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Cell division: Size-scaling cytoplasmic flows transport chromosomes to the right spot

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https://doi.org/10.1016/j.cub.2025.03.041

Early embryos undergo rounds of division, producing cells of reducing sizes that must scale the distance chromosomes segregate. A new study shows that this scaling results from a cell-size-dependent dampening of cytoplasmic flows that advect chromosomes.

During cell division, chromosomes must be properly segregated to each daughter cell to ensure faithful genome transmission. This segregation is commonly achieved by microtubules of the mitotic spindle that pull or push chromosomes apart in anaphase[1]. Chromosome segregation sets an interesting geometrical puzzle: it must be adapted to cell length, otherwise chromosomes would either end up outside cellular boundaries or too close to the cytokinetic cleavage furrow, resulting in the risk of segregation defects. In early developing embryos, such as those of the zebrafish *Danio rerio*, rounds of rapid reductive divisions transform early blastomeres that span several hundreds of microns in length into much smaller cells typically tens of microns long (Figure 1). Such drastic size variation raises the question of how the machinery that segregates chromosomes may probe cellular dimensions to ensure the proper positioning of chromosomes at the end of anaphase when the nuclear envelope reforms. In a recent paper in *Nature Cell Biology*, Afonso *et al.*[2] now show that, in early zebrafish embryos, chromosome segregation speed, but not duration, decays as blastomeres reduce in size, ensuring that chromosomes stop at a relative position that is 'adapted' or 'scaled' to cell size. Their data support the conclusion that chromosomes are not directly moved by spindle microtubules but are instead advected by cytoplasmic flows toward the cell periphery. These flows slow down as cells become smaller, because of hydrodynamic confinement by cell boundaries, and act as 'size sensors' to scale chromosome segregation (Figure 1).

Mechanisms of chromosome segregation have been studied for decades in model cell types like yeast or vertebrate adherent cells[1], leading to the observation that chromosome segregation often occurs in two consecutive steps — anaphase A and B. In anaphase A, chromosomes move away from the spindle midzone to approach static spindle poles, while in anaphase B, the distance between the spindle pole and the chromosomes remains constant, and spindle poles separate to finalize chromosome segregation. Some cell types spend more or less time in each phase, while others only exhibit one of the two phases. Using live microscopy to follow the divisions of cells of early zebrafish embryos, Afonso *et al.*[2] show that anaphase A lasts around 100 seconds, while anaphase B lasts around 170 seconds, independent of development stage. Interestingly, chromosome separation speed is constant in anaphase A, but exhibits a strong dependence on cell length in anaphase B. This finding suggests the existence of a size-scaling mechanism that progressively reduces the chromosome separation distance. Investigating putative mechanisms of chromosome transport, the authors observe large-scale cytoplasmic flows recirculating from the cell middle towards the cell periphery (Figure 1). Flows are readily visible by observing the motion of organelles, such as mitochondria or lipid droplets, suggesting that these flows could also advect chromosomes. Accordingly, these flows increase in

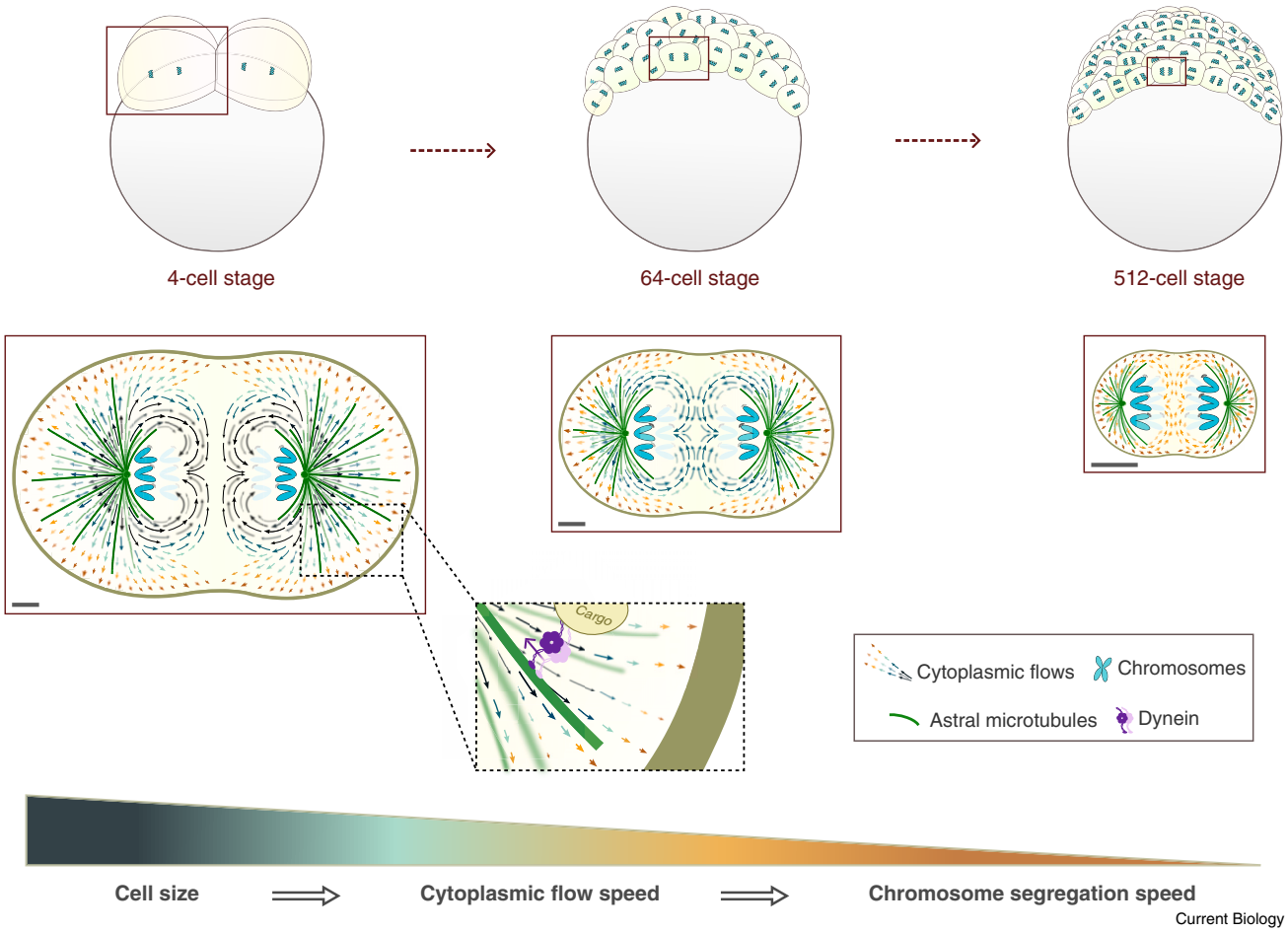

Figure 1. The speed of cell-size-dependent cytoplasmic flows scales chromosome segregation during early embryo development.
Three representative stages of zebrafish embryonic development are shown at the top. Blastomeres undergo fast mitotic cycles with sizes that range from ~300 μm (4-cell stage) to ~70 μm (512-cell stage). Chromosomes are transported by cytoplasmic flows that emerge during anaphase B as a result of reactive friction drags produced by dynein motors transporting endomembrane cargoes along astral microtubules. As cell size decreases, hydrodynamic confinement becomes more pronounced, slowing flows and chromosome separation speed. Scale bars, 20 μm.

amplitude in anaphase B, reaching a local velocity close to that of separating chromosomes.

Large-scale cytoplasmic flows have a long history as an effective mechanism for organelle transport and cellular organization, especially in the context of large cells, like oocytes, zygotes and early blastomeres[3]. Depending on the system, flows may be generated by cytoskeletal polymers and motors, such as actin and myosin or microtubules and kinesins. Cytoskeletal polymers and motors advect cytoplasm most often by actively moving vesicle cargos or endomembrane networks like the endoplasmic reticulum, which provide a large surface of interaction with the cytoplasm[3,4]. In the early zebrafish embryos, Afonso *et al.*[2] demonstrate that flows are independent of actin but that they depend on the activity of dynein motors moving along microtubule tracks. Dynein can transport endomembrane cargos like mitochondria, lysosomes or the endoplasmic reticulum to microtubule minus ends at the centre of the spindle asters[5]. Cargo motion in bulk cytoplasm creates reactive viscous drag forces that may reach tens of piconewtons and that can transport microtubules in the opposite direction through force balance[6]. This mechanism was proposed to contribute to aster centring during fertilization and to aster separation in anaphase in various embryos[5,7–9]. To test this hypothesis, the authors performed a detailed analysis of mitochondrial movements, finding that mitochondria may exhibit very rapid directed motion to the aster centre as they are transported by dynein, as well as slower outward motion as they are advected by cytoplasmic flows. Simple theoretical estimates support that the drag of mitochondria or that of other bulky cargos of similar size is sufficient to move microtubules outward with significant speeds. Aster anisotropy away from the spindle midzone directs microtubules and asters towards the cell edges, entraining the cytoplasm and chromosomes within it. Therefore, a significant outcome of this work is to establish dynein forces in bulk cytoplasm as a fundamental mechanism to generate stereotypical cytoplasmic flow patterns that separate chromosomes in anaphase.

If cytoplasmic flows explain chromosome transport, how might transport speed then scale with cell size?

In low Reynolds hydrodynamics, the amplitude and geometry of shear flows depend on mechanical stresses applied to the fluid, the rheological properties of the fluid (e.g. viscosity), and also strongly on boundary conditions (e.g. confinement by the fluid container)[10]. This is because, for most fluids, flow velocities must vanish to zero at the interface with a static boundary (in accordance with the no-slip boundary condition). As a consequence, for the same applied stress, flows should reduce in speed when the size of the container decreases, as exemplified by the numerical simulations of cytoplasmic flows in cells of reducing sizes reported by Afonso *et al.*[2]. Accordingly, in blastomeres of reducing sizes during development, or in embryos in which the cytoplasm was aspirated to reduce cell volume, the authors report a slowing of flows with a matched reduction in chromosome velocities. Therefore, a simple geometrical confinement by cell boundaries that progressively dampens cytoplasmic shear flows during development may account for size scaling of chromosome segregation.

Previous studies had already considered the question of chromosome separation scaling during early embryo development. In the nematode *Caenorhabditis elegans*, the extent and speed of spindle elongation, and thus chromosome segregation, also scale with cell size. This was proposed to derive from a surface-based sensing mechanism that progressively scales down the amount of force generators pulling astral microtubules from the cortex to separate spindle poles in anaphase[11]. A recent study in the syncytial embryos of the fruit fly *Drosophila melanogaster* also showed that chromosome segregation speed slows down during development[12]. Here, speed decay was shown to depend on a progressive slowing of anaphase rate, as well as on the activity of microtubule-depolymerizing kinesins that promote poleward fluxes to drive chromosome separation. It thus appears that early embryos have evolved diverse mechanisms to achieve a conserved anaphase scaling mechanism based on reducing chromosome segregation speeds. A plausible source of divergence in mechanisms used to scale chromosome speed may stem from the very different size of cells or nuclear compartments (in *Drosophila*), given that they are much smaller in *C. elegans* or in *D. melanogaster* compared with the zebrafish blastomeres considered in Afonso *et al.*[2]. For instance, smaller cells may be more prone to utilize microtubule interactions with the cell surface, while large cells may instead exploit forces exerted in bulk cytoplasm and their consequent flows.

From a mechanistic point of view, the evidence provided by Afonso *et al.*[2] that dynein may generate forces from bulk cytoplasm to move asters and create large-scale flows is compelling. This concept dates back to pioneering experiments from Hamagushi and Hiramoto in marine embryos[13] and has since then been applied to understand aster motion in various cell types[5,7–9]. Yet, many of the mechanistic details still remain obscure. First, it is unclear whether one particular type of endomembrane cargo mediates force exertion by dynein[5]. Earlier work in *C. elegans* considered endosomes, lysosomes and yolk granules as important cargo vesicles[8], while *in vitro* analysis of *Xenopus* asters instead supported a role for the endoplasmic reticulum[5]. Afonso *et al.*[2] focused on mitochondria as plausible cargos for force exertion, but they did not demonstrate *per se* a role for mitochondria, and thus other cargos may also be involved. Second, the physics of force exertion by dynein in bulk remains poorly understood. Indeed, as cargos move to the minus end of microtubules, they are expected to drag fluid towards the aster centre, yet the resulting flows, as measured by Afonso *et al.*[2], are directed outward from asters, suggesting they are mostly generated by microtubule displacements in the cytoplasm. How such flows are generated by the collective movements of microtubules that interact through hydrodynamic interactions in dense asters, and how much of the dynein-mediated force is really transmitted to microtubules, remain fundamental questions to be answered[14]. The impressive reproducibility of flow patterns as documented in Afonso *et al.*[2] may serve as a powerful model to address these mechanistic aspects of the problem.

Finally, this work provides an excellent example of the importance of cellular boundaries for cellular hydrodynamics and organization. It shows that flows may naturally dampen as cells become smaller, which could effectively reduce the overall fluidity of the cytoplasm at the scale of large organelles and constrain their motion[15,16]. How cell geometry intersects with cytoplasm hydrodynamics and cellular organization is an exciting avenue of research that may find key relevance in the mechanisms that pattern early developing embryos.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Symbiosis: An escalating arms race between a butterfly and bacterium

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https://doi.org/10.1016/j.cub.2025.03.061

Symbiotic bacteria such as *Wolbachia* can dramatically affect the reproduction of their arthropod hosts, in some instances causing male progeny to die as embryos. A recent paper describes an escalating arms race over *Wolbachia*-mediated male-killing in a tropical butterfly, with butterfly suppression of male-killing being overcome by acquisition of an additional male-killing gene via phage-mediated horizontal gene transfer.

Terrestrial arthropods often have intimate relationships with bacterial symbionts living within cells in their bodies. These relationships may be benign, antagonistic, or have multiple effects, and although some symbionts are aligned with host fitness, others are not. Many partnerships persist for millions of years[1]. Symbionts are typically maternally inherited in the egg cytoplasm and are almost never transmitted horizontally. Symbionts spread in host populations by causing symbiotic or 'infected' females to produce more infected female offspring than the number of female offspring produced by uninfected females[2]. The symbionts can spread over host generations by contributing to host nutrition (for example, by synthesizing B vitamins or essential amino acids), thus boosting production of both male and female offspring[1]. They can also spread by differentially benefitting female reproduction or fitness, since only female offspring can transmit the symbiont when hosts reproduce. These latter symbionts are often termed 'reproductive manipulators,' and they can profoundly influence the reproduction, ecology and evolution of their hosts[3]. In an exciting new study in this issue of *Current Biology*, Arai *et al.*[4] detail a dramatically escalating, ongoing evolutionary arms race for control of host reproduction between a sex-ratio distorting microbe and its insect host.

The new study focuses on what is perhaps the most antagonistic form of reproductive manipulation: male-killing. This strategy has evolved multiple times among bacterial lineages and is easy to describe; when infected with a male-killing symbiont, a female produces the normal number of eggs, but all (or nearly all) the males die, usually before egg hatch[5]. Infected females thus produce all female offspring, and whole populations may become strongly female-biased, although rare males are still required for mating and successful reproduction. In some populations with male-killing symbionts, not all females find mates[6]. The major benefit of the male-killing phenotype to the symbiont is the increased availability of resources for the surviving symbiont-carrying females, but avoidance of inbreeding may be another benefit for infected females[7]. To be an unerring executioner of only male offspring, the symbionts express genes that interfere only with male development. Arthropod sexual systems are hugely varied, and differences are found in both which sex is heterogametic and in the reliance on sex chromosomes (present in diploid systems, absent in haplodiploid systems). It is perhaps not surprising then that male-killing symbiont genes act on several targets, including dosage compensation mechanisms, splicing variants of the master sex determination gene *doublesex* and even maternally derived centrosomes in embryos of haploid males[8,9]. Despite the otherworldly horror-movie aspect of a