

Chiral Patterning Drives Peptide Coacervate Formation: Coarse-Grained Insights from the SIRAH Force Field

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ABSTRACT

Peptide-based polyelectrolyte complexes (PECs) are a class of stimuli-responsive materials with applications in drug delivery. However, the molecular mechanism by which stereochemical patterning governs their phase behavior remains unclear. While racemic patterning is known to promote liquid coacervation over solid precipitation through the disruption of ordered β -sheet structure, the experimental study of this effect at the molecular level remains challenging. A potential approach to this issue is the use of a high resolution coarse-grained (CG) force field which can model chiral inversions of the peptide backbone and capture sequence-dependent structural properties. Taking advantage of the backbone mapping scheme and torsion potential of the SIRAH-CG protein model, D-chiral parameters can be introduced through the inversion of the corresponding phase angle of the dihedral potential. This modified model is evaluated against microsecond atomistic C36m simulations and published FTIR secondary structure data using racemic and homochiral variants of six model PEC systems. We find that the racemic SIRAH model reproduces atomistic trends in peptide compaction, interfacial structure and aggregate density, exhibiting higher backbone contacts and peptide compaction relative to their homochiral adjacent. These trends appear consistent with the formation of dense, disordered aggregates characteristic of the liquid coacervate phase and suggest that racemic patterning promotes compact, entangled chain conformations that satisfy backbone hydrogen bonding outside of canonical β -sheet structures rather than simply eliminating it. Additionally, Hydrophobicity-dependent trends in secondary structure and solvent exposure are well reproduced in all variants. This work establishes the SIRAH model as a viable framework for studying the effect of stereochemical patterning on peptide-based coacervate using molecular dynamic simulations.