Are membraneless organelles truly membrane-less?

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(Abstract for oral presentation, poster presentation also welcome.)

The ability to control the spatio-temporal organization of biomolecules is paramount to the functioning of all living systems. Canonical molecular biology posits that lipids are the key molecules which enable this control via the formation of meso-scale, membrane-bound compartments that dynamically organize biomolecules and their reactions. Recent advancements, however, have shifted this paradigm by developing our understanding of biomolecular condensates - distinct, membrane-less cellular compartments that arise via the liquid-liquid phase separation (LLPS) of intrinsically disordered proteins. Existing near their thermodynamic critical points, condensates exhibit rapid formation and dissolution in response to physicochemical perturbations, in turn providing the cell with intricate spatio-temporal control, beyond what is offered by lipidic structures. The importance of such control is underscored by the ubiquitous presence of condensates in cells, and the functional diversity that they display [1].

The challenge, lies in understanding how these non-stoichiometric structures achieve such an array of functions. Condensates - initially treated by the field as monophasic entities - are now recognised to exhibit diverse mesoscale architectures, all of which serve clear roles in the functionality of their respective condensates [2]. In this study, we conduct a computational and theoretical investigation into a class of structures scarcely studied by the biomolecular condensate community - membranes. Specifically, motivated by recent works in the field, we directly confront the assumption that biomolecular condensates inherently lack membranes.

To achieve this, we employ a genetic algorithm that is integrated with molecular dynamics simulations in order to conduct a bottom-up, *de novo* exploration [3] of the intrinsically disordered protein sequence space that governs the formation of membrane structures. Notably, we discover three distinct chain topologies capable of giving rise to membrane structures. Furthermore, we demonstrate their physical properties, and elucidate the molecular grammar that governs their formation. Our investigation into the physical parameters of these protein-based membranes shows that the optimal solutions found using our genetic algorithm form structures with comparable bending moduli to lipid membranes.

Overall, these findings successfully challenge the fundamental preconceived notions of condensate biology and furthermore, suggest the discovery of a biocompatible material with diverse applications in drug delivery, synthetic biology, and nanotechnology.

References

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