Active wetting and collective durotaxis: speed, diffusion and super-diffusion of cellular clusters

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Collective migration of cohesive groups of cells underlies a variety of processes in embryonic morphogenesis, wound healing, and cancer invasion. Migration may respond to a variety of chemical and mechanical stimuli. Here we focus on the phenomenon of collective durotaxis [1, 2, 3], which refers to the migration of large groups of cells toward stiffer environments. We analyze this problem through the concept of active wetting [4], recently introduced to describe the spreading and retraction of cell clusters as a nontrivial competition between traction forces on the environment and tissue contractility. Since traction forces depend on substrate stiffness, the wetting properties, and the durotactic response must necessarily be related.

Experiments show that, generically, clusters dewet soft substrates and wet stiff ones, becoming maximally motile at an intermediate stiffness [5]. In particular, they show a nonmonotonic dependence of the durotactic velocity with the substrate stiffness. To elucidate the complex interplay between active wetting and collective durotaxis, we developed a continuum active wetting model that extends a previous one [4] from monolayers to 3D clusters, combining in-plane active traction and tissue contractility on the contact monolayer and out-of-plane surface tension [5]. In this model, the polarity field follows relaxational dynamics $\partial_t p_\alpha \propto -\delta F/\delta p_\alpha$, being

$$F = \int \left[\frac{a}{2} p_\alpha p_\alpha + \frac{K}{2} (\partial_\alpha p_\beta)(\partial_\alpha p_\beta) \right] d^2 r \tag{1}$$

the Frank free energy. By force balance, the stress tensor and the external force density originated at the tissue-substrate interface are related by $\partial_\beta \sigma_{\alpha\beta} + f_\alpha = 0$, and both quantities can be decomposed in a passive (viscosity η and friction ξ) and an active term (contractility ζ and active traction ζ_i),

$$\sigma_{\alpha\beta} = \eta(\partial_\alpha v_\beta + \partial_\beta v_\alpha) - \zeta p_\alpha p_\beta, \tag{2}$$

$$f_\alpha = -\xi v_\alpha + \zeta_i p_\alpha, \tag{3}$$

where v_α is the velocity field. The surface tension of the clusters enters as a boundary condition in the stress, $n_\alpha \sigma_{\alpha\beta} n_\beta = -\frac{\gamma}{R}\cos\theta$, being R the contact radius and θ the contact angle of the cluster with the substrate. Solving this model, we find that the durotactic velocity grows as the cluster spreads and achieves a maximum speed when the dynamic contact angle reaches approximately neutral wetting (90°) (see Fig. 1). After that, the saturation of traction and the growth of the friction coefficient with stiffness imply a decrease in the durotactic speed.

We have also generalized our theory to account for the biased random walks observed for cell clusters. Our stochastic model includes field-Langevin equations with both additive and multiplicative noises. Analyzing real data of local fluctuations of traction forces in cell monolayers, we can check which is the dominant noise source in the system and estimate temporal and spatial correlations of fluctuations of the physical parameters. The model provides explicit predictions for diffusion coefficients so that unknown model parameters can be obtained from experiments. From experimental data, we show that fluctuations in the traction force in some relevant parameter regimes satisfy an effective fluctuation-dissipation theorem with a nonequilibrium temperature. Finally, some experiments [5] show that clusters undergo long hops that could be described as Lvy flights, which we model within a stick-slip framework resulting from a nontrivial dependence of the friction coefficient with the relative direction of velocity and polarization.

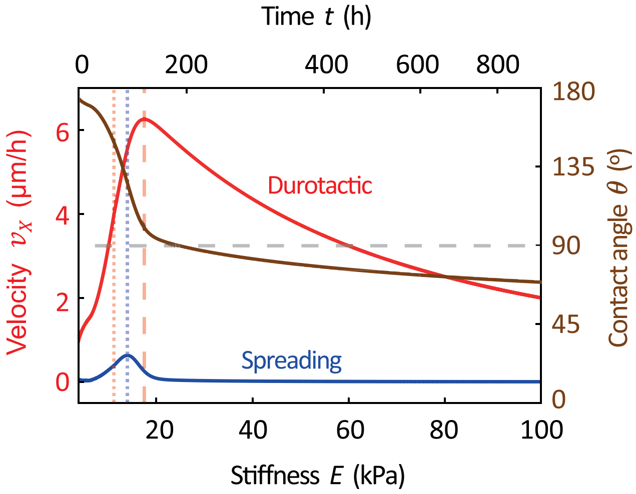

Fig. 1. Representative example of the velocity and shape dynamics of a migrating cluster with a constant volume, showing the nonmonotonic dependence of v_x with stiffness (in red), the spreading velocity (in blue) and the decrease in the contact angle (in brown).

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