Received: 17 June 2021 | Accepted: 23 September 2021

DOI: 10.1002/pamm.202100104

Exploring the interplay between cellular development and mechanics in the developing human brain

M. S. Zarzor[1,*], **S. Kaessmair**[1], **P. Steinmann**[1,2], **I. Blümcke**[3], and **S. Budday**[1]

[1] Institute of Applied Mechanics, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen 91058, Germany
[2] Glasgow Computational Engineering Centre, University of Glasgow, Glasgow G12 8QQ, UK
[3] Neuropathological Institute, University Hospitals Erlangen, Erlangen 91054, Germany

The human brain has a complex structure on both cellular and organ scales. This structure is closely related to the brain's abilities and functions. Disruption of one of the biological processes occurring during brain development on the cellular scale may affect the cortical folding pattern of the brain on the organ scale. However, the link between disruptions in cellular brain development and associated cortical malformation remains largely unknown. From a mechanical perspective, the forces generated during development lead to mechanical instability and, eventually, the mergence of cortical folds. To fully understand mechanism underlying malformations of cortical development, it is key to consider both the events that occur on the cellular scale and the mechanical forces generated on the organ scale. Here we present a computational model describing cellular division and migration on the cellular scale, as well as growth and cortical folding on the tissue or organ scale, in a continuous way by a coupled finite growth and advection-diffusion model. We introduce the cell density as an independent field controlling the volumetric growth. Furthermore, we formulate a positive relation between cell density and cortical layer stiffness. This allows us to study the influence of the migration velocity, the cell diffusivity, the local stiffness, and the local connectivity of cells on the cortical folding process and mechanical properties during normal and abnormal brain development numerically. We show how an increase in the density of the neurons increases the layer's mechanical stiffness. Moreover, weWe validate our simulation results through the comparison with histological sections of the fetal human brain. The current model aims to be a first step towards providing a reliable platform to systematically evaluate the role of different cellular events on the cortical folding process and vice versa.

1 Introduction

The human brain undergoes structural changes both on the micro- and macroscopic scales during development. Due to the strong relation between these changes and the brain's functionality, researchers from different fields struggled over the past few decades to understand the mechanisms underlying normal and abnormal cortical folding. Neuroscientists have mostly focused on the biological (cellular) processes to find an explanation for the folding phenomenon. However, from a mechanical perspective, it has been shown that mechanical forces play a critical role in cortical folding. Indeed, studying mechanical forces on the macroscopic scale or the cellular processes on the microscopic scale alone is not sufficient to explain the folding process. The formation of human brain folds starts around gestational week 25 and continues even after birth. This phenomenon is accompanied by the emergence of mechanical forces as a result of the cellular processes. Cell division, neuronal migration, and the formation of neuronal connectivity are the most significant processes occurring during brain development on the microscopic scale. The most common hypothesis attributes cortical folding to mechanical instabilities due to compressive stresses emerging during differential growth between the subcortex and cortex. Recent studies emphasize that continuous changes in the brain's microstructure during development also affect the mechanical properties of brain tissue, especially in the brain cortical layer. Here, the stiffness seems to increase with increasing the density of cells [1]. In this work, we adopt a computational model that couples an advection-diffusion equation with a morphoelastic growth, and we adjust it to control cortical stiffness. Furthermore, we compare the simulation results with histological fetal human brain sections to validate our model.

2 Computational model

Given the deformation field $\boldsymbol{\varphi}(\boldsymbol{X}, t)$, with $\boldsymbol{X} \in \mathcal{B}_0$ reference position of material point and following the theory of finite growth, we multiplicatively decompose the deformation gradient $\boldsymbol{F} = \boldsymbol{\nabla}_{\boldsymbol{X}} \boldsymbol{\varphi}$ into an elastic part and a growth part, as $\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}} \cdot \boldsymbol{F}^{\mathrm{g}}$, with $J = \det \boldsymbol{F}$. The growth part describes both the differential growth in the cortex under the effect of emerging neuronal connectivity, and the isotropically growing subcortex due to neuronal migration, where its formulated as $\boldsymbol{F}^{\mathrm{g}} = \vartheta^{\perp} \ [\boldsymbol{I} - \boldsymbol{N} \otimes \boldsymbol{N}] + \vartheta^{\parallel} \ \boldsymbol{N} \otimes \boldsymbol{N}$, with the growth multipliers in the tangential and radial direction $\vartheta^{\perp}$ and $\vartheta^{\parallel}$, respectively. Those multipliers are the key to linking the morphoelastic growth with the advection-diffusion problem, where they are formulated as a function of the cell-density field [2].

* Corresponding author: e-mail saeed.zarzor@fau.de, phone +49 9131 852 8516, fax +49 9131 852 8503

The balance of linear momentum and the balance of mass in the spatial configuration $\mathcal{B}_t$ are used in our model,

$$\mathrm{div}(\boldsymbol{\sigma}) = \mathbf{0} \qquad \text{and} \qquad \dot{J}/J\, c + \dot{c} = \mathrm{div}\, \boldsymbol{q} + r.$$

Here, the Cauchy stress $\boldsymbol{\sigma}$ is derived from strain energy function. In our model we adopt an isotropic hyperelastic neo-Hookean function $\psi_g(\boldsymbol{F}^{\mathrm{e}}) = \frac{1}{2}\lambda \ln^2(J^{\mathrm{e}}) + \frac{1}{2}\mu\,[\,\boldsymbol{F}^{\mathrm{e}} : \boldsymbol{F}^{\mathrm{e}} - 3 - 2\ln(J^{\mathrm{e}})]$, with $J^{\mathrm{e}} = \det \boldsymbol{F}^{\mathrm{e}}$. To consider the effect of continuous change in the brain microstructure on the mechanical properties, we introduce a piece-wise linear relation between cortical shear modulus and the cell density i.e. $\mu_{\mathrm{c}} = \mu_{\mathrm{c}}(c) \in [\mu_s\,,\, \mu_\infty]$, where μ_s is the subcortex shear modulus that remains constant over time and μ_∞ is the shear modulus of the fully developed brain [3]. The second equation is formulated in a way to mimic the cellular processes. The flux term $\boldsymbol{q}$ describes the migration in the subcortex and neuronal connectivity in the cortex, and the source term r represents the cell division.

3 Results and discussion

In this work, we capture the effect of variable cell-density-dependent cortical stiffness on the folding pattern of the brain's surface. To do so, we implement two cases, in the first one, we consider the variable stiffness during the formation of the cortex, and in the second one, we keep the value of the cortical stiffness constant during development. In both cases, the stiffness of the subcortex remains constant. Finally, to validate those cases, we compare the folding pattern of the results with the histologically stained fetal brain sections at week 34 of gestation [3]. For the finite element implementation, we use a geometry representing an exemplary two-dimensional part of the frontal lobe to be easily compared with the stained images. Figure 1 shows an example of the simulation results in the case of the variable and constant stiffnesses. For the validation, we chose to assess two criteria, the local gyrification index lGI and the thickness ratio between gyri and sulci α_t. The lGI value equals the ratio of the perimeter to the convex perimeter. Figure 2 demonstrates the average lGI and the thickness ratio values with confidence intervals for the simulation results in case of constant (CS) and variable (VS) stiffnesses compared with histologically stained images (HBS). The lGI value for VS yields 1.15 ± 0.05, which is close to the value of HBS case wtih 1.19 ± 0.05, whereas CS's lGI value equals 1.05 ± 0.03. The same difference appears for the thickness ratio. Moreover, the student's t-test emphasizes a significant difference between the results of constant and variable cases. In contrast, there is no significant difference between the results of the variable case and the histological sections.

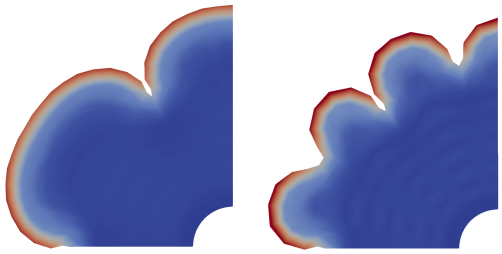

Fig. 1: Comparison between simulation results for the case of variable stiffness (right) and constant stiffness (left) for the same conditions and the same set of parameters.

In conclusion, the results of this study confirm that the stiffness of brain tissue in the cortex changes during development. Furthermore, there seems to be a positive relation between the cortical stiffness value and the cell density in the cortex.

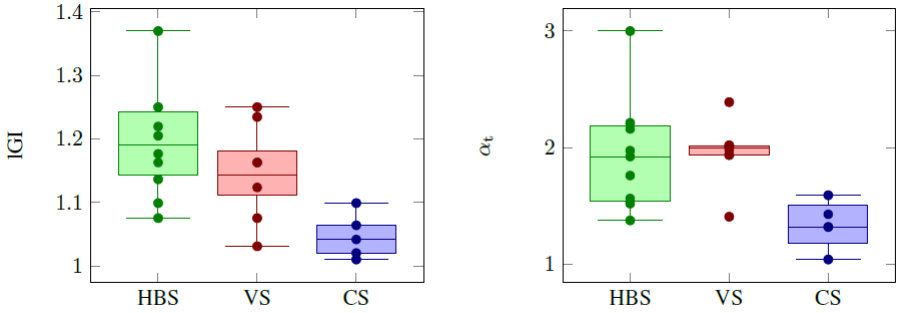

Fig. 2: Local gyrification Index (lGI, left) and thickness ratio α_{t} (right) averaged over all simulation results obtained for the case of constant (CS) and variable cortical stiffness (VS) compared to the values of histological human brain sections of the real human fetal brain.

Acknowledgements Open access funding enabled and organized by Projekt DEAL.

References

[1] S. Budday, and E. Kuhl. *Current Opinion in Biomedical Engineering*, **15**:16–25 (2020).
[2] R. de Rooij, and E. Kuhl. *The Mechanics and Physics of Solids*, **112**: 563-576 (2018).
[3] M.s. Zarzor, S. Kaessmair, P. Steinmann, I. Blümcke, and S. Budday. *Brain Multiphysics*, **2**: 100025 (2021).

