A level set method for hyperbolic curvature flows: Application to curvature-controlled tissue growth

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Abstract – Hyperbolic curvature flows are a class of geometric flows in which the normal acceleration of an interface is coupled to its local curvature. These flows arise in the growth of biological tissues when new tissue is produced at or near the interface, and in the evolution of foams and thin films. They are often associated with fragmentation or fusion of interfaces. In this paper, we propose a level set based method to resolve complex topological situations that arise in geometric hyperbolic curvature flows. The hyperbolic character of these flows requires the introduction of another Eulerian field than the level set function. This Eulerian field represents the normal velocity of the interface, or equivalently in tissue growth, the surface density of tissue synthesising cells, anticipated at future locations of the interface. We compare different numerical methods to solve the partial differential equations that govern the level set function and velocity field. These methods differ in whether or not these fields are re-initialised in a neighbourhood of the interface. We find that while the velocity field anticipates values away from the interface, its orthogonal extrapolation from the interface generally provides a more conservative numerical scheme at developing cusps of the interface, and thereby leads to more accurate simulations. Examples that include tissue fragmentation and fusion during the evolution of complex tissue shapes under hyperbolic curvature flows are provided.

Keywords: moving boundary problems, geometric flow, surfactant, tissue growth, morphogenesis, tissue engineering

1 Introduction

Many moving boundary problems in physics and biology can be modelled by geometric flows, in which the dynamics of the interface is described by interface properties alone. In morphogenesis, tissue growth occurs in confined spaces under strong geometric controls [1–4]. During appositional growth, the curvature of the tissue substrate provides a mechanistic influence on the tissue’s local growth rate that is captured by a hyperbolic curvature flow [5, 6]. In contrast to mean curvature flows, in which the normal velocity of the interface is proportional to curvature [7, 8], hyperbolic curvature flows are characterised by the fact that the normal acceleration of the interface is proportional to curvature [9–13]. The hyperbolic character of such flows gives rise to a rich set of interface movement patterns. Depending on the amount of lateral diffusive damping, these movement patterns include oscillatory shape motion, emergence of cusps in the interface that propagate sideways as shock waves, efficient smoothing of initial interface irregularities, and shock and rarefaction waves emerging at concavities and convexities in a similar way to curve offset flows [5–7].

Capturing these movement patterns with a single numerical scheme is challenging. In Refs [5, 6], explicit front-tracking Monge parameterisations in Cartesian and polar coordinates are used. The strongly coupled equations governing interface and velocity are solved using a combination of semi-implicit upwind finite difference and conservative high-resolution finite volume Kurganov–Tadmor schemes. Lagrangian front-tracking approaches are also used in the context of hyperbolic geometric flows in thin films [14–16]. A major setback of these schemes is the difficulty to describe topological changes in the interface. In biological contexts, such topological changes are common. They occur for example in tumour growth (fusion of tumour nodules or of tumour fingers) [17–19], wound healing [20, 21], tissue involution processes, tissue engineering bioscaffolds [22–25], and in bone consolidation or fragmentation [26–29].

The level set method is a common and successful technique to simulate numerically the evolution of interfaces undergoing topological changes [7, 30, 31]. It has been used to describe the evolution of biological tissues in several instances before [32, 17, 19, 22–24, 21]. However, in these studies, the population of tissue-synthesising cells is not considered, and the tissue’s interface velocity is usually assumed to be simply proportional to curvature. To model hyperbolic curvature flows with a level set method, an additional Eulerian field to the level set function must be introduced. This Eulerian field represents the normal velocity of the interface, or equivalently, the surface density of tissue-synthesising cells, and its anticipated value in a neighbourhood of the interface. The coupled partial differential equations governing the evolution of the level set function and the velocity field provide a new technique to solve hyperbolic curvature flows in complex topological situations.

It is common in level-set methods to extend interface velocity to a neighbourhood of the interface by orthogonal extrapolation [30]. This helps maintain the level set function as a signed distance function, which improves stability and accuracy [7, 30]. However, because the velocity field we
introduce anticipates the value of interface velocity at possible future locations of the interface, re-initialising it by orthogonal extrapolation from the interface may result in a less accurate determination of velocity. We thus explore several possibilities for solving the equations numerically that differ in whether or not the level-set function and interface velocities are re-initialised. We compare our numerical simulations with analytic solutions and with simulations performed with explicit parameterisations of the interface. We find that a good indicator of numerical accuracy is provided by how well the surface integral of the velocity of the geometric flow is conserved. This corresponds, in the hyperbolic curvature flow for tissue growth, to how well the total number of tissue-synthesising cells is conserved. We show that re-initialisation of the level set function as a signed distance function and re-initialisation of the velocity field by orthogonal extrapolation help conserve total cell number at developing cusps of the interface, and thereby provide more accurate simulations in general.

Our level-set method for hyperbolic curvature flow is applicable to general surface-bound dynamic processes that affect the evolution of an interface, and is particularly suited to model complex topological situations. This is common in tissue growth and remodelling but also includes etching processes [33, 34], active membranes [35, 36], thin films and foams [10–12, 14–16].

2 Mathematical model

We start by providing a brief account of the hyperbolic curvature flow model of tissue growth. This hyperbolic curvature flow model will be used in all our examples as it provides physical intuition to the flow, and it illustrates the inclusion of viscous damping in the form of lateral (Laplace–Beltrami) diffusion and cell depletion.

2.1 Hyperbolic curvature flow model of tissue growth

New tissue is often secreted by active cells residing at or near the tissue’s surface, such as in tissue engineering bioscaffolds, tumour spheroids, epithelial wound healing, and new bone formation [2–4, 32, 37, 19, 21]. The evolution of the tissue interface for such surface-localised growth is captured by a type of hyperbolic curvature flow in which the normal velocity of the interface depends linearly on curvature [3, 6]. The physical basis for this flow is the crowding of new tissue material at concavities of the substrate, and the spreading of new tissue material at convexities. This model of tissue growth derives directly from the conservation law of the tissue-synthesising cell surface density ρ (number of cells per unit surface) and the fact that the normal velocity of the interface is given by

\[ v = \rho \Delta \frac{\kappa}{s}, \]  

where \( k \) is the cell secretory rate (volume of new tissue secreted per cell per unit time) [5, 38].

In two-dimensional space, this mode of tissue growth can be described by an explicit front-tracking parameterisation \( \gamma(s,t) \) of the tissue interface \( S(t) \), where \( s \) is an arbitrary one-dimensional parameter and \( t \) is time. Assuming the secretory rate \( k \) to be constant, cell density \( \rho \) can be substituted for normal velocity \( v \) by Eq. (1). If the parameterisation \( \gamma(s,t) \) is orthogonal, i.e., time lines \( t \to \gamma(s,t) \) are perpendicular to the interface everywhere at all times, the equations governing the evolution of the tissue boundary are given by [5]:

\[ \gamma_t = v_n, \]  

\[ v_t = -v^2 \kappa + Dv_t - Av, \]

where subscripts denote partial derivatives, \( \ell \) is the arc length such that \( d\ell = gds \) with \( g = |\gamma_t| \), \( \tau = \gamma_t/|\gamma_t| \) is the unit tangent vector to \( S(t) \), \( n \) is the outward unit normal to the tissue substrate, and \( \kappa = \tau \cdot n_t \) is the signed curvature, such that \( \kappa > 0 \) where the tissue substrate is convex, and \( \kappa < 0 \) where the tissue substrate is concave. In Eq. (3), the term \( Dv_t \) represents cell diffusion parallel to the interface with diffusivity \( D \), and the term \( -Av \) represents the elimination of active cells at rate \( A \).

In Refs [5, 6], this model is solved using Monge parameterisations of the interface \( S(t) \) (tissue thickness functions) in Cartesian and polar coordinates. The equations are solved numerically using finite difference or conservative high-resolution finite-volume schemes. These simulations are limited to simple interface geometries as explicit parameterisations make it difficult to capture the evolution of tissues undergoing complex changes in morphology.

2.2 Implicit representations of interface and normal velocity

To describe arbitrary interface shapes and changes in topology, here we represent the interface \( S(t) \) implicitly as the zero contour of a time-dependent scalar field \( \phi \):

\[ S(t) = \{ r \mid \phi(r, t) = 0 \}. \]

The equation that governs the evolution of the level set function \( \phi \) is found by differentiating \( \phi|\gamma(s,t) = 0 \) with respect to \( t \). Utilising the fact that the unit normal vector of contour levels of \( \phi \) is \( n = \nabla \phi/|\nabla \phi| \) and that \( \tau \cdot n = v \), one gets [7, 30]

\[ \phi_t + V|\nabla \phi| = 0, \]

where \( V \) represents the normal velocities of all the contour lines of \( \phi \), and must coincide with the normal velocity \( v \) at the interface. In many applications of the level set method, the normal velocity of the interface is known algebraically, such as in mean curvature flow. This velocity is extrapolated in a neighbourhood of the interface to allow Eq. (5) to be solved in the Cartesian space \( r \) using regular PDE techniques [7, 30].

In our situation, the normal velocity is solution of a differential equation, Eq. (3), which represents dynamic processes confined to the interface only. Now that the interface is described implicitly, an alternative description of the normal velocity (or cell surface density) that does not refer to the explicit parameter \( s \), is also required. Performing similarly to the derivation of the level set equation (5), we seek a scalar
field $V(r, t)$ that coincides with $v(s, t)$ at any point $\gamma(s, t)$ of the interface. Writing

$$V(\gamma(s, t)) = v(s, t) \quad (6)$$

and differentiating with respect to $t$ gives, after using Eqs (2), (3), and (6),

$$V_t + V n \cdot \nabla V = -(d - 1) \kappa V^2 + D \nabla^2 V - AV, \quad (7)$$

where $\nabla^2 V = \nabla \cdot \nabla V$ is the Laplace-Beltrami operator, and $d$ is the space dimension ($d = 2$ in Eq. (3)). The unit normal $n$ and mean curvature $\kappa$ (in $d$ spatial dimensions) can be extended to a neighbourhood of the interface by [7]

$$n = \frac{\nabla \phi}{\|\nabla \phi\|}, \quad \kappa = \frac{1}{\|\nabla \phi\|} \nabla \cdot n, \quad (8)$$

where the sign of $\kappa$ is consistent with our convention provided that $\phi < 0$ inside the tissue and $\phi > 0$ outside the tissue. The Laplace-Beltrami operator can also be extended to a neighbourhood of the interface. The surface gradient $\nabla S V$ can be obtained as the orthogonal projection of $\nabla V$ onto the surface, i.e.

$$\nabla S V = (I - nn^\top)\nabla V, \quad (9)$$

and the surface divergence $\nabla S \cdot F$ as the trace of the Jacobian matrix $\nabla F$ restricted to the tangent plane, or equivalently, as the trace minus the normal component [39]:

$$\nabla S \cdot F = \text{Tr} S(\nabla F) - n^\top \nabla F n = \nabla \cdot F - n^\top \nabla F n. \quad (10)$$

In two-dimensional space ($d = 2$), these definitions are consistent with the representation $\nabla \phi = \tau \frac{\partial \phi}{\partial \tau}$, where $\frac{\partial \phi}{\partial \tau} = \tau \cdot \nabla \phi$ [40], as expected. With these extensions of the surface gradient and surface divergence away from the interface, the Laplace-Beltrami operator can be calculated as [41]

$$\nabla^2 S V = \nabla^2 V - (d - 1) \kappa n \cdot \nabla V - n^\top H(V)n, \quad (10)$$

where $H(V) = \nabla \nabla V$ is the Hessian matrix of $V$.

Equations (5) and (7) form a system of two nonlinear PDEs that describe implicitly both the position of the interface, and the value of a surface-bound quantity, equivalent in this case to the normal velocity. The zero contour of $\phi$ provides the set of all points belonging to the interface $S(t)$. Evaluating $V$ at these points then provides the normal velocity of the interface, see Fig. 1.

While the derivation proposed for Eqs (5) and (7) is based on an explicit parameterisation of the interface in two-dimensional space ($d = 2$), the level set equation (5) has the same form in higher dimensions [7], and Eq. (7) matches the evolution equation of a surfactant $\Gamma$ on a moving boundary in two or three dimensions ($d = 2, 3$) [42, 41, 43]. Equations (5) and (7) thus generalise the hyperbolic curvature flow model of tissue growth of Ref. [5] to three-dimensional space. These equations are also manifestly covariant with respect to changes of reference frames. Compared to the passive evolution of surfactants on moving boundaries, here the surfactant $\Gamma$ corresponds to the normal velocity of the interface, i.e., $\Gamma = V$, so that the evolution of the ‘surfactant’ influences the evolution of the interface. This results in a strongly coupled system which reflects the hyperbolic character of the flow. Coupling occurs via $V$ in Eq. (5), and via $n$ and $\kappa$ (expressed in terms of $\phi$) in Eq. (7).

Equation (7) can be viewed as defining the velocity field away from the interface by anticipating interface velocity at future locations of the interface, based on the crowding or spreading of cells induced by the current curvature. In contrast, orthogonal velocity extrapolations define the velocity field $V$ away from the interface such that

$$\nabla V \cdot \nabla \phi = 0 \quad (11)$$

in a neighbourhood of the interface. Such extrapolations ensure that the level set function remains a signed distance function with $|\nabla \phi| = 1$ at all times [7].

3 Numerical methods

We investigate several possible strategies to solve Eqs (5) and (7) numerically, drawing on existing numerical methods developed for the level-set method and for PDEs on moving boundaries [7, 30, 44]. The different strategies we devise differ by (i) whether or not the level set function $\phi$ is re-initialised as a signed distance function; and (ii) whether or not the velocity field $V$ is re-initialised by the orthogonal extrapolation (11) after determining its value at the interface using Eq. (7):

Method 1 No re-initialisation of $\phi$ or of $V$;

Method 2 Re-initialisation of $\phi$ as a signed distance function; no re-initialisation of $V$;

Method 3 Re-initialisation of $\phi$ as a signed distance function; re-initialisation of $V$ by orthogonal extrapolation.

In standard situations where the velocity field is known algebraically, the level set method is known to be more accurate when the level set function is re-initialised as a signed distance function. It is also known that maintaining the signed distance property of $\phi$ can be achieved by extrapolating the velocity field in the orthogonal direction [7, 30]. On the other hand, the velocity field determined by the differential equation (7) anticipates values at future locations of the interface by accounting for the curvature-induced acceleration or deceleration of the interface. Methods 1–3 therefore explore a trade-off between using a possibly more accurate determination of velocity (no re-initialisation of $V$, Methods 1,2), and using a signed distance function for the level set function (re-initialisation of $\phi$, Methods 2,3). Methods 1 and 3 are consistent, in the sense that all the contour levels of $\phi$ are evolved by the velocity
field $V$. Method 2 is not consistent in this sense, because while all the contour levels of $\phi$ are initially evolved by the solution $V$ to Eq. (7), these contour levels are subsequently reorganised to re-initialise $\phi$ as a distance function. However, Method 2 may potentially combine the advantages of dealing with a signed distance function for $\phi$, and anticipating future values of $V$ away from the current interface.

The general solution algorithm we use for solving jointly Eqs (5) and (7) is based on operator splitting and discrete time stepping, and is summarised as follows:

**Step 1 Initialisation.** $\phi$ is set as a signed distance function $\phi^0$ to the initial interface $S(0)$, and $V$ is initialised to be a uniform constant $v_0$ along the interface. In Methods 1 and 2, the velocity field $V$ is extended away from the interface by solving Eq. (7) with $\phi^0$ fixed until convergence (see Step 3). In Method 3, the orthogonal extrapolation of the initial interface velocity is achieved by simply setting $V$ to $v_0$ in the whole computational domain.

**Step 2 Level-set function update.** The level set function at time step $n$, $\phi^n$, is evolved using explicit stepping in time, leading first to a temporary update $\phi^{n+1/2}$. In general, $\phi^{n+1/2}$ is no longer a signed distance function. Re-initialisation of $\phi^{n+1/2}$ to a signed distance function is performed in Methods 2 and 3. This leads to the full time step update $\phi^{n+1}$.

**Step 3 Velocity field update.** The velocity field at time step $n$, $V^n$, is evolved by solving Eq. (7) using a semi-implicit time stepping scheme, leading first to a temporary update $V^{n+1/2}$. In Method 3, $V^{n+1/2}$ is re-initialised by extrapolating its value at the interface $\phi^{n+1} = 0$ in the orthogonal direction. This leads to the full time step update $V^{n+1}$.

The zero level set $\phi^{n+1} = 0$ provides the new location of the interface $S^{n+1}$, and the new interface velocity is provided by evaluating the field $V^{n+1}$ at this location. Steps 2 and 3 are repeated iteratively to evolve the solutions $\phi$ and $V$ in time.

We now describe the numerical discretisation algorithms involved in these steps in more detail. These algorithms are based on Ref. [45] with some modifications made to account for the discretisation of the Laplace–Beltrami operator [41]. We restrict the formulas to two dimensions for simplicity.

**Discretisation of gradients.** Equations (5) and Eq. (7) involve the spatial gradient operator $\nabla$, which we discretise using upwind based on the velocities $V n_1$ along $x$ and $V n_2$ along $y$, where $n_1$ and $n_2$ are the components of the unit normal $n = (n_1, n_2)$ [7, 30]. I.e., $\nabla \phi = (\phi_x, \phi_y)$, with

$$\phi_x = \begin{cases} \phi_x^-, & \text{if } V n_1 > 0, \\ \phi_x^+, & \text{if } V n_1 < 0. \end{cases}$$

where $\phi_x^-$, $\phi_x^+$, $\phi_y^-$, and $\phi_y^+$ are backward (−) and forward (+) high-resolution Hamilton–Jacobi weighted essentially non-oscillatory (HJ-WENO) discretisations of the partial derivatives (and likewise for $\nabla V$) [46, 30]. These discretisations are fifth order accurate in smooth regions of $\phi$ and $V$ but revert to lower order when interpolating across singularities, which occur for example after the emergence of cusps in the interface [5]. The term $V|\nabla \phi|$ in Eq. (5) involves the norm of the gradient, and is discretised using Godunov’s method with HJ-WENO discretisations [44, 30].

**Normal vector and curvature.** At cusps of $\phi$, the unit normal vector and curvature in Eq. (8) are ill-defined. To alleviate the problem of the discontinuity of $n$ for the numerical scheme, we follow Ref. [7] and define the unit normal vector $n = (n_1, n_2)$ by normalising the average of the four limiting normal vectors that can be calculated by the HJ-WENO backward and forward discretisations:

$$n_{1,2,3,4} = \frac{1}{\sqrt{(\phi_x^+)^2 + (\phi_y^+)^2}}$$

In contrast, we use second order central finite difference for $\phi_x$, $\phi_y$, $\phi_{xx}$, $\phi_{yy}$, and $\phi_{xy}$ in the numerical evaluation of curvature in the formula [7]

$$\kappa = \text{cl}\left( \frac{1}{d-1} \frac{\phi_{yy}^2 \phi_{xx} - 2\phi_x \phi_y \phi_{xy} + \phi_x^2 \phi_{yy}}{(\phi_x^2 + \phi_y^2)^{3/2}} \right),$$

where $\text{cl}(\xi) = \max(\kappa_{\min}, \min(\xi, \kappa_{\max}))$ is a clamping function that enforces the computed signed curvature $\kappa$ to remain between the minimum value $\kappa_{\min} = -1/\Delta x$ and the maximum value $\kappa_{\max} = 1/\Delta x$ for a spatial discretisation step $\Delta x$ [30].

**Level-set function time stepping.** We solve the level-set equation (5) numerically with a simple first-order forward Euler discretisation in time for convenience. Level set methods are known to be more sensitive to spatial accuracy than temporal accuracy [30]. We have found that using a third order total variation diminishing Runge–Kutta method [47] adds significantly more computation time and complexity without changing the results significantly. Our aim is to compare Methods 1–3 irrespective of the time discretisation scheme, so that below we only report results from the simpler first-order Euler discretisation. With this explicit time stepping scheme, the update from $\phi^n$ to $\phi^{n+1/2}$ is given by

$$\phi^{n+1/2} = \phi^n - \Delta t V^n |\nabla \phi^n|,$$

with current values $n^n$ and $V^n$ of the unit normal and velocity field, and a time increment $\Delta t$ [7, 30].

**Level-set function re-initialisation.** The level-set function update $\phi^{n+1/2}$ may no longer represent the signed distance function to the interface, even though the zero contour $\phi^{n+1/2} = 0$ represents the new location of the interface. In Methods 2 and 3, the level-set function $\phi^{n+1/2}$ is re-initialised to a signed distance function $\phi^{n+1}$ by iterating

$$\psi^{n+1} = \psi^n - \Delta t S(\psi^n) |\nabla \psi^n| - 1$$

for $\nu = 0, 1, \ldots$ to steady state $\psi^{\infty} = \phi^{n+1}$, starting from the initial condition $\psi^0 = \phi^{n+1/2}$, where

$$S(\psi) = \frac{\psi}{\sqrt{\psi^2 + |\nabla \psi|^2} (\Delta x)^2}$$

is a smoothed sign function [44, 45]. This iterative approach corresponds to finding the steady state of $\psi_z = -S(\psi)|\nabla \psi| - \Delta t S(\psi)|\nabla \psi|^2$. 

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1) with respect to the virtual time $\tau$, which occurs when $\psi$ is a signed distance function. Because $S(0) = 0$, the zero contour is unaffected by this re-initialisation procedure. We use the stopping criterion $\frac{1}{M} \sum_{(i,j) | |\nabla \psi| | < \beta} |\nabla \psi_{ij}| - 1 \leq \epsilon_{\text{rem}} \Delta x \Delta y$, where $\beta$ is the one-sided width of the band around the interface within which we require the signed distance function to be accurate, and $M$ is the number of spatial discretisation points $(i, j)$ in the sum. In practice, we choose $\beta = 5 \Delta x$ except for Step 1 (initialisation), where we choose $\beta = 20 \Delta x$.

**Velocity field stepping.** To solve Eq. (7), we rewrite it in the form $V_t = D \nabla^2 V + \alpha$, where $\nabla^2 V$ is the isotropic diffusion contribution of $\nabla^2 V$ in Eq. (10), and

$$a = -V \cdot \nabla V - (d - 1) \kappa V^2 - D(d - 1) \kappa n \cdot \nabla V$$

$$-D \left( n_1^2 V_{xx} + 2n_1 n_2 V_{xy} + n_2^2 V_{yy} \right) - AV$$

contains all the other contributions in Eq. (7). We use a simple semi-implicit scheme in which $D \nabla^2 V$ is solved implicitly using the alternative direction implicit method (ADI) [48], and the terms in $a$ are solved explicitly using first-order forward Euler discretisation as above. The ADI is a two-step method, so that the velocity time step update $V^n \rightarrow V^{n+1/2}$ is given by solving sequentially

$$\frac{\bar{V}^{n+1/2} - V^n}{\Delta t/2} = D \left( \bar{V}^{n+1/2}_{xx} + V_{yy} \right) + a^n,$$

$$\frac{V^{n+1/2} - \bar{V}^{n+1/2}}{\Delta t/2} = D \left( \bar{V}^{n+1/2}_{xx} + V_{yy} \right) + a^n.$$

Equation (17) is the predictor step determining $\bar{V}^{n+1/2}$ implicitly, and equation (18) is the corrector step determining $V^{n+1/2}$ implicitly. The derivatives $V_{xx}, V_{xy}, V_{yy}$, and $\bar{V}_{xx}$ in Eqs (17), (18), and (16) are discretised with second-order central difference, whereas first-order derivatives in Eq. (16) use upwind HJ-WENO discretisations. Each of the predictor and corrector steps requires solving a tri-diagonal matrix system with constant matrix coefficients.

**Velocity field re-initialisation.** In Method 3, the velocity field $V^{n+1/2}$ is re-initialised to a velocity field $V^{n+1}$ by extrapolating the interface values of $V^{n+1/2}$ in the orthogonal direction, so that it satisfies Eq. (11). This is achieved by iterating

$$W^{n+1} = W^n - \Delta t S(\phi) n \cdot \nabla W^n$$

over $n = 0, 1, \ldots$ to steady state $W^{\infty} = V^{n+1}$, starting from the initial condition $W^0 = V^{n+1/2}$ [30]. In practice, it is sufficient to perform 10 iterations every $10^9$ time step for $V$ to be well extrapolated orthogonally in the band $\beta = 5 \Delta x$ each side of the interface.

**Simulation parameters.** All the simulations are performed with an initial interface velocity of $V^0 = 0.016 \text{mm/day}$ [5], except simulations of trabecular bone formation and resorption, which use $V^0 = 0.001 \text{mm/day} = 1 \mu\text{m/day}$ [49]. The computational domain is chosen to extend at least 50% more than the maximum diameter of the interface in all cardinal directions. Other simulation parameters such as space and time discretisation parameters and tolerance parameters are mentioned in the figure captions.

### 4 Results

We first investigate the numerical accuracy of Methods 1–3 in Sec. 4.1. Application examples of complex geometries, fusion and fragmentation are presented in Sec. 4.2.

**4.1 Numerical simulations using Methods 1–3**

To estimate the accuracy of the numerical methods 1–3, we compare the shape of the interface and the normal velocity at regular time intervals either with analytical expressions (rotation-symmetric solution), or with results obtained using explicit parameterisations of the interface in simple geometries [5, 6]. We also check for conservation properties of the tissue-synthesising cells. For simplicity, we assume in this section that the tissue-synthesising cells are not depleted ($A = 0$), meaning that total cell number is constant. Total cell number $N(t)$ is estimated numerically by interpolating $V$ at the interface location $\phi = 0$, and integrating the interpolation numerically. Normalising by the initial value $N^0$ gives:

$$\frac{N(t)}{N^0} = \frac{1}{V^0} \int_{S(t)} V d\mathbf{f}.$$  

We start by investigating the infilling of a circular pore $[5, 6]$, and then consider the infilling of hexagonal and square pores to see how Methods 1–3 handle cusps in the interface of increasing sharpness. We finally simulate formation and resorption of realistic trabecular bone spicules.

**Circular pore infilling.** The evolution of the radius $R(t)$ and interface velocity $V(t) = -R_x(t)$ of an infilling circular pore are given by

$$R(t) = R^0 \sqrt{1 - 2 \frac{t}{R^0}}, \quad V(t) = V^0 \frac{R^0}{R(t)}$$

where $R^0$ is the initial radius [5]. In the simulations, we choose $R^0 = 9 \text{mm}/(2\pi)$ such that the initial pore perimeter is 9 mm, and set $V^0 = 0.016 \text{mm/day}$ as in Ref. [5].

By symmetry, cell diffusivity $D$ has no effect on the evolution of the interface and cell surface density in such a situation. However, it is clear from Figure 2 that the accuracy of the numerical simulations depends on diffusivity. The simulations are less accurate at low and high diffusivities, to different degrees depending on the method. The accuracy of Method 3 appears to be less sensitive to the degree of diffusivity and matches the analytical result very well. Methods 1 and 2 compare well with the analytical result so long as the total cell number is conserved (Fig. 2, bottom row). There is a significant numerical loss of cells developing at late times in Methods 1 and 2 at high diffusivities that results in an inaccurate evolution of interface and cell density at these times.

**Hexagonal and square pore infilling.** Figures 3 and 4 show the infilling of hexagonal and square pores, respectively. The initial pore perimeter is 9 mm like in the circular pore case, so that the initial number of tissue-synthesising cells is the same. The first column of Figs 3 and 4 represents simulations obtained by the high-resolution conservative numerical
Figure 2 – Tissue deposition within a circular pore obtained analytically (first column), and simulated by Methods 1–3 (columns 2–4) with different lateral diffusivities $D$ in mm$^2$/day (rows). The tissue interface is shown at regular time intervals of 6.8 days until 34 days and coloured according to the interface velocity. The evolution of normalised cell number is shown in the last row. Simulation parameters: $\epsilon_{\text{reinit}} = 5$, $\Delta x = \Delta y = 0.0357$ mm and $\Delta t = 0.017$ days.

schemes of [5]. Like in the circular pore case, all the methods perform well at intermediate diffusivity $D = 0.01$ mm$^2$/day. At low diffusivity $D = 0.0001$ mm$^2$/day, Method 1 performs better than Methods 2 and 3, particularly in the square pore case where corners of the interface are more acute. However, at high diffusivity, Method 1 violates cell conservation significantly, and the interface and velocities obtained by Method 3 are closest to the simulations of Ref. [5].

The numerical violation of cell conservation in Methods 1–3 is more severe initially for the interfaces with more acute cusps. At high diffusivities, the angle of the cusps remains the same throughout the simulation, and this is why cell conservation is harder to achieve numerically. At low diffusivity, cusp angle is initially reduced by a factor two due to the sideways propagation of shock waves [5, 6]. Simulations with intermediate diffusivity tend to smooth the interface, which helps conserve cell numbers numerically.

Bone formation on a single trabecular spicule. Figures 2–4 show that cell conservation serves as an important indicator of accuracy of interface motion and interface velocity. In Figure 5, we therefore use this indicator to compare Methods 2 and 3 in a situation where a Monge parameterisation in polar coordinates, and its conservative discretisation, are not possible.

To represent a realistic geometric situation, we take for initial interface the surface of a single trabecular bone spicule seen in an experimental cross section [50]. We then consider the apposition of new bone layers on this surface, as would occur for example by bone mechanical adaptation [51, 52]. For these simulations, we assume $D = 0.0001$ mm$^2$/day and $A = 0$. Method 2 violates the conservation of cells significantly (Fig. 5, bottom row), greatly overestimating the amount of new bone layers produced. Similar results hold for Method 1, in which cell conservation is also violated.
Figure 3 – Tissue deposition within a hexagonal pore simulated using an explicit parameterisation (first column) [5], and using Methods 1–3 (columns 2–4) with different lateral diffusivities \( D \) in mm\(^2\)/day (rows). The tissue interface is shown at regular time intervals of 5.2 days until 26 days and coloured according to the interface velocity. The evolution of normalised cell number is shown in the last row. Simulation parameters: \( \varepsilon_{\text{reinit}} = 5 \), \( \Delta x = \Delta y = 0.0357 \) mm and \( \Delta t = 0.013 \) days. Explicit parameterisation results are obtained using \( \Delta \theta = 0.0349 \) and \( \Delta t = 0.0163 \) days [5].

significantly (not shown). In contrast, Method 3 maintains cell numbers within 98.1% of their initial value.

4.2 Application to complex geometries, fusion and fragmentation

The comparison of Methods 1–3 in Section 4.1 reveals that numerical conservation can be difficult to achieve, particularly as cusps in the interface emerge. None of Methods 1–3 is explicitly conservative, so that tracking conservation is an important indicator of accuracy. Most often, curvature flow models smooth the interface, but the hyperbolic curvature flow considered here only does so provided lateral cell diffusion is balanced by curvature-induced crowding or spreading of cells at concavities or convexities of the interface, and this depends on the initial interface and diffusivity. We find that Method 3 results in the least amount of non-conservation in general, although Method 1 may perform better at low diffusivities.

In the remainder of the paper, we use Method 3 to illustrate the capabilities of the level-set formulation of the hyperbolic curvature flow model of tissue growth. We use this method to model complex evolving geometries, including fusion and fragmentation of tissues.

Fusion of two circular interfaces and time irreversibility.

To model a situation where there is a topological change in the interface, we consider the fusion of two expanding circles, representing for instance the fusion of two trabecular bone struts seen in cross section. As in Section 4.1, we take the total perimeter to be 9 mm, and \( A = 0 \). Each circle has radius \( 9/(4\pi) \) mm and the centres are 1.9 mm apart. The time point at which the two interfaces merge is \( t_m \approx 17 \) days from
Figure 4 – Tissue deposition within a square pore simulated using an explicit parameterisation (first column) [5], and using Methods 1–3 (columns 2–4) with different lateral diffusivities $D$ in mm$^2$/day (rows). The tissue interface is shown at regular time intervals of 5.2 days until 26 days and coloured according to the interface velocity. The evolution of normalised cell number is shown in the last row. Simulation parameters: $\epsilon_{\text{reinit}} = 5$, $\Delta x = 0.0357$ mm and $\Delta t = 0.013$ days. Explicit parameterisation results are obtained using $\Delta \theta = 0.0196$ and $\Delta t = 0.0163$ days [5].

Eq. (21). Figure 6 shows the evolution of the interface and velocity at different diffusivities. We perform the simulation first for outward tissue deposition during 34 days (Fig. 6, left column), then reverse the sign of the velocity from this state and continue the simulation for an additional 49 days (Fig. 6, right column). The reversal of velocity at $t = 39$ days may be interpreted as tissue resorption. Clearly, this reversal does not lead to the same tissue interfaces as during outward motion, i.e., tissue resorption is not simply tissue deposition reversed in time. The reason for this time irreversibility is due to the loss of information that occurs when characteristics collide into shock waves. The weak solutions selected by the level-set method are viscous solutions that satisfy an entropic condition which breaks time-reversal symmetry [7, 53, 54].

The evolution of normalised cell number in these simulations is shown in Fig S1 of the supplementary material. Cell number is reasonably well conserved overall, with some fluctuations ($D = 0.0001$ mm/day) or loss ($D = 0.01$ mm/day, $D = 1$ mm/day) around the time the two interfaces merge, at which extremely acute corners develop.

Curvature-controlled tissue growth in bioscaffold. We now consider an application of the model to the production of neotissue in bioscaffolds. The model is adapted slightly to prevent tissue formation where the tissue substrate is convex, as suggested experimentally [2–4, 55]. To this effect, we modify the evolution equation of the interface, Eq. (5), by multiplying the velocity field $V$ with a curvature-dependent Heaviside function:

$$\phi_t + H(\kappa) V |\nabla \phi| = 0,$$  \hspace{1cm} (22)
Figure 5 – Bone deposition around a single trabecular spicule obtained using Method 2 (left column) and Method 3 (right column). The initial shape of trabecular spicule is extracted from [50, Fig. 2]. The interface is shown at regular time intervals of 0.24 days and coloured according to the interface velocity (top row). The evolution of normalised cell number is shown in the bottom row. Simulation parameters: \( D = 0.0001 \), \( \varepsilon_{\text{reinit}} = 1000 \), \( \Delta x = \Delta y = 0.0075 \), \( \Delta t = 0.00017 \).

Figure 6 – Evolution of two circular interfaces during outward tissue deposition (left column), and subsequent inward tissue resorption (right column) with different diffusivities. The initial state for outward motion is two separate circles, which start to merge at \( t = 17 \) day. The initial state for inward motion is the final state of outward tissue deposition. Arrows indicate time evolution. Simulation parameters: Method 3, \( A = 0 \), \( \varepsilon_{\text{reinit}} = 10 \); Outwards simulation: \( \Delta x = \Delta y = 0.0278 \), \( \Delta t = 0.0085 \); Inwards simulation: \( \Delta x = \Delta y = 0.0312 \), \( \Delta t = 0.0123 \).

Figure 7 represents the simultaneous infilling of four disconnected pores represented by a single level-set function, with a diffusivity \( D = 0.0001 \) mm\(^2\)/day and a cell depletion rate \( A = 0.1 \) day\(^{-1}\). The decrease in cell number with time (Supplementary material, Fig S2) matches the theoretical decrease due to cell depletion.

Typically, the porous space of bioscaffolds is extremely complex and would be hard to represent using explicit parameterisations. As illustrated here, our model enables the consideration of cell-specific behaviour, such as curvature-dependent secretory rate (implemented via the function \( H(\kappa) \) above), and cell depletion rate \( A \). Depletion of active cells is important to explain tissue-deposition slowdown observed experimentally in vitro [5] and in-vivo [6]. This depletion, and more generally, the inclusion of cell behaviours is not captured by mean curvature flow models of tissue growth [3, 4, 22–24].

Fusion and fragmentation of trabecular bone spicules. Figure 8 shows simulations of bone apposition (top row) and bone resorption (bottom row) from an initial bone interface extracted from a histological section of trabecular bone from Ref. [50]. Bone apposition leads to fusion of initially distinct trabecular spicules, while bone resorption leads to their fragmentation, as would occur for instance during osteoporotic or age-related bone loss [26–28]. We note that during bone resorption, some trabecular spicules disappear, leading to an inevitable loss of cells that is not entirely due to numerical inaccuracies, see Fig S3 of the supplementary material.

5 Conclusions

We have developed a level-set based method for solving curvature flows of the hyperbolic type, in which interface velocity is determined dynamically by surface-bound processes. This method requires the introduction of an additional Eulerian field to the level set function, which represents the anticipated value of interface velocity at future locations of the interface. The level set function and velocity field are strongly coupled with each other. This coupling is responsible for the rich set of interface behaviour of hyperbolic curvature flows, which includes oscillatory motion, sideways shock propagation, and interface smoothing. Comparison with simulations that use explicit parameterisations shows that these different behaviours are well captured by the level set method proposed.
Figure 8 - Time snapshots of the concurrent evolution of several trabecular spicules from an experimental image [50] under bone resorption (top) and bone resorption (bottom). Simulation parameters: Method 3, \( \nu^0 = 10^{-3}\text{mm/day}, A = 0, D = 0.0001\text{mm/day}, \varepsilon_{\text{reinit}} = 600, \Delta x = \Delta y = 0.0086, \Delta t = 0.0023. \)

Importantly, we find that a good indicator of numerical accuracy of the method is provided by tracking the surface integral of the velocity field along the interface with time. In the hyperbolic curvature flow model of tissue growth, this surface integral corresponds to the total number of tissue-synthesising cells. Generally, numerical nonconservation is increased at developing cusps in the interface. We have proposed three main strategies to solve the coupled equations governing the level set function and velocity field. We find that re-initialisation of the level-set function to a signed distance function, and re-initialisation of the velocity field by orthogonal extrapolation help minimise nonconservation in most cases, despite the fact that orthogonal extrapolation erases anticipated values of velocity. At very low diffusivities, however, simulations were found to be more accurate without these re-initialisations.

The main advantage of this level-set method for hyperbolic curvature flows is to allow simulations of complex evolving topological situations, that include fragmentation of the interface, and fusion of initially distinct regions of the interface. We have applied the method to the simulation of biological tissue growth to several such complex geometric situations, greatly extending the applicability of such flows to real situations.

Finally, the numerical algorithms we have used may be improved, particularly at developing cusps and where interface regions merge, by using more advanced estimations of unit normals and curvature [56–58]. Particle level set methods [59] and conservative level set methods [60, 61] have been developed to help preserve mass in simulations of multi-phase fluid flows. While these techniques help preserve volumetric fluid mass, it is possible that similar techniques could also help preserve interfacial mass.

Declarations of interest

None

Author contributions

MAA and PRB conceived and designed the study; MAA performed the numerical simulations; MAA and PRB analysed the data; MAA drafted the article; and both authors edited the article and gave final approval for publication.

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References

[1] C. M. Nelson, R. P. Jean, J. L. Tan, W. F. Liu, N. J. Sniadecki, A. A. Spector, C. S. Chen, and R. Langer, “Emergent patterns of growth controlled by multicellular form and mechanics,” Proceedings of the National Academy of Sciences of the United States of America, vol. 102, no. 33, pp. 11594–11599, 2005.
[2] M. Rumpler, A. Woesz, J. Dunlop, J. van Dongen, and P. Fratzl, “The effect of geometry on three-dimensional tissue growth,” Journal of the Royal Society Interface, vol. 5, pp. 1173–1180, 2008.
[3] C. M. Bidan, K. P. Kommareddy, M. Rumpler, P. Kollmannsberger, Y. J. M. Bréchet, P. Fratzl, and J. W. C. Dunlop, “How linear tension converts to curvature: geo-
metric control of bone tissue growth," *PLoS One*, vol. 7, p. e36336, 2012.

[4] C. M. Bidan, K. P. Kommareddy, M. Rumpler, P. Kollmannsberger, P. Fratzl, and J. W. C. Dunlop, “Geometry as a factor for tissue growth: Towards shape optimization of tissue engineering scaffolds,” *Advanced Healthcare Materials*, vol. 2, no. 1, pp. 186–194, 2013.

[5] M. A. Alias and P. R. Buenzli, “Modeling the effect of curvature on the collective behavior of cells growing new tissue,” *Biophysical Journal*, vol. 112, no. 1, pp. 193–204, 2017.

[6] M. Alias and P. Buenzli, “Osteoblasts infill irregular pores under curvature and porosity controls: a hypothesis-testing analysis of cell behaviours,” *Biomechanics and Modeling in Mechanobiology*, vol. 17, no. 5, pp. 1357–1371, 2018.

[7] J. A. Sethian, *Level Set Methods and Fast Marching Methods: Evolving Interfaces in Computational Geometry, Fluid Mechanics, Computer Vision, and Materials Science*. Cambridge University Press, 1999.

[8] G. Huisken, “Asymptotic behavior for singularities of the mean curvature flow,” *J. Differential Geom.*, vol. 31, no. 1, pp. 285–299, 1990.

[9] P. G. LeFloch and K. Smoczyk, “The heat equation shrinks embedded plane curves to round points,” *J. Differential Geom.*, vol. 34, no. 4, pp. 149:1–149:9, 2015.

[10] K. Dexing, L. Kefeng, and W. Zenggui, “Hyperbolic mean curvature flow: evolution of plane curves,” *Acta Mathematica Scientia*, vol. 29, no. 3, pp. 493–514, 2009.

[11] C.-L. He, D.-X. Kong, and K. Liu, “Hyperbolic mean curvature flow,” *Journal of Differential Equations*, vol. 246, no. 1, pp. 373–390, 2009.

[12] S. Ishida, M. Yamamoto, R. Ando, and T. Hachisuka, “A hyperbolic geometric flow for evolving films and foams,” *ACM Trans. Graph.*, vol. 36, no. 6, pp. 199:1–199:11, 2017.

[13] M. A. Grayson, “The heat equation shrinks embedded plane curves to round points,” *J. Differential Geom.*, vol. 26, no. 2, pp. 285–314, 1987.

[14] F. Da, C. Batty, C. Wojtan, and E. Grinspun, “Double bubbles sans toil and trouble: Discrete circulation-preserving vortex sheets for soap films and foams,” *ACM Trans. Graph.*, vol. 34, no. 4, pp. 149:1–149:9, 2015.

[15] R. Đurićković, “Animation of soap bubble dynamics, cluster formation and collision,” *Computer Graphics Forum*, vol. 20, no. 3, pp. 67–76.

[16] B. Zhu, E. Quigley, M. Cong, J. Solomon, and R. Fedkiw, “Codimensional surface tension flow on simplicial complexes,” *ACM Trans. Graph.*, vol. 33, no. 4, pp. 111:1–111:11, 2014.

[17] P. Macklin and J. Lowengrub, “An improved geometry-aware curvature discretization for level set methods: Application to tumor growth,” *Journal of Computational Physics*, vol. 215, no. 2, pp. 392 – 401, 2006.

[18] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y.-L. Chuang, X. Li, P. Macklin, S. M. Wise, and V. Cristini, “Nonlinear modelling of cancer: bridging the gap between cells and tumour,” *Nonlinearity*, vol. 23, pp. R1–R91, 2010.

[19] S. Wise, J. Lowengrub, H. Frieboes, and V. Cristini, “Three-dimensional multispecies nonlinear tumor growth–I: Model and numerical method,” *Journal of Theoretical Biology*, vol. 253, no. 3, pp. 524 – 543, 2008.

[20] M. Poujade, E. Grasland-Mongrain, A. Hertzog, J. Jouanneau, P. Chavrier, B. Ladoux, A. Buguin, and P. Silberzan, “Collective migration of an epithelial monolayer in response to a model wound,” *Proc Nat Acad Sci*, vol. 104, pp. 15988–15993, 2007.

[21] F. Vermolen, M. W. G. van Rossum, E. J. Perez, and J. Adam, *Modeling of Self Healing of Skin Tissue*, pp. 337–363. Dordrecht: Springer Netherlands, 2007.

[22] Y. Guyot, I. Papantoniou, Y. Chai, S. Van Baal, J. Schrooten, and L. Geris, “A computational model for cell/ECM growth on 3D surfaces using the level set method: a bone tissue engineering case study,” *Biomechanics and Modeling in Mechanobiology*, vol. 13, no. 6, pp. 1361–1371, 2014.

[23] Y. Guyot, F. Luyten, J. Schrooten, I. Papantoniou, and L. Geris, “A three-dimensional computational fluid dynamics model of shear stress distribution during neotissue growth in a perfusion bioreactor,” *Biotechnology and Bioengineering*, vol. 112, no. 12, pp. 2591–2600, 2015.

[24] Y. Guyot, I. Papantoniou, F. P. Luyten, and L. Geris, “Coupling curvature-dependent and shear stress-stimulated neotissue growth in dynamic bioreactor cultures: a 3D computational model of a complete scaffold,” *Biomechanics and Modeling in Mechanobiology*, pp. 1–12, 2016.

[25] M. Paris, A. Götz, I. Hettrich, C. M. Bidan, J. W. Dunlop, H. Razi, I. Zizak, D. W. Hutmacher, P. Fratzl, G. N. Duda, W. Wagermaier, and A. Cipirita, “Scaffold curvature-mediated novel biomineralization process originates a continuous soft tissue-to-bone interface,” *Acta Biomaterialia*, vol. 60, pp. 64 – 80, 2017.

[26] I. S. Maggiano, C. M. Maggiano, J. G. Clement, C. D. L. Thomas, Y. Carter, and D. M. L. Cooper, “Three-dimensional reconstruction of Haversian systems in human cortical bone using synchrotron radiation-based micro-CT: morphology and quantification of branching and transverse connections across age,” *Journal of Anatomy*, vol. 228, no. 5, pp. 719–732, 2016.

[27] K. L. Bell, N. Loveridge, J. Reeve, C. D. Thomas, S. A. Feik, and J. G. Clement, “Super-osteons (remodeling clusters) in the cortex of the femoral shaft: Influence of age and gender,” *The Anatomical Record*, vol. 264, no. 4, pp. 378–386, 2001.

[28] J. H. Kinney and A. J. C. Ladd, “The relationship between three-dimensional connectivity and the elastic properties of trabecular bone,” *Journal of Bone and Mineral Research*, vol. 13, no. 5, pp. 839–845, 1998.

[29] G. Jordan, N. Loveridge, K. Bell, J. Power, N. Rushton, and J. Reeve, “Spatial clustering of remodeling osteons in the femoral neck cortex: a cause of weakness in hip fracture?,” *Bone*, vol. 26, no. 3, pp. 305 – 313, 2000.

[30] S. Osher and R. Fedkiw, *Level Set Methods and Dynamic Implicit Surfaces*. New York: Springer New York, 1 ed., 2003.

[31] F. Gibou, R. Fedkiw, and S. Osher, “A review of level-set methods and some recent applications,” *Journal of Computational Physics*, vol. 353, pp. 82 – 109, 2018.
A level set method for hyperbolic curvature flows: Application to curvature-controlled tissue growth – Supplementary material

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1 Fusion of two circular interfaces and time irreversibility

Figure S1 – Evolution of normalised cell number for the outward motion (left) followed by inward motion of the simulation of two expanding circles in Figure 6. The vertical dashed line corresponds to the time at which the two circles merge.

2 Curvature-controlled tissue growth in bioscaffold

Figure S2 – Evolution of normalised cell number during simultaneous infilling of four disconnected pores in a bioscaffold in Figure 7. The analytical normalised cell number is \( N(t)/N^0 = e^{-At} \).

3 Fusion and fragmentation of trabecular bone spicules

Figure S3 – Evolution of normalised cell number for simulations of bone apposition (outward motion – red) and bone resorption (inward motion – blue) that causes fusion and fragmentation of the bone in Figure 8.