BIOLOGICAL PHYSICS

Connected Development

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Standfirst
Mapping cell lineages onto a problem in graph theory suggests that physical principles regulate cell positioning during egg development in the fruit fly — providing an elegant example of how physics can advance our understanding of biology.

Embryonic development is a complex process. Its proper progression requires precise orchestration: even small deviations from the developmental plan, such as the misexpression of a single gene or misplacement of a few cells, can result in defects that are catastrophic for the organism. Yet, development is remarkably robust and occurs without fault with extraordinary regularity throughout the plant and animal kingdoms, from the simplest *volvox* algae to humans. The source of this robustness is a central question of developmental biology, and one of the great mysteries of life. Now, writing in *Nature Physics*, Jasmin Imran Alsous and co-workers have used experiment and theory to show how geometric constraints regulate cell positioning during egg development in the fruit fly[1]. Their work illustrates how physical principles can interact with cellular mechanisms to guide development along a reliable trajectory.

Egg production, or oogenesis, in the fruit fly *Drosophila melanogaster* is widely studied as a paradigm for development. During the first stages of oogenesis, a cluster of 16 germline cells – consisting of one cell that will eventually become the oocyte, or egg, and 15 supporting nurse cells – emerges via sequential cell divisions from a single stem cell. Unusually, the process of cellular separation, or cytokinesis, that normally consummates cell division does not fully complete in these divisions, and the daughter cells remain connected by tubular cytoplasmic bridges known as ring canals. As successive divisions occur, a small network of cells and bridges emerges, which provides the cells with primitive spatial information, and ensures that the oocyte remains intimately connected to its supporting cells. Because it encodes the cell-division history of the developing oocyte, this network is known as a cell lineage tree (CLT). As the process of oogenesis continues, the emerging CLT is surrounded by a sheet of smaller follicle cells, to form an enclosed aggregate known as an egg chamber, which provides a further spatial constraint on its development.

To biologists, ring canals and associated CLTs are interesting because they provide a mechanism by which the nurse cells can directly supply nutrients and cytoplasmic components to the developing oocyte. For this reason, much effort has been devoted to dissecting the molecular biology of the transport and signalling processes that orchestrate oocyte maturation[2]. However, despite this wealth of molecular knowledge, much less is known about the mechanisms that regulate collective cellular dynamics within the developing egg chamber.

Alsous and co-workers took a different approach. Rather than investigating the molecular identities of the cells in relation to their generation or spatial position, they asked whether the spatial arrangement of the CLT as a whole within the egg chamber is shaped by physical (rather than biological) principles. This question is natural for a physicist to ask because the CLT evolves under geometric constraints that might be expected to affect its configuration. However, it is not one that biologists would typically think to address, as it is not immediately clear how such principles would relate to underlying molecular processes — although they clearly have importance for how the cellular dynamics in the egg chamber will unfold.

To address this question, they first noted that a CLT can be represented mathematically as a graph in which nodes denote cells and edges denote ring canals, embedded on a convex enclosure (Fig. 1). Using this representation, they converted the question of how cells arrange themselves in the developing egg chamber to the problem of how trees embed on convex surfaces. Once in mathematical form, this biological question became amenable to investigation. Perhaps more importantly, the mapping revealed that the CLT configurations observed in development are not random, but rather are shaped by physical principles.

To show this, Alsous and co-workers noted that although CLTs all have the same degree distribution – essentially because the cell divisions that generate them are highly regulated – this constraint is not enough to fully determine their spatial configuration. By comparing the adjacency structures of observed CLTs with the structures of the Platonic, Archimedean and Johnson[3] solids, they found that the Disphenocingulum, also known as J_{90}, serves as an approximate model of the convex enclosure of the egg chamber. Importantly, they also found that some CLT configurations map to J_{90} in more ways than others, thus establishing an entropic principle for their preference in development.

However, the mapping between CLTs and J_{90} is not exact, because the layered structure of observed CLTs is not captured in the structure of J_{90}. To fix this issue the authors proposed an energy-based model for cellular positioning, adapted from the Thompson problem of arranging repulsive particles on a sphere[4], that takes account of connections between cells and differences in cell volumes. They found that the cellular arrangements that emerged from simulations of this model closely matched those observed in experiment. Collectively, this suggests that cellular positioning in the egg chamber is shaped, at least in part, by a combination of energetic and entropic considerations.

Of course, there is a long history of mathematicians and physicists turning their mind to similar problems in development[5]. When physicists consider problems in biology they sometimes find that the mathematical language required to specify the problem is not adequately developed. To make progress they must also develop new theory that can, thereby, stimulate new physics. Notable examples include Alan Turing's work on diffusion-driven instability as a mechanism for embryonic patterning[6] and René Thom's work on catastrophe theory as a theoretical framework to understand morphogenesis[7]. For their part, Alsous and co-workers found that the mathematical language they needed did exist and is — at least in part — very old, although perhaps not widely known. This does not diminish the importance of their work as a piece of physics, however. By bringing together new ideas and old to solve a problem in biology they provided more evidence of the role for physics in development. This is good physics, as well as good biology.

Yet, they also found that physics was not enough: the entropic principle they identified does not precisely explain the cellular positioning they observed. To fill in the missing pieces, we must return to the approach of the biologist and dissect the molecular and cellular details, because development depends on a synergy of molecular, cellular and physical principles. So, their work also points to the need for a more integrated understanding of life that blends physics with biology on all scales. Ultimately, such a synthesis may lead us to a theory for the physics of living matter. The search for such a theory is one of the most exciting frontiers of modern physics[8,9].

Fig.1 The geometry of the egg chamber

(a) Schematic of a Drosophila egg chamber; (b) Geometric relationships between germline cells in the egg chamber can be represented by a network known as a cell lineage tree.

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