CELL DIVISION IN TISSUES LIKE DISLOCATION UNBINDING IN 2D SOLIDS?

Fluidization of tissues by cell division and apoptosis
Jonas Ranft, Markus Basan, Jens Elgeti, Jean-Francois Joanny, Jacques Prost and Frank Jülicher, Proc. Nat. Acad. Sci. **107**, 49 20863 (2010).

Recommended with a commentary by M. Cristina Marchetti, Syracuse University

A growing body of experiments has demonstrated that mechanical forces play an important role in regulating tissue formation, morphogenesis and tumor growth. Growing tissues, notably cancerous tumors, are continuously remodeled by cell division and apoptosis (cell death) that couple to the elastic deformations of the material, changing its mechanical properties. The paper by Ranft et al. proposes a continuum model to describe tissue dynamics on time scales large compared to the inverse rate of cell division and apoptosis and demonstrates that at large scales the tissue effectively behaves as a viscoelastic fluid, but with a number of unusual properties.

Cell division involves mechanical forces and local stresses as cells must rearrange to make room for the new daughter cell. It is then clear that the division process creates volume changes in the tissue, resulting in isotropic stresses. The important observation at the basis of the work described in this paper is that cell division is anisotropic and occurs along a preferred cell axis, generating also anisotropic stresses that locally shear the tissue. This observation is born from experiments, such as those on two-dimensional larval structures of the fruit fly *Drosophila melanogaster* [1] and on *C. elegans* zygotes [2]. It is also supported by experiments with single cells on patterned substrates that have shown that an external constraint, such as that induced by the substrate anisotropy, can orient cells [3]. Ranft et al. describe the tissue as an elastic medium remodeled by the stresses due to cell division and death. They show that on times long compared to the inverse rate of cell division, k_d, the tissue behaves like a viscoelastic liquid, with a characteristic Maxwell relaxation time $\tau_a \sim 1/k_d$ that is calculated analytically in terms of cell properties. As the authors note, the effect of cell division on the tissue is not unlike the unbinding of dislocation pairs in solids. Like cell division, the creation of an unbound dislocation pair with

opposite Burgers vector is a directional process that creates local shear stresses in the solid and results in melting of the crystal in two dimensions.

Cell polarity and the lack of conservation of number of cells yields, however, rather unusual properties of the fluidized tissue. First, cell polarity can result in large-scale alignment, yielding an anisotropic oriented state of the growing tissue, not unlike a ferroelectric liquid crystal. Large-scale patterns of cell polarity have indeed been seen in layers of epithelial cells [4]. Although the large-scale alignment may arise from other factors, such as cell-cell signaling or morphogen gradients, it is enhanced by cell division that will occur preferentially along the axis of cell polarity. But even when the growing tissue remains isotropic at large scales, it exhibits some rather unusual mechanical behavior. The authors show that the so-called homeostatic state, corresponding to the situation where cell division and cell death balance, is an isotropic viscoelastic liquid with a finite relaxation rate τ for *compressional* stresses. This is very different from the conventional Maxwell model of viscoelasticity of fluids with a conserved number of particles, where shear stresses relax to zero at long times, but compressional stresses always have a zero frequency component that determines the liquid's bulk modulus. In contrast, in the homeostatic state a tissue is an infinitely compressible liquid. In equilibrium the isothermal compressibility, $\kappa_T = -\frac{1}{V}\left(\frac{\partial V}{\partial p}\right)_T$, is a direct measure of fluctuations in the number density $n = \langle N\rangle/V$, with $\frac{\langle n^2\rangle - \langle n\rangle^2}{\langle n\rangle^2} = k_B T \kappa_T / V$. Under normal conditions this quantity is of order $1/\langle N\rangle$, hence vanishes in the thermodynamic limit. At the critical point of equilibrium fluids, however, κ_T becomes very large and so do density fluctuations. These large fluctuations are responsible for the beautiful phenomenon of critical opalescence shown by fluids in their critical region. Ranft et al. argue that in the homeostatic state tissues also exhibit the remarkable property of diverging compressibility. This divergence implies that the system exhibits very large volume changes in response to a small change in pressure and is also reflected in the giant density fluctuations at constant pressure that arise due to noise from cell division and death. One then wonders if such a divergences may have dramatic experimental consequences analogous to the milky white appearance of critical fluids in reflected light. Is this infinite compressibility a general properties of fluids with non-conserved number of particles, such as a growing bacterial suspension? Of course it only occurs near the special homeostatic pressure and it is not clear how one could achieve this experimentally in a bacterial suspension. It was recently argued [5] that the tissue pressure of this special homeostatic state may be related to the invasiveness of a tumor in a host tissue. This is indeed supported by Ranft et al. since the large volume changes that would occur when the pressure is tuned slightly below or above

the homeostatic value would result in invasive growth or disappearance on the tissue, respectively.

The idea that tissues behave like liquids on a range of time scales has been around for some time [6]. For instance, in embryonic cell aggregates with very low cell division rates, different cell populations sort themselves and spread over each other according to their relative surface tension, just like droplets of immiscible liquids. In this case the liquid-like behavior occurs on times shorter than the time for cell divison/death and is associated with a tissue surface tension, traditionally thought to originate from cell-cell adhesion. Recent work has suggested that anisotropic cortical tension and the associated cell shape fluctuations may play an important role in determining the surface tension in some tissues [7]. Cell shape fluctuations provide an additional mechanism for the relaxation of shear stress, but cannot relax isotropic stresses and the tissue should in this case remain essentially incompressible on time scales shorter than cell division and death.

The picture that emerges from this work is that mechanical properties of tissues at large scales may be controlled by the interplay of two characteristic time scales, the time τ_a for relaxation of shear stresses and the time τ for relaxation of isotropic stresses. It is tempting to speculate that it may be possible to classify the mechanical behavior of different tissues in terms of the ratio of these two times, which will in general be controlled by multiple stress relaxation mechanisms and also regulated by complex signaling pathways. The work by Ranft et al. considers one mechanism for stress relaxation in growing tissues and provides an an expression for the contribution to τ_a from cell division/death in terms of cell parameters. More work is needed to fully characterize the stress/strain relation of tissues, incorporating the contribution from other mechanical relaxation mechanisms, and to understand the relation between the internal cell organization and the tissue's macroscopic rheological properties.

[1] D. Discher et al., Ann. Biomed. Eng. **37**, 847 (2009).
[2] M. Mayer, M. Depken, J. S. Bois, F. Jülicher and S. W. Grill, Nature **467**, 617 (2010).
[3] M. Théry, A. Jiménez-Dalmaroni, V. Racine, M. Bornens and F. Jülicher, Nature **447**, 493 (2007).
[4] A. Szabó, R. Ünnep, E. Méhes, W. O. Twal, W. S. Argraves, Y. Cao and A. Czirók, Phys. Biol. **7**, 046007 (2010).
[5] M. Basan, T. Risler, J.-F. Joanny, X. Sastre-Garau and J. Prost, HFSP J **3**, 265 (2009).

[6] R. Foty, G. Forgacs, C. Pfleger and M. Steinberg, Phys. Rev. Lett. **72**, 2298 (1994).
[7] M. L. Manning, R. A. Foty, M. S. Steinberg, and E.-M. Schoetz, Proc. Nat. Acad. Sci. **107**, 12517 (2010).