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Title: Can cells use a phase transition to find each other in fibrous darkness? Nonconvexity and change of type in a system from nonlinear biomechanics.

Abstract: Biological cells are known to die if they cannot sense other cells in their vicinity. Experiments on fibroblasts embedded in a fibrous extracellular matrix have shown that these cells locate each other using not only chemical signals, but also mechanical fields, such as displacement or stress, a process known as mechanosensing. The cells induce deformations in the ECM by contracting themselves. Apparently they do this so that other cells can detect the resulting strain fields in the ECM. It is noteworthy that cell contraction causes the appearance of so-called tethers, or thin bands in the ECM joining neighboring cells. Within tethers, the density of the ECM is much higher than outside.

This is suggestive of a phase transition, which in turn points to an underlying material instability. We observe that the ECM consists of fibrin, a spaghetti-like fibrous network. Individual fibers can resist tension, but buckle under compression.

We model the extracellular matrix as an orientationally uniform distribution of fibers that are weaker in compression. We thus arrive at a nonlinear stored energy function for large deformations, starting from the stress-strain law of a single fiber. This energy turns out to be nonconvex and has potential wells, at the undeformed state and at a compressed state. We then model each contracting cell as a contracting cavitiy in the domain of the extracellular matrix.

The associated vectorial variational problem is nonconvex (quasi- and rank-one convexity are also lost). It is likely that that a global minimizer does not exist, but only minimizing sequences. The corresponding Euler Lagrange equations comprise a quasilinear 2nd order system that changes type from elliptic to hyperbolic depending on the gradient of the unknown vector mapping.

The problem is solved using a finite element method that can handle discontinuous gradients. The result is multi-phase deformations with discontinuous Jacobian determinant (discontinuous density), and high density within narrow bands joining cells. This occurs when the latter are close enough or their pre-compression is high enough. These bands are tether-like in agreement with experiments. We also find evidence of fine phase mixtures: these look like hair growing radially outwards from each cell, and become finer and finer as the mesh size is refined. This suggests the presence of a sequence of local minima that approaches an energy infimum, while it is likely that a global minimizer does not exist, but only minimizing sequences.

In experiments there is a small finite number of such “hairs” and we approach this using a higher gradient regularization approach and a corresponding higher order numerical method. The results bear a strong resemblance to older experiments by Stopak, and more recent ones by Ravichandran, Notbohm, Lesman and Tirrell.

We are not aware of any explanation of tether formation, other than the compressive

phase change due to nonconvexity resulting from microbucking instability of fibrin, triggered by cell contraction.

Remarkably, experiments show that after the form, cells very quickly start growing appendages that grow along tethers in an attempt to join their neighbors. This confirms tether formation as a mechanosensing mechanism.