Representing the cortex convolutions through the wrinkling of growing soft bilayers

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Recent interest for brain embryology, why?

- New techniques in vivo, like MRI
- Cerebrum sulci = cognition support
- Development, pathologies of development
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New techniques and new possibilities for investigation

- Progress and challenges in probing the human brain, Nature (2015)

Figure – A HCP parcellation, 180 areas per hemisphere
Introduction

Theory of elasticity: Volumetric Growth of a bilayer

- Nonlinear elasticity of tissues. Variational formalism
- Differential growth between the two layers: grey matter and white matter
- Special focus on wavelength selection: a challenging and controversial problem, Biot (57), Biot (63)
- Scope: The gyrification index
Adult brain anatomy

Figure – A. Section of human brain. B. 3D reconstruction of human brain, modelled as a soft elastic solid with growth in the cortex, Tallinen et al. , Nature Physics, 2016
The central nervous system

Figure – A Brain and spinal cord, B nomenclature, C cut of the brain
The brain anatomy

Two layers in the adult brain:
- The grey matter (soft)
- The white matter (stiffer, according Budday et al, 2014)
The brain anatomy

Two layers in the adult brain:
- The grey matter (soft)
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But also,
- The meninges: 3 layers
- The cerebrospinal fluid
Central Nervous System and the Cerebrum Development

**Figure** – Main steps of formation as a function of Gestational Age GA

- **Formation du tube neural** 4 semaines
- **Formation du télencéphale** 2 mois
- **Prolifération cellulaire et migration neuronale** 3 mois
- **Début de la gyration** 4 mois

Apparition of the bilayer **before** the cerebrum sulci!

⇒ **Bilayer model** : grey matter with neuronal bodies, white matter : glial cells and axons
How to quantify the gyrification

Index of gyrification: $G_I = \frac{\text{Full cerebrum area}}{\text{Apparent external area}}$

Souris 1.0  Mouton 2.3  Humain 2.6  Lama 2.7

Indice de gyrification
Pathologies associated with gyrification

Examples

- The lissencephaly (smooth brain)
- The polymicrogyria (excessive number of small gyri)
- Local anomalies like autism, schizophrenia.....

Figure – Comparison of lissencephalic (A) and healthy brain (B) by MRI
Examples of recent MRI studies


Models

Two kinds of models :

Models for gyri formation

- **Mechanical models**, like " axonal tension " ( Manyuhina 2014) ⇒ more or less pre-strain, pre-stress models
- **Differential growth**.
- **Theoretical** : 2 layers with 2 different thicknesses, volumetric differential growth,

⇒ 2 famous papers of Biot, Biot (57) and Biot (63)

Folding instability of a layered viscoelastic medium under compression

By M. A. Biot

Shell Development Company

(Communicated by Sir Geoffrey Taylor, F.R.S.—Received 6 April 1957)

SURFACE INSTABILITY OF RUBBER IN COMPRESSION

by M. A. BIOT

New York, U.S.A.
One or two layers under compression

Biot (57) **One thin, stiff layer on an infinite soft substrate**

\[ \mu = \frac{\mu_1}{\mu_2} \text{ with } \mu \to \infty \]

- A critical threshold \( P_c \sim \mu^{-1/3} \)
- A wavelength \( \lambda_c \sim \mu^{1/3} \).

**Origin**: Long wavelength limit \( \lambda \gg H \). The human brain is not concerned by this limit: \( \mu \sim 0.7 \) (like bovine, pigs)
Biot’s singularity or surface instability

Biot’ singularity (63) one Neo-Hookean infinite layer, a finite threshold but $\lambda \rightarrow 0$ so creases!!!!!
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### Method

#### Main physical ingredients

- Ratio of stiffnesses $\mu = \frac{\mu_G}{\mu_W} \sim 0.7$
- **Anisotropic growth** in the cortex (more proliferation at the interface cortex/white matter, no known order of magnitude)
- **Differential growth**: Growth which is different in grey and white matter
- Infinite (or not) substrate ($L_W >> L_G$)
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Questions

1) Instability threshold?
2) Biot’s singularity? Can we get a finite wavelength?
3) Post-buckling analysis and Gyrification index?
4) Can we go back to pathologies?
Elastic bilayer

Scheme of the model. Cortex growth from «cortex growth expansion...Fernandez et al. EMBO (2016)

\((X,Y) \rightarrow (x,y)\)
Multiplicative decomposition gradient

Geometric deformation gradient: \( F = \begin{bmatrix} \frac{\partial x}{\partial X} & \frac{\partial x}{\partial Y} \\ \frac{\partial y}{\partial X} & \frac{\partial y}{\partial Y} \end{bmatrix} \)

**First hypothesis, [Rodriguez 1994]**

If we have a separation of time scales, if growth is very slow, \( F = F_e G \):

- Elastic tensor: \( F_e \)
- Growth tensor: \( G_1 = \begin{bmatrix} g_x & 0 \\ 0 & g_y \end{bmatrix} \) and \( G_2 = \begin{bmatrix} g & 0 \\ 0 & g \end{bmatrix} \)
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**Second hypothesis**
Living tissues are incompressible, so any change of volume is due to growth.

\( J_1 = g_x g_y \) et \( J_2 = g^2 \)
Incompressibility and stream functions

Definition of stream functions

Analogy with hydrodynamics, we define $\Phi(x_1, Y_1)$ et $\Psi(x_2, Y_2)$:

$$X_1 = J_1^{-1} \frac{\partial \Phi}{\partial Y_1}$$
$$y_1 = \frac{\partial \Phi}{\partial x_1}$$
$$X_2 = J_2^{-1} \frac{\partial \Psi}{\partial Y_2}$$
$$y_2 = \frac{\partial \Psi}{\partial x_2}$$

Advantage:

- We work in the correct space of deformations $\Rightarrow \emptyset$ we avoid Lagrange multiplier
Euler-Lagrange equations

Trivial growth configuration and perturbation:

\[ \Phi(x, Y) = xYg_1g_2 + \epsilon \phi(x, Y) \]
Euler-Lagrange equations

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Mode Fourier expansion:

\[ \phi(x, Y) = F_1(Y) \sin(kx) \text{ and } \psi(x, Y) = F_2(Y) \sin(kx) \]
Euler-Lagrange equations

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At order $\varepsilon$:

$$\frac{d^4 F_1(Y)}{dY^4} - k^2 (J_1^2 + p^2) \frac{d^2 F_1(Y)}{dY^2} + J_1^2 p^2 k^4 F_1(Y) = 0$$

$$\frac{d^4 F_2(Y)}{dY^4} - k^2 (J_2^2 + 1) \frac{d^2 F_2(Y)}{dY^2} + J_2^2 k^4 F_2(Y) = 0$$

$p = \frac{g_y}{g_x}$ is anisotropy parameter.
Solutions of Euler Lagrange

Solutions for infinite substrate:

\[ F_1(Y) = \cosh(J_1 kY) + A_1 \sinh(J_1 kY) + A_2 \cosh(pkY) + A_3 \sinh(pkY) \]
\[ F_2(Y) = B_1 \exp(J_2 kY) + B_2 \exp(kY) \]

\[ k = \frac{2\pi}{\lambda} \text{ wavenumber} \]

Boundary conditions \(\Rightarrow\) Dispersion relation in the limit \(\lambda \ll 1\)

\[ 0 = P_0(J_1) \times \mathcal{P}(\mu, J_1, J_2) \]
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Boundary conditions \( \Rightarrow \) Dispersion relation in the limit \( \lambda \ll 1 \)

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Primary bifurcation : \( P_0(J_1) = 0 \)
Secondary bifurcation : \( \mathcal{P}(\mu, J_1, J_2) = 0 \).
Primary bifurcation: \[ P_0(J_1) = -1 - pJ_1 - 3p^2J_1^2 + (pJ_1)^3 = 0. \]

- The threshold \( J_c \approx 3.38p \)
- Does not depend on the bottom layer and also on \( \mu \). \( \Rightarrow \) The instability comes only from the top layer.
- Such solution requires a surface tension \( \gamma \) to derive the wavelength:

\[
\lambda = 4p\pi H/\log \left( R_1(J_2, \mu, p) \times \frac{2p(3J_c^2 - 6J_c - 1)}{\gamma J_c(J_c + 1)} \right)
\]

\[
\lambda \approx 4p\pi H/\log \left( \frac{1.8p}{\gamma} \times R_1(J_2, \mu, p) \right)
\]
Primary Bifurcation

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\[
\lambda \approx 4p\pi H/\text{Log}
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\]

\( \Rightarrow \lambda \sim 4p\pi H \Rightarrow \text{Condition: } R_1(J_2, \mu, p) > 0 \)
Reminder: \( \mu = \frac{\mu_1}{\mu_2} \) and \( p = \frac{g_y}{g_x} \)

**Figure** – Primary bifurcation: phase diagram for \( R_1 \)
Discussion

Summary

- **For a stiff substrate** ($\mu < 1$) = primary bifurcation
  selection = surface tension of the upper layer
  Instability originates from the upper layer

- **Soft substrate** ($\mu > 1$) = secondary bifurcation
  Selection = surface tension of the interface between both layers

Nano-indentation (Buday 2015) : $\mu \approx 0.6$

Conclusion

For the brain, primary bifurcation responsible of the cortical sulci. Biot Singularity : Surface Instability
Discussion: Surface tension

⇒ Not solely a mathematical tool!

The meninges

Equivalent to a surface tension or to a third layer???

\[ \gamma = 4L\mu. \]

Figure – Schéma des méninges. © Blausen Medical, BruceBlaus
Discussion: pathologies

Pathologies of development = dysfunction migration of the neuronal migration \( \Rightarrow \text{modification of the growth} \)

Gyrification anomalies

- **Lissencephaly** (\( \emptyset \) sulcius) = threshold is not reached, thick cortex.
- **Polymicrogyria** (+ tiny sulci) very weak surface tension, proliferation along the interface.
- **Local anomalies** = heterogeneity and regional variation!!
Post-buckling treatment

Up to now, no amplitude for the folds. So we need to go further and to expand the energy to next order (nonlinearities). Via nonlinear analysis we reach the amplitudes after post-buckling, and the nature of the bifurcation super-critical bifurcation:

$$\varepsilon = \pm 1.3544 \frac{e^{-HkJ_1}}{k^2} \sqrt{p(J_1 - J_c)}$$

(1)

It corresponds to MRI measurements, J. Lefebvre, D. Germanaud, F. Rousseau Cortex (2016).
Gyrification index

After the post-buckling result, we can calculate this index maintaining the "shape profile"

\[
G_I = \frac{k}{2\pi} \int_{-\pi/k}^{\pi/k} \sqrt{1 + y'^2} \, dx = \frac{k}{2\pi} \int_{-\pi/k}^{\pi/k} \sqrt{1 + \varepsilon^2 \sin(kx)^2} \, dx
\]

Gyrification index

MRI measurements of pre-term newborns and fetuses, Lefèvre, Germanaud, F. Rousseau al.

Estimation → mass of the telecenphalon: $27g$ and $42g$, anisotropy $p = .55$ and $p = 0.3$. Extrapolation far from the threshold, out of the domain of validity. Simulations are necessary.
Impact of defects or inhomogeneities

Mimicking the imaginal disk of drosophila (mutant)

Inhomogeneity of the Young modulus in an horizontal sublayer inducing a buckling. Simulations of Joseph Ackermann with COMSOL
Conclusion

- bilayer model = **not so bad**
- Very simple $J_c = 3.38p$ and wavelength selection $\lambda \sim 4\pi pH$, where $H$ is the upper layer thickness.
- Qualitative explanation of gyri formation, $G_I$ not a very sensitive parameter.
- Local heterogeneity
- profound sulci and creases $\leftrightarrow$ autism.

Other problems of bilayers in human body: skin (Ciarletta et al. 2011), villi (MBA and Jia, 2013), esophagus and the spinal cord ...