

Cortical tension links curvature to tissue growth in the cellular Potts model

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The growth of biological tissue is sensitive to the physical properties of the environment. For example, the growth rate of contractile tissue under geometric confinement is proportional to local curvature as a result of tissue surface tension. It is not known how local cell behavior is coordinated to give rise to such behavior. Here we use computer simulations based on the cellular Potts model to investigate the role of cell adhesion and cortical contractility for curvature-dependent tissue growth. Our results show that tension-dependent local proliferation leads to the observed macroscopic curvature-driven growth kinetics via tissue surface tension, independent of soluble growth factors.

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I. INTRODUCTION

Growth and regeneration of biological tissues are complex and poorly understood phenomena. Cells migrate, divide, and deposit matrix in the available space, and coordination of cell behavior in space and time leads to higher-order organization. The activity of a single cell and the chemical and mechanical signals it sends and receives depend on the microenvironment defined by other cells, giving rise to a reciprocal feedback loop [1,2] in which early tissue serves as substrate for the growth of later tissue. While morphogenesis and self-organization have extensively been studied in computational biology [3,4], there are still many unanswered questions, and a better quantitative understanding of how the chemical, mechanical, and geometric properties of the substrate determine tissue organization would greatly benefit the design of engineered scaffolds to guide the formation of functional tissue.

A particularly interesting example of collective control of cellular dynamics is the curvature-dependent growth of tissue under geometric confinement. Contractile adherent cells such as fibroblasts (skin cells) or osteoblasts (bone cells) form a dense tissue in concave pores or clefts with a growth rate strictly proportional to the local curvature. This surprising relationship was first observed in an *in vitro* model of osteoid deposition by mouse preosteoblasts on bonelike substrates [5] and has since been reproduced in different systems using a variety of cell types [6–11]. After an initial lag phase that depends on pore size and substrate material, the rate of growth is the same for a given cell type and pore geometry [12]. A simple geometric construction that describes cells as linear tensile chords growing layer by layer explains the relationship

between curvature and the movement of the interface [13], suggesting surface tension as the mechanism behind curvature-driven tissue growth. This tissue surface tension is a result of the interplay of cell contractility and pore geometry, as confirmed by experiments [8,10,14]. Surface tension and curvature together lead to an outward-directed Young-Laplace force, driving the evolution of the tissue towards a minimal surface [11,15]. On a macroscopic level, surface tension explains not only growth kinetics but also cell and matrix alignment [16], in excellent agreement with experimental observations [17,18]. Tissue growth under geometric confinement is thus an example of the role of curvature in biological processes [19].

However, it is not clear how macroscopic curvature guides cellular decision-making towards proliferation and matrix production. Generally, adherent cells migrate, divide, differentiate, and deposit matrix fibers in response to chemical and mechanical signals. On flat substrates, cell adhesion and spreading are not only required for proliferation [20], but higher substrate stiffness also leads to increased cytoskeletal tension and promotes differentiation into a more contractile phenotype [21,22]. The actomyosin cell cortex is an important regulator for cell shape and tissue patterning [23,24], and the shape of individual cells confined to adherent micropatterns as well as the shape of microtissues confined by cantilevers can be explained by cortical contractility [25,26]. During curvature-driven tissue growth, a gradient of cell proliferation, myofibroblast differentiation, and matrix phenotype emerges [10,14], suggesting a key role of cellular contractility not only for macroscopic surface tension, which is known to drive the curvature dependence of tissue growth, but also for linking macroscopic curvature to the proliferation of individual cells.

The hypothesis that cortical tension links macroscopic curvature to microscopic proliferation can be tested using cell-level computer simulations by investigating how mechanical parameters influence cell behavior and tissue growth under different geometric boundary conditions, which cannot easily

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be done in experiments. Depending on the specific question, different approaches to model tissues with cellular resolution exist. For example, vertex-based models are well suited to study epithelial tissues with straight cell edges [27]. By explicitly including cortical tension in the energy term, vertex models provide valuable insights into epithelial topology [28] but are less suitable for highly dynamic growing tissues and irregular cell shapes. Another class of models describes cells as simplified spheres or pointlike objects without accounting for cellular morphology [29]. Such models are, e.g., used to study spatial interactions and tissue topology during embryonal development [30] but do not capture the interplay with external geometric features.

A well-established cell-level computational modeling framework is the cellular Potts model (CPM) or Glazier-Graner-Hogeweg (GGH) model. Since its introduction in 1992 [31], it has led to important insights into how cell behavior influences the growth and patterning of complex biological tissues, reviewed in Ref. [32]. Interactions of cells with other cells and the substrate are modeled by interfacial energies, while mechanical properties and contractility are included via energetic constraints. A lattice-based implementation allows for arbitrary cell shapes and a numerically efficient minimization of system energy under fluctuations. The CPM can, e.g., explain the role of cell adhesion and cortical contractility for eye patterning in *Drosophila* [33] and the shape of single cells on micropatterns [34], making it a promising approach to investigate a possible link between curvature-driven tissue growth and cellular contractility.

In this study, we aim to answer the question if tension-dependent proliferation, a simple mechanistic rule at the level of local cellular decision making, can explain curvature-dependent tissue growth. We used the CompuCell3D (CC3D) simulation environment [35] and incorporated a new tension-dependent proliferation rule into the model framework. The CPM explicitly includes cell-cell and cell-substrate adhesion, cortical contractility, and elasticity as separate terms in the system energy. The proliferation rule prohibits growth when cells are under compression, which is experimentally well established. The kinetics of biological growth is separated from the simulation timescale by averaging over fluctuations. We compare the results of our simulations to experimental data of tissue growth *in vitro* and systematically explore which parameter ranges give rise to the observed behavior. All assumptions of the model are on the cellular level and are experimentally established [36], while the simulation results are compared to experiments on the tissue scale. Our results agree well with observations, suggesting a mechanobiological feedback loop involving cell adhesion, contractility and proliferation as mechanism behind curvature-driven tissue growth under geometric confinement.

II. MATERIALS AND METHODS

A. Introduction to the cellular Potts model

The CPM, also referred to as Glazier-Graner-Hogeweg model [32], is a cell-level modeling approach on a lattice, where sites with the same cell index form cells of variable shapes. Historically, the model is derived from the statistical

mechanics of magnetic domains in the Ising and Potts models, with interaction energies between lattice sites of unequal spin values or, in the case of the CPM, cell indices [31,32]. The dynamics of the simulation result from the minimization of the system energy in a modified Metropolis algorithm. The system energy is defined by the energy function H :

$$H = H_{\text{Adhesion}} + H_{\text{Area}} + H_{\text{Perimeter}}, \quad (1)$$

$$H_{\text{Adhesion}} = \sum_{\langle i, j \rangle} J(\theta(\sigma_i), \theta(\sigma_j)) \cdot (1 - \delta(\sigma_i, \sigma_j)), \quad (2)$$

$$H_{\text{Area}} = \lambda_A \sum_{\sigma_i} (A(\sigma_i) - A_0(\sigma_i))^2, \quad (3)$$

$$H_{\text{Perimeter}} = \lambda_P \sum_{\sigma_i} (P(\sigma_i) - P_0(\sigma_i))^2, \quad (4)$$

The energy function consists of different terms for adhesion, area, and perimeter constraints, which in their interplay determine cell shape and dynamics. σ defines the index of a cell, while the cell type is determined by $\theta(\sigma)$. The adhesion term sums up the interaction energies J of all lattice sites with neighboring sites in the neighborhood $\langle i, j \rangle$. The Kronecker delta $\delta(\sigma_i, \sigma_j)$ (which equals 1 if $\sigma_i = \sigma_j$ and 0 otherwise) ensures that only interactions between sites belonging to different cells contribute to H_{Adhesion} . The contact energy J depends on the cell types θ of the contacting cells and defines whether it is an attractive or repulsive contact interaction. Increasing the size of the neighborhood determines the performance of the simulation and influences possible grid artifacts.

The area and perimeter constraints quantify an energy cost for the deviation of the area and perimeter of each cell from the target values A_0 and P_0 , with an elastic potential that is scaled by the prefactors λ_A and λ_P . Such an elastic area constraint was first introduced for the modeling of foams [37]. In the context of a two-dimensional cell model, the area constraint acts like a surface tension that denotes an energy cost to changes of the area, while the perimeter constraint introduces a line tension to the contour of the cell. The force balance between surface tension and line tension determines the resulting cell shape. An example would be the formation of a two-dimensional (2D) sphere due to the balance between surface tension σ and line tension λ where the radius is given by $R = \frac{\lambda}{\sigma}$. This is the 2D analog to the 3D Young-Laplace law, where the line tension is substituted by a surface tension, and the surface tension is exchanged by the internal pressure [34]. In the biomechanical context of cell and tissue simulations, the area constraint introduces a resistance against compression (or expansion), while the elastic line tension determines the cell shape due to the restriction of the contour length. The perimeter constraint therefore acts like the cortical tension of the cell that results from the contractile actin-myosin network in the plasma membrane [24].

The development of the system down the gradient of energy is defined by pixel copy attempts in a modified Metropolis algorithm. For each pixel copy attempt, the value of a random lattice site is copied onto a random neighbor. If the new configuration after the pixel copy is energetically favorable, then the pixel copy attempt is accepted. If the new configuration increases the global energy of the system, then the copy attempt is accepted with a probability that depends

on the energy cost:

$$p = \begin{cases} 1 & \text{for } \Delta H < 0, \\ e^{-\frac{\Delta H}{T}} & \text{for } \Delta H > 0. \end{cases} \quad (5)$$

The result of this acceptance function is that the state of the system will diffuse down the gradient of energy with some statistical fluctuations that are scaled by the temperature T . The key difference of this modified Metropolis algorithm in comparison to the standard Metropolis algorithm, where configuration changes can occur at any lattice site, is that pixel copy attempts are confined to interfaces between cells. Note that the acceptance threshold in Eq. (5) at which p becomes dependent on the Boltzmann factor does not have to be equal to zero for all CPM implementations. This further modification of the standard Metropolis algorithm was not used in the presented results but would lead to a system equilibration above the minimum energy [38].

Following the directions of possible pixel copy attempts along the cell boundary, one can use the local energy gradients for the calculation of forces to visualize the underlying mechanics of the simulation more intuitively [39]. Figure 1 visualizes conceptual equilibrium states of a suspended and adherent cell. In the context of cell simulations, the parameter T is typically referred to as the membrane fluctuation level. For each Monte Carlo step (MCS) of the simulation, multiple pixel copy attempts are performed sequentially. The number of pixel copy attempts per MCS is given by the number of pixels in the simulation box.

It should be noted that the neighbor order (NO), which determines the range of neighbor interaction based on a Euclidean distance threshold (see Supplemental Material Fig. S10 for different NO examples, Ref. [40]), can be set individually for different plugins in CC3D. The presented results are based on $\text{NO} = 10$ for the area of the copy attempts in the modified Metropolis algorithm and the calculation of the adhesion energy H_{Adhesion} , while the perimeter P is determined with $\text{NO} = 1$, whereby P is represented by the pixelated contour of the respective cell [41]. An exemplary simulation showing the influence of an increased NO for the perimeter is shown in Supplemental Material Fig. S11 [40].

The CPM is a powerful framework for the definition of biological models for tissues on an intermediate scale that consider single cells. To describe the behavior of growing tissues under geometric confinement, the model is easily expandable to contain cell proliferation and mitosis.

B. Tension-dependent proliferation

Depending on the energy terms for cell elasticity and cellular adhesion, different cell shapes emerge during stochastic energy minimization. Assuming a single cell without adhesion, a round shape with radius R can be parameterized in continuous space by the target area $A_0 = \pi R^2$ and the target perimeter $P_0 = 2\pi R$.

Due to discretization errors of a continuous circle onto a square lattice, the perimeter P_0 has to be rescaled by the prefactor ε_P . Note that the value of the prefactor, which is defined by the quotient of discrete and continuous perimeter ($\varepsilon_P = P_{\text{discrete}}/P_{\text{continuous}}$) has a constant value of $\varepsilon_P = \frac{4}{\pi}$ for all cell sizes (see Supplemental Material Fig. 1 for more detailed

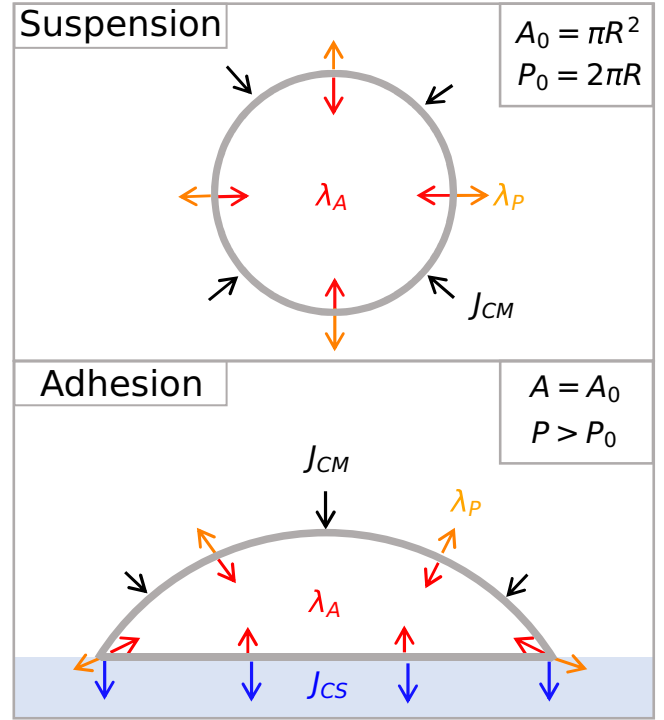


FIG. 1. Conceptual visualization of suspended and adherent cells in force equilibrium under area and perimeter constraints and adhesion. The area constraint introduces a tension corresponding to the compressibility of the cell, while the perimeter constraint describes a line tension along its contour. The overall cell shape in suspension results from the force balance between area and line tension (top). Adhesion energies act as additional differential line tensions for specific interfaces and change the force balance and resulting cell shape (bottom): substrate adhesion induces a change in cell shape similar to the wetting of a droplet on a hydrophilic substrate, since the cell-medium interface is energetically more costly than the cell-substrate interface. The resulting increase in perimeter leads to an increase in cortical tension, which is a biological signal required for proliferation of adherent cells. As described by Rens *et al.* [39], the indicated force directions reflect the gradients of the different terms of the energy function at the cell boundary.

information on the discretization of circles [40]). Using the formula for continuous circles and the previously introduced prefactor ε_P , the relation between target area A_0 and target perimeter P_0 becomes

$$P_0(t) = \varepsilon_P \cdot \sqrt{4\pi A_0(t)}. \quad (6)$$

Note that the target values for area and perimeter are dynamic and are updated based on the proliferation function defined below.

Apart from membrane fluctuations, a suspended cell (without medium interaction: $J_{CM} = 0$) will maintain its round shape, as this represents the most energetically favorable state where both perimeter and area requirements are satisfied. This situation changes when contact energies with the substrate or medium come into play, leading to alterations in cell shape. In the case of energetically favorable adhesion (negative J), the resulting deviation from the round shape will meet the area constraint, while the perimeter of the cell increases due to the

cell being stretched in the contact region (analog to surface wetting). A positive adhesion energy would conversely lead to a minimization of the contact perimeter and act like an external pressure, compressing the cell. In the interplay of different adhesion energies with different interfaces, the equilibrium cell shape results from the energetic balance of the adhesion influences and the perimeter and area constraints. Possible deviations in perimeter from the target perimeter $\Delta P = P - P_0$ serve as a measure for stretch of the cells and can be used as a biomechanical proliferation signal.

Whenever ΔP exceeds a threshold, a proliferation step is performed, increasing the cell perimeter depending on the local tissue tension ΔP . To prevent unequilibrated cell shapes and uncontrolled proliferation driven by random fluctuations of the cell perimeter, we introduce a combination of parameters that define the growth function in our CPM model. The growth threshold G_{th} and the timescale τ determine how strong the mean stretching ΔP_τ of the cell perimeter must at least be during a time interval τ for growth to occur. G_{th} defines a relative fraction of the current target perimeter P_0 and therefore the absolute threshold depends on the cell size. Note that the average perimeter deviation ΔP_τ is reset for each time window τ and the frequency of proliferation steps is globally determined by $1/\tau$. If the growth condition $\Delta P_\tau > G_{th} \cdot P_0$ is satisfied, then the cell increases in size as follows:

$$P_{0B} = P_{0A} + k \cdot \Delta P_\tau, \quad (7)$$

$$A_{0B} = \frac{P_{0B}^2}{4\pi \varepsilon_p^2}. \quad (8)$$

The subscripts *A* and *B* label the target values of perimeter and area before (*A*) and after (*B*) performing the proliferation step. The average stretching ΔP_τ of the cell perimeter on the timescale τ is used to prevent growth based on random fluctuations. Supplementary to the averaging timescale τ , we also introduce the growth factor $k < 1$, which rescales the growth of each proliferation step to avoid very fast proliferation that could prevent the equilibration of cell shapes on the timescale of τ . The rate of the performed proliferation steps is defined by $1/\tau$. As soon as the cell has doubled in size relative to the initial size ($A_0 = 2A_{0i}$), the cell divides along its minor axis, which results in two cells with A_{0i} and P_{0i} following equation 6. The initial cell area A_{0i} is defined as a global simulation parameter.

III. RESULTS

A. Single cell shape

We start by simulating a single cell adhering to a substrate to determine realistic regimes for the parameters of the simulation. The influence of substrate and medium adhesion on cell shape is shown in Fig. 2. We set $T = 1$ to enable a clear understanding of other energy parameters in units of temperature. For all simulations, the elasticities for area and perimeter constraints have values of $\lambda_A, \lambda_P = 1$, and the neighborhood order is 10. Based on Eq. (6) the target perimeter P_0 is defined with a static cell area of $A_0 = 400$ px. The perimeter prefactor for the correction of discretization errors has a value of $\varepsilon_P = \frac{4}{\pi}$ (for more detailed information on the perimeter discretization, see Supplemental Material Fig. S1 [40]). The

initial condition of the simulations is a square cell with an edge length of 20 px that rests directly on a fixed substrate with a thickness of 10 px.

Compared to an equilibrated spherical cell in the absence of adhesion [Fig. 2(c)], positive cell-medium interfacial energy (membrane tension) introduces an external pressure that compresses the cell and yields a minimized cell-medium interface [Fig. 2(d)]. In contrast, negative cell-substrate interfacial energy (adhesion) leads to a flattened cell shape [Fig. 2(e)] while increasing the cell-substrate interface and the cell perimeter. The equilibrium cell shape is determined by the energy balance between these adhesion terms and the perimeter/area constraints. A combination of positive J_{CM} and negative J_{CS} yields an intermediate cell shape between the two cases discussed above [Fig. 2(f)]. Cell compression due to unfavorable cell-medium interaction gets partially counteracted by the favorable cell-substrate interaction. The temporal developments of the average cell perimeter and area [Figs. 2(a) and 2(b)] reveal an equilibration process on the scale of roughly 100 MCS depending on the combination of adhesion energies. One should note that the fluctuation levels of the equilibrated perimeters are lowered under the influence of positive cell-medium interaction. The timescale of the equilibration process can serve as an estimation for reasonable timescales for the introduction of a growth function that separates the timescales for cell shape equilibration and cell proliferation. These equilibration timescales may vary for the equilibration of macroscopic tissue shape in contrast to single cell shape.

We performed systematic parameter scans of a wide range of positive J_{CM} and negative J_{CS} , which revealed different cell shape regimes [Figs. 2(g) and 2(h)]. For biologically realistic adherent cell shapes, we can discard the parameter ranges where cells vanish due to high J_{CM} , or become extremely flattened due to the domination of J_{CS} . Instead, we focus on cell shapes that fulfill the area constraint [white region in Fig. 2(g) with $A = A_0$] to represent the incompressibility of cells. These cells simultaneously show a significantly increased perimeter [Fig. 2(h)], corresponding to increased cortical tension that is known to drive cell proliferation. In conclusion, our simulations show contractile adherent cells with realistic shapes if the relationship between the adhesion terms is approximately $J_{CM} = -J_{CS}$.

B. Monolayer growth

To enable the formation of a monolayer starting from a single cell on a flat substrate, we next introduced tension-dependent proliferation (see Materials and Methods). The influence of the parameters of the growth function is shown in Fig. 3 for the timescale τ [Fig. 3(a)], the growth factor k [Fig. 3(b)] and the growth threshold G_{th} [Fig. 3(c)]. The growth kinetics are characterized by an approximately linear increase in tissue area that stagnates at a saturation value as soon as the available substrate surface is covered by a layer of cells. The condition for cell growth is a local increase of cell perimeter ($\Delta P_\tau > G_{th} \cdot P_0$), leading to an increase in cell size proportional to $k \cdot \Delta P_\tau$ for each proliferation step. The frequency of proliferation steps is determined by the timescale τ . Figures 3(a) and 3(b) show a growth rate $v_G = \frac{k}{\tau} \cdot \Delta P_\tau$ for

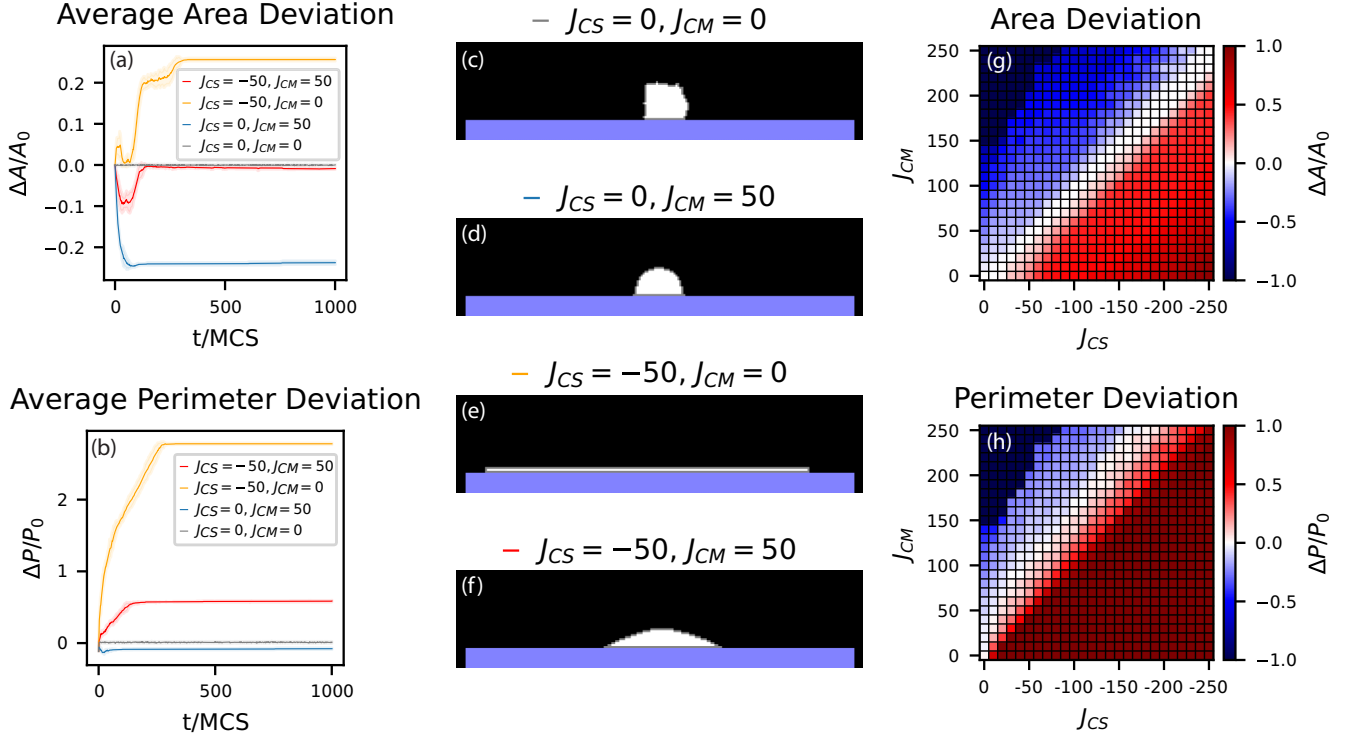


FIG. 2. Averaged evolution of cell perimeter (a) and area (b) for different combinations of cell-substrate energy J_{CS} and cell-medium energy J_{CM} (mean and standard deviation with $N = 10$ for each condition). The equilibrium state of the simulations at MCS 1000 [(c)–(f)] shows deviations from a spherical cell shape induced by different adhesion strength. An increase in substrate adhesion leads to flattening of the cell while increasing perimeter and area. In comparison, positive cell-medium interaction leads to a compression of the cell yielding a decreased cell area and perimeter and a minimized cell-medium interface (d). A combination of positive J_{CM} and negative J_{CS} also results in a rounded cell-medium interface, but the negative cell-substrate adhesion partially counteracts the compression due to positive cell-medium adhesion (f). Panels (g) and (h) show the equilibrium perimeter and area for cells under the influence of different adhesion energies J_{CS} and J_{CM} , showing different regimes for cell shape. In the dark blue region, where P and A are both zero, the unfavorable cell-medium interaction dominates, leading to disappearance of the cell. In the dark red region, cell-substrate interaction is dominant, leading to an extremely flattened cell with $P \geq 2P_0$. G also shows a white transition zone for perimeter values between these two extreme cases, where the cell perimeter fulfills the perimeter constraint $P = P_0$. Mapping the transition zones between the perimeter regimes to the area plot (h) reveals that there is a region in the adhesion-parameter space where the area of the cells fulfills the area constraint ($A = A_0$), while the perimeter of the cell is increased ($P > P_0$) without extreme flattening of the cell. This region represents an uncompressed cell on the substrate, which is stretched and can therefore grow.

the initial linear increase. Supplemental Material Fig. S2 [40] shows a detailed analysis of the slope in the initial growth phase confirming the linear proportionality $v_G \propto \frac{k}{\tau}$. For given interfacial energies and the resulting stretch ΔP_τ , the fraction $\frac{k}{\tau}$ is a global scaling factor for the dynamics of proliferation relative to the equilibration of the cell shape. Similar ratios for slow growth are achieved with a large timescale τ or low growth factor k , but they result in smoother growth dynamics with low k and τ [compare, for example, the two purple curves in Figs. 3(a) and 3(b)].

A systematic comparison of different growth rates v_G reveals different saturation values for tissue area, resulting in an increased thickness of the monolayer for faster growth rates on the same available substrate area. Extremely fast growth rates [Fig. 3(b) with $k = 1$] lead to uncontrolled proliferation that exceeds the monolayer configuration (data not shown). For sufficiently small growth rates, however, the saturation value remains constant. These results emphasize the importance of a suitably defined growth rate that allows for the

shape equilibration of tissue and cells. Another interesting observation is that a very low growth threshold ($G_{th} < 0.05$) does not result in uncontrolled growth within the scope of our simulations. This indicates, that any fluctuation driven growth already gets inhibited by the averaging of the growth signal ΔP_τ on timescale τ . Note, however, that simulations without a threshold ($G_{th} = 0$) may lead to purely fluctuation-driven, uncontrolled growth for long simulation times if τ has a low value (see Supplemental Material Fig. S3 [40]).

Next to the suppression of purely fluctuation-driven growth, the growth threshold defines the final achievable tissue shape. Growth dynamics that rely on low ΔP values therefore require a low G_{th} . Depending on the membrane fluctuation level T of the simulation, a suitable threshold has to be chosen to enable the desired growth dynamics while suppressing artifacts from fluctuation-driven growth. This motivates our choice to define the membrane fluctuation level T relatively low compared to the energy terms, which yields stiffer dynamics compared to typical CPM simulations.

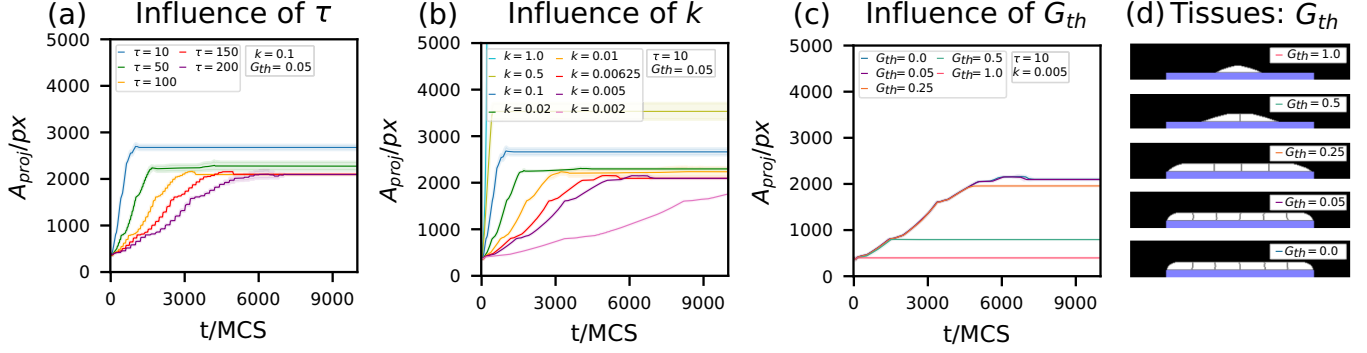


FIG. 3. Monolayer simulations with $J_{CS} = -50$ and $J_{CM} = 50$ show the influence of the timescale τ (a), growth factor k (b), and the growth threshold G_{th} on the resulting proliferation dynamics on a flat substrate. The projected tissue area A_{proj} is defined as the total area of all cells. Exemplary tissues resulting from different G_{th} are shown next to (c). The growth kinetics show an approximate linear increase in tissue area that transitions to a constant value when the available substrate is filled with cells. Panels (a) and (b) show the following proportionality of the growth rate: $v_G = \frac{k}{\tau} \cdot \Delta P$. Curves with the same color in (a) and (b) have a constant value for the ratio $\frac{k}{\tau}$ scaling the rate of growth. The comparison between (a) and (b) indicates that scaling the growth rate with k instead of τ yields smoother proliferation, which better represents continuous biological growth. Deviations from a strictly linear increase are probably related to cell divisions and a corresponding delay until the cell shape equilibrates again. The saturation values of the curves emphasize the role of a sufficiently slow defined growth rate to separate the timescales for proliferation and shape equilibration of tissue and cells. The tissue area shows an overshoot for very fast growth rates due to unequilibrated cell shapes. Fast growth rates in (b) ($k \geq 0.01$ for $\tau = 10$) show larger overshoots of the final projected tissue area with the extreme case of $k \geq 0.1$ yielding unchecked proliferation that even exceeds a monolayer configuration. If the growth rate is, however, sufficiently slow, then the saturation value of the tissue area does not depend on the growth rate. Variable growth thresholds G_{th} (C) illustrate how the final equilibrium shape of the tissue is determined by the activation of the growth function if the perimeter strain exceeds the defined growth threshold. A very high growth threshold of $G_{th} = 1$ suppresses the proliferation altogether, while an intermediate value of $G_{th} = 0.5$ stops proliferation after the first cell division. This can be explained by the fact that the initially isolated cell has two directions of free substrate to adhere to, such that the perimeter change exceeds the intermediate growth threshold. After the first division, however, the two daughter cells each have only one free substance direction, which lowers their ΔP_i below the threshold $G_{th} \cdot P_0$. For the other tested values, a low threshold in the interval of $G_{th} = [0, 0.25]$ enables the formation of a monolayer that fills the entire substrate. A higher or lower threshold in this interval can prevent or enable proliferation steps that are based on low perimeter strain and is therefore important for the final tissue shape.

C. Bulk growth

On flat substrates, tissue growth is confined to a monolayer of cells on the available area. This changes if the underlying substrate geometry allows for the formation of a concave, curved cell-medium interface. Figure 4(a) and Supplemental Material Movie 1 [40] show the resulting tissue on flat substrates on all four sides of the simulation box, with the adjustment that the substrates now touch in the lower right corner but remain spatially separated otherwise. The parameters of the growth function were the same as in Fig. 3 with $\tau = 10$, $k = 0.005$, and $G_{th} = 0.05$ to separate the timescales of growth and shape equilibration. The time course of the simulation shows that, in contrast to the confined monolayer growth on the isolated flat substrates, bulk tissue now emerges from the lower right corner where the two substrates touch. The growth rate is clearly related to the local tissue curvature, as the line tension induced by the unfavorable cell-medium interaction J_{CM} drives the minimization of the tissue contour length. This interpretation is supported by the observation that the final tissue shape exhibits a straight contour between the anchor points of the substrate. The formation of this minimum contour length is the 2D analog to the minimal surfaces observed in 3D [11,15]. A comparable simulation with constant growth instead of tension-dependent proliferation (see Supplemental Material Movie 2 [40]) highlights the role of tension-dependent proliferation for obtaining tissue shapes that are confined by the geometry of the underlying substrate.

Systematic variation of the adhesion energies J_{CS} and J_{CM} in Fig. 4(b) and the temporal development of the tissue area in Fig. 4(c) reveal how curvature-driven growth depends on the choice of interfacial energies. The parameter scan shows different types of tissue development for different parameter regimes. Cell-substrate adhesion is required for the formation of an initial monolayer. In the absence of cell-medium interaction, growth exceeding the monolayer does not occur. When both interfacial energies act simultaneously, bulk growth is enabled. The ratio between the two terms has an influence on the final tissue shape and determines whether growth follows the constraints imposed by the substrate. Most notably, a well-defined tissue shape emerges only if both adhesion terms have the same magnitude. The corresponding parameter regime overlaps with the parameters used for well defined single cell shapes with $A = A_0$ and $P > P_0$ in Fig. 2.

D. Growth in cleft and capillary geometries

To systematically investigate the influence of tissue curvature on proliferation, we analyzed the growth dynamics of clefts with various opening angles α and capillaries of variable width w (Fig. 5 and Supplemental Material Movie 3 and 4 [40]). The cleft geometries are inspired by the experimental setup used by Benn *et al.* [14]. We defined different capillary geometries for the comparison of clefts to cavities with a constant width. The clefts in Figs. 5(a)–5(c) show proliferation

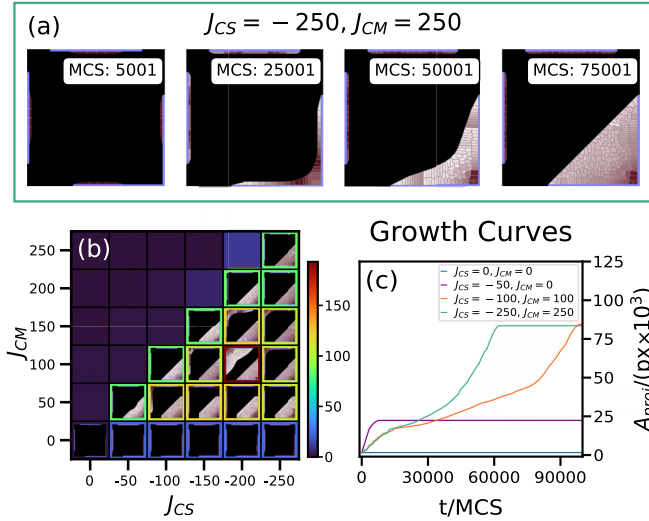


FIG. 4. Bulk tissue growth is mediated by substrate geometry. (a) Isolated substrates on the upper and left side of the box confine growth to a monolayer, while the touching substrates of the right and bottom sides form a corner that allows bulk growth with a curved tissue-medium interface. The red color of the individual cells depends on the time since the last cell division, with a darker shade indicating older cells. (b) Tissue area and tissue shape after 100k MCS for different combinations of J_{CS} and J_{CM} . The color scale represents the projected tissue area A_{proj} . The label corresponds to the y-axis label in (c). This parameter scan reveals that simulations with balanced adhesion energies ($J_{CS} = -J_{CM}$) yield bulk tissue growth in regions where the substrate is concave while being confined to a monolayer for flat substrates. Growth beyond the monolayer only occurs due to surface tension along the energetically unfavorable cell medium interface. However, unbalanced adhesion terms ($J_{CS} > -J_{CM}$) results in unconfined growth independent of substrate geometry. Unconfined growth dynamics in the case of $J_{CS} > -J_{CM}$ can be explained by the single cell shape results in Fig. 2(g), showing deviations from the target area A_0 in the respective parameter regime. The cells therefore do not fulfill the incompressibility assumptions on which the growth function is based. For additional timepoints similarly to (a), see Supplemental Material Figure S12 [40]. (c) compares the growth dynamics of simulations confined to a monolayer or contained bulk growth for balanced adhesion terms. In the case of balanced values for J_{CS} and J_{CM} , the proliferation speed is influenced by the magnitude of both adhesion terms. The growth parameters were set to $\tau = 10$, $k = 0.005$, and $G_{th} = 0.05$.

dynamics that depend on the angle of the cleft (22.5° – 90°). The data show a faster linear growth front progression for smaller cleft angles with a simultaneously larger mean curvature of the tissue contour and a higher local curvature in the center of the contour. The comparison between mean curvature and central curvature is important to verify that changes in the mean curvature are not only influenced by changes in the contour length, independent of the curvature in the center of the growth front.

The calculation of the local curvature is based on the method used by Driscoll *et al.* [42] for the analysis of cell boundaries. For each tissue surface pixel of the contour, two neighbors are defined by following the contour up and down a given distance. The reciprocal radius of a circle fitted to

the surface pixel and the two neighbors defines the local curvature. The result of this curvature analysis depends on the scale of the neighborhood distance and was set to 25 px to correspond to the scale of the contribution of the individual cell to the growth front. Surface pixels that are closer than 25 px to one end of the contour have a defined curvature of 0 on the given scale.

The capillary simulations [Figs. 5(e)–5(g)] show results similar to the cleft simulations with a growth front progression that is determined by the local curvature. Between the different capillary widths, differences in curvature and growth front progression occur during the initial growth phase, but then transition into a late growth phase with constant central curvature and a comparable slope in the development of growth front distance. Due to large differences in the total contour length, the mean curvature values of the different capillaries are not comparable with each other. Nevertheless, the mean curvatures also exhibit constant values for the late growth phase, corresponding to a constant progression of the growth front.

In contrast to the cleft simulations, we did not observe a difference in the late growth dynamics for different capillary widths—only the initial transition process differs in its dynamics. Based on this observation, the cleft angle dependencies can presumably be explained by the constant change in cleft width as the growth front progresses.

In summary, the cleft and capillary simulations clearly show that tension-driven proliferation as a mechanism can explain the experimental observation that local growth dynamics is determined by local tissue curvature. The visualizations of cleft and capillary tissues in Figs. 5(d) and 5(h) have a green hue assigned to each individual cell indicating the strength of the local proliferation signal ΔP , revealing a more prevalent localization of tensed, proliferating cells at the curved cell-medium interface. These results clearly show how curvature can lead to a growth signal at the single cell level as a way to control the resulting macroscopic tissue shape.

IV. DISCUSSION

A. Comparison to other models of curvature-driven growth

Since the first quantitative experimental report of curvature-dependent tissue growth [5], a number of conceptual and computational models have tried to explain this phenomenon. The curvature dependence was linked to surface tension with biological growth summarized by a chemical potential [15], but this continuum formulation does not describe cellular behavior. Curvature-driven growth was shown to be equivalent to a layer-by-layer deposition of tensed chords [13] resembling contractile cells. This cell-level conceptual model offers a convincing analogy, but does not explain how biological growth is triggered by curvature or surface tension. Combinations of the surface tension and chord model concepts explain the orientation of cells and matrix fibers in three dimensions [16]. Other work on the cellular scale links cell behavior to geometry via diffusive damping [43]. Recent work modeling other experimental systems on the cellular level explains the geometry dependence of growth by space availability [44] or by growth factors [45]. Experimental evi-

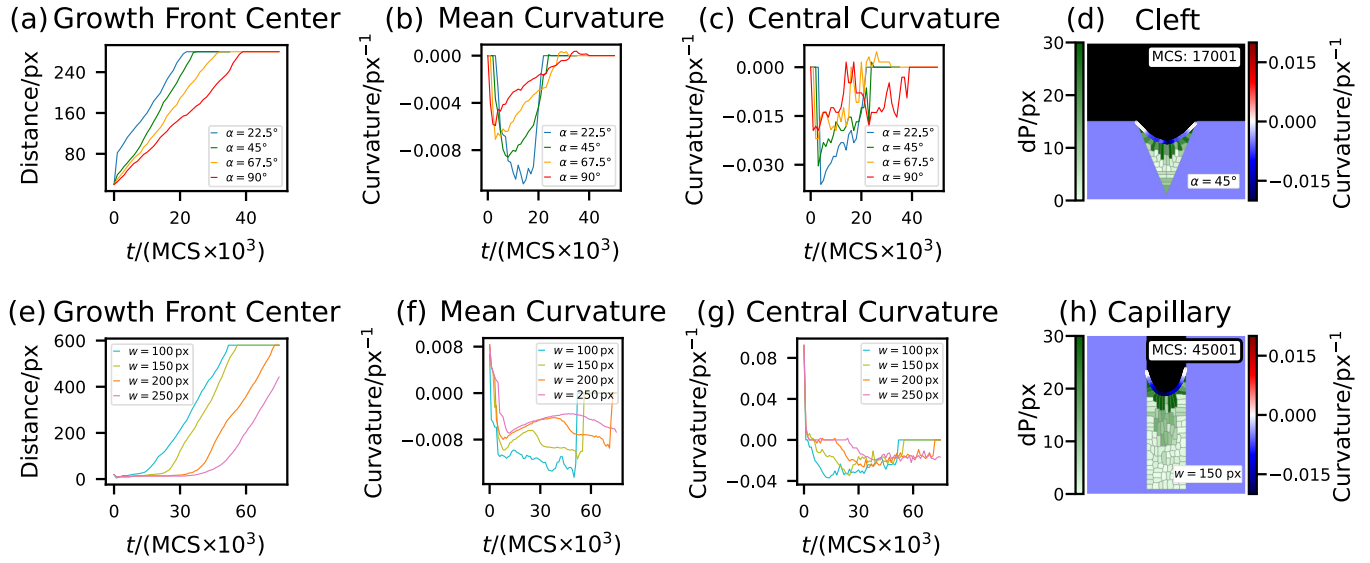


FIG. 5. Analysis of curvature-dependent growth on various cleft and capillary substrates. Cleft geometries with different angles [(a)–(c)] reveal curvature-dependent growth dynamics. Smaller angles lead to a faster displacement of the growth front (a) and to a stronger mean curvature and center curvature [(b) and (c)]. An exemplary tissue configuration in a 45° cleft shows the color-coded local curvature at the growth front and the individual cell perimeter deviation ΔP in a green hue. This visualization of the local stretching of cells reveals an increased growth signal at the tissue-medium-interface. Together with the angle-dependent growth rate, this illustrates the role of local tissue curvature as a biomechanical growth signal. The curvature controlled growth of the tissue stops as soon as the contour is smoothed out. The different capillary substrates with a width between 100 and 250 px [(e)–(g)] reveal a similar dependency between growth and curvature. The example configuration of a capillary tissue with width 150 px (h) reveals, analogous to the cleft shown, that the stretched cells that contribute to growth are localized at the curved growth front. The main difference to the growth in the cleft geometries is that, regardless of the capillary width, a constant central curvature emerges. The constant curvature that occurs after the initial transition process corresponds to a constant progression of the growth front. This supports the previous observation that growth rates depend on the local curvature. At the same time, this demonstrates the role of the underlying substrate geometry. The transition towards a constant curvature is related to the width of the cleft or capillary. The fact that the curvature between different cleft angles differs might be explained by the ongoing variation of the cleft width with the progression of the growth front. The growth parameters were set to $\tau = 10$, $k = 0.005$, and $G_{th} = 0.05$ with $J_{CS} = -250$ and $J_{CM} = 250$ as adhesion parameters.

dence in curvature-driven growth however shows an influence of pore geometry on local cell proliferation [10].

Cell-based models of biological tissue have used various strategies to implement growth on the cellular level. A simple and commonly used assumption is that cells progress through the cell cycle at a constant rate and divide after a fixed time interval. Variations in tissue shape and cell arrangement can then only result from cell migration and rearrangements due to variations in the available space, but not from growth heterogeneity. While this is sufficient in many cases where other factors are dominant, e.g., optic cup morphogenesis [46], it leads to an exponential growth rate and does not reproduce the inhibition of growth after a substrate is covered or after the tissue interface is flat. Another proliferation mechanism used in cell-based models is pressure inhibition, where cells stop growing when they are under pressure but otherwise divide at a constant rate, which explains for example why cells inside a tumor spheroid stop dividing [47]. It does not explain, however, why cells on flat substrates divide when they adhere but stop growing once the substrate is covered. Cell shape as growth signal in the CPM was first proposed in the context of tumor growth on flat substrates [48]. This concept is similar to our proliferation mechanism, but when we applied it in our simulations, we could not reproduce both monolayer growth and curvature-driven growth with the same parameter regime.

Other, nonmechanical signals for regulating growth that have been used in the CPM and other cell-based models are for example the availability of food [49], other soluble signals [50], or cell density [51].

Our computational approach is novel and different in that it assumes a simple control of cell proliferation by cortical cytoskeletal tension, expressed in terms of elastic energy from the extension of the cell perimeter relative to its resting length. This simple assumption does not only reproduce the spreading and proliferation of single cells on flat substrates (which none of the other models above can explain), but the exact same set of parameter values correctly predicts curvature-driven growth as experimentally observed in scaffolds of various geometries. We think that our model is the first to explain curvature-dependent growth on the tissue scale with a single biologically motivated mechanistic assumption at the level of cellular decision making and to explicitly link macroscopic and microscopic biological behavior in this experimental system.

While the focus of our work is on curvature-driven tissue growth, our model also describes the growth of a cell monolayer on flat substrates. Monolayer growth has been studied before in the CPM, for example in the context of tumor spreading [48], collective cell motion [52] and epithelial wound closure [53].

B. Tension-dependent proliferation reproduces curvature-driven growth

Our CPM-based simulations of cells on substrates reproduce a wide range of experimental observations without the need to fine-tune parameters to different scenarios (Fig. 4): Single cells spread on adherent substrates, divide unless adhesion is too weak, and continue until the substrate is covered by a cell monolayer, upon which growth stops. In regions with concave curvature, cells continue to proliferate and start forming a dense tissue in the third dimension [5] such that the amount of tissue produced, measured as 2D projection of the tissue area, initially grows linearly with time with a local growth rate proportional to local curvature [13] and cell division mainly at the growth front [10].

Additional simulations on sinusoidal substrates (shown in Supplemental Material Fig. S6 [40]) further support these results and reproduce findings of flattened cell shapes in regions with convex curvature in contrast to thicker cells for concave tissue contours [54]. Tissue growth stops once the negative curvature of the tissue contour equilibrates to zero. The resulting minimal contour length (between the anchor points of the substrate) with zero curvature is a two dimensional analog to a minimal surface in 3D [11,15]. Therefore, we expect the formation of minimal surfaces for CPM simulations in 3D when using a comparable tension-dependent growth function.

The simulation results of tissues growing in cleft and capillary geometries confirm these observations, and in addition imply growth rates which are proportional to the local tissue curvature (see Fig. 5). This can be explained by higher line tension in regions with higher curvature, driving proliferation to minimize the tissue contour. Differences in curvature and later growth rate are only significant between different cleft angles, but not different capillary widths. This is probably related to the instantaneous width between the anchor points of the growing tissue at a given height. In the capillary case, this width is constant, leading to constant curvature between different widths after the initial growth phase. In contrast, the width of the cleft varies dependent on height for each cleft substrate, resulting in changes in curvature and growth. The simulations in cleft and capillary geometries as well as on sinusoidal substrates present additional predictions of our model that can be tested experimentally.

The results in Fig. 4 also reproduce the experimental observations of Kommareddy *et al.* on the growth dynamics of osteoblast tissue in quadratic pores [12]. They found that the development of the projected tissue area is characterized by an initial lag phase followed by a universal growth rate for the bulk tissue growth. The duration of the initial lag phase is determined by substrate adhesion, while the subsequent universal growth rate is independent of the substrate, but is only determined by the cells used. Our model confirms these findings, with the difference that the initial spreading depends on the combination of J_{CS} and J_{CM} , while the bulk growth is determined solely by the interfacial line tension imposed by the tissue-medium interaction J_{CM} . Note that balanced values for J_{CS} and J_{CM} are still necessary for well defined cell shapes ($A = A_0$ and $P > P_0$, see Fig. 2) to ensure that the tissue grows under geometric confinement [see Fig. 4(b) for examples of unconfined proliferation].

C. Cell shape

The systematic simulations of single cells (Fig. 2) under the influence of adhesion and constraints for area and perimeter illustrate the biological interpretation of the different parameters: λ_A describes the cell's resistance against compression and expansion, while λ_P introduces a line tension along the perimeter of the cell in 2D, corresponding to a surface tension in 3D. The interfacial energies J_{CS} and J_{CM} can be interpreted as differential line tensions for contact with substrate or medium that drive changes in cell shape. Negative J_{CS} represents the adhesion of cells to the substrate, similar to surface wetting of a water droplet on a hydrophilic surface. Positive J_{CM} acts as an additional line tension for cell-medium interfaces, leading to a minimization of the interface. The resulting changes in cell shape drive proliferation based on an increased cell perimeter ($\Delta P > G_{th} \cdot P_0$). Therefore, J_{CM} is the driving factor for bulk tissue growth based on line tension at concave tissue-medium interfaces, while J_{CS} enables the spreading of cells on substrates.

Different cell shape regimes emerge under the counter-acting influence of favorable cell-substrate and unfavorable cell-medium adhesion. We assume a cell shape on the adhesive substrate as realistic if the area constraint is fulfilled ($A = A_0$) and the cell cortex is under tension ($P > P_0$). The biological motivation for the increased perimeter is central for tension-dependent proliferation in our model, where $\Delta P = P - P_0$ serves as a measure for the local mechanical tension on the level of single cells. This cortical tension is interpreted as growth signal, determining the resulting tissue shape. To keep the model as simple as possible, we selected for cell shapes that fulfill the area constraint $A = A_0$, such that cells behave as incompressible droplets of liquid.

The observation that tissue growth only depends on the geometric constraints imposed by the underlying substrate geometry for balanced substrate adhesion and cortical tension highlights the importance of well-defined single cell shapes. This is evident, for example, in Fig. 4(b) by confined growth in a parameter regime which simultaneously fulfills the requirements $A = A_0$ and $P > P_0$ for single cells (compare with Fig. 2). The experimentally observed orientation of surface cells perpendicular to the growth front is not reproduced in our model—this configuration would be energetically unfavorable due to the high cell-medium interfacial energy. Here, the polarization of contractile cells likely plays a role, which can be incorporated into the CPM by adding subcellular elements.

D. Spreading kinetics

The spreading kinetics of the monolayer in Fig. 3 reveal a linear increase of the tissue area. Due to the constant thickness of the cell layer, the projected tissue area A_{proj} is proportional to the length of occupied substrate in our simulation. This can be easily transferred to experimental observations on the spreading of monolayers, in which the radius of a circular monolayer increases linearly [55]. This suggests that the tension-dependent proliferation in the model can also reproduce the spreading dynamics of biological tissue in 3D.

The analysis of the various growth function parameters shows that the ΔP -dependent growth rate is determined by

$v_G = \frac{k}{\tau} \cdot \Delta P_\tau$, while the threshold G_{th} sets the minimum tension that must occur in order to activate growth. At the same time, the growth threshold prevents the occurrence of fluctuation-driven growth. The results also show that the growth rate $v_G \propto \frac{k}{\tau}$ must be sufficiently slow to allow for the equilibration of cell shapes on the timescale of growth. Too-fast growth leads to increased thickness of the cell monolayer in the case of spreading on a flat substrate.

Deviations of the growth kinetics from a strict linear progression are likely associated with nonlinear proliferation dynamics on the single-cell level, since the enlargement of the cell depends on the relative change in perimeter, which is confined by a parabolic potential H_P counteracting a linear adhesion term H_J . The systematic variations of the growth threshold suggest that the bends in the curves correspond to discrete mitosis events whose occurrence depends on the growth threshold G_{th} . This supports the idea that deviations from a linear progression can be explained by nonlinear elasticities and varying cell sizes.

An additional analysis of capillary simulations reveals how the substrate spreading kinetics can determine the emergence of curvature-driven bulk tissue growth. The comparison of the lateral and central growth front distance in different capillaries (Supplemental Material Fig. S7 [40]) shows how the lag in the initial growth phase is associated with the linear progression of the lateral growth front boundary. The approximately linear progression of the boundary is driven by substrate adhesion and is in line with the linear growth dynamics observed in monolayer growth (see Fig. 3). The subsequent emergence of curvature-driven growth depends on the previous spreading on the available substrate. This explains why the lag phase before the constant growth is proportional to the capillary width. Increased substrate adhesion relative to the cell-medium interaction (Supplemental Material Fig. S8 [40]) shows a faster spreading of the cells on the substrate followed by curvature-driven growth dynamics that are independent of J_{CS} .

It should be noted that monolayer growth on tilted substrates reveals anisotropic spreading on all substrates, that are not aligned with the lattice with selective increased growth at a substrate angle of 45° (see Supplemental Material Fig. S4 [40]). This has implications for the development of tissues on tilted substrates, such as the clefts, shown in Figs. 5(a)–5(d). However, the main message of curvature-driven growth in the clefts should not be affected by the orientation of the substrate, as faster spreading only occurs at an angle of exactly 45° . This angle of the substrate relative to the orientation of the lattice is only present in the 90° cleft, which still shows overall slower proliferation in the cleft comparison. To confirm that our results are qualitatively independent of lattice symmetry, we also performed a simulation on a hexagonal lattice [56] and found that the key observation, namely tissue growth in a concave corner but monolayer formation on flat substrates, remains unchanged, as does the spatial distribution of cell shapes (see Supplemental Material Fig. S9 [40]).

E. Limitations of the model

When combining the CPM with tension-driven proliferation, some limitations need to be considered. First, some

assumptions behind the simulations discussed here are not applicable to model more complex tissues and would instead require additional extensions and adaptations. One key point would be to transition the model from 2D to 3D. This would allow the formation of multiple directions of curvature, leading to minimal surface tissue shapes based on the geometry of the underlying substrate. In addition, the customizable properties of the CPM can be used to implement processes such as apoptosis and cell differentiation. These expansions would make the CPM more suitable to model complex tissues. Although these concepts are beyond the scope of the work presented here, the used CC3D framework would in principle allow the implementation of such additional functionalities in an easy and user friendly manner.

Some inherent properties of the CPM can be limiting for certain applications. Those include lattice artifacts such as the anisotropy of growth on tilted substrates (Supplemental Material Fig. S4 [40]), inconvenient parallelization (see Ref. [57] for parallelization approaches), and the lack of direct mechanical forces in the model. To rule out the possibility that the observed macroscopic growth patterns and dynamics are based on lattice artifacts, comparable simulations were rescaled at half and double resolution. Supplemental Material Fig. S5 [40] shows reproducible macroscopic behavior for a wide range of lattice resolutions.

When defining CPM simulations that include tension-driven proliferation, a sensible choice of fluctuation level T must be made. The trade-off between simulation time and sufficiently slow growth to avoid unequilibrated cell shapes might be limiting for certain applications. Our current results imply that simulations have to be relatively stiff to prevent fluctuation-driven growth.

A possible solution to access the mechanical forces would be to calculate them from the local energy gradient defined by the energy function of the system [39]. Another limitation of the CPM is that the representation of fibrous extracellular matrix (ECM) is difficult. One approach to include ECM fibers was proposed by Tsingos *et al.* by combining the CPM with a bead-spring model [58]. This hybrid model is a promising approach to investigate the intricate feedback mechanisms between cells and ECM in the regulation of tissue homeostasis and proliferation. Overall, the tension-dependent proliferation presented here could be a suitable concept to be combined with more sophisticated simulations or hybrid models to get closer to the behavior of real biological tissues.

V. CONCLUSIONS

The key new insights of our simulations are that cortical tension-driven proliferation not only explains the spreading and proliferation of cell monolayers, but in addition correctly predicts (1) that tissue is formed on curved substrates of negative, but not positive sign, (2) that the rate of tissue growth is proportional to local interfacial curvature, (3) the global tissue shape, and (4) the proliferation of cells predominantly along the tissue surface. This is nontrivial, since on the cellular level, the model does not include any conceptual description of these higher-level emergent properties, but only elasticity and

interfacial tension—properties that are defined independently for each cell.

Our results highlight how a tension-dependent proliferation function implemented in the CPM framework is able to explain the macroscopic dynamics of curvature-driven tissue growth. The resulting tissue shape is determined by the external cues imposed by the geometry of the underlying substrate. Therefore, our model presents a promising approach to predict tissue shape and growth dynamics for microtissue engineering. The model's customization options also allow this approach to be used to simulate individual geometries and

more complex biological tissues in the future, which is facilitated by the good scalability of the CPM [57,59]. We encourage other researchers to reproduce and adapt our simulations using the predefined configurations and documentation provided in Ref. [60].

DATA AVAILABILITY

The data that support the findings of this article are openly available [60].

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