A Mathematical Model of Cerebral Cortical Folding Development

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Outline

1. Hypotheses

   ATH (Axonal Tension Hypothesis)

   DGH (Differential Growth Hypothesis)

   IPH (Intermediate Progenitor Hypothesis)

2. Biomechanical Models

   Kim's Linear Brain Folding Model

3. Our New Model

All large mammals including humans have a cerebral cortex - the brain's outer folded layer.

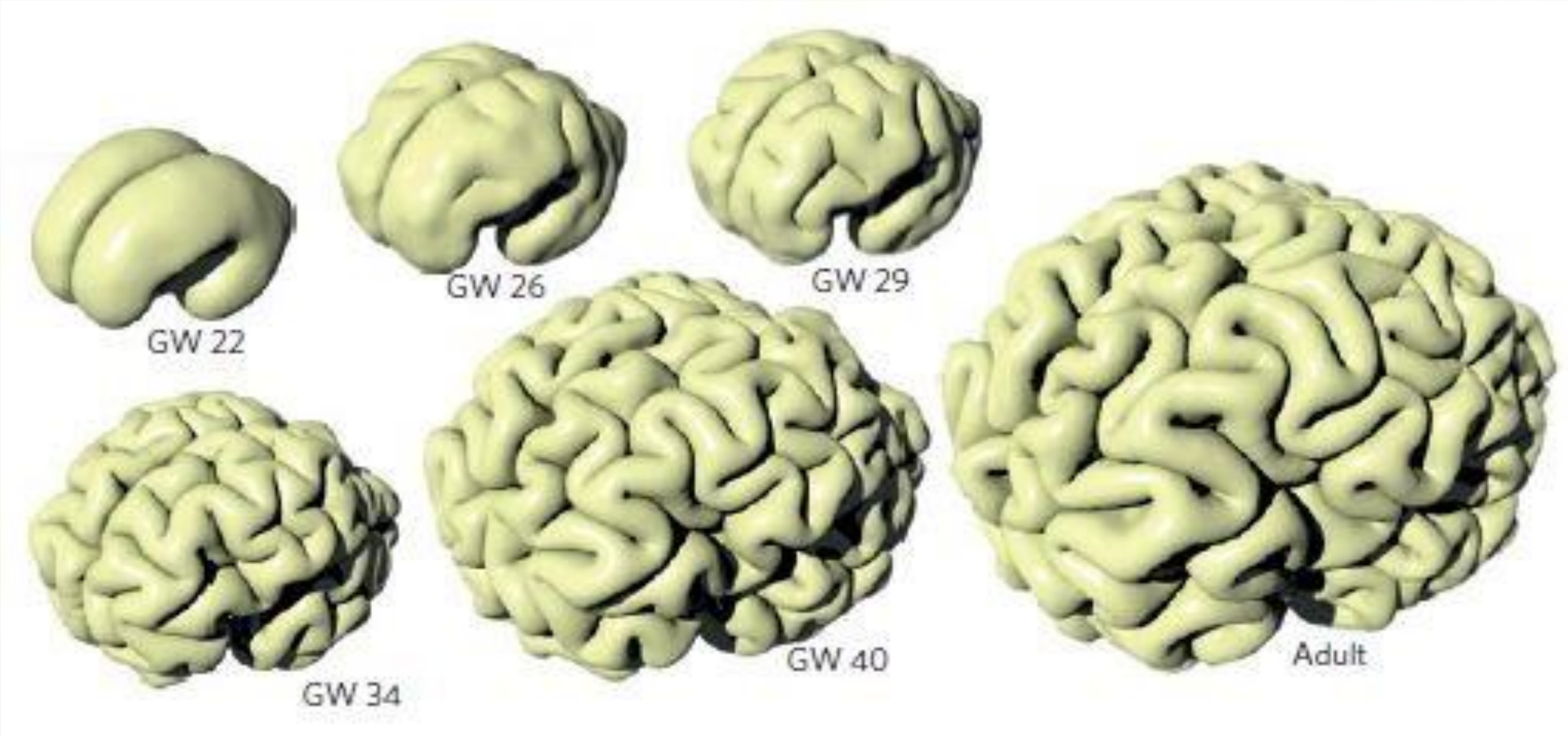


Figure adapted from [17] Toumas Tallinen, 2016

In large mammals, cortex intricately folded into gyri (hills) and sulci (valleys).

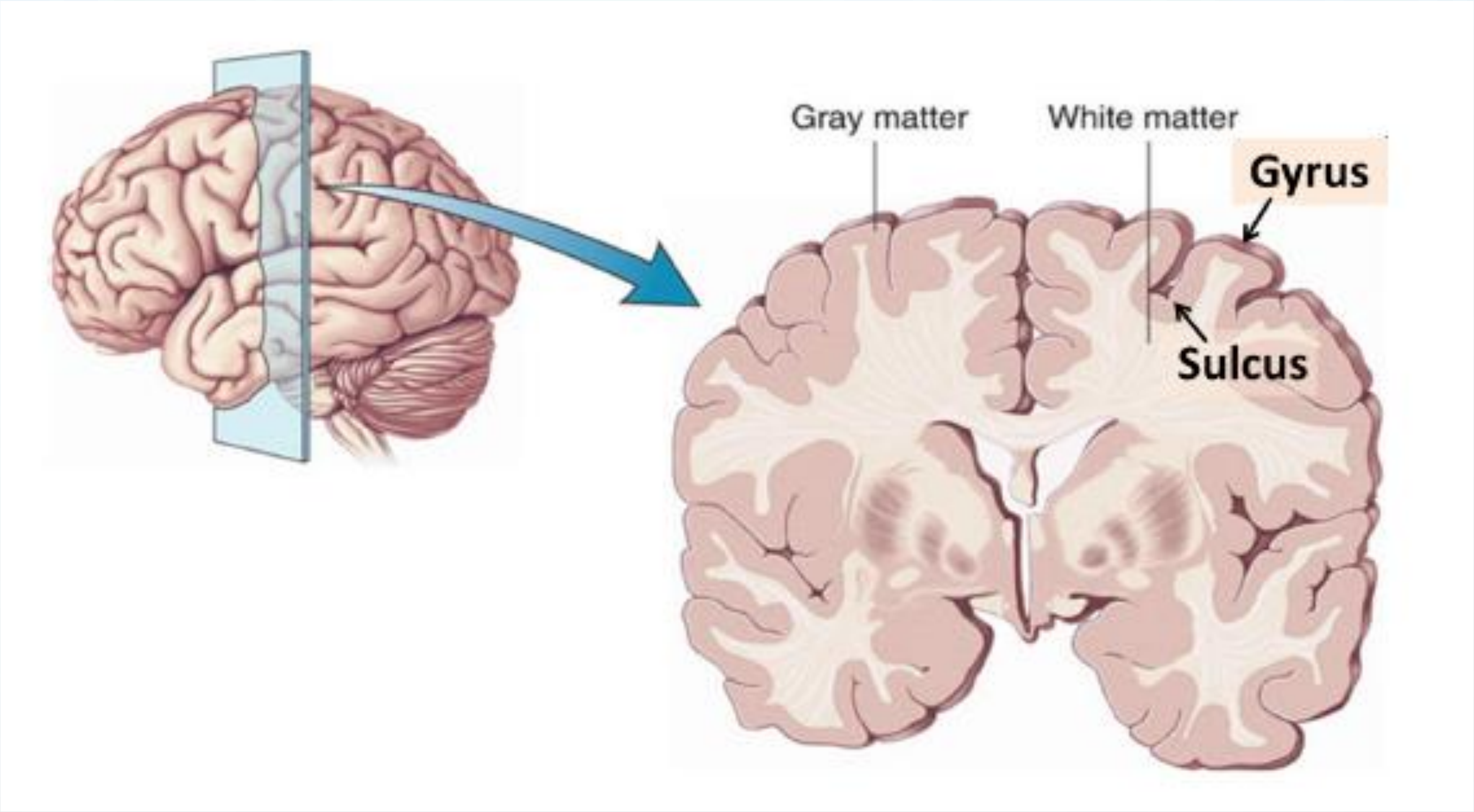


Figure adapted from www.medinewsdigest.com/?p=3249

Three Main Hypotheses of Cortical Folding

- To date, there have been three leading biological hypotheses that explain the development of cortical folding.
- Two of them are biomechanical.

1. Biomechanical Hypothesis: Axonal Tension Hypothesis (ATH)

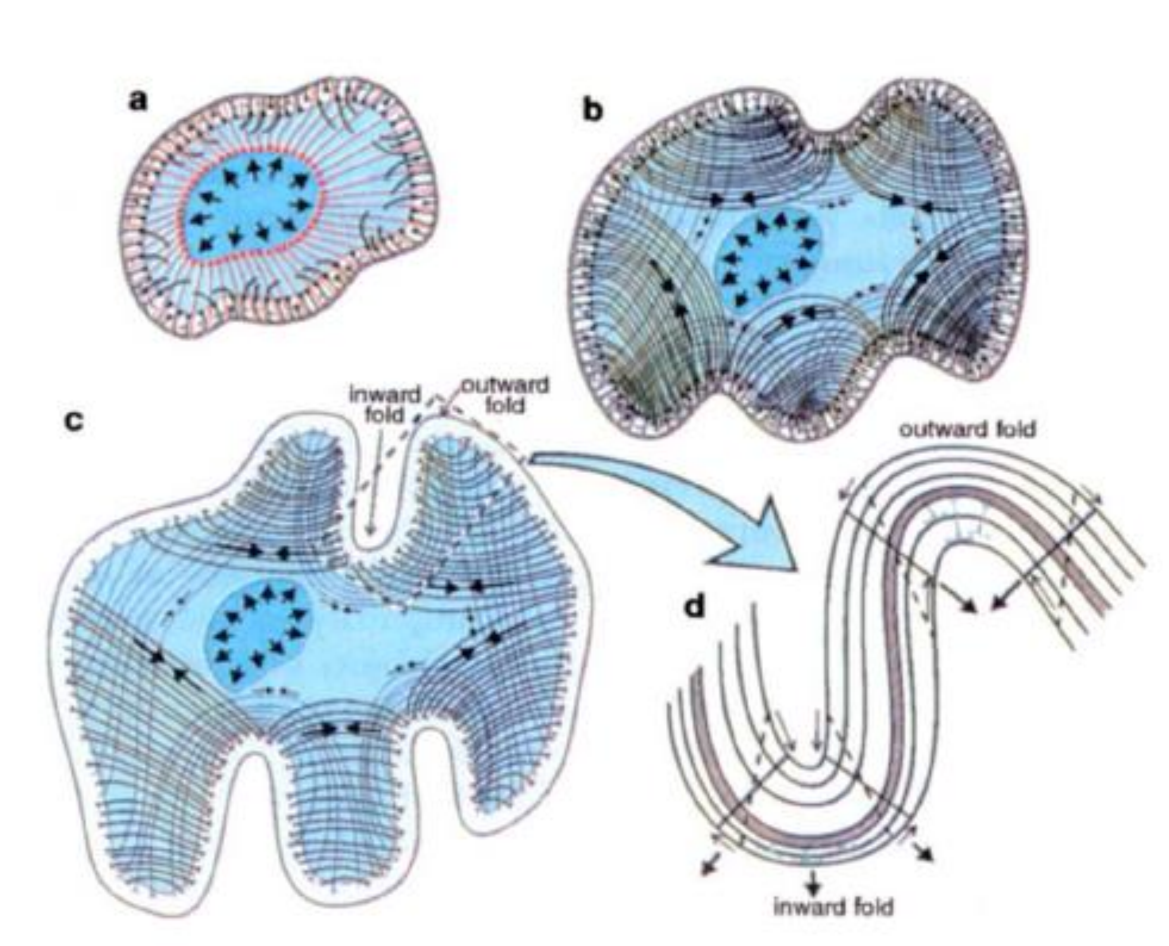


Figure adapted from [4] D.C. Van Essen, 1997

2. Biomechanical Hypothesis: Differential Growth Hypothesis (DGH)

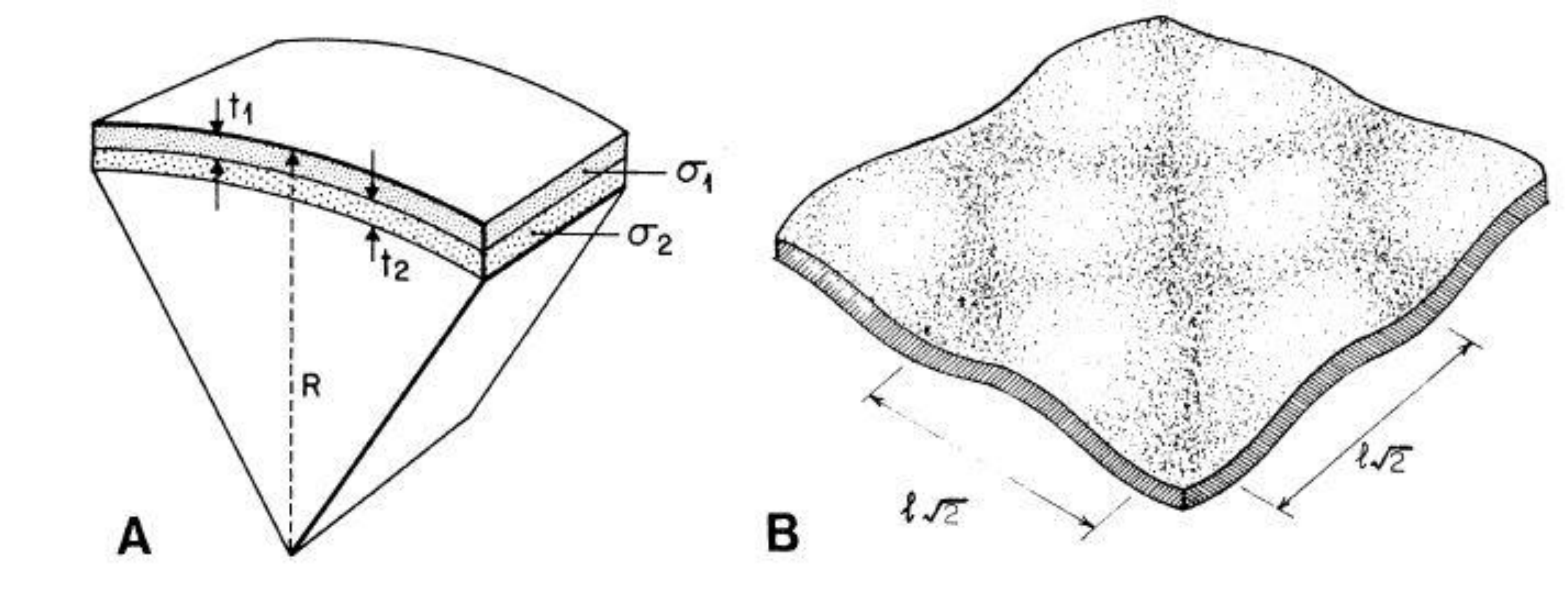


Figure adapted from [5] D.P. Richman, 1975

3. Biochemical Hypothesis: Intermediate Progenitor Hypothesis (IPH)

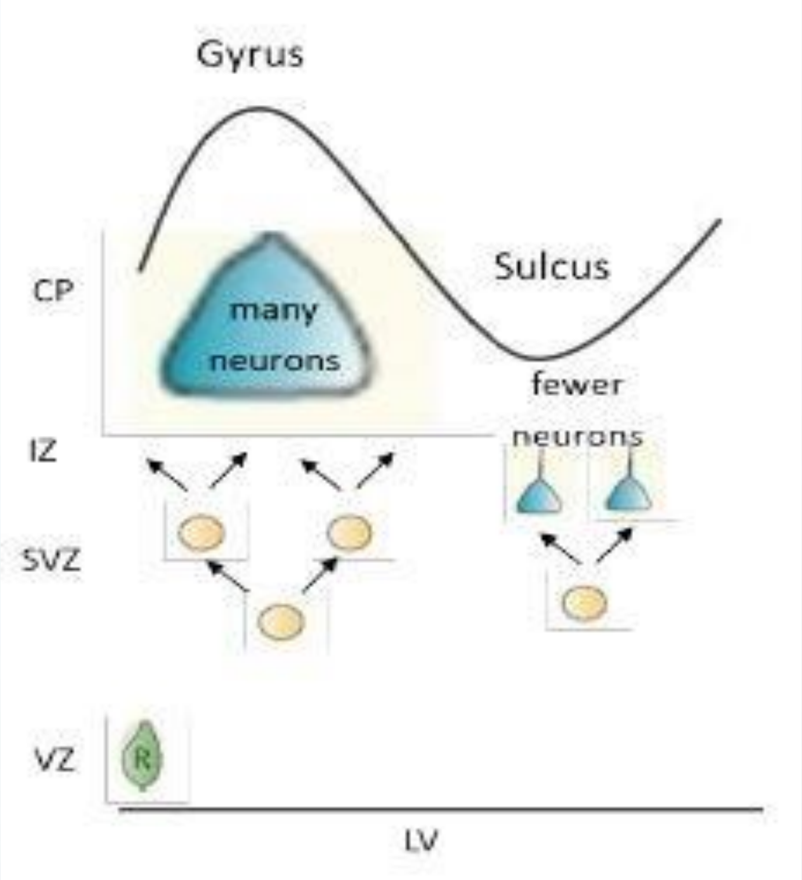


Figure adapted from [6] A. Kriegstein, 2006

CP: Cortical Plate,
IZ: Intermediate Zone,
SVZ: Sub Ventricular Zone,
VZ: Ventricular Zone,
LV: Lateral Ventricles.

An Ideal Model

- The one that utilizes all three leading hypotheses
- No such combined model to date.

A Previous Biomechanical Model

- Kim's model [1] assumes that the major mechanism causing cerebral cortical folding is the axonal tension forces (ATH).

- The cortico-cortical connections are explained by the biochemical hypothesis (IPH).

[1] S. Kim, PhD Thesis, Florida State University, 2015

A Previous Biomechanical Model

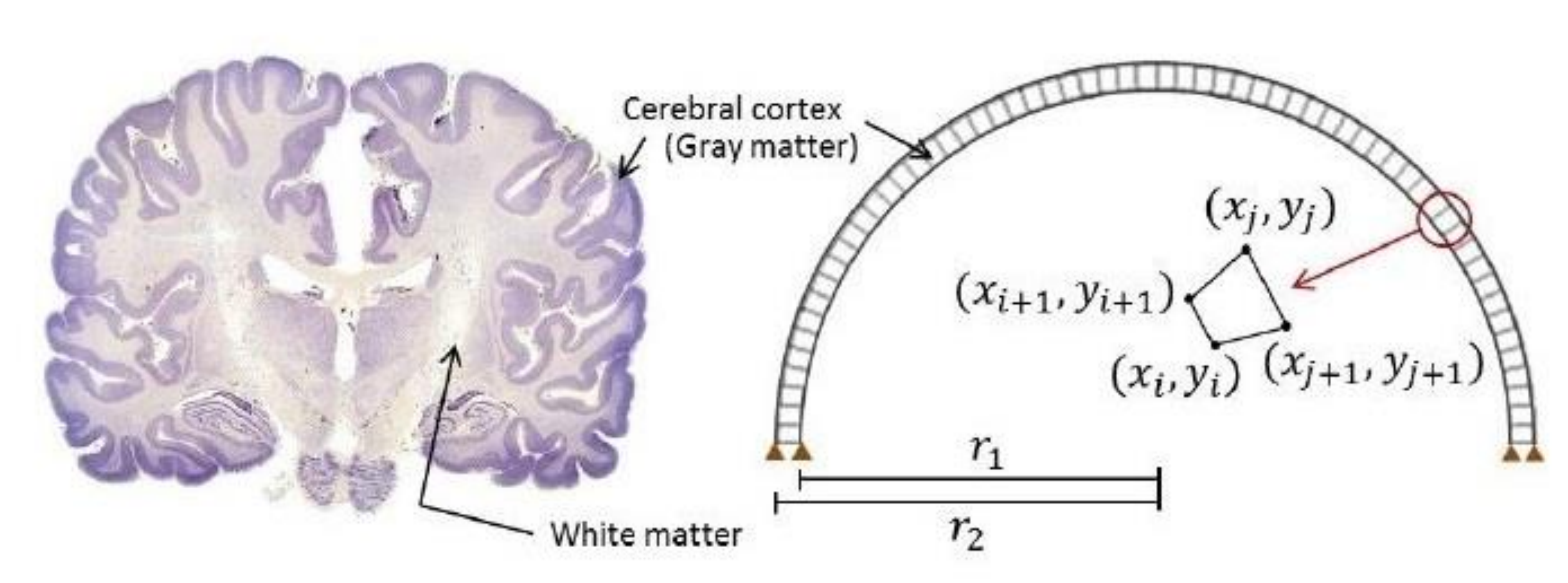


Figure adapted from [1] S. Kim, 2015

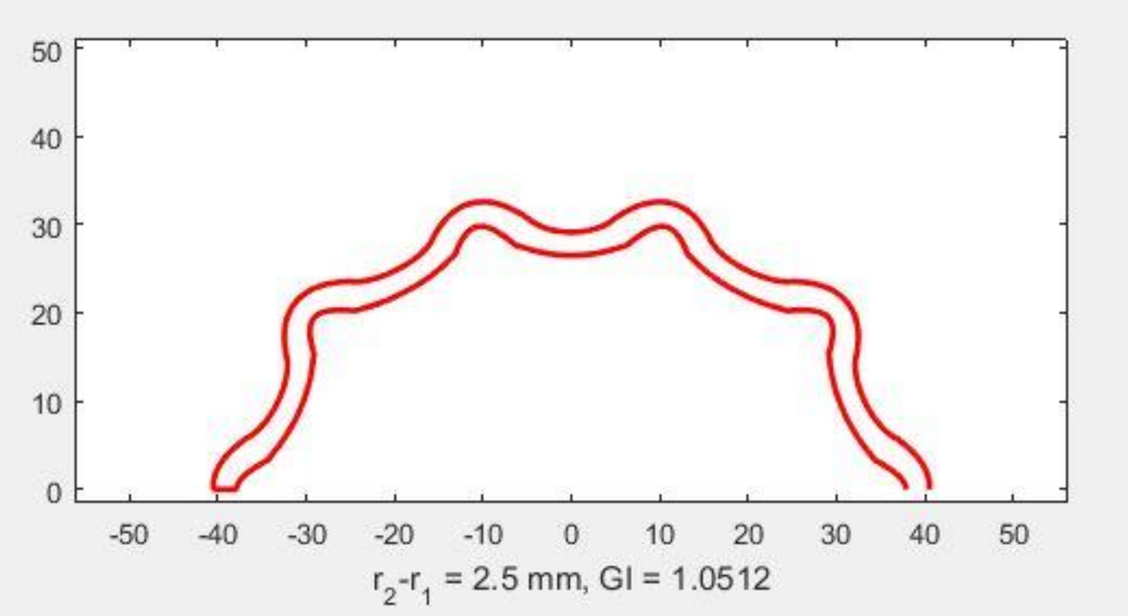
IPM and ATH

- The biochemical hypothesis (IPM) and that of biomechanical hypothesis (ATH) coincide on the claim that:
  an area which includes a densely packed cell population develop into gyri.

- Turing Reaction-Diffusion system [1] is used to determine the level of morphogen. The magnitude of applied forces are determined by the Turing patterns.

[1] A.M. Turing, 1952

A Previous Biomechanical Model - Simulations



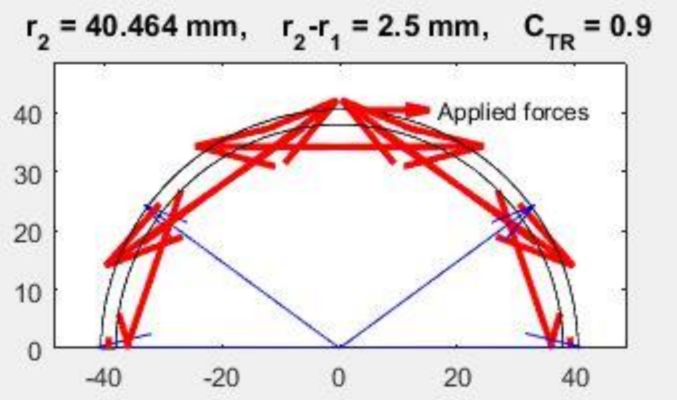


Figure adapted from [1] S. Kim, 2015

A New Model for Cortical Folding

- Tangential growth of the cortex drives the folding process
- 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.

A New Model for Cortical Folding

- Brain tissue is assumed as isotropic, hyperelastic material.

  F : the deformation gradient tensor
  F^*: elastic tensor
  G : growth tensor
  σ : Cauchy stress tensor
  $J^* := detF^*$
  W: Strain energy density function

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

A New Model for Cortical Folding

A standard neo-Hookean material model [1] is used.
Strain energy density function:

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

μ : shear modulus
κ : bulk modulus
I_1^* : trace of ${F^*}^T F^*$

[1] Holzapfel G. A., 2000

A New Model for Cortical Folding

- Both cortex and subcortical foundation were hyperelastic.
- In the cortex, growth rate was taken as linear, and no growth in radial direction.
- Both tangential and radial growth were stimulated by corresponding stress components.

Experimental Setup

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

- $\boldsymbol{r} = 0.0404$ m: radius of brain at 28th week
- $\boldsymbol{t}$ = 2.5 mm: thickness of the gray matter
- $\boldsymbol{E_g} = 1.389$ kPa: Young's Modulus of gray matter
- $\boldsymbol{E_w} = 1.895$ kPa: Young's Modulus of white matter
- $\boldsymbol{v}$ = 0.4583: Poisson ratio of brain tissue
- $\boldsymbol{d}$ = 1.1 g/$\boldsymbol{cm^3}$: density of brain tissue

Geometry

Simulations are performed in

- a two-dimensional (2D) semi-circular domain
- a 2D semi-elliptical domain

Boundary Loads

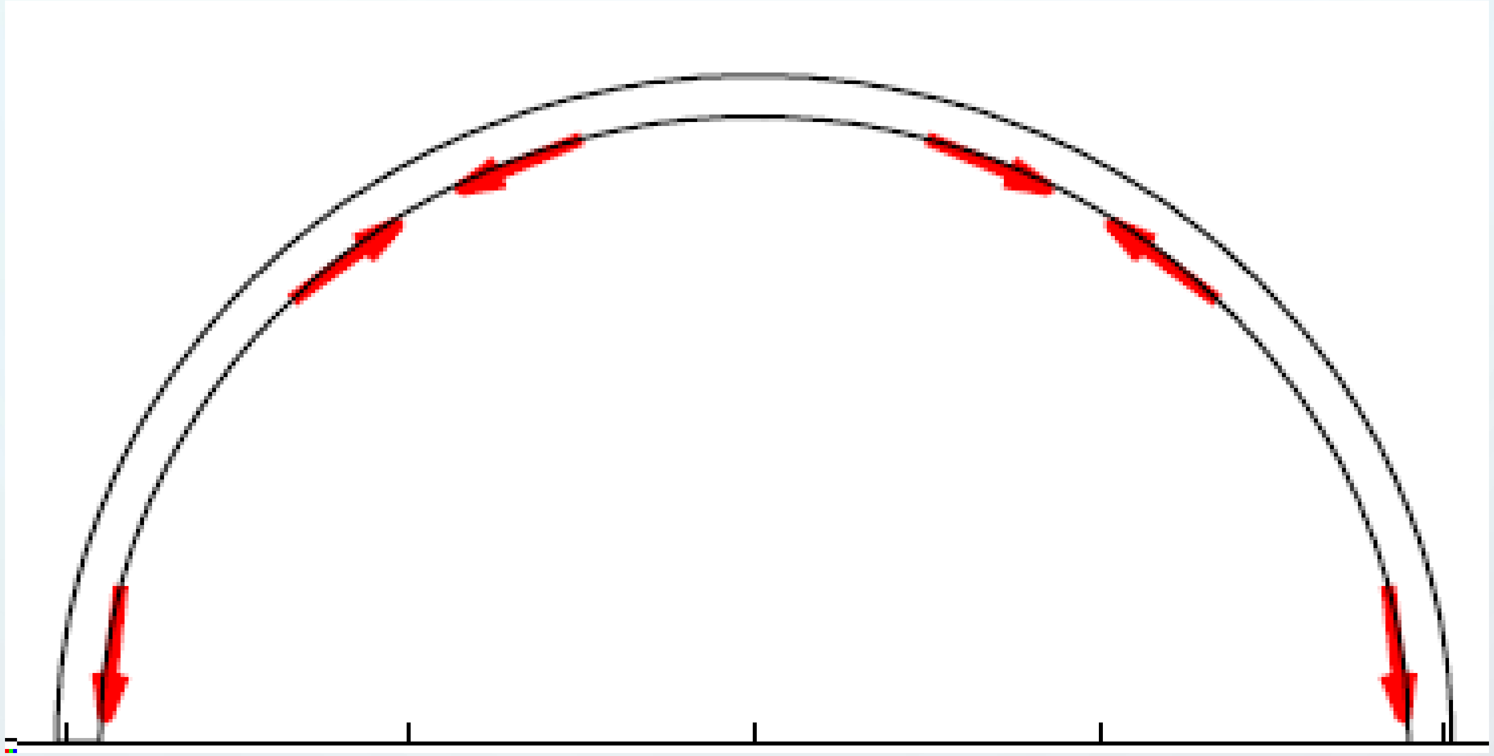
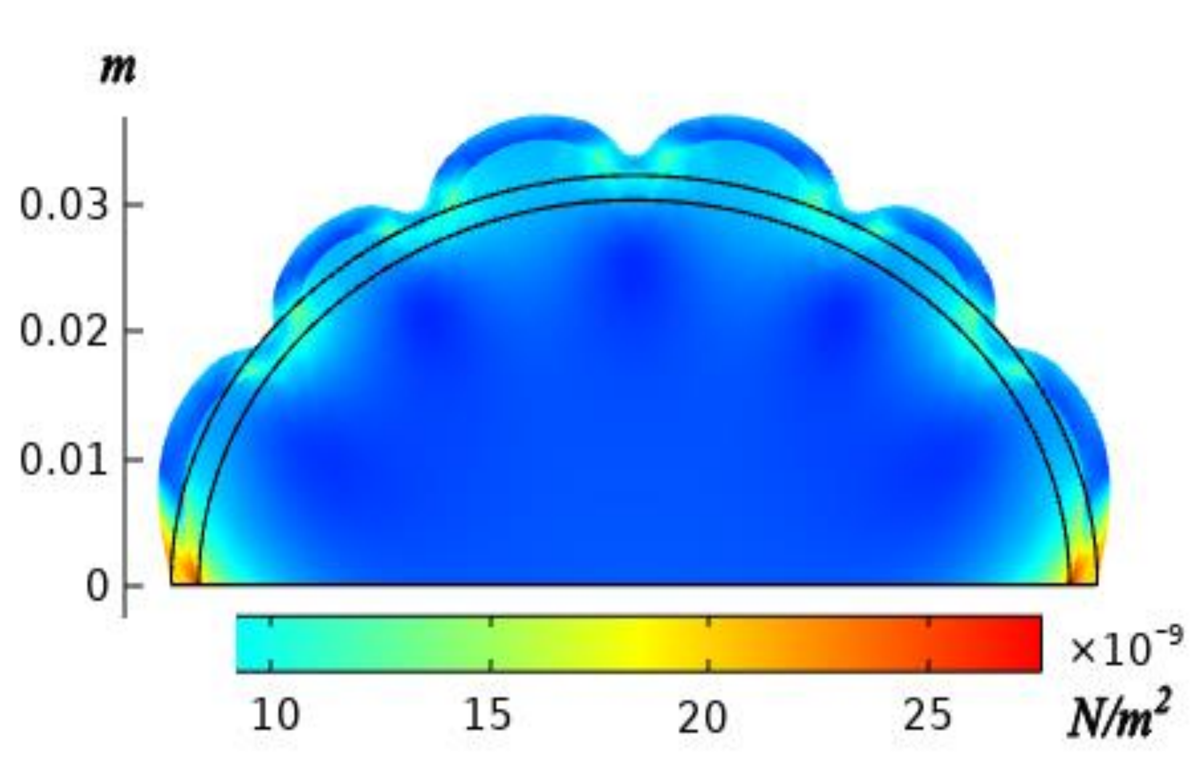


Figure adapted from [3] P. V. Bayly, 2013

Simulations

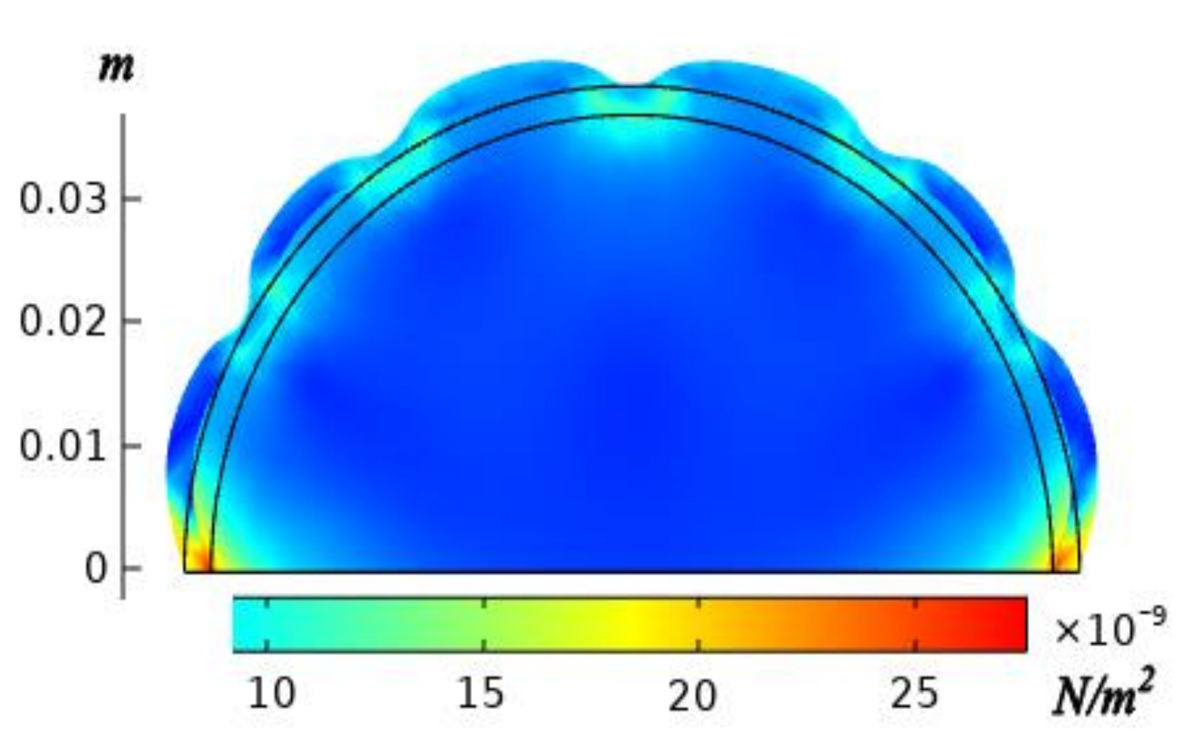
Semi-elliptical domain: The human brain is more like a semi-ellipsoid, that is why we first prefer 2D semi-elliptical domain for



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

Simulations

Semi-circular domain: To compare with other models that use a semi-circular domain, the following simulation was done:



Simulation with a 2D semi-circular domain.

Conclusion & Future Directions

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

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THANK YOU!