Stability of an interface between competing mechanically-regulated tissues

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We theoretically analyse the stability of a propagating interface between two competing tissues in which cell division and death are mechanically regulated. The interface between the tissues is either driven by homeostatic pressure differences or by cell motility. An interface driven by homeostatic pressure imbalance experiences a Saffman-Taylor-like instability involving the tissues’ substrate frictions, and a separate long-wavelength instability related to an effective viscosity of cell number change. When interface propagation arises from directed cell motility, a further instability depends on the strength and direction of motility forces in each tissue. Each of these mechanisms can equally well exert stabilising effects, hence providing means for mechanical feedback to promote orderly interface propagation in developing tissues.

Competition between tissues occurs frequently in biology [1–4]. During tissue replacement processes such as in the developing Drosophila abdominal epidermis [5, 6], imbalance of cell growth and death or cell motility drive the expansion of one tissue at the expense of the other, leading to the motion of the interface between the two tissues.

Contour instabilities of growing tissues have been widely discussed, principally as an important invasive signature of cancer [7–11]. One well-studied mechanism is nutrient diffusion across a tumour boundary. Protruding regions can access greater nutrient concentrations, triggering further growth [3, 8, 12], reminiscent of the Mullins-Sekerka instability in non-living systems [13]. Tissue boundary instabilities of mechanical origin have also been considered. For example, an epithelium-stroma interface could exhibit undulations due to viscous stresses from cell turnover [14, 15]. A recent cell-based simulation of imbalanced mechanically regulated cell growth between two tissues observed a stable interface [16], while a related simulation of cells embedded in an inert medium found finger-like protrusions arising for higher friction in the medium relative to the cells [17, 18]. Opposing potential contour instabilities, line tension acting between cell populations has been proposed to contribute to boundary maintenance [13, 21].

Here we ask under which conditions the interface between two competing growing tissues is stable. Theory and simulation have explored how an imbalance in “homeostatic pressure” between tissues drives propagation of the interface separating them, and replacement by the tissue with the largest homeostatic pressure [16, 22–24]. The homeostatic pressure arises from the sensitivity of cell number change (i.e., division and death) to mechanical forces [22, 24]. Interface propagation may thus occur without the exertion of coherently directed cell motility forces. Alternatively, active, directed migration has been proposed to act as the driving force for interface motion in wound healing [35–37] or tissue replacement [4].

In this Letter, we study theoretically the interface in-stabilities of competing mechanically-regulated tissues. We consider a situation where tissue replacement is driven by differences in homeostatic pressure and/or by cell motility. Homeostatic pressure imbalance yields a Saffman-Taylor-like instability involving substrate friction, and a long-wavelength instability dependent on an effective viscosity of cell number change. Considering directed motile forces that are homogeneous in each tissue [38–41], we find a further instability that depends on their strength and direction.

A schematic of the situation considered in this Letter is shown in Fig. 1A. Two compressible tissues A and B contiguously cover an infinite domain, meeting at a flat interface. We use a 2D description, with z a coordinate parallel to x in the comoving frame of the interface.
general tissue, and equations should be read as such unless decorated with $A$ or $B$.

We begin with continuity of the areal cell density, $\rho$, where $v_i$ is the velocity field and

$$k_d = \frac{1}{\tau} \frac{\rho_d - \rho}{\rho_d}$$

is an expansion of the net division/death rate about the homeostatic density $\rho_d$, with $\tau$ a characteristic timescale. The $\rho$ units of each tissue may be independently rescaled, so we set $\rho_d \equiv 1$. The cell velocity is determined by stresses in the tissue. We consider here a linearised, isotropic elastic stress,

$$\sigma_{ij} = \sigma_{0ij} - \sigma_h - \chi \Delta \rho,$$

where $\sigma_h$ is a tissue’s homeostatic stress (negative of pressure), $\chi$ its elastic modulus and $\Delta \rho \equiv \rho - 1$. The homeostatic pressure imbalance between the tissues is $-\Delta \sigma_h = - (\sigma_h - \sigma_{0h})$. The quantity $\chi \tau$ is an effective bulk viscosity for cell number change; on a characteristic timescale $\tau$, a tissue loses its elastic character as cells are lost or created.

$$f = \delta x f$$ directed normal to the interface. Because motility exerted solely at the interface would map to a homeostatic pressure imbalance [35], we focus on the opposite limit, taking $f$ as uniform in a given tissue to represent “bulk” directed motility forces, as may arise from cryptic lamellipodia away from tissue edges [34–41].

Moving steady state. We define the comoving coordinate $z \equiv x - V_0 t$, with $V_0$ the velocity of a flat interface positioned at $z_0 = 0$ and propagating in $z$. We perturb a static state of balanced homeostatic pressure and no directed motility, such that $\rho = \rho_d \equiv 1$ and $v_i = 0$ everywhere. Assuming the density perturbation $\Delta \rho$ and velocity remain small (cf. Refs. [16, 24]), we write

$$\partial_t \Delta \rho + \partial_x v_z + \partial_y v_y = - \frac{1}{\tau} \Delta \rho$$

where $v_z \equiv v_z - V_0$. The steady state of a flat interface propagating in $z$ is derived in the supplement [38]. Steady state density perturbations $\propto e^{\pm z/\ell}$ decay from the interface (Fig. 2) governed by each tissue’s hydrodynamic length $\ell = (\chi \tau / \xi)^{\frac{1}{2}}$. Their sign (see Eq. S2 [38]) depends on the homeostatic pressure imbalance $-\Delta \sigma_h$, and on $\Delta v_f \equiv f_A/\xi_A - f_B/\xi_B$, a difference in “bare” velocities $f/\xi$ associated to directed motility. $\Delta v_f > 0$ if one tissue’s motility force, scaled by friction, points toward the interface more strongly than that in the other tissue points away. Note that a label swap $A \leftrightarrow B$ entails $f_A \leftrightarrow f_B$, $\xi_A \leftrightarrow \xi_B$, leaving $\Delta v_f$ unchanged. In Fig. 2A, the growing tissue has decreased density so, by Eq. 2, is proliferative near the interface, while the shrinking tissue has increased density so undergoes net apoptosis near the interface. In Fig. 2B, both tissues are apoptotic near the interface [42]. We find the steady interface velocity,

$$V_0 \equiv v_z|_{z=0} = - \frac{\Delta \sigma_h + \ell \xi_A f_A + \ell \xi_B f_B}{\xi_A \ell_A + \xi_B \ell_B}$$

which, for $f_A = f_B = 0$ and $\xi_B = \xi_A$, reduces to that recently calculated in Ref. [14]. Note that the approximation of small velocity and density perturbations formally requires $|\Delta \sigma_h| \ll \chi_A, \chi_B$ and $|\Delta v_f| \ll \ell \xi_A, \ell \xi_B$. Interference stability in 2D. We now determine the response to an interface fluctuation (Fig. 1B). Fourier and Laplace transforms $y \rightarrow q'$ and $t \rightarrow s$ of Eq. 3 (defined in [38]) give

$$L_z \delta \rho = \delta \rho|_{t=0} , \quad L_z \equiv s + \frac{\chi}{\xi} q'^2 - \frac{\chi}{\xi} q'^2 + \frac{1}{\tau}$$

applied to the deviation $\delta \rho$ from the moving reference state, with $\delta \rho$ its Fourier transform and $\delta \rho$ the Laplace transform of $\delta \rho$. We analyse a perturbation $\delta z_0 = e(t) \cos(q q')$ with $e(0) = e_0$ and let $q' = q$. Interface stresses couple to a line tension $\gamma \geq 0$ from, e.g., in-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2}
\caption{A) Steady state density perturbation profile $\Delta \rho$ (solid line) and velocity $v_z$ (dashed) for tissues $A$ ($z < 0$) and $B$ ($z > 0$). Parameters: $\Delta \sigma_h = -0.5 \chi_A, f_B = \xi_A, \chi_B = \chi_A, \tau_B = 2 \tau_A$. $f_A = f_B = 0$. B) As A, but with $\Delta \sigma_h = 0, f_A = 0.1 \chi_A / \ell_A$. C) As A, but with $\Delta \sigma_h = 0, f_B = 0.1 \chi_A / \ell_A$. D) As A, but with $\Delta \sigma_h = 0, f_A = f_B = 0.1 \chi_A / \ell_A$. In this particular case the tissue moves uniformly and the density perturbation cancels to zero.}
\end{figure}
creased myosin at heterotypic cell bonds [20],

\[(\sigma + \delta \sigma)|_{\delta z_0, A} - (\sigma + \delta \sigma)|_{\delta z_0, B} = -\gamma q^2 \delta z_0, \]

where \(\delta \sigma\) is the deviation from the steady state stress \(\sigma\).

Applying boundary conditions on Eq. 7 in terms of \(\delta z_0\), we find the transformed interface evolution as

\[\hat{\varepsilon}(s) = \frac{g(s)}{f(s)} \varepsilon_0,\]

where \(f(s)\) and \(g(s)\) are given in the supplement [38]. The long-time behaviour of the perturbation is determined by the pole \(s^*\) of \(\hat{\varepsilon}(s)\) with the highest real part. In the regime of small \(\Delta \sigma_h\) and \(\Delta v_f\) applicable here, we do not find complex poles and thus treat \(s^*\) as real [38]. \(s^* < 0, > 0\) indicate stability or instability respectively. Dispersion relations \(s^*(q)\) (Fig. 3A,B) are maximised over \(q\) to yield phase diagrams (Fig. 3C,D) of the most-unstable wavenumber \(q^*\). We approximate the dispersion relation in limits of \(q\) [38] to find the analytic criteria discussed below.

**Stability of an interface driven by homeostatic pressure imbalance.** We first discuss growth of tissue \(A\) driven by a difference of homeostatic pressure \(\Delta \sigma_h < 0\) (Fig. 3), without directed motility \((f_A = f_B = 0\)). Analytic dispersion relations [38] show that, for strong enough homeostatic pressure imbalance, the interface is unstable if tissue \(B\) has greater friction \(\xi_B > \xi_A\) or effective viscosity \(\chi_B \tau_B > \chi_A \tau_A\). Instability criteria for each mechanism (given \(\Delta \sigma_h < 0\)) can be derived as

\[-\Delta \sigma_h \gtrsim \frac{27}{4} \left(\frac{\ell_A \ell_B - \xi_B \xi_A}{\ell_A^2 \ell_B (\xi_B - \xi_A)^3}\right),\]

\[\xi_B > \xi_A,\]

or

\[-\Delta \sigma_h \gtrsim \frac{2\gamma}{\chi_B \tau_B - \chi_A \tau_A}, \quad \chi_B \tau_B > \chi_A \tau_A.\]

where the criterion Eq. 10 is approximate [38]. Two types of instability transition arise. Fig. 3A and Eq. 10 show a "type I" transition in the Cross-Hohenberg classification [44], where a band \(q_{\min} < q < q_{\max}\), \(q_{\min} \neq 0\) becomes unstable. Fig. 3B and Eq. 11 show a "type II" transition, where the unstable band is \(0 < q < q_{\max}\) and onset occurs at \(q \to 0\). In that case, one expects near threshold that the characteristic wavelength scales with system size. Eqs. 10 and 11 are combined with phase diagrams of the most unstable wavenumber \(q^*\) in Fig. 3C-D.

These mechanisms share with the Saffman-Taylor instability the qualitative property that the interface is destabilised if the shrinking tissue is somehow "stiffer": i.e. having higher friction, higher elastic modulus or changing cell number more slowly in response to stress. Given \(f_A = f_B = 0\), the dispersion relations can be recast in terms of \(V_0\), revealing a similarity between the friction difference mechanism and the Saffman-Taylor instability (Eqs. S14, S16 [38]).

**FIG. 3.** A) Numerically-determined dispersion relations for homeostatic pressure imbalance. Parameters: \(\xi_A = 1.5\xi_B, \chi_B = 0.5\chi_A, \tau_B = \tau_A, f_A = f_B = 0, \gamma = 0.001\ell_A\chi_A\). The homeostatic pressure imbalance increases, \(\Delta \sigma_h = -0.1\chi_A, -0.2\chi_A, \ldots, -0.5\chi_A\), in the direction of the arrow, crossing a "type I" instability transition [44]. B) As \(A\) but with \(\xi_B = \xi_A, \chi_B = 1.5\chi_A, \Delta \sigma_h = -0.008\chi_A, -0.009\chi_A, \ldots, -0.012\chi_A\), crossing a "type II" instability transition with onset at \(q \to 0\) [44]. C) Phase diagram in \((\Delta \sigma_h, \xi_B)\) of the most unstable wavenumber \(q^*\) (white if no instability), using \(\chi_B = 0.5\chi_A, \tau_B = \tau_A, f_A = f_B = 0, \gamma = 0.001\ell_A\chi_A\). The dashed line indicates the approximation of the type I transition line by Eq. 10. D) Phase diagram in \((\chi_B, \xi_B)\) using \(\Delta \sigma_h = -0.5\chi_A, \tau_B = \tau_A, f_A = f_B = 0, \gamma = 0.001\ell_A\chi_A\). The dashed line is as in C, and the solid line indicates the type II transition (Eq. 11). Cartoons illustrating stability, or short or long-wavelength instability, are superimposed on C and D.

**FIG. 4.** A) Numerically-determined dispersion relations for directed motility. Parameters: \(\xi_B = \xi_A, \chi_B = \chi_A, \tau_B = \tau_A, f_B = 0.25\chi_A, f_A = 0, \gamma = 0.001\ell_A\chi_A\). The motility force in tissue \(A\) increases, \(f_A = 0, 0.1\chi_A, \ldots, 0.4\chi_A\), in the direction of the arrow. This increases \(\Delta v_f\), leading to an instability transition. B) Phase diagram in \((f_A, f_B)\) with other parameters as in A. The black line is the transition approximated by Eq. 12. The dotted line is \(V_0 = 0\), with the upper half-space \(V_0 > 0\) (tissue \(A\) growing) and the lower \(V_0 < 0\). In each quadrant, cartoons illustrate the direction of tissue motilities.
Stability of an interface driven by directed motility forces. We now consider balanced homeostatic pressure, \( \Delta \sigma_0 = 0 \), but non-zero directed motility forces, \( f_A \neq 0 \) and/or \( f_B \neq 0 \). Stability is now governed by \( \Delta v_f \equiv f_A / \xi_A - f_B / \xi_B \), with the instability criterion

\[
\Delta v_f > \frac{2 \gamma (\ell_A \xi_A + \ell_B \xi_B)}{\xi_A \ell_B \ell_A (\ell_A + \ell_B)}
\]

(12)

Fig. 3A shows dispersion relations for \( f_A \) increased for fixed \( f_B \), increasing \( \Delta v_f \) to cross a type II instability transition approximated by Eq. (12). Fig. 3B shows a phase diagram for varying both directed motility strengths. In contrast to the homeostatic pressure case, we can have various stability scenarios even for a static interface, \( V_0 = 0 \). For instance, both tissues could actively migrate towards the interface (\( f_A > 0, f_B < 0 \)), giving \( \Delta v_f > 0 \) and promoting instability. Conversely, the tissues could each direct their motility away from the interface (\( f_A < 0, f_B > 0 \), \( \Delta v_f < 0 \)), promoting stability. For a moving interface \( V_0 > 0 \), a shrinking tissue that actively migrates away from the growing tissue (\( f_A = 0, f_B > 0 \), “pushing”) is stabilising, whereas the converse situation (\( f_B = 0, f_A > 0 \), “pulling”) is destabilising.

Discussion. We have studied the stability of a propagating interface between epithelial tissues undergoing mechanically-regulated cell number change. Given increasing experimental evidence of such regulation [25–33], there is wide interest in models of the type used here [16, 18, 22, 24]. As well as homeostatic pressure imbalance [16, 22, 23], we included directed motility forces, which can drive interface propagation even for balanced homeostatic pressures. We accounted for an auxiliary line tension, as arises from increased myosin at heterotypic cell bonds [20, 21], or a supracellular actin cable as in Drosophila larval epithelial tissues [45]. The results yield analytic insight into instabilities arising from the effective material parameters of competing mechanically-regulated tissues. The mechanisms identified can equally promote stability, supplementing line tension [20] to maintain boundaries in developing tissues.

Two mechanisms were found to arise from homeostatic pressure imbalance. On length-scales shorter than a hydrodynamic length \( \ell \), a Saffman-Taylor-like instability can occur if the substrate friction \( \xi \) of the growing tissue is smallest. The dispersion relation, Eq. S16 [33], supports previous proposals of Saffman-Taylor behaviour for cells in an inert medium [17, 18], and is in accord with observations from the tumour literature that tissues with weaker cell-matrix adhesions tend to be more invasive [10]. Longer length-scales are dominated by another instability, which can occur if the effective bulk viscosity for cell number change, \( \chi^* \), is smallest in the growing tissue. These mechanisms, along with line tension \( \gamma \), determine whether an interface driven by homeostatic pressure imbalance propagates stably (Fig. 3, Eqs. 10, 11).

A cell-based simulation of homeostatic pressure imbalance [10] found an effective interfacial tension attributed to anisotropic active cell growth. The mechanisms we have found, when stabilising, may also be thought of as supplying an effective tension. It could be interesting to use the simulation method of Ref. [10] to systematically explore our theory’s predictions, or to extend it to include, e.g., cell growth anisotropy.

We also studied the effects of directed motility forces on stability. Recent work noted that motility may contribute to the homeostatic pressure [47]. The directed motility we include is the coherent contribution of motility forces in a given direction, arising for instance from a biochemical polarisation signal. Stability depends on \( \Delta v_f \), which compares velocity scales that relate each tissue’s motility force to its friction (Fig. 3). Repulsive migration, as known to occur due to Eph receptor and ephrin signalling in boundary maintenance [19], should yield \( \Delta v_f < 0 \), favouring stability. Our results similarly imply that a propagating interface is more stable if the shrinking tissue actively migrates away from it. Such migratory forces are proposed in Drosophila larval epithelial cells being replaced by histoblasts [6]. This would promote an orderly interface, which is presumably desirable to ensure tissue replacement occurs predictably and completely. This could be a fruitful experimental setting in which to perturb the model (e.g., modifying active motility forces or cell division), and determine the effects on stability.

We have focused here on effects arising directly from mechanical regulation of cell number change, ignoring nutrient or growth factor diffusion that is often considered in tumour modelling [8, 9, 12]. This should be a reasonable assumption for planar epithelia receiving nutrients from their out-of-plane surroundings [24]. It would be interesting to add biomolecule diffusion to the mechanical instabilities studied here, as performed for a previous study of an epithelium-stroma interface [14, 15].

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