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How the cell nucleus gets in shape

Richard Dickinson **and** ***Tanmay Lele*** **explain that the mammalian cell nucleus deforms with fixed surface area and volume and that limiting nuclear shapes in cells are governed by interfacial tension.**

Consider an object consisting of an inextensible, impermeable membrane enclosing a liquid, such as a vesicle (Fig. 1). If the shape of the membrane boundary is not spherical, it must have excess surface area relative to a sphere of the same enclosed volume. This excess area allows the object to adopt a wide range of shapes without changing its surface area or its volume and enables it to exhibit varying stiffness depending on both the amount of excess area and the degree of confinement.

The eukaryotic nucleus has long been thought of as an elastically 'stiff' organelle. However, in many situations, it deforms more like the object described above. The nuclear lamina, an approximately 15-nm-thick protein meshwork surrounding chromatin and composed primarily of type V intermediate filament proteins called lamins[1], behaves as the inextensible bounding surface. In rounded nuclei in tissues[2], excess laminar surface area (typically 20–40%) appears as visible folds and wrinkles. In this state, the nucleus can change shape with little mechanical resistance. Once the lamina becomes fully taut, however, the mechanical response changes: further deformation requires substantially larger forces to compress the nuclear volume or expand the lamina surface area. This transition from 'soft' to 'stiff' behavior is clearly evident during the spreading of a mammalian cell on a substratum. The nucleus takes on a smooth limiting shape beneath the confinement of the cell cortex, which can be computationally predicted by minimizing the surface area of the contractile cell cortex subject to constraints of constant cell volume, nuclear volume and nuclear surface area[3].

From the limiting shape, one can estimate the tension in the taut nuclear lamina τ_n and the nuclear pressure P_n (ref. 3). Assuming mechanical equilibrium, the Laplace relation $\Delta P = 2\tau H$ (ΔP is the pressure difference across the interface, τ is the interfacial tension and H is the mean surface curvature) can then be applied to the various interfaces: (1) between the cytoplasm and surroundings; (2) between the nucleus and cytoplasm; and (3) between the nucleus and surroundings where it is in contact with the cellcortex, yielding $\tau_n \sim 0.1$ nN μm^{-1} and $P_n \sim 60$ Pa. These mechanical stresses in the nucleus are otherwise very difficult to measure inside living cells.

Fig. 1 | Cross-section of idealized deformable object with constant volume and an inextensible surface possessing excess surface area. These geometric constraints capture the first-order mechanics governing nuclear shape, allowing large deformations through redistribution of excess surface area while conserving both enclosed volume and total surface area.

The presence of excess area in the inextensible nuclear lamina elegantly explains how the nucleus is able to deform through narrow tissue pores during the migration of cells in tissues[4]. Traditional explanations have emphasized the energetic cost of elastically deforming the entire nucleus as the primary barrier to cell migration under confinement. However, as described above, a nucleus with sufficient excess area should be able to deform and pass through a pore with little mechanical resistance. By contrast, when excess surface area is insufficient for a given nuclear volume and narrow pore geometry, no admissible shape exists within the confinement. In this case, the nucleus cannot pass without either reducing its volume (for example, via nuclear envelope rupture) or increasing its surface area, as occurs in cells lacking lamin A/C. This defines a threshold surface area that depends on nuclear volume and pore geometry, which can be computed by minimizing the surface area of a nucleus subject to confinement by the pore walls[5]. These predictions have been validated in microdevice experiments that present cells with constrictions of defined widths. Surface-area inextensibility conferred by lamin A/C – rather than nuclear size or bulk nuclear stiffness – is the key factor limiting migration through confinement.

Chemical engineers are familiar with the Laplace equation from bubble columns, emulsification and droplet microfluidics. Despite the complexity of living cells, it is remarkable that similar geometric and interfacial principles can explain cell and nuclear shapes, and the limits to cell migration in confined environments.

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Competing interests

The authors declare no competing interests.