Collective cell motion in biological tissues: A novel form of glassy dynamics?

- *Energy barriers and cell migration in densely packed tissues*,
  Dapeng Bi, J. H. Lopez, J. M. Schwarz, M. Lisa Manning, Soft Matter (in press, 2014); arXiv:1308.3891.

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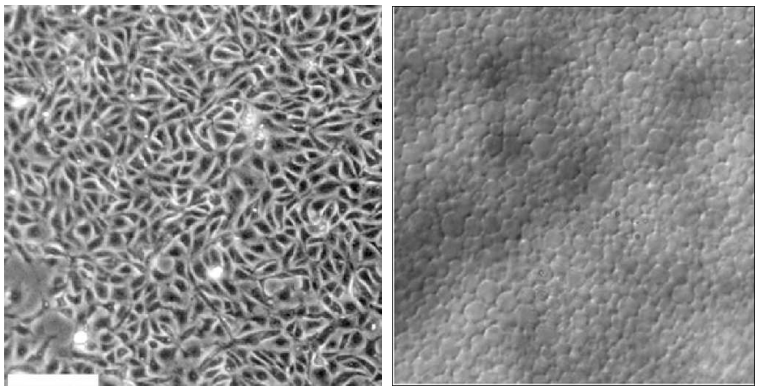

Figure 1: Left: Microscopy image of a dense biological tissue, the scale bar is 100 μm (from [1]). Right: Microscopy image of a dense emulsion (from [2], courtesy L. Cipelletti, Université Montpellier 2), the typical droplet size is about 3 μm.

Recent progress has allowed increasingly detailed experimental characterizations of the dynamics of a variety of biological tissues, resolved at the single cell scale. Several studies have in particular analyzed the behaviour of *confluent* tissues (when there is no gap between the cells) and measurements of both the collective motion of the cell assembly, and of the single cell dynamics have appeared. These studies reveal in particular that single cell dynamics exhibit similarities with the caged dynamics observed for instance in dense colloidal suspensions or viscous liquids [3], while collective cell motion seems to present interesting analogies [1] with the dynamic heterogeneity characterizing materials approaching a glass transition. These studies are motivated by broad biological considerations [4, 5], because collective motion plays an important role in processes such as wound healing, embryogenesis, and cancer invasion.

Because cells are soft objects, tissues then superficially resemble foams or compressed emulsions, in the sense that they are made of soft objects at a packing fraction that is essentially unity (there is no gap between the 'particles'), and the cells (like bubbles or droplets) are such large entities that thermal fluctuations do not influence their dynamics in any significant way. This (incorrect) analogy suggests that confluent tissues should behave rheologically as soft jammed *solids*, much like mayonnaise or shaving cream, as the images in Fig. 1 suggest.

However, unlike droplets or bubbles, individual cells are of course *living* objects, and can therefore diffuse in an active manner, i.e. much faster than if they were solely fueled by thermal fluctuations.

As a result, experiments demonstrate that tissues do not behave as elastic solids, but in fact as *viscoelastic* materials [4]. That is, they can spontaneously flow at large enough time, much as polymeric liquids do. In agreement with these observations, direct visualisation of the cell collective motion reveals intriguing flow patterns reminiscent of observations in dense fluids, while single cells are found to diffuse over significant distances.

Therefore, flow, collective dynamics and single cell diffusion necessarily result from the interplay between the jammed structure of these highly disordered and very dense materials, and the biological activity that drives the dynamics at the level of the individual objects. However, there exists at present no good analogy to understand the outcome of this competition. Because energy is injected at the level of individual objects, the jamming transition is not a good analogy [6] because jamming refers to the change of mechanical properties of completely athermal assemblies. A second analogy which is not obviously correct is with the glassy dynamics of equilibrium colloidal suspensions and supercooled liquids, because the nonequilibrium nature of the energy injection in tissues might profoundly affect the nature of the physics [7]. Finally, a third incorrect analogy is with sheared amorphous solids, where the energy injected at large scale cascades down to smaller scale to trigger plastic deformations in the material.

Thus, it should come as no surprise that not much is known about the response of amorphous dense assemblies to nonequilibrium driving forces typical of biological tissues.

The paper by Dapeng Bi and coworkers [8] is an interesting theoretical effort in this direction, covering both structural and dynamical aspects of flow in biological tissues. This study provides in particular answers to the following two related questions:

(1) What are the relevant energy barriers that an amorphous assembly of cells composing biological tissues has to cross in order to flow?

(2) How do single cells move as a result of the biological activity in the energy landscape dictated by their disordered structure?

Question (1) is answered using a numerical analysis of a simple vertex model of biological tissue, where mechanical equilibrium of an amorphous assembly of cells is maintained at each step. By imposing an active deformation of the tissue up to the point where the tissue rearranges irreversibly, the authors access a distribution of energy barriers $\rho(E)$ for tissue rearrangement. Their main finding is that this distribution is broader than a Gaussian distribution, and decays instead exponentially, $\rho(E) \sim \exp(-E/E_0)$.

The authors then address question (2) by assuming a simple dynamical equation, inspired by the physics of glassy systems. They assume that the single cell dynamics can be expressed as the dynamics of a point particle in an energy landscape with an exponential distribution of barriers, $\rho(E)$. At thermal equilibrium, transitions between states are governed by Arrhenius rates, and the model becomes the trap model [9]. In this study, biological activity is assumed to lead to Arrhenius rates associated with an *effective temperature*, and the cell propulsion is taken into account as a reduction of the barrier height. With this *adhoc*, but physically reasonable, modelling of single cell propulsion, the modified trap model can then be analysed. The main outcome is the existence of a glass transition towards a nonergodic glassy state, associated to dynamical slowing down in the vicinity of the transition. The simplicity of the model implies that this transition actually maps onto the original equilibrium transition whose nature is, somewhat surprisingly, not affected by the biological activity.

The broad interpretation of this study is that dense biological tissues have an amorphous structure reminiscent of simple jammed solids, but they can nevertheless flow because biological activity is able to induce flow, collective motion and single cell diffusion that are *somehow* reminiscent of the effect of

thermal fluctuations in a dense liquid near the glass transition (although the details of this 'somehow' are discussed at a qualitative level only and should be understood better).

This paper should encourage at least two interesting lines of research, that are currently being actively pursued. First, the analogy between glassy dynamics and collective cell motion suggests that experimental investigations of confluent tissues should benefit from the experience gathered in experimental studies of glassy suspensions, in order to characterize better the nature of the nonequilibrium glassy dynamics observed in tissues. It can in particular be expected that the type of single particle dynamics and spatially heterogeneous dynamics observed in these far from equilibrium materials present interesting differences with their equilibrium counterparts. Second, this study also raises fundamental questions about the use of an effective temperature to describe the physics of dense particle assemblies that are driven by non-thermal forces, and about the fate of the glass transition physics in systems that are not uniquely driven by thermal fluctuations, but contain additional 'propulsion' mechanisms.

References

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