Mechanistic Pathways Leading to the Maturation of Biomolecular Condensates by Amyloid Fibrils

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Motivation

Biomolecular condensates formed via LLPS are increasingly implicated as precursors to pathological amyloid fibrils, yet the kinetic mechanisms linking condensate aging to fibril growth remain unclear.

- Condensates often transition from liquid-like to solid-like states, but the microscopic pathways driving fibrillar assembly are not well understood.
- Experimental studies suggest that condensate interfaces act as active sites, where anisotropy and molecular deposition from the dilute region lower barriers to ordered β-sheet formation [1, 2, 3].
- How sequence-encoded rigidity and sustained molecular influx cooperate under non-equilibrium conditions to promote fibril growth remains unexplored [4].

Understanding these interfacial and kinetic mechanisms is essential for connecting molecular grammar to condensate stability and for identifying routes to delay pathological aging.

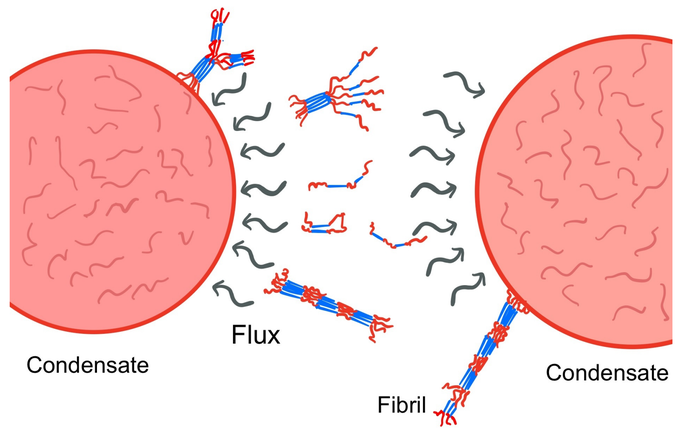

Figure 1: Schematic diagram of protein flux towards the surface of the condensates and fibril growth.

Main Objectives

Existing simulation approaches face key limitations: atomistic simulations capture sequence-specific interaction grammars but cannot access the timescales or system sizes required for interface-mediated fibril growth, whereas coarse-grained models typically lack explicit structural motifs or non-equilibrium molecular influx. As a result, a unified computational framework is still missing one that integrates

- sequence-encoded β-prone interactions
- interfacial alignment and anisotropy
- sustained non-equilibrium flux

These three primary ingredients are increasingly recognized as essential for condensate-to-fibril transitions.

The role of rigidity and sequence

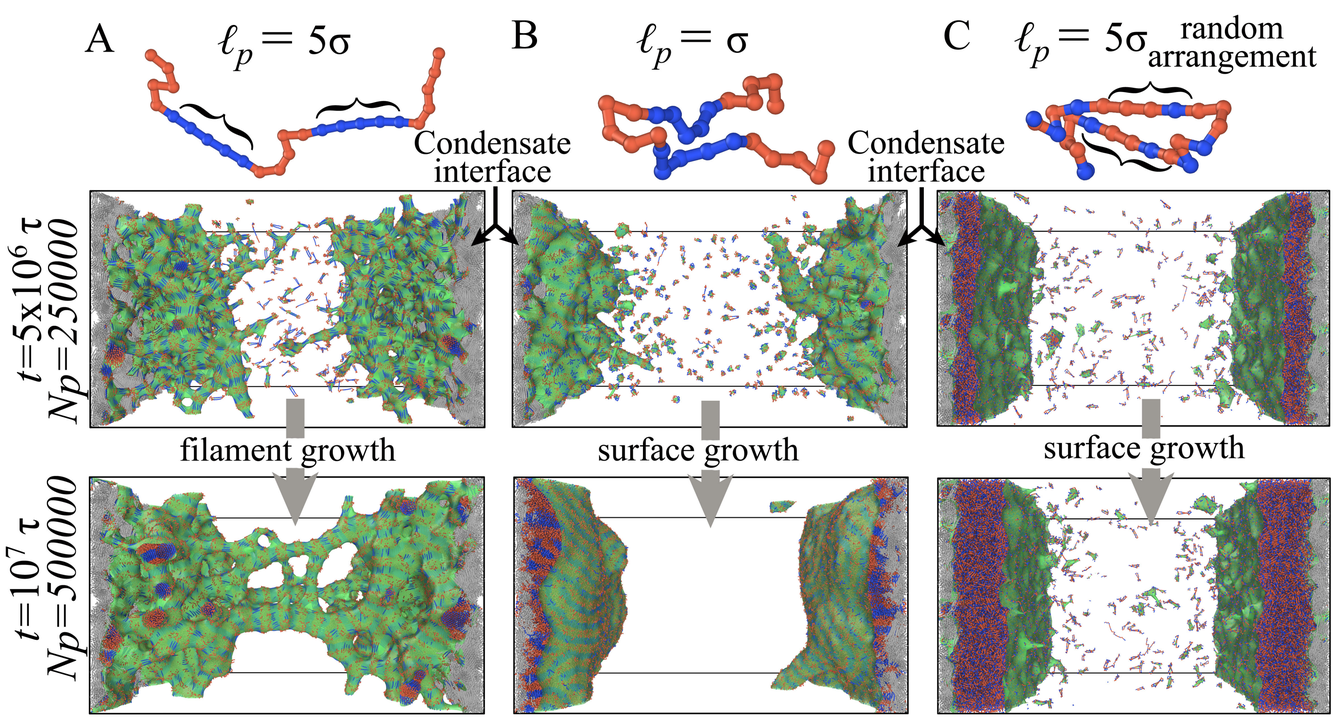

Figure 2: Simulation snapshots of filament growth at biomolecular condensate interfaces. CGMD simulations illustrating the role of sequence-encoded rigidity in fibril formation. (A) Polymers containing two rigid, β-prone segments (blue; persistence length $\ell_p = 5\sigma$) connected by flexible segments (red) nucleate at the condensate interface and progressively assemble into surface-anchored fibrillar protrusions. With time, these filaments elongate, bundle, and form mesh-like structures that can bridge opposing interfaces. (B) When the rigid β-prone segments are replaced entirely by flexible segments, interfacial aggregation persists but no fibrillar structures emerge. (C) Polymers with randomly distributed rigid and flexible segments, despite the presence of a rigid β-sheet–like interaction, fail to form filaments and instead promote the growth of extended planar interfaces. These results demonstrate that both the presence and spatial organization of rigid segments are critical for fibril nucleation and growth at condensate interfaces.

The role of mass flux and rigidity

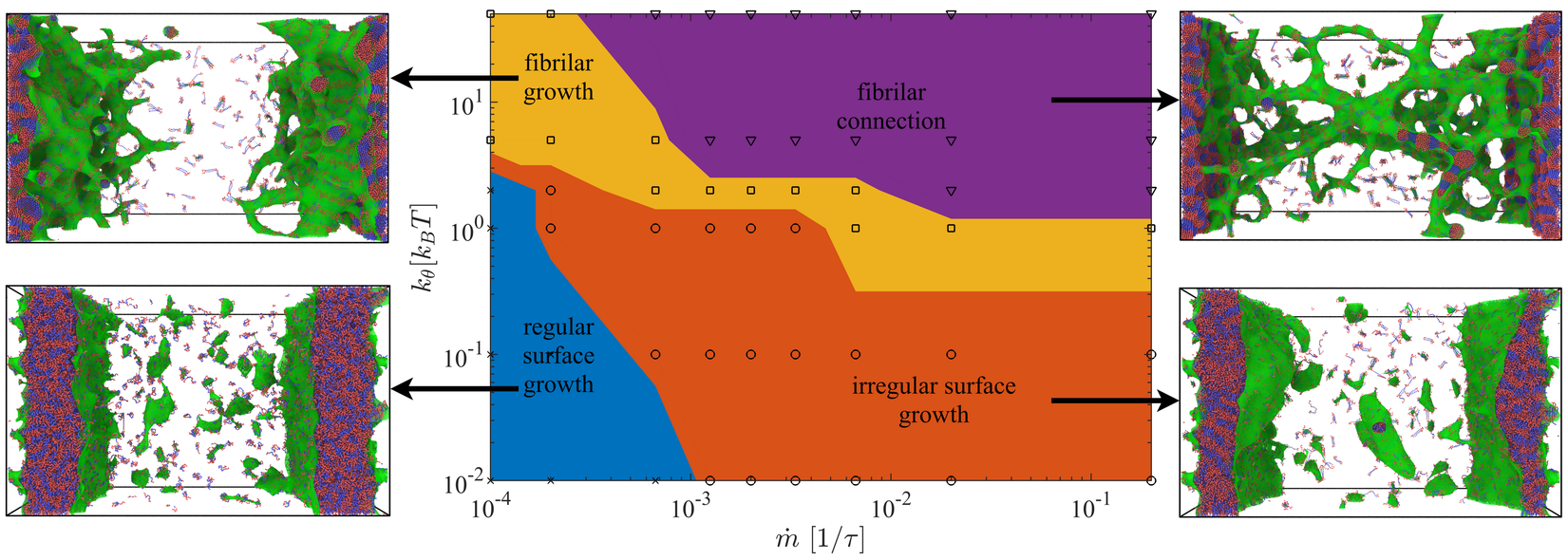

Figure 3: Non-equilibrium phase diagram of interfacial growth morphologies. Phase diagram obtained from coarse-grained molecular dynamics simulations under sustained mass flux onto a condensate interface, plotted as a function of polymer influx and bending energy of the β-sheet–prone segment. Four distinct growth regimes are identified. (I) Planar surface growth, observed predominantly for fully flexible chains, is characterized by smooth interfacial thickening. (II) Irregular surface deposition, emerging at low but finite semiflexibility, where disordered aggregates accumulate without long-range order. (III) Fibrous interfacial growth, appearing once sufficient molecular rigidity is present, is marked by the nucleation and elongation of surface-anchored fibrils. (IV) Bridging and network formation occur at higher rigidity and sustained flux, where fibrils grow, bundle, and form connections between opposing interfaces. Arrows indicate representative simulation snapshots corresponding to each regime, highlighting the qualitative morphological transitions across the phase space.

Dynamic arrest during fibril growth

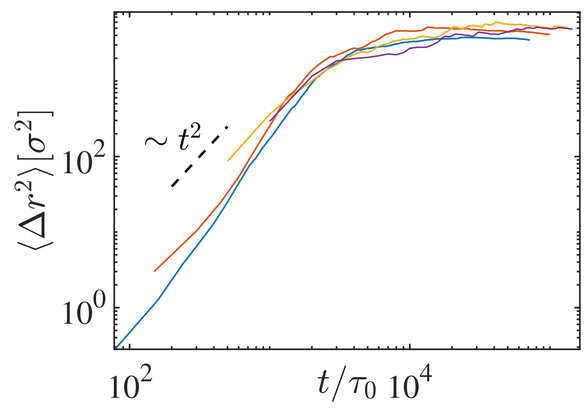

Figure 5: Mean-squared displacement under sustained mass influx. The MSD exhibits an initial ballistic regime, scaling as MSD $\sim t^2$, followed by a crossover to a long-time plateau indicative of dynamical arrest. While the mass influx is sensitive to the resulting growth morphology, distinguishing fibrillar growth from planar surface deposition, however, the MSD curves corresponding to different mass influx rates collapse onto a single master curve, indicating that the dynamics become insensitive to the influx rates.

Surface growth under non-equilibrium deposition

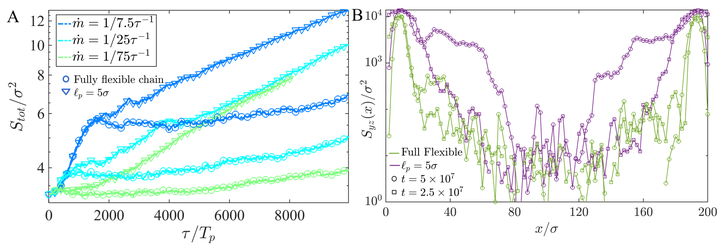

Figure 5: **(A)** Total mean-squared displacement S_{tot} as a function of normalized time τ/T_p for different mass influx rates $\dot{m}$, comparing fully flexible chains (circles) and chains containing a rigid β-prone segment with persistence length $\ell_p = 5\sigma$ (triangles). Increased molecular rigidity enhances displacement growth and sensitivity to mass flux, while fully flexible chains exhibit slower, weakly flux-dependent dynamics. **(B)** Spatial correlation function $S_{yz}(x)$ along the interface for fully flexible chains (green) and rigid-segment chains ($\ell_p = 5\sigma$, purple) at two representative times (open symbols). Rigid segments induce long-range, heterogeneous interfacial correlations consistent with fibrillar bridge organization, whereas flexible chains produce weaker, more disordered interfacial surface structure.

Summary

- Using non-equilibrium CGMD, we map the maturation landscape of condensates as a function of molecular rigidity and mass influx [5].
- Phase diagrams reveal distinct aging pathways, including planar surface deposition, irregular interfacial aggregation, and fibrillar protrusion growth [2].
- Rigid β-sheet–prone segments are required for fibril nucleation and elongation.
- Sequence organization determines whether long-time condensate maturation results in fibrillization or crust formation at the condensate corona [1].

References

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