Mathematical Models of Cortical Folding Process of the Human Brain

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Biological Preliminaries

- The brain is one of nature's greatest mysteries
- Little is understood about how folds of the brain (cerebral cortex) are formed
- The principal types of cells in the Central Neuron System are neurons and glial cells
- Radial glial cell, a special type of glial cell, has an important role in brain development
- Radial glial cells are also responsible for the production of special proliferative cells called intermediate progenitor cells (IPC)

Cerebral Cortex

- Cerebral Cortex is the outer layer of the brain and often referred to as gray matter
- Cerebral Cortex plays a key role in memory, consciousness, attention, thought etc.
- The human cerebral cortex is 2 to 4 mm thick and has 6 layers in humans
- In large mammals, the surface of the cerebral cortex is folded into gyri (hills) and sulci (valleys)

Two major competing hypotheses about cortical folding

1. Intermediate Progenitor Hypothesis

- Intermediate Progenitor Hypothesis is used in order to establish the Intermediate Progenitor Model (IPM) of cortical folding
- IPM states that the areas of high intermediate progenitor cell (IPC) self-amplification lead to neuron proliferation, corresponding with the formation of gyri and areas of low IPC self-amplification lead to a lack of neuron proliferation that corresponds with the formation of sulci

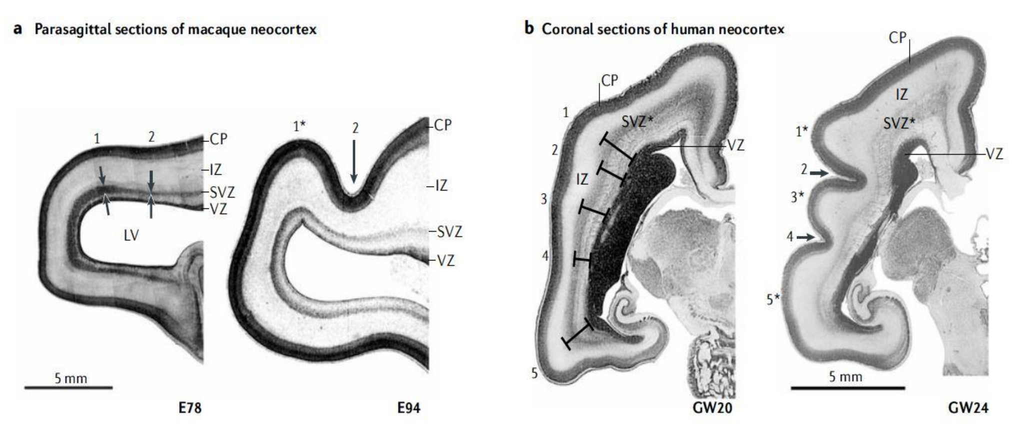

Figure 1: Cortical Folding according to the IPM (Kriegstein et al., 2006)

2. Axonal Tension Hypothesis

- Axonal Tension Hypothesis given by Van Essen (1997) claims that the mechanical tension along the axons in the white matter is the reason for the folding process. Axonal tension of highly interconnected areas in the cortex pulls the cortical walls together, forming gyri. Cortical areas joined by few corticocortical connections (or no connections) lack the axonal tension to pull towards each other, forming sulci

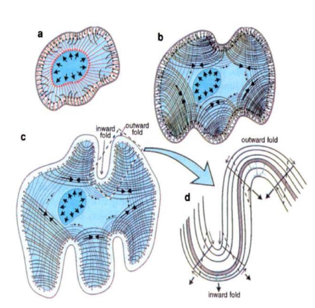

Figure 2: ATH mechanism for cortical folding (Van Essen, 1997)

Models Based on Chemical Hypothesis

Turing Systems

- A. M. Turing developed a system of two reaction-diffusion equations to describe chemical gradient pattern formation of morphogens during morphogenesis of the developing embryo

$$\frac{\partial u}{\partial t} = d_u \nabla^2 u + f(u,v)$$
$$\frac{\partial v}{\partial t} = d_v \nabla^2 v + g(u,v)$$

- $u(x,t), v(x,t)$ = concentration at position x and time t of an activator and inhibitor morphogen,respectively
- $f(u,v), g(u,v)$ = reaction kinetics
  d_u, d_v= diffusion constant for the activator and inhibitor, respectively
- The system tends to a linearly stable uniform steady state in the absence of diffusion ($d_u = d_v = 0$)
- The system is unstable in the presence of diffusion if $d_u \neq d_v$
- The ability of a Turing system to generate spatially inhomogeneous patterns in the presence of diffusion is often referred to as Turing behavior

Nondimensionalized Turing System

- Consider the nondimensionalized reaction-diffusion equation

$$u_t = \nabla^2 u + \gamma f(u,v)$$
$$v_t = d\nabla^2 v + \gamma g(u,v)$$

where γ >0 is proportional to the domain scale, $d = \frac{d_u}{d_v}$ >0 is the ratio of diffusion coefficients

Labyrinthine Turing Model

- Cartwright (2002) proposed a model that explained the labyrinthine patterns in the cortex of mammalian brains with the Turing system. For the activation and inhibition kinetics, he used Van Der Pol-Fitz Hugh-Nagumo Equations as following

$$u_t = \nabla^2 u + \gamma(v - \frac{u^3}{3} + u)$$
$$v_t = d\nabla^2 v + \gamma^{-1}(u + \mu + \beta v)$$

- μ and β are kinetics parameters
  activation dominates for $\gamma > 1$, while inhibition dominates for $\gamma < 1$

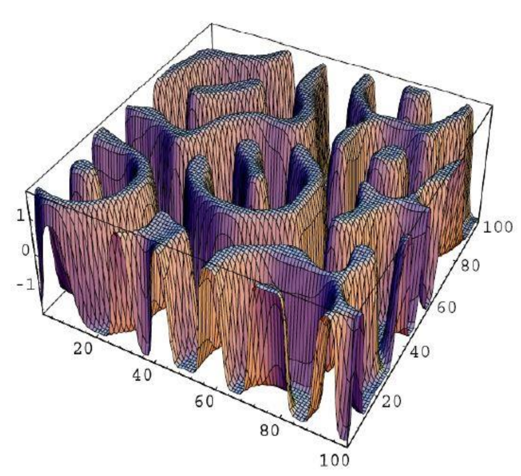

Figure 3: (Cartwright, 2002)

Prolate Spheroid Turing System

- A prolate spheroid is generated by rotating an ellipse around its major axis
- Based on the paper Kriegstein et al., Striegel and Hurdal presented a model called Global Intermediate Progenitor stating that regional patterns of IP cells in SVZ of the cortex produce cortical pattern formation
- They assumed that there are activator and inhibitor reactants that regulate certain radial cells in the Ventricular Zone (VZ). With the activator reactants, IP cells are created and travel to the SubVZ, and lead to gyrus formation
- The GIP model was mathematically modeled using a two-equation Turing reaction-diffusion system with Barrio-Varea-Maini (BVM) kinetics on a prolate spheroidal domain of constant size as following

$$u_t = d\delta u + \alpha u(1 - r_3 v^2) + v(1 - r_2 u)$$
$$v_t = \delta \nabla^2 v - \beta v\left(1 + \frac{\alpha r_3}{\beta} uv\right) + u(\gamma + r_2 v)$$

- α, β, r_2, r_3 are interaction parameters
- They solved the Helmhotz Equation $\nabla^2 X + k^2 X = 0$ with respect to prolate spheroidal coordinates in order to look at Turing patterns on the prolate spheroidal surface
- This model can be used to explain as to why certain cortical diseases may have abnormal folding as well as describe the location, the order, and directionality of normal cortical folding

Simulation Results for the disease Polymicgyria

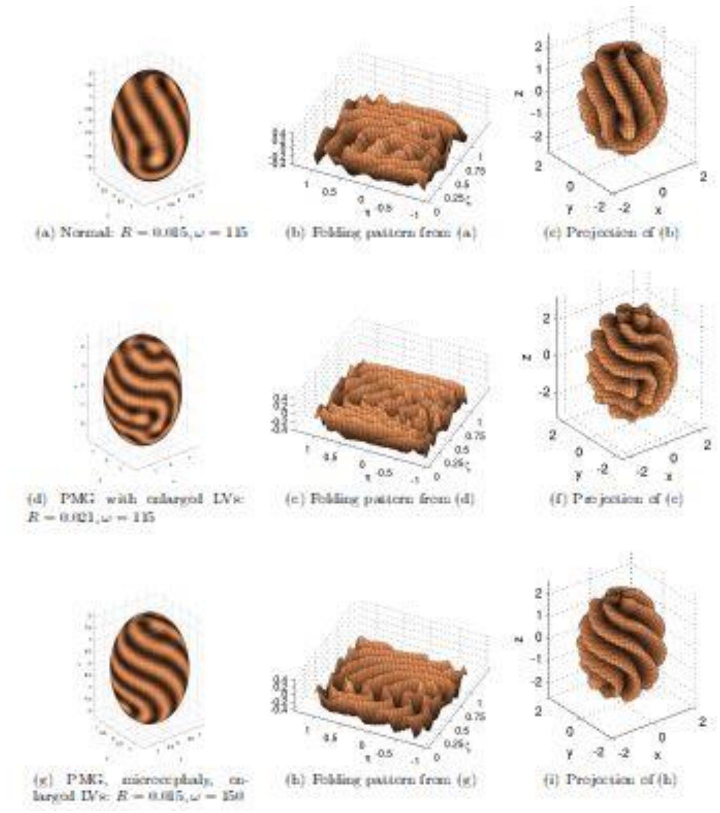

Figure 4: Modling polymicrogyria (PMG) on an exponentially growing prolate spheroid. The generated PMG prepatterns exhibit an increased number and decreased width of stripes (figures(d)-(i)) relative to the normal patterns (figures(a)-(c)). The center and right columns show how a labyrinthine cortical folding pattern could develop from the corresponding Turing genetic chemical prepattern in the left column. (Toole, 2013)

Labyrinthine Turing System with a Surface Deformation

- Lefevre and Mangin also proposed a Turing system model that differs from the one of Cartwright and the GIP model since they have adopted the Gray-Scott model

$$u_t = d_1 \Delta u + F(1-u) - uv^2$$
$$v_t = d_2 \Delta v + uv^2 - (F+k)v$$

which exhibits a high number of patterns for different values of F and k

- They combine the Turing system model with a surface deformation that is result of folding formation process

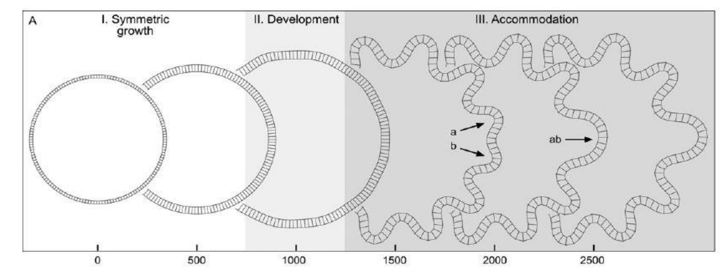

Figure 5: (Toro et al., 2005)

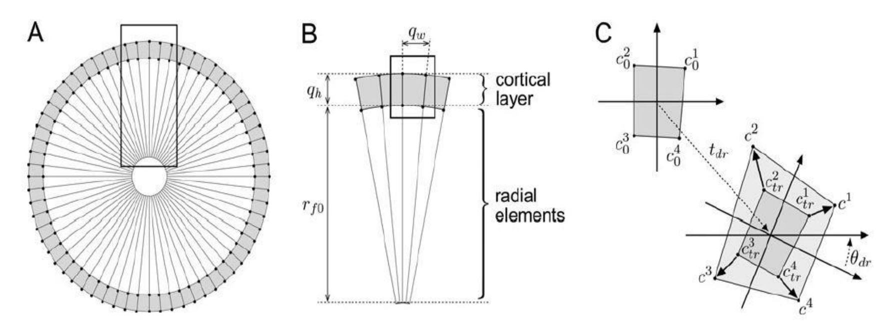

Figure 6: (Toro et al., 2005)

Models Based on Mechanical Hypothesis

2D Model

- Toro and Burnod (2005) proposed a model that supposes elasticity and plasticity are the fundamental mechanical properties of the cortex and fibers
- Elasticity enables the cortex to recover the initial shape that has been deformed, plasticity helps modify the shape when a strong or long-lasting force is applied
- The model is implemented with two-dimensional finite elements. They simplified the circular domain to be composed of two separated areas: a cortical layer that represents the cerebral cortex and radial elements that represent the inner neural parts consisting of white matter (See the images above)

3D Model

- Nie et al proposed a computational model also used surface modeling that is widely used in computer graphics to model soft thin shells. Thus, bending energy is also considered
- The proposed model is a 3-dimensional finite element implementation having triangle elements as the mesh

Cortical Development with and without constraints in 3D Model

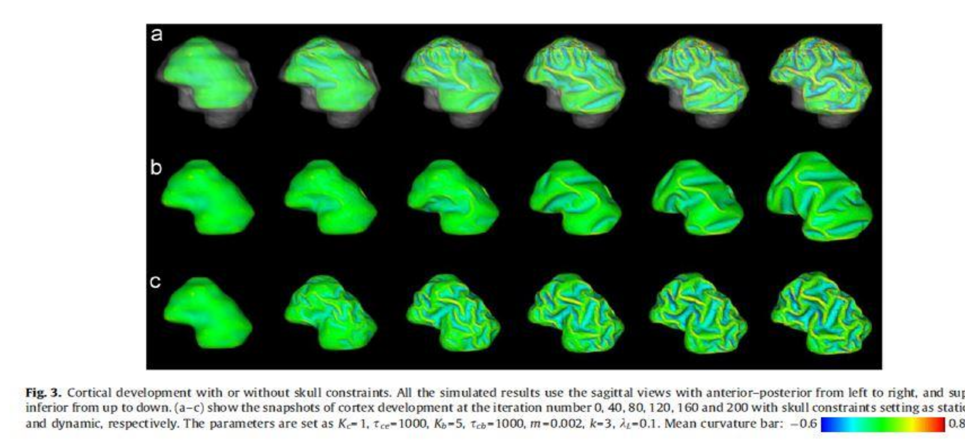

Figure 7: (Nie et al., 2010)

Future Work

- Investigate the parameter space in previous models and observe the results
- Construct a model that combines both chemical and mechanical hypotheses of cortical folding using Traveling Waves solutions
- Need realistic developmental brain images to be able to incorporate a more realistic geometry instead of a prolate spheroid

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