Mechanics of epithelia and morphogenesis

2018-2019 Biophysics exam – Physics of Complex Systems M2

No documents, calculators or phones allowed.

It is not birth, marriage or death which is
the most important time in your life, but gastrulation.
Lewis Wolpert, 1989

In the early stages of their development, animal embryos are composed of a fluid-filled cavity lined by a continuous single layer of epithelial cells (*i.e.*, cells that mark the interface between the organism and the outside world) with spherical or cylindrical symmetry. As the outer surface of that layer undergoes contraction driven by actin and myosin, the embryo changes shape and develops folds which later develop into the digestive system ("gastrulation") and the central nervous system ("neurulation").

In Sec. 1, we study a model for the emergence of these contractile forces at the molecular level. We discuss the consequences of this contraction for the rigidity of the epithelial tissue in Sec. 2. As this contraction is asymmetric between the inner and the outer face of the epithelium, it endows it with a spontaneous curvature, which we incorporate in a continuum description in Sec. 3. Finally, in Sec. 4 we study under what conditions this curvature can lead to the formation of a closed tube, as is the case during neurulation.

The four sections can be tackled independently. Each begins with basic questions close to the contents of the lectures. Answer them all to demonstrate your mastery of the basic course material.

1 Molecular motor model for cortical contraction

We consider the interface between a single actin filament and a myosin filament comprising many motor heads, each of which is either attached to or detached from the actin [Fig. 1(a)]. We represent the periodic structure of the actin filament by a periodic potential $V(x)$ which is ℓ-periodic and piecewise affine, yielding

$$V(x) = \begin{cases} Ux/a & \text{for } 0 \leqslant x < a \\ U(\ell - x)/(\ell - a) & \text{for } a \leqslant x < \ell \end{cases}, \tag{1}$$

as illustrated in Fig. 1(b). We study the density $\rho(x)$ of motors in this potential, which evolves according to

$$\partial_t \rho = -\partial_x J + k_{\text{on}} - k_{\text{off}} \rho, \tag{2}$$

where k_{on} and k_{off} are the motor attachment and detachment rate, which we assume are independent of x.

1.1 What is $J(x)$? Assuming the dynamics of the bound motors is a viscous, overdamped dynamics with a mobility μ, write down its expression as a function of μ and the motor diffusion coefficient D, as well as the other variables of the problem.

1.2 Write down and name the relationship that exists between μ and D at equilibrium.

1.3 In the following we neglect diffusion, and write $J = -\mu\rho\partial_x V$. This is equivalent to making a certain assumption about the temperature of the system. Formulate this assumption in words and as a mathematical relationship.

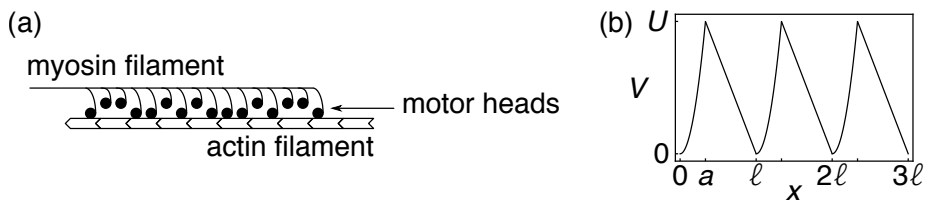

Figure 1: Molecular-scale motor model. (a) Interface between the myosin thick filament (cluster comprising many motor heads) and the actin filament. (b) Effective potential for the motor motion.

1.4 Show that for left ($x < a$) piece of the potential the stationary state of the motor distribution takes the form

$$\rho = \rho_0 - Ke^{\alpha x}, \tag{3}$$

where you will give the values of ρ_0 and α as functions of the parameters of the problem and where K is an integration constant.

1.5 What is the form of the stationary motor distribution on the right ($x > a$) part of the potential? We denote by K' the integration constant involved.

1.6 In the absence of diffusion, the motor density at the peak of the potential is zero since any motor arriving left or right of there is immediately transported downhill. Determine K and K' using this condition. Compute the resulting total flux of motors into the lowest point of the potential ($x = 0 \Leftrightarrow x = \ell$). This non-vanishing current implies an accumulation of motors in that point.

1.7 Assuming the motors at the bottom of the potential detach at a constant rate k_{off} just like the motors elsewhere, compute the number of motors accumulated at the bottom of the potential in the steady-state.

1.8 Express the force exerted by the motors on one period of the filament as a function of $\rho(x)$ and $V(x)$. Note that since the accumulated motors are at the bottom of the potential, they do not contribute to this force.

1.9 Compute this force explicitly, and simplify the expression in the strong-friction limit where motors hardly slide downhill before detaching, namely $\mu U/a^2 k_{\text{off}} \ll 1$, $\mu U/(\ell - a)^2 k_{\text{off}} \ll 1$.

1.10 In which case does the filament move to the left? To the right? Under what condition does the force vanish and why?

2 Vertex model and epithelial rigidity

A common model for epithelial tissues is to represent them as a tiling of polygonal cells in two dimensions. A simple hexagonal example is given in Fig. 2. The energy associated with each cell is

$$E_{xy} = \frac{k_A}{2}\left(A - \frac{3\sqrt{3}}{2}b^2\right)^2 + \frac{k_P}{2}(P - 6b)^2, \tag{4}$$

which has two quadratic terms describing the fact that each hexagon has a preferred area A and perimeter P. These two preferences are enforced by the constant rigidities k_A, k_P and b is a constant length. Note that there is no spring energy in the model besides E_{xy}.

2.1 Show that the ground state of this energy is a tiling of regular hexagons with sides of a length to be specified.

2.2 We now regard the vertex model as an elastic network of vertices and bonds. How many degrees of freedom does the model have per cell?

2.3 How many constraints per cell does it have? Is the network hypostatic? Isostatic? Hyperstatic? What do you expect its shear modulus to be?

2.4 The perimeter of epithelial cells is lined by actomyosin cables that exert a contractile force similar to the one computed in the last section. We represent it by defining the pseudo-energy $E'_{xy} = E_{xy} + FP$ with $F > 0$ a constant force. In the presence of that force, what is the expression of the preferred perimeter of the cell (not taking into account the area constraint)? How does this change the ground state of the system qualitatively?

2.5 For positive F, the sheet acquires a shear modulus. Why is this similar to the elasticity of rubber? Use that explanation to give the scaling of the shear modulus with the parameters of the problem.

2.6 Depending on the value of the target perimeter of the cell, the epithelial sheet may behave as a rigid elastic sheet or a two-dimensional liquid [1]. The threshold between the two behaviors is given by a critical force $F_c \neq 0$. Can you guess whether the liquid-like behavior corresponds to a small or large target perimeter? Will F_c be positive or negative?

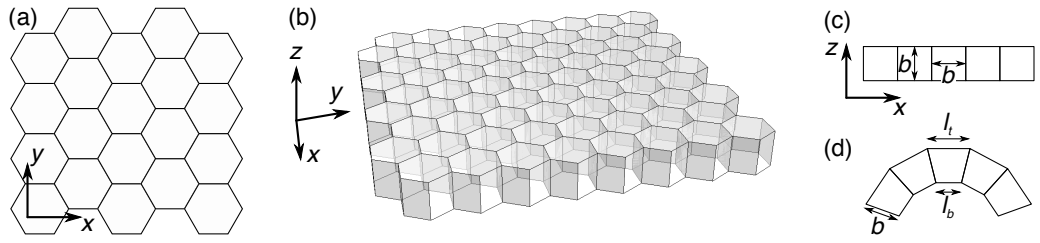

Figure 2: Cell-level epithelium models. (a) Two-dimensional hexagonal vertex model. (b) Illustration of a 3D epithelium. (c) Two-dimensional epithelium model in a plane perpendicular to the plane of the tissue. (b) Bent epithelium within that model.

3 Bending modulus and spontaneous curvature of an epithelium

In the early embryo, epithelial sheets are free to deform in three dimensions. Here we consider the energetic cost of bending an epithelium whose top and bottom surfaces are not equivalent. such a sheet is represented in Fig. 2(b), and one possible description would be to assign to each of these two surfaces a pseudo-energy E'_{xy} similar to that of the last section with two different values of the force F.

We consider bending of the epithelial sheet along a single direction (*i.e.*, into a cylindrical shape), and take advantage of the translational invariance of the problem to consider a simplified two-dimensional model in the x, z plane (as opposed to the x, y plane considered in the last section) [Fig. 2(c)]. In this model, each cell is represented by a quadrilateral with fixed height b and whose horizontal mid-line also has a fixed length equal to b, which enforces cell volume conservation. The top and bottom sides of the quadrilateral have lengths l_t and l_b [Fig. 2(d)]. Similar to the discussion of the last section, the different contractile forces within the top and bottom surfaces imply that each targets a different preferred area, which we represent by a pseudo-energy

$$E_{xz} = \frac{k}{2}(l_t - l_t^0)^2 + \frac{k}{2}(l_b - l_b^0)^2, \tag{5}$$

where the preferred lengths l_t^0 and l_b^0 can *a priori* assume different values. Here we aim to coarse-grain this model into a membrane-like description for the epithelial monolayer.

3.1 What is the general form of the *bending* energy of a weakly curved top-down symmetric membrane? How is this form changed for an asymmetric membrane? You may denote the spontaneous curvature by c_0.

3.2 We consider a bent membrane as in Fig. 2(d). Relate l_t and l_b to b and the curvature radius R.

3.3 By writing down the energy of a single bent cell, determine the spontaneous curvature c_0 in this model.

3.4 Assuming each cell has a thickness b in the y direction, take the continuum limit by writing the energy per unit surface of the epithelium. What is the bending modulus of the epithelial sheet? Check that its unit is correct.

4 Model for neural tube closure

The neural tube is the embryonic precursor to the central nervous system, and forms from a locally flat epithelial sheet according to the process sketched in Fig. 3(a). In practice, actomyosin contraction is activated on the top part of a narrow band of cells, inducing a spontaneous curvature as discussed in the previous section and thus driving the invagination of the neural tube. Here we investigate under what conditions the tube is able to fully close.

We model the uncontracted epithelium as a flat sheet with tension γ and vanishing spontaneous curvature. Within this sheet, a band of cells of width s starts contracting at the top, which inducing a spontaneous curvature c_0 within that band only. We approximate the resulting deformation to a partial cylinder as pictured in Fig. 3(b). Our goal in this section is to determine under which conditions the cylinder can undergo the full closure required for development ($\phi = \pi$).

4.1 The energy E_{cyl} of the partial cylinder is the sum of two terms, one due to bending and the other to surface tension. Assuming the length of the cylinder in the direction orthogonal to the figure is L_y, write the bending energy as a function of the bending modulus κ, r, s, c_0 and L_y.

4.2 Now write the surface energy associated with the undeformed epithelium as a function of γ, r, ϕ, L_y. The surface energy of the deformed tube is irrelevant since its area is constant. It will be useful to consider that the area of the undeformed epithelium is equal to the constant total area of the plane minus that of the gap indicated in Fig. 3(b).

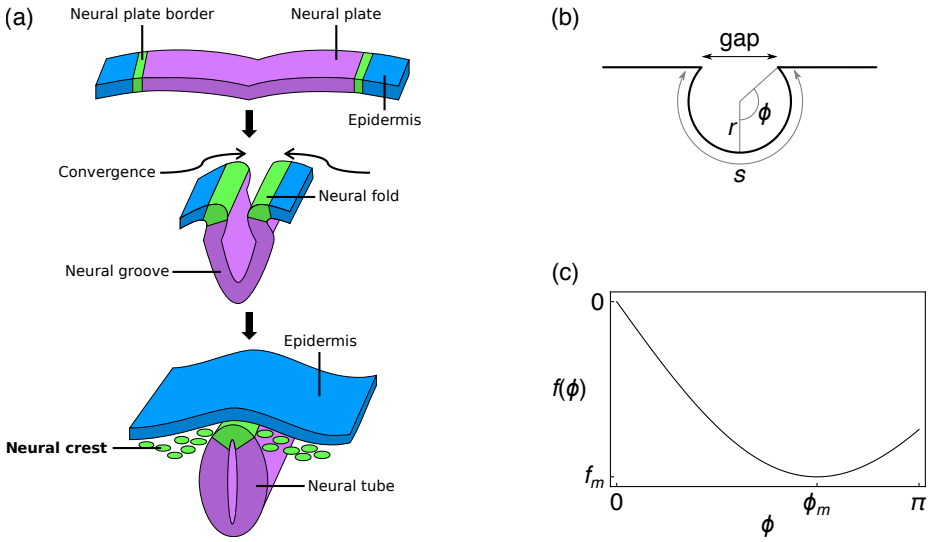

Figure 3: Tissue-level model of neural tube closure. (a) Schematic of the process of neural tube closure [from Wikipedia] (b) Cylindrical closure model used here. (c) Plot of $f(\phi) = \cos\phi/\phi - \sin\phi/\phi^2$. The derivative of the function vanishes in $\phi = \phi_m \simeq 2.08158$ at a value $f_m \simeq -0.436182$.

4.3 Adding another geometrical relation to eliminate r, show that

$$\frac{E_{\rm cyl}}{\kappa L_y} = \beta \left[\left(\phi - \frac{c_0 s}{2} \right)^2 - \frac{\gamma s^2}{2\kappa} \frac{\sin\phi}{\phi} \right], \tag{6}$$

where β is a ϕ-independent prefactor to be determined.

4.4 Minimize the energy with respect to ϕ and schematize the possible resulting regimes depending on the position of a line with respect to the curve of Fig. 3(c). Plot four lines corresponding to the four possible regimes of solutions: (i) one stable solution $\phi < \phi_m$, (ii) two solutions, one stable and one unstable, (iii) one stable solution $\phi > \phi_m$, and (iv) no solution.

4.5 Specify the interval of parameters corresponding to case (iii).

4.6 What happens to the tube in case (iv)?

4.7 Starting from a situation in case (iii) and enhancing contractility, *i.e.*, increasing c_0, specify the value of c_0 for which the tube closes completely.

4.8 In contrast to the cylindrical approximation used above, the membrane profile is fully solvable in the Monge gauge, where the membrane is described by an altitude function $z(x)$. Write down the corresponding free energy functional.

4.9 Can you describe tube closure within this approximation? Why?

References

[1] Dapeng Bi, J. H. Lopez, J. M. Schwarz, and M. Lisa Manning. A density-independent rigidity transition in biological tissues. *Nat. Phys.*, 11:1074–1079, September 2015.