

Active matter modifies, and is oriented by, its environment

Environment-Stored Memory in Active Nematics and Extra-Cellular Matrix Remodeling

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Seminars on active matter often begin with familiar and evocative images of flocks of birds and schools of fish. A less “visible” (but possibly more relevant to human health concerns) example of active matter is a collection of animal cells crawling on a viscoelastic extracellular matrix. Here, we follow the most common definition of active matter as a collection of units that each have access to an energy source, which they utilize to move [1, 2]. Drawing inspiration from biological systems across scales and in tight collaboration with biologists and chemists, researchers in this rapidly growing branch of condensed matter physics seek to consider and create new types of materials that show remarkable collective behavior, not expected at thermodynamic equilibrium.

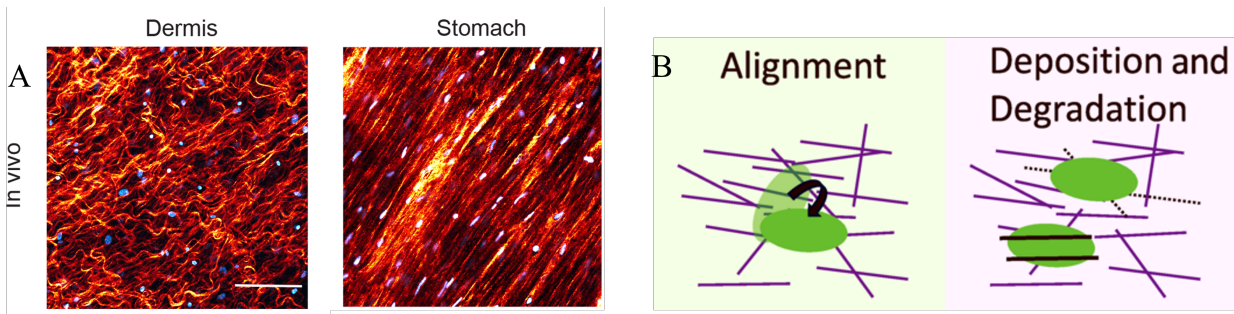


Figure 1: A. Second harmonic imaging of collagen fibers (orange) in different mouse tissues in vivo show various patterns of extracellular matrix organization [7]. The position of the fibroblasts are indicated by their labelled nuclei (cyan). B. Schematic of key processes in the hydrodynamic active matter model developed in the highlighted paper. Left: Cells (green) align with matrix segments (purple). Right: Cells degrade existing matrix segments (dashed black) and deposit new segments (bold black). Reproduced with permission [6].

Ever since the pioneering model by Vicsek and collaborators [3], a major preoccupation has been orientable active matter, that is, how agents with directed self-propulsion interact

to create ordered states [4, 5]. In the common paradigm of Vicsek-style models, a liquid-gas type of phase separation occurs, with higher density and lower noise favoring a liquid-like state with orientational order [2]. By considering the biologically relevant mechano-chemical interactions of migrating cells with their extracellular matrix (most commonly, fibroblasts on collagen fibers), Ram Adar and Jean-François Joanny now show that cells can align and create ordered states even at vanishingly small cell densities [6]. This is a striking example of how active matter that interacts with and “actively” modifies its complex environment in a biologically inspired manner, can itself be modified beyond its established paradigm.

In this work, the authors present a hydrodynamic model for “active nematics” interacting with their environment. “Nematic” implies long-range orientational order of rod-like constituent units, which are head-tail symmetric. In contrast with polar order, the orientational order is therefore parametrized by a tensor (commonly denoted as \mathbf{Q}), rather than a vector field. The biological motivation comes from self-propelling and mutually aligning, elongated cells that deposit, align with, and degrade fibers that constitute the extracellular matrix [7]. We use “hydrodynamic” here to mean a continuum model based on conservation principles, that is applicable to many particles at long length and timescales. The model is otherwise “dry” in that no fluid flow is involved and the extracellular matrix is considered to behave like a “momentum sink”, in that the matrix segments (comprising fibers) move negligibly in response to cell forces. Two processes key to the model, in addition to the cell self-propulsion, are illustrated in Fig. 1B. Each cell experiences an aligning field which contains the combined effect of the other cells and matrix fibers (analogous to the Maier-Saupe mean field theory for liquid crystals). Each cell also randomly deposits a fiber along its body axis, or degrades a fiber (of any orientation), at its location.

The authors follow one of the well-trodden routes of creating a hydrodynamic model from the mesoscale kinetics. They start with the mean-field kinetics of the distribution of the two species (cells and matrix segments), f_c and f_m , in position \mathbf{r} , and orientation, \mathbf{n} . The change of cell density, f_c , from a given position happens through advection and diffusion, while the change in orientation happens through alignment with a local field and rotational diffusion. The matrix segments are assumed to not translate or reorient in the timescale of the phenomena of interest, and are instead just deposited (along local cell orientation) or degraded by the cells. Coarse-graining the kinetics by considering moments of the probability distributions up to second order leads to mass, momentum, and angular momentum balance equations in terms of density, polar and nematic order parameters, respectively.

A key aspect of the model is the Maier-Saupe like mean field treatment of the local alignment, wherein each cell orients with a total aligning field, $\mathbf{Q}_t = \beta_c \mathbf{Q}_c + \beta_m \mathbf{Q}_m$, where the \mathbf{Q}_c and \mathbf{Q}_m are nematic tensors corresponding to alignment of cells and matrix segments, respectively. The solution of the resulting hydrodynamic model at steady state yields the phase diagram of Fig. 2. A striking feature of this phase diagram is that, because of the matrix contribution to the total nematic field (the $\beta_m \mathbf{Q}_m$ term), there is an alignment of cells (non-zero intensive nematic order parameter, $\mathbf{q}_c = \mathbf{Q}_c/\rho_c$) even when cell density ρ_c goes to zero. This result, derived from a self-consistent solution of the mean-field theory, can be understood simply. Even very dilute cells will deposit a finite density of oriented fibers after long enough time, which records the memory of past positions and orientations of the cells, which in turn will align the cells in time.

A crucial feature of the phase separation in aligning active matter is the co-existence region of the isotropic gas-like and nematic liquid-like phases [2]. This can be derived from a mean-field theory for the lattice gas version of Vicsek model [8]. Adar and Joanny perform linear stability analyses of their model to show how the matrix shifts the spinodal and binodal lines in Fig. 2. They physically interpret the stability criterion as a competition of the “ideal gas” (osmotic) pressure and active stress originating from cells moving past each other along the local orientation direction. The purely isotropic or nematic phases can turn unstable when the active stress can overcome osmotic pressure and cause the cells to clump. Consider for ex-

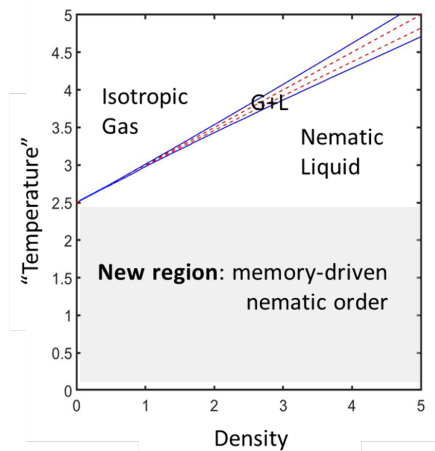


Figure 2: Model phase diagram in the cell density and temperature (noise) space when cells deposit and degrade matrix segments (slightly modified with permission from Ref. [6]). Solid blue lines are the binodal and red dashed lines are the spinodal. The grey nematic region does not occur in the usual Vicsek style models, and is a result of alignment with the matrix segments.

ample, a clump of cells aligned in the y -direction. Their motility results in an extensile force dipole aligned along y , creating inward directed forces along the orthogonal x -direction. This will draw in more cells against the concentration gradient leading to a high density region next to a lower density. The analysis reveals two new important effects of the matrix on the stability analysis. The matrix ensures stability of the nematic region at low cell density. Furthermore, the matrix allows for co-existence between domains of different orientations. For example, it is possible for a domain of cells oriented along y -direction to co-exist next to a domain of cells along x . By analyzing the angular dynamics of the relative orientations of the cells and the matrix, the authors show that local cell re-orientations can be frozen, giving rise to domains of different orientation. They terms this phenomenon “arrested domain coarsening”, which could be important for creating various patterns in the cell-extracellular matrix composite tissue, as shown in the examples in Fig. 1A.

This work shows that the mechanism of alignment in tissue is not just through collisions of self-propelling rod-like cells [9, 10], but could also be templated by the environment. Such feedback between active units and their environment that they remodel, can also be important in other forms of active matter. In a complementary example, we recently showed nematic bands on microtubule gliding assays, where microtubules are driven by kinesin motors anchored to a lipid membrane substrate [11]. In accompanying theory for motor-propelled rods, we considered the modification of the rods’ collective dynamics by the motors’ ability to redistribute by diffusion.

The work by Adar and Joanny is a good example of how consideration of realistic mechanobiology can inspire new physical theory. Theorists have been fascinated by cells and tissues acting as active fluids for some time, with strong recent interest in collectively

migrating, dense monolayers of epithelial cells [12]. Such active nematic fluids are characterized by generic instabilities, proliferation of defects and chaotic flows. However, many cell culture experiments as well as in vivo situations such as wound healing or blood clot contraction involve dilute cell assemblies embedded in a solid extracellular matrix. For these systems of broad-ranging interest in tissue engineering and regenerative medicine, it is important to include the effect of the environment in the modeling. The theory for cell-matrix elastic interactions of adherent cells [13] suggests that cell-cell interactions through mutual elastic deformations of the matrix can help create tissue patterns, such as aligned cell networks during vascular development [14]. Including elasticity of the matrix would therefore be an important extension to the present model. It will also be important to check the predictions of this mean-field model in agent-based simulations, where stochastic fluctuations can be explicitly included. The model is also an important step in the direction of considering mechano-chemical feedback in motile active matter. Biological matter is inherently mechano-chemical [15] in that active mechanical forces are generated by chemical reaction kinetics which are themselves mechano-sensitive. Considering such mechano-chemical feedback is of direct biological relevance and is fertile terrain for development of new active matter models potentially featuring non-reciprocal interactions.

References

- [1] M. C. Marchetti, J.-F. Joanny, S. Ramaswamy, T. B. Liverpool, J. Prost, M. Rao, and A. Simha, *Rev. Mod. Phys.* 85, 1143 (2013)
- [2] H. Chaté, *Annu. Rev. Condens. Matter Phys.* 11, 189 (2020)
- [3] T. Vicsek, A. Czirók, E. Ben-Jacob, I. Cohen, and O. Shochet, *Phys. Rev. Lett.* 75:1226 (1995)
- [4] J. Toner and Y. Tu, *Phys. Rev. Lett.* 75, 4326 (1995)
- [5] S. Ramaswamy, *Annu. Rev. Condens. Matter Phys.* 1:323–45 (2010)
- [6] R. M. Adar and J.-F. Joanny, *Phys. Rev. Lett.* 133, 118402 (2024).
- [7] E. Wershof, D. Park, R. P. Jenkins, D. J. Barry, E. Sahai, P. A. Bates, *PLoS Comput Biol* 15(10): e1007251 (2019).
- [8] A. P. Solon and J. Tailleur, *Physical review letters* 111, 078101 (2013).
- [9] F. Peruani, A. Deutsch, and M. Bär, *Phys. Rev. E* 74, 030904 (2006).
- [10] A. Baskaran and M. C. Marchetti, *Phys. Rev. Lett.* 101, 268101 (2008).
- [11] F. L. Memarian, J. D. Lopes, F. J. Schwarzendahl, M. G. Athani, N. Sarpangala, A. Gopinathan, D. A. Beller, K. Dasbiswas and L. S. Hirst, *PNAS* 118(52), e2117107118 (2021)

- [12] T. B. Saw, A. Doostmohammadi, V. Nier, L. Kocgozlu, S. Thampi, Y. Toyama, P. Marcq, C. T. Lim, J. M. Yeomans, and B. Ladoux, *Nature*, 544(7649), 212-216 (2017).
- [13] U. S. Schwarz and S. A. Safran, *Rev. Mod. Phys.* 85, 1327 (2013)
- [14] P. S. Noerr, F. Golnaraghi, J. E. Zamora Alvarado, K. E. McCloskey, A. Gopinathan, and K. Dasbiswas, *PNAS* 120 (45) e2301555120 (2023)
- [15] J. Howard, S. W. Grill, and J. S. Bois, *Nat. Rev. Mol. Cell Biol.* 12, 392–398 (2011).