Article

From Discrete to Continuum Models of Three-Dimensional Deformations in Epithelial Sheets

Nebojsa Murisic,[1] Vincent Hakim,[2] Ioannis G. Kevrekidis,[3] Stanislav Y. Shvartsman,[1] and Basile Audoly[4,*]
[1]Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey; [2]CNRS & Laboratoire de Physique Statistique, Ecole Normale Supérieure, Paris, France; [3]Chemical and Biological Engineering, Princeton University, Princeton, New Jersey; and [4]Sorbonne Universités, UPMC Univ Paris 06, CNRS, UMR 7190 Institut Jean Le Rond d'Alembert, Paris, France

ABSTRACT Epithelial tissue, in which cells adhere tightly to each other and to the underlying substrate, is one of the four major tissue types in adult organisms. In embryos, epithelial sheets serve as versatile substrates during the formation of developing organs. Some aspects of epithelial morphogenesis can be adequately described using vertex models, in which the two-dimensional arrangement of epithelial cells is approximated by a polygonal lattice with an energy that has contributions reflecting the properties of individual cells and their interactions. Previous studies with such models have largely focused on dynamics confined to two spatial dimensions and analyzed them numerically. We show how these models can be extended to account for three-dimensional deformations and studied analytically. Starting from the extended model, we derive a continuum plate description of cell sheets, in which the effective tissue properties, such as bending rigidity, are related explicitly to the parameters of the vertex model. To derive the continuum plate model, we duly take into account a microscopic shift between the two sublattices of the hexagonal network, which has been ignored in previous work. As an application of the continuum model, we analyze tissue buckling by a line tension applied along a circular contour, a simplified set-up relevant to several situations in the developmental contexts. The buckling thresholds predicted by the continuum description are in good agreement with the results of stability calculations based on the vertex model. Our results establish a direct connection between discrete and continuum descriptions of cell sheets and can be used to probe a wide range of morphogenetic processes in epithelial tissues.

INTRODUCTION

The emergence of epithelial tissues, in which polarized cells adhering to each other and to the extracellular matrix are arranged in continuous sheets, was one of the key steps in the evolution of multicellular animals. In adult organisms, epithelia line the internal surfaces of organs, maintaining their integrity and mediating interactions between different compartments. During embryonic development, epithelia serve as the starting point in the morphogenesis of tissues and organs (1). Epithelial morphogenesis can be accompanied by changes in cell numbers, because of cell division and death. At the same time, early steps in a number of important and well-studied morphogenetic events, including early stages of gastrulation (2), happen at constant cell numbers and do not involve changes in cell connectivity. This is the class of processes considered in this article, in which we aim to develop a coarse-grained description of three-dimensional (3D) tissue deformations, starting from cell-level description of an epithelium.

Recent studies of epithelial morphogenesis (3–7) provide highly resolved kinematic descriptions that set the stage for the development and analysis of mathematical models that can explain and predict the observed cell and tissue deformations. Some of the simplest proposed mathematical descriptions are the so-called vertex models, see (3,8–14), in which the degrees of freedom are the coordinates of the vertices of cells, modeled as planar polygons. The energy of such a model epithelium is evaluated from contributions of terms that account for properties of individual cells, like the preference for a target area value and their tendency to minimize perimeter length because of cortical tension. It also includes cell pairwise interactions, modeled as terms depending on the length of cell-cell edges, as in e.g., (3). Of course, tissue morphogenesis is quite varied, and a number of phenomena, such as cell motion, have been described by models different from vertex models, see (15) for a review. Vertex models have been used to explain the statistics of cell shapes and compartment boundaries in developing epithelia and provide a clear connection between experimental data and simple physical theories (3,12,16,17). In this study, we use the existing models as a starting point for describing out-of-plane deformations of epithelial sheets.

Our results can be summarized as follows. First, we show that a 3D extension of vertex models requires some care in the definition of cell area, which is straightforward when cells are planar, but must be redefined when vertices can move in three dimensions. To properly describe 3D deformations, we also introduce a cell-based description of bending stresses. Second, we use a homogenization approach to derive an effective continuum description of an epithelium, valid on length

Submitted November 14, 2014, and accepted for publication May 13, 2015.
*Correspondence: audoly@lmm.jussieu.fr
Editor: Ruth Baker.

0006-3495/15/07/0154/10 $2.00
http://dx.doi.org/10.1016/j.bpj.2015.05.019

scales larger than a single cell. We resolve the difficulties pointed out in previous studies by properly taking into account the non-Bravais character of the hexagonal lattice. Motivated by a number of experimental studies, e.g., (17), we use the homogenized model to describe epithelial buckling induced by heterogeneities of cell properties. Linear stability analysis of the homogenized problem is in quantitative agreement with the results of direct bifurcation analyses of the extended vertex model that resolves individual cells, suggesting that our approach can describe a wide range of phenomena in developing epithelia.

MATERIALS AND METHODS

The nonplanar vertex model

Originally developed to study foams (18), vertex-based geometrical models have been employed to describe cell sheets since the early work of Honda (8,9). In this approach (3,4,11–13,16), interfaces between cells are defined as straight segments and each cell assumes a polygonal shape. Cell dynamics is described in a simplified way in terms of the motion of the polygon vertices.

Based on these previous works, we introduce a vertex model to describe nonplanar configurations of epithelial cell sheets. We consider a smooth surface endowed with a mesh, as described schematically in Fig. 1. More precisely, the lattice is specified by the positions $\mathbf{x}_v$ of its vertices, where v is a vertex index. The length L_e of an edge labeled by e is $L_e = \left|\mathbf{x}_{v_2(e)} - \mathbf{x}_{v_1(e)}\right|$, where $v_1(e)$ and $v_2(e)$ denote the indices of the vertices at the endpoints of the edge e. The perimeter P_f of a face f is simply the sum of the lengths of its edges e, $P_f = \sum_{e\in f} L_e$.

Next, the energy of a nonplanar configuration of cells is defined by the following:

$$\mathcal{E}_{\mathrm{vm}} = \frac{1}{2}\sum_f \left(A_f - 1\right)^2 + G\sum_e L_e + \frac{H}{2}\sum_f P_f^2 + B\sum_{e'}\left(1 - \mathbf{N}_{f_1(e')}\cdot\mathbf{N}_{f_2(e')}\right). \quad (1)$$

The first and third term run over all faces f, the second term over all edges e, and the last term runs over interior edges e', i.e., edges belonging to two adjacent faces $f_1(e')$ and $f_2(e')$. The quantities G, H, and B are elasticity parameters. The first term (area elasticity) penalizes any deviation from the natural area $A^0 = 1$. For simplicity, we work in a set of units such that both the target area A^0 and the corresponding modulus have the value 1. The second term captures the adhesion energy between cells, when $G<0$. The coefficient G has units of energy per unit length, or force. The third term represents cortical tension (perimeter elasticity). The last term is a bending term to which we will return below. A simpler description is often used with $H = 0$ and $G>0$, which then represents an effective line tension. In the following, we provide analytical results for the general case $G\neq 0, H\neq 0$ and focus on the case $H = 0$ in our simulations.

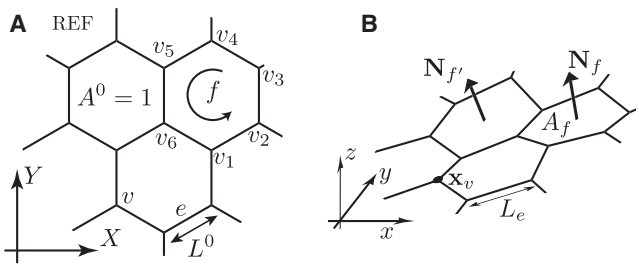

FIGURE 1 The 3D vertex model. (*A*) Schematic drawing of the hexagonal vertex model, showing the vertices, edges, and cell faces in reference configuration. (*B*) Deformation of the reference regular hexagonal configuration into a nonplanar configuration, and unit outward normal vectors.

For planar configurations of the vertices, the bending term vanishes and the energy defined by Eq. 1 coincides with the classical, planar vertex model (3,13). For nonplanar configurations, the area A_f and the unit normal $\mathbf{N}_f$ to a face f appearing in Eq. 1 can be defined in different ways (19) that are all equivalent in the continuous limit. We use the following definitions, which differ slightly from those used in (17) and are more convenient. Let n be the number of vertices of the face f ($n = 6$ for a hexagonal mesh), and $(v_1(f), \ldots, v_n(f))$ be the list of vertices ordered in the counter-clockwise direction, as in Fig. 1. We first define the vector area $\mathbf{A}_f$ of the face f by

$$\mathbf{A}_f = \frac{1}{2}\left(\mathbf{x}_{v_1(f)} \times \mathbf{x}_{v_2(f)} + \mathbf{x}_{v_2(f)} \times \mathbf{x}_{v_3(f)} + \cdots + \mathbf{x}_{v_n(f)} \times \mathbf{x}_{v_1(f)}\right), \quad (2)$$

this quantity being invariant under rigid-body translations of the lattice. Next, we define the scalar area A_f and the unit normal $\mathbf{N}_f$ by

$$A_f = \left|\mathbf{A}_f\right|, \qquad \mathbf{N}_f = \frac{\mathbf{A}_f}{A_f}. \quad (3)$$

Observing that the flux of a constant vector field $\mathbf{u}$ through the face f is expressed as $\mathbf{A}_f\cdot\mathbf{u}$, we can interpret these definitions geometrically: $\mathbf{N}_f = \mathbf{u}$ is the unit vector producing the maximum flux across the face, and A_f is the maximal value of the flux.

Once the area of a face is defined, the energy of a nonplanar configuration of vertices can be computed. The usual first three terms on the right-hand-side of Eq. 1 penalize bending deformations only weakly, see Results. They produce a bending modulus for the epithelial sheet that is entirely determined by the two-dimensional (2D) biophysical parameters $(A^0 = 1, G, H)$ and that moreover depends on the somewhat arbitrary definition of the discrete area $\mathbf{A}_f$. Therefore, to produce a better defined model, adaptable to diverse biological contexts, we have added the last term in the right-hand-side of Eq. 1. It is a discrete bending energy: the dot product is the cosine of the angle between the normals to adjacent cells and so, for small deflections, the parenthesis grows as one half of the square of this angle. This term tends to keep normals of adjacent cells aligned, much like spins in the classical Heisenberg model of ferromagnetism (20). This bending energy has been used in previous work to model elastic shells using triangulated surfaces (21,22), and it has been shown to be equivalent to the usual bending energy in the continuous limit (23). We will show in the following that a suitable choice of B allows one to adjust the vertex model rigidity to match that of the tissue under consideration.

Contractile contour

An additional contractile contour in the epithelium is implemented in the vertex model through the additional energy term,

$$\mathcal{E}_\Gamma = \Gamma\sum_{e\in C} L_e. \quad (4)$$

The geometry of the lattice is defined by two integers P_1 and P_2 with $0<P_1<P_2$, see Fig. 2 *A*: the diameter of the contour C is $(2P_1 + 1)$ cells, and the diameter of the entire lattice is $(2P_2 + 1)$ cells. The number of cells inside the contractile contour C is $n_1 = 1 + 3P_1(P_1 + 1)$, and the total number of cells is $n_2 = 1 + 3P_2(P_2 + 1)$.