MECHANICAL MODELING OF CEREBELLAR FOLIATION CAUSED BY MULTICELLULAR ACTIVITIES

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Introduction

The cerebellar cortex has a unique morphology characterized by accordion-like parallel folds called folia, which are closely associated with the cerebellar function. The folia are formed through inward migration of granule cells (GCs) proliferated in an external granular layer (EGL), and subsequent their accumulation to generate an internal granular layer (IGL). Although, in this foliation process, GC migration guided by Bergmann glia (BG) fibers is believed to play important roles in the folia lengthening [1], its mechanical mechanism is still unclear. To clarify how the fiber-guided GC migration contributes to the cerebellar foliation, in this study, we have developed a continuum mechanics model of tissue morphogenesis that links tissue growth and deformation to multicellular activities including proliferation and migration. By conducting computer simulations based on this mechanical model, we investigated the effects of fiber-guided GC migration on the folia lengthening [2].

Methods

The tissue growth and deformation during the cerebellar foliation were formulated based on the theory of continuum mechanics [3]. The cell proliferation and migration were modeled using a balance equation for the cell number density, and incorporated them into the above tissue model. By combining the proposed model with a finite element method, we simulated the folia lengthening in the cerebellar cortex caused by GC proliferation and migration. The cerebellar cortex at the initial state was simply modeled as a slightly curved two-dimensional strip with a length of 400 μm and a thickness of 50 μm, which is composed of three layers: EGL, molecular/Purkinje cell layer (ML&PCL), and IGL. The GCs proliferated in the EGL were assumed to migrate toward the IGL along the BG fiber orientation that depends on the tissue deformation.

Results and discussion

To investigate the effects of fiber-guided GC migration on the folia lengthening, we performed computer simulations under physiological condition, where the GCs strictly migrated along the BG fibers, and pathological condition, where the GC migration direction was disturbed by a random angle ranging from $-\varphi_{max}/2$ to $\varphi_{max}/2$ (Fig. 1). Under the physiological condition (Fig. 1a), the GCs spread radially toward the IGL around the fissure, while the GCs converged toward the IGL around the lobule. In contrast, under the pathological condition (Fig. 1b), impaired GC migration decreased the cell number density in the IGL and increased it in other layers. As a result, the folia lengthening was more promoted under physiological condition compare to pathological condition. These results showed that radial migration of GCs guided by Bergmann glial fibers, whose orientation depends on the surrounding tissue deformation, is a critical factor to produce elongated folia accompanied by the IGL with non-uniform thickness. Our mathematical model is a promising framework to explore the emergence of brain structure and function from mechanical and biochemical viewpoints, and potentially help clarify the mechanism of various neurological diseases.

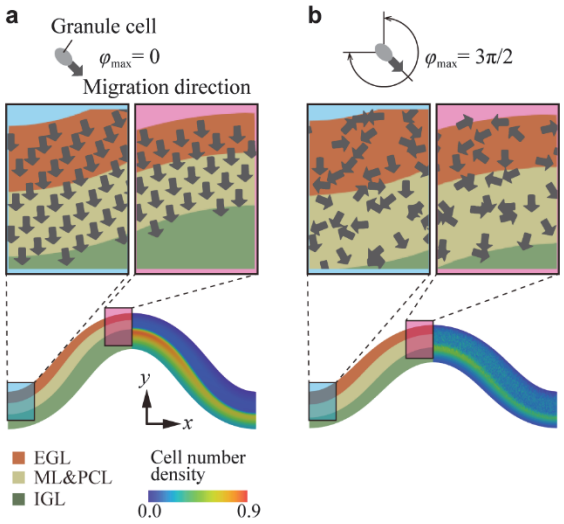

Figure 1: Computer simulations on the lengthening of cerebellar folia caused by fiber-guided GC migration under (a) physiological and (b) pathological conditions.

References

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