Collective migration of cells in spreading epithelia

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Collective cell migration is present in many biological processes. It requires a guidance mechanism to coordinate mechanical stresses in large groups of cells. An example that has received intensive attention recently is the free advance of the front of a confined epithelial tissue when the confinement is removed. Cells are able to transmit forces through cell-cell junctions and through adhesion on the substrate, and tend to modify their trajectories in order to minimize the local intracellular stress[1]. Recently, it has been possible to measure quantitatively for the first time the mechanical stresses exerted at the cell-cell junctions, and on the substrate within single-cell resolution[1]. A detailed theoretical modeling of this process and the mechanical stresses involved, however, is still lacking.

Inspired by the above experiments, in this work we focus on understanding the collective migration of an advancing tissue of epithelial cells, considering the internal flow of actin in the crawling of cells, and the generation of traction forces applied on the substrate through focal adhesions. It has been pointed out[2] that during the spreading process of a tissue made up of Madin-Carby kidney epithelial cells, each individual cell in the sheet is not selfpropelling, whereas the traction force distribution on the cell sheet reveals that a single cell in the tissue does exert a net force on the substrate.

In this study we model an epithelial tissue as an active polar nematic gel[3,4]. Momentum and mass conservation then read

$$\begin{aligned} \partial_a \left(\sigma^{tot}_{\alpha,\beta} - P\delta_{\alpha,\beta}\right) &= \xi v_\alpha - f_c p_\alpha \\ \partial_t \rho + \partial_\alpha \left(v_\alpha \rho\right) &= \gamma \end{aligned}$$

where p_α is a polarization field which measures the degree of orientation of a patch of cells, v_α is the macroscopic velocity field of the tissue, P stands for the pressure field and $\sigma^{tot}_{\alpha,\beta}$ is the total stress tensor. Due to the spreading process the thickness of the quasi-twodimensional tissue may vary along the cell sheet and consequently it might modify locally the density of cells. In order to take this into account in our model phenomenologically, we assume a certain function γ which for simplicity will be considered homogeneous[5]. There are two different external friction forces from the substrate: the term ξv_α, coming from the macroscopic displacement of a group of cells relative to the substrate and the term $f_c p_\alpha$, which is due to internal actin flux from the lamellipodia.

The proposed framework is a coarse-grained description that treats the tissue as a continuous active material. We expect that different phenomenology already observed in experiments[1,2] may be understood within this approach. As a first step, we have studied the morphological instability of the advancing front of cells to transversal modulations, a phenomenon that is observed to lead to fingering patterns. The growth rate of a transversal perturbation on the leading edge is shown in the figure for two different biological values of the shear viscosity. The dominant transversal scale of the fingering of the leading edge is seen to be consistent with the dominant transversal wavelength obtained from experimental data, and provides an indirect way to obtain effective parameters of the model that cannot be easily accessed directly. The mechanism of destabilization of the front can be understood in terms of the microscopic friction force of the leading cells, provided that the strength of this physical element is above a critical value. Note that this term depends crucially on the nematic order of the cells. These results set the basis for a more detailed and quantitative understanding of a variety of experimental phenomena[2].

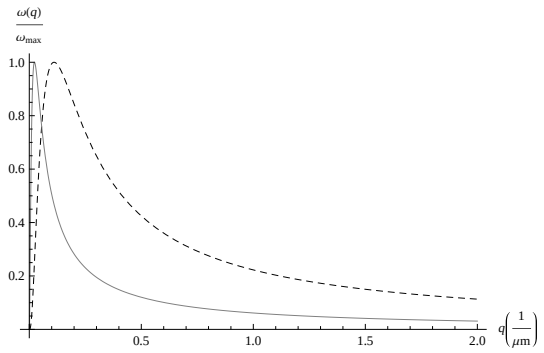

FIG. 1. Linear growth rate of a transversal perturbation on a rectangular steady configuration under biologically parameters normalized by its maximum positive value. The dashed curve corresponds to a shear viscosity of $10^4 Pa \cdot s$ and the solid curve to one of $10^7 Pa \cdot s$.

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