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# Mechanisms of Brain Morphogenesis

Benjamin A. Filas, Gang Xu, and Larry A. Taber

**Abstract** In structures with obvious mechanical function, like the heart and bone, the relationship of mechanical forces to growth and development has been well studied. In contrast, other than the problem of neurulation, the developmental mechanisms in the nervous system have received relatively little attention. In this review we discuss recent advances in our understanding of the physical mechanisms of morphogenesis during brain development. Specifically, we focus on two processes: formation of the primary brain vesicles and folding of the cerebral cortex.

## 1 Introduction

During development, the brain undergoes a dramatic transformation from a simple tubular structure to (in large mammals) a highly convoluted shape. Most investigators recognize that mechanics plays a major role in this process, but the physical mechanisms of brain morphogenesis remain poorly understood.

In this review, we discuss the state of the field and some of the current research challenges. Where appropriate, we emphasize interspecies differences in morphogenetic mechanisms, as understanding these differences can provide insight into the development of individual organisms (Lui et al., 2011). After discussing background and embryology we focus on the formation of the primary vesicles in the early brain

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and cortical folding, which occurs relatively late in development. These processes warrant further study, as abnormalities in brain shape and folding patterns have been linked to a wide array of neurological disorders including schizophrenia, epilepsy, autism, and mental retardation. Morphogenesis offers a number of challenges for computational modelers, and we hope this review stimulates more interest in these problems among biomechanical engineers.

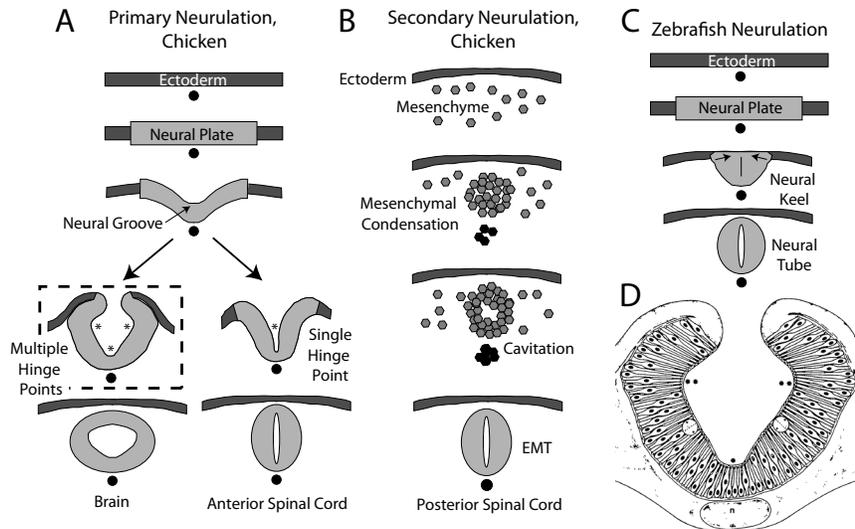
## 2 Neurulation and Brain Tube Formation

Neurulation is the earliest stage of development specific to the nervous system. This process begins within the first three weeks of conception in humans, as a central region of ectoderm called the neural plate folds to create the neural tube (Fig. 1). The wall of the tube is a neuroepithelium composed of a single layer of undifferentiated neural progenitor cells (Lowery and Sive, 2009). The cells are columnar, and the cell nuclei migrate between the apical side (facing the lumen) and basal side (facing the exterior) during the cell cycle, giving the neuroepithelium a pseudostratified, or multi-layered appearance (Sauer, 1935; Miyata, 2008). Eventually, the anterior and posterior regions of the neural tube become the brain and spinal cord, respectively.

Morphogenesis of the neural tube occurs in a specific spatiotemporal pattern along the length of the embryo. In the chicken, mouse, and human embryo, the neural plate elevates, folds, and fuses to form a tube with a hollow lumen (Fig. 1A). Depending on the longitudinal position along the tube, this closure is facilitated by the formation of one or three hinge points (Fig. 1A, asterisks). Generally, multiple hinge points are present at the anterior end of the tube (prospective brain), while only one hinge point forms posteriorly (prospective spinal cord). The end result is a tube that decreases in cross-sectional area from the brain through the spinal cord. Collectively this folding is known as primary neurulation, which has been shown to require the coordination of forces intrinsic to the neuroepithelium as well as extrinsic forces generated by surrounding tissues (Schoenwolf and Smith, 1990).

In contrast, during later stages of development, an entirely different mechanism sculpts the furthest posterior spinal cord region. Here, undifferentiated mesenchymal (loosely connected, highly migratory) cells condense and cavitate to form an internal lumen in a process known as secondary neurulation (Fig. 1B). Hence, the anterior brain and spinal cord form via coordinated bending of the neuroepithelium, whereas the posterior end of the spinal cord forms via the agglomeration, cavitation, and epithelialization of loosely connected cells.

In species such as *Xenopus* (frog) and zebrafish, however, such a difference between neurulation mechanisms is not immediately apparent (Schmitz et al., 1993; Lowery and Sive, 2004; Harrington et al., 2009). Here, neural precursor cells migrate medially to form a neural keel (Fig. 1C, arrows), intercalate (exchange neighbors), and remodel to form a slit-like lumen. Interestingly, it remains controversial as to whether the brain forms via a primary or secondary neurulation mode in these species. Dynamic (time lapse) imaging studies suggest that these cells roll into a



**Fig. 1** Neurulation mechanisms. (A) Primary neurulation in the chicken. A central region of ectoderm (neural plate) bends to form the neural groove. Multiple (brain) or single hinge points (spinal cord) facilitate subsequent tube closure (asterisks). (B) Secondary neurulation in the chicken. Mesenchymal cells coalesce and cavitate to form the posterior spinal cord. (C) Neurulation in zebrafish. Cells migrate medially (arrows) to form the neural keel and reorganize to form a slit-like lumen. (D) Schematic from Schoenwolf and Smith (1990) showing representative cell morphologies during stages of hinge point formation in the prospective chicken brain, adapted with permission from Development. Interrelated processes of cell shape change, contraction at the apical (inner) wall, and nuclear positioning cooperatively shape the bending neuroepithelium.

tube, as occurs during primary neurulation, but in doing so, the cells intercalate and migrate, displaying behaviors more typical of those involved in secondary neurulation (Lowery and Sive, 2004; Harrington et al., 2009). Hence, neurulation in these species may involve a combination of the primary and secondary neurulation mechanisms. Computational models for neural tube closure in amphibians have provided insight into some of these processes (Clausi and Brodland, 1993; Chen and Brodland, 2008; Brodland et al., 2010).

What does seem to be clear, however, is that hinge points do not form during neural tube formation in *Xenopus* or zebrafish as occurs in chicken, mouse, and human embryos (Fig. 1A,C, Harrington et al., 2009). Hinge point formation is characterized by interrelated, intrinsic processes such as cell wedging, possibly caused by apical contraction or the radial positioning of nuclei in the neuroepithelial wall (interkinetic nuclear migration) (Fig. 1D, Schoenwolf and Smith, 1990). The nucleus constitutes the bulk of the cell volume (Fig. 1D) and its radial position in the neuroepithelial wall depends on the stage of the cell cycle. If, for example, a subset of cells takes longer to undergo DNA synthesis at the outer wall of the neuroepithelium, then the nucleus would force the basal side of these tall, thin cells to expand and potentially generate a hinge point (Smith and Schoenwolf, 1988). Apical narrowing via contraction may also be involved, however, as proteins that

regulate cytoskeletal contraction (rho, phosphorylated myosin light chain, and F-actin) colocalize and accumulate at the inner wall of the neuroepithelium at hinge points (Sadler et al., 1982; Lee and Nagele, 1985; Kinoshita et al., 2008). It is currently unclear whether hinge point formation acts as a driving or a stabilizing force during normal neural tube closure (Greene and Copp, 2009). Early finite element models have shown that apical constriction can produce invaginations (Odell et al., 1981) and hinge-like morphologies (Clausi and Brodland, 1993), but this mechanism warrants further study.

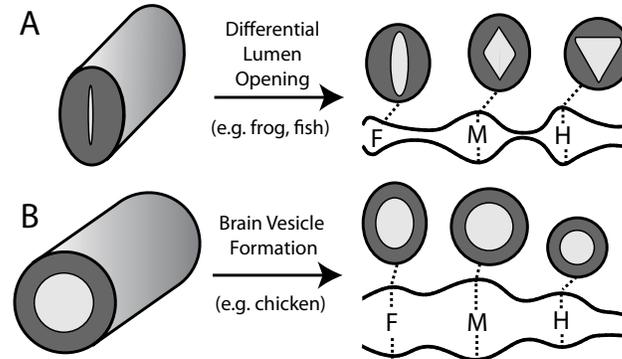
### 3 Brain Tube Morphogenesis

The brain tube of vertebrates subsequently subdivides into three primary vesicles (forebrain, midbrain, and hindbrain) (Fig. 2). Depending on the species, the brain vesicles develop from either a hollow tube or a comparatively closed, slit-like tube (Fig. 1). This suggests that, as in neurulation, morphogenetic mechanisms driving vesicle formation may vary between species.

#### 3.1 Lumen Opening in Zebrafish Brains

To date, mechanistic studies of brain vesicle formation have been conducted primarily in zebrafish embryos. In this species, the internal lumen of the tube differentially opens to generate the primary vesicles. The lumen of the hindbrain opens first, followed closely by the midbrain and the forebrain (Lowery and Sive, 2005). Interestingly, the forebrain, midbrain, and hindbrain lumens open into different cross-sectional shapes (Fig. 2A). Specifically, the midbrain lumen is shaped like a diamond, the hindbrain a triangle, while the forebrain opens into a tear-drop shape (Filas et al. (2012); see also Fig. 5G,J,M in Lowery and Sive (2005)). It is currently unclear whether all regions initially open as diamonds (as occurs in the midbrain; (Nyholm et al., 2009)) and later remodel into different shapes, or if the shape inhomogeneities are preserved throughout the opening process. Moreover, the significance of regionally varying shapes along the length of the brain tube is not yet known. Notably, at comparable developmental stages, early chicken, mouse, and human brains are generally round in transverse cross section (Fig. 2B, Copp et al., 2003; Filas et al., 2011, 2012).

The morphogenetic mechanisms that drive luminal opening in the zebrafish midbrain are beginning to be uncovered. In particular, inhibiting myosin by blebbistatin exposure prevents this process (Nyholm et al., 2009). This result has led to speculation that cytoskeletal contraction at lateral hinge points may facilitate luminal opening in zebrafish (Nyholm et al., 2009). Consistent with this idea, finite element modeling has shown that simulating local contraction at the inner wall of a tube



**Fig. 2** Mechanisms of brain vesicle formation. (A) Differential opening of a slit-like brain tube is concomitant with primary vesicle formation in frog and fish. Shapes vary in transverse cross sections between the forebrain (F), midbrain (M), and hindbrain (H). (B) Primary brain vesicles similarly form in species with comparatively open brain tubes, but vesicle shapes are rounded and relatively homogeneous.

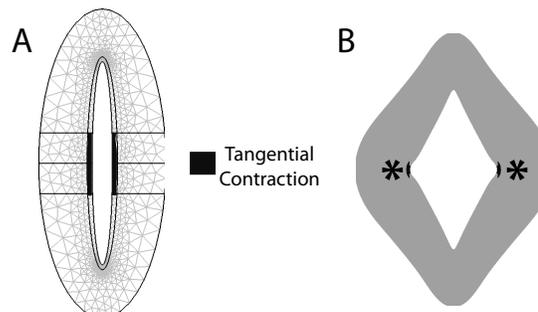
with an initially slit-like cross section generates lateral hinge points and a diamond-shaped lumen (Fig. 3).

Once the lumen opens, later expansion of the hindbrain requires relaxation of the cytoskeleton (Gutzman and Sive, 2010). Hence, it seems that the zebrafish brain tube actively contracts to establish a lumen, and later relaxes to facilitate expansion in response to increasing fluid pressure in the lumen (see Section 3.2).

### 3.2 Brain Vesicle Formation

Evidence suggests that brain tube morphology at the mid-hindbrain boundary in zebrafish is not purely a consequence of differential luminal expansion. The decreased radius in this region is associated with wedge-shaped cells produced by a com-

**Fig. 3** Model for lumen opening. (A) Finite element model of a tube with a slit-like cross section. Tangential contraction is prescribed at the apical (inner wall) at two mediolateral (darkened) locations. (B) Local contraction generates lateral hinge points (asterisks) and opens the lumen into a diamond shape. Figure adapted from Filas et al. (2012), with permission from Biomechanics and Modeling in Mechanobiology.



bination of basal constriction and apical expansion (Gutzman et al., 2008). Actin is concentrated on the basal side of these cells, consistent with actomyosin driven basal contraction. (Interestingly, in most other instances of invagination that involve cytoskeletal contraction, the contraction occurs at the cell apex (Davies, 2005).) In embryos that lack laminin, which is a major component of the basement membrane surrounding the outside (basal side) of the brain tube, the mid-hindbrain boundary still forms, but is not as sharp as in wild type embryos (Gutzman et al., 2008). Hence, differential lumen opening may set the initial pattern for the brain vesicles, while ongoing actomyosin activity remodels the tube into its characteristic three-dimensional structure.

Outside of zebrafish, however, the mechanisms of brain vesicle formation have received relatively little attention. To begin exploring this process, we measured morphogenetic strains at the inner wall of the neural tube during the stages of vesicle formation in the chicken embryo (Filas et al., 2008). As expected, negative circumferential strains occur at the mid-hindbrain boundary, with negative longitudinal strains in the surrounding ventricles. These results suggest that the brain may shorten in a specific, regionally dependent manner to facilitate vesicle formation. Corresponding changes in mechanical properties were measured by probing the stiffness of the neuroepithelium via microindentation (Xu et al., 2010a). Surprisingly, the characteristic brain geometry gives a nearly uniform indentation stiffness along the brain tube.

Recently, we have developed a finite element model for brain vesicle formation (BAF unpublished). The model consists of a circular tube with contraction simulated within a narrow region next to the lumen. When the mid-hindbrain boundary region undergoes circumferential contraction and the surrounding vesicles isotropic contraction (consistent with actin staining), the model yields geometric changes consistent with experimental measurements (Fig. 4B).

Extrinsic forces also may play a role in shaping the brain tube. The brain forms on the dorsal side of the embryo surrounded by a loosely packed network of cells and extracellular matrix known as the head mesenchyme. During vesicle formation in chicken and human embryos, the early brain seals at both ends to become a fluid-filled pressure vessel. The brain then begins a period of rapid expansion, and studies have shown that this growth depends on cerebrospinal fluid pressure (Gato and Desmond, 2009). Specifically, prematurely sealing the brain cavity causes the expansion to begin early (Desmond and Levitan, 2002), whereas relieving the pressure severely retards growth (Desmond and Jacobson, 1977).

In these embryos, however, the majority of vesicle morphogenesis occurs prior to the brain becoming a sealed, pressurized system. Hence, the primary source of external forces acting on the neuroepithelium during vesicle formation would likely be from surrounding tissues. To explore these effects, we removed the head mesenchyme and cultured isolated chicken brains through the stages of vesicle formation (Filas et al., 2011). In these brain tubes, the vesicles and overall morphology developed normally, suggesting that vesicle formation is intrinsic to the neuroepithelium.

### ***3.3 Rhombomere Formation***

As the primary brain vesicles form, a series of smaller, periodic bulges arise in the hindbrain. These rhombomeres (Fig. 4A), have received considerable attention since the early 1990s as regions of cell lineage restriction and differential gene expression (reviewed in Kiecker and Lumsden (2005)). With the spotlight on these structures as local signaling centers, interest in the morphogenetic mechanisms of rhombomere formation has receded. Still, some useful mechanistic details can be garnered from the earlier literature.

In rhombomeres of chicken embryos, cell proliferation rates and apical F-actin concentrations are higher in interboundary regions than in the boundaries (Guthrie et al., 1991). In addition, the amount of extracellular space between neighboring cells tends to increase in the boundaries during development (Heyman et al., 1993). These results led to early speculation that a bowing or buckling mechanism, due to constrained cell proliferation, drives rhombomere formation.

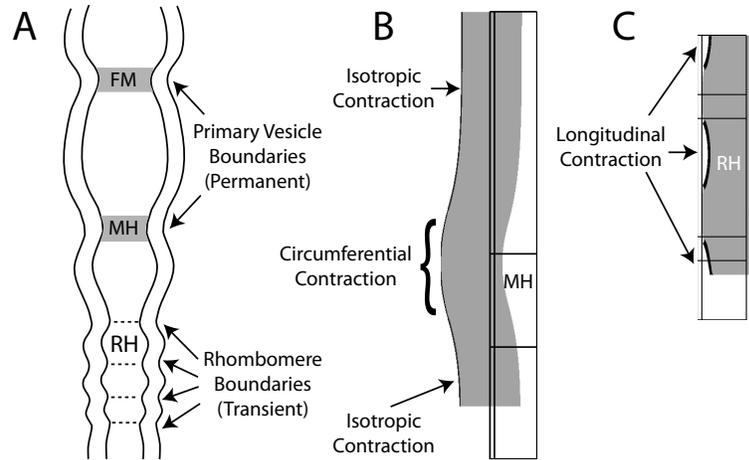
Alternatively, apical contraction between boundaries could play a role in rhombomere formation. For example, the model in Fig. 4C shows that longitudinal contraction along the inner wall between boundaries causes these regions to bend outward, producing a shape consistent with experimental observations.

Interestingly, rhombomeres are transient structures during brain development (as opposed to the primary vesicle boundaries which persist through maturity) (Kiecker and Lumsden, 2005). Before they disappear, rhombomere boundaries facilitate spatially dependent patterns of axonal migration, cell differentiation, and gene expression. In a recent study in zebrafish, rhombomere boundaries abnormally persisted in hyper-contracted mutants (Gutzman and Sive, 2010), suggesting that rhombomere formation and subsequent dissolution may be a consequence of regulated patterns of cytoskeletal contraction.

## **4 Cortical Folding**

### ***4.1 Cerebral Cortex Development and Theories for Folding***

Following vesicle formation, the brain rapidly expands due to an increasing lumen pressure. This expansion is primarily a growth response, rather than a simple inflation (Desmond and Jacobson, 1977; Pacheco et al., 1986). During these stages of rapid growth, the forebrain subdivides into the diencephalon and the more anterior telencephalon, which gives rise to the neocortex. Neurons generated in the developing neocortex differentiate and migrate along radially aligned glial fibers to form the characteristic layers of the mature brain in an inside-out manner (Bystron et al., 2008). In large mammals, folding of the cortex begins after these stages of neuronal migration and proliferation. The primary folding patterns are generally conserved across species, but secondary folds can differ considerably.

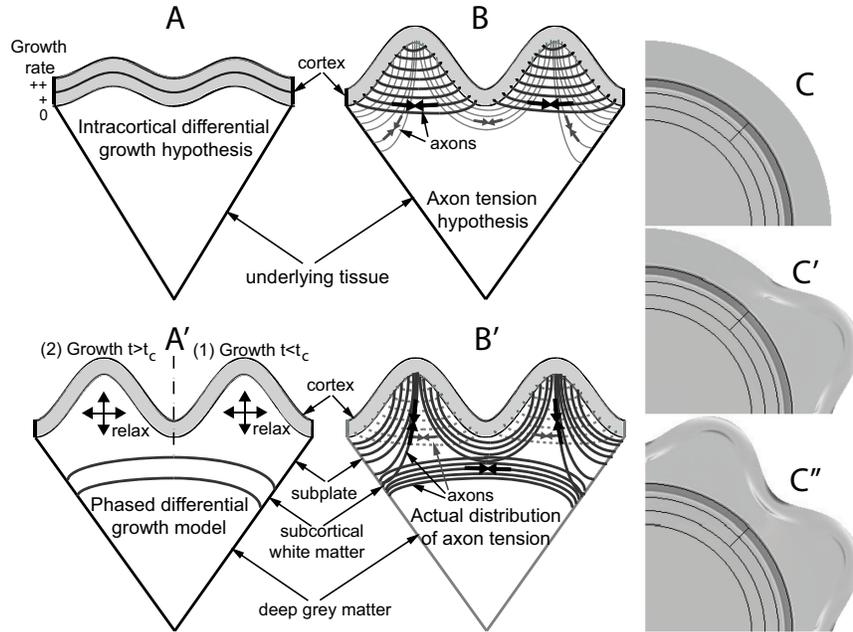


**Fig. 4** Boundary formation in the brain tube of the chicken embryo. (A) The primary brain vesicles (forebrain, midbrain, and hindbrain) are separated by the permanent fore-midbrain (FM) and mid-hindbrain (MH) boundaries. Rhombomeres (RH) are transient, sequential bulges in the early hindbrain. (B,C) Axisymmetric finite element models of vesicle (B) and rhombomere (C) morphogenesis. Contraction occurs at the apical (inner) wall. (B) The mid-hindbrain boundary contracts in the circumferential direction, but the apical side of the wall contracts isotropically elsewhere to create vesicles. (C) Longitudinal contraction between the more passive rhombomere boundaries causes local bulges (rhombomeres) to form.

Several hypotheses have been proposed for cortical folding mechanisms, and many are based on the idea that folds are produced by differential or constrained growth. A straightforward idea is that the brain grows faster than the skull, which therefore exerts compressive forces on the brain that cause it to buckle. To study this hypothesis, Raghavan et al. (1997), modeled the cerebral cortex as a thin curved beam that grows within a semicircular boundary representing the skull. With some *ad hoc* assumptions, these authors obtained realistic folding patterns. Experimental evidence, however, indicates that the brain can fold without external constraints (Barron, 1950).

The cerebral cortex is more accurately modeled as a thin shell. Such a model was proposed by Richman et al. (1975), who assumed that the outer layers of the cortex grow faster than the inner layers, causing compressive stresses that buckle the cortex (Fig. 5A). Their analysis yielded wavelengths consistent with those measured in the normal brain, as well as in brains with a microgyric (short wavelength) or lissencephalic (long wavelength) cortex. However, these investigators neglected nonlinear effects, which become increasingly important as folds grow large.

Several other computational models for growth-driven cortical folding have been proposed. Toro and Burnod (2005) modeled the cortex as a ring of 2-D truss elements with growth constrained by radially aligned elastoplastic fibers. Extending a similar model to 3-D, Nie et al. (2009) examined the effects of constraint of skull constraint, growth rate, regional variations in growth, and initial geometry of folding patterns. In addition, Geng et al. (2009) examined folding of small 3-D regions



**Fig. 5** Postulated models for cortical folding. (A) Intracortical differential growth hypothesis (Richman et al., 1975). Brain cortex is divided into two layers with the outer layer growing faster (indicated by ++ than the inner layer (+). Underlying tissue does not grow (0). Differential growth results in cortical buckling. (B) Axon tension hypothesis (Van Essen, 1997). Tension (black arrows) in axons pulls two cortical regions together to form an outward fold. The inward fold that forms between the outward folds separates weakly interconnected cortical regions (grey arrows). (A') Phased differential growth model. Cortical growth in region 1 ( $t < t_c$ ) followed by cortical growth in region 2 ( $t > t_c$ ) produces two folds. The underlying subplate grows to relax the induced stresses. (B') Experimental distributions of axon tension. Axons are under tension (black arrows) and aligned in the directions shown. Importantly, no circumferential tension (grey arrows) or axons (grey dotted lines) were detected in the cores (subplate) of the outward folds. (C-C'') Corresponding finite element model for cortical folding caused by phased differential growth. The dark and light grey colors indicate circumferential tension and compression, respectively (Xu et al., 2010b). Figure reproduced from Xu et al. (2010b), with permission from the Journal of Biomechanical Engineering, ASME.

of the cortex by combined osmotic expansion and artificially applied loads and constraints. It is important to note, however, that these models focus mainly on folding geometry and do not present stress distributions, which can be used to help distinguish between multiple solutions.

In an alternative hypothesis, Van Essen (1997) has postulated that the brain expands due to hydrostatic pressure and growth, but tension in axons restricts this expansion locally, forcing the cortex to fold (Fig. 5B). Consistent with observations, such a mechanism would tend to create outward folds in regions that are strongly interconnected, producing compact wiring, whereas inward folds form in weakly connected regions. Until recently, this mechanism had not been tested experimentally (see Section 4.2).

## ***4.2 Phased Differential Growth as a Mechanism for Cortical Folding***

The ferret is a popular animal for studies of cortical folding, as the ferret brain does not begin to fold until after birth (Smart and McSherry, 1986a,b; Barnette et al., 2009). To test the axonal tension hypothesis, we used tissue dissection to determine stress patterns in the folding ferret brain. The results indicate that axonal tension is significant, but the principal directions of this tension (and the corresponding axon orientations) are different from those predicted by the axon tension hypothesis (Fig. 5B'; Xu et al., 2010b). Notably, there is no significant tension between the walls of the outward folds (gyri). This result suggests that, although axonal tension is present, it likely does not play the mechanistic role during folding proposed by Van Essen (1997).

Next, we proposed a new model for folding driven by differential growth. This model is similar to that of Richman et al. (1975) with the following exceptions: (1) Tangential growth in the cortex is out of phase between adjacent regions (phased differential growth); and (2) the underlying subplate grows in response to the developed stresses. During the simulation, growth in one region produces an outward fold, which is then followed by a second growth-induced fold in the neighboring region, and so on (Fig. 5C). Consistent with this idea, imaging studies have shown that folds form in such a sequential manner during development (Neal et al., 2007; Kroenke et al., 2009). This model yields folding geometry and stress distributions that agree well with experimental results (Xu et al., 2010b). More recent data suggest, however, that the differential growth hypothesis may require further refinement to include a radial gradient in growth (Reillo et al., 2010).

## **5 Conclusions**

In summary, results from a number of laboratories are providing new insights into the biomechanical mechanisms of brain morphogenesis. Careful consideration must be taken in interpreting the results from these studies, as brain morphology can be highly variable between different model organisms.

The treatment of the subject here is not exhaustive and much work remains to be done to fill in the gaps. Notably, we have omitted discussion of secondary vesicle generation in the brain tube, as well as secondary cortical folding. Deeper questions remain relatively unexplored, such as the possible role of mechanical feedback in driving and potentiating brain morphogenesis. Indeed, mounting evidence suggests that the neuroepithelium can actively respond to changes in mechanical stress (Filas et al., 2011), and that changes in mechanical loading can directly affect cell proliferation rates (Desmond et al., 2005). Lastly, we note that the biomechanical events that cause folding anomalies associated with pathological conditions warrant further attention.

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