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Tissue curvature and apicobasal mechanical tension imbalance instruct cancer morphogenesis

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Supplementary Modelling Procedures

3D vertex model for epithelial mechanics

In this section we briefly describe the 3D vertex model for epithelial mechanics [1] used for simulations.

Geometry of the 3D vertex model

In the 3D vertex model the tissue is represented by a set of apical and basal vertices, associated with the apical and basal surfaces of the epithelium. Vertices correspond to the apical to basal intersection of three or more cells. Here for simplicity we have set the apical and basal tissue topologies to be identical. The vertices forming an apical, basal or lateral surface are not necessarily coplanar. In order to define the surface enclosing a cell, each cell boundary is defined by triangulation of the vertices on the contour of the boundary. The triangulation is obtained by joining neighbouring vertices on the contour with the centre of mass of the surface contour. Each cell is therefore enclosed by a set of triangles (Fig. 3a) which allows us to define the cell volume, and apical, basal and lateral surface areas.
Vertices move in space according to forces acting on them, as described in the sections below. In addition, the tissue topology is allowed to change through topological transitions involving neighbour exchange [1].
In simulations discussed here, the tissue is assumed to be confined in a periodic box in the z direction, with system size L_z.

Virtual mechanical work

The differential of the virtual work for the 3D vertex model is written

$$\delta W = \sum_k T_k \delta A_k - \sum_\alpha P^\alpha \delta V^\alpha, \tag{1}$$

where the index k labels interfaces and the index α labels cells. The volume of cell α and the surface area of interface k are denoted V^α and A_k respectively. The pressure acting in cell α is denoted P^α and the surface tension on interface k, T_k.
The cell pressure P^α is taken to be linear in the deviation of the volume from the preferred volume,

$$P^\alpha = -K_{3\mathrm{D}}(V^\alpha - V_0), \tag{2}$$

where V_0 is the preferred cell volume and the proportionality constant $K_{3\mathrm{D}}$ is a bulk elastic modulus.

Resulting forces

The force $\mathbf{F}_i$ that acts on vertex i with position $\mathbf{x}_i$ can be obtained by taking the derivative of the virtual work with respect to the vertex position:

$$\mathbf{F}_i = -\frac{\delta W}{\delta \mathbf{x}_i}. \tag{3}$$

The centres of mass of the surfaces are not taken as independent degrees of freedom, but their variation is taken into account in the calculation of the forces acting on the single vertices. The tissue is in mechanical

equilibrium if the forces on all vertices i vanish:

$$\mathbf{F}_i = \mathbf{0}. \tag{4}$$

Relaxation to mechanically equilibrated shapes

For the choice of the virtual work function we use here where surface tensions are constant, δW can be integrated to yield

$$W = \sum_\alpha -P^\alpha V^\alpha + T_a^\alpha A_a^\alpha + T_b^\alpha A_b^\alpha + \frac{T_l^\alpha}{2} A_l^\alpha \tag{5}$$

where A_a^α, A_b^α, A_l^α are the apical, basal and lateral surface area of cell α. T_a^α, T_b^α, T_l^α are the apical, basal and lateral surface tensions of cell α. For a fixed topology of the network of junctions and vertices, the work W can be minimised with respect to the position of the vertices and the system size L_z to find mechanically equilibrated configurations of the network. This is done numerically in a C++ implementation of the Polak-Ribiére conjugate gradient algorithm [2].

Simulations of early lesion deformation in the 3D vertex model

Starting configurations

Simulations are performed starting from a hexagonal packing on a cylinder with N_z cells along the longitudinal direction and N_c cells along the circumferential direction. We have chosen here $N_z = 40$ cells, and a varying number of circumferential cells N_c corresponding to tubes of varying diameters d. Apical and basal vertices are positioned at different radii away from the axis of symmetry of the cylinder. This initial configuration is then relaxed to a mechanically equilibrated shape by minimising the work function with respect to system size and vertex positions.

Mechanical parameters prior to transformed cell specification

description	**parameter**	**parameter value**
circumferential number of cells	N_c	variable (from 6 to 50)
longitudinal number of cells	N_z	40
cell volume	V_0/l_0^3	1
volume elasticity	$K_{3D}/(\bar{T}/l_0^4)$	1000
apical surface tension	$T_a/\bar{T}$	5.8
basal surface tension	$T_b/\bar{T}$	2.0
lateral surface tension	$T_l/\bar{T}$	set by Eq. 8.

Table 1: List of normalised parameters in 3D vertex model simulations, determining the tissue state prior to the deformation of the transformed epithelial area. The normalised apical and basal surface tensions are assumed to be proportional to normalised apical and basal pMLC2 intensities shown in Fig. 2j.

We discuss here mechanical parameters describing the tissue prior to the induction of transformed cells, which are set to be equal in all cells. Cells have a preferred volume V_0 with a volume elasticity K_{3D}, as well as apical, basal and lateral surface tensions T_a, T_b, T_l. The corresponding parameters are listed in

TABLE 1, where we use the length scale $l_0 = V_0^{\frac{1}{3}}$ and the tension $\bar{T}$ for normalisation. The high volume elasticity $K_{3D} l_0^4/\bar{T} = 1000 \gg 1$ ensures that the volume of the cells remains practically constant. The apical/basal mechanical tensions are estimated from experimental measurements by assuming that the average normalised pMLC2 intensity I_{MyoII} (shown in Fig. 2j) is proportional to the locally created tensions T with the proportionality constant $\bar{T}$:

$$T = \bar{T} I_{\mathrm{MyoII}} \ . \tag{6}$$

The corresponding values for normalised apical and basal surface tensions $T_a/\bar{T}$ and $T_b/\bar{T}$ are shown in Table 1.

The free mechanical adimensional parameter remaining is the lateral surface tension ($T_l/\bar{T}$), which we estimate from experimental shape measurements as follows.

The aspect ratio of simulated cells $\beta_{\mathrm{sim}} = h/\sqrt{A}$ with h the tissue height and A the cell cross-sectional area can be estimated by solving the following equation, obtained by calculating the preferred shape of a regular flat packing of hexagonal cells with mechanical parameters as specified above [1]:

$$\beta_{\mathrm{sim}} \simeq \frac{\sqrt{2}}{3^{\frac{1}{4}} T_l} \left(T_a + T_b\right). \tag{7}$$

We then require that the simulated aspect ratio in the equation is equal to the experimentally measured aspect ratio, which varies with the number of circumferential cells N_c (Figs. 1e, 1f, Extended Data Fig. 8a):

$$\beta_{\mathrm{sim}} = \beta_{\mathrm{exp}}(N_c) \quad . \tag{8}$$

To apply Eq. 8, we approximated $\beta_{\mathrm{exp}}(N_c)$ with a piecewise linear function:

$$\beta_{\mathrm{exp}}(N_c) = \beta_0 + N_c/24, \quad N_c < N_c^1 \tag{9}$$

$$\beta_{\mathrm{exp}}(N_c) = \beta_1, \quad N_c > N_c^1 \tag{10}$$

with $N_c^1 = 15$, $\beta_0 = 0.375$, $\beta_1 = 1$.

Simulation of deformation of transformed epithelium

To simulate the shape change of the transformed epithelium, we select a modified transformed cell in the simulated cylindrical epithelium. The apical, basal, and lateral surface tension and preferred volume of the transformed cell are then modified, according to

$$T_a^{\mathrm{tf}} = T_a(1 + \delta_a) \tag{11}$$

$$T_b^{\mathrm{tf}} = T_b(1 + \delta_b) \tag{12}$$

$$V_0^{\mathrm{tf}} = V_0(1 + \delta_v) \quad , \tag{13}$$

where the superscript tf refers to transformed cells.

To obtain values for the modified surface tensions, we assumed as above that apical and basal surface tensions are proportional to the fluorescence intensity of pMLC2. We quantified separately the change in pMLC2 fluorescence intensity in transformed cells and the surrounding wildtype cells around lesions

classified as exophytic or endophytic (Fig. 2j and Extended Data Fig. 6c). We find that pMLC2 fluorescence intensity is affected in transformed cells (Fig. 2j), and report the corresponding values in Table 3. Trends in pMLC2 intensity changes in transformed cells are similar in exophytic and endophytic lesions. We noticed however slight quantitative differences in pMLC2 intensities measured in transformed cells in endophytic and exophytic lesions (Table 3). Possibly, this difference can be attributed to the fact that some lesions classified as exophytic are in fact recombined, but untransformed cells in small ducts. Indeed, some recombined cells do not transform (Extended Data Fig. 2b), and we found that cellular morphology is not sufficient in 2D cross-section of small ducts to unambiguously distinguish transformed cells. We therefore use pMLC2 intensities determined in large ducts, where cellular transformation can be identified from the earliest stages, for simulations in Fig. 3. The corresponding values are reported in Table 2. For completeness, simulation results with the two sets of parameters obtained from exophytic and endophytic lesions are shown in Extended Data Fig. 8b. We find that our simulations results are only weakly affected by this choice in set of parameters.

description	**parameter**	**parameter value**
normalised apical surface tension in transformed cells	$T_a^{\mathrm{tf}}/\bar{T}$	3.6
normalised basal surface tension in transformed cells	$T_b^{\mathrm{tf}}/\bar{T}$	3.5

Table 2: List of normalised mechanical parameters of the transformed cells for 3D vertex model simulations, inferred from pMLC2 measurements shown in Fig. 2j.

parameter set	$T_a^{\mathrm{wt}}/\bar{T}$	$T_b^{\mathrm{wt}}/\bar{T}$	$T_a^{\mathrm{tf}}/\bar{T}$	$T_b^{\mathrm{tf}}/\bar{T}$
derived from endophytic lesions	5.8	2.0	3.6	3.5
derived from exophytic lesions	4.5	1.6	3.6	2.6

Table 3: List of varied normalised parameters of transformed cells in 3D vertex model simulations in Extended Data Fig. 8b.

To obtain values of the modified volume, we used measurements of cell width w, length l and height in transformed and wildtype cells, as well as the tube diameter d (Fig. 1f). We assume that cell shapes can be approximated by rectangular frustums, such that their volume can be estimated from:

$$V_0 \simeq h\frac{A_a + A_b}{2} \tag{14}$$

$$A_a \simeq wl\left(1 + \frac{h}{d}\right) \tag{15}$$

$$A_b \simeq wl\left(1 - \frac{h}{d}\right) \quad . \tag{16}$$

Using these relations, we find from experimental measurements average relative volume change $|\delta_v| < 0.07$ and, given the small difference, we use in simulations

$$\delta_v = 0. \tag{17}$$

Following these changes, the tissue shape is relaxed quasistatically to mechanical equilibrium. We then implement cell division of the transformed cell by introducing a new junction apically and basally with a random orientation. The tissue is then again relaxed quasistatically to mechanical equilibrium. This procedure is repeated by randomly selecting a cell within the set of transformed cells and performing a new

cell division and quasistatic relaxation step.

The simulation is stopped when a target number of transformed cells N_t is reached. This number of cells was chosen to match an estimate of the average number of cells in transformed clones in different experiments. This number is taken as $N_t \simeq 18$ and $N_t \simeq 59$, respectively, for comparison with the Fbw7-Kras clone sizes 10 days and 21 days after tamoxifen injection (Fig. 3d and Extended Fig. 8b-c), and $N_t \simeq 21$ for comparison with the Fbw7 clone size after 28 days (Fig. 4b).

In order to compare simulations with experiments (Fig. 3d and Extended Data Fig. 8b-c), we performed simulations with a varying circumferential number of cells N_c. We then used a linear fit to the experimentally determined relationship between the number of cells and the duct diameter (Extended Fig. 8a) to relate the number of cells in the simulation to a duct diameter. This is then used as the coordinate on the x axis in Fig. 3d, and Extended Data Fig. 8b and 8c.

Measurement of deformation of the simulated epithelium

To calculate the deformation resulting from the induction of transformed cells, we first calculate the position of the axis of symmetry prior to transformed cell specification by averaging the (x, y) positions of apical centroids in the entire tissue. We then quantify the average distance of all apical centroids from the axis of symmetry. This number is used to calculate the simulated tissue diameter prior to cell transformation, d_{wt}.

After the transformed epithelium has relaxed to a mechanically equilibrated state, we calculate a reference axis by averaging the (x, y) positions of apical centroids in the entire tissue. We then quantify the distance from the reference axis of the apical centroids, and select the point of maximum invagination or evagination. We then used the distance d_{max} from the axis of symmetry of the maximally invaginated or evaginated point to obtain an estimate of the apical to apical distance in the region of transformed epithelium indentation, according to:

$$d_{\mathrm{tf}} = d_{\mathrm{max}} + \frac{d_{\mathrm{wt}}}{2} \quad . \tag{18}$$

The relative deformation is then calculated as for experiments,

$$\epsilon = \frac{d_{\mathrm{tf}} - d_{\mathrm{wt}}}{d_{\mathrm{tf}} + d_{\mathrm{wt}}} \quad . \tag{19}$$

Continuum theory of transformed epithelium deformation in a cylindrical tissue

In this section, we describe a continuum theory for the growth and deformation of a transformed epithelial area in a cylindrical tissue (Extended Data Fig. 10a). Prior to the induction of transformed cells, the tissue is assumed to have the shape of a cylinder. A perturbation of the cylindrical shape is induced by growth and force generation within the transformed cells. Here we aim to calculate the deformed tissue shape, restricting ourselves to small deformations away from the cylindrical shape that would occur at tumour initiation. For simplicity, we also assume translational invariance along the long axis of the tube and consider a single cross-section of the tube.

To calculate deformations induced by the transformed cells, we describe the tissue as a material with an isotropic in-plane elasticity, a bending rigidity and internal active tensions and torques, arising from surface

tensions within the tissue. In particular, we discuss the effect of a difference in spontaneous bending moment ζ_c arising in the tissue. In a simple model where the tissue is represented by two apical and basal surfaces under isotropic tension and separated by a distance h, the spontaneous bending moment arises from the difference in apical and basal surface tensions T_a and T_b, with $\zeta_c = \frac{h}{2}(T_b - T_a)$. The spontaneous bending moment tends to drive tissue deformation away from a flat shape. A positive value of $\zeta_c > 0$ drives tissue deformation towards the apical side; i.e. in the case of pancreatic ducts, towards the inner part of the duct. Conversely, a negative value of ζ_c drives a deformation towards the basal side; i.e. towards the outer part of the duct. In lesions of pancreatic ducts, we find that pMLC2 levels are increased basally and decreased apically (Fig. 2j). We therefore expect that the basal surface tension is increased and the apical surface tension is decreased in the transformed region. As a result, there is a larger spontaneous bending moment ζ_c in the transformed region than in the wild-type tissue. This difference drives an invagination of the transformed region towards the centre of the tube.

Using a continuum theory taking into account the spontaneous bending moment, we show that the tissue deformation can therefore be understood from the competition of two driving mechanisms, arising from the growth of the transformed area and the change in the distribution of cytoskeleton-generated tensions within the transformed cells. While the growth of the transformed area drives an overall increase of the radius of the tube, cytoskeleton-generated tensions within the transformed cells generate a spontaneous bending moment which drives tissue invagination towards the centre of the tube. This invagination is resisted by the tissue bending rigidity, which provides a stronger resistance to deformation for smaller tube radii.

Mechanical equations

We use here notations of differential geometry as in [3]. Briefly, the tissue is represented by a surface $\mathcal{S}$ with positions $\mathbf{X}(s^1, s^2)$, and we denote the coordinates s^1, s^2 by latin indices i, j. The tangent vectors are denoted $\mathbf{e}_i = \partial_i \mathbf{X}$, the normal vector $\mathbf{n} = (\mathbf{e}_1 \times \mathbf{e}_2)/|\mathbf{e}_1 \times \mathbf{e}_2|$. The metric of the surface is denoted $g_{ij} = \mathbf{e}_i \cdot \mathbf{e}_j$ and the curvature tensor $C_{ij} = (\partial_i \mathbf{n}) \cdot \mathbf{e}_j$. We also introduce the antisymmetric tensor on the surface ϵ_{ij}, with $\epsilon_{12} = \sqrt{g} = -\epsilon_{21}$, with g the determinant of the metric. The surface element is denoted $dS = \sqrt{g} ds^1 ds^2$. We denote covariant components by lower indices, contravariant components by upper indices, and the covariant derivative by ∇_i. In the following we use cylindrical coordinates (θ, z), such that a point on the surface is given by

$$\mathbf{X}(\theta, z) = r(\theta) \cos\theta \mathbf{e}_x + r(\theta) \sin\theta \mathbf{e}_y + z \mathbf{e}_z \quad . \tag{20}$$

where $\mathbf{e}_x$, $\mathbf{e}_y$, $\mathbf{e}_z$ denotes a Cartesian basis.

We denote the tangential surface tension tensor t^{ij}, the tangential bending moment density tensor in the surface m^{ij} and its related tensor $\bar{m}^{ij} = -m^{ik}\epsilon_k{}^j$. We assume that no external force or torque density act on a surface element, and consider configurations of mechanical equilibrium with no flow. The tangential and normal force balance equations can then be written [3]

$$\nabla_i t^{ij} + C_i{}^j \nabla_k \bar{m}^{ki} = 0 \quad , \tag{21}$$

$$\nabla_i \nabla_j \bar{m}^{ji} - C_{ij} t^{ij} = 0 \quad . \tag{22}$$

We consider the following constitutive equations for the tension and bending moment density tensors

$$t_{ij} = K\frac{a-a_0}{a_0}g_{ij} \quad , \tag{23}$$

$$\bar{m}_{ij} = (\kappa C_k{}^k + \zeta_c)g_{ij} \quad , \tag{24}$$

where a is the local average cell area on the tissue surface, a_0 is a reference cell area, K is the isotropic elastic modulus, κ is the bending modulus of the tissue, and ζ_c is the spontaneous bending moment. As discussed above, in an epithelium, a spontaneous bending moment can arise from differences between the basal and apical surface tensions. For simplicity, we have not included possible stresses arising from shear elasticity or deviation from a preferred curvature in Eq. 23.

With the constitutive equations 23-24, the tangential and normal force balance equations can be rewritten

$$K\partial_i\left(\frac{a-a_0}{a_0}\right) + C_i{}^j\partial_j(\kappa C_k{}^k + \zeta_c) = 0 \quad , \tag{25}$$

$$\Delta(\kappa C_k{}^k + \zeta_c) - K\frac{a-a_0}{a_0}C_k{}^k = 0 \quad , \tag{26}$$

where we have introduced the Laplace-Beltrami operator, $\Delta = \frac{1}{\sqrt{g}}\partial_i(\sqrt{g}g^{ij}\partial_j f)$.

Cylinder shape

We now consider the special case of a cylinder of radius R with uniform cell area and spontaneous bending moment ζ_c^0. In that case the force balance equations reduce to $a = a_0$, and the cell area is in its preferred state. Assuming that cells are isotropically arranged such that their density along the circumferential direction is $1/\sqrt{a}$, the radius of the cylinder is then equal to

$$R = \frac{N_c l_0}{2\pi}, \tag{27}$$

where N_c is the circumferential number of cells in the cylinder, and $l_0 = \sqrt{a_0}$. According to Eq. 27, the radius of the tube increases linearly with the number of cells N_c.

Deformation induced by a perturbation of spontaneous bending moment

We now calculate the perturbation to the cylindrical shape induced by a spontaneous bending moment difference in the transformed region. We consider small deformations away from the cylindrical shape, and a homogeneous perturbation along the axis of the cylinder. We also assume here that the length of the cylinder in the longitudinal direction is maintained. The modified shape can then be described by

$$\mathbf{X}(\theta, z) = (R + \delta r(\theta))\cos\theta\mathbf{e}_x + (R + \delta r(\theta))\sin\theta\mathbf{e}_y + z\mathbf{e}_z \quad . \tag{28}$$

with $\delta r \ll R$. The only non-zero component of the curvature tensor is $C_\theta{}^\theta \simeq \frac{1}{R}(1 - \frac{\delta r}{R}) - \frac{\partial_\theta^2 \delta r}{R^2}$. To first order in the radial deformation δr, in the area deviation $(a-a_0)/a_0$, and in gradients of ζ_c, the force balance

equations read:

$$\partial_\theta \left(K \frac{a - a_0}{a_0} - \frac{\kappa}{R^3} \left(\delta r + \partial_\theta^2 \delta r \right) + \frac{\zeta_c}{R} \right) = 0 \quad , \tag{29}$$

$$\frac{1}{R} \partial_\theta^2 \left(-\frac{\kappa}{R^2} \left(\delta r + \partial_\theta^2 \delta r \right) + \zeta_c \right) - K \frac{a - a_0}{a_0} = 0 \quad , \tag{30}$$

which can be solved for the radial displacement δr and the average cell area a. In addition, if the total number of cells in the tissue $\int_S dS/a$ is conserved, we obtain expanding again in δr and $(a - a_0)/a_0$:

$$\int_{-\pi}^{\pi} d\theta \frac{a - a_0}{a_0} = \int_{-\pi}^{\pi} d\theta \frac{\delta r}{R} \quad , \tag{31}$$

where the term on the right-hand side is proportional to the change in tissue area between the deformed tissue and the cylinder.

We now consider a perturbation of the spontaneous bending moment for $-\pi < \theta < \pi$, with profile (Extended Data Fig. 10a):

$$\zeta_c(\theta) = \zeta_c^0 + \Delta\bar{\zeta}_c \quad -\theta_c < \theta < \theta_c \quad , \tag{32}$$

$$\zeta_c(\theta) = \zeta_c^0 \qquad\qquad \theta_c < \theta < \pi \text{ and } -\pi < \theta < -\theta_c \quad . \tag{33}$$

where $-\theta_c < \theta < \theta_c$ denotes the transformed region in the epithelium, and $\Delta\bar{\zeta}_c$ is the spontaneous bending moment difference between the transformed and wild-type tissue. In lesions induced in the pancreas ducts described in this work, we expect $\Delta\bar{\zeta}_c > 0$. Indeed we find that pMLC2 levels are increased basally and decreased apically in the transformed cells (Fig. 2j), and as a result we expect the apical surface tension to decrease and the basal surface tension to increase in the transformed region. Therefore the spontaneous bending moment $\zeta_c \sim \frac{h}{2}(T_b - T_a)$ is higher in transformed cells.

We then find the following solution for Eqs. 29-30:

$$\delta r(\theta) = \frac{\Delta\bar{\zeta}_c R^2}{2\pi\kappa} \left[(-2(\pi - \theta_c)(\cos\theta \cos\theta_c - 1) - \sin\theta_c (2\theta \sin\theta + 3\cos\theta)) \right] \quad 0 < \theta < \theta_c \quad , \tag{34}$$

$$\delta r(\theta) = \frac{\Delta\bar{\zeta}_c R^2}{2\pi\kappa} \left[(2(\pi - \theta)\sin\theta \sin\theta_c + \cos\theta (2\theta_c \cos\theta_c - 3\sin\theta_c) - 2\theta_c) \right] \quad \theta_c < \theta < \pi \quad , \tag{35}$$

where we have imposed a zero displacement of the centre of mass of the shape $\int_{-\pi}^{\pi} d\theta \delta r(\theta) \cos\theta = 0$ and $\int_{-\pi}^{\pi} d\theta \delta r(\theta) \sin\theta = 0$, and imposed the continuity of the torque $\bar{m}_\theta{}^\theta$ and its derivative at θ_c. In addition, $\delta r(\theta) = \delta r(-\theta)$ for $-\pi < \theta < 0$. We find that the increase in diameter along the axis of symmetry is

$$\delta r(0) + \delta r(\pi) = \frac{\Delta\bar{\zeta}_c R^2}{\kappa} \left[1 - \cos\theta_c - \frac{2\theta_c}{\pi} \right] \quad . \tag{36}$$

The magnitude of the deformation therefore depends on the ratio between the spontaneous bending moment difference $\Delta\bar{\zeta}_c$, which drives the deformation, and the bending modulus κ, which resists the deformation. For $\theta_c < \pi/2$ and $\Delta\bar{\zeta}_c > 0$, Eq. 36 yields a negative value, corresponding to an inward deformation. Therefore the spontaneous bending moment difference tends to drive invagination of the transformed epithelium. In the next section we introduce in addition the effect of growth and division of the transformed cells.

Deformation induced as a result of transformed cell proliferation

We now introduce a description of the growth of a early lesion from proliferation of a single cell, with a spontaneous bending moment difference acting in transformed cells.

We consider a cross-section of a cylindrical tube containing N_c cells around its circumference. We assume that within the cross-section, a single transformed cell divides several times to produce N_t transformed cells. As a result, the total number of cells in a cross-section of the tube increases from N_c to N_c-1+N_t. According to Eq. 27 and assuming that the transformed cells have the same preferred area a_0 as wild-type cells, the tube radius then increases from R to $R' = R + (N_t - 1)l_0/(2\pi)$.

In addition, the N_t transformed cells generate an additional internal spontaneous torque $\Delta\bar{\zeta}_c$. This leads to a deformation given by Eq. 36, with R replaced by R' and $\theta_c = l_0 N_t/(2R')$.

Combining these two deformations, we find that the overall change in inner tube end-to-end distance along the axis of symmetry is (Extended Data Fig. 10b)

$$\begin{aligned} \frac{d_{\rm tf} - d}{d} &= \frac{N_t - 1}{2\pi R} l_0 + \frac{\Delta\bar{\zeta}_c R'^2}{2\kappa R}\left[1 - \cos\left(\frac{l_0 N_t}{2R'}\right) - \frac{l_0 N_t}{\pi R'}\right] \\ R' &= R + \frac{(N_t - 1)l_0}{2\pi} \quad , \end{aligned} \tag{37}$$

where $d = 2R$. Corresponding deformation profiles are shown in Extended Data Fig. 10c.

Assuming that $l_0 N_t \ll 2\pi R$ and $l_0 N_t \ll \kappa/\Delta\bar{\zeta}_c$; i.e. when the size of the transformed area is small compared to the perimeter of the cylinder and the characteristic length $\kappa/\Delta\bar{\zeta}_c$, this expression can be simplified to give

$$\frac{d_{\rm tf} - d}{d} \simeq \frac{N_t - 1}{2\pi R} l_0 - \frac{\Delta\bar{\zeta}_c l_0 N_t}{2\kappa\pi} \quad . \tag{38}$$

For $\Delta\bar{\zeta}_c > 0$, there is a competition between the growth of the transformed area (first term in Eq. 38), which drives an outward deformation, and the deformation induced by the spontaneous bending moment difference in the transformed area (second term in Eq. 38), which drives an inward deformation. For large radius, the second term dominates, as the resistance to deformation due to the bending elasticity decreases for larger tubes (Extended Data Fig. 10b). In this limit, the overall deformation changes sign at a threshold radius

$$R^* = \frac{\kappa}{\Delta\bar{\zeta}_c}\frac{N_t - 1}{N_t} \simeq \frac{\kappa}{\Delta\bar{\zeta}_c} \quad . \tag{39}$$

where the last approximation is for a large number of transformed cells N_t. A corresponding phase diagram for the direction of tumour deformation is plotted in Extended Data Fig. 10d.

In the same limit $l_0 N_t \ll 2\pi R$ and $l_0 N_t \ll \kappa/\Delta\bar{\zeta}_c$, it is also interesting to note that the curvature at the centre of the transformed region reads

$${C_\theta}^\theta(\theta = 0) \simeq \frac{1}{R} - \frac{\Delta\bar{\zeta}_c}{\kappa} \quad , \tag{40}$$

such that the threshold radius for inversion of curvature of the transformed tissue region is

$$R_c = \frac{\kappa}{\Delta\bar{\zeta}_c} \quad . \tag{41}$$

Therefore, we find that in this simplified description, a similar threshold radius is found for inversion of the curvature at the centre of the transformed region, and to determine whether the transformed area deformation along the axis of symmetry is inward or outward.

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