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Viscoelastic memory selects hierarchical folding in growing tissues

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Abstract: Mechanical instability plays a pivotal role in the morphomechanics of growing biological tissues, shaping complex architectures across multiple length scales. However, the mechanical origins of ubiquitous multiscale hierarchical instability in tissue morphogenesis remain unresolved. Existing models predominantly focus on single-scale elastic instabilities (e.g., wrinkling and buckling), neglecting the time-dependent viscoelastic relaxation that governs real tissue dynamics. Here, we establish a viscoelastic epithelial-submucosal model incorporating growth-induced stress to investigate spatiotemporal morphological evolution. We characterize hierarchical instability as a multiscale steady-state morphology with coexisting wrinkling and global buckling, and obtain analytical solutions for their viscoelasticity-dependent critical instability criteria. We further propose time-window and energy-competition criteria and construct a phase diagram, mapping the selection of wrinkling, hierarchical, and buckling patterns across the parameter space. This work provides a theoretical tool linking tissue mechanics to morphological outcomes, addressing limitations of elastic approximations and elucidating time-dependent constitutive impacts on instability criteria.

Keywords: Morphological evolution, Power-law viscoelasticity, Growth, Hierarchical instability.

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Introduction

The geometric morphologies of biological tissues serves as the structural basis for their physiological function and pathological progression^{1, 2}, tightly coupled to the development^{3, 4}, pathological evolution^{5, 6} and cancer diagnosis of living organisms⁷. Across cellular to tissue scales, living tissues sculpt complex functional morphologies through tightly regulated mechanical processes. Notably, under confined spatial environments, growth-induced mechanical instability emerges as a recurring mechanism for pattern formation, generating diverse structures ranging from microscopic surface wrinkling to macroscopic buckling^{8, 9}. Classic examples include the folded gyri of the cerebral cortex constrained within the skull^{10, 11} and epithelial folding in spherically confined organoids³, as illustrated in Figs. 1(a) and (b). Strikingly, beyond these single-scale patterns, hierarchical instability-driven morphologies as shown in Fig. 1(c), characterized by the coexistence of multiple length scales, widely emerge during tissue development as well^{12, 13, 14}. A paradigmatic example is the crypt-villus architecture lining the mammalian digestive tract [Fig. 1 (d)], in which long-wavelength epithelial folds ($\sim$ mm scale)¹⁵ coexist with shorter-wavelength villus and crypt structures ($\sim$ μ m scale)¹⁶. This multiscale structure maximizes nutrient absorption area, showing the critical biological significance of hierarchical morphogenesis. Our numerical simulations [Figs. 1(a')-(d')] recapitulate these experimentally observed representative morphologies, confirming that mechanical instability alone can generate morphological characteristics seen in vivo.

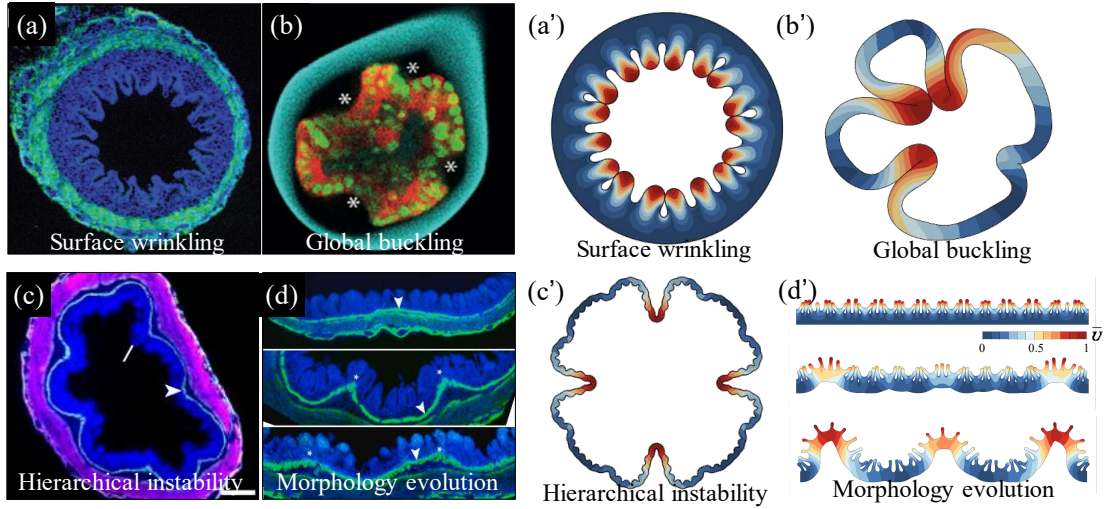


Fig. 1 Morphological evolution pattern of soft tissues in growth. (a) Surface wrinkling in chick gut lumen. Adapted from Shyer et al.⁹ with permission from AAAS. (b) Global buckling in the epithelium growing under spherical confinement. Adapted from Trushko et al.³ with permission from Elsevier. (c) Hierarchical instability in chick gut. Adapted from Gill et al.¹² with permission from PNAS. (d) The morphology evolution of the chick hindgut transverse sections. Adapted from Gill et al.¹³ with permission from Elsevier. (a'), (b'), (c') and (d') represent the results of our corresponding numerical simulations, shown alongside representative experimental morphologies for qualitative comparison.

Wrinkling or buckling have been recognized as a powerful mechanical mechanism underpinning tissue morphogenesis during growth^{17, 18, 19, 20, 21}. However, most previous morphogenetic studies have been focused on single-scale morphology formation under the static or quasi-static perspective^{22, 23, 24, 25, 26}. These classical frameworks adequately describe the final steady-state morphology of idealized elastic systems but fail to capture the time-dependent spatiotemporal evolution observed in real developing tissues. Most critically, they are difficult to explain the origin or stability of hierarchical multiscale structures, which remain a central unresolved problem in biological physics and developmental mechanics. In fact, the effective viscoelastic rheology of epithelial cell and tissues originates from rearrangements over a broad range of subcellular and extracellular scales, particularly exhibiting power-law rheological characteristics^{27, 28, 29, 30}. Turnover of the actomyosin cortex, remodeling of cell-cell junctions, basement-membrane reorganization, and extracellular-matrix crosslinking can all contribute to broad relaxation spectra^{31, 32, 33}. Their collective effects are coarse-grained into the reference modulus and power-law exponents of the epithelia and tissues. While the rate dependence and memory effects introduce a

temporal dimension to morphological evolution which is absent in elastic theories. Accordingly, we speculate that hierarchical morphologies of soft tissues may arise from the spatiotemporal coupling of multiscale instabilities within viscoelastic effects. To date, however, quantitative critical conditions for microscopic wrinkling, macroscopic buckling, and hierarchical transitions, as well as the regulatory role of viscoelasticity in morphological evolution, remain elusive.

In this work, we address these questions by developing an effective theoretical framework for the morphomechanics of growing viscoelastic layered tissues. We focus specifically on the epithelial-submucosal bilayer configuration, which is representative of many biological systems including the digestive tract, respiratory tract, brain and skin¹⁷. We derive closed-form analytical solutions for the critical instability conditions, characteristic timescales, and nonlinear amplitude evolution of both wrinkling and buckling patterns. We elucidate the mechanical origin of hierarchical instability, proposing two complementary quantitative criteria, the time-window criterion and the energy-competition criterion, which govern morphological pattern selection. Using these criteria, we construct an analytical phase diagram that maps steady-state morphologies across the parameter space of tissue geometry, material properties, and growth kinetics. This work not only resolves longstanding discrepancies between elastic predictions and experimental observations, but also provides a predictive tool for applications spanning artificial organs^{11, 34} and bio-inspired materials design^{35, 36}.

Results

Competing instability modes yield three distinct folding pathways

We idealize the mucosal epithelium and its underlying submucosa as a perfectly bonded bilayer subjected to differential growth. The epithelial film and submucosal substrate are denoted by subscripts f and s , with thickness h and H , respectively. Both layers are represented by effective power-law viscoelastic constitutive relations^{29, 37}, while differential growth is emulated via mismatched thermal dilatation (see detailed in Method and Supplementary Note 1). The primary dimensionless control parameters are

geometric ratio ($\mathcal{G} = H/h$), material property ratios (modulus ratio $\mathcal{M} = E_f/E_s$ and power-law exponent ratio $\mathcal{R} = \alpha/\beta$), and growth rate ratio ($\mathcal{K} = G_f/G_s$), to map morphological evolution driven by growth strain mismatch and time-dependent mechanical contrast.

Through extensive numerical simulations, we recapitulate the temporal and spatial evolutions of surface wrinkles and post-buckling in viscoelastic tissues, driven by growth disparity ($\mathcal{K}$) and time-dependent mechanical mismatch ($\mathcal{M}$, $\mathcal{R}$) between the epithelial and submucosal layers. Notably, the post-buckling morphological evolution exhibits the pronounced time-dependent behavior and geometric nonlinearity, with distinct morphological bifurcations (surface wrinkling, hierarchical instability, and global buckling) across the parameter spaces ($\mathcal{G}$, $\mathcal{K}$, $\mathcal{M}$ and $\mathcal{R}$), consistent with the trend of representative experimental observations, as delineated in Fig. 2.

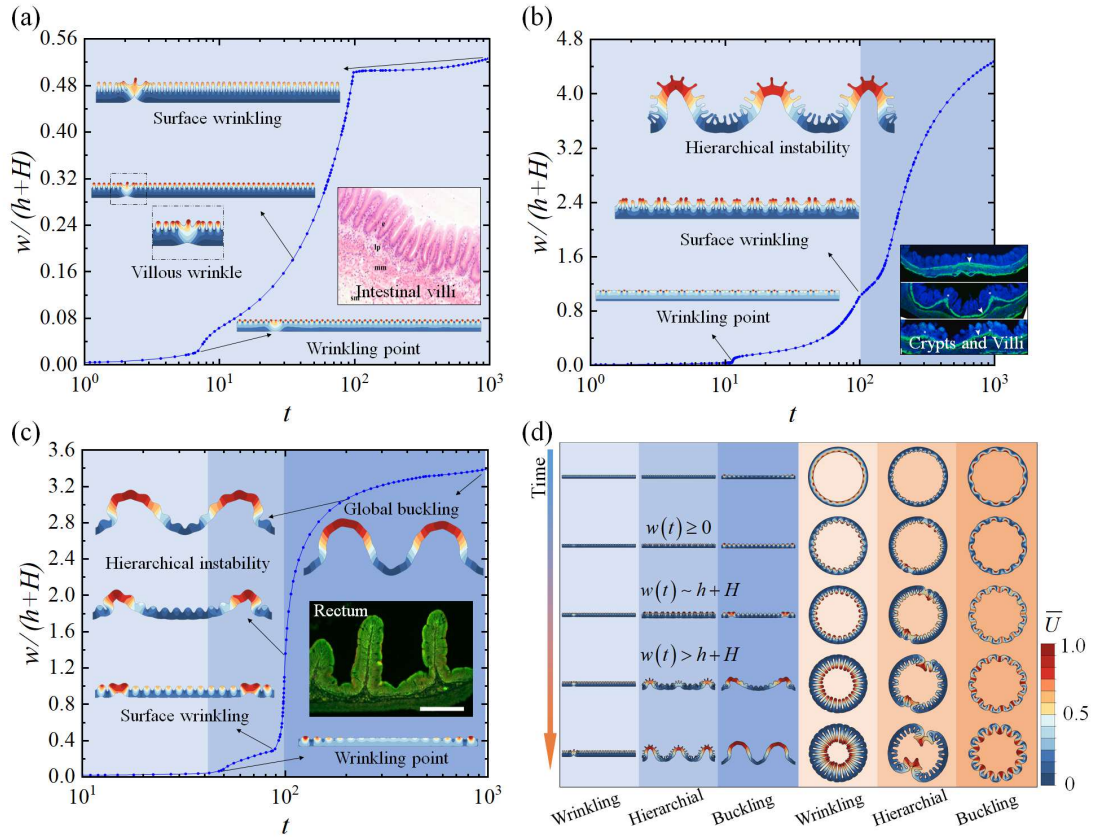


Fig. 2 Classification of post-buckling evolution pathways of biological tissues. (a) Surface wrinkling: After initiation, wrinkle amplitude increases monotonically to a stable state, analogous to epithelial folding and intestinal villus protrusion. (b) Hierarchical instability: Post-wrinkling, global buckling is triggered while surface wrinkles persist stably, forming multiscale instability, similar to

concurrent intestinal crypts and villi. (c) Global buckling: Surface wrinkles gradually attenuate, eventually evolving into global buckling, reminiscent of protrusive wrinkling in biological membranes. Insets in (a-c) adapted from Pozzer et al.³⁸ with permission from Wiley, Gill et al.¹³ with permission from Elsevier, and Gregório et al.³⁹ with permission from Company of Biologists LTD., respectively. (d) Different morphological bifurcations of temporal and spatial evolution diagrams. Numerical simulation parameters: (a) $\mathcal{G} = 50$, $\mathcal{M} = 32$, $\mathcal{K} = 3.0$ and $\mathcal{R} = 0.6$, (b) $\mathcal{G} = 25$, $\mathcal{M} = 64$, $\mathcal{K} = 3.0$ and $\mathcal{R} = 0.6$, (c) $\mathcal{G} = 10$, $\mathcal{M} = 10$, $\mathcal{K} = 1.0$ and $\mathcal{R} = 0.6$.

Besides, we identify three distinct steady-state instability modes across a broad parameter space of the growing viscoelastic epithelial-submucosal system, each governed by geometric ratio $\mathcal{G}$, modulus ratios $\mathcal{M}$ and growth rate ratios $\mathcal{K}$, with unique spatiotemporal evolution pathways for each mode. First, surface wrinkling emerges and persists in the thin-film/thick-substrate regime ($\mathcal{G} \gg 10$) at high $\mathcal{K}$ or $\mathcal{M}$ [Fig. 2(a)], consistent with prior studies on surface instability^{23,40}. The mechanical constraint from the thick submucosa locks surface wrinkling with no further bifurcation during growth, and the wrinkle amplitude converges to a stable saturation value. Second, hierarchical instability is captured as the terminal morphology under intermediate values of $\mathcal{G}$, $\mathcal{K}$ and $\mathcal{M}$ [Fig. 2(b)]. Initial surface wrinkling reduces the epithelial effective bending stiffness, lowering the critical Euler buckling threshold and triggering a secondary bifurcation to macroscopic bending. Crucially, the initial wrinkling mode does not dissipate, instead of the coupling co-evolution with wrinkling and buckling, terminating in a stable multiscale morphology with coexisting short-wavelength wrinkles and long-wavelength buckles. Third, global buckling is ultimately observed at low $\mathcal{G}$ or high $\mathcal{K}$ or $\mathcal{M}$ [Fig. 2(c)]. Conversely, insufficient mechanical constraint of submucosa sustains localized surface wrinkles. While surface wrinkling initiates first, global buckling onset rapidly dominates the post-buckling evolution. Driven by viscoelastic relaxation and stress redistribution, the initial short-wavelength wrinkles fully dissipate, leaving a stable macroscopic long-wavelength buckling morphology.

Analogous sets of three spatiotemporal bifurcation pathways are also observed in the ring-confined configuration, with the full morphological bifurcation map for both planar and ring geometries summarized in Fig. 2(d). This classification of steady-state instability modes directly reflects the competition between localized stress-driven

surface wrinkling and global stiffness-driven buckling, rooted in the inherent viscoelasticity and geometric nonlinearity of soft biological tissues.

Relaxation mismatch governs wrinkling onset and wavelength

We adopt the Föppl–von Kármán theory and the viscoelastic bilayer film–substrate framework⁴¹ to reveal the above underlying mechanisms. The time-dependent deflection $w(x, t)$ of mucosa epithelium is governed by the fourth-order plate equation⁴²,

$$\int_0^t D_f(t-\tau) \frac{d(\nabla^4 w)}{d\tau} d\tau + N_x^{\text{total}} h \frac{\partial^2 w}{\partial x^2} = p(x, t), \quad (1)$$

where $D_f(t)$ is the time-dependent bending stiffness. The in-plane force $N_x^{\text{total}} = N_g + N_m$ represents the sum of the growth-induced compressive force $N_g(t)$ and nonlinear force $N_m(t)$ within the epithelium. The epithelium deflection is described by $w(x, t) = A(t) \cos(kx)$ with the time-dependent amplitude $A(t)$, the wavenumber $k = 2\pi/\lambda$, and the wavelength λ . The deflection-induced transverse force of the growing submucosa is expressed as $p(x, t) = f(kH, v_s) k \gamma_s \int_0^t \bar{E}_s(t-\tau) d(\partial w / \partial x) / d\tau d\tau$ ^{22, 43} with the effective modulus of the submucosa $\bar{E}_s$ (Supplementary Note 1). Here, $f(kH, v_s)$ depends on the interface bonding conditions between the mucosa and the submucosa. Notably, $f(kH, v_s)$ decreases with kH and approaches a constant $f(\infty, v_s) = 1/2$ for $\mathcal{G} > 10$ (Supplementary Note 1). Additionally, $\gamma_s = \tau_{cr} / (\tau_{cr} + G_s)$ where G_s and τ_{cr} represent the growing rate of the submucosa and the characteristic time of mucosal folding, respectively⁴⁰.

Within the framework of linear stability analysis, the critical compressive force N_g^{cr} and wavelength λ_{cr} can be derived analytically by solving the eigenvalue problem (Supplementary Note 1). Biological soft tissues exhibit power-law viscoelastic

174 rheology^{31, 32, 33}, characterized by relaxation moduli as $E_f(t) = \bar{E}_f t^{-\alpha}$ and
 175 $E_s(t) = \bar{E}_s t^{-\beta}$ (see detailed in Method), where α and β denote the power-law exponents
 176 of the mucosal epithelium and submucosa, respectively. Substituting these constitutive
 177 relations into the equilibrium equations and performing an inverse Laplace transform,
 178 we obtain the time-domain critical conditions for surface wrinkling (Supplementary
 179 Note 1),

$$180 \quad N_g^{cr} = \frac{3}{4} \rho_\alpha \bar{E}_s \left(\frac{c_\alpha}{3} \gamma_s^2 \mathcal{M} \right)^{\frac{1}{3} \frac{\alpha+2\beta}{3}}, \lambda_{cr} = 2\pi h \kappa_\alpha \left(\frac{c_\alpha}{3\gamma_s} \mathcal{M} \right)^{\frac{1}{3} \frac{\alpha-\beta}{3}}, \quad (2)$$

$$\left(t_{surf} + \frac{1}{G_s} \right)^2 t_{surf}^{3-2(\alpha-\beta)} = \frac{9}{64} \frac{1}{\mathcal{M}^2} \frac{c_\alpha \rho_\alpha^3 (1-\alpha)^3}{G_c^3 G_s^2}$$

181 where $t_{surf} = 1/\tau_{cr}$ marks the onset of surface instability, $c_\alpha = \Gamma(1-\alpha)\Gamma(1-\beta)^{-1}$,
 182 $\rho_\alpha = \Gamma(1-\beta)\Gamma[1-(\alpha+2\beta)/3]^{-1}$ and $\kappa_\alpha = \Gamma[1-(\alpha-\beta)/3]^{-1}$ are dimensionless
 183 viscoelastic parameters. The other dimensionless parameters ($\mathcal{G}, \mathcal{K}, \mathcal{M}$ and $\mathcal{R}$) are
 184 explicitly defined by the tissue geometry, material properties, and growth kinetics.

185 Fig. 3 summarizes the marginal stability boundaries for the normalized critical
 186 pressure $\bar{N}_g^{cr}$, critical wrinkling time t_{surf} , and critical wavelength λ_{cr} as functions
 187 of the modulus ratio $\mathcal{M} = E_f/E_s$, growth rate ratio $\mathcal{K} = G_f/G_s$, epithelial thickness
 188 h , and power-law exponent ratio $\mathcal{R} = \alpha/\beta$. The critical pressure $\bar{N}_g^{cr}$ increases with
 189 both $\mathcal{M}$ and $\mathcal{K}$ [Fig. 3(a)], indicating that stiffer epithelia or stronger differential
 190 growth raise the threshold for wrinkling. The critical time t_{surf} decreases with $\mathcal{M}$
 191 but increases with $\mathcal{K}$ [Fig. 3(b)], showing that a stiffer epithelium accelerates
 192 instability onset, while faster differential growth delays it. The critical wavelength λ_{cr}
 193 scales linearly with h , increases with $\mathcal{M}$, and decreases with $\mathcal{K}$ [Figs. 3(c) and (d)].
 194 Of particular importance, the exponent ratio $\mathcal{R}$ quantifies the viscoelastic mismatch
 195 between the two layers and exerts a decisive influence on the wrinkling morphology.

As shown in Figs. 3(e) and (f), λ_{cr} increases monotonically with $\mathcal{R}$, a trend mediated entirely through the critical wrinkling time t_{surf} . In the special case of identical rheology ($\alpha = \beta \neq 0$), the common relaxation factor cancels from the spatial wavelength-selection problem. The wavelength of Eq. (2) reduce exactly to the elastic solution derived by Budday et al.²², while the growth-induced resultant and critical time remain history dependent. This result demonstrates that classical elastic models emerge as a limiting case of the present viscoelastic model, valid only when all layers share identical rheological properties.

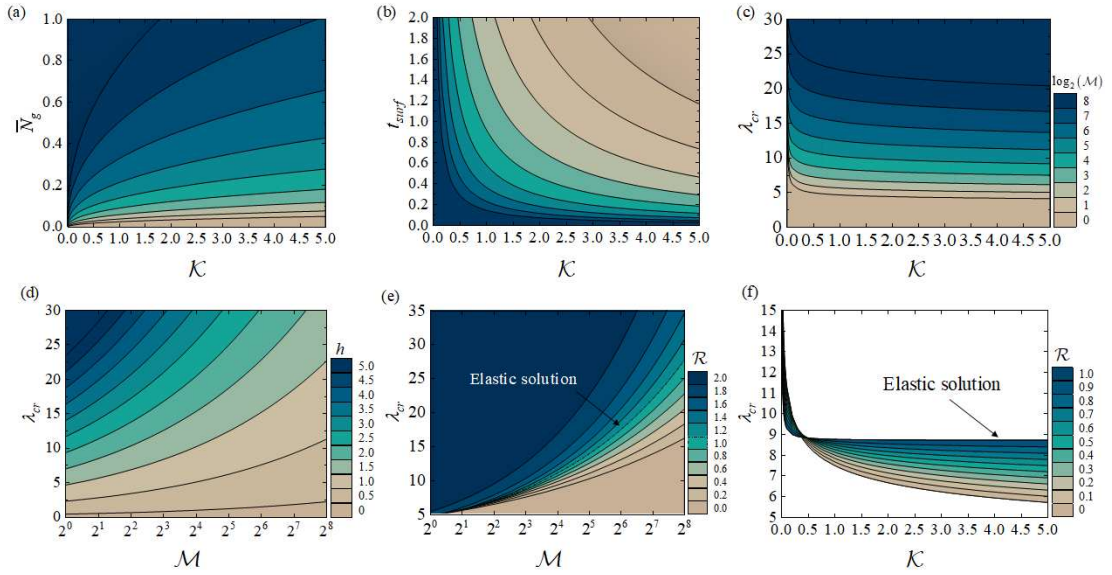


Fig. 3 Critical conditions governing surface instability in viscoelastic biological tissues. (a), (b) and (c) depict the critical normalized growth-induced pressure $\bar{N}_g^{cr} = N_g^{cr} / (hE_c)$, the critical surface wrinkling time t_{surf} , and the critical wavelength λ_{cr} under varying modulus ratios $\mathcal{M}$. (d) Dependence of λ_{cr} on $\mathcal{M}$ for different film thicknesses h . Variations of λ_{cr} with (e) $\mathcal{M}$ and (f) $\mathcal{K}$ under different power-law exponent ratios $\mathcal{R}$ with $\beta = 0.5$.

Besides, the critical wavelength in our simulations are consistent with this theoretical prediction [Fig. S2 in Supplementary Note 1]. Collectively, these results reveal that surface wrinkling in growing tissues arises from the interplay of geometric confinement h , material contrast ($\mathcal{M}$ and $\mathcal{R}$), and growth asymmetry ($\mathcal{K}$). Compared with purely elastic systems, viscoelastic tissues exhibit substantially time-dependent wrinkling onset, controlled sensitively by the rheological mismatch between

layers. More importantly, tissue viscoelasticity endows post-buckling amplitude evolution with temporal memory and enables the spatial bifurcations that underlie hierarchical morphogenesis, as analyzed in the following section.

Viscoelastic memory controls nonlinear amplitude evolution

Following the onset of surface wrinkling ($t \geq t_{surf}$), post-instability morphological evolution is governed by geometric nonlinearity, cumulative growth, and viscoelastic memory, leading to strongly time-dependent amplitude dynamics. As growth proceeds, the evolving wrinkle profile induces significant in-plane stretching, and the resulting nonlinear membrane force becomes dominant for rapid growth wrinkle amplitude, with its spatial average given by $\langle N_m(x, t) \rangle = \int_0^t \bar{E}_c(t - \tau) d \langle (\partial w / \partial x)^2 / 2 \rangle / d\tau d\tau$ [see Fig. 2]. To capture the full nonlinear and time-dependent response, we back to the viscoelastic equilibrium equation for bilayer tissues Eq. (2) again. Considering growth dynamics of epithelia, growth and relaxation operate on comparable timescales. Performing modal expansion on Eq. (2) and considering the dynamic approximation, yields the canonical Landau equation for the time-dependent amplitude evolution

$$\frac{dA(t)}{dt} = \psi(t)A(t) - \eta(t)A^3(t). \quad (3)$$

Here, the linear growth rate $\psi(t)$ reflects the balance between destabilizing driving force and resistance, while the nonlinear geometric saturation coefficient $\eta(t)$ (Supplementary Note 1). Accordingly, solving via separation of variables with initial amplitude $A(t_{surf}) = A_0$, the saturation amplitude can be obtained as

$$A_{sat}(t_{sat}) = \sqrt{\psi_{sat} / \eta_{sat}}, \text{ where } t_{sat} \text{ is defined as the amplitude saturation time of}$$

surface wrinkling, expressed as $t_{sat} \approx t_c^{surf} + \ln(A_{sat}/A_0)/\psi_{sat}$. A fundamental departure from elastic theories emerges in the post-saturation creep, that is viscoelastic relaxation sustains slow amplitude growth long after growth-induced pressure saturates [see in Fig. 4(a)]. Obviously, it demonstrates that the amplitude spatiotemporal evolution of viscoelastic soft tissues is not merely delayed but qualitatively reshaped by rheological

disparity, encoded in the power-law exponents α and β .

As wrinkling amplitude approaches saturation ($t_{surf} \leq t < t_{sat}$), cumulative deformation reduces effective global stiffness of soft tissue significantly while the growth-induced axial compression force $P_g(t) = \int_0^t E_{eq}(t-\tau) \dot{\epsilon}_g^{eq}(t) d\tau$ continues to rise. At a critical compression threshold, a secondary bifurcation to global buckling occurs, defining hierarchical instability as the superposition morphology with a stable coexistence of short-wavelength wrinkling and long-wavelength buckling. We treat this secondary instability via a viscoelastic Timoshenko beam model, yielding critical buckling force $P_g^{cr}(t)$, critical time $t_{global} = f^{-1}(P_g(t) = P_g^{cr}(t))$, and amplitude $B(t)$ (Supplementary Note 2). Fig. 4 presents the coupled spatiotemporal evolution of $\mathcal{A}(t)$ and $\mathcal{B}(t)$. Following the buckling of soft tissues onset, the global buckling is coupled and superimposed with surface wrinkling, undergoing nonlinear co-evolution, resulting in a sharp increase in the amplitude curve, as shown in Fig. 4(a). This creates spatial deformation conditions for generating more complex morphological evolution. Moreover, viscoelasticity shifts the entire bifurcation sequence by adjusting the critical time span $t_{surf} \leq t < t_{sat}$ and threshold t_{global} , controlled by modulus ratio $\mathcal{M}$ and growth ratio $\mathcal{K}$, as observed in Figs. 2(b) and (c). This temporal separation of bifurcations is the mechanical origin of hierarchical morphogenesis, distinguishing it from elastic systems where surface wrinkling and global buckling either co-occur or mutually suppress.

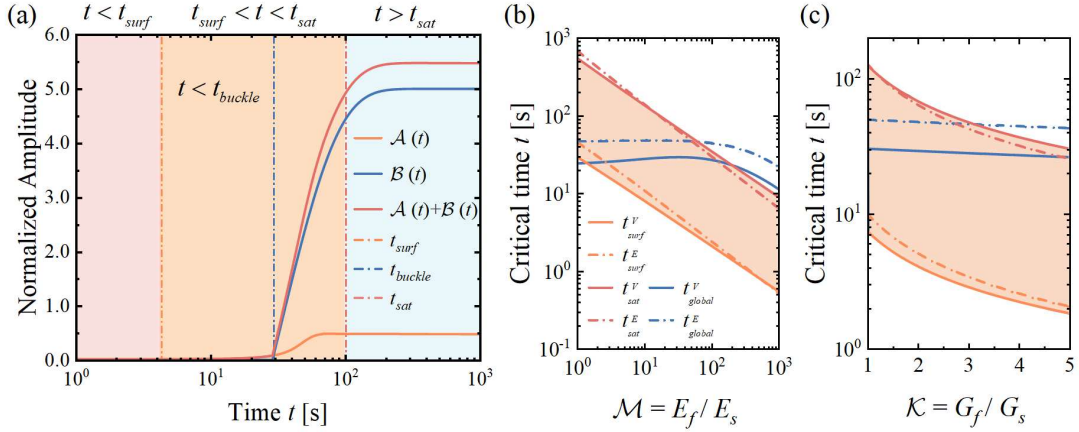


Fig. 4 Amplitude spatiotemporal evolution and three critical characteristic times. (a) The evolution curves of normalized surface wrinkling amplitude $\mathcal{A}(t) = A(t)/h$ and the global buckling amplitude $\mathcal{B}(t) = B(t)/(H+h)$. Comparing the viscoelastic (solid line t^V with $\alpha = 0.3, \beta = 0.5$) and elastic theoretical frameworks (dash lines t^E with $\alpha = \beta = 0$), the curves of three characteristic times under (b) different modulus ratios $\mathcal{M}$. and (c) different growth rate ratios $\mathcal{K}$.

Sequential instability opens a time window for hierarchical folding

From the standpoint of post-buckling evolution, it is evident that the spatiotemporal evolution of viscoelastic post-buckling in growing tissues establishes a critical time window for the development of complex geometric morphologies, as shown in Figs. 4(b) and 4(c). This time window (relative timing of t_{surf} , t_{global} and t_{sat}) determines the post-buckling evolution bifurcation path. Consequently, the theoretical framework for deriving bifurcation criteria in terms of instability time is conceptually straightforward, of which the definition by the dimensionless time ratio as:

$$\mathcal{T} = \frac{t_{global} - t_{surf}}{t_{sat} - t_{surf}}. \quad (4)$$

In which, $0 < \mathcal{T} < 1$ represents the surface wrinkling occurs first, and then the global buckling is triggered before wrinkling saturates ($t_{surf} < t_{global} < t_{sat}$). The geometric nonlinearity of the epithelium induces in-plane stress redistribution and the equivalent stiffness $\overline{EI}_{eq}(t)$ reduction, thereby lowering $P_g^{cr}(t)$ and triggering the global buckling. Then, the hierarchical instability is formed (e.g., villus formation evolve with glandular folding concurrently in embryonic development^{12, 19}). $\mathcal{T} < 0$ (i.e.,

283 $t_{global} < t_{surf}$) represents only the global buckling occurs. The axial force triggers overall
 284 bending before the epithelium accumulates sufficient membrane force for wrinkling
 285 (e.g., abnormal glandular folding in early tumorigenesis⁷). Conversely, $\mathcal{T} > 1$ (i.e.,
 286 $t_{global} > t_{sat}$) means only the surface wrinkling occurs. The soft tissue enters a stable
 287 wrinkling state and the axial force cannot overcome the saturated stiffness (e.g., stable
 288 gyrification of the cerebral cortex^{10, 11}).

289 Indeed, the establishment of the time window provides the necessary prerequisite
 290 for the multiscale morphological evolution of soft tissues. As a strictly bifurcation path
 291 criterion, that is, whether the hierarchical folds can be stably maintained, further
 292 analysis of the energy competition of soft tissues is required. However, considering the
 293 complexity of the viscoelastic theoretical framework and the unpredictability of the
 294 deformation of tissues, it is difficult to establish the strictly quantified potential energy.
 295 Therefore, based on the saturation amplitudes $\mathcal{A}$ for wrinkling and $\mathcal{B}$ for buckling
 296 (Supplementary Note 3), we approximatively establish the potential energy competition
 297 for a qualitative analysis, denoted as,

$$298 \quad \mathcal{E} = \Pi_{\text{multi}}(\mathcal{A}, \mathcal{B}) - \min[\Pi_{\text{surf}}(\mathcal{A}), \Pi_{\text{global}}(\mathcal{B})]. \quad (5)$$

299 During the evolution process of the hierarchical instability, the surface instability can
 300 remain stable without being released by the generation of buckling instability ($\mathcal{E} < 0$),
 301 then the epithelial tissue will eventually present hierarchical instability. On the contrary,
 302 if the surface instability is released, the epithelial tissue will eventually reach the stable
 303 state along the evolution path of buckling folding morphology ($\mathcal{E} > 0$). Accordingly,
 304 the mechanical mechanism of hierarchical instability can be understood that during the
 305 buckling evolution process after surface wrinkling, the surface wrinkles trigger the
 306 global buckling through stiffness reduction, and trigger the coupling evolution of
 307 surface wrinkles and global buckling. The stability of this coupling evolution co-
 308 regulated by the time window criterion and the energy minimization principle.

Mode competition maps temporal ordering to morphological selection

We first perform extensive numerical simulations to map the morphological bifurcation landscape across the full parameter space, yielding a preliminary phase diagram of post-buckling evolution [Fig. 4]. Notably, the bifurcation laws observed under planar confinement are quantitatively consistent with those under annular confinement, confirming that our theoretical framework is generalizable to different geometric constraints. This consistency arises because the fundamental competition between localized surface wrinkling and global stiffness-driven buckling, rooted in tissue viscoelasticity and geometric nonlinearity, operates independently of the specific boundary geometry. Our parametric analysis reveals that the modulus ratio $\mathcal{M}$ and growth rate ratio $\mathcal{K}$ exert critical control over the formation of hierarchical instability [see in Figs. 3(a) and (b)]. A larger $\mathcal{M}$ or $\mathcal{K}$ extends the morphological bifurcation time window ($t_{surf} < t_{buckle} < t_{sat}$). This extension arises because stiffer epithelia or faster differential growth delay the onset of global buckling relative to wrinkling saturation, providing additional time for viscoelastic relaxation and geometric nonlinearity to develop. It conditions that are essential for the formation of stable hierarchical morphologies. In contrast, the thickness ratio $\mathcal{G}$ dominates the global mechanical constraint of the system. For large $\mathcal{G}$ (thin epithelium on thick submucosa), the stiff submucosa provides strong lateral confinement that suppresses global buckling, locking the system in the surface wrinkling pattern. Conversely, for small $\mathcal{G}$ (thick epithelium on thin submucosa), the weak submucosal constraint allows large-scale bending to occur before localized wrinkling can stabilize, leading exclusively to global buckling [see in Figs. 3(c) and (d)]. These trends are consistent across both planar and toroidal geometries, as illustrated in Fig. 5. To address the gaps in phase diagram in Fig. 5, we need to construct a more comprehensive parameter-domain phase diagram based on the time window criterion established in our theoretical derivation.

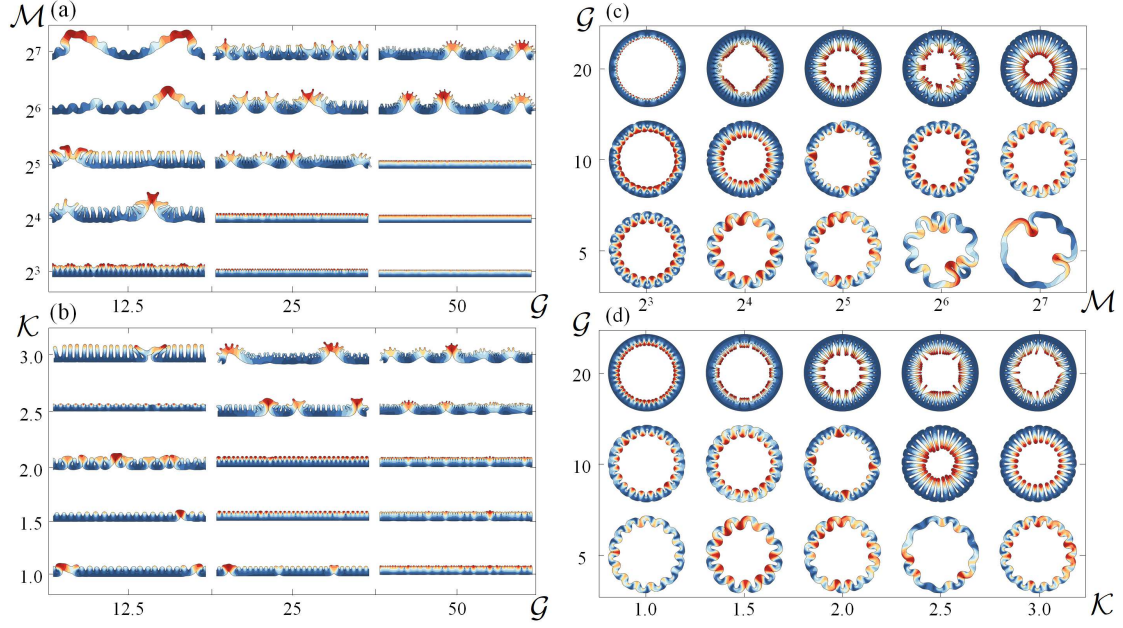


Fig. 5. Evolution diagrams of post-buckling shapes under different parameter domains. Numerical simulations of the morphology with (a) thickness ratios $\mathcal{G}$ vs modulus ratios $\mathcal{M}$ under $\mathcal{K} = 2.0$ and (b) thickness ratios $\mathcal{G}$ vs growth rate ratios $\mathcal{K}$ under $\mathcal{M} = 32$ for planar constraints. Numerical simulations of the morphology with (c) thickness ratios $\mathcal{G}$ vs modulus ratios $\mathcal{M}$ under $\mathcal{K} = 2.0$ and (d) thickness ratios $\mathcal{G}$ vs growth rate ratios $\mathcal{K}$ under $\mathcal{M} = 32$ for toroidal constraints.

While numerical simulations provide a qualitative overview of morphological selection, they are computationally expensive and limited to discrete parameter points. To overcome these limitations, we construct a comprehensive analytical phase diagram to describe the bifurcation paths of spatiotemporal evolution, directly from the closed-form time-window criterion derived Eq. (4) as

$$\begin{aligned} f_1(\mathcal{G}, \mathcal{M}, \mathcal{K}, \mathcal{R}) &= t_{\text{surf}} - t_{\text{global}} = 0 \\ f_2(\mathcal{G}, \mathcal{M}, \mathcal{K}, \mathcal{R}) &= t_{\text{global}} - t_{\text{sat}} = 0 \end{aligned} \quad (6)$$

where $f(\cdot)$ is an implicit function derived from our closed-form solutions for t_{surf} , t_{sat} and t_{global} . This analytical phase diagram [Fig. 6] provides a continuous, quantitative map of morphological outcomes across the entire parameter space, unifying the mechanical conditions for surface wrinkling, hierarchical instability, and global buckling. Unlike the discrete numerical phase diagram [Fig. 5], the analytical phase diagram precisely delineates the phase boundaries and allows for direct prediction of morphological transitions for any combination of geometric, material, and

growth parameters. Our analysis further clarifies the physical mechanism underlying hierarchical instability initiation and stabilization.

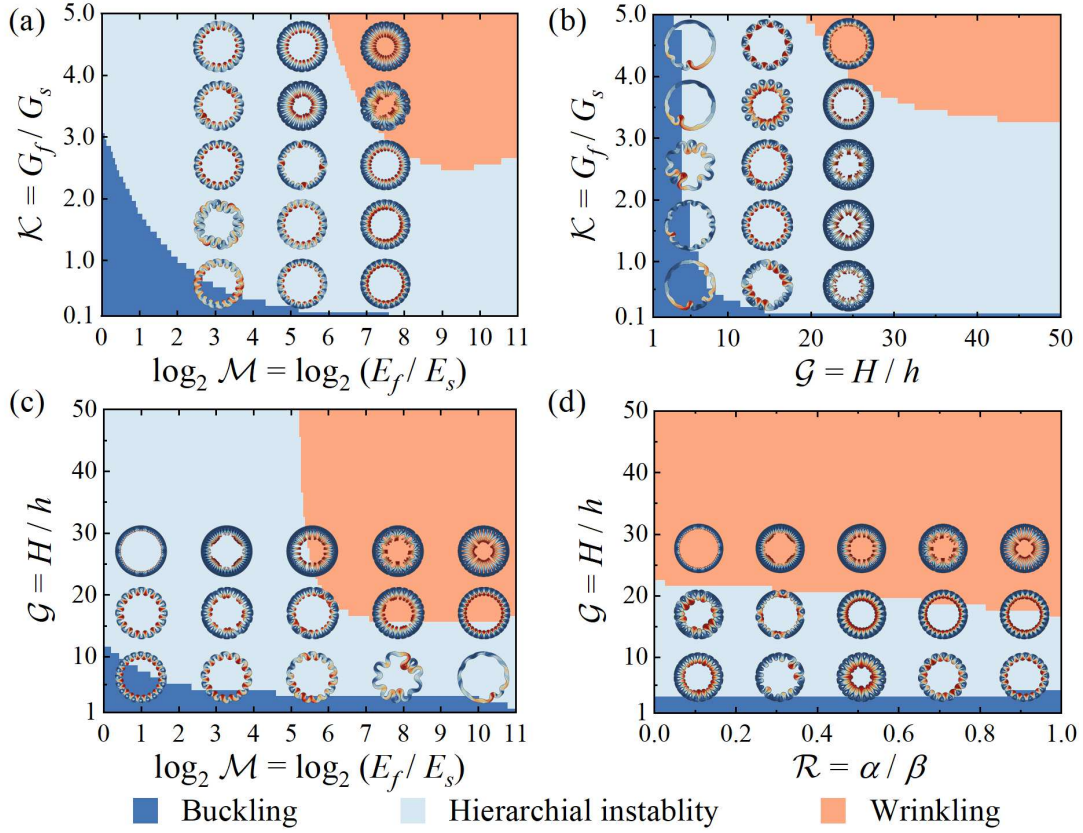


Fig. 6 Morphological evolution bifurcation phase diagram under different parameter domains. Theoretical predictions of the morphology with (a) thickness ratios $\mathcal{G}$ vs growth rate ratios $\mathcal{K}$, (b) modulus ratios $\mathcal{M}$ vs thickness ratios $\mathcal{G}$, (c) modulus ratios $\mathcal{M}$ vs thickness ratios $\mathcal{G}$, and (d) viscoelastic properties $\mathcal{R}$ vs growth rate ratios $\mathcal{K}$, respectively.

Hierarchical instability initiates when the wrinkling amplitude becomes comparable to the epithelial thickness ($A \sim h + H$), at which point geometric nonlinearity significantly reduces the effective global stiffness and triggers the secondary bifurcation to global buckling ($0 < T < 1$). The long-term stability of the resulting hierarchical morphology is then determined by the energy-competition criterion ($\mathcal{E} < 0$), which quantifies the relative energetic costs of maintaining the two coupled modes. Only when the time-window criterion is satisfied (allowing sequential bifurcations) and the energy-competition criterion is met (allowing stable coexistence) does the system converge to the hierarchical steady state. These results establish a predictive method for morphological pattern selection in growing viscoelastic tissues,

providing a quantitative tool for interpreting developmental morphogenesis and engineering bioinspired hierarchical structures. By linking tissue rheology, growth kinetics, and geometric constraints to final morphological outcomes, this work bridges fundamental continuum mechanics with developmental biology and soft materials engineering.

Discussion

Growth-induced mechanical instability underpins multiscale morphology in soft biological tissues, a spatiotemporal evolution tightly couples to their inherent viscoelasticity^{44, 45}. For decades, theoretical investigations of tissue morphogenesis have relied almost exclusively on time-invariant elastic approximations, which can adequately describe single-scale steady-state instabilities but fail fundamentally to capture the viscosity-dependent temporal dynamics that govern real tissue development. Most critically, these classical models are difficult to explain the origin of ubiquitous hierarchical morphologies, multiscale structures that arise from the coexistence of microscopic wrinkling and macroscopic buckling, whose mechanical basis has remained a long-standing open question in biological physics. In this work, we develop a viscoelastic bilayer model epithelial-submucosal tissues that fully incorporates growth-induced stress and power-law viscoelastic relaxation. It provides a comprehensive theoretical description of growth-induced instabilities, unifying the analysis of three distinct stable steady-state modes (surface wrinkling, hierarchical instability, and global buckling), addressing limitations of elastic approximations and elucidating time-dependent constitutive impacts on instability criteria.

We have derived closed-form analytical solutions for the complete sequence of instability events, from the linear onset of surface wrinkling to the nonlinear coupled evolution of wrinkling and buckling amplitudes. These solutions rigorously demonstrate that classical elastic models emerge as a special limiting case of our general viscoelastic framework, valid only when all tissue layers exhibit identical rheological properties. Our results reveal that viscoelastic exponents govern instability

onset timing, while modulus, growth rate, and thickness ratios define dictate the characteristic length scales of the resulting morphologies. We further capture the full time-dependent amplitude evolution of both modes, consistent with the trend of experimental observations^{3, 9, 12, 13}. Crucially, we elucidate the mechanical origin of hierarchical instability. It arises from the temporal separation of two sequential bifurcations, that is the initial onset of surface wrinkling, followed by a secondary bifurcation to global buckling before the wrinkling amplitude has saturated. This temporal separation is a direct consequence of tissue viscoelasticity, which introduces a finite time delay between stress accumulation and mechanical response. Moreover, we propose time-window and energy-ratio criteria to delineate morphological pathway selection. Then, we have constructed a comprehensive phase diagram that maps morphological outcomes across the full parameter space of tissue geometry, material properties, and growth kinetics.

This work establishes viscoelasticity as an indispensable regulator of growth-induced tissue instability, which shapes the spatiotemporal evolution of instability via rate dependence^{46, 47}. Our predictions of critical conditions, evolutionary pathways, and hierarchical instability transitions show far better agreement with native living tissue morphologies than classical elastic solutions. The constructed phase diagrams and bifurcation evolution rules may provide a quantitative theoretical foundation for biomimetic design (e.g., wrinkled structures in flexible electronics¹⁷) or disease intervention as mechanical regulation of tumor invasion^{48, 49}. By bridging viscoelastic mechanics, growth-driven instability, and multiscale tissue morphogenesis, this work advances a quantitative model applicable to developmental biology, soft matter physics and tissue engineering. Looking forward, our work will extend to address more complex biological systems, including three-dimensional tissue architectures, active cell contractility, and cell-matrix mechanical interactions. Further integration with experimental measurements of tissue rheology and growth dynamics will enable more precise predictions of developmental processes and pathological evolution.

Method

Bilayer geometry and assumptions

We investigate the morphodynamics of a mucosal epithelium atop a submucosal substrate by idealizing the system as a confined layered medium subjected to growth-induced differential compression, with subscripts f and s , denoting the epithelial film and submucosal substrate, respectively. The tissue is modeled as a perfectly bonded bilayer under plane-strain conditions as shown in Fig. 7. Each layer follows a normalized power-law relaxation kernel over the finite time interval represented in the simulations,

$$E_i(t) = \bar{E}_i \left(\frac{t}{t_0} \right)^{-q_i}, \quad q_f = \alpha, \quad q_s = \beta. \quad (7)$$

Here t_0 is the reference time and q_i is dimensionless. We use $q_f = \alpha$ for the film and $q_s = \beta$ for the supporting layer. The Laplace transform is

$$\tilde{E}_i(s) = \bar{E}_i \Gamma(1 - q_i) t_0^{q_i} s^{q_i - 1}, \quad q_f = \alpha, \quad q_s = \beta, \quad (8)$$

where $\Gamma(\cdot)$ denotes Gamma function. We evaluate this quantity at $s \sim 1/t$ in the frozen-time onset calculation. This gives $E_i = \bar{E}_i t^{-q_i}$ with normalized time $t = t/t_0$. We further assume that mechanical equilibration proceeds faster than tissue growth and rheological remodeling, so the evolving system is treated as a sequence of quasi-static states when estimating each instability onset. For the planar geometry, the onset analysis employs an equivalent simply supported configuration of effective length L . For the circular geometry, we solve the model numerically rather than applying the straight-beam buckling formula directly, and use the results to assess the geometric robustness of the trajectory classification.

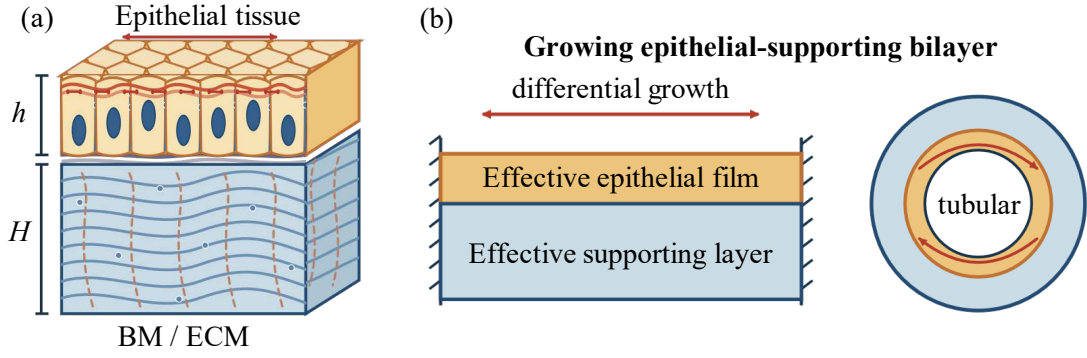


Fig. 7. Schematic of the viscoelastic epithelial bilayer model. (a) Real mucosal tissue consisting of an epithelial layer of thickness h atop a basement membrane/extracellular matrix (BM/ECM) substrate of thickness H . (b) Idealized growing epithelial-supporting bilayer subjected to differential growth, modeled as an effective viscoelastic film on an effective viscoelastic substrate in both planar (left) and annular/tubular (right) configurations.

Finite element implementation

To explore surface morphological formation and evolution of viscoelastic soft tissues in growth, we perform numerical simulations using the finite element method with ABAQUS/STANDARD. We implemented the planar and circular bilayers under plane-strain conditions in ABAQUS 6.13. We discretize the nonlinear problem of finite growth using 8-node biquadratic hybrid plane-strain elements (CPE8H) for the mucosal epithelium and the submucosa, and 4-node bilinear reduced-integration plane-strain elements (CPE4R) for the substrate (Fig.S1 in Supplementary Note 1). The layered tissue (mucosal epithelium and the submucosa) and substrate are adopted as the incompressible power-law linear viscoelastic material, which are characterized by the Prony series and more rigid elastic material, respectively⁴². In which, the power-law viscoelastic materials are characterized by the Prony series^{33, 50},

$$E(t) = E_0 \left(1 - \sum_{i=1}^n g_i \right) + \sum_{i=1}^n g_i E_0 e^{-t/\tau_i} \quad (9)$$

where E_0 is the modulus at $t=0$, τ_i denotes the relaxation time, and g_i is the relaxation coefficient corresponding to τ_i . Hang et al.^{33, 50} confirmed the creep function $J \sim t^\alpha$ corresponds to a relaxation modulus of $E \sim t^{-\alpha}$, when the given relaxation time conforms to the power-law distribution as $P(\tau) \sim \tau^{\alpha+1}$ ⁵¹. Then we apply thermal dilatation for emulating growth-driven volumetric growth and strain

mismatch, gradually increasing in time with the growth rate (G_c and G_s). We verified that the prescribed thermal field reproduced the intended layer-wise growth histories. Besides, to investigate the biologically relevant post-buckling behavior of the growing viscoelastic tissue, we adopt the pseudo-dynamic method by introducing a tiny dissipated energy fraction as 0.02%.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contribution

H. Wang and G.-K. Xu conceived the project and developed the theoretical methodology. H. Wang performed the numerical simulations, formal analysis, and data curation, with contributions from X.-Q. Feng on investigation and methodology. G.-K. Xu supervised the project, acquired funding, and contributed to formal analysis and validation. All authors wrote the original draft, and G.-K. Xu reviewed and edited the manuscript.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Reference

1. Huang, H., Gao, S. & Bao, M. Exploring Mechanical Forces Shaping Self-Organization and Morphogenesis During Early Embryo Development. *Annu Rev Cell Dev Biol* **40**, 75-96 <https://doi.org/https://doi.org/10.1146/annurev-cellbio-120123-105748> (2024).
2. Riiska, C. A., Nguyen, C., Peleg, O. & Rieser, J. M. The Physics of Animal Behavior: Form, Function, and Interactions. *Annu Rev Condens Matter Phys* **15**, 325-350 <https://doi.org/https://doi.org/10.1146/annurev-conmatphys-040821-120442> (2024).

- 508 3. Trushko, A., *et al.* Buckling of an Epithelium Growing under Spherical
 509 Confinement. *Dev Cell* **54**, 655-668 e656
 510 <https://doi.org/10.1016/j.devcel.2020.07.019> (2020).
- 511 4. Ben Amar, M., Qiuyang-Qu, P., Vuong-Brender, T. T. K. & Labouesse, M.
 512 Assessing the Contribution of Active and Passive Stresses in *C. elegans* Elongation.
 513 *Phys Rev Lett* **121**, 268102 <https://doi.org/10.1103/PhysRevLett.121.268102>
 514 (2018).
- 515 5. Yang, Q., *et al.* Cell fate coordinates mechano-osmotic forces in intestinal crypt
 516 formation. *Nat Cell Biol* **23**, 733-744 <https://doi.org/10.1038/s41556-021-00700-2>
 517 (2021).
- 518 6. Hohn, S., Honerkamp-Smith, A. R., Haas, P. A., Trong, P. K. & Goldstein, R. E.
 519 Dynamics of a *Volvox* embryo turning itself inside out. *Phys Rev Lett* **114**, 178101
 520 <https://doi.org/10.1103/PhysRevLett.114.178101> (2015).
- 521 7. Lampart, F. L., *et al.* Morphometry and mechanical instability at the onset of
 522 epithelial bladder cancer. *Nat Phys* **21**, 279-288 [https://doi.org/10.1038/s41567-](https://doi.org/10.1038/s41567-024-02735-2)
 523 [024-02735-2](https://doi.org/10.1038/s41567-024-02735-2) (2025).
- 524 8. Sudderick, Z. R. & Glover, J. D. Periodic pattern formation during embryonic
 525 development. *Biochem Soc Trans* **52**, 75-88 <https://doi.org/10.1042/bst20230197>
 526 (2024).
- 527 9. Shyer, A. E., *et al.* Villification: How the Gut Gets Its Villi. *Science* **342**, 212-218
 528 <https://doi.org/doi:10.1126/science.1238842> (2013).
- 529 10. Akula, S. K., Exposito-Alonso, D. & Walsh, C. A. Shaping the brain: The
 530 emergence of cortical structure and folding. *Dev Cell* **58**, 2836-2849
 531 <https://doi.org/10.1016/j.devcel.2023.11.004> (2023).
- 532 11. Tallinen, T., *et al.* On the growth and form of cortical convolutions. *Nat Phys* **12**,
 533 588-593 <https://doi.org/10.1038/nphys3632> (2016).
- 534 12. Gill, H. K., *et al.* The developmental mechanics of divergent buckling patterns in
 535 the chick gut. *P Natl Acad Sci USA* **121**, e2310992121
 536 <https://doi.org/doi:10.1073/pnas.2310992121> (2024).
- 537 13. Gill, H. K., *et al.* Hox gene activity directs physical forces to differentially shape
 538 chick small and large intestinal epithelia. *Dev Cell* **59**, 1-16
 539 <https://doi.org/https://doi.org/10.1016/j.devcel.2024.07.012> (2024).
- 540 14. Qin, B., *et al.* Hierarchical transitions and fractal wrinkling drive bacterial pellicle
 541 morphogenesis. *P Natl Acad Sci USA* **118**, e2023504118
 542 <https://doi.org/doi:10.1073/pnas.2023504118> (2021).
- 543 15. Ensari, A. & Marsh, M. N. Exploring the villus. *Gastroenterol Hepatol Bed Bench*
 544 **11**, 181-190 (2018).
- 545 16. Antfolk, M. & Jensen, K. B. A bioengineering perspective on modelling the
 546 intestinal epithelial physiology in vitro. *Nat Commun* **11**, 6244
 547 <https://doi.org/10.1038/s41467-020-20052-z> (2020).
- 548 17. Tan, Y., Hu, B., Song, J., Chu, Z. & Wu, W. Bioinspired Multiscale Wrinkling
 549 Patterns on Curved Substrates: An Overview. *Nano-Micro Lett* **12**,

- 550 <https://doi.org/10.1007/s40820-020-00436-y> (2020).
- 551 18. Dai, A. & Ben Amar, M. Minimizing the Elastic Energy of Growing Leaves by
 552 Conformal Mapping. *Phys Rev Lett* **129**, 218101
 553 <https://doi.org/10.1103/PhysRevLett.129.218101> (2022).
- 554 19. Tozluoglu, M. & Mao, Y. On folding morphogenesis, a mechanical problem. *Philos*
 555 *Trans R Soc B* **375**, <https://doi.org/10.1098/rstb.2019.0564> (2020).
- 556 20. Pezzulla, M., Stoop, N., Steranka, M. P., Bade, A. J. & Holmes, D. P. Curvature-
 557 Induced Instabilities of Shells. *Phys Rev Lett* **120**, 048002
 558 <https://doi.org/10.1103/PhysRevLett.120.048002> (2018).
- 559 21. Engstrom, T. A., Zhang, T., Lawton, A. K., Joyner, A. L. & Schwarz, J. M. Buckling
 560 without Bending: A New Paradigm in Morphogenesis. *Phys Rev X* **8**,
 561 <https://doi.org/10.1103/PhysRevX.8.041053> (2018).
- 562 22. Budday, S., Steinmann, P. & Kuhl, E. The role of mechanics during brain
 563 development. *J Mech Phys Solids* **72**, 75-92
 564 <https://doi.org/10.1016/j.jmps.2014.07.010> (2014).
- 565 23. Li, B., Cao, Y.-P., Feng, X.-Q. & Gao, H. Surface wrinkling of mucosa induced by
 566 volumetric growth: Theory, simulation and experiment. *J Mech Phys Solids* **59**,
 567 758-774 <https://doi.org/10.1016/j.jmps.2011.01.010> (2011).
- 568 24. Li, B., Jia, F., Cao, Y. P., Feng, X. Q. & Gao, H. Surface wrinkling patterns on a
 569 core-shell soft sphere. *Phys Rev Lett* **106**, 234301
 570 <https://doi.org/10.1103/PhysRevLett.106.234301> (2011).
- 571 25. Andrenšek, U., Zihlerl, P. & Krajnc, M. Wrinkling Instability in Unsupported
 572 Epithelial Sheets. *Phys Rev Lett* **130**, 198401
 573 <https://doi.org/10.1103/PhysRevLett.130.198401> (2023).
- 574 26. Wang, T., Dai, Z., Potier-Ferry, M. & Xu, F. Curvature-Regulated Multiphase
 575 Patterns in Tori. *Phys Rev Lett* **130**, 048201
 576 <https://doi.org/10.1103/PhysRevLett.130.048201> (2023).
- 577 27. Kollmannsberger, P., Mierke, C. T. & Fabry, B. Nonlinear viscoelasticity of
 578 adherent cells is controlled by cytoskeletal tension. *Soft Matter* **7**, 3127-3132
 579 <https://doi.org/10.1039/c0sm00833h> (2011).
- 580 28. Kollmannsberger, P. & Fabry, B. Linear and Nonlinear Rheology of Living Cells.
 581 *Annu Rev Mater Res* **41**, 75-97 [https://doi.org/10.1146/annurev-matsci-062910-](https://doi.org/10.1146/annurev-matsci-062910-100351)
 582 [100351](https://doi.org/10.1146/annurev-matsci-062910-100351) (2011).
- 583 29. Khalilgharibi, N., *et al.* Stress relaxation in epithelial monolayers is controlled by
 584 the actomyosin cortex. *Nat Phys* **15**, 839–847 [https://doi.org/10.1038/s41567-019-](https://doi.org/10.1038/s41567-019-0516-6)
 585 [0516-6](https://doi.org/10.1038/s41567-019-0516-6) (2019).
- 586 30. Harris, A. R., *et al.* Characterizing the mechanics of cultured cell monolayers. *P*
 587 *Natl Acad Sci USA* **109**, 16449-16454 <https://doi.org/10.1073/pnas.1213301109>
 588 (2012).
- 589 31. Desprat, N., Richert, A., Simeon, J. & Asnacios, A. Creep function of a single living
 590 cell. *Biophys J* **88**, 2224-2233 <https://doi.org/10.1529/biophysj.104.050278> (2005).
- 591 32. Stamenovic, D., Suki, B., Fabry, B., Wang, N. & Fredberg, J. J. Rheology of airway

- smooth muscle cells is associated with cytoskeletal contractile stress. *J Appl Physiol* **96**, 1600-1605 <https://doi.org/10.1152/japplphysiol.00595.2003> (2004).
33. Hang, J.-T., Kang, Y., Xu, G.-K. & Gao, H. A hierarchical cellular structural model to unravel the universal power-law rheological behavior of living cells. *Nat Commun* **12**, 6067 <https://doi.org/10.1038/s41467-021-26283-y> (2021).
 34. Poling, H. M., *et al.* Mechanically induced development and maturation of human intestinal organoids in vivo. *Nat Biomed Eng* **2**, 429-442 <https://doi.org/10.1038/s41551-018-0243-9> (2018).
 35. Liu, Z. F., *et al.* Hierarchically buckled sheath-core fibers for superelastic electronics, sensors, and muscles. *Science* **349**, 400-404 <https://doi.org/10.1126/science.aaa7952> (2015).
 36. Chan, H. F., *et al.* Folding artificial mucosa with cell-laden hydrogels guided by mechanics models. *P Natl Acad Sci USA* **115**, 7503-7508 <https://doi.org/10.1073/pnas.1802361115> (2018).
 37. Bonfanti, A., Kaplan, J. L., Charras, G. & Kabla, A. Fractional viscoelastic models for power-law materials. *Soft Matter* **16**, 6002-6020 <https://doi.org/10.1039/d0sm00354a> (2020).
 38. Pozzer, R. F., *et al.* Morphological analysis of the digestive tract of *Hypophthalmus marginatus* (Valenciennes, 1840). *Anat Histol Embryol* **52**, 603-610 <https://doi.org/10.1111/ahe.12918> (2023).
 39. Gregório, S. F., *et al.* Adaptation to different salinities exposes functional specialization in the intestine of the sea bream (*Sparus aurata* L.). *Journal of Experimental Biology* **216**, 470-479 <https://doi.org/10.1242/jeb.073742> (2013).
 40. Bayly, P. V., Okamoto, R. J., Xu, G., Shi, Y. & Taber, L. A. A cortical folding model incorporating stress-dependent growth explains gyral wavelengths and stress patterns in the developing brain. *Phys Biol* **10**, 016005 <https://doi.org/10.1088/1478-3975/10/1/016005> (2013).
 41. Huang, R. Kinetic wrinkling of an elastic film on a viscoelastic substrate. *J Mech Phys Solids* **53**, 63-89 <https://doi.org/10.1016/j.jmps.2004.06.007> (2005).
 42. Wang, H., Liu, Y.-Q., Hang, J.-T., Xu, G.-K. & Feng, X.-Q. Dynamic high-order buckling and spontaneous recovery of active epithelial tissues. *J Mech Phys Solids* **183**, 105496 <https://doi.org/10.1016/j.jmps.2023.105496> (2024).
 43. Huang, Z. Y., Hong, W. & Suo, Z. Nonlinear analyses of wrinkles in a film bonded to a compliant substrate. *J Mech Phys Solids* **53**, 2101-2118 <https://doi.org/10.1016/j.jmps.2005.03.007> (2005).
 44. Tozluoğlu, M., *et al.* Planar Differential Growth Rates Initiate Precise Fold Positions in Complex Epithelia. *Dev Cell* **51**, 299-312.e294 <https://doi.org/10.1016/j.devcel.2019.09.009> (2019).
 45. Gjorevski, N., *et al.* Tissue geometry drives deterministic organoid patterning. *Science* **375**, eaaw9021 <https://doi.org/10.1126/science.aaw9021> (2022).
 46. Elosegui-Artola, A., *et al.* Matrix viscoelasticity controls spatiotemporal tissue organization. *Nat Mater* **22**, 117-127 <https://doi.org/10.1038/s41563-022-01400-4>

- (2023).
47. Yavitt, F. M., *et al.* In situ modulation of intestinal organoid epithelial curvature through photoinduced viscoelasticity directs crypt morphogenesis. *Sci Adv* **9**, eadd5668 <https://doi.org/doi:10.1126/sciadv.add5668> (2023).
 48. Dai, X., *et al.* Viscoelastic Mechanics: From Pathology and Cell Fate to Tissue Regeneration Biomaterial Development. *ACS Appl Mater Interfaces* **17**, 8751-8770 <https://doi.org/10.1021/acsami.4c18174> (2025).
 49. Courbot, O. & Elosegui-Artola, A. The role of extracellular matrix viscoelasticity in development and disease. *npj Biol Phys Mech* **2**, 10 <https://doi.org/10.1038/s44341-025-00014-6> (2025).
 50. Hang, J.-T., Xu, G.-K. & Gao, H. Frequency-dependent transition in power-law rheological behavior of living cells. *Sci Adv* **8**, eabn6093 <https://doi.org/doi:10.1126/sciadv.abn6093> (2022).
 51. Balland, M., *et al.* Power laws in microrheology experiments on living cells: Comparative analysis and modeling. *Physical Review E* **74**, 021911 <https://doi.org/10.1103/PhysRevE.74.021911> (2006).

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