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

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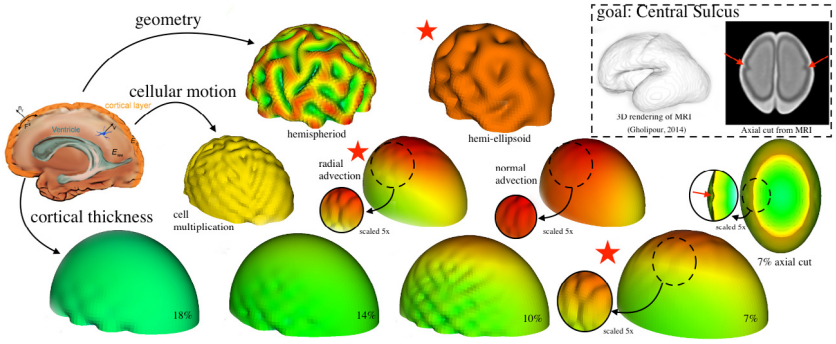
GRAPHICAL ABSTRACT



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ABSTRACT

We consider the mechanisms by which folds, or sulci (troughs) and gyri (crests), develop in the brain. This feature, 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, which causes circumferential compression, leading to a bifurcation of the solution path to a folded configuration. The problem can be framed as one of buckling in the regime of linearized elasticity. However, the brain is a very soft solid, which is 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—typically, ellipsoidal. Depending on the boundary conditions, the folded configurations have symmetric or anti-symmetric patterns. 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 mechanisms and geometry that control the development of primary sulci and gyri. In this preliminary communication we carry out computations with idealized geometries, boundary conditions and parameters, seeking a pattern resembling one of the first folds to form: the Central Sulcus.

1. Introduction

Folding, or sulcification and gyrification, of the brain is common in mammals including primates, cetaceans, pachyderms and

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ungulates. Folds form in the cortical layer of gray 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 indicate that the human brain is almost perfectly smooth until 24 weeks of gestation [5–7], from which stage gyrification proceeds until well after birth. 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 [8]—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 [9]. Bayly et al. [10] explained gyrification patterns by analytic and computational studies based on inhomogeneous growth, and Tallinen et al. [11] used experiments in a surrogate, polymeric gel model combined with nonlinear finite element computations to further support the inhomogeneous growth theory.[1]

Mismatched elastic moduli between a thin elastic layer and an underlying substrate are common in many non-biological thin film applications [12]. Such stiffness contrast also is a feature that may control the patterns of wrinkling of fruit and vegetable skins [13]. However, it is not essential to brain folding [14–16]; the Young's Modulus of cortical gray matter and of the white matter underlying it are of the same order of magnitude [17].

There is now a sizeable literature [10,11,17–23] 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 [21,22,24], but much of the computational work is based on finite strains, and operates 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 [19–21]. 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 on reference configurations of high symmetry. Primary sulci and gyri – the early forming, prominent folds – are not localized into either symmetric or antisymmetric modes of folding [5,25]. Studies of the sequence of normal formation of primary sulci and gyri, however, are currently lacking.

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

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. In this first communication, we vary (a) geometries guided by quantitative data from anatomical measurements, (b) mechanisms of cell accumulation by local proliferation, and by migration, and (c) thickness of the cortical layer. Our goal is to reproduce a pattern that suggests the incipient Central Sulcus (Fig. 1a). Apart from its location, which is roughly in the coronal plane, and its orientation, which is close to vertical, this target is recognized qualitatively rather than quantitatively in this preliminary computational study. We exploit the smoothness of the 24 week-old fetal brain [5–7], a convenient reference configuration, 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 [10,11,17–20,23]. *Effectively, this addresses only the mechanism of local cell proliferation. In contrast, we also pay attention to the developmental processes by which neurons arise near the ventricles and migrate outward to the cortex* [26,27]. *There, they intercalate circumferentially, causing tangential growth* [28] *in the two-dimensional surface manifold that is the cortical layer. We use the advection–diffusion–reaction equation to model cell migration and proliferation, 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), mechanisms of cell migration (Section 5) and cortical thickness (Section 6). The role that energy variations play in the development of bifurcations is 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 Ω_0. Reference positions of material points are vectors $\boldsymbol{X} \in \Omega_0 \subset \mathbb{R}^3$, and the displacement field vector is $\boldsymbol{u} \in \mathbb{R}^3$. Points in the deformed (and grown) configuration, Ω, are labeled $\boldsymbol{x} = \boldsymbol{\varphi}(\boldsymbol{X}) = \boldsymbol{X} + \boldsymbol{u}$. The deformation gradient tensor is $\boldsymbol{F} = \boldsymbol{1} + \partial \boldsymbol{u}/\partial \boldsymbol{X}$, where $\boldsymbol{1}$ is the second-order isotropic tensor. Fig. 1b illustrates these kinematics and a few other key aspects of the treatment. Inhomogeneous growth is modeled by the multiplicative, *elastogrowth* decomposition $\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}}\boldsymbol{F}^{\mathrm{g}}$. Denoting the cell concentration in Ω by c, tangential growth in the cortical layer is written as

$$\boldsymbol{F}^{\mathrm{g}}(c(\boldsymbol{\varphi}(\boldsymbol{X}))) = \begin{cases} \dfrac{1}{2-f(c)}\left(\boldsymbol{1} - (f(c)-1)\boldsymbol{N}\otimes\boldsymbol{N}\right), & \boldsymbol{X} \in \text{cortical layer} \\ \boldsymbol{1}, & \boldsymbol{X} \notin \text{cortical layer} \end{cases} \tag{1a}$$

$$f(c) = \begin{cases} 1, & c \le c_{\mathrm{cr}} \\ \dfrac{c}{c_{\mathrm{cr}}}, & c > c_{\mathrm{cr}} \end{cases} \tag{1b}$$

with $\boldsymbol{N}$ representing the surface normal on $\partial\Omega_0$. The form of $\boldsymbol{F}^{\mathrm{g}}$ in Eq. (1a) ensures that cell intercalation-driven growth occurs only in the cortex, and within the cortical tangent plane. The form of $f(c)$ in Eq. (1b) ensures that tangential expansion occurs only after the cell concentration in the cortex has exceeded the threshold of c_{cr}, thus modeling the effect of free volume. We use $c_{\mathrm{cr}}(\boldsymbol{x}) = c(\boldsymbol{\varphi}(\boldsymbol{X}), 0)$, the initial concentration.

We consider hemispherical and hemi-ellipsoidal reference configurations, Ω_0, with cortical layers of varying thicknesses, forming thin shells of gray matter resting on elastic foundations of white matter in each case. The white matter is itself a thick shell with the inner surface, $\partial\Omega^{\mathrm{i}}$ representing the ventricles (Fig. 1c). Since the time scales of growth are much greater than the intrinsic