



A biochemical timer phases condensates in and out in cells

Guillaume Charras, Martin Lenz

► To cite this version:

Guillaume Charras, Martin Lenz. A biochemical timer phases condensates in and out in cells. *Nature*, 2022, 609 (7927), pp.469-470. 10.1038/d41586-022-01794-w . hal-03805464

HAL Id: hal-03805464

<https://hal.science/hal-03805464>

Submitted on 23 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Phasing condensates in and out

Guillaume Charras^{1,2} and Martin Lenz^{3,4}

Affiliations:

¹ London Centre for Nanotechnology, University College London, London, WC1H 0AH, UK

² Department of Cell and Development Biology, University College London, London, WC1E 6BT, UK

³ Université Paris-Saclay, CNRS, LPTMS, 91405, Orsay, France

⁴ PMMH, CNRS, ESPCI Paris, PSL University, Sorbonne Université, Université de Paris, F-75005, Paris, France

Correspondence to: martin.lenz@universite-paris-saclay.fr or g.charras@ucl.ac.uk

Living cells are masters at multitasking. They simultaneously perform a myriad of vital functions with a relatively limited set of tools, flexibly assembling the same basic components into a variety of macromolecular complexes each fulfilling a distinct task. A prime example is the actin cytoskeleton, a set of biopolymers that can be rapidly assembled into a host of different network structures, from tree-like dendritic networks that propel the cell forwards and engulf bacteria, to ring-like structures that constrict the mother cell at division, and linear arrays of filaments that exert force on their surroundings, e.g., to close an open wound. To prevent these functions from interfering with one another, the cell often segregates them into specialised compartments. Some of these are enclosed in a lipid membrane, while others are merely flowy clumps of proteins that stick together. These so-called liquid condensates have emerged as powerful compartmentalisation tools. They allow molecules to randomly bind onto and detach from their loose, sponge-like structure under the influence of thermal agitation, while their overall integrity is ensured by the thermodynamics of phase transitions in the same way that a droplet of oil stubbornly refuses to dissolve into water. While liquid condensates provide the cell with convenient open compartments for biochemical reactions, they also confront it with a challenge: as their sticky components diffuse around in the cell, what is to prevent droplets from aggregating in the same place to form one giant clump?

In their article (1), Yan and co-workers find that actin networks, which are usually thought of as rigid meshes central to cells' mechanical integrity, form a type of condensate that helps structure the nascent cytoskeleton of the single-celled *C. elegans* embryo. Uncontrolled growth or merging of the actin cytoskeleton into a large single condensate would present a huge problem for the cell, as it would prevent it from appropriately allocating resources and growing a properly structured cytoskeleton to support embryonic development. Instead, the authors show that thousands of small clusters of actin filaments appear and disappear on the cell surface over a period of minutes with asynchronous dynamics. Their analysis further reveals that the cell prevents catastrophic clumping not by using some kind of spatial ruler to assess and limit the size of condensates, but by subjecting them to a biochemical timer (**Figure 1A**). The mechanism can be thought of as the interplay of two components: an actin filament initiator, and the filaments themselves. A condensate is first formed when the initiator of actin assembly WSP-1 (the ortholog of the Wiskott Aldrich Syndrome protein, WASp), starts accumulating at a location at the cell surface through self-association (**Figure 1B**). This locally triggers the assembly of an actin network, which is itself continuously disassembled by other specialized proteins present in the cytoplasm. At the onset of cluster formation, filament disassembly is negligible compared to the burst in WSP-1-induced assembly. As actin filaments accumulate however, WSP-1 is removed from the condensate,

although the exact mechanism for this exclusion remains unclear. This leaves a WSP-1-poor, actin-rich condensate in which disassembly outpaces assembly, leading to the condensate's eventual dissolution. Beyond creating condensates with the right functionality, the cell thus also actively destroys them in a timely fashion to prevent limited resources from being hoarded by one function.

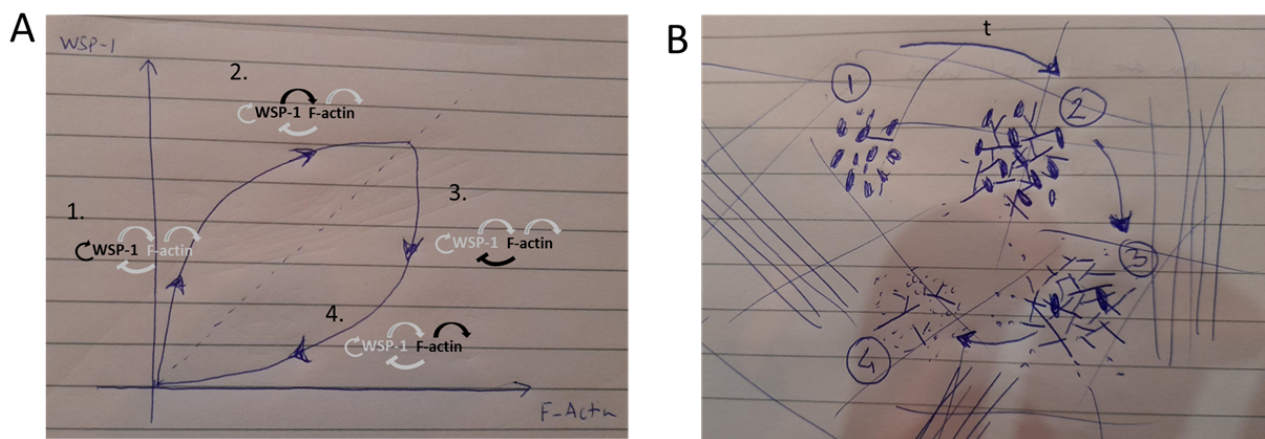
The results of this technically demanding study pose many exciting questions. Indeed, controlling the density of cytoskeletal condensates does not only require destroying them in time, but also regulating how frequently they arise in the first place. How is this nucleation process controlled? Beyond separating actin-rich from actin-poor regions, we may also wonder whether the phase separation analogy could shed light on the spatial patterning of distinct cytoskeletal structures, which have recently been shown to be closely intertwined (2). Can such differences be interpreted as different phases of the same network? While the model proposed by the authors relies on the interplay between two components, it is clear that many hidden proteins lurk behind the associated reaction constants. Some can be guessed from our current knowledge of actin network biochemistry: removing the branches of a dendritic network may involve coronin and cofilin, among others. Others remain more mysterious: why does the depletion of the branch-forming Arp2/3 complex in the authors' experiments mostly affect reaction constants linked to actin disassembly as opposed to assembly? Do growing filaments dislodge WSP-1 from the condensate through direct mechanical interactions similar to those that move the Wave complex laterally at the lamellipodium tip (3)? Answering these questions will require a combination of imaging and modeling. Due to its suitability to high quality imaging and tractable genetics, the study of condensate formation in the early *C. elegans* embryo could thus deepen our understanding of cytoskeletal organization.

Broadly speaking, this paper calls for an extension of our notion of intracellular condensates from liquid-like aggregates of intrinsically disordered proteins to gel-like structures involving stiff protein filaments. It remains to be determined whether two such aggregates would smoothly merge together like two liquid droplets upon contact, a property that has until now been regarded as the hallmark of liquid condensates. This study also enriches our understanding of condensate size regulation beyond previously proposed static mechanisms relying, for example, on physical confinement by an elastic scaffold and a nonequilibrium imbalance between the diffusion and degradation of the condensate's components (4,5,6). More than these static mechanisms, the new "timer to destruction" mechanism proposed by Yan et al. suggests a very dynamic regulation of intracellular condensates, and once again reveals the power of integrating physics and biochemistry to understand cellular processes from their molecular interactions.

References:

- (1) Paper that is the subject of this N&V
- (2) Vignaud T, Copos C, Leterrier C, Toro-Nahuelpan M, Tseng Q, Mahamid J, Blanchoin L, Mogilner A, Théry M, Kurzawa L. Stress fibres are embedded in a contractile cortical network, *Nat Mater.* **20**, 410 (2021).
- (3) Mehidi A, Kage F, Karatas Z, Cercy M, Schaks M, Polesskaya A, Sainlos M, Gautreau AM, Rossier O, Rottner K, Giannone G. Forces generated by lamellipodial actin filament elongation regulate the WAVE complex during cell migration, *Nat Cell Biol.* **23**, 1148 (2021).

- (4) David Zwicker, Rabea Seyboldt, Christoph A. Weber, Anthony A. Hyman & Frank Jülicher, Growth and division of active droplets provides a model for protocells, *Nat. Phys.* **13**, 408 (2017)
 - (5) Pierre Ronceray, Sheng Mao, Andrej Košmrlj & Mikko P. Haataja, Liquid demixing in elastic networks: cavitation, permeation, or size selection?, arXiv:2102.02787 (2021) and *Europhys. Lett.* **137**, 67001 (2022)
 - (6) Estefania Vidal-Henriquez & David Zwicker, Cavitation controls droplet sizes in elastic media. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2102014118 (2021)
-



- A. Phase portrait of the cytoskeletal condensates. 1. Localised enrichment of WSP-1 arises through self-association. 2. WSP-1 activates the Arp2/3 complex, an actin filament initiator that promotes formation of dendritic actin networks. 3. Growth of the actin network depletes the condensate in WSP-1. 4. Concomitantly, F-actin is depolymerised through the action of actin binding proteins present in the cytoplasm.
- B. Life cycle of cytoskeletal condensates. The actin cortex is a submembranous network of actin filaments in which linear arrays of actin are embedded. WSP-1 rich regions form in the membrane (1) and activate polymerisation of actin filaments via the Arp2/3 complex (2). This leads to the formation of dense, branched networks in the cortex. Growth of F-actin towards the membrane dislodges WSP-1 from the membrane (3), reducing nucleation of new filaments and leading to eventual depolymerisation of the condensate (4). Black ellipses represent WSP-1. Lines represent actin filaments. Dots represent actin monomers.