A Mathematical Model of Cerebral Cortical Folding Development

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Introduction

The cerebral cortex is the outer covering of the brain. In large mammals, it is intricately folded into gyri (hills) and sulci (valleys). To date, there have been three leading biological hypotheses that explain the development of cortical folding. The mechanism behind this folding process is not fully understood yet.

Our mathematical model for cerebral cortex development is more biologically relevant compared to most other models and yields decent folding patterns. Also, it is a unique model in the sense of utilizing three leading hypotheses for cortical folding. To date, brain folding models are all based on either one or two of these hypotheses.

Theory

1st hypothesis and how it is used in the model: Van Essen [1] proposed the Axonal Tension Hypothesis (ATH) in 1997. According to this biomechanical hypothesis, areas that are packed with neurons make lots of cortico-cortical connections and tend to create bucklings; therefore, mechanical tension along cortico-cortical connections is the major force for cortical folding. In our model, mechanical tension is represented as tangential force vectors acting on certain areas of the cortex symmetrically.

2nd hypothesis and how it is used in the model: Intermediate Progenitor Hypothesis (IPH) is a biochemical hypothesis and was proposed in 2006 [2]. It claims that folding patterns on the Cortical Plate (CP) are caused by an irregularly distributed cell population, and the Intermediate Progenitor Cells (IPCs) have a major role in this process.

Both ATH [1] and IPH [2] hypotheses coincide on the claim that regions which are densely packed with neurons develop into gyri, while regions having fewer neurons become sulci. Therefore, it is plausible to assume that the magnitude of applied forces is proportional to the density of neurons. According to IPH, the density and production of cortical neurons are controlled by IPCs, and there are some morphogens which control the production of IPCs. Thus, the morphogen levels affect neuron production in the cortex. So, it is plausible to assume that the magnitude of applied forces is proportional to the morphogen levels as well.

3rd hypothesis and how it is used in the model: Differential Growth Hypothesis (DGH) was proposed in 1972 and is the oldest among the leading hypotheses. [3]. Brain cortex consists of white and gray matter, and each of them has different elasticity coefficients. The DGH claims that cortical folding occurs due to the significant difference in elasticity among different layers. In our model, we used actual Young's Modulus (E) values, also referred to as modulus of elasticity, for the cortex and inner core of the human brain, which is $1389 \pm 289 \frac{N}{m^2}$ for the cortex (gray matter) and $1895 \pm 592 \frac{N}{m^2}$ for the inner core (white matter) [4]. So, white matter is 39% stiffer than gray matter on average. Therefore, it is plausible to conclude that the cortex and the core are classified as two different layers.

A Nonlinear Model

Our model suggests that tangential growth of the cortex drives the folding process, and tangential force vectors are the primary factor of buckling. Deeper layers grow in response to the resulting growth-induced stress, i.e., the core is allowed to grow. Brain tissue is assumed to be isotropic, hyperelastic material, and the theory of volumetric growth developed by Rodriguez [5] is used. The constitutive stress-strain relationship is given as following:

$$\sigma = J^{*-1} F^* \frac{\partial W}{\partial F^{*T}}$$

where F^* is an elastic tensor, J^* is $\det F^*$ and W is a strain energy density function.

A standard neo-Hookean material model [6] is used and the related strain energy density function W is the following:

$$W = \frac{\mu}{2}\left(I_1^* J^{*-\frac{2}{3}} - 3\right) + \frac{\kappa}{2}(J^* - 1)^2$$

where μ is bulk modulus $\left(\frac{E}{3(1-2\nu)}\right)$, κ are the parameters of the hyperelastic model, and I_1^* is trace of $F^{*T}F^*$. The tissue is assumed to be nearly incompressible, thus, $\kappa \gg \mu$.

Initial conditions: For both displacement and velocity fields, initial values are taken as zero.

Boundary conditions: The diameter on which the domain placed is assumed to be a fixed line, therefore, displacement and velocity of this line are taken as zero.

Turing system: A Turing reaction-diffusion system was used in the model to determine the morphogen levels in the cortex. Turing systems have been widely used in biomathematical pattern formation models since Alan M. Turing proposed it in 1952 [7]. The system consists of two differential reaction-diffusion equations:

$$\frac{\partial U}{\partial t} = d_u \nabla^2 U + p(U,V),$$

$$\frac{\partial V}{\partial t} = d_u \nabla^2 V + q(U,V),$$

where $U(x,t)$ and $V(x,t)$ are concentrations of an activator morphogen and an inhibitor morphogen, respectively, at spatial position x and time t. The functions p and q represent the reaction kinetics. In this system and equations, we assume activator u to be proportional to the magnitude of the axonal tension force.

Experimental Set-up

Parameters: The following parameters are used and were obtained from actual data of the human brain:

r = 0.0404 m: radius of brain at 28th week [10]
t = 2.5 mm: thickness of the gray matter [10]
E_g = 1.389 kPa: Young's Mod. of gray matter [4]
E_w = 1.895 kPa: Young's Mod. of white matter [4]
$\boldsymbol{\nu}$ = 0.4583: Poisson ratio of brain tissue [11]
d = 1.1 g/cm^3 : density of brain tissue [12]

Geometry: Simulations are performed in
(i) a two-dimensional (2D) semi-circular domain,
(ii) a 2D semi-elliptical domain

Boundary loads: In order to model axonal tension as a force pulling together on the semi-circular and semi-elliptical domains, we use vector f loaded at some nodes as shown in Figure 1. The magnitude of f is given, and its direction is controlled by combinations of the two components: f_x and f_y. These force components are calculated for each vector, and their values are entered as the "boundary load" components in Comsol.

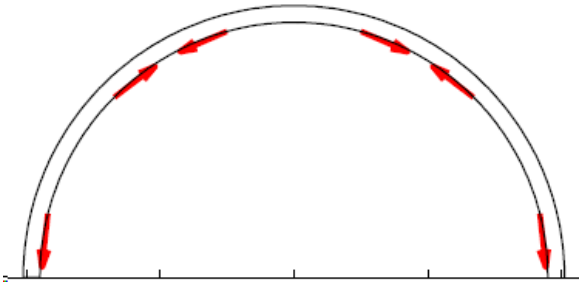

Figure 1: An illustration for the place and strength of the applied axonal tension forces based on a Turing pattern [8]

Material type and material model: Since brain tissue may be roughly taken as an isotropic, hyperelastic material [9], both cortex and inner core are taken as a hyperelastic, nearly-incompressible material. A standard neo-Hookean material model was used.

Linear growth: During the development of brain, growth occurs in both length and radius. To include this biological fact in the model, we use "hygroscopic swelling" feature of Comsol for the inner core.

Tangential growth is assumed to exist for both the cortex and the inner core while radial growth is assumed to exist for the core.

Method, Simulations and Simulation App

Finite element simulations are performed using COMSOL Multiphysics software (V.5.4, COMSOL Inc., Burlington, MA) within two domains, which are a two-dimensional semi-circular domain and a two-dimensional semi-elliptical domain. A 2D, time-dependent scheme is used together with Nonlinear Structural Mechanics module.

The significant parameters (radius of the cortex, the thickness of the gray matter, Young's Modulus, Poisson Ratio) are placed on the Application Builder of Comsol so that the effects of different values are seen quickly during the simulations.

Simulation Results

1. Semi-elliptical domain: The human brain is more like a semi-ellipsoid, that is why we first prefer 2D semi-elliptical domain for simulations:

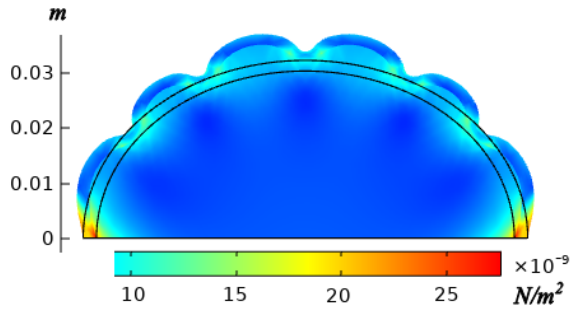

Figure 2. Simulation with a 2D semi-elliptical domain. The colors represent the Von Mises stress.

Comment: Compared to the MR images shown in Figure 4, Figure 2 demonstrates decent bucklings on the cortex together with volumetric growth. The initial symmetry of the elliptical domain is preserved on the image as well.

2. Semi-circular domain: To make a comparison with the semi-elliptical domain, the following simulation was done:

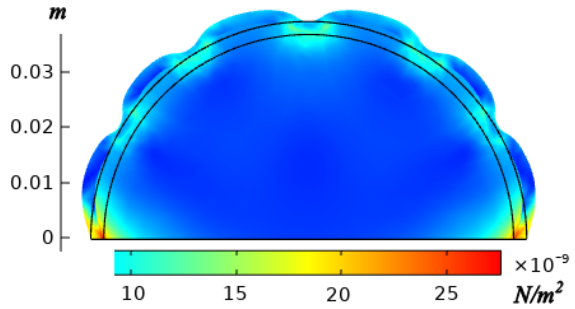

Figure 3. Simulation with a 2D semi-circular domain.

Comment: Figure 3 also shows decent bucklings on the cortex, but with a little decreased volumetric growth in the center.

MR images:

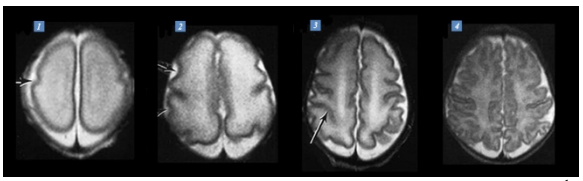

Figure 4. MR images of a preterm infant born at the 25th, 28th, 32nd and 40th week of gestational age (GA). The MR images are taken at a supraventricular level in the transverse plane. [13]

Conclusions

The current model is distinct from previous models since it utilizes all three leading hypotheses of the cortical folding, and more biologically relevant compared to most other models in terms of being time-dependent, nonlinear, and the fact hyperelastic material is used. Obtaining better patterns and the extension of simulations to the 3D are the next steps.

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