provoked by premature fusion of the cranial sutures, with an incidence of one in 2000 live births, and no ethnic predominance.\textsuperscript{1} It can have aesthetic implications and also functional consequences, as it can affect brain growth, intra-cranial pressure, and produce respiratory and visual impairment. Early diagnosis is critical for consideration for early surgical correction.\textsuperscript{2,3}

The preferred method for diagnosis and assessment of craniosynostosis is three-dimensional reconstruction from computed tomography (CT). Premature fusion of skull sutures can be detected on the reconstructions, and can sometimes manifest with ridging of the fused suture.\textsuperscript{4} Craniosynostosis usually entails some degree of dysmorphology, as the need for volume expansion tied to normal brain growth results in compensatory areas of skull overgrowth and abnormal morphology.

Most types of craniosynostosis can be diagnosed by assessing the fusion of sutures. One exception is metopic synostosis, which accounts for 20-27% of all cases of craniosynostosis.\textsuperscript{5} The metopic suture fuses early in healthy subjects and therefore suture fusion is not indicative of pathology. As a consequence, metopic craniosynostosis can only be diagnosed in terms of the degree of malformation (trigonocephaly), which is often assessed subjectively.

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by the surgeon. In this context, it is desirable to rely on objective quantitative descriptions of shape abnormality to assist in producing a diagnosis and establishing the need for surgical correction. See Fig. 1 for a comparison between example morphologies in normal and metopic craniosynostosis subjects.

Different authors proposed methods to evaluate the degree of trigonocephaly using anthropometric indices on CT images. Previous reports either lack well-defined landmarks to ensure accuracy and reliability or are too complicated for intuitive clinical application. Recently, Kellogg et al. proposed the characterization of trigonocephaly using inter-frontal angles measured according to different sets of landmarks. Although they obtain good diagnostic accuracy, the angles they compare are obtained from arbitrarily defined landmarks.

The purpose of our work is to identify robust anatomical landmarks located on the frontal bones of patients with metopic craniosynostosis to optimally and reproducibly discriminate pathological shape abnormality from healthy phenotypes. We achieve this via a shape analysis framework for pediatric skulls, based on a statistical shape model of normal anatomy built from 94 healthy subjects.

Some key aspects of our methodology are:

- We perform the spatial normalization of each subject by an age-invariant strategy via isotropic scale registration (7 degrees of freedom) that incorporates only structures in the base of the skull, minimizing the influence of cranial vault malformation on the registration.

- We provide a morphological analysis across anatomically meaningful regions of the skull. This is attained via a graph-cut method based on labeling priors and low contact interface detection to automatically segment and label the skull bone segments and sutures.

- Our description of cranial morphology is expressed from a multi-atlas computed from 94 normal cases. For each metopic craniosynostosis subject, we use the closest normal variant in the multi-atlas to compute the degree of malformation across anatomical regions.
• The degree of malformation for each subject, on each point of the skull surface, is averaged across metopic craniosynostosis subjects according to closest-point correspondence, and represented on a template of normal anatomy. This allows for finding the optimal landmarks as those which exhibit maximum average malformation.

2. MATERIALS AND METHODS

2.1 Data

A database of 112 head CT scans was gathered from the image repository system in our institution, acquired with different scanners and varying resolution. We were able to collect 18 cases diagnosed with metopic synostosis and 94 healthy subjects, all ranging in ages 1-12 months. Controls were selected from subjects reported to the emergency room for trauma, and were screened to exclude craniofacial trauma and prior craniofacial surgery.

2.2 Methodology

For every subject we obtained a segmentation of bone tissue with open sutures using an age-adapted threshold in the range 150-400 HU. These thresholds were determined empirically in relation with the gradual ossification of the skull in infants.

In order to produce meaningful comparisons across subjects, all skull volumes were brought into a common spatial reference frame. We selected a random CT image of a healthy subject (the template) in order to define the reference space. On this template, a set of manual landmarks was selected on structures at the base of the skull (the nasion (N), the opisthion (O) and the two clinoid processes of the dorsum sellae (D1, D2)). N, D1 and D2 together define an axial plane that dissects the skull approximately above the supra-orbital notches (P1). O, D1, and D2 define an oblique plane passing through the lower occipital bone (P2). The intersection of the regions above P1 and P2 describes the region of interest (ROI) for cranial morphology assessment. Next, we performed a 7-degree-of-freedom registration (rotation, translation and isotropic scale) using an overlap metric\textsuperscript{13} computed only outside the ROI (i.e. across the base of the skull).

Furthermore, the bone tissue (with open sutures) was labeled into one of the five bone segments present in the structures of interest: (right and left frontal, right and left parietal, and occipital bones). Labeling of the bones was performed using a graph-cut strategy.\textsuperscript{14} Only voxels present in the bone-without-sutures tissue were incorporated to the graph. The energy of the graph was composed of a homogeneous edge term (favoring low contact cuts, i.e. at the sutures) and a region cost derived from the distance to the appropriate segment on the transformed labeled template. Analytically, the cost of assigning label $f_p$ at node $p$ is $D_p(f_p)$

\begin{equation}
D_p(f_p) = \frac{d_{f_p}}{(d_{f_p} + \max_f(d_f | f \neq f_p))},
\end{equation}
where $d_f$ is the distance to the closest node with label $f$ in the labeling prior (the labeled template). See Fig. 2 for an example of a normal subject with labeled bone segments.

From the result of the labeling of the bones we produced a polygonal surface model of the subject’s skull on which each vertex is labeled to belong to one of the bone segments or to a suture region (if lying close to two neighboring segments that share a suture of interest). See our previous publication\textsuperscript{14} for more details.

In parallel, a statistical shape model was constructed using the 94 normal subjects transformed into the reference space. We applied the principal component transform (PCT) to the set of Danielsson’s signed distance functions\textsuperscript{15,16} obtained from each normal subject’s bone-labeled volume. The result is a multi-atlas of normal skull anatomy that can be queried for every subject by projecting it into the shape space and selecting the normal subject at minimal Euclidean distance of the projection.

Subsequently, at each vertex on each subject’s surface model we computed the Euclidean distance to the closest vertex in the surface model of the closest normal found in the multi-atlas. As a result we obtained a malformation field defined across all bone segments and suture regions. See Fig. 3 for an example of a metopic craniosynostosis subject’s surface model with labeled anatomical regions and local malformations from the subject to the closest normal in the multi-atlas.

Then, we used the transformation previously obtained from the registration procedure to bring each subject into the reference space of the template. At each vertex on the template we computed an average malformation value by averaging the malformations on the closest vertices in all the metopic subjects. The result is the definition of an average malformation field on the normal template. The points of maximum average malformation on the template can be computed on different skull regions. We obtained three points of maximum malformation: one at the left frontal bone, one at the right frontal bone and another one on the metopic suture. These points follow the clinical observations in the diagnosis procedure for metopic craniosynostosis.

These optimal landmarks can be obtained in the reference space of every normal and metopic subject using the transformation previously computed in the registration procedure for that subject. The malformation for every subject at each landmark can be obtained by evaluating the subject’s malformation field on the vertex lying closest to the transformed landmark.

2.3 Validation and Tests
An operator manually labeled the five bone segments (LP, RP, LF, RF, Oc) in the suture-free bone volumes for seven normal and seven randomly-picked craniosynostosis subjects. Using this ground truth we evaluated the

![Figure 3. Surface model of a metopic craniosynostosis subject. (a) Labeling of anatomical regions according to bone segments produced by the graph-cut labeling algorithm. The metopic suture is shown in purple and the right and left frontal bones in yellow and orange respectively. (b) Local malformation (local distance to closest vertex in closest normal subject from the multi-atlas).](image)
Figure 4. Average malformation field for metopic craniosynostosis. Anatomical landmarks (white spheres) corresponding
to the maximum malformations in each region (left/right frontal bone and metopic suture) are also shown.

<table>
<thead>
<tr>
<th></th>
<th>Left Frontal (mm)</th>
<th>Right Frontal (mm)</th>
<th>Metopic Suture (mm)</th>
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</thead>
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<td>Metopic Subjects</td>
<td>5.11±2.18</td>
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<td>Normal Subjects</td>
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<tr>
<td>p-value</td>
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<td>&lt;0.001</td>
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</table>

Table 1. Average malformation and significance of differences for metopic and normal subjects at the three obtained landmarks, and for a linear regression of the three malformations.

Subsequently, we obtained malformation values for transformed optimal landmarks on each of the subject’s malformation field. Then, we performed Mann-Whitney U-tests\textsuperscript{17} on the malformation values at the optimal landmarks on normal versus metopic subjects to determine the significance of differences. Finally, we computed receiver operating characteristic (ROC) curves for metopic craniosynostosis detection using the malformation values on each of the landmarks, and a linear regression combining the three malformation values.

### 3. RESULTS

The registration procedure was validated using the manual landmarks, the opisthion (O) and the clinoid processes of the dorsum sellae (S1 and S2). The error (mm) was 4.60±1.97 for O, 2.65±1.13 for S1 and 2.56±1.31 for S2. The average sensitivity and specificity of the skull bone labeling algorithm were 0.97±0.03% and 0.99±0.01%, respectively.

In Fig. 4 we show the average metopic malformation field represented on the template. We also show the three optimal landmarks, as the maximum average malformation locations at the three anatomical regions of interest (left/right frontal bone and metopic suture). Notice the good behavior of the computed field, and the symmetric arrangement of the landmarks.

Table 1 presents the average malformations computed at the optimal anatomical landmarks on the left/right frontal bones and the metopic suture, respectively. The p-values from the Mann-Whitney statistical test for the malformations on the three anatomical landmarks and for the linear regression computed from the three malformations, for normal vs. abnormal cases, are also shown in Table 1.

In Fig. 5 we show ROC curves of normal versus metopic subjects for the malformations at the three optimal landmarks and also for a linear regression of the three malformations at the three landmarks. The best area under the curve (AUC) of the ROC for metopic craniosynostosis diagnosis was found to be 0.97 using the linear
Figure 5. ROC curves for the three landmarks and their multivariate linear regression. Areas under curve (AUC) are 0.95, 0.92, 0.85 for the landmarks at the left/right frontal bones and on the metopic suture, respectively, and 0.97 for the linear regression.

regression of the malformations at the three optimal landmarks. Using only one anatomical landmark, the AUC was 0.95, 0.92 and 0.85 for the landmarks at the left/right frontal bones and on the metopic suture, respectively.

4. DISCUSSION

From shape modeling and analysis of a large database of infant skulls we found the optimal anatomical landmarks for the quantification of skull malformation in metopic craniosynostosis. The value of the malformations at the three landmarks varies significantly between normal and metopic craniosynostosis subjects (p<0.001). Furthermore, the AUC for linear regression combination of the three malformations is 0.97, indicating excellent diagnostic power from just three landmarks.

We proposed a computational model of local malformation in the craniosynostotic skull to optimize the diagnosis of metopic craniosynostosis. To the best of our knowledge, this is the first systematically derived strategy of its kind. A radiographic method similar to the inter-frontal angle proposed in12 can be envisaged according to the obtained optimal landmarks, which by construction optimally describe the recedence of the frontal bones and the protrusion of the suture area in trigonocephaly.

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REFERENCES


