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【Review Paper】

Computational mechanics simulations on epithelial folding (Strengths, insights, and future challenges)

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Abstract
Epithelial folding is a fundamental process governing the transformation of flat epithelial sheets into intricate three-dimensional structures during morphogenesis. This phenomenon plays a pivotal role in the development of various organs across biological systems. Despite its importance, the underlying mechanisms of epithelial folding remain incompletely understood due to its dynamic and complex nature. In recent years, computational simulations have emerged as powerful tools to study epithelial folding, providing a means to test theories, generate predictions, and integrate data from various sources. The basic workflow of simulation-based research involves formulating hypotheses grounded in insights derived from experimental observations, constructing mechanical models based on these hypotheses, conducting simulations, and subsequently comparing simulation results with experimental observations. This review encompasses studies exploring how spatial distributions of contractile cells and temporal histories of growth and contraction contribute to the three-dimensionalization of epithelial sheets by modeling the mechanics of tissue growth and cell contractile forces. Additionally, it addresses the studies examining the impact of asymmetry in physical constraints imposed by the surrounding structures of epithelial sheets and the non-uniformity of growth on the undulation pattern formation of epithelial sheets by modeling the mechanical interaction between the growing tissue and the surrounding structures. Furthermore, a recent advancement proposes a new framework where computations are employed for initial stages of hypothesis formation by inferring the causality. In this context, we also discuss a recent study that quantitatively infers differential growth, causing the morphogenesis, solely from pre- and post-growth shape data. Through this comprehensive review, we demonstrate the utility of simulations in studying epithelial folding, emphasizing their potential for synergistic integration with various perspectives and exploring synergistic opportunities.

Keywords: Simulation, Epithelial folding, Apical constriction, Energy landscape, Mechanical interaction, Pattern formation, Differential growth

1. Introduction

Epithelial folding is a crucial process in morphogenesis, orchestrating the transformation of a flat epithelial sheet into complex three-dimensional structures. This phenomenon plays a central role in the development of various organs and structures, spanning a wide range of biological systems, from simple organisms to complex multicellular entities such as humans. Notable examples include the formation of villi of the intestinal tract (Shyer et al., 2013; Walton et al., 2016), folds in oviduct (Koyama et al., 2016), and brain gyri (Tallinen and Biggins, 2015) through epithelial folding. Moreover, the process contributes to three-dimensionalization of diverse organs, such as neural tube closure (Inoue et al., 2016; Martin and Goldstein, 2014), optic cup development (Eiraku et al., 2011), gastrulation (Beane et al., 2006), and even the formation of insect exoskeletons (Adachi et al., 2020; Matsuda et al., 2017).

The process of epithelial folding is intricately regulated and governed by a complex interplay of biochemical signals and mechanical forces. These can include cellular processes such as cell division (Mao et al., 2011, 2013), migration (Morishita et al., 2017; Sato et al., 2015), and apoptosis (Toyama et al., 2008), as well as physical forces such

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as contractile forces induced by cells (Nishimura et al., 2007; Sawyer et al., 2010; Simões et al., 2006). Interactions between cells and surrounding structures such as substrates are also key contributors to the folding process (Koyama et al., 2016; Tallinen and Biggins, 2015).

Despite the critical role of epithelial folding in development and its impact on adult organ function, the underlying mechanisms governing this process remain incompletely understood. This is largely due to the complex and dynamic nature of the process, which involves changes at the molecular, cellular and tissue scales over time.

In recent years, computational simulations have emerged as a powerful tool for studying complex biological processes such as epithelial folding. These simulations, which can incorporate detailed, quantitative information about the properties and behaviors of cells and tissues, provide a way to test theories and generate predictions about the mechanisms driving epithelial folding. By enabling researchers to manipulate various parameters and observe their effects on the folding process, simulations offer a level of control and precision that would be challenging, if not impossible, to achieve in experimental settings. They also offer a way to integrate and interpret data from a variety of sources, including experimental studies and theoretical models.

This review aims to introduce the practical utilization of simulations in understanding the mechanisms of epithelial folding. Particularly, we present the application of simulations to examine hypotheses related to mechanical aspects, which is the basic framework of the simulation-based study. In Section 2, we discuss studies on the mechanics of organ morphogenesis through the three-dimensionalization of epithelial sheets, and Section 3 focuses on studies on the undulation pattern formation on epithelial sheets. Furthermore, Section 4 introduces a recent study exploring the incorporation of computational approaches at the hypothesis-forming stage. Lastly, in Section 5, we discuss insights from these studies and explore the synergistic opportunities arising from the integration of diverse perspectives.

2. Three-dimensionalization of epithelial sheets

2.1 Role of spatial patterns of contractile cells in epithelial folding

One of the key factors influencing epithelial folding is the distribution of contractile forces within the epithelial sheet. These forces, generated by the contraction of actomyosin networks located at the apical side of the cells, induce contraction of the apical surface of the cells, leading to the bending and folding of the epithelial sheet (Martin and Goldstein, 2014).

In a study by Inoue et al., computational simulations were used to investigate the role of contractile forces in tissue invagination, a type of epithelial folding (Inoue et al., 2017). Their simulations were based on a model of monolayer epithelial sheet in which certain cells could undergo cell proliferation and contraction. By varying the spatial pattern of contractile cells in their simulations, the researchers were able to observe the effects of these patterns on the shape of the invaginated tissue. Two specific patterns were examined: circular and ring patterns of contractile cells. In both cases, cell proliferation occurred within the same circular region characterizing the pattern of contractile cells.

Their results showed that a circular pattern of contractile cells led to an apically concave shape, while a ring pattern of contractile cells resulted in an apically convex shape (Fig. 1). These findings emphasize the importance of the spatial distribution of contractile forces in determining whether invagination or evagination occurs. They also highlight the potential of computational simulations as a tool for studying the role of mechanical forces in epithelial folding.

Moreover, the study by Inoue et al. provides a compelling example of how simulations can be used to test hypothesis about the mechanisms of epithelial folding. By comparing the results of their simulations with experimental observations, the researchers were able to validate their model and confirm the predicted role of contractile forces in tissue invagination. This demonstrates the power of simulations as a tool for hypothesis testing in the study of epithelial folding.

2.2 Role of temporal history of growth and contraction

In epithelial folding driven by contraction, another mechanism influencing whether invagination or evagination occurs is the temporal control of growth and contraction. Even with the same spatial pattern of contractile cells, changes in the temporal relationship between tissue growth and contraction can result in altering invagination and evagination.

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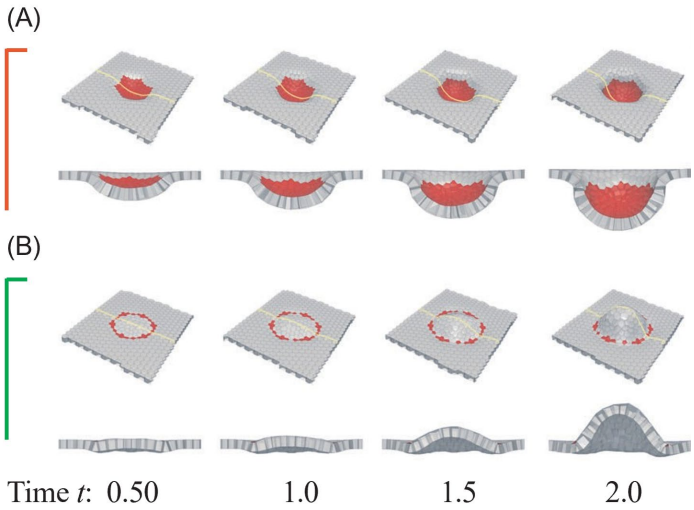

Fig. 1 Simulation snapshots at time t investigating the impact of spatial patterns of contractile cells. (A) Cells on the circular pattern contract and also proliferate, resulting in invagination. (B) Cells in the ring pattern contract and the cells inside the ring proliferate, resulting in evagination. Reprinted and modified from (Inoue et al., 2017) (CC BY 4.0).

Research by Takeda et al. focused on the mechanical stability of tissues, visualizing the energy landscape of morphogenesis events to provide a new framework for understanding the mechanical forces driving morphogenesis (Takeda et al., 2020). Using simulations based on continuum mechanics, where the entire tissue uniformly grows in-plane under fixed boundary conditions, they constructed energy landscapes for tissue growth with a circular contraction pattern. The results revealed that both invagination and evagination were mechanically stable in tissues with circular contraction patterns. Moreover, the study elucidated a dependence on the temporal history of growth and contraction, revealing that invagination occurs when contraction precedes growth, whereas evagination occurs when growth precedes contraction. This temporal dependency was elucidated as paths on the energy landscape (Fig. 2).

Furthermore, their study extended its framework to represent the wrinkling in tubular tissues, providing insights into the temporal role of mechanical and biological factors in epithelial folding. This work offers a framework for investigating the temporal roles of mechanical and biological factors in driving epithelial folding processes, demonstrating the potential of simulations for gaining new insights into complex biological phenomena.

3. Undulation pattern formation of epithelial sheets

3.1 Impact of physical constraints by surrounding structures in epithelial folding

Another factor that plays a crucial role in epithelial folding is the constraints by the surrounding structures. In a study by Morikawa et al., computational simulations were used to examine the impact of environmental constraints on epithelial folding patterns (Morikawa et al., 2022). Their simulations were based on a model of an epithelial sheet surrounded by an elastic environment. Under conditions where the out-of-plane deformation of the epithelial sheet is constrained by elastic walls, folding occurs through the growth of epithelial sheet by cell proliferation, giving rise to the formation of wrinkle patterns. In their research, they explored the relationship between the asymmetry of environmental constraints and the folding pattern of epithelial sheet by setting asymmetric constraints on the epithelial tissue. The results showed that the degree of asymmetry could serve as a determining factor in the formation of dot patterns, labyrinth patterns, or hole patterns (Fig. 3A). This finding underscores the importance of environmental constraints in shaping the folding patterns of epithelial sheets and highlights the potential of simulations as a tool for studying the influence of the environment on epithelial folding. Moreover, the study provides an example of how simulations can be used to investigate complex biological phenomena that are difficult to study experimentally. By using simulations, the researchers were able to manipulate the properties of the environment and observe their effects on epithelial folding, providing insights that would be challenging to obtain through experimental methods.

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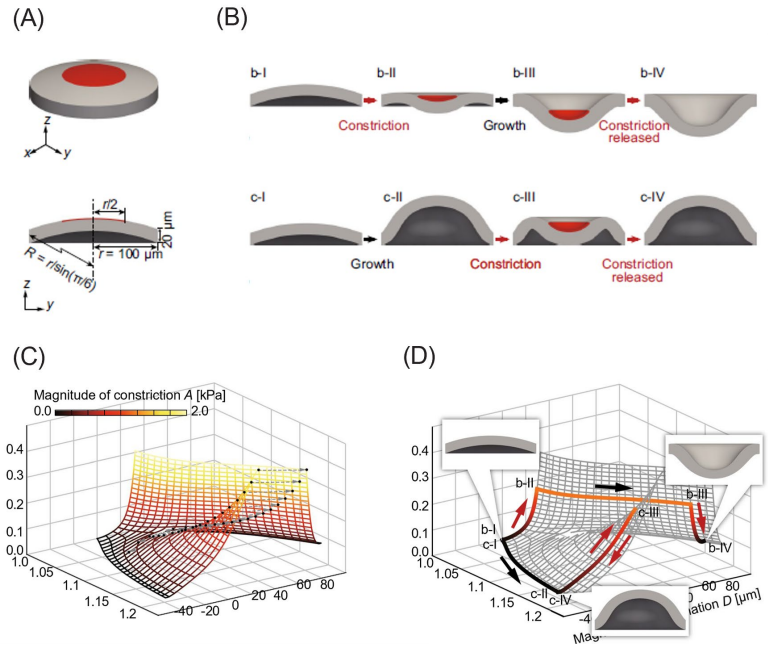

Fig. 2 Relationship between tissue shape and the temporal history of growth and contraction represented in the energy landscape. (A) Initial shape. Red region indicates the contractile apical surface. (B) Snapshots of simulations of growth and contraction. By changing the time history of growth and contraction, invagination and evagination are switched. (C) Visualization of the energy landscape. (D) Paths on the energy landscape corresponding to each time history of growth and contraction. Reprinted and modified from (Takeda et al., 2020) (CC BY 4.0).

In a study by Koyama et al., the folding of the luminal epithelium of the tubular mouse oviduct was investigated with a focus on the influence from the surrounding smooth muscle (SM) layer (Koyama et al., 2016). The luminal epithelium of mouse oviducts forms parallel fold structures with ridges in the longitudinal direction. However, in mutants with disrupted a gene, the folds exhibit branching. The researchers focused on the ratio of the longitudinal length of the epithelial layer to that of the surrounding SM layer (L-Epi/SM ratio) and conducted simulations of epithelial folding under the physical constraint of the SM layer. The results suggested that, depending on the L-Epi/SM ratio, orderly folding patterns in normal individuals and branched folding patterns in mutants are formed (Fig. 3B). The researchers also estimated the tension of the epithelium in each folding structure through both simulations and experiments. This dual approach indicated that epithelial tension plays a role in aligning wrinkle patterns. These findings emphasize the importance of L-Epi/SM ratio and the associated epithelial tension in the formation of ordered folding pattern in tubular oviduct. Moreover, the research demonstrates the utility of simulations in providing theoretical validation for hypothesis derived from experimental observations.

3.2 Epithelial folding pattern formation with coupling of cell division and local curvature

In the context of the formation of epithelial undulating patterns, certain scenarios involve not only cell proliferation, as observed in the intestines, but also frequent apoptosis. In the crypts of intestinal villi, cells undergo proliferation, while at the tip of the villi, cells experience apoptosis. A study conducted by Hannezo et al. introduced a model where the growth rate increases with curvature, expressing large growth rates at the bottom of concave crypts and small (negatively large) growth rates at the tip of convex villi (Hannezo et al., 2011). They conducted simulations of epithelial sheets growing under mechanical constraints imposed by the substrate. They created a phase diagram illustrating the effect of coupling between cell division and curvature, in addition to the relationship between the accumulated pressure due to growth and undulating patterns (Fig. 4). As a result, it became evident that asymmetrical undulating patterns, specific to the apical and basal sides, appear, showcasing only the crypts rather than the villi. This pattern corresponds to the morphology of the colon. While previous studies successfully reproduced the morphology of the small intestine with developed villi, the extension of their model in this study allowed for the reproduction of colon morphology as well.

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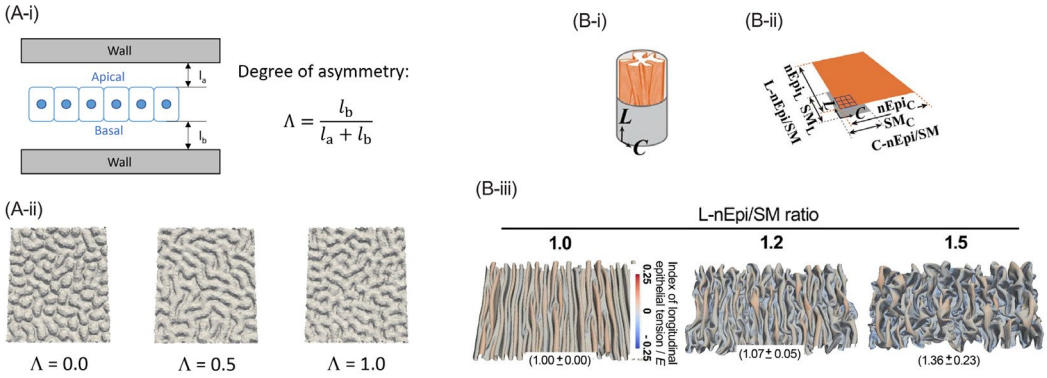

Fig. 3 Impact of physical constraints by surrounding structures. (A) Impact of asymmetry of out-of-plane deformation by surrounding structures on epithelial folding patterns. (A-i) Schematic of the model of the surrounding structures. Elastic walls are set on each apical and basal side of the epithelial sheet, and asymmetry is set with respect to the distance between the walls and the epithelial sheet. (A-ii) Simulation results of epithelial folding with different asymmetry settings. By changing the degree of asymmetry, dot, labyrinth, hole patterns were formed. Reprinted and modified from (Morikawa et al., 2022) (CC BY 4.0). (B) Impact of ratio of longitudinal length of epithelial sheet and the surrounding smooth muscle (SM) layer. (B-i) Schematic of the epithelial sheet (orange) and SM layer (gray). (B-ii) Schematic of two-dimensionally spread epithelial sheet and SM layer. (B-iii) Simulation results of epithelial folding with different L-nEpi/SM (longitudinal natural epithelium/SM) ratio settings. By changing the L-nEpi/SM ratio, ordered and branching patterns of epithelial folding were formed. Reprinted and modified from (Koyama et al., 2016) with permission from Elsevier.

Furthermore, their research provides a mechanical perspective for understanding epithelial folding. The wavelength of undulating patterns estimated from their elastic energy model closely resembles those observed in living organisms and can explain the size of villi in the biological context. Additionally, this observation explains the fact that the size of villi is consistent across many mammals, regardless of differences in body size. Thus, from a mechanical standpoint, it is possible to understand the universal principles of morphogenesis that transcend biological species.

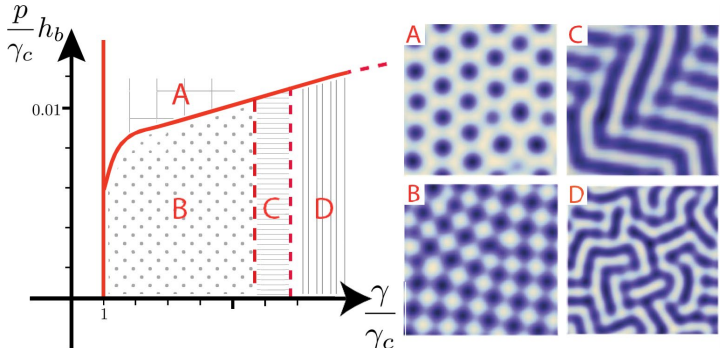

Fig. 4 Phase diagram generated from simulations of epithelial folding models with coupling between cell division and curvature. (A) Colon-like folding pattern, showcasing only the crypts. (B-D) Small-intestine-like developed villi pattern, herringbone pattern, and labyrinth pattern. The horizontal axis is the pressure exerted by tissue growth, and the vertical axis is the coupling between cell division and curvature. Reprinted from (Hannezo et al., 2011) with permission from American Physical Society.

4. Differential growth in curved surface morphogenesis of 3D organs

Recent approaches to understanding epithelial folding focus not only on the mechanical perspective but also on the geometric aspect, particularly considering differential growth, which is a growth mode where the growth rates are spatially biased, as a key factor of three-dimensional morphogenesis.

Morikawa et al.'s study proposed a method to infer the differential growth, i.e., spatial distribution of area expansion rates, from pre- and post-growth shapes' information in three-dimensional morphogenesis (Morikawa et al.,

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2023). Applying this method to the formation of horn primordia in beetles, they demonstrated its efficacy by comparing the inferred area expansion rate distribution with experimentally known cell proliferation frequency distribution (Fig. 5).

This research provides a tool to formulate working hypotheses for understanding the factors governing the complex three-dimensional morphogenesis. In conventional research, a mechanical model of growth can be constructed and theoretically verified by simulation only after a working hypothesis is obtained through sufficient experimental observation. Their method can provide a working hypothesis that can serve as a stepping stone for research using mechanical simulations, even for subjects for which detailed experimental observations are difficult.

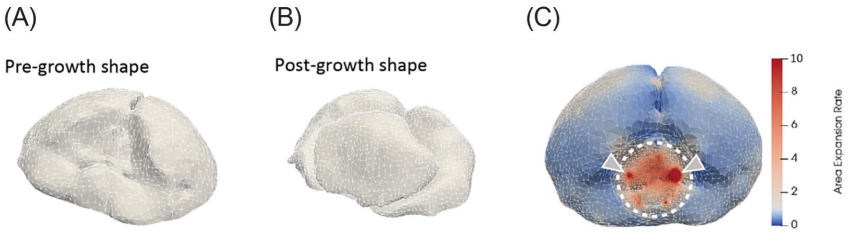

Fig. 5 Inference of the area expansion rate distribution governing its growth in the curved surface morphogenesis. (A) Pre-growth shape of the beetle's horn primordium. (B) Post-growth shape of the beetle's horn primordium. (C) Inference result of the area expansion rate distribution governing the growth of the horn primordium. Reprinted and modified from (Morikawa et al., 2023) (CC BY 4.0).

5. Multiple perspectives and strengths and limitations of simulations: comprehensive insights into epithelial folding

This review introduces the process of theoretically examining hypotheses based on experimental observations using simulations. Through diverse examples, we illustrate how this process is practically implemented. Additionally, we introduced a computational method for inferring the causes of phenomena at the hypothesis formation stage. Fig. 6 provides an overview of these processes. The reviewed papers have provided a range of perspectives on the process of epithelial folding, each contributing unique insights into the mechanisms behind this complex biological phenomenon. By examining these papers collectively, we can discern common themes and shared findings, as well as identify opportunities for synergy through the integration of various models and approaches.

Epithelial folding manifests in various forms, including substantial invagination or evagination leading to three-dimensional large deformation and the formation of undulation patterns with relatively small out-of-plane displacement. For significant three-dimensional deformations, studies by Inoue et al. and Takeda et al. suggest that simulations reveal the potential control of invagination or evagination through the interplay of tissue growth and cellular contractile forces (Inoue et al., 2017; Takeda et al., 2020). Moreover, spatial distribution of contraction patterns and temporal histories of growth and contraction are proposed as mechanisms governing the regulation of invagination or evagination. These outcomes underscore the power of computer simulations in purely expressing insights from a mechanical standpoint.

However, applying such methods to real developmental systems necessitates constructing the mechanical model of the system from substantial experimental knowledge (Okamoto et al., 2013; Shindo et al., 2019; Shinoda et al., 2018). In theoretical studies investigating mechanisms related to simple invagination and evagination, as seen in the works of Inoue et al. and Takeda et al., it was possible to model tissue growth with simple settings where cells uniformly proliferate within a circular region (Inoue et al., 2017; Takeda et al., 2020). On the other hand, to construct such models that reflect actual developmental systems, a quantitative understanding about how the tissue grows in these systems is essential. Formulating mathematical models requires obtaining quantitative data, which can be challenging in many cases.

In instances where acquiring quantitative data proves difficult, Morikawa et al.'s proposed method for inferring the distribution of area expansion rates may serve as a valuable tool for generating working hypotheses about how they growth, a fundamental aspect for initiating mechanical studies (Morikawa et al., 2023). By inferring the area expansion

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rate distribution solely from data on the shapes before and after growth, it becomes possible to construct a mechanical model of growth based on this distribution. This approach allows for the exploration of the mechanical mechanisms of the target developmental system. Particularly, determining whether invagination or evagination occurs, as highlighted in the studies by Inoue et al. and Takeda et al., remains undetermined from the area expansion rate distribution alone, necessitating investigation through mechanical simulations.

It's important to note that the method proposed by Morikawa et al. yields an isotropic growth pattern expressed as a scalar field representing the area expansion rate distribution (Morikawa et al., 2023). However, actual scenarios may involve anisotropic growth represented by vector fields, such as convergent extension or orientation of cell division. In cases where anisotropic growth predominates, the inferred growth pattern may deviate from reality. Validating the results requires examining the correspondence between the obtained area expansion rate distribution-based mechanical simulations and experimental observations.

Concerning the formation of undulation patterns with relatively small out-of-plane displacement, many studies have focused on the mechanical interaction between epithelial tissue and surrounding structures. These studies investigate the relationship between parameters characterizing the surrounding structures and the formed undulation patterns to understand the mechanisms underlying epithelial folding (Hannezo et al., 2011; Koyama et al., 2016; Morikawa et al., 2022). The utility of using mechanical simulations lies in the ability to purely extract the effects of the specific mechanical properties of interest, such as the asymmetry of physical constraints or the ratio of lengths between the epithelium and the surrounding layer (Koyama et al., 2016; Morikawa et al., 2022). This approach, as seen in the work of Morikawa et al., provides new perspectives for hypothesis formation, suggesting that the mechanical asymmetry of surrounding structures may determine undulation patterns, or, as demonstrated in the work of Koyama et al., allowing for theoretical validation of hypotheses derived from experiments (Koyama et al., 2016; Morikawa et al., 2022).

However, the capability to selectively extract specific properties comes at the cost of disregarding certain aspects of the real-world subject. Nonlinearity of mechanical actions and randomness in tissue shapes and cellular activities such as cell division are often treated with a certain degree of idealization, but it is possible that important effects may be contained in such discarded properties. For instance, in the studies of Morikawa et al. and Koyama et al., tissue growth was assumed to be uniform, but as shown in Hannezo et al.'s research, there are epithelial folding patterns that cannot be explained without considering the non-uniformity of tissue growth (Hannezo et al., 2011). Regarding the feasibility of assuming uniformity in tissue growth, Morikawa et al.’s proposed method for inferring the distribution of area expansion rates may offer insights into it (Morikawa et al., 2023). In general, to verify that our models accurately represent the key mechanisms, we need to examine the correspondence with experiments.

Moreover, instances of complex morphogenesis involving both three-dimensional large deformation and undulation pattern formation are known (Adachi et al., 2020; Matsuda et al., 2017). Conventional studies have explored such complex subjects by focusing on specific aspects and investigating local mechanisms (Inoue et al., 2020; Morikawa et al., 2022). However, by integrating the insights introduced in this review, it becomes feasible to comprehensively examine even these intricate subjects, shedding light on overarching mechanisms.

In conclusion, simulations, despite their limitations, serve as invaluable tools in the study of epithelial folding. They provide a method to explore the intricate interactions driving the process, offering insights that may be challenging to obtain through experimental methods alone. Furthermore, the synergistic effects of diverse perspectives obtained through simulations hold promise for advancing further research in this field.

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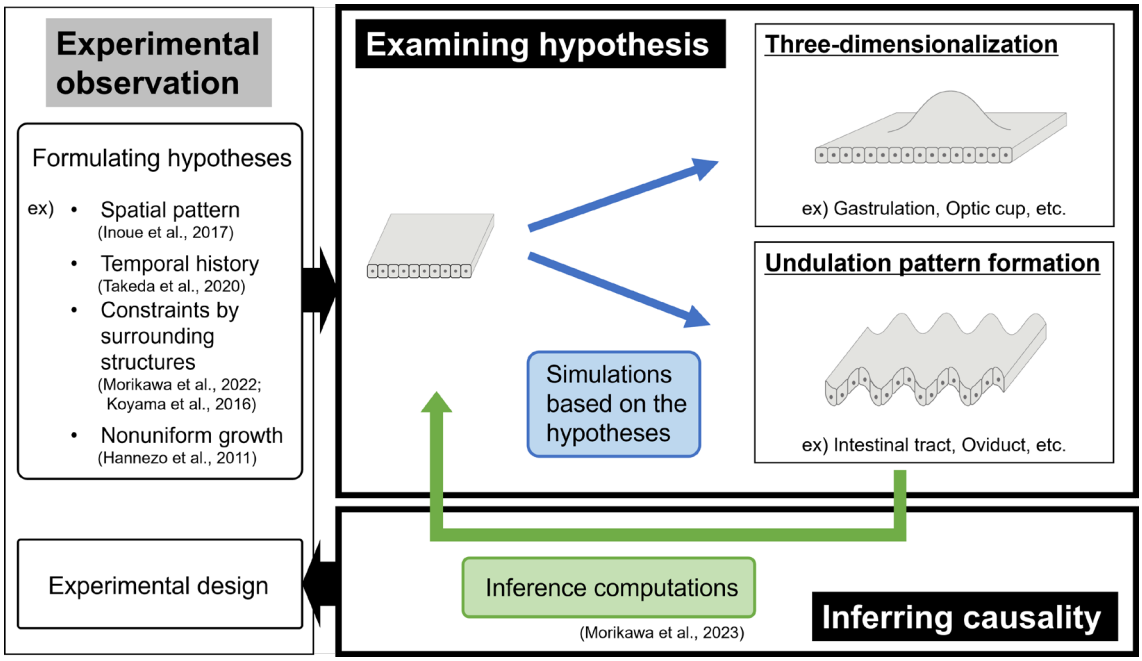

Fig. 6 Overview of simulation utilization in the study of epithelial folding. The basic process involves employing simulations to theoretically examine hypothesis formulated based on experimental observations. Additionally, a framework is proposed for using computational methods to infer the causes of phenomena at stages of hypothesis formation. This framework includes leveraging the results of inference in the design of experiments aimed at investigating the phenomena.

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Conflict of interest

There is no conflict of interest.

References

Adachi, H., Matsuda, K., Nishida, K., Hanson, P., Kondo, S. and Gotoh, H., Structure and development of the complex helmet of treehoppers (Insecta: Hemiptera: Membracidae). Zoological Letters, Vol. 6, No. 1 (2020), DOI:10.1186/s40851-020-00155-7

Beane, W. S., Gross, J. M. and McClay, D. R., RhoA regulates initiation of invagination, but not convergent extension, during sea urchin gastrulation. Developmental Biology, Vol. 292, No. 1 (2006), DOI:10.1016/j.ydbio.2005.12.031

Eiraku, M., Takata, N., Ishibashi, H., Kawada, M., Sakakura, E., Okuda, S., Sekiguchi, K., Adachi, T. and Sasai, Y., Self-organizing optic-cup morphogenesis in three-dimensional culture. Nature, Vol. 472, No. 7341 (2011), DOI:10.1038/nature09941

Hannezo, E., Prost, J. and Joanny, J. F., Instabilities of monolayered epithelia: Shape and structure of villi and crypts. Physical Review Letters, Vol. 107, No. 7 (2011), DOI:10.1103/PhysRevLett.107.078104

Inoue, Y., Suzuki, M., Watanabe, T., Yasue, N., Tateo, I., Adachi, T. and Ueno, N., Mechanical roles of apical constriction, cell elongation, and cell migration during neural tube formation in Xenopus. Biomechanics and Modeling in Mechanobiology, Vol. 15, No. 6 (2016), DOI:10.1007/s10237-016-0794-1

Inoue, Y., Tateo, I. and Adachi, T., Epithelial tissue folding pattern in confined geometry. Biomechanics and Modeling in Mechanobiology, Vol. 19, No. 3 (2020), DOI:10.1007/s10237-019-01249-8

Inoue, Y., Watanabe, T., Okuda, S. and Adachi, T., Mechanical role of the spatial patterns of contractile cells in

invagination of growing epithelial tissue. Development Growth and Differentiation, Vol. 59, No. 5 (2017), DOI:10.1111/dgd.12374

Koyama, H., Shi, D., Suzuki, M., Ueno, N., Uemura, T. and Fujimori, T., Mechanical Regulation of Three-Dimensional Epithelial Fold Pattern Formation in the Mouse Oviduct. Biophysical Journal, Vol. 111, No. 3 (2016), DOI:10.1016/j.bpj.2016.06.032

Mao, Y., Tournier, A. L., Bates, P. A., Gale, J. E., Tapon, N. and Thompson, B. J., Planar polarization of the atypical myosin Dachs orients cell divisions in Drosophila. Genes & Development, Vol. 25, No. 2 (2011), DOI:10.1101/gad.610511

Mao, Y., Tournier, A. L., Hoppe, A., Kester, L., Thompson, B. J. and Tapon, N., Differential proliferation rates generate patterns of mechanical tension that orient tissue growth. The EMBO Journal, Vol. 32, No. 21 (2013), DOI:10.1038/emboj.2013.197

Martin, A. C. and Goldstein, B., Apical constriction: Themes and variations on a cellular mechanism driving morphogenesis. Development, Vol. 141, No. 10 (2014), DOI:10.1242/dev.102228

Matsuda, K., Gotoh, H., Tajika, Y., Sushida, T., Aonuma, H., Niimi, T., Akiyama, M., Inoue, Y. and Kondo, S., Complex furrows in a 2D epithelial sheet code the 3D structure of a beetle horn. Scientific Reports, Vol. 7, No. 1 (2017), DOI:10.1038/s41598-017-14170-w

Morikawa, K., Kuroda, D. and Inoue, Y., Impact of environmental asymmetry on epithelial morphogenesis. Scientific Reports, Vol. 12, No. 1 (2022), DOI:10.1038/s41598-022-15343-y

Morikawa, K., Morita, S., Sakura, K., Maeno, A., Gotoh, H., Niimi, T. and Inoue, Y., Unveiling the role of differential growth in 3D morphogenesis: An inference method to analyze area expansion rate distribution in biological systems. Journal of Theoretical Biology, Vol. 575 (2023), DOI:10.1016/j.jtbi.2023.111650

Morishita, Y., Hironaka, K. I., Lee, S. W., Jin, T. and Ohtsuka, D., Reconstructing 3D deformation dynamics for curved epithelial sheet morphogenesis from positional data of sparsely-labeled cells. Nature Communications, Vol. 8, No. 1 (2017), DOI:10.1038/s41467-017-00023-7

Nishimura, M., Inoue, Y. and Hayashi, S., A wave of EGFR signaling determines cell alignment and intercalation in the Drosophila tracheal placode. Development, Vol. 134, No. 23 (2007), DOI:10.1242/dev.010397

Okamoto, M., Namba, T., Shinoda, T., Kondo, T., Watanabe, T., Inoue, Y., Takeuchi, K., Enomoto, Y., Ota, K., Oda, K., Wada, Y., Sagou, K., Saito, K., Sakakibara, A., Kawaguchi, A., Nakajima, K., Adachi, T., Fujimori, T., Ueda, M., Hayashi, S., Kaibuchi, K., and Miyata, T., TAG-1-assisted progenitor elongation streamlines nuclear migration to optimize subapical crowding. Nature Neuroscience, Vol. 16, No. 11 (2013), DOI:10.1038/nn.3525

Sato, K., Hiraiwa, T., Maekawa, E., Isomura, A., Shibata, T. and Kuranaga, E., Left-right asymmetric cell intercalation drives directional collective cell movement in epithelial morphogenesis. Nature Communications, Vol. 6, No 1 (2015), DOI:10.1038/ncomms10074

Sawyer, J. M., Harrell, J. R., Shemer, G., Sullivan-Brown, J., Roh-Johnson, M. and Goldstein, B., Apical constriction: A cell shape change that can drive morphogenesis. Developmental Biology, Vol. 341, No. 1 (2010), DOI:10.1016/j.ydbio.2009.09.009

Shindo, A., Inoue, Y., Kinoshita, M. and Wallingford, J. B., PCP-dependent transcellular regulation of actomyosin oscillation facilitates convergent extension of vertebrate tissue. Developmental Biology, Vol. 446, No. 2 (2019), DOI:10.1016/j.ydbio.2018.12.017

Shinoda, T., Nagasaka, A., Inoue, Y., Higuchi, R., Minami, Y., Kato, K., Suzuki, M., Kondo, T., Kawaue, T., Saito, K., Ueno, N., Fukazawa, Y., Nagayama, M., Miura, T., Adachi, T. and Miyata, T., Elasticity-based boosting of neuroepithelial nucleokinesis via indirect energy transfer from mother to daughter. PLoS Biology, Vol. 16, No. 4 (2018), DOI:10.1371/journal.pbio.2004426

Shyer, A. E., Tallinen, T., Nerurkar, N. L., Wei, Z., Gil, E. S., Kaplan, D. L., Tabin, C. J. and Mahadevan, L., Villification: How the Gut Gets Its Villi. Science, Vol. 342, No. 6155 (2013), DOI:10.1126/science.1238842

Simões, S., Denholm, B., Azevedo, D., Sotillos, S., Martin, P., Skaer, H., Hombría, J. C. G. and Jacinto, A., Compartmentalisation of Rho regulators directs cell invagination during tissue morphogenesis. Development, Vol. 133, No. 21 (2006), DOI:10.1242/dev.02588

Takeda, H., Kameo, Y., Inoue, Y. and Adachi, T., An energy landscape approach to understanding variety and robustness in tissue morphogenesis. Biomechanics and Modeling in Mechanobiology, Vol. 19, No. 2 (2020), DOI:10.1007/s10237-019-01222-5

[DOI: 10.1299/jbse.23-00562]

Tallinen, T. and Biggins, J. S., Mechanics of invagination and folding: Hybridized instabilities when one soft tissue grows on another. Physical Review E - Statistical, Nonlinear, and Soft Matter Physics, Vol. 92, No. 2 (2015), DOI:10.1103/PhysRevE.92.022720

Toyama, Y., Peralta, X. G., Wells, A. R., Kiehart, D. P. and Edwards, G. S., Apoptotic Force and Tissue Dynamics During Drosophila Embryogenesis. Science, Vol. 321, No. 5896 (2008), DOI:10.1126/science.1157052

Walton, K. D., Whidden, M., Kolterud, Å., Shoffner, S. K., Czerwinski, M. J., Kushwaha, J., Parmar, N., Chandhrasekhar, D., Freddo, A. M., Schnell, S. and Gumucio, D. L., Villification in the mouse: Bmp signals control intestinal villus patterning. Development, Vol. 143, No. 3 (2016), DOI:10.1242/dev.130112

[DOI: 10.1299/jbse.23-00562]