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# Cytoplasms are viscous and crowded, and yet they move

**Self-organized intracellular twisters**

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*Recommended with a Commentary by Massimo Vergassola, CNRS and Ecole Normale Supérieure, Paris*

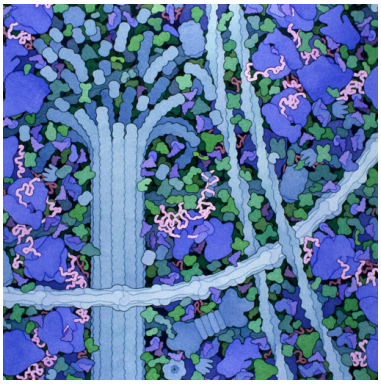

Figure 1: An illustration of the crowded cytoplasmic environments. Three types of filaments that make up the dynamic network of proteins in the cytoplasm are shown: a microtubule, an intermediate filament, and two actin filaments (largest/knobby/smallest). Freely available illustration by David S. Goodsell.

Living systems require proper coordination of their internal processes across their span. In particular, material like organelles, vesicles and other cellular components, ought to be transported across cells, oocytes and embryos [1]. A striking example of the importance of transport is provided by oocytes (eggs) where proper localization of components of the cytoplasm are needed to ensure subsequent development of the embryo [2]. Transport of cytoplasmic components in small cells is thought to be controlled by a combination of diffusion and active force generation. However, orders-of-magnitude estimates [3, 4] show that the cell is highly crowded and viscous, as beautifully illustrated in Fig. 1 by one of Goodsell's classical drawings [5]. That organization can hamper transport and make diffusion (possibly slowed-down to sub-diffusion [6]) alone unable to ensure cytoplasmic reorganization across larger distances (hundreds of micrometers). Those distances are typical of oocytes and syncytial tissues characterized by cytoplasmic continuity, that is a large mass of cytoplasm not separated into individual cells and containing many nuclei. A solution that has emerged from evolution in a broad range of biological instances is cytoplasmic flow, i.e., a continuous circulation of the cellular cytoplasmic fluid, see, e.g., Refs. [7, 8, 9, 10]. Streaming is encountered in many types of large cells, particularly in plants and algae, where it was first reported by the abbot Bonaventura Corti [11], and its source of energy is very often mediated by active processes such as polymerization and motor protein activity, see, e.g., Ref. [12].

Active processes can trigger large-scale cytoplasmic flow through a variety of molecular and mechanical embodiments. For instance, the actin cytoskeleton is the main actor in the peristaltic contractions of the slime mold *Physarum polycephalum*. The slime mold grows as a single complex of tubes that can reach more than 30 cm in diameter in a laboratory setting. Tubes are made of a gel-like outer layer enclosing the cytoplasmic fluid, and the fluid oscillates back and forth with a period of about 100 s [13]. The dynamics of the internal fluid is well-described by a Stokes flow with the boundary conditions set by the time-dependent sections of the tubes [14]. The actomyosin network is also responsible for the cytoplasmic flow observed in the embryo of *Drosophila* during its very early stages of development [15]. Biochemical oscillations driven by the cell cycle and initiated at the location of nuclei in the embryo spread over clouds of about 50 $\mu m$ to generate myosin II gradients close to the cortex. These gradients cause cortical contractions of the gel that entrain by friction the sol, and generate the cytoplasmic flow in the bulk that are ultimately responsible for proper positioning of the nuclei along the AP axis [16]. A final example of actin at work is provided by the segregation of maternal determinants within the zebrafish oocytes. Extensive streaming leads to the segregation of ooplasm from yolk granules along the animal-vegetal axis of the oocyte. The process was recently shown to be driven by a bulk actin polymerization wave traveling from the animal to the vegetal pole of the oocyte, which yields segregation by both pulling ooplasm animally and pushing yolk granules vegetally [17].

Contrary to the previous examples, the recommended paper by Dutta et al. considers the *Drosophila* oocyte, where streaming has been proposed to spontaneously arise from hydrodynamic interactions among cortically anchored microtubules loaded with cargo-carrying molecular motors [18]. The cytoplasm of the developing *Drosophila* oocyte remains relatively quiescent for the first three days of oogenesis. Then, when the oocyte reaches the size of about $150 - 300\mu m$ long and $100 - 200\mu m$ wide, large-scale vortical streaming arises with typical speed of $100 - 400nm/s$ [19, 20, 21]. This vortex was proposed to be generated by beds of cortically anchored flexible microtubules serving as tracks for plus-end-directed Kinesin-1 motor proteins moving free microtubules and other payloads. The recommended paper builds upon previous work [22] where a swirling instability was identified for a coarse-grained model, based on an active and deformable porous-medium model, meant to effectively capture the effects and fluid-mediated coupling of active and flexible microtubules. The novel advance brought forth by the recommended paper is to develop a fast, and scalable numerical approach to investigate fluid-structure interactions of thousands of flexible fibers and demonstrate the robust emergence and evolution of cell-spanning vortices, which the authors call "twisters". Specifically, the authors consider

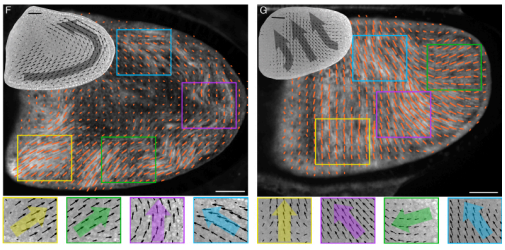

Figure 2: An image from the recommended paper of microtubules near the surface of *Drosophila* oocytes. Orange lines represent the local orientation of microtubules, with length representing the local degree of microtubules alignment. The cytoplasmic velocity field is shown by black arrows in a plane $15\mu m$ from the surface for corresponding regions. The colored arrows are average microtubules orientation in the corresponding regions. Scale bars are $25\mu m$.

a set of $N \gg 1$ microtubules clamped to the inner surface of a spheroidal cell and model them as inextensible elastic slender bodies. The cytoplasm is modeled as a passive Newtonian fluid. Equations for the shape of the microtubules are derived by using slender-body theory [23], which expresses the balance due to drag forces between elastic and motor forces. The total flow results from the superposition of the velocities due to the various microtubules, the backflow and the Stokes flow due to incompressibility and the no-slip condition at the boundary of the oocyte. The equations are integrated using boundary integral methods featuring Stokeslet and Stresslet components [24]. The resulting flow near the cell surface is locally set by the orientation of the microtubules (Fig. 2), and, since the flow is generated by motors moving along the microtubules, the flow speed increases from the center of the vortex towards the microtubule bed, then diminishes near the cell surface due to the no-slip boundary condition. Predictions were experimentally tested in live *Drosophila* oocytes by particle image velocimetry (PIV) using endogenous particles (yolk granules and other particles) as flow tracers. As in the aforementioned examples driven by actin, fine-tuning is not required and physics ensures the robustness of the process : as long as microtubule density and motor activity are within the wide domain of parameters that corresponds to stable streaming, self-organization takes care of the rest, establishing a cell-spanning cytoplasmic flow. The name twisters used by the authors reminds inertia-dominated phenomena, like tornadoes, whilst their twisters take place at vanishing Reynolds number and involve a precise balance between active surface driving and viscous dissipation. The functional role of cytoplasmic flows here is to ensure intracellular transport, namely the uptake of yolk, the main source of protein in the embryo.

In sum, the paper by Dutta et al. illustrates a beautiful instance of physics coopted by living systems to perform an essential biological function and I highly recommend their work to physicists and biologists alike.

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