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Box: How are condensed phases different from macromolecular complexes?

One of the key questions in understanding biomolecular condensates is what distinguishes them from canonical macromolecular assemblies such as the ribosome or RNA polymerase. Such differences underlie their distinct functional possibilities. First, condensed phases are often macroscopic, and can be orders of magnitude larger than the largest known macromolecular assemblies (microns vs. tens of nanometers). Their sizes can also be highly variable, depending on factors such as concentration of their components, their rates of nucleation and growth, and cellular structures such as the cytoskeleton (and likely other factors still to be determined). In contrast, the size of most macromolecular assemblies is fixed based on the structure and stoichiometries of their components. Relatedly, while macromolecular assemblies usually have fixed stoichiometries of their components, condensed phases can occur with the same components at varying stoichiometries (e.g. [1,2]). Macromolecular assemblies are stereochemically defined across their length, whereas the length scales on which condensed phases are ordered remain to be determined. Secondly, the functionally-relevant dynamics of macromolecules is often in the μs-ms timescale, whereas fluctuations in condensed phases can extend into the minutes regime; it remains unclear which timescale is most functionally relevant. Thirdly, for biomolecular condensates there is no obvious equivalent to the phase boundary, which produces the distinct chemical environment within the structure, in a canonical macromolecular assembly. Finally, while the activities of macromolecules are often regulated by alterations between discrete conformations, condensed phases are constantly fluctuating between different configurational states, and it remains unclear what mechanisms are used biologically to control their activities.

1. Li, P. *et al.* Phase transitions in the assembly of multivalent signalling proteins. *Nature* **483,** 336–340 (2012).

2. Elbaum-Garfinkle, S. *et al.* The disordered P granule protein LAF-1 drives phase separation into droplets with tunable viscosity and dynamics. *Proceedings of the National Academy of Sciences* (2015). doi:10.1073/pnas.1504822112