thermal images than those acquired with existing AI-enhanced thermal-imaging techniques[3,4]. HADAR therefore redefines machine perception in low-visibility environments.

Although HADAR is a nascent technology, its potential applications are many and varied. It seems clear that the system will find immediate applications in the autonomous driving and robotics sectors. But it could also be applied in national security and emergency-response settings, in which the success of a mission can hinge on the responder's ability to navigate under conditions of near-zero visibility (see go.nature.com/3cwan9c).

HADAR's ability to detect temperature accurately, despite the confounding factors of emissivity and texture, holds great promise for industries such as smart health care. For instance, it could be used in real-time, contactless systems for monitoring body temperature, providing an efficient means to screen people at airports or public events. The technology could also be used in agricultural settings, in wildlife monitoring and in geoscience research. And the scalability and passive nature of HADAR will no doubt inspire future imaging and vision technologies.

However, the system is not without its challenges. The greatest barriers lie in the cost of the equipment, and in hardware-level issues, including the fact that the system must be calibrated on the fly. Another stumbling block is the fact that a variety of environmental conditions can affect the temperature, emissivity and texture of an object, and so impair the model's ability to identify it correctly. This problem could be solved by modifying the material library to account for these factors. Integrating the technology with cutting-edge devices is yet another challenge in this list of formidable obstacles.

All these difficulties must be overcome if HADAR is to become widely accessible, but Bao and colleagues' proof-of-principle demonstration is sufficient to show that the approach is poised to revolutionize computer vision and imaging technology in low-visibility conditions. HADAR will no doubt improve autonomous driving and other machine-assisted technologies and, as it continues to evolve, it could pave the way for fully passive machine-perception technology that has an acute sense of its physical surroundings. It therefore has the potential to reshape our future — pushing us closer to a world in which machines can provide key safety information by assessing their surroundings with ever greater accuracy.

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1. Bao, F. *et al. Nature* **619**, 743–748 (2023).
2. Gurton, K. P., Yuffa, A. J. & Videen, G. W. *Opt. Lett.* **39**, 3857–3859 (2014).
3. Marnissi, M. A. & Fathallah, A. in *Proc. IEEE/CVF Conf. Computer Vision and Pattern Recognition* 817–825 (IEEE, 2023).
4. Kwasniewska, A., Szankin, M., Ruminski, J., Sarah, A. & Gamba, D. in *Proc. IEEE/CVF Conf. Computer Vision and Pattern Recognition* 3852–3862 (IEEE, 2021).

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Biophysics

Dynamics of protein droplets at multiple scales

Marina G. Guenza

Many biological processes rely on proteins that aggregate into droplets governed by dynamics that span myriad scales. A clever combination of spectroscopy and simulation offers a way to probe these diverse dynamics. **See p.876**

Coacervates are dense protein droplets that form spontaneously in cells through a process called phase separation[1]. These droplets have key roles in various biological phenomena, but an understanding of the molecular-scale mechanisms through which they perform their functions remains largely elusive. This is because their macroscopic properties are intricately linked to their structure on an atomic scale. Revealing these molecular mechanisms therefore requires the investigation of properties across a wide range of time and length scales. On page 876, Galvanetto *et al.*[2] address this challenge by combining several spectroscopic techniques with computer simulations to capture the dynamics of proteins in coacervates — from their atomic movements all the way up to the fusion of phase-separated molecular droplets.

One reason that coacervates have piqued the interest of so many scientists is that they are implicated in such varied phenomena, including cell replication and the dynamic compartmentalization of living cells. Protein aggregation has also been linked to the development of neurodegenerative diseases. In marine organisms, coacervates have a crucial role in providing robust adhesion, allowing organisms to withstand strong tides and waves. Finally, the presence of dense liquid droplets is thought to have been important during early evolution, because prebiotic aggregates can readily form from protein and polysaccharide mixtures.

But coacervates are intriguing for another reason: they form without the need for an enclosing membrane. The aggregation process is simpler than that for structures that are covered in membranes — it is driven by thermodynamics, and leads to the formation of protein-rich droplets that are dispersed in a low-concentration protein environment. Coacervates therefore have the advantage that their molecules can diffuse more freely between the condensed and dispersed phases than they would with a membrane. At the same time, the physical proximity of molecules in the condensed phase still gives rise to intermolecular interactions.

Most of the proteins that are involved in the formation of coacervates belong to a class known as intrinsically disordered proteins (IDPs)[3]. Unlike other protein classes, IDPs exist mainly in an unfolded state when they are in solution. However, when IDPs bind to other molecules, they can adopt distinct folded structures that have special functions. Despite decades of dedicated research[4], scientists do not have a full understanding of IDPs. Galvanetto *et al.* investigated the behaviour of two IDPs: a protein known as histone H1, which helps to package DNA in human cell nuclei, and its nuclear chaperone, prothymosin α. In doing so, the researchers combined topics that sit at two of the most exciting frontiers in modern molecular biology: IDPs and coacervates.

So far, investigations of coacervates have focused mainly on scales larger than that of the molecules in the droplets[5], leaving the underlying molecular mechanisms that govern coacervates' biological functions largely unexplored. This is because it is challenging to probe these systems on multiple scales of interest, given that each experimental and simulation technique can explore only a well-defined and small range of timescales (Fig. 1).

Macroscopic phase separation is known to be guided by a delicate balance of attractive and repulsive molecular forces at the atomic scale. Therefore, although these forces operate at sub-nanometre scales, they have an

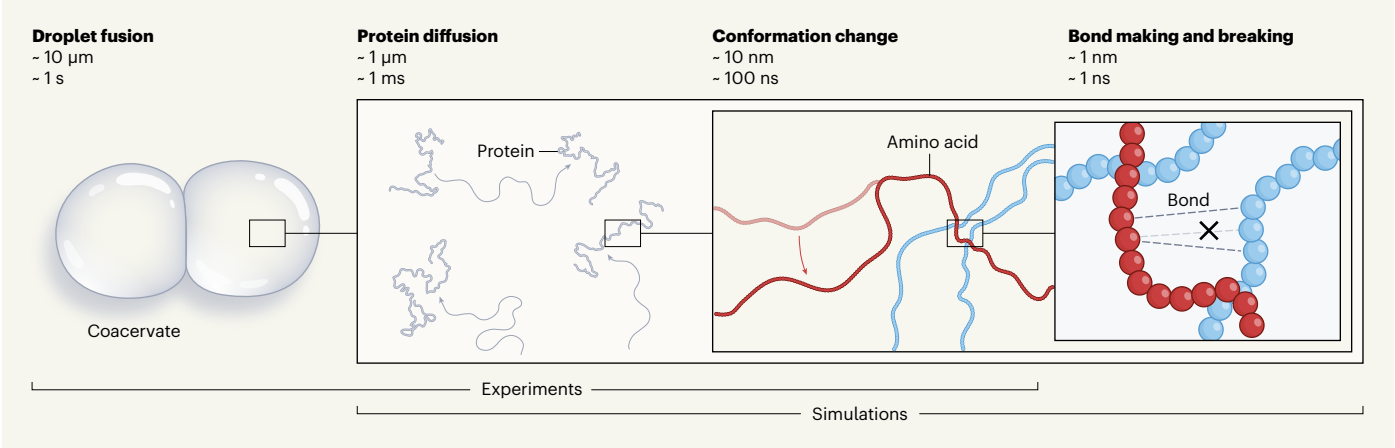

Figure 1 | Bridging the scales of protein-droplet dynamics. Dense protein droplets called coacervates form spontaneously in cells and their behaviour is governed by dynamics on a wide range of time and length scales. Probing such scales is not possible with a single experimental technique or with simulations of atoms, so Galvanetto *et al.*[2] used spectroscopy and computer simulations at different resolutions to obtain a comprehensive picture of droplet dynamics. The researchers' experiments granted access to the time and length scales on which droplets fuse, and on which proteins diffuse inside the droplets and change their conformations. Simulations probed the latter two scales, as well as atomic-scale processes, such as the formation and breaking of intermolecular bonds between amino acids in proteins. (Adapted from Fig. 4 of ref. 2.)

impact on properties manifesting at the length scale of nanodroplets, which are an average of 1,000–10,000 times larger than the size of an atom. Macromolecular dynamics inside the droplets range from bond fluctuations (on sub-nanosecond timescales) to protein diffusion (on millisecond timescales) — spanning six orders of magnitude in time. Comprehensive coverage of such extensive ranges of time and length scales is not possible with a single experimental technique, even for the most advanced methods.

Galvanetto and co-workers came up with a clever way of circumventing this problem: they probed their mixtures of histone H1 and prothymosin α using several spectroscopic techniques, each of which could offer information at a specific resolution[6]. They then combined the results, bridging the information obtained at one resolution to that collected at the next largest scale with the help of computer simulations. In this way, they achieved a comprehensive understanding of the macromolecular dynamics inside the droplets.

The computer simulations were also conducted at variable resolutions by combining two techniques that served as a thread, weaving together the information collected in different experiments. Crucially, the simulations provided atomic-scale information that could not be observed directly in experiments. However, simulations of atoms are slow and cannot reach the large scale of the whole droplet. Even the most advanced computer architectures are incapable of simulating these systems at atomic resolution across the range of timescales that are relevant for coacervates.

To overcome this issue, Galvanetto *et al.* combined atomistic simulations with coarse-grained simulations[7]. Coarse-grained models are a way of simplifying the description of a complex system, such as a protein, by averaging the behaviour of groups of atoms, rather than describing each atom independently. This averaging process accelerates simulations, and allows exploration of timescales that are longer than those otherwise accessible through atomistic simulations alone.

The authors' study yields two fascinating findings concerning protein dynamics in coacervates. First, the local movements of amino acids remain as rapid in high-density and high-viscosity coacervates as when they are dispersed at low density in solution. This is because their motion is governed by atomic-scale friction arising from the surrounding solvent, which is present on a local scale even in the high-concentration droplet. Second, on a larger scale, the proteins themselves move with subdiffusive dynamics, which means that their mean squared displacement grows more slowly with time than it would if the protein were moving randomly (that is, by simple diffusion).

"Macroscopic phase separation is guided by a delicate balance of attractive and repulsive molecular forces at the atomic scale."

This result is at odds with conventional models of protein dynamics[8] that predict diffusive motion at any timescale because they focus on a single molecule. Galvanetto and colleagues' study suggests instead that, in dense droplets, the dynamics of individual proteins are not independent of each other. And they are correlated through the long-lasting interactions that are set up by the presence of the surrounding macromolecules, as described by more modern theories[9–11].

Galvanetto and colleagues' skilful integration of different experimental and simulation techniques allowed them to investigate the dynamics of IDPs in coacervates, and to successfully unravel the mechanisms governing these systems at various resolutions. The authors' groundbreaking combination of experimental and computational methods paves the way for collaborative research that can probe properties across a wide range of scales — a challenge that arises frequently in biophysics.

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1. Astoricchio, E., Alfano, C., Rajendran, L., Temussi, P. A. & Pastore, A. *Trends Biochem. Sci.* **45**, 706–717 (2020).
2. Galvanetto, N. *et al. Nature* **619**, 876–883 (2023).
3. Wright, P. E. & Dyson, H. J. *Nature Rev. Mol. Cell Biol.* **16**, 18–29 (2015).
4. Shea, J. E., Best, R. B. & Mittal, J. *Curr. Opin. Struct. Biol.* **67**, 219–225 (2021).
5. Alberti, S., Gladfelter, A. & Mittag, T. *Cell* **176**, 419–434 (2019).
6. Lakowicz, J. R. (ed) *Principles of Fluorescence Spectroscopy* (Springer, 2006).
7. Guenza, M. G., Dinpajooh, M., McCarty, J. & Lyubimov, I. Y. *J. Phys. Chem. B* **122**, 10257–10278 (2018).
8. Doi, M. & Edwards, S. F. *The Theory of Polymer Dynamics* (Oxford Univ. Press, 2003).
9. Guenza, M. *J. Chem. Phys.* **110**, 7574–7588 (1999).
10. Zamponi, M. *et al. J. Phys. Chem. B* **112**, 16220–16229 (2008).
11. Kruteva, M. *et al. Macromolecules* **54**, 11384–11391 (2021).

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