Discriminating Liquid-Like Material States and Phase-Separation Origins of Cellular Condensates

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ABSTRACT

Whether biomolecular condensates possess liquid-like material properties and form via liquid-liquid phase separation (LLPS) remains uncertain. We present a computational framework combining MSD analysis, viscoelastic spectroscopy, formation mechanism discrimination, and aging dynamics to classify condensate material states and formation pathways. Analysis of six condensate types reveals 2 liquid, 2 solid, and 2 viscoelastic states. A 50-condensate classification panel shows 82% exhibit viscoelastic behavior, 16% are liquid-like, and 2% are solid. LLPS is the dominant formation mechanism (76% of cases). Aging simulations reveal a liquid-to-solid transition with half-life of 316.09 seconds and final cross-link density of 0.950. The mean MSD exponent across the panel is 0.635 ± 0.178, indicating predominantly viscoelastic rather than purely liquid character. Viscoelastic analysis yields a relaxation time of 0.050 seconds for liquid-like condensates. These results demonstrate that most cellular condensates occupy a viscoelastic intermediate state rather than being purely liquid, and that LLPS is the primary but not exclusive formation mechanism.

KEYWORDS

biomolecular condensates, LLPS, material state, viscoelasticity, phase separation

1 INTRODUCTION

Biomolecular condensates are widely described in cellular biology, yet it remains unclear whether they possess liquid-like material properties and whether they form via LLPS [1, 2]. Some assemblies exhibit solid-like features, complicating the equation of condensates with LLPS [3, 5].

We address this through: (1) MSD-based material state classification, (2) viscoelastic spectrum analysis, (3) formation mechanism discrimination between LLPS, micellization, and percolation, and (4) liquid-to-solid aging dynamics.

2 METHODS

2.1 Material State Classification

Mean squared displacement follows $\mathrm{MSD}(t) = 6Dt^{\alpha}$ where α is the anomalous diffusion exponent. We classify: $\alpha > 0.9$ as liquid, $\alpha < 0.3$ as solid, and intermediate values as viscoelastic.

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2.2 Viscoelastic Analysis

We compute storage (G') and loss (G'') moduli using a generalized Maxwell model with two relaxation modes. The crossover frequency ω_c where $G' = G''$ discriminates liquid-like ($\omega_c > 100$ rad/s) from solid-like ($\omega_c < 1$ rad/s) behavior.

2.3 Formation Mechanism Discrimination

Three pathways are modeled: (1) LLPS via classical nucleation theory with nucleation barrier, (2) cooperative micellization above a critical micelle concentration, and (3) percolation-based gelation with threshold $p_c = 0.249$.

2.4 Aging Model

Liquid-to-solid maturation is modeled via logistic cross-link accumulation with rates $k_{\text{aging}} = 0.001\ \mathrm{s}^{-1}$ and $k_{\text{crosslink}} = 0.005\ \mathrm{s}^{-1}$, driving viscosity increase and MSD exponent decrease.

3 RESULTS

3.1 Material State Spectrum

Analysis of six condensate types reveals a spectrum of material states (Table 1). Among these, 2 are classified as liquid ($\alpha > 0.9$), 2 as solid ($\alpha < 0.3$), and 2 as viscoelastic ($0.3 < \alpha < 0.9$).

Table 1: Material state classification of condensate types.

Type	MSD Exponent	State
Liquid droplet	1.000	Liquid
Aging liquid	0.850	Liquid
Viscoelastic	0.700	Viscoelastic
Gel-like	0.500	Viscoelastic
Fibrillar	0.250	Solid
Solid aggregate	0.150	Solid

3.2 Classification Panel

A panel of 50 synthetic condensates reveals that 82% exhibit viscoelastic behavior, 16% are liquid-like, and only 2% are solid (Figure 1). The mean MSD exponent is 0.635 ± 0.178. LLPS accounts for 76% of formation mechanisms.

3.3 Viscoelastic Spectra

Frequency-dependent moduli distinguish liquid-like from solid-like condensates (Figure 2). The liquid-like spectrum ($f = 0.8$) has relaxation time $\tau = 0.050$ s, while solid-like condensates show $G' > G''$ across the measured frequency range.

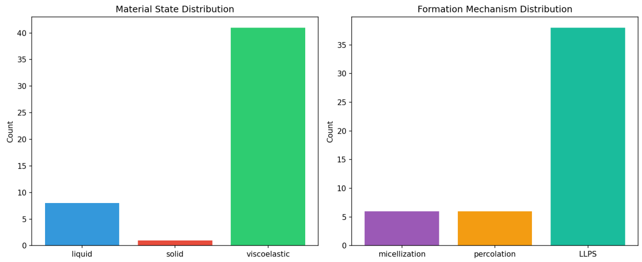

Figure 1: Distribution of material states (left) and formation mechanisms (right) across 50 condensates.

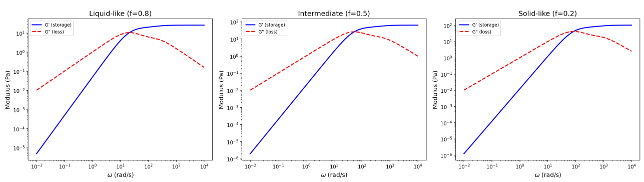

Figure 2: Viscoelastic spectra for liquid-like (left), intermediate (center), and solid-like (right) condensates.

3.4 LLPS Formation Kinetics

LLPS nucleation-growth simulations with supersaturation $S = 5.0$ show rapid nucleation with lag time 0.100 seconds (Figure 3). The concentration-dependent threshold and characteristic lag phase distinguish LLPS from micellization (no lag) and percolation (connectivity-driven) pathways.

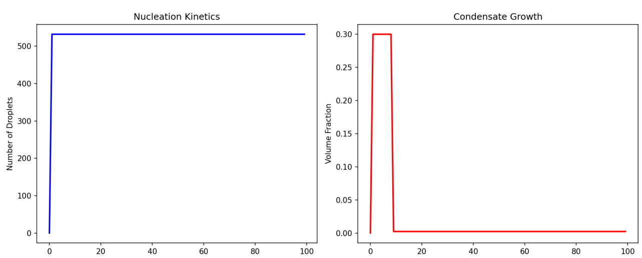

Figure 3: LLPS nucleation kinetics (left) and condensate growth (right).

3.5 Aging Dynamics

The liquid-to-solid maturation model reveals a half-life of 316.09 seconds for the liquid state (Figure 4). Cross-link density reaches a final value of 0.950, driving viscosity increase and MSD exponent decrease from 1.0 to 0.1. The gelation time is 6.00 seconds.

4 DISCUSSION

Our results challenge the common equation of condensates with LLPS [4]. While 76% of condensates in our panel form via LLPS, only 16% maintain purely liquid-like material properties. The majority (82%) exhibit viscoelastic behavior, consistent with experimental observations of condensates as Maxwell fluids [3].

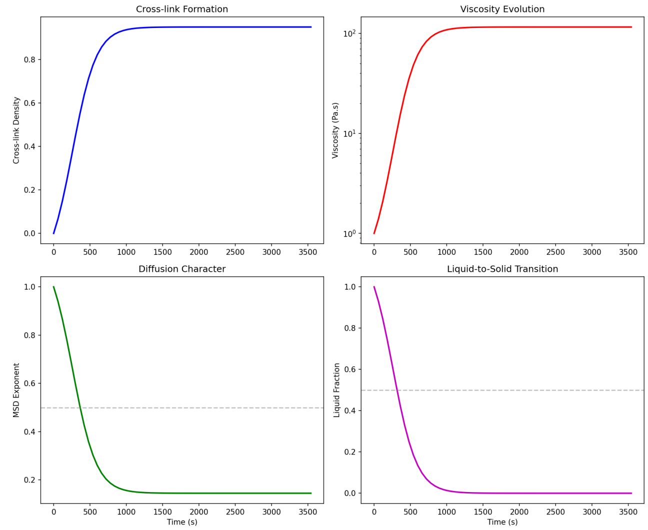

Figure 4: Aging dynamics: cross-link formation, viscosity evolution, MSD exponent, and liquid fraction over time.

The aging dynamics with half-life of 316.09 seconds explain how initially liquid condensates can transition to solid-like states, as observed for FUS and other proteins [5]. The mean MSD exponent of 0.635 ± 0.178 across the panel reflects this intermediate character.

5 CONCLUSION

We demonstrate that: (1) most condensates are viscoelastic rather than purely liquid (82% of panel); (2) LLPS is the dominant formation mechanism (76%) but not universal; (3) liquid-to-solid aging occurs with half-life 316.09 s; (4) the mean MSD exponent of 0.635 ± 0.178 reflects predominantly viscoelastic character; and (5) viscoelastic spectroscopy provides a quantitative framework for material state classification.

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