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Geometric control of intracellular patterning

1. **How to assemble a scale-invariant gradient**
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Recommended with a Commentary by Arjun Narayanan, New York University Abu Dhabi

Living matter shows an impressive architectural ability - starting from molecules that must react to their nanometer-scale local environment, structures are robustly generated on both the cellular scale (10's of μm) and the tissue scale (meters). To appreciate these scales, one may imagine that molecules assembling a cytokinetic ring at the center of a 10 μm cell is analogous to a group of people meeting at the precise center of New York City while walking with a blindfold on. This would rarely occur by chance, and instead information about instantaneous position relative to the city must be made available locally to each person. The concept of a positional information field permeating living cells and tissues has long been appreciated [1].

Many models have been constructed that generate positional information fields. In the recommended paper, Arnab Datta, Sagnik Ghosh and Jane Kondev add to this list of models [2]. Their model is distinguished by three features: i) a parsimonious list of requirements, ii) a close matching to the experimental situation in many biological contexts, and iii) a purely geometric control of patterning in cells and tissues.

Consider a polarized cell, such as a mammalian cell migrating along an axis of polarization or the just-fertilized embryo of nematodes as they polarize in preparation for an asymmetric cell division. Here, the positional information field must correspond to the concentration profile of some molecular species between the poles. How is such a profile set up, and how does this profile scale as the cell size changes, during natural growth or under perturbation? It is sufficient to look at the constant variation of cell shapes and sizes on a tissue culture plate to understand that a positional information field that does not scale with cell shape and size would not convey positions for long.

One way to create a concentration profile in a cell is the so-called 'synthesis-diffusion-degradation' scheme. Here we consider proteins synthesized at one cell pole - where they are consequently maintained at concentration C_0 - diffusing away from this source with diffusion constant D, and being degraded at a constant rate k everywhere in the cell. In one dimension, the steady state concentration profile resulting from synthesis, diffusion and degradation is an

exponential $C(x) = C_0 e^{-x/\lambda}$ where x is the distance from the synthesis pole and the characteristic length scale $\lambda = \sqrt{D/k}$. In three dimensional cells - e.g. for spherical and ellipsoidal cells, azimuthally symmetric about an axis passing through the synthesis pole - the exponential character and characteristic length scale are maintained

Were the cell to grow during its cell cycle, or be squished by its environment, the diffusion constant and degradation rate would have to change in order for the concentration profile to scale correctly. The basic insight in the recommended paper is that, if the degradation term were due to diffusive capture of molecules at the surface of the cell and their directed transport back to the pole - none of the kinetic parameters would matter, and the gradient would be simply set by cell size.

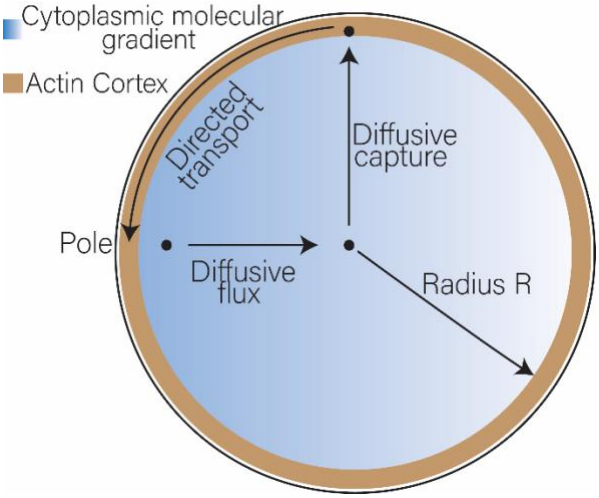

Figure 1: Schematic: A concentration profile is generated within the cytoplasm of a cell of radius R, by the coupling of diffusive flux away from a pole to directed transport back to the pole via diffusive capture and transport at the actin cortex.

The simplest realization of this model is sketched in Figure 1. The surface of the cell includes machinery for directed transport –a meshwork of actin filaments (the actin cortex). Some species of molecule - whose concentration profile will convey positional information - diffuses within the bulk of the cell and is only removed from the concentration field by the chance event that it diffuses and sticks to the actin cortex on the surface. These captured molecules are then efficiently transported along the surface, by the actin cortex, to one pole and released, conserving molecule number in the cell. In this model, synthesis and degradation are both linked to diffusive capture. Moreover, the typical rate at which molecules diffuse from the bulk to the surface of a cell of radius R gives the capture or degradation rate $k = D/R^2$. Since the decay length scale $\lambda = \sqrt{D/k}$, the resulting concentration profile along the axis of polarization is an exponential with a decay length $\lambda \sim R$. Thus, the concentration profile is independent of any kinetic parameters and set solely by geometry. Scaling of this profile with cell size follows. We note that the geometric control in this picture is distinct from models that rely on cell size dependent kinetic rates and also from models that rely on long range mechanical communication of positional information.

It is well-established that many molecular species can switch between diffusive and directed transport in cells and tissues. We expect the effect just discussed to contribute to scale-invariant positional information fields whenever the rate of molecular switching between these behaviors depends on diffusion over a distance that scales with cell size. In such biological contexts, the only question that remains is how relevant this effect is when compared to other influences. This is a question for careful experiment. Where should we look?

We note that in addition to cells, this model can apply to tissues, or subcellular regions. Additionally, there are many sources of directed transport - flows of actin filaments within the cortex, cytoplasmic streaming, actin treadmilling, and trafficking along microtubules to name a few. Finally, there are many molecular species that can couple to each of these transport mechanisms when they are not diffusing. Given the wide domain of potential applicability, there are multiple biological contexts where experimental efforts could be directed. The authors suggest a few, including budding yeast, fission yeast, cilia and flagella. One particularly intriguing factor that may guide our choice is the potential for a feedback effect - briefly mentioned by the authors - the very transport channel that allows directed transport, may be shaped by the concentration profiles it creates. For instance, a spatial pattern of actin severing proteins created by treadmilling actin filaments, may affect the very treadmilling that set it up.

Motivated by this last point, in addition to the authors own suggestions, we suggest two promising experimental directions:

1) The one-cell C. elegans embryo becomes polarized just prior to its first cell division. While polarity is being established, the molecular motor, Non-muscle Myosin II (NMY-2) drives a polarized flow of matter in the actin cortex. NMY-2 is itself transported by this flow and released at the anterior pole of the embryo as the cell polarizes [3]. Additionally, polarized cells of serially reducing sizes are created during subsequent cell divisions in the early C. elegans embryo. This system could allow for simultaneous testing of geometry dependent scaling, and feedback between a transport channel and the molecular field it creates.
2) The lamellipodia of cells are characterized by retrograde actin flow transporting actin and its regulators back to the cell body. Lamellipodia are flat sheets that vary widely in aspect ratio as cells migrate and sense their substrates. It is possible to measure the forces they apply on their environment. The gradients of force generators formed within the lamellipodia, and their dependence on lamellipodial aspect ratio may hold insights about the regulation of cell migration

We encourage readers to use and add to this list.

References

[1] Louis Wolpert, J. Theor. Biol. 25:1-47 (1969)
[2] Arnab Datta, Sagnik Ghosh and Jane Kondev, eLife 11:e71365 (2022)
[3] Fereshteh R. Najafabadi, Mark Leaver, and Stephan W. Grill, Mol. Bio. Cell, 33, 8 (2022)