# A method for assessing nonlinear growth in the fetal cortex

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*Abstract*— **The cerebral cortex is folded into gyri and sulci in the brains of higher mammals. Quantitative study of the process by which the cortex folds during brain development is critical to a complete understanding of normal brain development and neuro-developmental disorders. In this work, we propose a new method by which to localise nonlinearities in the cortical folding process, and thereby identify regions of differential growth across the cortex. Our method is based on spherical harmonic (SPHARM) representation of the cortical surface. Linearity is assessed by comparison of each SPHARM reconstructed surface with an artificial surface constructed using a linear combination of SPHARM coefficients from data at adjoining developmental time points. The resultant quantification of cortical folding development is easy to interpret, and the method has low computational cost. We demonstrate application to a set of experimental MRI data of fetal sheep brains, across key developmental timepoints as the cortex first folds during development.**

## I. INTRODUCTION

High-level cognitive function originates in the cerebral cortex, the expansion of which is thought to herald the evolutionary emergence of intelligence [1], [2]. A fundamental feature accompanying expansion of the cortex is folding of the sheet-like structure. A complete understanding of cortical folding in normal brain development [3], [4], [5] is essential for improved understanding of neurodevelopmental disorders [6], [7], which have clinical value in early diagnoses. Given the importance of an understanding of the cortical folding process in developmental neuroscience research, it is critical that robust methods exist by which to quantify both cortical folding complexity and the pattern of folding throughout development.

Cortical folding complexity metrics based on morphometric analyses have been previously proposed, including gyrification indices [6], spectral analysis using the Laplace Beltrami operator [8], spherical harmonics [9], and spherical wavelets [3]. Brain growth is known to be nonlinear, further motivating quantitative study of localised cortical development. Previous methods include volumetric analysis of localised regions during development [10]. Other studies have quantified regional rates of brain growth using nonlinear registration [4], [5]. These methods input deformation maps to a linear model of growth and compute statistical significance of points within the deformation maps to characterise regional growth rates of tissue. One drawback of methods based on nonlinear registration is that they have high computational cost.

The key contribution of this paper is a technique by which to assess nonlinearity in cortical folding development. Our method, based on spherical harmonics (SPHARM) shape descriptors, constructs cortical morphometry at each developmental time point using linear combination of the coefficient sets at neighbouring time points, and compares the simulated shape with reconstruction from data. These comparisons are used to identify localised regions of differential growth. Based on SPHARM, the method is easy to interpret and has low computational cost. We make a second contribution in the current paper, assessing the ability to predict morphology from low order approximations of the cortex of more developed brains.

The organisation of this paper is as follows. In Section II, the theory, experimental and analytical methods are presented. Experimental results are given in in Section III, followed by conclusions in Section IV.

## II. METHOD

The proposed method for assessing nonlinearity growth during cortical folding development is presented in Fig. 1. We begin below by describing the data acquisition and preprocessing steps, followed by a brief theoretical background of spherical harmonics for shape analysis. To conclude the Methods section, we present the proposed cortical surface approximation and shape comparison measurements used to compute nonlinear rate of cortical development.

### *A. Data acquisition and pre-processing*

T2-weighted MRI data of ex-vivo fetal sheep brains were acquired. The sheep is an ideal model for studying gyrification due to the relatively simple folding pattern. The sheep gestational period is 144-151 days. Cortical folding in the sheep begins around day 60. We therefore analysed cortical folding at 10-day intervals from 60 to 90 days, based on structural MRI data. Fetal sheep brains were perfusion fixed, extracted and subsequently scanned on a Bruker 4.7T MRI scanner equipped with a BGA-12S gradient set. Coronal slices were acquired at a resolution of 0.258 x 0.258 x 1 $mm^3$. Fig. 2 depicts exemplar slices of the MR images at each gestational time-point.

The MR images were manually segmented to provide 3D masks of the right hemisphere at each time point. In order to

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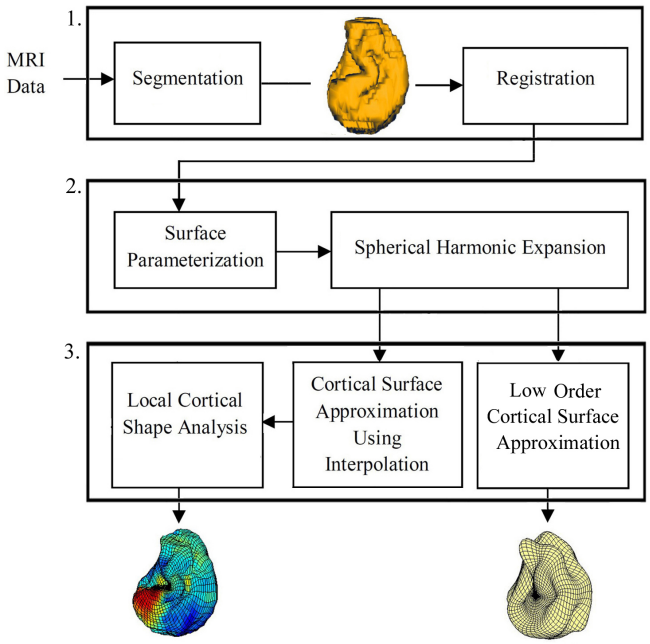


Fig. 1. The proposed procedure for assessing linearity of brain development and cortical folding approximation. This procedure contains three main steps: 1) Data acquisition and pre-processing, 2) Spherical harmonic shape representation, and 3) Cortical folding approximation.

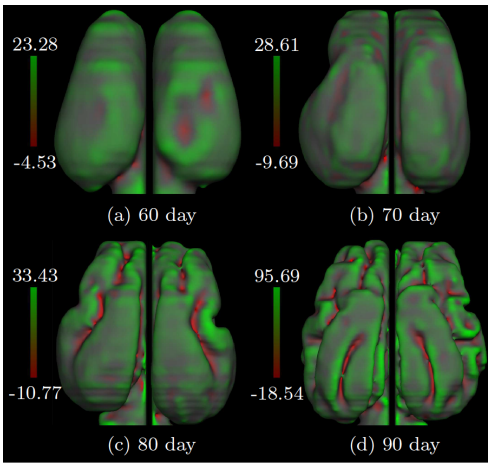


Fig. 2. Freesurfer cortical surfaces of fetal sheep brains at day (a) 60, (b) 70, (c) 80 and (d) 90. The colours encode the curvature. (From [11]).

achieve correspondence between cortical surfaces, the masks were aligned by translation and rotation.

### B. Spherical harmonic shape representation

Spherical harmonic (SPHARM) is a common shape representation that has been used widely in morphological analysis of the brain structures. Brechbhler et al. first introduced SPHARM as a parametric representation of a boundary in 1995 [9]. SPHARM representation consists of two steps:

1) Surface parameterisation to the surface of a unit sphere. This is an optimisation problem that aims to preserve area and provide minimal distortion [9], [12]. The result is mapping of each point on the surface to spherical coordinates, $\theta$ and $\phi$.
2) SPHARM expansion of the surface defined on $\theta \in [0, \pi] \times \phi \in [0, 2\pi]$:

$$\vec{v}(\theta, \phi) = \sum_{l=1}^{\infty} \sum_{m=-l}^{l} \vec{c}_l^m Y_l^m(\theta, \phi), \quad (1)$$

where $\vec{c}_l^m$ is SPHARM coefficient vector, $Y_l^m$ is a SPHARM basis function, $l$ is the degree and $m$, $-l \leq m \leq l$ is the order of the basis function:

$$Y_l^m(\theta, \phi) = \sqrt{\frac{2l+1}{4\pi} \frac{(l-m)!}{(l+m)!}} P_l^m(cos\theta) e^{im\phi}. \quad (2)$$

Here $P_l^m$ is the Legendre polynomial,

$$P_l^m(w) = \frac{(-1)^m}{2^l l!} (1-w^2)^{\frac{m}{2}} \frac{d^{m+1}}{dw^{m+1}} (w^2-1)^l. \quad (3)$$

SPHARM coefficients are three-dimensional vectors that summarise the shape information and become the surface shape descriptors. The order of the reconstruction determines the level of detail of the surface that is retained in the reconstruction. For SPHARM parameterisation and coefficient computation we used SPHARM-PDM toolbox [12]. The bandwidth of the reconstruction refers to the maximum order, L, used in the analysis.

### C. Cortical folding prediction

Cortical folding through development was predicted using linear interpolation between SPHARM coefficients at the measured time-points in order to analyse cortical surface data for linearity of growth,. The predicted surfaces were locally compared with experimental data at various gestational ages and the resulted distance maps were presented as nonlinear rate of growth of cortical surface data. Beyond using all of SPHARM coefficients of the measured time-points for cortical folding prediction, we predicted cortical surface folding pattern at earlier ages, using low order SPHARM reconstructions of more developed brains. Local and global metrics for cortical surface shape comparisons were employed. Distance between every vertex was computed to analyse the approximated shapes locally. Average Euclidian distance (AED) between two SPHARM reconstructions was computed in order to compare shapes globally :

$$AED = \frac{1}{n} \sum_{i=1}^{n} \|v_l - u_i\|, \quad (4)$$

where $v_i$ and $u_i$ are the vertices on the two surfaces and $n$ is the number of vertices in each reconstruction.

For cortical complexity measurements, AED was used to compute reconstruction error between SPHARM reconstructions of cortical surface with maximum order ($L = 30$) and lower bandwidths [13]. Surface areas were normalised by surface area of the higher order SPHARM reconstruction of cortex. The area under reconstruction error plot (ARE) was computed as a global measure of cortical complexity.

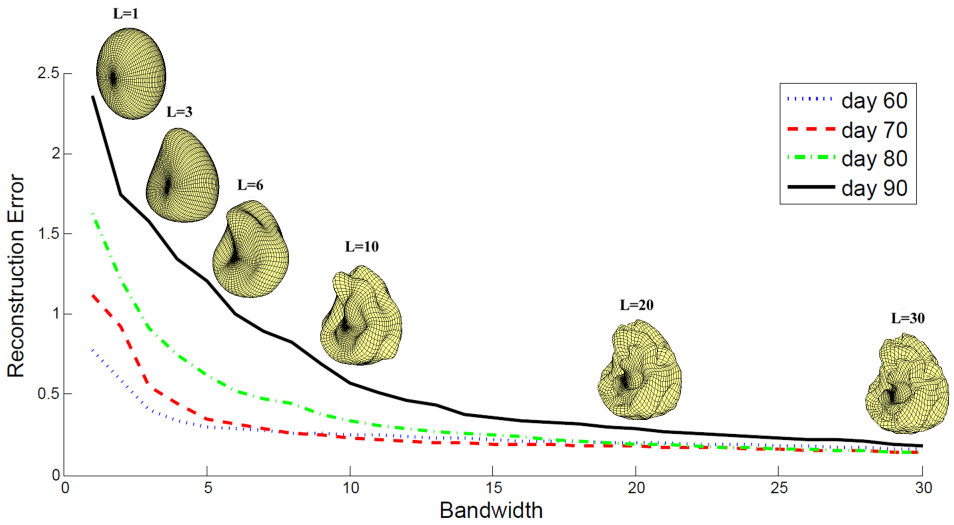


Fig. 3. SPHARM reconstruction error versus bandwidth, L. The cortical surface at day 90, reconstructed with different numbers, $N = (L+1)^2$, of SPHARM coefficients is illustrated.

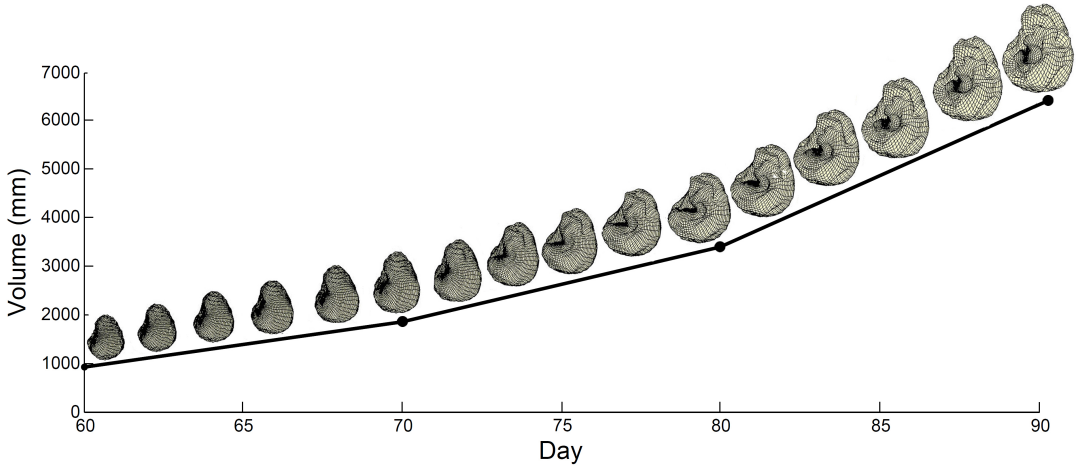


Fig. 4. Volume and shape changes in the developing sheep cortex, day 60 to day 90. Black dots: measured data.

## III. EXPERIMENTAL RESULTS

### A. SPHARM reconstruction

As the fetal sheep brains at 60-90 days gestation are morphometrically quite simple, the SPHARM coefficients were computed up to order 30. The reconstructed brains with $L = 30$ represent the gyrification pattern well. Fig. 3 displays the cortical surface at day 90, reconstructed with different numbers of SPHARM coefficients. In order to assess the accuracy of the cortical shape reconstruction at each time-point, we computed the SPHARM reconstruction error, defined as distance between the SPHARM reconstruction of the brain with $L = 30$ and lower frequencies (see Fig. 3). ARE was computed to be ARE=[5.16, 5.90, 9.13, 15.28] for the four time-points in order. It is evident that the complexity of the brain at days 60 and 70 is very similar, while it is by day 80 that a rapid increase in complexity has occurred in development, continuing through day 90, consistent with increased gyrification. As expected, more developed brains require higher frequencies to be accurately reconstructed.

### B. Assessing nonlinearity in cortical development

Approximations of cortical folding development using interpolation between SPHARM coefficients of the measured time-points are given in Fig. 4. The predicted cortical shape at each day of gestation provides an approximation to the cortical gyrification development in a detailed, in this case every second day, sequence. 2D piecewise linear diagram of volume development with ageing illustrates the idea of our linear interpolation in spherical harmonics space.

To assess nonlinearity of cortical development, we approximated the cortical shapes at days 70 and 80, as exemplar day points, using SPHARM coefficients of day 60 and 80, and 70 and 90 respectively. Then we compared the approximations with SPHARM reconstruction of original cortical shape of those days. Fig. 5 demonstrates the original day 80 brain, the

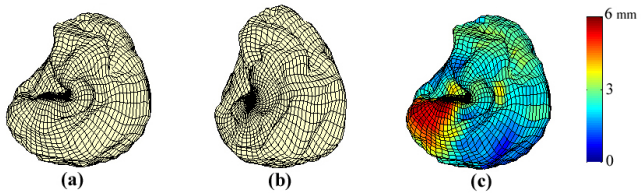


Fig. 5. Localising nonlinear rate of growth, (a) $L = 30$ SPHARM reconstruction of original cortical shape of day 80, (b) cortical surface approximation of day 80 using the interpolation of coefficients in between data points 70 and 90 and (c) point-to-point distance between the two images, colour coded on $L = 30$ SPHARM reconstruction of original cortical shape of day 80.

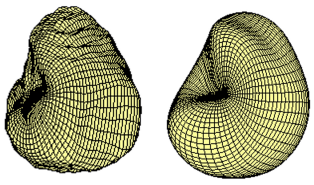

Fig. 6. Cortical surface of day 70 (left) and cortical surface of day 80 reconstructed with bandwidth, $L = 5$ (right). A sulcus is clearly observed at the frontal pole of the day-80 reconstruction, while the day-70 data presents slice artefact without a well-defined sulcus.

$L = 30$ approximation of day 80 using the data from days 70 and 90, and the point-to-point distances. As is evident in Fig. 5c some cortical regions (dark blue: small error) have linear growth from day 70 to day 80, while other regions of the cortex display differential growth. The colour encoded local values represent the computed distance map, which localised nonlinear rate of growth in sheep brains.

### C. Low order cortical surface approximation

More developed brains require higher orders for accurate reconstruction (Fig. 3). Thus it is of interest to examine whether low order SPHARM reconstructions of the cortical surfaces of more developed brains can predict the folding pattern at earlier measured developmental time-points. We reconstructed cortical surfaces using varying bandwidths up to $L = 30$ and computed the similarity between approximations using low orders, and true reconstructed shapes. As expected, day 60 and day 80 brains were most similar to low order reconstructions of day 70 and 90 data, respectively. While it is tempting to assume that cortical development can be traced using an increasing bandwidth, Fig. 6 demonstrates with a counter-example why this is not possible. In this figure, the cortical surface of day 80 was reconstructed with low bandwidth ($L = 5$). A sulcus can be observed at the frontal pole of the brain; in contrast, the original day-70 cortex is largely unfolded.

## IV. CONCLUSION

We have proposed a technique by which to assess nonlinearity in cortical folding development, based on spherical harmonic reconstructions of the cortical surface. Nonlinear growth is identified by the divergence of a simulated cortical surface, approximated using linear interpolation of SPHARM coefficient sets, from the surface reconstructed from the data. Our method is easy to interpret and straight forward to implement. Applied to a fetal sheep brain MRI dataset, the pattern of the cortical development was shown to exhibit differential growth corresponding to localised nonlinear growth rate in certain cortical regions. The results show that reconstruction error, which assesses folding complexity, increases with the development of cortical folds during gestation. This led to formulation and test of the hypothesis that lower order reconstruction of more developed brains could be used to predict the shape of the cortical surface at earlier time points. It was demonstrated that the cortical surface cannot be accurately predicted in this manner, even in the simple folding model of the sheep. Future work will involve the application of the method to human clinical datasets. It is noted that the human brain is more complex than the fetal sheep brain, however the method is equally relevant across species.

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