Abstract

In this paper buckling instabilities of monolayers are discussed. Wrinkles, which usually occur have been known for some time, but the formation and the structure have not been fully understood till recently. Therefore we first focus on the generic aspects on wrinkles and their formation. Later on, we debate buckling in biological systems. In particular, the shape and the structure of villi and crypts in small intestine and colon are described.

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1 Introduction

A significant property of living tissues is a permanent cell turnover due to division and death, which has important effects on their mechanical response [1]. Since cells often grow and divide in a constrained environment, cellular divisions and programmed death (known as apoptosis) induce internal stresses in tissues that influence deeply their shape. A particularly interesting example to consider is intestine, which is the body's fastest renewing organ. It consists of a variety of folded multicellular structures, called villi, which play a crucial role in the exchange of nutrients. Even though the development of intestine has been studied in various animals, the formation of villi and their structure has not yet been described till recently [1, 2]. From a physicist's point of view, these folded shapes in a periodic arrangement are strongly reminiscent of patterns observed after buckling of plates. Those patterns can be seen in Fig. 1. Elastic instability, known as Euler buckling, leads to the lateral deflection of an elastic beam or a surface under load. A similar buckling instability is expected in growing constrained systems and has been invoked to explain fingerprints or the shapes of algae [1]. Particularly interesting is the suggestion that intestinal structures can be reproduced with minimal physiological environment, which reinforces the idea that mechanical forces play a crucial role [3]. In this seminar a theoretical model for the buckling instability of monolayers is presented.

Figure 1: Villi and crypts in the jejunum [4]. The jejunum is the middle section of the small intestine in most higher vertebrates, including mammals, reptiles and birds. Key to figure: V - villi, cr - crypts, g - goblet cells in epithelium, mm - muscularis mucosae, subm - submucosa.

2 Buckling and Wrinkles

Wrinkles have been known for quite some time. In the Renaissance, for instance, wrinkles were frozen lines of energy, psychological as well as kinetic; getting the wrinkles right in a scene in picture helped the artist get the artistic energy (appearance of motion) right [5]. This also showed what an accomplished artist the person was. Prescientifics that they were, however, the Renaissance masters did not fully understand the physical laws of wrinkling. Lakshminarayan Mahadevan, a physicist at Harvard University, and Enrique Cerda, a physicist at Cambridge University, were first one to propose the "general
theory of wrinkling" [6]. By knowing the dimensions of the fabric and the forces acting on it, their theory predicts the amplitude and the wavelength of the resulting wrinkles — that is, how big and how far apart they will be. The beauty of the theory is that it works not only for cloth, plastic wrap and other fabrics but also for shriveled apples and people’s skin which can be seen in Fig. 2.

Figure 2: Some examples of wrinkles. Wrinkles induced in the skin of an apple (≈ 5 cm) by the shrinking of the flesh (panel a; [6]). Wrinkling of skin (b; [6]). Scanning electron microscopy image of suspended graphene bilayer - scale bar is 1 µm (c; [7]). Pattern of folds obtained for a rubber curtain - scale bar is 25 cm (d; [7]).

Mahadevan likened that a thin sheet of fabric or tissue is like a spring: "When you deform it, it stores elastic energy. The sheet can deform either by stretching or by bending." [6] Being thin, a sheet is typically less resistant to bending. However, because we have two competing effects, the optimal deformation is a compromise. The energy of a spring or of a stretched sheet is proportional to the strain from stretching squared, but the energy in a bent sheet is proportional to the curvature squared. A sheet with lots of little wrinkles contains more curvature and thus more bending energy than a sheet with one big wrinkle. It was the 18th century Swiss mathematician Leonhard Euler who first realized this, and who also had the fundamental insight that underlies all wrinkle physics today: A deformed sheet adopts the shape that minimizes its total bending energy [5]. A clamped plastic sheet may sound like an idealized example, but in nature there are lots of thin sheets that are clamped — not at the ends, but to a foundation. For instance, our skin is attached to the underlying flesh. As we age, our skin begins to sag as the fatty tissue beneath it loses its stiffness and thus results in skin wrinkles [5].
3 Folding of Sheet on Fluid Substrate

It is time to begin with a general description of wrinkles. Composite structures, consisting of a fluid substrate covered by a thin rigid layer, are commonly found in biological tissues and synthetic coatings. Unlike a freely suspended sheet, a supported layer has an intrinsic length scale arising from the competition of bending and substrate energy [2]. Thus a compressed sheet floating on a fluid buckles at a wavelength

$$\lambda = 2\pi \left(\frac{B}{\rho g}\right)^{1/4},$$

(1)

$B$ being the bending stiffness, $\rho$ the fluid mass density, and $g$ the gravitational acceleration. An analogous argument holds for an elastic foundation. In the elastic case, it has long been recognized that this extended periodic wrinkling is always unstable against localized folding for a sufficiently large system [2]. With a fluid substrate, the same instability occurs. Such fold localization has been observed in diverse fluid-supported films — from monolayers and trilayers of nanometer-sized gold particles, through submicron-thick polymer films, to 10 $\mu$m-thick plastic sheets. In Fig. 3 wrinkling of polyester film on water is shown.

![Figure 3: Polyester film on water transitioning from an extended wrinkled state, panel a, to a localized folded state upon further compression, panel c [8]. Initial wrinkle wavelength is $\lambda \sim 1.6$ cm.](image)

Let us consider a thin incompressible elastic sheet of length $L$, width $W$, and bending modulus $B$. The sheet is compressed along the $x$ direction and is assumed to deform in the $xz$ plane, whereas remains uniform along the direction of $y$-axes as shown in Fig. 4. Due to incompressibility, the configuration of the sheet can be defined by the angle $\phi(s)$ that the local tangent to the sheet makes with the $x$-axis; $s$ is the arclength. One can also define a height profile, $h(s)$, such that $\dot{h} = \sin \phi$. The half-space below the sheet is filled with a fluid of mass density $\rho = K/g$. We want to determine steady state of the system and thus ignore time dependence.
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Figure 4: Schematic view and parametrization of the system showing the definition of angle $\phi(s)$, a height profile $h(s)$, and the arclength $s$. Deformation in $xz$ plane occurs due to compression of the sheet along the $x$ direction [2].

Since we consider localized deformations we send $L \to \infty$ and set $\phi = \dot{\phi} = h = 0$ at $s \to \pm \infty$. We may now write the total energy of the system, which consists of the bending energy

$$E_b = \frac{WB}{2} \int_{-\infty}^{\infty} \dot{\phi}^2 ds$$

and of the substrate energy

$$E_s = \frac{WK}{2} \int_{-\infty}^{\infty} h^2 \cos \phi ds.$$  

Lateral pressure $P$ is related to the energy by $P = dE/d\Delta$, where $\Delta$ stands for the displacement along the direction of compression and is given by

$$\Delta = \int_{-\infty}^{\infty} (1 - \cos \phi) ds.$$  

We scale the energy by $B$, the lengths by $(B/K)^{1/4}$ and the lateral pressure $P$ by $(BK)^{1/2}$. For brevity, units where $B = K = W = 1$ are used. From classical mechanics we know that to find the stable configuration we must minimize the action

$$S = \int_{-\infty}^{\infty} \mathcal{L}(\phi, h, \dot{\phi}, \dot{h}) ds,$$

where Langrange function is given by

$$\mathcal{L} = \frac{1}{2} \dot{\phi}^2 + \frac{1}{2} h^2 \cos \phi - P(1 - \cos \phi) - Q(s)(\sin \phi - \dot{h}).$$

In Eq. (6) $P$ and $Q$ are Lagrange multipliers which replace the global constraint on $\Delta$ and the relation between $h$ and $\phi$. As mentioned in Ref. [2], in the case of elastic foundation, the hydrostatic term $(h^2/2) \cos \phi$ should be replaced by $h^2/2$. We can now identify the momenta

$$p_\phi = \frac{\partial \mathcal{L}}{\partial \dot{\phi}} = \dot{\phi}$$

6
and

\[ p_h = \frac{\partial \mathcal{L}}{\partial \dot{h}} = Q, \tag{8} \]

which we use to obtain the Hamiltonian

\[ H = p_\phi \dot{\phi} + p_h \dot{h} - \mathcal{L}. \tag{9} \]

Since the Lagrange function does not depend explicitly on \( s \) the energy is a constant of motion

\[ E = \frac{1}{2} p_\phi^2 + p_h \sin \phi - \frac{1}{2} h^2 \cos \phi + P(1 - \cos \phi) = 0. \tag{10} \]

The last equality follows from the boundary conditions at \( s \to \pm \infty \) mentioned above. We can quickly see consequence of Eq. (10); wherever the sheet is horizontal \((\phi = 0)\), we have \(|p_\phi| = |h|\), which implies a geometrical constraint

\[ \phi = 0; \quad |\dot{\phi}| = |\dot{h}| = |\ddot{h}|. \tag{11} \]

The equation of motion for a specific problem is obtained by Hamilton’s equation \( \dot{p}_\phi = -\partial H/\partial \phi \):

\[ \ddot{\phi} + \left( \frac{1}{2} h^2 + P \right) \dot{\phi} + p_h \cos \phi = 0. \tag{12} \]

By eliminating \( p_h \) from Eqs. (10) and (12) and differentiating Eq. (12) with respect to \( s \), we find

\[ \dddot{\phi} + \left( \frac{3}{2} \dot{\phi}^2 + P \right) \ddot{\phi} + h = 0. \tag{13} \]

Equation (13) concurs with so called Euler’s elastica problem [2]. The last term arises from hydrostatic pressure. Differentiating Eq. (13) one more time removes the dependence on \( h \):

\[ \dddot{\phi} + \left( \frac{3}{2} \dot{\phi}^2 + P \right) \dddot{\phi} + \sin \phi = 0. \tag{14} \]

As we assume that \( \phi \) and its derivatives vanish at infinity, we integrate the above equation to obtain

\[ \dddot{\phi} - \frac{1}{2} \dddot{\phi}^2 + \frac{3}{8} \dot{\phi}^4 + \frac{1}{2} P \dot{\phi}^2 + 1 - \cos \phi = 0. \tag{15} \]

Equation (15) does not seem to give a closed-form solution. However, with a simple trick, it can be solved quite easily. Let us consider well known physical-pendulum (PP) equation, \( \ddot{\phi} + q^2 \sin \phi = 0 \), whose solutions are

\[ \phi(s) = \pm 4 \tan^{-1} \left( A \exp(\pm iqs) \right). \tag{16} \]
By integrating Eq. (16) once and differentiating it twice we can show that any of the PP solutions solves Eq. (14) as well for \( P = q^2 + q^{-2} + c \), where \( c \) is an integration constant, which can be set to 0 without loss of generality. The solutions are complex with specific complex wave vectors

\[
q = \pm k \pm i\kappa,
\]

\[
k = \frac{1}{2}(2 + P)^{1/2},
\]

\[
\kappa = \frac{1}{2}(2 - P)^{1/2}.
\]  

(17)

From Eq. (17) one might quickly notice that the pressure is limited to the range \(-2 < P < 2\). The above solution can be written in slightly different form, describing localized symmetric and antisymmetric shapes of the angular profile:

**Symmetric fold:**
\[
\phi(s) = 4 \tan^{-1}\left(\frac{\kappa \sin(ks)}{k \cosh(\kappa s)}\right),
\]

(18)

**Antisymmetric fold:**
\[
\phi(s) = 4 \tan^{-1}\left(\frac{\kappa \cos(ks)}{k \cosh(\kappa s)}\right).
\]

(19)

It can be shown that these functions solve the nonlinear Eq. (15) exactly. From the obtained solutions some very simple relations among the pressure \( P \), the displacement \( \Delta \), the central height \( h(0) \) and the energies can be derived. It turns out that decay parameter \( \kappa \) is linearly dependent on the displacement

\[
\kappa = \frac{\Delta}{8},
\]

(20)

whereas pressure has a quadratic dependence

\[
P = 2 - \frac{\Delta^2}{16}.
\]

(21)

The maximum amplitude of a symmetric deformation is \(|h(0)| = \Delta/2\), whereas the central deformation of antisymmetric fold \( h(0) \) by definition 0. We are also interested in the bending and substrate energy given by \( E_b = \Delta \) and \( E_s = \Delta(1 - \Delta^2/48) \). The progression of the symmetric and antisymmetric folds as the pressure decreases is shown in Fig. 5. Shapes of the curves match what we can see in experiments.
As seen from Fig. 5, the symmetric fold is found to contact itself at a slightly positive pressure; $P = 0.04$ (corresponding to $\Delta = 5.6$), whereas for self-contact of the antisymmetric fold a substantial negative pressure is required; $P = -0.7$ ($\Delta = 6.6$). One might examine the solutions beyond self-contact as well. However these solutions produce self-intersecting configurations which, of course, are unphysical. In particular, at $P = -2$ the oscillations in $\phi$ disappear which is shown in Fig. 6.

Figure 5: Symmetric (a) and antisymmetric (b) configurations of the sheet as a function of decreasing pressure. The curves are shown from a point close to the instability threshold ($P_c = 2$) down to self-contact [2].

Figure 6: Unrealistic symmetric (a) and antisymmetric (b) self-intersecting configurations for $P \to -2$. It should be noted that in case of antisymmetric configuration as pressure approaches $-2$ the two loops are pushed toward the boundaries [2].
4 Instabilities of Intestinal Epithelia

Let us now consider the intestine, which is main topic of the seminar. Intestine is relatively simple organ. It is covered by a single layer of epithelial cells which lay on top of the thin basement membrane. The intestinal tube is surrounded by a soft tissue called the stroma schematically shown in Fig. 7. In a model proposed in Ref. [1], the stroma is considered as an elastic medium of height \(H\) and Young’s modulus \(E_s\). Since the thickness of this tissue is much larger than the typical wavelength of the villi \((\lambda \sim 100 \, \mu m)\), it can be considered as infinite. The basement membrane is a thin elastic sheet of height \(h_b \sim 1 \, \mu m\), bending modulus \(K_b\), and Young’s modulus \(E_b\). The cell monolayer has an elastic modulus \(E_c\) and the thickness of the monolayer is estimated \(h_c \sim 10 \, \mu m\). Let us assume the cell density is constant. Therefore, its bending modulus can be expressed as \(K_c = E_c h_c^3 / 9\) which coincides with Poisson number for incompressible material \(\sigma = 0.5\) - usual expression is \(K_c = E_c h_c^3 / 12(1 - \sigma^2)\). As such it is much larger than the bending modulus of the membrane. As the cells respond to tension by dividing or undergoing apoptosis over long time scales, the elasticity of the cell monolayer is dominated by curvature and has no stretching energy. The curvature of intestinal tube should be neglected, since its radius \((R \sim 2 \, cm)\) is orders of magnitude larger than the other relevant dimensions.

![Figure 7: Schematic of monolayered intestinal epithelium. Crude estimates for the parameters involved are \(E_s = 400 \, Pa\), \(E_c = 10^4 \, Pa\) and \(E_b = 10^3 \, Pa\) [1].](image)

The buckling instability is caused by the cell layer. When cells either divide or die in a tissue, they exert stresses on their environment, where the characteristic pressure is the homeostatic pressure \(P_h\). We will assume that all new cells are attached to the membrane as well. Since the membrane is considered as infinite, this is not severe assumption. It should be mentioned that in comparison to the problem we discussed in the previous section there are two main differences. First of all, we are now actually dealing with three layers: cell monolayer, thin basement membrane and stroma. Another difference is, that in previous problem the sheet deformed due to lateral compression, whereas now deformation occurs due to division and apoptosis of cells. The forces in the plane of the monolayer can be described in terms of a negative surface tension \(-\gamma\), which is connected to homeostatic pressure by \(\gamma = P_h h_c\). Let us assume that the undulation is of type \(w(x) = w_0 \cos(qx)\). To the lowest order, the corresponding elastic energy of the cell monolayer reads

\[
\epsilon = \frac{1}{2} K_c w_0^2 q^4 - \frac{1}{2} \gamma w_0^2 q^2 + \frac{1}{3} E_s w_0^2 q. \quad (22)
\]
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Buckling occurs when the energy becomes negative; in other words, if the tension $\gamma$ is larger than the critical $\gamma_c = (3K_c E_s^2)^{1/3}$. The corresponding wavelength at threshold is then $\lambda = 2\pi(K_c/E_s)^{1/3} \approx 90 \mu m$, which is close to the wavelength observed in vivo. The critical homeostatic pressure for villi formation is typically $P_{hc} = 1400$ Pa. In the above description, the size and wavelength are dictated only by elastic considerations. This is consistent with observations that animals of very different sizes (for example, mice and humans) have villi of equivalent dimensions [1]. This approach reproduces accurately the undulations of the small intestine.

However, the morphology of the colon is visually completely different. There are no villi observed, but only crypts extending into the stroma. Due to this asymmetry we should take into account the nonuniform division rates along the villi, which, according to Ref. [1], can by modeled by a growth rate depending on the curvature of the cell monolayer. As a reference state the homeostatic state $\gamma = \gamma_0$ is used, where the monolayer is flat and the cell division rate $k_d$ balances the cell apoptosis rate $k_a$. We can write linear dependence of growth rate

$$k_d - k_a = -\xi(\gamma - \gamma_0) + \alpha \nabla^2 w,$$

where $\xi$ and $\alpha$ measure the dependence of the growth rate on pressure and on curvature, respectively. The growth rate decreases with pressure and is larger in the crypts and smaller in the villi. If the cell density in the monolayer is constant, the cell volume conservation law applies: $\nabla \cdot \mathbf{v} = k_d - k_a$. As opposed to the pressure gradient in the monolayer, the friction force with the basement membrane appears $\zeta \mathbf{v} = -\nabla \gamma$, where $\zeta$ stands for friction constant.

It is quite difficult to obtain the precise values of $\xi$, $\alpha$, and $\zeta$ and therefore to decide which regime would be more relevant. For this reason calculations in the regime of small and large friction were performed. In both cases the same physical behavior is observed [1]. Hereafter calculations in small friction regime are presented. We define a new parameter $p = \alpha \zeta$. In order to study the morphology of the small intestine analysis with $\alpha = 0$ should be done. Specifics of the colon can be explained later on using large $\alpha$. For each point in the monolayer, a displacement vector $\mathbf{u} = (u_1, u_2, w)$ can be defined. Here $w$ is the vertical displacement of the interface and $(u_1, u_2)$ is the lateral displacement. From the force balance on the basement membrane the steady state shape and structure of the villi are than obtained. The basement membrane is described by the classical Foppl-von Kármán equation, which is more properly described in Ref. [10]. We now rescale all lengths by the thickness of the basement membrane $h_b$ and obtain the following equations of motion

$$\frac{\partial w}{\partial t} = -\Delta^2 w - \gamma \nabla^2 w - f_{el,z},$$

$$\frac{\partial u_\alpha}{\partial t} = 9 \left( \frac{h_b}{h_c} \right)^{1/3} \frac{E_b}{E_c} \frac{\partial}{\partial x_\beta} \left[ \frac{\partial w}{\partial x_\alpha} \left( \frac{\partial u_\alpha}{\partial x_\beta} + \frac{\partial u_\beta}{\partial x_\alpha} + \frac{\partial w}{\partial x_\alpha} \frac{\partial w}{\partial x_\beta} \right) \right],$$

$$\frac{\partial u_\alpha}{\partial t} = 9 \left( \frac{h_b}{h_c} \right)^{1/3} \frac{E_b}{E_c} \frac{\partial}{\partial x_\alpha} \left( \frac{\partial u_\alpha}{\partial x_\beta} + \frac{\partial u_\beta}{\partial x_\alpha} + \frac{\partial w}{\partial x_\alpha} \frac{\partial w}{\partial x_\beta} \right) - f_{el,\alpha},$$

where $\alpha$ and $\beta$ represent indexes 1 or 2 so that $\alpha \neq \beta$. The various terms describe the friction force, the curvature of the cell layer, the pressure implemented by the cells, the
stretching force of the basement membrane, and the elastic force due to the stroma \( f_{el} \) that is proportional to displacement vector \( \mathbf{u} \), respectively. The linear relation for \( f_{el} \) is best written in Fourier space for a wave vector \( \mathbf{k} \) as

\[
\mathbf{f}_{el} = 3\left(\frac{E_s}{E_c}\right)\left(\frac{h_b}{h_c}\right)^{1/3} \mathbf{M} \mathbf{u},
\]

where \( \mathbf{M} \) is the \( 3 \times 3 \) matrix given by

\[
\begin{pmatrix}
\frac{(2k^2 - k^2_y)}{k} & \frac{k_x k_y}{k} & 0 \\
\frac{k_x k_y}{k} & \frac{(2k^2 - k^2_x)}{k} & 0 \\
0 & 0 & 2k
\end{pmatrix}
\]

In one dimension, the buckled state is a simple sine-like function. However, numerical integration obtained by semi-implicit integration method showed that in two dimensions, a variety of patterns are possible, including those representing small intestine and colon morphologies seen in vivo. Figure 8 shows these results.

**Figure 8**: Numerical integration of the epithelial surface \( w(x, y) \) under buckling. Small intestine morphology (a) showing well-developed villi, and colon morphology (b) characterized by crypts. Wavelengths of shape modulation are micrometers which coincides with actual dimensions observed in vivo [1].

For characteristic physiological values of parameters a phase diagram (seen in Fig. 9) regrouping different equilibrium solutions is obtained. The parameter that has been varied here is the buckling pressure exerted by the monolayer, presented on the horizontal axis. This is in fact the main result. At low buckling pressure, finger shapes [seen in Fig. 8(a) or, as a 2D projection on Figure 9(b)] are stable. Nevertheless, for large stresses, it becomes difficult to bend the membrane in all directions, and labyrinth or herringbone structures are favored [seen as 2D projections on Figure 9(c) and 9(d)]. This has been observed experimentally as well. Indeed, villi are not always finger-shaped, but sometimes
adopt complex folded patterns surprisingly identical to the predicted ones. Even though villi wavelength is roughly constant throughout the intestine, their height is not [1]. At the entrance of the intestine (near the stomach), villi are very long, but their size decreases gradually in more distal parts. This leads to conclusion that lateral pressure decreases along the intestine. Therefore it is expected that labyrinth-like villi are more likely to be found near the stomach, and that in distal parts, villi should be finger-shaped. This is actually seen in physiological studies.

![Figure 9: Phase diagram showing the various possible villi morphologies. Pattern seen in panel (a) is colon-like, whereas patterns (b)–(d) are, small-intestine-like; finger-shaped, herringbones, and labyrinth-like, respectively. The vertical axis is the coupling between cell division and curvature, and the horizontal axis is the pressure exerted by the cell monolayer. Also shown is the phase diagram in the surface tension, pressure phase [1].](image)

The model does not claim that this is the mechanism for the formation of villi during embryogenesis, but it is argued that when the system reaches a steady state, stresses must be balanced as described by equations mentioned above [1]. In fact, several experiments have shown that when increasing cell apoptosis for a short time, villi disappear and, in a matter of days, they regain their initial equilibrium state. More, overseeing villi as a product of a buckling instability could provide new views on intestinal pathologies. It should be noted that in the described model, the elasticity of the basement membrane plays a crucial role, since it stabilizes the amplitude of the folds. According to Ref. [1] in celiac diseases, degeneration of the villi is correlated with an increase of the apoptotic index but also with an increase of the basement membrane thickness. This translates into a lower pressure and a higher energetic cost to bend the membrane, which can cause the abrupt disappearance of villi. Conversely, if the basement membrane breaks, which is a necessary event in appearance of colon cancer, the model predicts uncontrolled outgrowth of the intestinal lining, somehow very similar to polyp formation.
5 Conclusion

In the first part of the paper, general aspects on wrinkling were described. The solution presented here provides an exact insight into shapes and energies of a large class of wrinkling and folding systems. Later on, a specific problem of monolayered epithelia was discussed. This simple buckling model predicts a full phase diagram explaining most of the structures observed in the small intestine and colon. This suggests a deep connection between tissue architecture and the stresses produced by the dividing cells and their apoptosis. Intestinal shape and renewal rate are at least partially controlled by a mechanical balance, which is disrupted in the case of intestinal diseases. Since it has been proven that an excess of mechanical pressure could induce colonic cancer, a detailed understanding of this balance is of great interest for cancer research. This buckling formalism is not limited only to understanding the shape and structure of villi and crypts but could also be applied to other morphogenetic phenomena as well, for example in neurulation.
References


