

News & views

Cell biology

Biochemical timer phases condensates in and out

Guillaume Charras & Martin Lenz

The interior of the cell is organized with the help of dynamic structures that condense like droplets. A timing strategy ensures that cells maintain healthy function by avoiding uncontrolled growth of these condensates. **See p.598**

Living cells are experts at multitasking. They perform myriad vital functions with a limited set of tools through the creation of specialized compartments. In some cases, the compartments are enclosed by a lipid membrane, but molecules can also be grouped into amorphous clumps known as liquid condensates, whose contents fluctuate as molecules diffuse in and out of them. The integrity of these condensates is maintained by thermodynamics, in the same way as an oil droplet resists dissolving in water. But their dynamic behaviour poses a challenge: what prevents a cell's components from forming one giant clump? Yan *et al.*¹ report on page 598 a biochemical timing mechanism used by cells to avoid catastrophic clumping during the formation of the actin cytoskeleton – the protein network that gives cells their structure.

The cytoskeleton is formed from a set of biopolymers that can be rapidly assembled into various network structures: from tree-like networks that propel the cell forwards, to ring-like structures that constrict it when it divides, and linear arrays that exert the forces required to close an open wound. The rigidity of these meshes is usually considered central to their role in maintaining a cell's mechanical integrity. However, by looking at the earliest stage of network formation, Yan *et al.* showed that the nascent actin network forms sparse condensates that help to structure the cytoskeleton. Uncontrolled growth or merging of the cytoskeleton into a single condensate would therefore present a huge problem for the cell, because homogeneous distribution of the cytoskeleton across the cell surface is crucial to healthy embryonic development, and to the proper allocation of cellular resources.

Yan and colleagues studied the cytoskeleton in the single-cell stage of the embryo of the

nematode worm *Caenorhabditis elegans*. They found that thousands of small clusters of actin filaments appeared and disappeared on the cell surface over a period of minutes with asynchronous dynamics. The authors' analysis reveals that these clusters were prevented from merging into one clump through a mechanism that involves the interplay of two components: a protein that initiates the assembly of actin filaments, known as WSP-1, and the filaments themselves.

The team showed that a condensate is first formed when WSP-1 starts accumulating at

the cell surface by binding preferentially to itself (Fig. 1a). This aggregation triggers the assembly of an actin network at the location of the WSP-1 cluster, and the network is continuously disassembled by other specialized proteins present in the cytoplasm. At the onset of cluster formation, the rate at which filaments are disassembled is negligible compared with the burst in WSP-1-induced assembly.

As more and more actin filaments accumulate, WSP-1 is removed from the condensate, leaving an actin-rich condensate deficient in the protein. At this point, disassembly begins to outpace assembly, leading to the condensate's eventual dissolution. Through this mechanism, the cell creates condensates with the correct functionality, while also actively destroying them in a timely fashion. The authors mapped this cycle as a function of the concentration of actin and WSP-1 (Fig. 1b). The cycle effectively creates a biochemical timer with which the cell can prevent its limited resources from being hoarded by one function.

The results of this technically demanding study pose many questions. Indeed, controlling the density of cytoskeletal condensates not only involves devising a way of destroying them at the right time, but also requires precise regulation of how frequently they arise in the first place. The means by which this nucleation process is controlled is

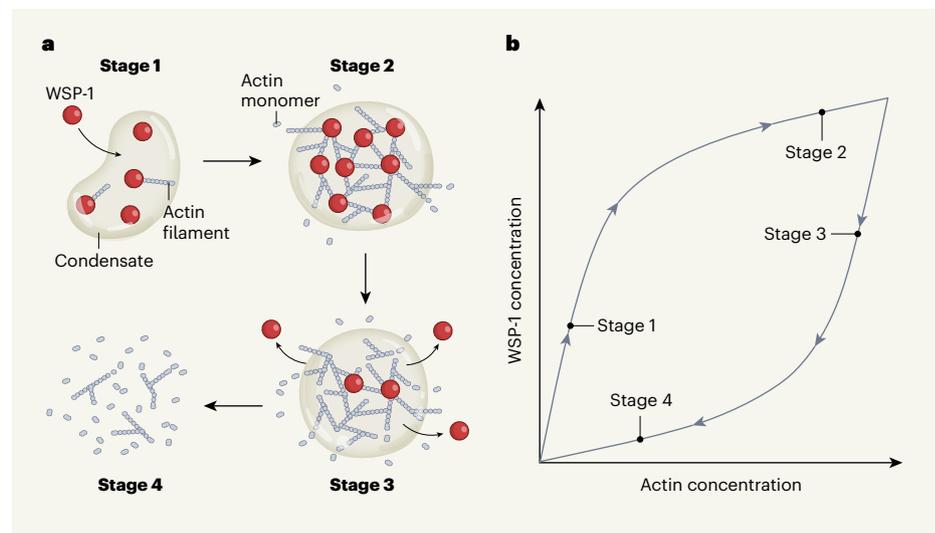


Figure 1 | A biochemical timer for actin cytoskeleton condensates. The actin cytoskeleton is the protein network that maintains a cell's structure. Yan *et al.*¹ showed that actin networks form condensates that are prevented from merging into a large clump by a biochemical timing mechanism. **a**, A protein that initiates actin-filament assembly, known as WSP-1, first accumulates at the cell surface to form a condensate, triggering the local assembly of an actin network (stage 1); these filaments are continuously disassembled, albeit at a lower rate than that for their assembly (stage 2). WSP-1 is forced out of the condensate through an unknown mechanism (stage 3). As a result, disassembly outpaces assembly, leading to the condensate's dissolution (stage 4). **b**, This cycle can be mapped as a function of the concentration of actin and WSP-1.

a topic ripe for further investigation.

The exact mechanism by which WSP-1 is excluded from the condensates is similarly unknown. One possibility is that the growing actin filaments dislodge WSP-1 from the condensate through direct mechanical interactions. Indeed, at the front of crawling cells, a complex related to WSP-1 has been shown to be physically displaced by the actin filaments whose formation it triggers². Could similar forces induce WSP-1 exclusion?

Although the authors' model is based on the interplay between just two components, it is clear that many hidden proteins lurk behind its parameters. The identity of some of them can be guessed at from our current knowledge of actin-network biochemistry. For example, parameters associated with the removal of actin filaments are likely to be affected by changes in the abundance or activity of proteins that are involved in network disassembly, such as coronin and cofilin³. Others remain more mysterious: when the authors depleted the cells of a protein complex involved in filament assembly, the model parameters that changed the most were linked to actin disassembly instead.

Answering these questions will require a combination of imaging and modelling. The early *C. elegans* embryo used by the authors provides an ideal system in this respect – its transparency makes it amenable to high-quality imaging, and it can be probed with a rich variety of genetic tools. Further studies on condensate formation in this model organism will no doubt deepen our understanding of cytoskeletal organization.

Yan and colleagues' work calls for an extension to our understanding of intracellular condensates. Although many observed condensates are liquid-like aggregates of intrinsically disordered proteins, the cytoskeletal aggregates observed by Yan and co-workers probably take the form of gel-like structures involving stiff protein filaments. It remains to be determined whether these gel-like aggregates can merge smoothly on contact, like two liquid droplets – a property that has so far been regarded as the hallmark of condensates.

The study also enriches our understanding of how the size of condensates is controlled. Previously proposed mechanisms for size regulation suggest, for example, that condensates are physically confined by an elastic scaffold^{4,5}, or that their size is determined by an imbalance between the diffusion and degradation of their components⁶. Unlike these static mechanisms, Yan and colleagues' biochemical timer suggests that intracellular condensates are regulated through highly dynamic means, and once again reveals the power of integrating physics and biochemistry in our efforts to understand cellular processes from their molecular interactions.

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Condensed-matter physics

Simple solids mimic complex electronic states

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Solid-state systems that are designed to simulate the quantum behaviour of electrons in a solid could rival established techniques that require exhaustive computation or precise control of atoms in dilute gases. **See p.479 & p.485**

Just as flight simulators can offer a trainee pilot insight into what it might be like to fly an aeroplane in real life, quantum simulators help physicists to understand the complex quantum behaviour of electrons in solids. Ideally, such simulators should be as customizable as possible – featuring many 'knobs' with which to modify the properties of the system. Atoms cooled and manipulated by laser beams have proved extremely useful as quantum simulators, but solids could provide more knobs than can their cold-atom counterparts. In two papers in this issue, Lagoin *et al.*¹ (page 485) and Li *et al.*² (page 479) report solid-state simulators that produce unusual states in systems of particles with and without electric charge, hinting at the versatility of this solid alternative for quantum simulation.

Quantum mechanics describes the wave-like nature of particles and successfully explains the electronic properties of materials in which electrons move independently of each other. Certain other properties are understood to some extent, such as the ability of materials known as superconductors to conduct electric charge without resistance – a phenomenon that arises from the coordinated interaction of electrons in the material. However, as the complexity and range of interaction between electrons increase, the nature of the resulting electronic state in real materials is difficult to understand microscopically.

Even without a complete understanding of them, such states are often technologically desirable. For example, many materials behave as superconductors only at very low temperatures of a few kelvin. Some other

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2. Mehidi, A. *et al.* *Nature Cell Biol.* **23**, 1148–1162 (2021).
3. Gautreau, A. M., Fregoso, F. E., Simanov, G. & Dominguez, R. *Trends Cell Biol.* **32**, 421–432 (2022).
4. Ronceray, P., Mao, S., Košmrlj, A. & Haataja, M. P. *Europhys. Lett.* **137**, 67001 (2022).
5. Vidal-Henriquez, E. & Zwicker, D. *Proc. Natl Acad. Sci. USA* **118**, e2102014118 (2021).
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materials display such behaviour when cooled by liquid nitrogen to a temperature of around 70 kelvin, and even though their behaviour is more complicated than that of those at lower temperatures – posing an unresolved puzzle for physicists – they are clearly more useful for everyday applications (Fig. 1a). But developing a microscopic understanding is crucial because it provides a path for tailoring and improving a material's properties.

The two options available for developing this understanding are to perform numerical calculations using the principles of quantum mechanics, or to find simple systems that simulate the properties of real solids, as first suggested by US physicist Richard Feynman³. Numerically calculating the properties of roughly 100 interacting electrons becomes intractable very rapidly, even with increasingly fast computers⁴. However, simulators with a large number of electrons (Li and colleagues' device has approximately 10,000 in its active area) have shown real promise in furthering our understanding of complex electronic states⁵.

Varying the platforms used to realize simulators offers different advantages and an assortment of knobs with which to tune the system. In the simplest simulator – the Hubbard simulator⁶ – the particles can occupy sites in an array that is determined by the energy of the system, and they can move around to neighbouring sites. There is an energy cost associated with a site being doubly occupied, and also a cost (albeit a smaller one) for filling the site adjacent to an occupied site. The array in such a simulator mimics the periodic lattice of atoms in a typical solid.