How does a nucleus grow?

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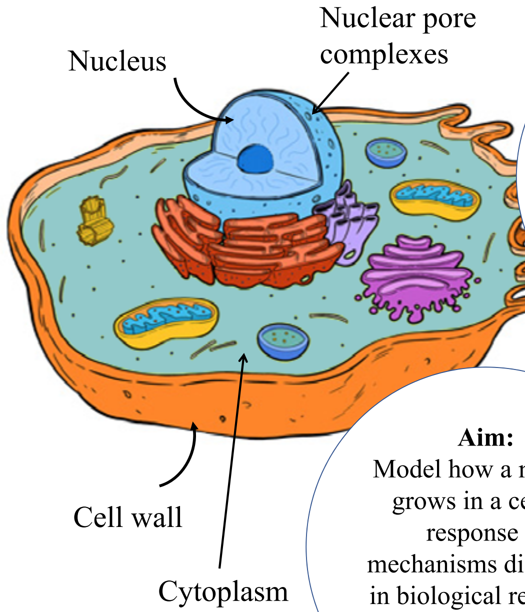
Introduction

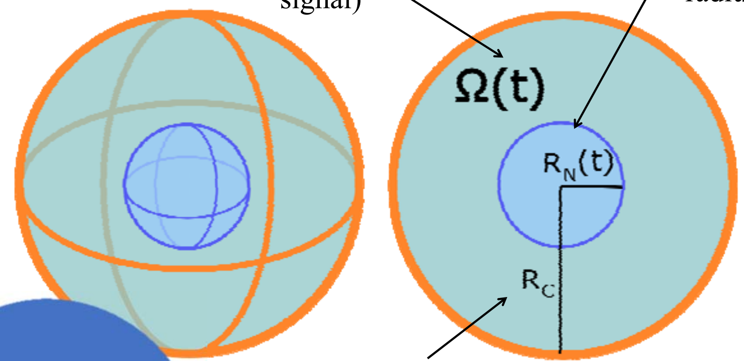


Why?
Nuclear size can help to diagnose various cancers and determine their stage [3], so it is useful to understand how nuclei grow.

What do we know?
- Nucleus grows by isotropic 3D expansion [1]. - Molecules in the cytoplasm pass through nuclear pore complexes (NPCs) in the nuclear envelope [2].

Aim:
Model how a nucleus grows in a cell, in response to mechanisms discussed in biological research. Use experimental data to compare results

Set up



$$\boldsymbol{v}(\boldsymbol{X},t) = \frac{R_C - ||\boldsymbol{X}||}{R_C - R_N}\dot{R}_N\frac{\boldsymbol{X}}{||\boldsymbol{X}||}.$$

Assume that $\boldsymbol{v}(\boldsymbol{X},t)$ varies linearly with distance from the nucleus

$\boldsymbol{v}(\boldsymbol{X},t)$ ... Velocity at which material points move in the cytoplasm

Governing equation

Advection term

$$\frac{\partial u}{\partial t} + \nabla\cdot(u\boldsymbol{v}) = D\nabla^2 u\,, \qquad ||\boldsymbol{X}|| \in \Omega(t)$$

$u(\boldsymbol{X},t)$ ... Concentration of growth signal in domain $\Omega(t)$

Diffusion constant

Diffusion term

Boundary conditions

$\boldsymbol{n}$ ... unit normal pointing out of the domain

$$D\nabla u\cdot\boldsymbol{n} = 0\,, \qquad ||\boldsymbol{X}|| = R_C$$

$$D\nabla u\cdot\boldsymbol{n} = -\kappa u\,, \qquad ||\boldsymbol{X}|| = R_N(t)$$

No flow through the cell wall

Signal is absorbed at the nuclear membrane

$\kappa(t)$ ... absorption rate

Modelling assumptions

Spherical symmetry is assumed

S ... total amount of growth signal entering the nucleus

$$S = 4\pi \underbrace{R_N^2}_{\text{Surface area of nucleus}}\kappa \underbrace{u(R_N,t)}_{\text{Signal concentration at surface of nucleus}}$$

κ ... Absorption rate

For $\kappa(t)$:
(a) Does the density of NPCs remain constant?
(b) Do the number of NPC's remain constant?

		(a)	(b)
		$\kappa(t) = \kappa_0$	$\kappa(t) \propto \frac{1}{R_N^2}$
(1)	$\dot{R}_N = \alpha S$	$\dot{R}_N = 4\alpha\pi\kappa R_N^2 u(R_N,t)$ $\kappa(t) = \kappa_0$	$\dot{R}_N = 4\alpha\pi\kappa R_N^2 u(R_N,t)$ $\kappa(t) = \kappa_0\left(\frac{R_N(0)}{R_N(t)}\right)^2$
(2)	$\dot{A}_N = \alpha S$	$\dot{R}_N = \frac{1}{2}\alpha\kappa R_N u(R_N,t)$ $\kappa(t) = \kappa_0$	$\dot{R}_N = \frac{1}{2}\alpha\kappa R_N u(R_N,t)$ $\kappa(t) = \kappa_0\left(\frac{R_N(0)}{R_N(t)}\right)^2$
(3)	$\dot{V}_N = \alpha S$	$\dot{R}_N = \alpha\kappa u(R_N,t)$ $\kappa(t) = \kappa_0$	$\dot{R}_N = \alpha\kappa u(R_N,t)$ $\kappa(t) = \kappa_0\left(\frac{R_N(0)}{R_N(t)}\right)^2$

How does the nucleus grow?
The amount of growth signal absorbed into the nucleus could be proportional to:
(1) Increase in nuclear radius
(2) Increase in nuclear surface area
(3) Increase in nuclear volume

Well-mixed model

$\frac{\kappa_0 R_C}{D} \ll 1$

diffusion is fast compared absorption, cell size small

well-mixed model can be approximated

$u(r,t)$

$u(t)$

$$\dot{u}(t) = \frac{3R_N^2 u(t)(\dot{R}_N(t) - \kappa(t))}{R_C^3 - R_N^3}$$

$$\dot{R}_N(t) = f(R_N,t)$$

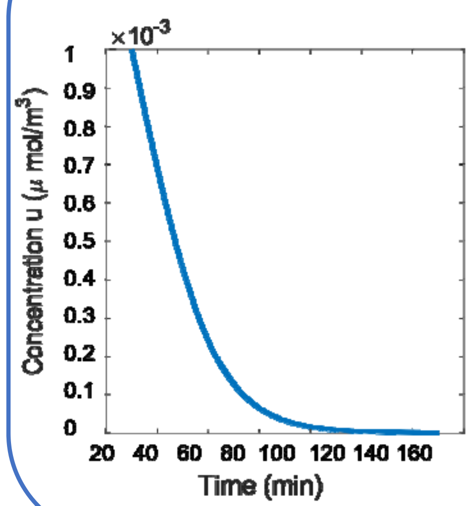
$f(R_N,t)$ depends on the modelling assumptions (1) – (3)

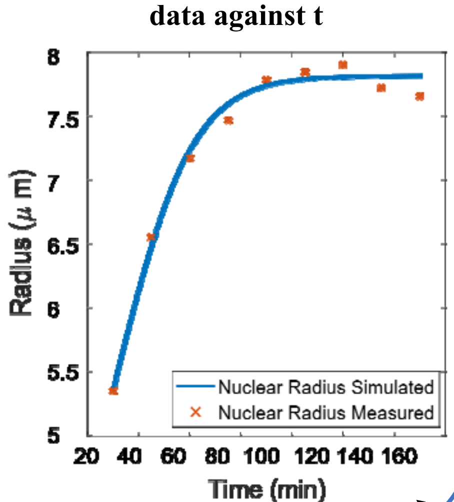
Simulation

Well-mixed model is simulated for a given cell size

Appropriate parameter choices are made to make results fit with experimental data

Signal concentration decreases with time until it is all used up





Nuclear radius increases with time until it reaches a limiting value when all the signal is absorbed

Which model is the best?

Method:
For each case (a), (b), (1) – (3) the model is simulated.

Parameters are chosen to make the results fit best to the experimental data provided and the total error is calculated

How is the signal absorbed?
This needs to be explored further as there is not a big enough difference in the error for both models to draw a conclusion.

How does the nucleus grow?
It is most likely that nuclear volume increases proportional to the amount of signal entering the nucleus, as in case (3)

References

[1] Chan, Y.-H. M. and Marshall, W. F. (2010). Scaling properties of cell and organelle size. *Organogenesis*, 6(2):88-96.

[2] Chen, P., Tomschik, M., Nelson, K., Oakey, J., Gatlin, J. C., and Levy, D. L. (2019). Cytoplasmic volume and limiting nucleoplasmin scale nuclear size during xenopus laevisdevelopment. *bioRxiv.*

[3] Levy, D. L. and Heald, R. (2012). Mechanisms of intracellular scaling. *Annual Review of Cell and Developmental Biology*, 28(1):113-135.

Acknowledgements

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