Supplementary note 1: Computational vertex model.

3D vertex model on a rigid substrate

To understand the tissue mechanics leading to cell and monolayer morphology and to the mechanical coupling with the substrate, we developed a 3D computational vertex model. This model is based on a conventional effective energy or virtual work function of the form

$$\delta W = \sum_{c=1}^{N} \sum_{f=1}^{N_c} \gamma_{f,c} \delta A_{f,c}, \tag{1}$$

where N is the number of cells, N_c the number of faces of cell c, $\gamma_{f,c}$ the surface tension of face f of cell c, and $\delta A_{f,c}$ the variation of the surface area of that face. We assume that the surface tensions $\gamma_{f,c}$ remain constant during a simulation but are heterogeneous throughout the tissue. Work functionals for 3D vertex models can also account for the line tension generated by apical or basal cables. We also implemented such terms but found no essential differences for the purpose of this study, and hence we ignored them for the sake of simplicity.

To capture the cell shapes with curved junctions observed in the experiments, we discretized each cell with a triangulation as shown in Extended Data Figure 6a. However, we did not account for cell rearrangements, which are easily dealt with in 2D but much more challenging in 3D. Thus, during tissue relaxation, cells maintain their prismatic topology and connectivity and can only change their shape. In the actual system, local junctional rearrangements may contribute to the tissue deformation [1].

Accounting for cell volume preservation, we can define an effective or pseudo-energy over the entire triangulation describing the tissue of the form [2–4]

$$W(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_M) = \sum_{c=1}^{N} \sum_{f=1}^{N_c} \gamma_{f,c} A_{f,c}(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_M) + \sum_{c=1}^{N} \frac{\kappa}{2} \left[V_c(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_M) - V_{c,0} \right]^2 \tag{2}$$

where $\boldsymbol{x}_i$ denotes the position of node i in this triangulation, V_c is the volume of cell c, and κ is an osmotic compressibility modulus that ensures that cell volumes remain fixed within 0.1% to the initial volume, $V_{c,0}$ for cell c.

We started our analysis by considering a planar tissue with cells of uniform shape and size as shown in Extended Data Figure 6. To examine the mechanics of intestinal crypts, we prescribed a distribution of surface tensions that mimics the measured basal and apical F-actin distribution. It is known that cortical tension depends in a highly nontrivial way on the amount, but also the architecture, of cytoskeletal components. However, given the order-of-magnitude variations of F-actin accumulation in our crypts, it is reasonable to consider F-actin accumulation as a proxy for cortical tension in a first approximation. Noting that the F-actin distributions were measured on an actual deformed crypt and that we are prescribing surface tensions on an idealized undeformed tissue, we broadened the apical and basal peaks in F-actin distribution in our computer model. Regarding lateral surface tensions, we noted that the apical/basal surfaces of our monolayers were quite smooth at the intersections with lateral junctions. We reasoned that if lateral surface tensions were relatively large, then as a result of mechanical equilibrium at these intersections we should observe noticeable surface deformations at apico-lateral and baso-lateral intersections. Since these were absent, we concluded that lateral tensions should be significantly smaller than basal and apical tensions. We note in this regard that at lateral faces, adhesion tension acts as a negative surface tension that lowers the total lateral surface tension.

During our analysis, we kept fixed the distribution of surface tension over cell faces shown in Extended Data Figure 6b. Given the high heterogeneity of this surface tension pattern, the initial regular cell monolayer is not in mechanical equilibrium. We then proceeded to the equilibration of the system on a rigid substrate. For this, we minimized the function in Eq. (2) using Newton's method to find the equilibrium positions of nodes in our triangulation. While our description of each cell face as a triangulated surface allows us to describe curved shapes, it also poses a numerical challenge as the distortion of our triangulations needs to be controlled during the numerical minimization. Indeed, since the function in Eq. (2) only depends on the surface area of each face and the volume of each cell, it is invariant with respect to tangential motions of internal nodes to each face that leave these geometric quantities unchanged, and thus does not provide any control of mesh distortion. To deal with this issue, we adopted the approach proposed elsewhere [5], which considers a fictitious surface hyperelastic model for each cell junction whose reference configuration is updated iteratively to the previously converged configuration. This fictitious elastic energy results in an effective viscosity of the cellular cortices and the algorithm can then be viewed as the dynamical relaxation of a viscous cell aggregate with active surface tensions and fixed cellular volumes. These dynamics control mesh distortions and upon convergence of the algorithm, the fictitious elastic energy vanishes and does not bias the final results.

In our simulations on rigid substrates, we allowed the nodes on the basal plane to slide tangentially but forced their z position to zero so that they stay on the plane of the substrate. Furthermore, we fixed the lateral edges of the tissue. Upon equilibration, we found the tissue and cellular shapes and the normal tractions, Extended Data Figure 6c. As the tissue deformed, the pattern of surface tensions more closely followed the experimentally measured patterns of F-actin distribution.

3D vertex model on a deformable substrate

We then placed the equilibrated crypt in contact with a highly deformable elastic substrate. We modeled the substrate using finite deformation continuum mechanics and a NeoHookean hyperelastic model, for which the strain energy density per unit undeformed volume is given by [6]

$$\psi(\boldsymbol{C}) = \frac{\lambda}{2}(\ln J)^2 - \mu \ln J + \frac{\mu}{2}(\text{trace } \boldsymbol{C} - 3), \tag{3}$$

where $\boldsymbol{C} = \boldsymbol{F}^T\boldsymbol{F}$ is the right Cauchy-Green deformation tensor, $\boldsymbol{F}$ is the deformation gradient, $J = \sqrt{\det \boldsymbol{C}}$ is the Jacobian determinant and λ and μ are the Lamé coefficients at infinitesimal deformations. These coefficients are related to infinitessimal Young's modulus E and Poisson's ratio ν by the relations $\lambda = E\nu/[(1+\nu)(1-2\nu)]$ and $\mu = E/(1+\nu)$. We discretized the deformable substrate with linear tetrahedral finite elements. The bulk tetrahedral mesh was generated to be conforming in its top plane to the surface triangulation of the basal plane of the tissue equilibrated on a rigid substrate. We imposed kinematical compatibility at the cell-matrix interface by identifying the basal nodes of the tissue triangulation to the corresponding nodes of the matrix mesh. We then further equilibrated the joint tissue-matrix system by minimizing the joint effective energy given by

$$W + \int_{\Omega_0} \psi(\boldsymbol{C})\, dV, \tag{4}$$

where Ω_0 is the domain representing the substrate, with respect to the positions of the nodes of the tissue triangulation and of the bulk finite element mesh. This minimization was again performed using Newton's method with a line-search. As a result, the crypt was able to deform the substrate, Extended Data Figure 6d.

Sensitivity to the pattern of active tensions

We simulated tens of computational crypts with patterns of cellular surface tensions following the measured F-actin distribution. We found a very robust agreement with the main features of the experiments in terms of tissue shape in stiff and soft substrate, of cellular shapes and of normal traction. However, the details of these observables depended on the specific pattern of surface tensions. By way of an illustration of this sensitivity, we report in Extended Data Figure 7d the tissue morphology and normal tractions for two models with significantly different distribution of basal surface tensions. When basal tension is increased, we observe that the peak of positive normal tractions is smaller, and that the indentation on soft gels is smaller since tension works against the extension of the basal surface required for bending. However, both models recapitulate the essential features of the actual crypts. In Extended Data Figure 7a we report the pattern of surface tensions used to produce the results in Fig. 5. We also illustrate the procedure to filter the normal tractions in the simulations, Extended Data Figure 7b, and the finite element mesh used to model the substrate, Extended Data Figure 7c.

Estimation of the maximum apical surface tension

The length-scale of the model is fixed by the typical size of cells and height of the typical crypt. Given this length-scale, $\gamma_{\max}$, Extended Data Figures 6b and 7a, sets the force-scale in the model, and hence the units of the computational normal tractions. By comparing the normal tractions in the simulations and in the experiments, we can scale the force scale in our model and hence attach physical units to the surface tensions. This allows us to estimate the magnitude of the surface tensions. By focusing on the normal traction data in Fig. 4b and its standard deviation, we find that $\gamma_{\max} \sim 4.6$ mN/m with a standard deviation of 1.7 mN/m. This cellular surface tension is about two times larger than surface tensions measured in suspended cells during mitosis [7]. We note that apical actin cables could contribute to this effective apical surface tension.

Simulating laser cuts

To simulate laser cuts and starting from a previously equilibrated system, we instantaneously imposed nearly zero surface tension in the finite elements lying in the cut region. By removing the mechanical effect of the cut region, the internal force balance of the system is broken and it will move to regain a new state of equilibrium. In theoretical models of tissue recoil, the instantaneous recoil depends on pre-existing tension (irrespective of its origin, active or elastic) and on an effective viscosity. The detailed modelling of the viscosity of the different structural elements of the tissue is complex and beyond the scope of the present work. However, by taking advantage of the viscosity intrinsic to our algorithm described above [5], we could predict the recoil velocity pattern (but not the physical magnitude of these velocities) from the model displacements in the first iterations. To post-process the results in Figs. 5 and 8, we represented the displacements of the nodes in the apical plane after the first iteration.

Basal cell elongation in the transit amplifying zone

Despite introducing a peak of basal surface tension in the transit amplifying zone, consistent with our quantification of F-actin distribution, our computational model did reproduce some degree of basal elongation, but not nearly as marked as in actual crypts, Fig. 5i,n. Imaging of cytoskeletal components in this region (Extended Data Fig. 3) clearly showed strongly aligned supra-cellular structures, which can likely influence the active force generation since active tension is expected along these aligned structures, but also bundling active forces may act perpendicular to those structures. All surface tensions being isotropic in our model, it likely misses some mechanical aspects of the basal plane in the transit amplifying region, which may explain the extreme elongation of cells.

Supplementary note 2: Axisymmetric Monolayer Stress Microscopy.

We describe here a simple approach for Monolayer Stress Microscopy (MSM), that is to infer the tissue surface stress from the measured tractions, in an axisymmetric configuration pertinent to the analysis of our crypts. The starting variable is then the radially-averaged tangential traction T_r, Fig. 1f.

Background

We consider polar coordinates given by $x(r,\theta) = r\cos\theta$ and $y(r,\theta) = r\sin\theta$. The natural basis is given by $\boldsymbol{x}_r(r,\theta) = (\cos\theta, \sin\theta)$ and $\boldsymbol{x}_\theta(r,\theta) = (-r\sin\theta, r\cos\theta)$. Hence the metric tensor is given by

$$\{g_{ab}\} = \begin{pmatrix} 1 & 0 \\ 0 & r^2 \end{pmatrix}, \qquad \{g^{ab}\} = \begin{pmatrix} 1 & 0 \\ 0 & 1/r^2 \end{pmatrix}.$$

The corresponding Christoffel symbols are

$$\{\Gamma^r_{ab}\} = \begin{pmatrix} 0 & 0 \\ 0 & -r \end{pmatrix}, \qquad \{\Gamma^\theta_{ab}\} = \begin{pmatrix} 0 & 1/r \\ 1/r & 0 \end{pmatrix}.$$

Therefore, using standard formulae in differential geometry, we can compute the covariant derivative of a radial vector field $\boldsymbol{u}(r,\theta) = u(r)\,\boldsymbol{x}_r(r,\theta)$ as

$$\{u^a{}_{|b}\} = \begin{pmatrix} u' & 0 \\ 0 & u/r \end{pmatrix}.$$

The symmetrized displacement gradient is the small-strain tensor, which thus takes the form

$$\{\varepsilon_{ab}\} = \begin{pmatrix} u' & 0 \\ 0 & ur \end{pmatrix}, \qquad \{\varepsilon^{ab}\} = \begin{pmatrix} u' & 0 \\ 0 & u/r^3 \end{pmatrix},$$

and its trace is

$$\text{tr } \boldsymbol{\varepsilon} = \varepsilon^a{}_a = u' + u/r.$$

Consider a stress tensor in axisymmetry, and thus of the form

$$\{\sigma^{ab}\} = \begin{pmatrix} \sigma^{rr}(r) & 0 \\ 0 & \sigma^{\theta\theta}(r) \end{pmatrix}.$$

The radial component of its divergence $\sigma^{ab}{}_{|b}$ can be written as

$$\sigma^{rb}{}_{|b} = \partial_r \sigma^{rr} + \frac{1}{r}\left(\sigma^{rr} - r^2\sigma^{\theta\theta}\right) = \partial_r \sigma^r{}_r + \frac{1}{r}\left(\sigma^r{}_r - \sigma^\theta{}_\theta\right) \tag{5}$$

Consider now linear elastic constitutive relation

$$\boldsymbol{\sigma} = 2\mu\boldsymbol{\varepsilon} + \lambda(\text{tr } \boldsymbol{\varepsilon})\boldsymbol{g}.$$

Using the equations above, we find

$$\sigma^r{}_r = \sigma^{rr} = (2\mu + \lambda)u' + \lambda\frac{u}{r}, \tag{6}$$

and

$$\sigma^\theta{}_\theta = r^2\sigma^{\theta\theta} = (2\mu + \lambda)\frac{u}{r} + \lambda u', \tag{7}$$

and we obtain its radial divergence as

$$(\text{div } \boldsymbol{\sigma})_r = \left[(2\mu + \lambda)u' + \lambda\frac{u}{r}\right]' + \frac{2\mu}{r}\left(u' - \frac{u}{r}\right).$$

If material properties are uniform, then we obtain

$$(\text{div } \boldsymbol{\sigma})_r = (2\mu + \lambda)\left(u'' + \frac{u'}{r} - \frac{u}{r^2}\right).$$

Monolayer Stress Microscopy

The tissue modeled as a 2D continuous medium is initially in an axisymmetric state of mechanical equilibrium characterized by a stress $\boldsymbol{\sigma}$. The equilibrium condition can be expressed as

$$(\text{div } \boldsymbol{\sigma})_r = \partial_r \sigma^r{}_r + \frac{1}{r}\left(\sigma^r{}_r - \sigma^\theta{}_\theta\right) = T_r, \tag{8}$$

where T_r are the measured radial tractions exerted by cells on the substrate. Thus, we have one equation for two unknowns, $\sigma^r{}_r$ and $\sigma^\theta{}_\theta$. One standard way to proceed is then to assume a constitutive relation, e.g. linear elasticity [8], leading to

$$\left[(2\mu + \lambda)u' + \lambda\frac{u}{r}\right]' + \frac{2\mu}{r}\left(u' - \frac{u}{r}\right) = T_r \tag{9}$$

or if mechanical properties are assumed to be constant to

$$(2\mu+\lambda)\left(u''+\frac{u'}{r}-\frac{u}{r^2}\right)=T_r, \tag{10}$$

which, along with boundary conditions $u(0)=0$ and $u(r^\infty)=U$ allow us to find the auxiliary displacement $u(r)$. The boundary condition at a far away location $u(r^\infty)=U$ only fixes the undetermined hydrostatic and uniform state of tension σ_0, and is thus arbitrary unless an independent measurement is available. Finally, recalling Eqs. (6,7) we obtain the sought-after tension as

$$\sigma^r{}_r = \sigma_0+(2\mu+\lambda)u'+\lambda\frac{u}{r}, \tag{11}$$

$$\sigma^\theta{}_\theta = \sigma_0+(2\mu+\lambda)\frac{u}{r}+\lambda u'. \tag{12}$$

The quantity $\sigma^r{}_r$ is the radial tension reported in Fig. 8, whereas $\sigma^\theta{}_\theta$ is a hoop tension.

We lack an independent measurement to determine σ_0 but our laser cuts indicate that radial tension is positive where it is minimum, at the transit amplifying zone. Therefore, in our calculations of MSM reported in Fig. 8 we chose σ_0 so that the minimum radial tension is zero with the understanding that there should be a positive offset to this curve.

Given T_r, we solve Eq. (9) using 1D finite elements. For this, we multiply Eq. (9) by a test function w, integrate over the domain $(0,R_{\text{out}})$ noting that $dS=2\pi r dr$, and integrate by parts, to obtain

$$\int_0^{R_{\text{out}}}(2\mu+\lambda)u'w'rdr+\int_0^{R_{\text{out}}}\frac{2\mu+\lambda}{r}uwdr+\int_0^{R_{\text{out}}}\lambda\left(vw'+v'w\right)dr=-\int_0^{R_{\text{out}}}T_rwrdr.$$

Approximating the unknown with finite element basis function $u(r)=\sum_{J=1}^M N(r)u_J$ and taking the test functions to be $w(r)=N_I(r)$, we find the following algebraic system of equations

$$\sum_{J=1}^M K_{IJ}u_J=F_I,$$

imposing the constraints that $u_1=0$ and $u_M=U$ and where

$$K_{IJ}=\int_0^{R_{\text{out}}}(2\mu+\lambda)N_I'N_J'rdr+\int_0^{R_{\text{out}}}\frac{2\mu+\lambda}{r}N_IN_Jdr+\int_0^{R_{\text{out}}}\lambda\left(N_IN_J'+N_I'N_J\right)dr$$

and

$$F_I=\int_0^{R_{\text{out}}}T_rN_Irdr.$$

In the calculations reported in Fig. 8, we chose $\lambda=10\mu$. We checked that the inferred tensions were largely insensitive to the choice of material parameter provided that $\lambda\gtrsim 3\mu$. Since the crypt is bound to have very different material properties than the rest of the tissue, we tested the sensitivity of the recovered tensions to heterogeneous elastic constants. For this, we chose λ and μ to be 10 and 20 times larger in the crypt than in the rest of the tissue. The results were again insensitive.

Supplementary references

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