Continuum Modeling for Neuronal Lamination During Cerebral Morphogenesis Considering Cell Migration and Tissue Growth

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For neuronal lamination during cerebral morphogenesis, later-born neurons must migrate through already-accumulated neurons. This neuronal migration is biochemically regulated by signaling molecules and mechanically affected by tissue deformation. To understand the neuronal lamination mechanisms, we constructed a continuum model of neuronal migration in a growing deformable tissue. We performed numerical analyses considering the migration promotion by signaling molecules and the tissue growth induced by neuron accumulation. The results suggest that promoted migration and the space ensured by tissue growth are essential for neuronal lamination. The proposed model can describe the coupling of mechanical and biochemical mechanisms for neuronal lamination.

Keywords: Continuum model; Tissue growth; Cell migration; Cerebral morphogenesis; Neuronal lamination

1. Introduction

Cerebral tissue has a well-ordered layered structure consisting of several subtypes of neurons, the formation of which plays an essential role in acquiring physiological brain functions (Rakic 2009). To understand cerebral morphogenesis, it is important to clarify the mechanisms governing the formation of the neuronal layers. Neuronal lamination is accomplished through neuronal migration and accumulation during cerebral morphogenesis. Neurons are produced from radial glial progenitor cells in the ventricular zone (VZ) (Borrell and Reillo 2012; Borrell and Gotz 2014), which is located in the inner region of the cerebrum. The neurons then migrate along the radial

glial cells toward the marginal zone (MZ) (Rakic 1972; Borrell and Reillo 2012; Borrell and Gotz 2014), which is located close to the cerebral surface. After reaching the MZ, the neurons stop their migration and accumulate to form an inside-out layered structure in a cortical plate (CP), where the late-born neurons are arranged outside of the early-born neurons (Marin et al. 2010).

The neuronal migration during cerebral morphogenesis is regulated by extracellular signaling molecules including reelin (Marin et al. 2010; Valiente and Marin 2010; Chai et al. 2016). Reelin, which is secreted from the neurons in the MZ (D'Arcangelo et al. 1995), is thought to act as a chemoattractant in neuronal migration (D'Arcangelo and Curran 1998; Caffrey et al. 2014). In *reeler* mutants, which have reelin-deficient cerebrums, the neuronal lamination is inverted, forming in an outside-in manner, through inhibition of the neuronal migration (Sheppard and Pearlman 1997). To address the mechanisms governing the formation of inside-out lamination, it is necessary to clarify how neuronal migration is regulated by signaling molecules.

To understand neuronal lamination, it is crucial to consider the interaction between cellular and tissue-level mechanisms because the neuronal lamination and tissue formation affect each other. For an example of the tissue formation influencing a cellular-level process, the direction of the neuronal migration can be determined by the orientation of radial glial fibers, which varies depending on the tissue deformation (Misson et al. 1988; Del Toro et al. 2017). In contrast, the volumetric growth in the CP, which is suggested to result in gyrus formation, is caused by the production and accumulation of neurons (Reillo et al. 2011; Borrell and Gotz 2014). This represents an influence of cellular processes on tissue formation. To obtain a conceptual understanding of the cellular and tissue interaction in morphogenesis, computational approaches are useful (Takeda et al. 2020). **(#1-1)**A variety of computational models of

cell dynamics have been proposed in the fields of cell/tissue biology and tissue engineering to study cell movement based on cell-cell adhesion (Armstrong et al. 2006), collective cell migration during wound healing (Buganza Tepole and Kuhl 2016), and scaffold-dependent cell migration (Elsayed et al. 2019). For understanding cerebral development from a biochemical viewpoint, the cellular mechanisms of neuronal lamination, such as the adhesiveness of neurons, have been investigated using computational models (Zubler and Douglas 2009; Caffrey et al. 2014; Matsunaga et al. 2017). As for tissue-level mechanisms, computational and theoretical studies have been performed to elucidate the mechanical mechanisms of tissue deformation during cerebral morphogenesis (Budday et al. 2014; Tallinen et al. 2014; Goriely et al. 2015; Tallinen et al. 2016; Rooij and Kuhl 2018). To connect the cellular behavior and tissue deformation, the development of a model coupling neuronal migration and tissue deformation is required.

In this study, we constructed a computational model for neuronal lamination caused by neuronal migration in a growing deformable tissue. The tissue growth and deformation were formulated based on continuum mechanics. According to a previous study (Rooij and Kuhl 2018), the cellular migration was described using the balance equation for the cell number density by assuming a constitutive relationship between the cell number density and volumetric growth. To investigate the effects of the promotion of neuronal migration by signaling molecules on the neuronal lamination, the promoted neuronal migration was modeled as an additional migration velocity. Using the proposed model, we performed computer simulations in a one-dimensional space to investigate the effects of the promotion of neuronal migration and tissue growth on the inside-out neuronal lamination.

2. Continuum model for neuronal lamination in cerebral morphogenesis

2.1. Kinematics and constitutive relation of tissue growth

We consider a continuum body in a reference configuration, $\mathcal{B}_0 \subset \mathbb{R}^3$, with coordinates $\boldsymbol{X}$ denoting the position of material points in the body. The position of the same point at time t in the current configuration, $\mathcal{B}_t \subset \mathbb{R}^3$, is denoted as $\boldsymbol{x}$. We assume a deformation map, $\chi: \mathcal{B}_0 \to \mathcal{B}_t$, that maps a material point, $\boldsymbol{X}$, in $\mathcal{B}_0$ to a point $\boldsymbol{x} = \chi(\boldsymbol{X}, t)$ in $\mathcal{B}_t$. The deformation gradient tensor, $\boldsymbol{F}$, is defined as $\boldsymbol{F} \coloneqq \partial\chi(\boldsymbol{X}, t)/\,\partial\boldsymbol{X}$. To model the material growth, we assume multiplicative decomposition of the deformation gradient tensor, $\boldsymbol{F}$, into a growth part, $\boldsymbol{F}^{\mathrm{g}}$, and an elastic deformation part, $\boldsymbol{F}^{\mathrm{e}}$, as follows:

$$\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}}\boldsymbol{F}^{\mathrm{g}}. \tag{1}$$

The Jacobian of the growth deformation gradient tensor, $J^{\mathrm{g}} \coloneqq \det \boldsymbol{F}^{\mathrm{g}}\ (> 0)$, is the ratio of the volume in the reference configuration to that in the virtual stress-free configuration. To model the cerebral tissue growth induced by the neuronal accumulation, we assume that the volumetric growth depends on the cell number density. With reference to (Rooij and Kuhl 2018), the Jacobian, J^{g}, is described as a function of the cell number density $c\ (\geq 0)$ in the current configuration, $\mathcal{B}_t$:

$$J^{\mathrm{g}}(c) = (1 + kc)^{\alpha}, \tag{2}$$

where k and α are parameters for the constitutive relationship between tissue growth and cell number density.

2.2. Balance equation for the cell number density

The balance equation for the cell number density, c, in the current configuration, $\mathcal{B}_t$, is given as follows:

$$\frac{\partial c}{\partial t} + c\frac{1}{J}\frac{\partial J}{\partial t} = -\frac{\partial}{\partial \boldsymbol{x}} \cdot \boldsymbol{q}, \tag{3}$$

where $J(>0)$ is the Jacobian of the deformation gradient tensor, $\boldsymbol{F}$, and $\boldsymbol{q}$ is the flux of the cell number density (Rooij and Kuhl 2018). (#1-2)In this study, cell proliferation and cell death were not included because we focused on the neuronal migration during the lamination. Thus, the source of cell number density was not considered, and the number of cells was constant throughout the simulations. To model the neuronal migration, we describe the flux, $\boldsymbol{q}$, as follows:

$$\boldsymbol{q} = c\boldsymbol{v}\left(1 - \frac{c}{c_{\max}}\right) + c\boldsymbol{v}_{\mathrm{p}} - D\frac{\partial c}{\partial \boldsymbol{x}}, \tag{4}$$

where $\boldsymbol{v}$ is the velocity of the neuronal migration, $\boldsymbol{v}_{\mathrm{p}}$ is the additional velocity of neuronal migration promoted by signaling molecules, $c_{\max}$ is the upper limit of the cell number density when neuronal migration is not promoted, and D is a diffusion coefficient. The first term indicates the flux due to cell density-dependent migration without signaling molecules, and the second term indicates the flux promoted by signaling molecules. (#1-2)The third term indicates the dependence of cell migration on the gradient of cell number density. Substitution of Eq. 4 in Eq. 3 shows that the first and second terms correspond to convection terms, and the third term corresponds to a diffusion term.

2.3. Modeling neuronal lamination

To understand the essential mechanism of the inside-out neuronal lamination, the migration and accumulation of neurons is simulated using a one-dimensional model with a coordinate x (Fig 1). (#2-1-A)Previous studies (D'Arcangelo and Curran 1998; Caffrey et al. 2014) proposed that the inside-out lamination may be achieved through the attractive effect of reelin, which enables the late-born neurons to migrate from the VZ to MZ through the accumulated early-born neurons (Fig. 1, middle panel). The lack

of expression of reelin in the *reeler* cerebrum disrupts the neuronal migration, thus resulting in inverted lamination (Fig. 1, bottom panel).

[Figure 1 near here]

By defining the cell number densities of the early-born and late-born neurons as c_{E} and c_{L}, respectively, the flux of late-born neurons, q_{L}, in the x-direction can be described as follows:

$$\begin{aligned} q_{\mathrm{L}} &= c_{\mathrm{L}} v \left(1 - \frac{c_{\mathrm{E}} + c_{\mathrm{L}}}{c_{\max}}\right) + c_{\mathrm{L}} v_{\mathrm{p}} - D \frac{\partial c_{\mathrm{L}}}{\partial x} \\ &= c_{\mathrm{L}} (v + v_{\mathrm{p}}) \left(1 - \frac{c_{\mathrm{E}} + c_{\mathrm{L}}}{(1 + v_{\mathrm{p}}/v) c_{\max}}\right) - D \frac{\partial c_{\mathrm{L}}}{\partial x}, \end{aligned} \tag{5}$$

where v and v_{p} are scalar values in the x-direction for the corresponding vector values in Eq. (4). As shown in Eq. (5), the increase in the additional velocity, v_{p}, can be interpreted as an increase in the upper limit of the cell number density. **(#2-1-B)**In contrast to the late-born neurons, we assume that the early-born neurons are already accumulated and do not migrate during the late stage of the lamination, by setting their flux equal to 0.

(#2-1-C) To investigate the effects of tissue growth on neuronal lamination at the late stage, when the accumulated early-born neurons do not contribute to tissue growth, we considered only the tissue growth caused by the late-born neurons. Using a growth stretch, θ, in the x-direction determined based on the deformation gradient, $\boldsymbol{F}^{\mathrm{g}}$, the constitutive relationship described in Eq. (2) can be rewritten as follows:

$$\theta = (1 + k c_{\mathrm{L}})^{\alpha}. \tag{6}$$

The differential equations for tissue growth and neuronal migration were solved using the finite element method. In the numerical analysis of the tissue growth, the displacement at $x = 0$ was fixed. For the neuronal migration analysis, Eq. (3) was

160 solved in the one-dimensional domain $0 \leq x \leq l$, where l is the length of the tissue in
161 the current configuration, subject to zero-flux boundary conditions at $x = 0$ and l.

3. Results

3.1. Neuronal migration through the accumulated neurons

(#2-1-D)For inside-out lamination during cerebral morphogenesis, it is essential that late-born neurons migrate through early-born neurons. Based on previous studies proposing the role of reelin as an attractant of neurons (D'Arcangelo and Curran 1998; Caffrey et al. 2014), the effect of reelin was modeled as the promotion of neuronal migration. Using this model, we performed a numerical analysis in a one-dimensional space with coordinate x. In this analysis, the tissue growth was not considered, and thus, the current tissue length, l, was equal to the initial tissue length, L. We considered two types of neurons: the early-born neurons accumulated close to the MZ, and the late-born neurons migrating from the VZ to MZ. At the initial state of the simulations ($t/T = 0$), the cell number density distributions were determined according to an approximated rectangular function. (#2-2)Cell bodies are sparsely distributed behind the accumulated neurons (Sekine et al. 2012; Matsunaga et al. 2017). Thus, the low-density space was set as $0.9 < x/L \leq 1.0$, and the early-born neurons, which had ceased migrating, were set as $0.7 \leq x/L \leq 0.9$ based on cross-sectional images of the cerebrum (Iwashita et al. 2014). The late-born neurons, which migrated along the positive x-direction, were set as $0.2 \leq x/L \leq 0.5$. For simplicity, the migration velocity, v, and the additional migration velocity induced by signaling molecules, v_{p}, in Eq. (5) were assumed to be constant. To investigate the effects of signaling molecules that can promote neuronal migration, the additional velocity, v_{p}, was set as 0 and $0.2v$. The model parameters were defined as listed in Table 1.

[Table 1 near here]

We investigated the changes in the cell number density distribution with the additional velocity, v_{p}. When the cell migration was not promoted by signaling molecules ($v_{\mathrm{p}} = 0$), the late-born neurons ceased their migration just before reaching the early-born neurons (Fig. 2A), and thus, the late-born neurons did not migrate through the early-born neurons. On the other hand, in the case where the cell migration was promoted by signaling molecules ($v_{\mathrm{p}} = 0.2v$), the late-born neurons successfully migrated through the early-born neurons (Fig. 2B). These results suggest that the promotion of cell migration by signaling molecules is a possible essential factor for the inside-out lamination in the cerebral cortex.

In actual cerebral tissue, the space behind the accumulated neurons is small, and thus we performed numerical simulations by setting two different positions of the accumulated early-born neurons: $0.7 \leq x/L \leq 0.9$ and $0.8 \leq x/L \leq 1.0$. When the space between the early-born neurons and the end of the tissue was smaller, fewer late-born neurons migrated through the early-born neurons (Fig. 2C). On the other hand, when there was no space behind the early-born neurons, the late-born neurons could not migrate through the accumulated early-born neurons; some of the late-born neurons were distributed overlapping with the accumulated neurons, while the rest of the migrating neurons accumulated before the early-born neurons (Fig. 2D). These results suggest that sufficient space is required for all of the cells to migrate through the accumulated cells.

3.2. Effects of tissue growth on neuronal migration

In the inside-out lamination process, the accumulation of neurons close to the MZ contributes to the volumetric growth of the CP. **(#2-1-E)**In Section 3.1, we found that the low-density space behind the early-born neurons is required for the inside-out

lamination. Thus, we consider the expansion of the low-density space through the tissue growth caused by the late-born neurons as a possible mechanism of neuronal lamination. To investigate the effects of the tissue growth on the migration of late-born neurons that pass through the accumulated early-born neurons, we performed numerical simulations of the cell migration in a growing tissue by varying the constitutive parameter k in Eq. (6) (Fig. 3A and 3B). In the initial state of these simulations ($t/T = 0$), the tissue length satisfies $l/L > 1$ as a result of the tissue growth induced by the late-born neurons. The accumulated early-born neurons are present at $l/L - 0.3 \leq x/L \leq l/L - 0.1$, and the late-born neurons are located just before the early-born neurons. In addition to these simulations, to investigate the effects of the space behind the accumulated early-born neurons, we performed simulations by setting the early-born neurons at $l/L - 0.2 \leq x/L \leq l/L$ in the initial state (Fig. 3C).

[Figure 3 near here]

Comparing the results for $k = 0.5$ (Fig. 3A) and $k = 1.0$ (Fig. 3B), we show that a larger space behind the early-born neurons enabled a larger number of the late-born neurons to migrate through the accumulated early-born neurons. When there was no space behind the early-born neurons, the late-born neurons could not migrate through the accumulated early-born neurons, even with the growth of the tissue (Fig. 3C). Thus, these results suggest that space behind the accumulated neurons is required for neuronal migration through the accumulated early-born neurons, and this space is ensured by the tissue growth induced by the neuronal accumulation in the MZ.

4. Discussion

In cerebral development, neuronal lamination is important for the formation of the functional layered tissue. To investigate the mechanism governing the inside-out neuronal lamination in the cerebral cortex, we simulated the migration of late-born neurons past the accumulated early-born neurons. The simulation results suggest that the neuronal migration must be promoted by signaling molecules to form a neuronal layer behind the accumulated neurons (Fig. 2A and 2B). In addition, a larger number of late-born neurons can pass through the accumulated early-born neurons with increased space behind the accumulated neurons (Fig. 2C and 2D), which suggests that sufficient space behind the accumulated neurons is also required for the formation of inside-out lamination. **(#2-1-F)**Based on our simulations listed in Section 3.1, we assumed that the low-density space behind the accumulated early-born neurons is expanded by tissue growth induced by the late-born neurons. To test this mechanism, we performed computer simulations considering the tissue growth depending on the cell number density. The results showed that a greater number of late-born neurons can migrate past the accumulated early-born neurons as the tissue grows larger (Fig. 3). Taken together, we have clearly demonstrated that inside-out neuronal lamination can be accomplished through promoted neuronal migration and the tissue growth induced by neuronal accumulation.

To investigate the neuronal lamination in cerebral development, it is essential to consider the mechanisms at both the cellular and tissue levels simultaneously. The cellular mechanism of neuronal lamination has been investigated in some previous computational studies (Zubler and Douglas 2009; Caffrey et al. 2014; Matsunaga et al. 2017), which focused on biochemical aspects of the cellular interaction, such as the adhesion of neurons. On the other hand, the tissue-level mechanisms of cerebral

morphogenesis, such as gyrus formation, have been investigated from a mechanical perspective using mechanical modeling (Budday et al. 2014; Tallinen et al. 2014; Goriely et al. 2015; Tallinen et al. 2016; Rooij and Kuhl 2018). However, the tissue deformation and neuronal lamination processes affect one another, i.e., the neuronal migration depends on tissue deformation (Misson et al. 1988; Del Toro et al. 2017) and tissue growth is caused by neuronal accumulation (Reillo et al. 2011; Borrell and Gotz 2014). Therefore, to understand the mechanism of neuronal lamination, it is crucial to investigate the interaction between tissue deformation and neuronal lamination. In this study, we proposed a novel computational model for neuronal lamination and investigated the effects of tissue growth on the neuronal lamination by performing computer simulations of the tissue growth with respect to the cell number density.

During neuronal lamination, it has been suggested that reelin secreted from neurons in the MZ plays an important role in regulating neuronal migration. Considering that reelin has been proposed to be a chemoattractive factor during neuronal migration (D'Arcangelo and Curran 1998; Caffrey et al. 2014), in this study, the effect of reelin was modeled as an additional migration velocity. As shown in Eq. (5), this additional velocity corresponds to an increase in the maximum cell number density, which is dependent on cell–cell adhesion. Recent studies have shown that reelin regulates changes in the adhesiveness of neurons (Sekine et al. 2012; Matsunaga et al. 2017). Therefore, the simulation results shown in Fig. 2 suggest that reelin enables the late-born neurons to migrate past the early-born neurons by enhancing the velocity of the neuronal migration or by inducing a decrease in the cell–cell adhesion, which results in an increase in the maximum cell number density. Additionally, reelin has been suggested to regulate formation of the MZ, in which cell bodies are sparsely distributed (Sekine et al. 2012; Matsunaga et al. 2017). Therefore, our simulation results suggest

that reelin also contributes to the inside-out lamination by creating the space behind the accumulated early-born neurons by decreasing the cell density in the MZ.

(#2-3, #2-4, #2-5) We performed numerical analyses in a one-dimensional space because the inside-out lamination is essentially one-dimensional. To investigate the mechanical effects of tissue deformation on the neuronal lamination, such as tissue folding during gyrus formation, two- or three-dimensional analysis must be performed. This analysis could also consider both radial migration and non-radial/tangential migration, such as locomotion in CP, terminal translocation in MZ, and multipolar migration in VZ. Although such modes of neuronal migration contribute to the formation of neuronal layers, we modeled only locomotion of neurons in this study. To model the different migration modes, it is important to consider the heterogeneity of direction and speed of neuronal migration depending on the migration mode. These types of models would enable us to investigate the duration of neuronal lamination and the distribution of region-dependent thickness of neuronal layers. Furthermore, in addition to neuronal migration, modeling of the subsequent neuronal behaviors, such as cell fate decisions and maturation of neurons, will contribute to a comprehensive understanding of cerebral morphogenesis.

This study developed a computational model for neuronal lamination in growing tissue based on a continuum model. To understand the essential mechanism governing the neuronal lamination, we performed numerical analyses in a one-dimensional space by focusing on the locomotion of neurons. Further development of this model can lead to the establishment of a computational platform to understand the mechanisms governing the formation of functional tissues.

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Declaration of Interest

There are no conflicts of interest to declare.

References

Armstrong NJ, Painter KJ, Sherratt JA. 2006. A continuum approach to modelling cell-cell adhesion. J Theor Biol. 243(1):98-113.

Borrell V, Gotz M. 2014. Role of radial glial cells in cerebral cortex folding. Curr Opin Neurobiol. 27:39-46.

Borrell V, Reillo I. 2012. Emerging roles of neural stem cells in cerebral cortex development and evolution. Dev Neurobiol. 72(7):955-971.

Budday S, Raybaud C, Kuhl E. 2014. A mechanical model predicts morphological abnormalities in the developing human brain. Sci Rep. 4:5644.

Buganza Tepole A, Kuhl E. 2016. Computational modeling of chemo-bio-mechanical coupling: a systems-biology approach toward wound healing. Comput Methods Biomech Biomed Engin. 19(1):13-30.

Caffrey JR, Hughes BD, Britto JM, Landman KA. 2014. An in silico agent-based model demonstrates Reelin function in directing lamination of neurons during cortical development. PLoS One. 9(10):e110415.

Chai X, Zhao S, Fan L, Zhang W, Lu X, Shao H, Wang S, Song L, Failla AV, Zobiak B et al. 2016. Reelin and cofilin cooperate during the migration of cortical neurons: a quantitative morphological analysis. Development. 143(6):1029-1040.

D'Arcangelo G, Curran T. 1998. Reeler: new tales on an old mutant mouse. Bioessays. 20(3):235-244. eng.

D'Arcangelo G, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T. 1995. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature. 374(6524):719-723.

Del Toro D, Ruff T, Cederfjall E, Villalba A, Seyit-Bremer G, Borrell V, Klein R. 2017. Regulation of Cerebral Cortex Folding by Controlling Neuronal Migration via FLRT Adhesion Molecules. Cell. 169(4):621-635 e616.

Elsayed Y, Lekakou C, Tomlins P. 2019. Modeling, simulations, and optimization of smooth muscle cell tissue engineering for the production of vascular grafts. Biotechnol Bioeng. 116(6):1509-1522.

342 Goriely A, Budday S, Kuhl E. 2015. Chapter 2, Neuromechanics: From Neurons to
343 Brain. In: Bordas SPA, Balint DS, editors. Advances in Applied Mechanics. Elsevier; p.
344 79-139.

345 Iwashita M, Kataoka N, Toida K, Kosodo Y. 2014. Systematic profiling of
346 spatiotemporal tissue and cellular stiffness in the developing brain. Development.
347 141(19):3793-3798.

348 Marin O, Valiente M, Ge X, Tsai LH. 2010. Guiding neuronal cell migrations. Cold
349 Spring Harb Perspect Biol. 2(2):a001834.

350 Matsunaga Y, Noda M, Murakawa H, Hayashi K, Nagasaka A, Inoue S, Miyata T,
351 Miura T, Kubo KI, Nakajima K. 2017. Reelin transiently promotes N-cadherin-
352 dependent neuronal adhesion during mouse cortical development. Proc Natl Acad Sci U
353 S A. 114(8):2048-2053.

354 Misson J-P, Edwards MA, Yamamoto M, Caviness VS. 1988. Identification of radial
355 glial cells within the developing murine central nervous system: studies based upon a
356 new immunohistochemical marker. Dev Brain Res. 44(1):95-108.

357 Rakic P. 1972. Mode of cell migration to the superficial layers of fetal monkey
358 neocortex. J Comp Neurol. 145(1):61-83. eng.

359 Rakic P. 2009. Evolution of the neocortex: a perspective from developmental biology.
360 Nat Rev Neurosci. 10(10):724-735.

361 Reillo I, de Juan Romero C, Garcia-Cabezas MA, Borrell V. 2011. A role for
362 intermediate radial glia in the tangential expansion of the mammalian cerebral cortex.
363 Cereb Cortex. 21(7):1674-1694.

364 Rooij Rd, Kuhl E. 2018. A physical multifield model predicts the development of
365 volume and structure in the human brain. J Mech Phys Solids. 112:563-576.

366 Sekine K, Kawauchi T, Kubo K, Honda T, Herz J, Hattori M, Kinashi T, Nakajima K.
367 2012. Reelin controls neuronal positioning by promoting cell-matrix adhesion via
368 inside-out activation of integrin α5β1. Neuron. 76(2):353-369.

369 Sheppard AM, Pearlman AL. 1997. Abnormal reorganization of preplate neurons and
370 their associated extracellular matrix: an early manifestation of altered neocortical
371 development in the reeler mutant mouse. J Comp Neurol. 378(2):173-179. eng.

Takeda H, Kameo Y, Inoue Y, Adachi T. 2020. An energy landscape approach to understanding variety and robustness in tissue morphogenesis. Biomech Model Mechanobiol. 19(2):471-479.

Tallinen T, Chung JY, Biggins JS, Mahadevan L. 2014. Gyrification from constrained cortical expansion. P Natl Acad Sci USA. 111(35):12667-12672.

Tallinen T, Chung JY, Rousseau F, Girard N, Lefèvre J, Mahadevan L. 2016. On the growth and form of cortical convolutions. Nat Phys. 12(6):588-593.

Valiente M, Marin O. 2010. Neuronal migration mechanisms in development and disease. Curr Opin Neurobiol. 20(1):68-78.

Zubler F, Douglas R. 2009. A framework for modeling the growth and development of neurons and networks. Front Comput Neurosci. 3:25.

385 **Tables**

386 Table 1. Model parameters

Symbol	Value	Descriptions
L	100 μm	Initial length of the tissue
T	1 day	Representative time of the neuronal lamination
v	500 μm/day	Velocity of the neuronal migration in Eq. (5)
D	500 μm^2/day	Diffusion coefficient in Eq. (5)
c_{max}	1 /μm	Upper limit of the cell number density in Eq. (5)
α	1	Constitutive parameter in Eq. (6)

387

388 **Figure captions**

389 Figure 1. One-dimensional model of the neuronal lamination. Neurons born from radial
390 glial progenitor cells (black) in the VZ migrate toward the MZ; after reaching the MZ,
391 the neurons stop their migration and accumulate in a CP (top panel). The neuronal
392 lamination proceeds in an inside-out manner, in which the late-born neurons (red)
393 migrate past the accumulated early-born neurons (blue) (middle panel). The lack of
394 expression of reelin in the *reeler* cerebrum disrupts the neuronal migration, thus
395 resulting in inverted lamination (bottom panel).
396
397 Figure 2. Numerical analysis of neuronal lamination in one-dimensional space. The
398 curves show the spatial distributions of the early born neurons (blue) and the late-born
399 neurons (warm colors) at time t. The late-born neurons migrate toward the accumulated
400 early-born neurons along the positive x-direction. (**A**) Neuronal migration when the
401 migration was not promoted by signaling molecules ($v_\mathrm{p} = 0$). (**B**) Neuronal migration
402 past the accumulated neurons when the migration was promoted by signaling molecules
403 ($v_\mathrm{p} = 0.2v$). (**C**, **D**) Effects of the space between the early-born neurons and the end of
404 the tissue on neuronal lamination. (**C**) Neuronal migration with a smaller space behind
405 the accumulated neurons than that in (**B**). (**D**) Neuronal migration with no space behind
406 the early-born neurons.
407
408 Figure 3. Effects of tissue growth on neuronal lamination. The snapshots show the
409 spatial distribution of the cell number density for the late-born neurons (red) and early-
410 born neurons (blue) at the varying times, t. (**A**, **B**) Migration of the late-born neurons
411 through the accumulated early-born neurons with varying constitutive parameter of
412 tissue growth, k, in Eq. (6): (**A**) $k = 0.5$ and (**B**) $k = 1.0$. The dotted lines represent

413 growth stretch, θ. The gray regions indicate the outside of the tissue. (**C**) Neuronal
414 migration with the tissue growth ($k = 1.0$) when there is no space behind the
415 accumulated early-born neurons.
416

Figures

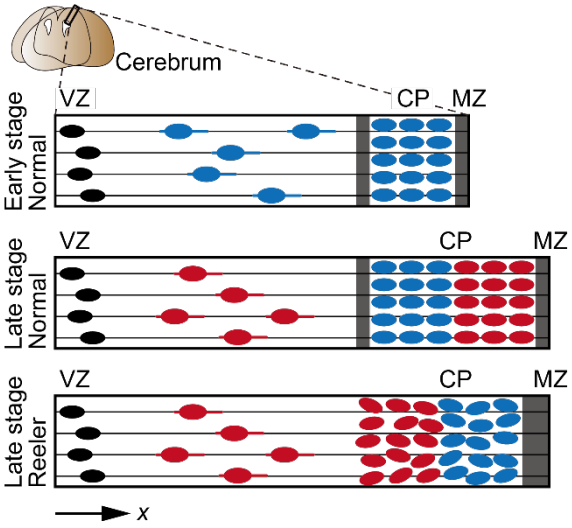
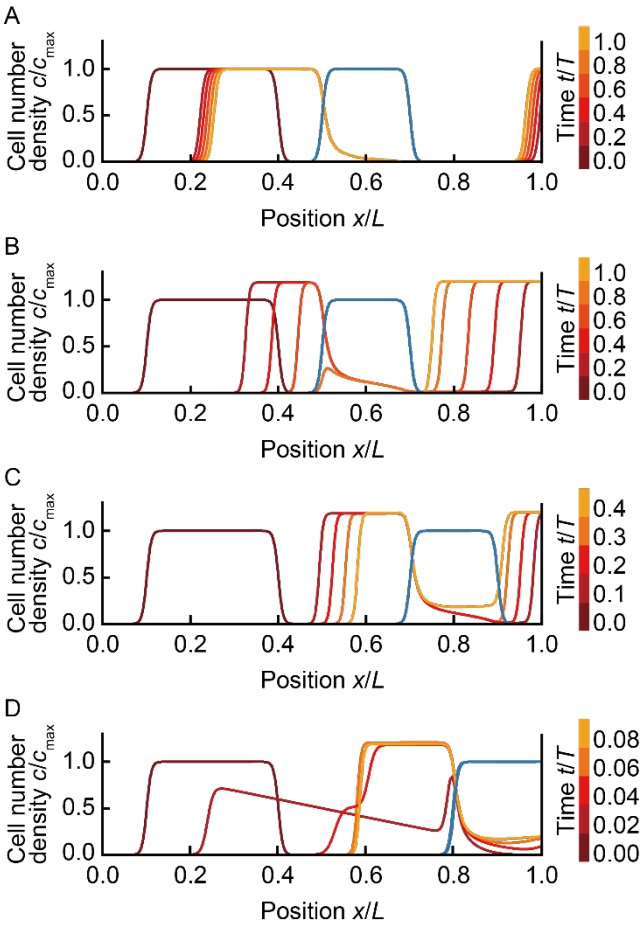


Figure 1



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423 Figure 2

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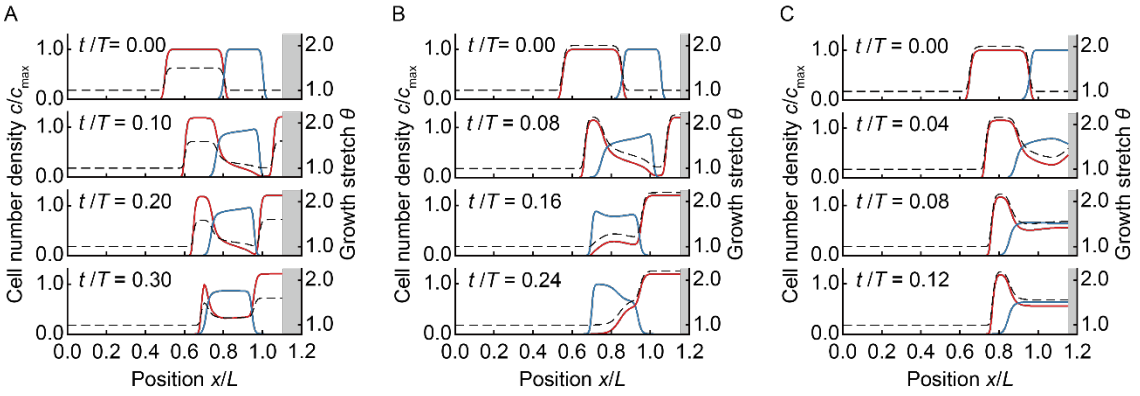
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Cell number density c/c_max
Growth stretch θ
Position x/L
0.0 0.2 0.4 0.6 0.8 1.0 1.2
1.0
2.0

Figure 3