

Geometry of T1 transitions in epithelia

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The flows of tissues of epithelial cells often involve T1 transitions. These neighbor exchanges are irreversible rearrangements crossing an energy barrier. Here, by an exact geometric construction, I determine this energy barrier for general, isolated T1 transitions dominated by line tensions. I show how deviations from regular cell packing reduce this energy barrier, but find that line tension fluctuations increase it on average. By another exact construction, I prove that the nonlinear tensions in vertex models of tissues also resist T1 transitions. My results thus form the basis for coarse-grained understanding of cell neighbor exchanges for continuum descriptions of epithelia.

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The deformations of epithelial tissues [Fig. 1(a)] in development are often associated with cell intercalations [1,2] during which initially neighboring cells are separated by changes of the topology of the network of cell-cell contacts [Fig. 1(b)]. Cell intercalations are involved in particular in the processes of convergence and extension [3,4] that pervade morphogenesis; an example is germband extension in *Drosophila* [5–8].

In the language of two-dimensional foams [9], these cell neighbor exchanges are T1 transitions. Mechanically, they are irreversible rearrangements of the tissue which involve the crossing of a barrier $\mathcal{E}_b$ in the energy landscape [Fig. 1(c)] near the T1 transition, which has a cuspy shape [10–12]. The vanishing of this energy barrier is associated with tissue fluidization [13], which has important biological roles in development and disease [14,15], for example in zebrafish morphogenesis [16–18].

Biological tissues are not of course two-dimensional, and their three-dimensional nature gives rise to complex cell neighbor relationships [19–21], in which for example apical and basal cell surfaces have different cell-cell contact networks. In turn, this gives rise to a richer zoo of cell neighbor exchanges [22]. Still, this two-dimensional picture has proven useful to elucidate the physical principles governing the interplay between the tensions in cell-cell junctions, their fluctuations, and the resulting active T1 transitions and fluidization of tissues [10–13,23–32]. In particular, recent work has shown how mechanochemical feedbacks can generate such active T1 transitions [33].

There is however a more geometric component to the mechanics of T1 transitions, too: Epithelial tissues often feature large amounts of cell shape variability, as exemplified by the *Drosophila* wing disk epithelium [34] shown in Fig. 1(a). This disorder takes the geometry of a T1 transition far away from the regular T1 transition sketched in Fig. 1(b), but its effect has remained unexplored.

Here, I show how this cell-scale disorder affects the energy barrier to isolated T1 transitions: I start from an exact geometric construction of a general T1 transition in the case in which the mechanics are dominated by homogeneous line tensions. I go on to extend these exact results to inhomogeneous and nonlinear line tensions.

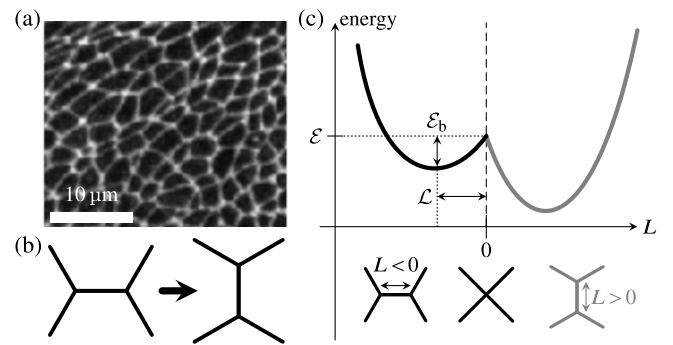


FIG. 1. T1 transitions. (a) Example of a two-dimensional epithelial tissue, the *Drosophila* wing disk epithelium, taken from Ref. [34]. Lines are cell boundaries. Scale bar: 10 μm . (b) Schematic of a T1 transition: before the T1 transition, the “top” and “bottom” cells are neighbors; after the transition, the “left” and “right” cells are neighbors. (c) Generic energy landscape of a T1 transition, plotted against the T1 transition coordinate L , the signed length of the central edge. The energy landscape has a cusp at the T1 transition point $L = 0$. The energy minimum for $L < 0$ is at $L = -\mathcal{L}$, where $\mathcal{L} > 0$. This and the energy $\mathcal{E}$ at the T1 transition define the energy barrier $\mathcal{E}_b$. The energy landscape for $L > 0$ is similar. Shape insets: T1 transition and definition of L .

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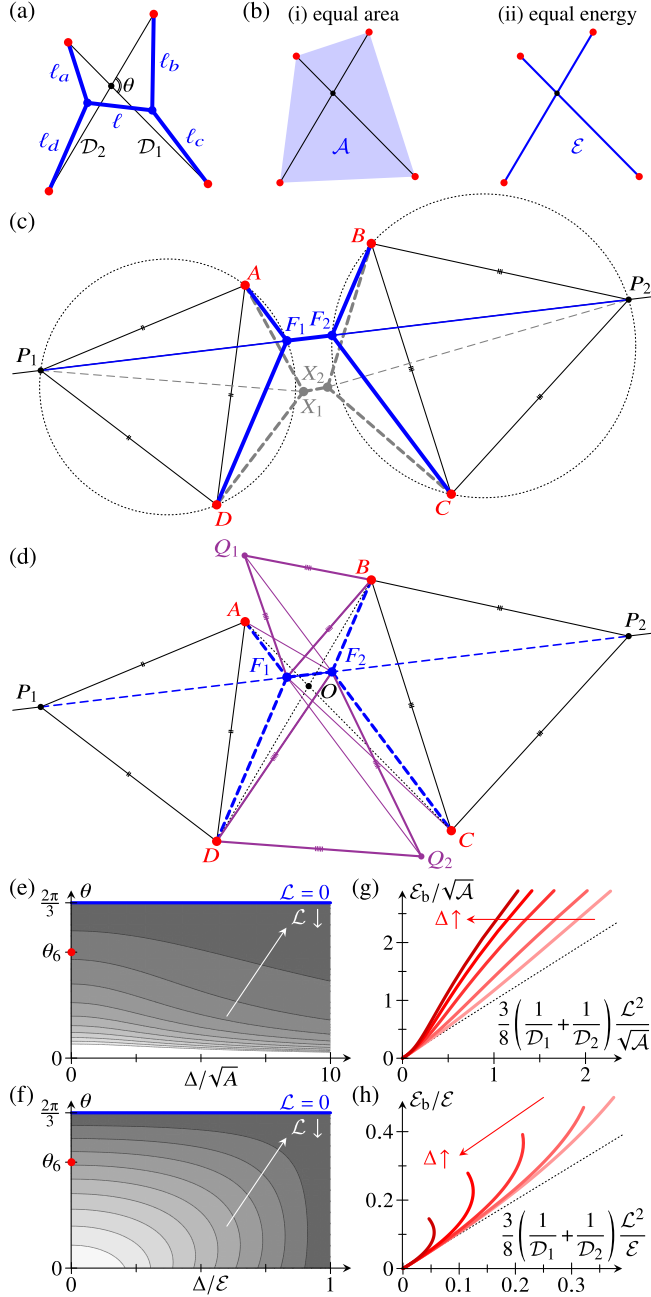


FIG. 2. Geometry of an isolated T1 transition dominated by (homogeneous) line tensions. (a) Plot of an isolated T1 transition: The outer vertices (red) are fixed as the central edge formed by the inner vertices (blue) undergoes a T1 transition. These outer vertices define a quadrilateral with diagonals $\mathcal{D}_1, \mathcal{D}_2$ that are at an angle θ to each other. (b) Ensembles of isolated T1 transitions: (i) In the equal-area ensemble, the area $\mathcal{A}$ of the quadrilateral is fixed. (ii) In the equal-energy ensemble, the energy $\mathcal{E}$ of the transition configuration is held constant. (c) Geometric construction of the positions F_1, F_2 of the inner vertices minimizing the line-tension energy for fixed outer vertices A, B, C, D . See text for further explanation. (d) Calculation of the energy barrier $\mathcal{E}_b$ and the distance $\mathcal{L}$ from the T1 transition based on this geometric construction. See text for further explanation. (e) Contour plot of $\mathcal{L}$ against θ and the asymmetry $\Delta = |\mathcal{D}_1 - \mathcal{D}_2|$ in the equal-area ensemble (i). The red mark corresponds to a regular hexagonal lattice $\theta = \theta_6$, $\Delta = 0$. On the (blue) line $\theta = 2\pi/3$, $\mathcal{L} = 0$. (f) Analogous plot for the equal-energy ensemble (ii). (g) Plot

An isolated T1 transition is defined by six cell vertices: four “outer” vertices held fixed and two “inner” vertices that undergo the T1 transition [Fig. 2(a)]. The four outer vertices define a (convex) quadrilateral with diagonals $\mathcal{D}_1, \mathcal{D}_2$ making an angle θ with each other. In a regular hexagonal lattice of cells, $\theta = \theta_6 \equiv \tan^{-1} 4\sqrt{3}$ and $\mathcal{D}_1 = \mathcal{D}_2$. This regular case underpins mean-field arguments for tissue fluidization [13,19,31]. To analyze the general geometry, it will be useful to introduce two geometric ensembles [Fig. 2(b)]: (i) an equal-area ensemble in which the area $\mathcal{A}$ of the quadrilateral defined by the four outer vertices is held constant, and (ii) an equal-energy ensemble in which the energy $\mathcal{E}$ at the point of the T1 transition [Fig. 1(c)] is held constant instead.

I begin by assuming that the mechanics are dominated by homogeneous line tensions. I denote by $\ell_a, \ell_b, \ell_c, \ell_d, \ell$ the lengths of the cell edges, shown in Fig. 2(a), so that the energy is $E = \ell_a + \ell_b + \ell_c + \ell_d + \ell$. Labelling the four outer vertices A, B, C, D as shown in Fig. 2(c), I erect equilateral triangles ADP_1 and BCP_2 outwards on line segments $[AD]$ and $[BC]$. Line P_1P_2 intersects their circumcircles again at F_1 and F_2 , respectively. I claim that F_1, F_2 are the positions of the inner vertices that minimize E . The proof relies on the following rephrasing of Pompeiu’s theorem of classical Euclidean geometry [35]:

Lemma 1. Let ABC be an equilateral triangle. For any point P , $|AP| + |BP| \geq |CP|$, with equality if and only if P lies on the minor arc $\widehat{AB}$ of the circumcircle of ABC .

Let X_1, X_2 be points in the plane, so that $\ell_a = |AX_1|$, $\ell_b = |BX_2|$, $\ell_c = |CX_2|$, $\ell_d = |DX_1|$, $\ell = |X_1X_2|$, as shown in Fig. 2(c). Thus, by the above lemma,

$$E = (|AX_1| + |DX_1|) + |X_1X_2|(|BX_2| + |CX_2|) \geq |P_1X_1| + |X_1X_2| + |P_2X_2| \geq |P_1P_2|, \quad (1)$$

in which the final inequality follows from the triangle inequality. Equality holds throughout if and only if the following three conditions hold: (1) X_1 lies on the minor arc $\widehat{AD}$ of the circumcircle of triangle P_1AD , (2) X_2 lies on the minor arc $\widehat{BC}$ of the circumcircle of triangle P_2BC , and (3) points P_1, X_1, X_2, P_2 lie on a line in this order. These conditions imply $X_1 = F_1, X_2 = F_2$. An equivalent construction was obtained in Ref. [36] as the solution of the Steiner minimal tree problem [37] on four vertices; I add that Ref. [36] analyzes carefully degenerate cases that I have neglected [38].

This construction requires P_1, F_1, F_2, P_2 to be in this order. Let O denote the intersection of the diagonals AC, BD , as in Fig. 2(d). Angles $\angle AF_1P_1, \angle ADP_1$ intercept the same chord of the circumcircle of the cyclic quadrilateral AF_1DP_1 so $\angle AF_1P_1 = \angle ADP_1 = 60^\circ$ since triangle ADP_1 is equilateral. Similarly, $\angle CF_2P_2 = 60^\circ$, whence $AF_1 \parallel CF_2$. Analogously, $BF_2 \parallel DF_1$. This shows that $F_1 = F_2 = F$ if and only if $F = O$, in which case $\theta = \angle AF_1D = 180^\circ - \angle DP_1A = 120^\circ$. It is clear that P_1, F_1, F_2, P_2 are in this order for small θ and

of the energy barrier $\mathcal{E}_b$ against $\mathcal{L}^2$, for the equal-area ensemble (i) and for different values of Δ . The dotted line shows the asymptotic relation $\mathcal{E}_b/\mathcal{L}^2 \sim 3(\mathcal{D}_1 + \mathcal{D}_2)/(8\mathcal{D}_1\mathcal{D}_2)$. (h) Analogous plot for the equal-energy ensemble (ii).

that F_1, F_2 vary continuously on line P_1P_2 as θ increases. Hence, P_1, F_1, F_2, P_2 are in this order and the minimum $E = |P_1P_2|$ in Eq. (1) can be attained only if $\theta \leq 120^\circ$.

To understand the case $\theta \geq 120^\circ$, I prove a slightly more general statement: If X_1, X_2 minimize E , then they are the respective Fermat points [39–41] of triangles AX_2D , BX_1C . To show this, I assume to the contrary, and without loss of generality, that X_1 is different from the Fermat point X'_1 of triangle AX_2D . Moving $X_1 \rightarrow X'_1$ gives a valid T1 configuration or “Steiner tree” because X'_1 is an interior point of AX_2D . This move reduces E because, by definition of the Fermat point, $|AX'_1| + |DX'_1| + |X'_1X_2| < |AX_1| + |DX_1| + |X_1X_2|$, which contradicts minimality, so proves my claim. Now there are two possibilities: (1) $X_1 \neq X_2$ and (2) $X_1 = X_2 = X$. In case (1), from properties of Fermat points [39,40], X_1, X_2 are the respective second intersections of the circumcircles of triangles ADP_1 and BCP_2 with lines PX_2, PX_1 . This implies that P_1, X_1, X_2, P_2 lie on a line, whence, again, $X_1 = F_1, X_2 = F_2$, and hence $\theta \leq 120^\circ$ by the above. Case (2) must therefore arise for $\theta \geq 120^\circ$. In that case, $\mathcal{L} = 0$ and $\mathcal{E}_b = 0$ by definition. The “other” T1 configuration is now the energy minimum; by taking $\theta \rightarrow 180^\circ - \theta$, I

note that it exists for $\theta \geq 60^\circ$. I will thus focus on $\theta \leq 120^\circ$ below.

By definition, the energy $\mathcal{E}$ at the T1 transition point [Fig. 1(c)] minimises $|AX| + |BX| + |CX| + |DX|$ over all positions of the collapsed fourfold vertex X . It is well known [42] that this sum of the distances from a point to the vertices of a convex quadrilateral is minimized at the intersection of its diagonals. This shows that $X = O$, i.e., $\mathcal{E} = |AO| + |BO| + |CO| + |DO| = |AC| + |BD|$. The energy barrier [Fig. 1(c)] is the difference between this energy and the ground-state energy determined by Eq. (1) for $\theta \leq 120^\circ$. Hence, $\mathcal{E}_b = |AC| + |BD| - |P_1P_2|$. Moreover, the distance from the T1 transition, i.e., the length of the inner edge, is $\mathcal{L} = |F_1F_2|$. I am left to express these quantities in terms of the geometry of quadrilateral $ABCD$ [Fig. 2(a)]. To compute $\mathcal{L}$, I rely, again, on properties of Fermat points [39,40]: if I erect equilateral triangles BF_1Q_1 and DF_2Q_2 on segments $[BF_1]$ and $[DF_2]$, respectively, as shown in Fig. 2(d), then lines AQ_2 and CQ_1 intersect line P_1P_2 at F_1 and F_2 , respectively. It turns out to be convenient to take these computations to the complex plane. Using MATHEMATICA (Wolfram, Inc.), I find, in the Supplemental Material [43],

$$\mathcal{E}_b = \mathcal{D}_1 + \mathcal{D}_2 - [\mathcal{D}_1^2 + \mathcal{D}_2^2 + (\sqrt{3} \sin \theta - \cos \theta) \mathcal{D}_1 \mathcal{D}_2]^{1/2}, \quad (2a)$$

$$\mathcal{L} = \frac{(3 \cos \theta + \sqrt{3} \sin \theta)^3}{9(2 + \cos 2\theta + \sqrt{3} \sin 2\theta)} \frac{\mathcal{D}_1 \mathcal{D}_2}{[\mathcal{D}_1^2 + \mathcal{D}_2^2 + (\sqrt{3} \sin \theta - \cos \theta) \mathcal{D}_1 \mathcal{D}_2]^{1/2}}. \quad (2b)$$

Remarkably, these results depend on the geometry of the fixed outer vertices only through θ , $\mathcal{D}_1 = |AO| + |CO|$, $\mathcal{D}_2 = |BO| + |DO|$, but are independent of $|AO| - |CO|$, $|BO| - |DO|$. Thus, neither the energy barrier to nor the distance from the T1 transition are affected by changes, at constant θ , of the relative position of the diagonals of the outer quadrilateral.

In the ensembles introduced in Fig. 2(b), I can use $2\mathcal{A} = \mathcal{D}_1 \mathcal{D}_2 \sin \theta$ or $\mathcal{E} = \mathcal{D}_1 + \mathcal{D}_2$ to express the dependence of Eqs. (2) on the geometry of this quadrilateral more symmetrically in terms of θ and $\Delta = |\mathcal{D}_1 - \mathcal{D}_2|$ only. Since $\mathcal{D}_1 = \mathcal{D}_2$ for a regular hexagonal lattice, Δ quantifies the geometric disorder of outer vertices.

Contour plots of $\mathcal{L}$ reveal that, in both the equal-area ensemble [Fig. 2(e)] and the equal-energy ensemble [Fig. 2(f)], the distance from the T1 transition decreases as Δ increases at constant θ . Similarly (not shown), the energy barrier decreases as Δ increases at constant θ . Thus, in this tension-dominated regime, geometric disorder facilitates isolated T1 transitions. Both $\mathcal{E}_b$ and $\mathcal{L}$ vanish as $\theta \rightarrow 120^\circ$, as expected [Figs. 2(e) and 2(f)]. Expanding Eq. (2) in this limit yields

$$\frac{\mathcal{E}_b}{\mathcal{L}^2} \sim \frac{3}{8} \left(\frac{1}{\mathcal{D}_1} + \frac{1}{\mathcal{D}_2} \right) \quad \text{for } \theta \approx 120^\circ. \quad (3)$$

This displays the scaling $\mathcal{E}_b \sim \mathcal{L}^2$ that Ref. [12] has shown to be generic. For larger $\mathcal{L}$, $\mathcal{E}_b$ increases faster than this scaling, in both ensembles [Figs. 2(g) and 2(h)], with the increase being larger at larger Δ .

Next, I extend my results to the more general energy $E = \gamma_a \ell_a + \gamma_b \ell_b + \gamma_c \ell_c + \gamma_d \ell_d + \gamma \ell$, with (inhomogeneous) line tensions $\gamma_a, \gamma_b, \gamma_c, \gamma_d, \gamma$ in the corresponding sides. This extends the above in the same way as the Fermat–Torricelli problem is extended by the Steiner problem [41] of minimizing the weighted sum of the distances to the vertices of a triangle, which is a special case of the Weber problem of operations research [51,52].

To minimize E in this case, I erect a triangle ADP_1 such that $|AD| : |P_1D| : |P_1A| = \gamma : \gamma_a : \gamma_d$ outwards on line segment $[AD]$ and a triangle BCP_2 such that $|BC| : |P_2C| : |P_2B| = \gamma : \gamma_b : \gamma_c$ outwards on line segment $[BC]$. This assumes, of course, the existence of such triangles, and hence that the line tensions $\gamma_a, \gamma_b, \gamma_c, \gamma_d, \gamma$ satisfy the triangle inequalities, i.e., that they are not too different. This is probably a significant mathematical restriction of the geometric problem, but not perhaps a significant physical restriction of the biological problem, the more so as I will analyze small fluctuations around homogeneous tensions. I claim that the points F_1 and F_2 at which line P_1P_2 intersects the circumcircles of triangles ADP_1 and BCP_2 are again the positions of the inner vertices that minimize E . Indeed, Ptolemy’s inequality [40], applied to quadrilateral AX_1DP_1 , yields $|AX_1||P_1D| + |DX_1||P_1A| \geq |P_1X_1||AD|$, and hence, on scaling by $|AD|$, $\gamma_a|AX_1| + \gamma_d|DX_1| \geq \gamma|P_1X_1|$, with equality if and only if A, X_1, D, P_1 lie on a circle in this order. Similarly, $\gamma_b|BX_2| + \gamma_c|CX_2| \geq \gamma|P_2X_2|$, with equality if and only if B, X_2, C, P_2 are cocyclic.

Thus,

$$E = (\gamma_a|AX_1| + \gamma_d|DX_1|) + \gamma|X_1X_2| + (\gamma_b|BX_2| + \gamma_c|CX_2|) \\ \geq \gamma(|P_1X_1| + |X_1X_2| + |P_2X_2|) \geq \gamma|P_1P_2|, \quad (4)$$

with equality, again, if and only if $X_1 = F_1$ and $X_2 = F_2$ and P_1, F_1, F_2, P_2 lie on a line in this order. By contrast to the homogeneous case, I am not aware of a simple condition equivalent to the last one. Again, this construction has additional geometric properties [53], but it does not lend itself to further general calculations.

It is therefore meet and right to specialize these results to the limit of small fluctuations, and analyze the

energy barrier close to a T1 transition. Accordingly, I write $\theta = 2\pi/3 - \vartheta$, where $\vartheta \ll 1$, and introduce fluctuations $\gamma_a = 1 + \vartheta\Gamma_a$, $\gamma_b = 1 + \vartheta\Gamma_b$, $\gamma_c = 1 + \vartheta\Gamma_c$, $\gamma_d = 1 + \vartheta\Gamma_d$, $\gamma = 1 + \vartheta\Gamma$, in which $\Gamma_a, \Gamma_b, \Gamma_c, \Gamma_d, \Gamma$ are independent, identically distributed fluctuations of zero mean and variance σ^2 . For these fluctuations, I compute [43] the energy barrier $\mathcal{E}_b$ to a T1 transition by asymptotic expansion in ϑ . As I am not aware of an exact construction of the T1 transition point for this inhomogeneous case, I obtain $\mathcal{E}$ by minimizing energy order by order in ϑ .

I thus find [43] that $\mathcal{E}_b = O(\vartheta^2)$, i.e., that the energy barrier from homogeneous tensions and the effect of fluctuations only arise at order $O(\vartheta^2)$. Continuing the asymptotic expansion to this order, I obtain [43]

$$\mathcal{E}_b = \vartheta^2 \left\{ \frac{\mathcal{D}_1\mathcal{D}_2}{2(\mathcal{D}_1 + \mathcal{D}_2)} + \frac{(\mathcal{D}_1\mathcal{D}_2\bar{\Gamma} + \mathcal{D}_1\delta_2\bar{\Gamma}_1 + \mathcal{D}_2\delta_1\bar{\Gamma}_2)[\mathcal{D}_1\mathcal{D}_2(4\sqrt{3} + \bar{\Gamma}) + \mathcal{D}_1\delta_2\bar{\Gamma}_1 + \mathcal{D}_2\delta_1\bar{\Gamma}_2]}{24\mathcal{D}_1\mathcal{D}_2(\mathcal{D}_1 + \mathcal{D}_2)} \right\} + O(\vartheta^3), \quad (5a)$$

with $\delta_1 = |AO| - |CO|$, $\delta_2 = |BO| - |DO|$, $\bar{\Gamma} = \Gamma_a + \Gamma_b + \Gamma_c + \Gamma_d - 4\Gamma$, $\bar{\Gamma}_1 = 2\Gamma_c + \Gamma_d - 2\Gamma_a - \Gamma_b$, $\bar{\Gamma}_2 = \Gamma_c + 2\Gamma_d - \Gamma_a - 2\Gamma_b$. The first term in brackets is the leading-order energy barrier in the homogeneous case; the second term is associated with the tension fluctuations. It is clear that this second term can overcome the first, i.e., that small tension fluctuations can overcome the homogeneous energy barrier to drive T1 transitions. This is consistent with previous work highlighting the importance of tension fluctuations for tissue fluidization [11,27,54–57]. Averaging Eq. (7) yields

$$\langle \mathcal{E}_b \rangle = \vartheta^2 \left[\frac{\mathcal{D}_1\mathcal{D}_2}{2(\mathcal{D}_1 + \mathcal{D}_2)} + \frac{4(\mathcal{D}_1\delta_2 + \mathcal{D}_2\delta_1)^2 + \mathcal{D}_1^2\delta_2^2 + \mathcal{D}_2^2\delta_1^2 + 10\mathcal{D}_1^2\mathcal{D}_2^2\sigma^2}{12\mathcal{D}_1\mathcal{D}_2(\mathcal{D}_1 + \mathcal{D}_2)} \right] + O(\vartheta^3), \quad (5b)$$

showing that the average correction from fluctuations is positive. Thus, on average, line-tension fluctuations increase the energy barrier to T1 transitions. This suggests in particular that slow fluctuations suppress T1 transitions compared to fast fluctuations because edges are in states in which their inhomogeneous tensions increase $\mathcal{E}_b$ most of the time. This is consistent with the numerical observations, in the vertex model [44–48], of Ref. [57].

Finally, I turn to the case of (homogeneous) nonlinear line tensions, for which $E = \ell_a^2 + \ell_b^2 + \ell_c^2 + \ell_d^2 + \ell^2$. Nonlinear tensions of this ilk were introduced into tissue mechanics in Ref. [49]. Unlike the standard perimeter elasticity in vertex models of tissues [44–48,58], they are local, in that E can be expressed in terms of the lengths of the edges involved in the isolated T1 transition only. As shown in Fig. 3(a), I denote by M_1, M_2 the respective midpoints of line segments $[AD]$, $[BC]$, and divide line segment $[M_1M_2]$ into four equal segments by points G_1, M, G_2 . By construction, M_1G_2 is a median of triangle AG_2D , and $|G_1G_2| = 2|M_1G_1|$. It is well known [39,40] that this implies that G_1 is the centroid of triangle AG_2D . Analogously, G_2 is the centroid of triangle BG_1C . I claim that G_1, G_2 are now the positions of the inner vertices that minimize E . Thus, in this nonlinear case, the pair of Fermat points of the linear case is replaced by a pair of centroids. To prove this, I shall need an arcane piece of triangle trivia [40]:

Lemma 2. Let ABC be a triangle with centroid G . Then $|PA|^2 + |PB|^2 + |PC|^2 = |GA|^2 + |GB|^2 + |GC|^2 + 3|GP|^2$ for any point P .

Let X_1, X_2 be points in the plane. Applying this result to points X_1, X_2 in triangles AG_2D, BG_1C , respectively,

$$E = (|AX_1|^2 + |DX_1|^2) + (|BX_2|^2 + |CX_2|^2) + |X_1X_2|^2 \\ = (|AG_1|^2 + |DG_1|^2 + |G_1G_2|^2 + 3|G_1X_1|^2 - |X_1G_2|^2) \\ + (|BG_2|^2 + |CG_2|^2 + |G_1G_2|^2 + 3|G_2X_2|^2 - |X_2G_1|^2) \\ + |X_1X_2|^2 \\ = |AG_1|^2 + |DG_1|^2 + |BG_2|^2 + |CG_2|^2 + |G_1G_2|^2 \\ + (|X_1X_2|^2 + |X_2G_2|^2 + |G_1G_2|^2 + |G_1X_1|^2 \\ - |X_1G_2|^2 - |X_2G_1|^2) + 2(|G_1X_1|^2 + |G_2X_2|^2) \\ \geq |AG_1|^2 + |DG_1|^2 + |BG_2|^2 + |CG_2|^2 + |G_1G_2|^2, \quad (6)$$

in which I have applied Euler's quadrilateral theorem [40,59] to quadrilateral $X_1X_2G_2G_1$ to note that the terms in parentheses in the penultimate equation are nonnegative. This completes the proof.

It is now clear that $\mathcal{L} = |G_1G_2| = |M_1M_2|/2$, which cannot vanish if $ABCD$ is convex. This establishes that nonlinear tensions resist T1 transitions. Next, I introduce the barycenter Z of quadrilateral $ABCD$. It minimizes the sum of the squares of the distances to its vertices [60], so that the energy at the T1 transition point [Fig. 1(c)] is $\mathcal{E} = |AZ|^2 + |BZ|^2 + |CZ|^2 + |DZ|^2$. With this result, I can compute [43]

$$\mathcal{E}_b = \frac{\mathcal{D}_1^2 + \mathcal{D}_2^2 + 2\mathcal{D}_1\mathcal{D}_2 \cos \theta}{8} = \frac{\mathcal{L}^2}{2}, \quad (7)$$

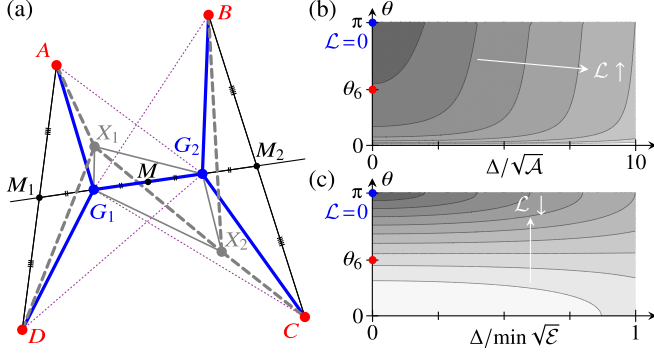


FIG. 3. Geometry of an isolated T1 transition dominated by (homogeneous) nonlinear line tensions. (a) Construction of the positions G_1, G_2 minimizing the nonlinear line-tension energy for fixed outer vertices A, B, C, D . See text for further explanation. (b) Contour plot of the length $\mathcal{L}$ of the central edge against θ and the asymmetry $\Delta = |\mathcal{D}_2 - \mathcal{D}_1|$ [Fig. 2(a)] in the equal-area ensemble [Fig. 2(b), case (i)]. The red mark corresponds to a regular hexagonal lattice $\theta = \theta_6$, $\Delta = 0$. The blue mark is the single point $\Delta = 0$, $\theta = \pi$ at which $\mathcal{L} = 0$. (c) Analogous contour plot in the equal-energy ensemble [Fig. 2(b), case (ii)]. See text for further explanation.

so $\mathcal{E}_b = \mathcal{L} = 0$ in and only in the degenerate case $\theta = \pi$, $\mathcal{D}_1 = \mathcal{D}_2$. Again, these results only depend on the diagonals $\mathcal{D}_1, \mathcal{D}_2$ of the quadrilateral formed by the outer vertices of the T1 transition and the angle θ between them [Fig. 2(a)]. Interestingly, the generic scaling $\mathcal{E}_b \sim \mathcal{L}^2$ for small $\mathcal{L}$ [12] is an exact proportionality in this case. In the equal-area ensemble [Fig. 2(b), case (i)], $\mathcal{L}$ increases with the disorder $\Delta = |\mathcal{D}_1 - \mathcal{D}_2|$ of the outer quadrilateral [Fig. 3(b)]. The equal-energy ensemble [Fig. 2(b), case (ii)] is more interesting, because $\mathcal{E}$ also depends on $\delta_1 = |AO| - |CO|$, $\delta_2 = |BO| - |DO|$, viz.,

$$\mathcal{E} = \frac{\mathcal{D}_1^2 + \mathcal{D}_2^2}{2} + \frac{\delta_1^2 + \delta_2^2 + 2\delta_1\delta_2 \cos \theta}{4}. \quad (8)$$

I therefore rescale Δ with $\min \mathcal{E} = (\mathcal{D}_1^2 + \mathcal{D}_2^2)/2$, attained for $\delta_1 = \delta_2 = 0$, to plot the contours of $\mathcal{L}$ in Fig. 3(c). Now $\mathcal{L}$ increases with Δ only for large enough θ , for which $\mathcal{L}$ is small, and hence the energy barrier to a T1 transition is lower. Hence, disorder further resists T1 transitions in this nonlinear case.

I have thus shown, by relying on exact geometric constructions, how geometry, fluctuations, and nonlinearities control general isolated, line-tension-dominated T1 transitions in epithelial tissues. Even these simple models have revealed complex behavior.

The linear and nonlinear line tensions that I have studied here are different, however, from the perimeter elasticity in the single-cell energy of vertex models of tissues [44–48, 58]. Moreover, these vertex models feature additional interplay between this perimeter elasticity and area elasticity. In the Supplemental Material [43], I therefore analyze a mean-field vertex model of an isolated T1 transition. My results confirm that the distance $\mathcal{L}$ from a T1 transition increases with increasing disorder in general, but also uncover more complex behavior in some parameter regimes [43]. Future work will need to explain these numerical observations, in particular by generalizations of my geometric constructions to cases in which area elasticity dominates.

In general, the energy barrier $\mathcal{E}_b = \mathcal{E}_b^{\text{local}} - \mathcal{E}_b^{\text{nonlocal}}$ decomposes into a local contribution that is the energy barrier for an isolated T1 transition and a nonlocal correction resulting from the displacement of the vertices neighboring those undergoing the T1 transition as the surrounding cells deform. Active T1 transitions [8, 11, 25, 26, 28, 33] overcome this local energy barrier. Nonlocal relaxation may drive additional, passive rearrangements that cannot be captured by this local picture. In particular, the mean-field arguments that predict fluidization in the vertex model even quantitatively [13, 31, 61] do rely on such nonlocal effects. Nonetheless, recent numerical simulations of the vertex model [32] have suggested that these two contributions are proportional to each other, $\mathcal{E}_b^{\text{nonlocal}} \propto \mathcal{E}_b^{\text{local}}$. While the mechanism setting this proportionality remains unclear, this suggests that mean-field models of isolated T1 transitions that I have studied here capture the full physics of T1 transitions in tissues and that they can be extended into quantitative models of T1 transitions by including this proportionality.

In this context, a large body of recent work has focused on the continuum mechanics of epithelial tissues, computing the viscoelastic moduli of the vertex model [62–69] and deriving coarse-grained limits of the vertex model [49, 70–73] and of differential-tension models of tissues [74–77]. My geometric results form the basis for understanding the mean-field effects of cell-scale disorder on cell rearrangements in these models and in related continuum theories [78] for tissues. At the same time, three-dimensional vertex models of bulk tissues [79–83] and descriptions of their cell rearrangements [22] are beginning to emerge, but understanding their coarse-grained mechanics remains a formidable challenge for future work.

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Data availability. The data that support the findings of this article are openly available [50].

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