COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 104 (2011) 489–497

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

A model of cerebral cortex formation during fetal development using reaction–diffusion–convection equations with Turing space parameters

Diego Alexander Garzón-Alvarado[a,*], *Angelica Maria Ramirez Martinez*[b], *Dorian Luis Linero Segrera*[c]

[a] *Department of Mechanical and Mechatronic Engineering, Universidad Nacional de Colombia, Numerical Modelling and Methods in Engineering Group (GNUM), Colombia*
[b] *Universidad Central de Colombia, Bioengineering Research Group (UCIB), Colombia*
[c] *Department of Civil and Agricultural Engineering, Universidad Nacional de Colombia, Colombia*

ARTICLE INFO

Article history:
Received 11 December 2010
Received in revised form
11 June 2011
Accepted 2 July 2011

Keywords:
Cerebral cortex
Polymicrogyria
Lissencephaly
Turing pattern
Numerical solution
Finite element
Continuum mechanics

ABSTRACT

The cerebral cortex is a gray lamina formed by bodies of neurons covering the cerebral hemispheres, varying in thickness from 1.25 mm in the occipital lobe to 4 mm in the anterior lobe. The brain's surface is about 30 times greater that of the skull because of its many folds; such folds form the gyri, sulci and fissures and mark out areas having specific functions, divided into five lobes. Convolution formation may vary between individuals and is an important feature of brain formation; such patterns can be mathematically represented as Turing patterns. This article describes how a phenomenological model was developed by describing the formation pattern for the gyri occurring in the cerebral cortex by reaction diffusion equations with Turing space parameters. Numerical examples for simplified geometries of a brain were solved to study pattern formation. The finite element method was used for the numerical solution, in conjunction with the Newton–Raphson method. The numerical examples showed that the model can represent cerebral cortex fold formation and reproduce pathologies related to gyri formation, such as polymicrogyria and lissencephaly.

1. Introduction

The human brain's surface has folds, called sulci, and smooth regions extending between the sulci known by the name of convolutions or gyri [1]. Lobes corresponding to different functional areas can be distinguished in the brain: the frontal lobe, the parietal lobe, the temporal lobe and the occipital lobe at the back [2]. The brain's surface is about 30 times greater than the surface of the skull because of its many folds; such folds are formed during an embryonic stage around the 20th week [2] and can vary from one individual to another [1,3]. Cerebral cortex development pathologies can occasionally appear (i.e., polymicrogyria and lissencephaly) [1,2]. These patterns' formation in the cerebral cortex is still a matter for ongoing discussion and medical study [3–5], because the exact way of formation is a complex mechanism that involves mechanical forces, chemical process and genetic aspects. A complete description of cerebral cortex pattern formation can lead to elucidating cerebral cortex pathologies and improve the sufferers' quality of life.

* *Corresponding author*. Tel.: +57 12606381.
E-mail address: dagarzona@bt.unal.edu.co (D.A. Garzón-Alvarado).
0169-2607/$ – see front matter
doi:10.1016/j.cmpb.2011.07.001

The normal form of the human brain has well-defined gyris and sulcis allowing normal operation of each individual's motor and cognitive conditions [4]. There may be high variability in gyri "form" within each individual but a physiological limit will still be maintained [5]. Beside such limits regarding form, some diseases such as polymicrogyria involve cerebral malformation characterized by excessive cortical folds and shallow grooves [6]. Lissencephaly can also occur, this being a rare brain formation disorder characterized by microcephaly and agyria (the absence of convolutions or *gyris* (folds) normally occurring in the brain) [7].

The nature of the appearance of cerebral cortex shape is a constant theme in research involving the work of physicians, physicists, mathematicians and engineers to elucidate cortical pattern formation. Research in this area can be classified into two fundamental aspects: mechanical and biochemical. From a mechanical point of view, Le Gros [8] has shown that gyri formation is due to cortical surface expansion constrained by the skull and basal ganglia; it has also been shown that differential cerebral cortex growth causes gyri [9]. The same article also explained that pathologies regarding neocortical formation occur through changes in the mechanical properties of brain tissue. Toro and Burnod [10] have used anisotropy to show cortex formation regarding cerebral cortex tissue's mechanical properties [11].

Other hypotheses have been developed from a biochemical point of view regarding brain fold formation. Lefevre and Mangin [3] have stated the necessary conditions for a reaction–diffusion (RD) system for generating the distribution patterns required for cortical gyri formation. Their article assumed that the Gray–Scott RD system can determine cerebral cortex formation. Cartwright [12] has shown the similarity between Turing patterns in labyrinth form and cerebral cortex development. Their article used van der Pol–Fitzhugh–Nagumo equations as the ruling RD system and resolved the RD problem in 2D. Similarly, Rakic [11] has shown that cortical gyri pattern formation is present through intrinsic genetic control during the formation of the brain. The hypotheses presented in these articles have been supported by recent discoveries in the fields of genetics and biochemistry. Chenn and Walsh [13] have shown that the cerebral cortex of transgenic mice having an altered form of β-catenin expands in area, but not in width.

Lefevre and Mangin's excellent article [3] calls for reflection on the formation of the patterns emerging on the cortex of the brain; their article uses van der Pol–Fitzhugh–Nagumo's RD system. They also used the finite element method for solving the previously linearized RD equation system. They used the Laplace–Beltrami operator for taking surface deformation into account regarding the state of surface dilation. The present article uses classic continuum mechanics' formulation for shape-changing domains; Lagrangian formulation (also called material [33]) has thus been used in a full-Lagrangian approach. The Newton Raphson method has also been used for treating nonlinear terms. The glycolysis RD system has been used which shows that different types of reaction terms can lead to similar results in cerebral cortex patterns. The debate about the best reaction function would thus seem to be still open. An additional point concerns the variety of numerical tests carried out in this article; in fact, tests were carried out on several RD system parameters and the effect of brain growth introduced, as reflected in the last example establishing that skull growth speed can affect neocortical pattern configuration.

Based on an article by Chen and Walsh [13], it can be assumed that β-catenin is a protein activator precursor for gyri formation in the cerebral cortex and (associated with this molecule) that an inhibitor completes the RD system. The two molecules form RD systems forming highly stable patterns in time and unstable ones in space, similar to Turing patterns [3,13]. The present article's initial hypothesis has been based on the assumption that biochemical agents are primarily responsible for cerebral cortex formation in superior animals, especially, humans.

Following a similar approach to that used by Lefevre and Mangin [3] and Rakic [12], the glycolysis reaction model has been used (with Turing space parameters) to simulate the appearance of patterns in the cerebral cortex. A solution method using 3D surfaces was provided using the finite element (FE) method with full-Lagrangian formulation for resolving the RD equations. Several cases were simulated: normal pattern formation and the formation of development-associated pathologies (i.e., microgyria and lissencephaly).

2. Materials and methods

2.1. RD system

Following a biochemical approach, it was assumed that an RD system could control the formation of patterns occurring in the cerebral cortex. For this purpose, an RD system was defined for two species, given by (1):

$$\begin{aligned} \frac{\partial u_1}{\partial t} - \nabla^2 u_1 &= \gamma \cdot f(u_1, u_2) \\ \frac{\partial u_2}{\partial t} - d\nabla^2 u_2 &= \gamma \cdot g(u_1, u_2) \end{aligned} \tag{1}$$

where u_1 and u_2 were the concentrations of chemical species present in reaction terms f and g, d was the dimensionless diffusion coefficient and γ was a dimensionless constant [13]. It should be remembered that u_1 and u_2 could have been β-catenin (as activator) and its inhibitor [13], respectively. It was also assumed that a set of highly coupled morphogens (for example, Pax6, Ngn2, Id4 [3]), could guide gyri pattern formation in the cerebral cortex.

RD systems have been widely studied for determining their behaviour with different parameters regarding reaction terms [13,14], geometric scenarios [14,15] and for different biological applications [16–18]. One area which has led to extensive work being developed on RD equations is the formation of patterns which are stable in time and unstable in space [19] [20], called Turing patterns; Turing [21] developed the necessary conditions for spatial pattern formation in his book, "The chemical basis of morphogenesis." Pattern formation conditions