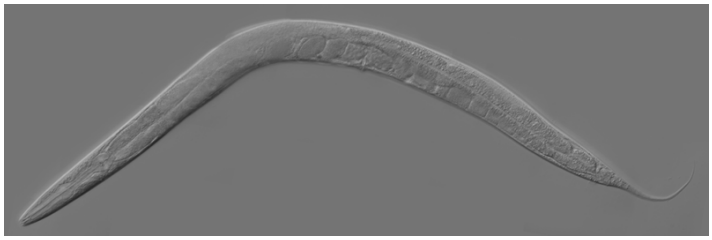
Limits on the Volume of a Cell's Nucleus

By monitoring a tiny worm's embryonic cells, researchers have deduced that the availability of material for the membrane of a cell's nucleus constrains the volume of the nucleus.

By **Charles Day**

It's reasonable to expect that the volume of a cell's nucleus depends in some way on the volume of the cell. After all, the larger the cell, the more material it holds from which to build a nucleus. Scientists have studied the nuclei-to-cell volumes for cells from microorganisms to mammals. However, the relationship has been found to differ for cells that form in the early life stages of the tiny worm *Caenorhabditis elegans*. To identify why, Matthias Weiss of the University of Bayreuth, Germany, and his collaborators tracked the sizes of nuclei in different cell lineages of *C. elegans* embryos [**1**]. They found that while the availability of material indeed limits the size of a cell's nucleus, the key structure is not the nucleus but the membrane that envelops it. How cells balance and maintain the volumes of their nuclei is potentially important for understanding when that balance breaks down, which happens, for example, when cells turn cancerous.

Scientists first started studying the size correlations between parts of living creatures in the late 19th century. For a wide range of mature cells, the nucleus volume V_N is about one tenth the cell volume V_C. But recent experiments have established that for nuclei in young embryos and larvae of *C. elegans*, the two quantities depend on each other in a sublinear way ($V_C = kV_N^{\alpha}$, where k is a constant and $\alpha < 1$).



An adult *Caenorhabditis elegans*.
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To investigate how and why V_N varies with V_C, Weiss and his collaborators studied so-called founder cells of five different lineages in early *C. elegans* embryos. Founder cells are cells whose cell type has just been determined. The researchers genetically tagged the cells' nuclei and surrounding membranes or envelopes with two different fluorescent proteins.

To measure V_N and V_C, the team used two complementary techniques: confocal microscopy and light-sheet microscopy. The former has higher spatial resolution but can damage cells and becomes unreliable at distinguishing individual cells after few rounds of cell division. The latter has a lower spatial resolution but does not damage cells and retains its reliability for three-dimensional imaging even after a larva has developed.

The researchers found that they could fit their V_N versus time data with a simple exponential function consisting of a constant term and a variable term that started out at zero and then increased steadily until it reached a constant, asymptotic value. The asymptotic behavior of V_N matched that found previously for mature cells across different species—that is, $V_N = 0.1V_C$. Still, the $V_N = 0.1V_C$ in the asymptotic limit puzzled Weiss and his collaborators. The five *C. elegans* lineages they studied have mature cells with different volumes. Yet the cells, from large to small, contain the same amount of *C. elegans* DNA, suggesting their nuclei should all have the same volume.

The researchers found that they could account for both the asymptotic and relaxation behavior by factoring in cell division. When a cell divides in two, the total volume of the system stays the same, but the surface area doubles. A cell's surface is made of a plasma membrane, which consists mostly of lipid molecules. A cell's nucleus is also enveloped by a lipid membrane, which is interconnected with the endoplasmic reticulum. The endoplasmic reticulum consists of an extensive network of membranes in which new lipids are synthesized. Weiss and his collaborators propose that once cell division finishes, the production and degradation of lipids needs to reach a new steady state. A dynamical model of that process developed by the team links the surface areas of the three membranes—plasma, nucleus, and endoplasmic reticulum—to the cell's volume such that $V_C^{2/3}$. The surface area of the nucleus therefore also scales with $V_N^{2/3}$, so it follows that V_N and V_C are proportional to one another.

Last year Sean Sun of Johns Hopkins University, Maryland, and his collaborators proposed a different explanation for the proportionality between V_N and V_C that they observed in mammalian culture cells [**2**]. Their model considered the synthesis, degradation, and transport of proteins and ribosomes, the molecular machines that translate RNA into proteins. "It's possible that [all the] mechanisms exist and feed into the final observed V_C/V_N relationship," Sun says.

Weiss and his collaborators also proposed a mechanism to account for the cell-size-dependent relaxation dynamics of V_N following each cell division. After chromosomes have been replicated inside the nucleus, the nuclear membrane breaks down during cell division and the duplicated chromosomes migrate to opposite ends of the cell, where they unspool into a form of DNA called chromatin and occupy new nuclei. Being less compact than chromosomes, chromatin exerts an outward pressure on the new nuclear envelope, akin to the behavior of polymers under confinement. The endoplasmic reticulum network, lacking lipids after cell division, is stretched out and will not let lipids reach the nuclear envelope to ease the pressure exerted by chromatin.

Faced with a dearth of lipids, the nuclear envelope grows slowly by appropriating nascent lipids, which are produced after cell division in the endoplasmic reticulum to balance the missing membrane material. These fresh extra lipids diffuse along the endoplasmic reticulum and become incorporated into the nuclear envelope, thereby increasing the envelope's area and allowing the chromatin to expand. Once the steady-state balance among all the membranes is reached, the growth of the nucleus stalls, even if the chromatin continues to exert outward pressure. In this scenario, the relaxation rate is determined by the diffusion of nascent lipids on the membrane of the endoplasmic reticulum, indicating that the characteristic relaxation time should scale as $V_C^{2/3}$. Weiss and his colleagues found the same dependency in their observations.

"The [study] has some nice experimental findings," says biophysicist Jasmin Imran Alsous of the Flatiron Institute in New York. She and her colleagues recently studied the nuclear membranes of the so-called nurse cells that are connected to the fruit fly's oocyte (future egg) [**3**]. Within a cluster of nurse cells, V_N and V_C both vary, and these cells duplicate their DNA 10–12 times without undergoing any cell divisions. "That's another experimental system where some of the [new] model predictions could be tested," she says.

Charles Day is a Senior Editor for ***Physics Magazine***.

REFERENCES

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