A computational study of growth-driven folding patterns on shells, with application to the developing brain

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Abstract

We consider the development of folds, or sulci (troughs) and gyri (crests), of the brain. This phenomenon, common to many gyrencephalic species including humans, has attracted recent attention from soft matter physicists. It occurs due to inhomogeneous and predominantly tangential growth of the cortex, causing circumferential compression and leading to a bifurcation of the solution path into a folded configuration. The problem can be framed as one of buckling in the linearized elasticity regime. However, the brain is a very soft solid subject to large strains due to inhomogeneous growth. As a consequence, the morphomechanics of the developing brain demonstrates an extensive post-bifurcation regime. Nonlinear elasticity studies of growth-driven brain folding have established the conditions necessary for the onset of folding and for its progression to configurations broadly resembling gyrencephalic brains. The reference, unfolded, configurations in these treatments have a high degree of symmetry—often spherical. Depending on the boundary conditions, the folded configurations have patterns of symmetry or anti-symmetry. However, these configurations do not approximate the actual morphology of, e.g., human brains, which display unsymmetric folding. More importantly, from a neurodevelopmental standpoint, many of the unsymmetric sulci and gyri are notably robust in their locations. Here, we initiate studies on the physical conditions and parameters responsible for the development of primary sulci and

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gyri. In this preliminary communication we work with idealized geometries, boundary conditions and parameters to perform computations aimed at understanding the formation of the first fold to form: the Central Sulcus.

Keywords
morphology; patterning; cortical folding; elasticity; bifurcation

1 Introduction

Folding, or sulcification and gyrification, of the brain is common in mammals including primates, cetaceans, pachyderms and ungulates. Furrows form in the outermost cortical layer of grey matter, and in species such as humans that demonstrate pronounced gyrencephaly, the sulci can be significantly deeper than the cortical thickness. From a neurophysiological point of view, a folded cortex confers a cognitive advantage by increasing the surface area enclosed within the skull, translating to greater capacity for intelligence. Human brains in a nonpathological state have a gyrification index (ratio of actual surface area to the surface area of an enveloping surface) approaching 2.55 [1]. Neurodevelopmental pathologies are associated with significant departures from this value. In humans, polymicrogyria (shallow, more frequent folding) is associated with developmental delays and epilepsy [2]. Pachygyria (shallow, less frequent and flatter folds) can cause seizures, mental retardation and in rare cases, mania [3]. Lissencephaly (absence of folds) is linked to abnormal EEG patterns, mental retardation and agitation, and manifests in under-developed social skills [4].

Fetal MRI data indicates that the human brain is almost perfectly smooth until 24 weeks of gestation [5]. Therefore, there is a clear neurophysiological motivation to understand the physics governing cortical folding and the conditions for normal or pathological cortical folding.

There have been competing hypotheses for this phenomenon. Most prominent have been (a) the axonal tension model of cortical folding under forces imposed by interconnected neurons [6]—a theory in turn challenged by (b) the principle of inhomogeneous growth of the cortical layer in which circumferential compression due to growth causes an elastic buckling bifurcation, and extreme strains lead to highly folded structures in the post-bifurcation regime. Studies of cutting followed by elastic relaxation on ferret brains established that axonal tension does not cause folding, while
computational studies strongly suggested that inhomogeneous growth does
[7]. Bayly et al [8] explained gyrification patterns by analytic and computa-
tional studies based on inhomogeneous growth, and Tallinen et al [9] used
experiments in a surrogate, polymeric gel model combined with nonlinear
finite element computations to further support the inhomogenous growth
theory[7].

Mismatched elastic moduli between a thin elastic layer and underlying
substrate are common in many non-biological thin film applications [10].
Such stiffness contrast also is a feature that may control the patterns of
wrinkling of fruit and vegetable skins [11]. However, it is not essential to
brain folding [12, 13, 14]; the Young’s Modulus of cortical grey matter and
of the white matter underlying it are of the same order of magnitude [15].

There is now a sizeable literature [8, 9, 16, 17, 18, 19, 20, 21] seeking
to explain aspects of brain folding by inhomogeneous growth in linearized
and, more appropriately, nonlinear elasticity. Some of this literature draws
from linearized buckling of beams and plates [19, 20, 22], but much of the
computational work operates with finite strains and in the post-bifurcation
regime. This work has shed light on the mechanical conditions governing
the development of the organ-wide pathologies of polymicrogyria, pachygyria
and lissencephaly [17, 19, 18]. However, the precise form of the folded cortex
is important beyond its implications for these pathologies. In humans and
other gyrencephalic species, the normally developed brain does not fold into
perfectly symmetric or antisymmetric mode shapes that may be expected
from elastic buckling and post-bifurcation straining. Primary sulci and gyri–
the early forming, prominent folds–are not localized into either symmetric
or anti-symmetric modes of folding [5, 23]. Studies of the sequence of normal
formation of primary sulci and gyri, however, are currently lacking.

Here, we initiate studies on the geometry and physical mechanisms that,
governed by the phenomenology of inhomogeneous growth, lead to primary
sulci and gyri in the normally developed human brain. We exploit the
smoothness of the 24 week-old fetal brain [5]–a convenient reference con-
figuration relative to which we consider growth. Most previous studies have
reduced the problem to one of local, inhomogeneous growth controlled by
a time- or load-dependent scalar parameter [8, 9, 16, 17, 15, 18, 21]. In
contrast, we also pay attention to the developmental processes by which
neurons arise near the ventricles and migrate outward to the cortex [24, 25].

\[1\] Albeit, solved as elastic unloading from the folded configuration with first-order dy-
namics added to numerically stabilize the system against bifurcations.

\[2\] Although there are some differences in the nonlinear response at large strains, these
differences do not have a significant influence on the results presented here.
There, they intercalate circumferentially, causing tangential growth \[26\] in the two-dimensional surface manifold that is the cortical layer. We use the advection-diffusion-reaction equation to model cell migration and production, and couple it to a local model of tangential growth.

Our treatment begins with the governing and constitutive equations in Section 2. The computational framework is briefly presented in Section 3 followed by studies of the effects of: geometry (Section 4), modes of cell migration (Section 5) and cortical thickness (Section 6). Elementary energetic aspects of the bifurcations are studied in (Section 7). Closing remarks appear in Section 8.

## 2 Model and Governing Equations

We adopt the classical formulation of continuum mechanics. The reference configuration representing the smooth, fetal brain is denoted by \(\Omega_0\). Reference positions of material points are vectors \(X \in \Omega_0 \subset \mathbb{R}^3\), and the displacement field vector is \(u \in \mathbb{R}^3\). Points in the deformed (and grown) configuration, \(\Omega\), are labelled \(x = \varphi(X) = X + u\). The deformation gradient tensor is \(F = 1 + \partial u / \partial X\), where 1 is the second-order isotropic tensor. Figure 1 illustrates these kinematics and a few other key aspects of the treatment. Inhomogeneous growth is modelled by the multiplicative, elastogrowth decomposition \(F = F_e F_g\). Denoting the cell concentration in \(\Omega\) by \(c\), tangential growth in the cortical layer is written as

\[
F_g(c(X)) = \begin{cases} 
  f(c) \left(1 - n \otimes N\right), & X \in \text{cortical layer} \\
  1, & X \notin \text{cortical layer}
\end{cases}
\]  

\[
f(c) = \begin{cases} 
  1, & c \leq c_{cr} \\
  \frac{c}{c_{cr}}, & c > c_{cr}
\end{cases}
\]

with \(n\) and \(N\) representing the surface normals on \(\partial \Omega\) and \(\partial \Omega_0\), respectively. The form of \(F_g\) in Equation (1a) ensures that cell intercalation-driven tangential growth occurs only in the cortex. The form of \(f(c)\) in Equation (1b) ensures that tangential expansion occurs only after the cell concentration in the cortex has exceeded the threshold of \(c_{cr}\), thus modelling the effect of free volume. We use \(c_{cr}(x) = c(x, 0)\), the initial concentration.

We consider hemispherical and hemi-ellipsoidal reference configurations, \(\Omega_0\), with cortical layers of varying thicknesses, forming thin shells of grey matter resting on elastic foundations of white matter in each case. The white matter is itself a thick shell with the inner surface, \(\partial \Omega_i\) representing
the ventricles (Figure 1b). Since the time scales of growth are much greater
than the intrinsic viscoelastic relaxation times of the soft, jelly-like brain,
its constitutive response is modelled by an elastically compressible, neo-
Hookean strain energy density expressed as a function of $F^e$,

$$F^e(c) = F \left( F^E(c) \right)^{-1},$$  \hspace{1cm} (2a)  

$$W(F^e) = \frac{1}{4} \lambda (\det F^e \cdot F^e - 1) - \frac{1}{2} \left( \frac{1}{2} \lambda + \mu \right) (\log \det F^e \cdot F^e) + \frac{1}{2} \mu (F^e : F^e - 3),$$  \hspace{1cm} (2b)  

where $\lambda$ and $\mu$ are Lamé parameters. The first Piola-Kirchhoff stress $P$,
and its governing quasistatic equilibrium equation are,

$$P = \frac{\partial W}{\partial F^e},$$  \hspace{1cm} (3a)  

$$\text{Div} P = 0, \quad \text{in } \Omega_0.$$  \hspace{1cm} (3b)  

Neuronal migration and production are modelled by an advection-diffusion-
reaction equation (4) written on the deformed and grown configuration, $\Omega$:

$$\frac{\partial c}{\partial t} = D \nabla^2 c - v \cdot \nabla c + R, \quad \text{in } \Omega,$$  \hspace{1cm} (4)  

where $D$ is an effective diffusivity modelling random cell migration, $v$ is a
directed migration velocity and the reaction term, $R$, models cell multiplica-
tion. The parameters used in our computations are summarized in Table 1.
Near elastic incompressibility is modelled in the ratio of Lamé parameters,
which corresponds to a Poisson ratio $\nu = 0.49$ in the regime of linearized
elasticity. The dynamic quantities $D$ and $v$ have been scaled up in magnitude relative to physiological values in order to speed up our computations.
The scaling constant $v^c$ gives the migration velocity’s magnitude.

2.1 Initial and Boundary Conditions

Working with a non-dimensional cell concentration, we impose initial con-
ditions

$$c(x, 0) = \begin{cases} 1.0 & x \in \partial \Omega_i^i \\ 0.5 & x \notin \partial \Omega_i^i \end{cases}$$  \hspace{1cm} (5)
The boundary conditions on growth-driven mechanics are,

\[ u(X) = 0, \text{ for } X \in \partial \Omega_i^i \]  
\[ u_1(X) = 0, \text{ for } X_1 = 0 \]  
\[ PN = 0, \text{ for } X \in \partial \Omega \backslash \partial \Omega_i^i \]

and on the advection-diffusion-reaction of cells:

\[ c(x, t) = 1.0, \text{ for } x \in \partial \Omega_i^j \]  
\[ (-D \nabla c + cv) \cdot n = 0, \text{ for } x \in \partial \Omega \backslash \partial \Omega_i^j \]

representing cell birth on \( \partial \Omega_i^i \). The distinct boundaries have been delineated in Figure 1b.

The initial conditions (5) and boundary conditions (7a-7b) applied to Equation (4) drive the neuronal population from the ventricles bounded by \( \partial \Omega_i^i \) toward the cortical surface bounded by \( \partial \Omega_o^o \). In the cortex, cell intercalation drives tangential growth, creating a compressive circumferential stress that induces a buckling bifurcation, and post-bifurcation straining into folded structures of sulci and gyri. These folding phenomena are subjected to a parametric study in Sections 4-7.

### 3 Computational framework

All computations were carried out using an open source patterning and morphology code introduced previously [27]. It is built off the deal.II open source finite element library [28, 29]. Code parallelization is based

| Parameter                              | Value                    |
|----------------------------------------|--------------------------|
| Diffusivity \((D)\)                   | \(0.1 \text{ mm}^2 \cdot \text{s}^{-1}\) |
| Lamé parameter \(\lambda\)            | \(8.2 \times 10^4 \text{ Pa}\)   |
| Lamé parameter \(\mu\)                | \(1.67 \times 10^3 \text{ Pa}\)   |
| Velocity constant \((v^c)\)           | \(0.1 \text{ mm} \cdot \text{s}^{-1}\) |
| Cellular Multiplication Constant \((R)\) | \(0.1 \text{ s}^{-1}\) |
| Outer Radius of hemispherical brain \((R_o)\) | \(20 \text{ mm}\) |
| Inner Radius of hemispherical brain \((r_i)\) | \(10 \text{ mm}\) |
on MPI, and the SuperLU direct solver \cite{30} was used. Post-processing was carried out in the visualization toolkit \textit{VisIt} 2.12.0 \cite{31}. We also used measurements taken from the fetal brain atlas developed by Habas et al. \cite{5} using the MRI viewing software \textit{ITK-Snap} \cite{32} to obtain the geometric parameters, namely aspect ratios and cortical thickness, in our model. The code for all numerical examples presented here is available at https://github.com/mechanoChem/patternMorph.

4 The Effect of geometry: Hemispherical and hemi-ellipsoidal models

Our first models used a hemispherical approximation of the brain’s geometry. With Equations (1a-7b) and $R = 0$, the model produced patterns of sulci and gyri in Figure 2a bearing a great deal of similarity to the lattice-like arrangement seen in Tallinen et al. \cite{21}. However, this degree of regularity is not seen in the human brain. Thus, the folded structure bore little global similarity, either spatially or in its temporal evolution, with the anatomical human brain shown in Figure 2a (left). Specifically, the primary structures, such as the Central Sulcus, Circular Sulcus, Pre- and Post-central Gyri, the Calcarine Sulcus and others, \cite{5} were not seen.

In seeking to better predict the mature brain’s morphology, we first considered the approximation of its geometry. The human brain’s shape is better approximated by a hemi-ellipsoid than a hemisphere, as indicated by fetal MRI data \cite{5, 33, 34, 35}. From data in Chapman et al. at 24 Gestational Weeks \cite{34}, the point before sulcification and gyrification, we infer the ratio of the best-approximating ellipsoid’s axes to be $1:0.75:1$ along the $e_1, e_2, e_3$ directions. The shortest axis, $e_2$, is along the ears (Figure 2b, right).

We therefore transformed the hemisphere to a hemi-ellipsoid with the aspect ratios $1:0.75:1$. While the spherical geometry imposed radial advection and diffusion, the transformation to ellipsoidal symmetry suggests at least two mappings of the advective velocity, $\mathbf{v}$, both resulting in angularly non-uniform cellular concentration over the cortex (see Section 5). This motivates consideration of a third model, which enforces angularly uniform cell concentration in the cortex, thus isolating the effect of spherical/ellipsoidal geometry from the resulting cortical cell distribution.

The obvious approach to such a cell distribution is to eliminate advection and diffusion in Equation (4) by setting $\mathbf{v} = 0$ and $D = 0$, with $R > 0$. This independence from cell motion in favor of cell multiplication has been adopted by several authors previously \cite{8, 9, 16, 17, 15, 18, 22, 36, 37}.
The resulting morphology is shown in Figure 2b, and compared with the spherical model from Figure 2a. Note that both these models employ a cortical thickness of 10%. As demonstrated by the computations, the ellipsoidal geometry generates a structure resembling the early Central Sulcus (circled in Figure 2b). With this shape, therefore, we observe patterning more representative of the human brain folding than with the spherical geometry. Motivated by this result, the remainder of this communication is focused on the ellipsoidal geometry.

5 The effect of cell motion

The transformation from a hemisphere to a hemi-ellipsoid is obtained by scaling the spherical radius by $\alpha = 1, \beta = 0.75, \gamma = 1$ in the directions $e_1, e_2, e_3$ [34]. This transformation suggests at least two mappings of advective velocity. These are developed in detail in Sections 5.1 and 5.2, and in Section 5.3, their influences on formation of the early Central Sulcus are compared with the cell multiplication model of Section 4.

5.1 Radial advection velocity

In order to radially orient the advection velocity vector, we first define a direction vector, $\hat{x^e}$ in Equation (8a), for any point $x^e$ in the ellipsoid $\Omega$. We also introduce the standard polar angles $\theta$ and $\phi$, given by Equations 8b and 8c, and illustrated in Figure 3a.

\[
\hat{x^e} = \frac{x^e}{\|x^e\|} \quad \text{(8a)}
\]
\[
\theta = \cos^{-1}(\hat{x^e}_3) \quad \text{(8b)}
\]
\[
\phi = \sin^{-1}\left(\frac{\hat{x^e}_1}{\cos \theta}\right) \quad \text{(8c)}
\]
\[
\mathbf{v}^r = \mathbf{v}^c \begin{bmatrix} \cos \phi \sin \theta \\ \sin \phi \sin \theta \\ \cos \theta \end{bmatrix} \quad \text{(8d)}
\]

Here, $v^c = \|v^c\|$ is the magnitude of the radial velocity vector $v^c$ from the spherical geometry, and $v^r$ is the radial velocity in an ellipsoidal geometry. An easy calculation reveals that the sphere-to-ellipsoid transformation biases $v^r$ along the longer axes of the ellipsoid, in comparison with $v^c$. This is seen to some degree in Figure 3a, where $v^r$ is more aligned with the long axis, an
effect that becomes more pronounced with aspect ratio. This bias creates a band of higher cell concentration lying in the plane of the longer axes, shown in Figure 3b (right).

Another consequence of the sphere-to-ellipsoid transformation is nonuniform ellipsoidal shell thickness. To account for this effect, we identify points on the inner and outer surfaces, \( x_{\text{min}} \) and \( x_{\text{max}} \), along a vector, \( \hat{x}^e \) (or \( v^e \)), as shown in Figure 3a (right) and described in Equations (9a) and (9b). There, \( r_i \) and \( R_o \) are the inner and outer spherical radii, which are transformed into the semi-axes of inner and outer ellipsoids.

We define a position-dependent thickness scaling factor, \( t^r_{\text{scale}} \), as the difference between \( \| x_{\text{max}} \| \) and \( \| x_{\text{min}} \| \) divided by the thickness of the sphere, \( R_o - r_i \) (Equation (9c)). It falls to its minimum value in the \( e_2 \) direction, as seen in Figure 3a. This scaling is then applied to the mapped radial velocity, \( v^r \), to give the final, scaled velocity vector, \( v^r_{\text{scale}} \), shown in Equation (9d).

\[
\begin{align*}
x_{\text{max}} &= \left\{ \begin{array}{c}
\alpha \cdot R_o \cos \phi \sin \theta \\
\beta \cdot R_o \sin \phi \sin \theta \\
\gamma \cdot R_o \cos \theta
\end{array} \right\} \\
x_{\text{min}} &= \left\{ \begin{array}{c}
\alpha \cdot r_i \cos \phi \sin \theta \\
\beta \cdot r_i \sin \phi \sin \theta \\
\gamma \cdot r_i \cos \theta
\end{array} \right\} \\
t^r_{\text{scale}} &= \frac{\| x_{\text{max}} \| - \| x_{\text{min}} \|}{R_o - r_i} \\
v^r_{\text{scale}} &= t^r_{\text{scale}} v^r
\end{align*}
\]

### 5.2 Normal advection velocity

It is trivial that, for the spherical geometry, a radial vector field also is normal to concentric spherical shells between the inner and outer surfaces. However, a radial vector field in an ellipsoid is distinct from one that is normal to concentric ellipsoidal surfaces. In order to generate an advection velocity field that is normal to concentric ellipsoidal surfaces, we begin by computing the ellipsoidal surface, say \( \psi \), on which a point, \( x^e \in \Omega \), lies.

Using the scaling factors \( \alpha, \beta, \gamma \) we write the equation of an ellipsoid, obtained by transforming a spherical surface of radius \( R^c \), as

\[
\left( \frac{x_1}{\alpha R^c} \right)^2 + \left( \frac{x_2}{\beta R^c} \right)^2 + \left( \frac{x_3}{\gamma R^c} \right)^2 = 1
\]

We introduce Equation (11a), which maps any point from the hemi-ellipsoid, \( x^e \), back to its originating point \( x^c \) in the hemisphere. This leads to Equation 9.
(11b) for \( R^c \) in terms of \( x^e \).

\[
x^e = \begin{cases} 
  x^e_1/\alpha \\
  x^e_2/\beta \\
  x^e_3/\gamma 
\end{cases}
\]  

(11a)

\[
R^c = \sqrt{\left(\frac{x^e_1}{\alpha}\right)^2 + \left(\frac{x^e_2}{\beta}\right)^2 + \left(\frac{x^e_3}{\gamma}\right)^2}
\]  

(11b)

Then, \( \psi(x^e) - 1 = 0 \) is the ellipsoidal surface, containing the point \( x^e \), where \( \psi \) is given by Equation (12a). We then generate an advection vector field \( v^n \) that is everywhere normal to \( \psi - 1 = 0 \). This is illustrated in Figure 3a (left) and shown in Equation (12b).

\[
\psi(x^e) = \left(\frac{x^e_1}{\alpha R^c}\right)^2 + \left(\frac{x^e_2}{\beta R^c}\right)^2 + \left(\frac{x^e_3}{\gamma R^c}\right)^2
\]  

(12a)

\[
v^n = v^c \frac{\nabla \psi}{\|\nabla \psi\|}
\]  

(12b)

Similarly to Equation 9d, we scale \( v^n \) to generate \( v^{n}_{\text{scale}} \). We define \( \tilde{x}_{\text{max}}^e \) as the intersection of the line containing \( x^e \) and parallel to \( v^n \), and the outer hemi-ellipsoidal surface \( (R^c = R_o \text{ in Equation } (12a)) \). Analogously, define \( \tilde{x}_{\text{min}}^e \) as the intersection of the line containing \( x^e \) and parallel to \( v^n \), and the inner hemi-ellipsoidal surface \( (R^c = r_i \text{ in Equation } (12a)) \). The scaling follows as shown in Equations (13a-13b).

\[
t^{n}_{\text{scale}} = \frac{\|\tilde{x}_{\text{max}}^e\| - \|\tilde{x}_{\text{min}}^e\|}{R_o - r_i}
\]  

(13a)

\[
v^{n}_{\text{scale}} = t^{n}_{\text{scale}} v^n
\]  

(13b)

5.3 Influences of cell motion on morphology

We have three models for cell accumulation in the cortex: radial advection, normal advection, and multiplication without migration. The biological literature does not explicitly inform one of these models over the others. Therefore, we compared these three models for patterning in the ellipsoidal geometry against the development of the early Central Sulcus in fetal MRI [5, 33], seen in Figure 2b (left).

From Figure 3c, it is obvious that including the physics of cell motion, by advection and diffusion, is important for achieving anatomical sulcus formation. In both the radial and normal mappings of the advection velocity,
a structure resembling the beginnings of a Central Sulcus forms, although this feature is more clearly defined in the radial mapping. It is also important to note that the cell multiplication model, which neglects cell advection and diffusion and instead models the proliferation of cells in the cortical layer, shows no evidence of a structure resembling any of the primary sulci. We therefore conclude that cell motion is important to the physics of cortical folding and for attaining physiologically accurate morphologies. Since the radial mapping of advection velocity best reproduces early Central Sulcus formation, this model will be carried through to Sections 6 and 7.

6 The effect of cortical thickness

Several cortical folding studies have examined the buckling of a thin, elastic layer on an elastic substrate [8, 16, 36, 38, 39, 11]. These analytic and computational investigations have considered a variety of geometries including plates and shells to elucidate the role of the layer-to-substrate thickness ratio in forming folding patterns. We therefore consider the implications of cortical thickness for the folding patterns and for developing anatomically accurate structures.

Based upon measurements taken from fetal MRI data at 24 Gestational Weeks [5, 35], the smooth state before formation of the Central Sulcus as seen in Figure 2b (left), we found an average cortical thickness of 2 mm. This value, examined in concert with the global dimensions of the 24 week-old fetal brain, corresponds to a 7% cortical thickness in our model. We conducted a sensitivity study of the folding pattern to cortical thickness values of 7, 10, 14 and 18 percent to determine this parameter’s role in the development of the Central Sulcus.

Seen in Figure 4a, we observe three key influences of cortical thickness on patterning:

a) Sulcification wavelength increases with the cortical shell thickness. This result is in agreement with the key finding in the work of Yin et al [11].

b) The actual pattern of sulcification is also sensitive to cortical thickness. Moving in the negative $e_1$ direction from the crown (in the caudal direction), the transition from smooth to folded cortex happens further from the pole as the cortical thickness increases.

c) The 7% cortical thickness case displays a morphology most similar to that seen in fetal MRI data [35], namely the development of an
early Central Sulcus-like structure, circled in red in Figure 4a. It is important to reiterate that this value of the thickness parameter comes from anatomical data.

In Figure 4b, more detailed observation is made of the 7% cortical thickness computation. A horizontal slice is shown through the region of folding that most resembles the early Central Sulcus (red arrows). In the far right of the figure, we compare this slice with a similar section through the fetal human brain. Red arrows point to the Central Sulcus on both left and right hemispheres in the MRI data. This comparison makes apparent that taking into account a hemi-ellipsoidal geometry, a radial mapping of cellular advection and a cortical thickness of 7% results in a structure bearing similarity to the early Central Sulcus that develops in the fetal human brain.

**Remark.** The ellipsoidal geometries in Figures 2b (right), 3c; 4a (7%), 4b and 5d demonstrate folding along the dorsal plane, which is not an anatomical feature. A more accurate fetal geometric model would include the longitudinal fissure in this position, and these folds would not develop.

### 7 Energetics of folding

We investigated the energetics of folding to seek further insight to this process. We computed the total strain energy, $E(t)$, by integrating the Neo-Hookean strain energy density function, Equation (2b), over the domain. This calculation, shown in Equation (14), is carried out at each time instant, during the temporally evolving finite element computation.

$$E(t) = \int_{\Omega_0} W(F^e(X, t)) dV \quad (14)$$

The boundary conditions in Equation (7a) and (7b) drive an increasing cell concentration and growth in the cortex. Therefore, $E(t)$ is an increasing function, masking any interesting behavior around bifurcations. However, since time plays the role of a loading parameter, derivatives of $E$ with respect to $t$ can reveal insights to the system’s elastic stiffness and susceptibility to bifurcations.

The second time derivative of the elastic strain energy, $d^2E/dt^2$, is a measure of system stiffness. Negative values highlight instances of bifurcation as well as a relative measure of their severity. Figure 5 shows the
The evolution of $d^2E/dt^2$ with a hemi-ellipsoidal geometry, radial advection velocity, and 7% cortical thickness. The curve is compared with the folding pattern at four key instants. Also see Supplementary Movie 1.

a) Figure 5a shows the growing brain at the time step prior to the system stiffness becoming negative. Because the global stiffness value is positive at this time, the system is in a condition of stability; neither a bifurcation nor pronounced folding have occurred.

b) Figure 5b shows the growing brain at the instant when the system stiffness has reached a local minimum. Here, we note that a band of deformation has begun to form, although no substantial folding has occurred. Although the system stiffness is negative, and it would be expected to be elastically unstable with respect to the global deformation, the first-order dynamics imposed by cell transport allows the system to relax in the regimes of elastic instability. Therefore, converged solutions are obtained.

c) Figure 5c shows the system at the time step prior to a large disturbance in system stiffness. Some degree of deformation with the onset of folding is evident here, since the system has been in a state of “elastic instability” from the time displayed in Figure 5b.

d) Figure 5d shows the system immediately following a large fluctuation in the system stiffness into the negative regime. This disturbance is indicative of a major bifurcation event accompanied by a notable degree of folding.

This elementary study of the elastic strain energy provides an important measure of system stiffness and stability (if only elastic deformation is considered) and identifies bifurcations. It holds potential for greater insight into the system’s dynamic evolution in more complex sequences of folding.

8 Conclusions

This letter initiates a study of normal morphological development of the human brain, specifically of the sequence of sulcification and gyrification. Our focus is on the physical processes of migration and tangential intercalation of neurons in the cortex, leading to growth. These processes are governed by the advection-diffusion-reaction equation and inhomogeneous growth in the setting of nonlinear elasticity, respectively. Using these mathematical
models, shapes informed by medical imaging data and a finite element framework, we have identified and studied the influence of three model parameters on anatomically representative cortical folding: overall system geometry, cell motion and thickness of the cortical layer.

This letter represents only the first stage in our studies. For this reason, we have focused on the Central Sulcus, the first of the primary folds to develop in the fetal human brain. We are able to make three important conclusions: As discussed in Section 4, a hemi-ellipsoidal geometry leads to folded morphologies that include a structure resembling the early Central Sulcus in fetal development. The associated transformation in our study from a hemispherical to the hemi-ellipsoidal geometry suggests two mappings of cell advection velocity and the consideration of a strict cell multiplication model. In Sections 4 and 5, we explored these treatments and concluded that including cell motion is important for proper modelling sulcification and gyrification. Additionally, a radial mapping of the advection velocity induces folding morphologies that better resemble the early Central Sulcus. It is notable that nothing resembling a primary sulcus forms in the model neglecting migration. This suggests that the gradient of cell concentration induced by the mechanism of migration influences the subsequent distribution of growth strains to create the Central Sulcus-like structure as seen in Figure 3c.

Perhaps most importantly, in Section 6, our model substantiates the importance of a physiologically grounded treatment of cortical thickness. Medical imaging data suggests a cortical layer corresponding to a 7% thickness in our model. A numerical study of variable cortical thickness confirmed that the value motivated by MRI data indeed produced results bearing similarities to those seen in early Central Sulcus formation. Finally, in Section 7, we discussed the second derivative of the elastic strain energy as a measure of the system’s stiffness, elastic stability and as an indicator of bifurcations. We anticipate that this approach will prove important in future studies of the sequence of primary sulcification and gyrification.

The identification of geometry, mechanism of cell motion and cortical thickness as parameters that influence the development of the early Central Sulcus remains a preliminary finding. There is still a great deal of understanding to be gained of the physics underlying cortical folding. This study has highlighted the importance of incorporating realistic geometries into the model and paying attention to imaging data. In the future, we plan to incorporate additional data both to inform model parameters as well as drive the model by rigorous methods of data science.
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Figure 1: (a) Illustration of the brain as a deforming (growing) continuum body in reference and deformed configurations and (b) illustration of domain boundaries on a mathematically idealized deformed configuration $\Omega$. 
Figure 2: a) Representative normal human brain (Creative Commons photo: Shannan Muskopf), left, and hemispherical model of cortical folding, right, b) Fetal MRI data [33] at 24 and 25 Gestational Weeks (left) and cortical folding from an ellipsoidal reference geometry with an early Central Sulcus-like structure circled (right)
Figure 3: a) Illustration of two mappings of advection velocity b) nonuniform cellular distributions for normal (left) and radial (right) mappings, c) resulting patterning of two mappings of advection (top) and cellular multiplication (bottom). All three models use a 7% cortical thickness.
Figure 4: a) Morphology resulting from variations of cortical thickness and b) horizontal section cut of 7% cortical thickness model as compared to fetal MRI data of a similar section [35].
Figure 5: Plot of the second time derivative of elastic energy vs. time (center) and four points of interest.