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Cell nuclei as cytoplasmic rheometers

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Some researchers probe the mechanics of cells by perturbing them from the outside, such as using an atomic force microscope probe to record the amount of deformation of the cell in response to applying a prescribed force at a defined speed. Other researchers probe the mechanics of cells by perturbing them from the inside, an example of which is particle-tracking microrheology, in which the spontaneous motion of submicron, passive fluorescent beads ballistically injected earlier into the cell decodes the cell moduli. Both types of probes are typically composed of nonliving material. In this issue of *Biophysical Journal*, Moradi and Nazockdas cleverly propose to use the cell nucleus itself as a rheological probe for the mechanics of the cytoplasm (1). The cell nucleus is typically the largest and the stiffest organelle in eukaryotic cells. The surrounding cytoplasm contains other organelles and the cytoskeleton, which is comprised different kinds of semiflexible polymers, including actin, microtubules, and intermediate filaments. For cells that are confined by geometries on the scale of the size of the cell, the nucleus is minimally deformed and can therefore be approximated as a rigid sphere. It is in this limit that the authors ask the following questions. As a cell moves inside a microchannel, what does the motion of the cell nucleus, in response to deformations in the cell cortex, reveal about the rheology of the cytoplasm? Is it viscoelastic? Is it porous? Is it a poroelastic network? Is it something else? Answers to such questions will help us better understand cell function, such as how the cytoplasm reorganizes in response to changes in a cell physical environment.

To begin to answer the above questions, the authors focus on time-dependent deformations of the cell cortex, a regime rich with actin and myosin just beneath the cell membrane. Such deformations will generate internal flows to drive nuclear motion because the model assumes that some outer volume of the cell contains a Newtonian fluid. There also exists a viscoelastic or poroelastic medium, for example, within some inner volume of the cell, as well as a rigid sphere or the nucleus at the cell's core (see Fig. 1). Note that within this framework, no explicit cell cortex mechanics is required. One can infer the rheological properties of the cell cytoplasm by measuring the velocity of the cell nucleus moving in the cell in response to the cortical shape change. If the measured velocity of the cell nucleus as a function of time agrees with the theoretical curve found for a viscoelastic fluid, then one can argue that the cytoplasm acts as a viscoelastic fluid. If the measured nucleus velocity as a function of time takes a form that agrees with the theoretical curve found using a porous medium, then one can argue that the cytoplasm acts more as a porous medium. The authors provide multiple analytical calculations to determine the motion of the nucleus, assuming these different constitutive models. A key promise of the authors' approach is that particular constitutive models for the cytoplasm can effectively be ruled out by comparing the predictions with the experimental data.

From the theoretical perspective, the potential use of analytical solutions to the Stokes and modified Brinkman equations to determine the rheology of the cytoplasm is exciting. On the other hand, divvying up the cell into an outer fluid component and an inner, more complicated component, downplays the interactions between the different types of cytoskeletal filaments. To begin to address this, at least for the case of an inner poroelastic network, the authors consider fibers, such as microtubules, that may extend through the outer Newtonian fluid component to reach the cell cortex. In this situation, the displacement of the outer Newtonian fluid becomes tied to the poroelastic network displacement, should the fibers be pinned to the cell cortex, which, in turn, affects the motion of the nucleus.

With the model at hand, one can envision that the cytoskeletal filaments, such as vimentin intermediate filaments, do form a poroelastic network enclosing the nucleus (but

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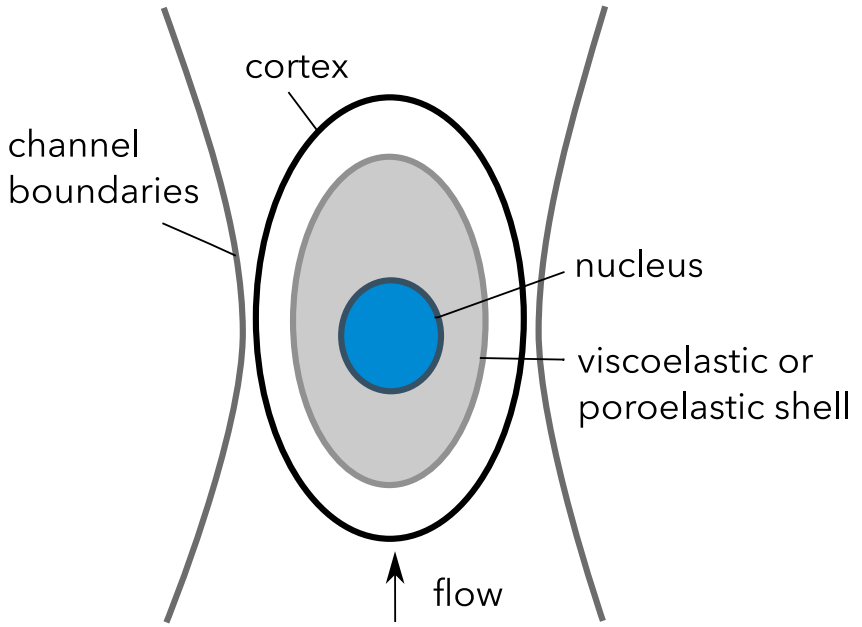

FIGURE 1 Schematic representation of a cell in a microfluidic flow. The cell consists of a deformable cortical membrane, a rigid nucleus, and a viscoelastic or poroelastic medium (shown in *gray*). Between the cortical membrane and the viscoelastic or poroelastic medium is fluid (shown in *white*). To see this figure in color, go online.

not necessarily the entire cytoplasm) (2). Vimentin, and other intermediate filaments, play diverse roles in the cell, ranging from physical linkages with actin filaments and microtubules (3) to modulating cellular adhesions with the extracellular environment (4,5). Moreover, the cytoskeleton interacts directly with the nucleus via the LINC complex, such that the nucleus itself plays a role in cellular mechanotransduction (6). Understanding such interactions at the mesoscale may help inform the continuum modeling presented here. These cytoskeletal interactions are a crucial component of the mechanics of the cytoplasm, as are, potentially, the organelles. A recent model of a cell being uniaxially compressed demonstrates that the presence of such organelles, modeled as deformable spheres, trigger the onset of compressional stiffening in the cytoskeletal networks (7).

From the experimental perspective, using the nucleus as a cytoplasmic probe is an advantageous technique for high-throughput cellular deformability testing. Advances in microfluidic and high-speed imaging techniques now allow for the automated tracking of nuclei at the scale of thousands of cells per second (8), which is orders of magnitude faster than more conventional tests, such as atomic force microscopy and microrheology. The mechanical properties of cells are rapidly emerging as an important biomechanical marker of different pathological states, particularly in cancer (9). The ability to more accurately predict cytoplasmic rheology from microfluidic-based nuclear motions could thus help expedite the development of diagnostic tools for early disease detection.

An overarching goal in the study of cell mechanics is to understand the connection between nuclear structure and cytoplasmic stresses. Thus, a natural next step is to introduce nuclear deformability. The nucleus is large, easily labeled, and ubiquitous, making it an ideal target for estimating cellular stresses in a wide range of applications, including in vivo cell motility assays and in vivo tissue morphology studies. A major challenge is that the nucleus does not act as a passive observer of the flow, and both the nucleus and cytoplasm can actively remodel upon direct application of force and generate their own forces through motors. Understanding the feedback mechanisms between the nucleus and cytoskeletal forces will be key to this outstanding issue.

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