CHEMICAL ENGINEERING
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Stereoregularity Inhibits Complex Coacervation of Polypeptides

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Stereoregularity Inhibits Complex Coacervation of Polypeptides

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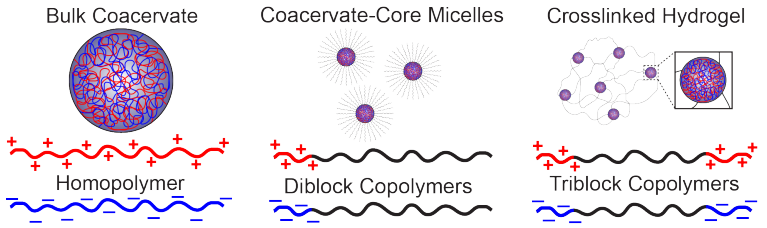
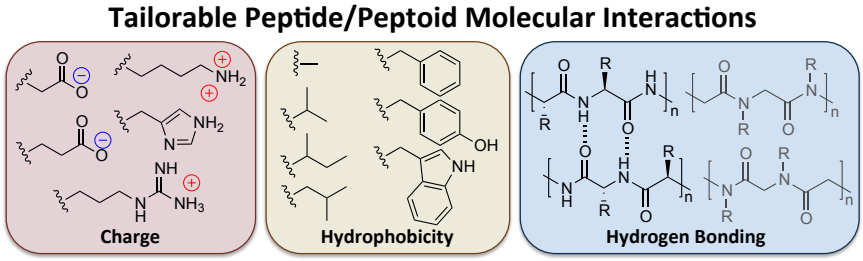
Living cells have evolved sophisticated intracellular organization strategies that are challenging to reproduce synthetically. Biomolecular function depends on both the structure of the molecule itself and the properties of the surrounding medium. The ability to simulate the *in vivo* environment and isolate biological networks for study in an artificial milieu without sacrificing the crowding, structure, and compartmentalization of a cellular environment, represent engineering challenges with tremendous potential to impact both biological studies and biomedical applications.

Complex coacervation is a liquid-liquid phase separation phenomenon resulting from the electrostatic complexation of oppositely charged polyelectrolytes. The resultant fluid phase (coacervate) is a dense, polymer-rich liquid retaining both water and salt. Coacervates are common in everyday life, present in applications ranging from electronic displays to food and cosmetics, and are known to play a key role in the protein-based underwater adhesives used by sessile marine animals. Emerging experience has shown that the dense, amino acid-rich coacervates formed from polypeptides and other biomolecules can produce an effective biomimetic microenvironment. The liquid-liquid phase separation in a coacervate droplet enables sequestration of encapsulated materials, such as proteins, from the external environment in a manner similar to intracellular organelles. Molecular design strategies further enable the use of microphase separation and domain structuring as additional design parameters. For all of these systems, sequence specificity can be used to tailor the available interactions and thus control the emergent properties of the coacervate environment on both the bulk and molecular scale.





In addition to sequence, amino acid chirality is another handle for controlling material properties. Naturally occurring proteins are composed almost entirely of left-handed, or L-amino acids. This chiral-specificity is critical for protein folding and enzymatic recognition of binding motifs. Consequently, chirality is important for maintaining the biological relevance of a particular recognition sequence. However, in the absence of sequence-imposed diversity, the fluid nature of a coacervate appears to be incompatible with homochiral polypeptides. Instead, coacervation requires a mismatch in the degree of stereoregularity between the oppositely charged polypeptides. Complexation between oppositely-charged polypeptides with matching degrees of stereoregularity (L+L, L+D, D+L, D+D, D/L+D/L) results in the formation of solid precipitates with a β-strand structure reminiscent of fibrils typical of amyloidogenic diseases such as Huntington's disease, type II diabetes, and Alzheimer's disease. It remains to be seen patterns of chirality can be used to control macroscopic material properties such as viscosity through the formation of short crosslinking β-strand regions without altering the chemical composition.

The application of both chirality and sequence specificity in polypeptide-based coacervates will allow for the generation of biomimetic microenvironments, the properties of which can be tailored on both the bulk and the molecular scale. Examination of these effects on the process of coacervation could elucidate pathways whereby natural proteins have evolved to utilize diverse amino acid sequences to favor assembly into an equilibrium structure over a kinetically trapped fibrillar state. Alternatively, the use of these materials for the sequestration and modification of biomolecule activity inside artificial organelle-like structures could have a significant impact in the fields of bioenergetics, biocatalysis, and biomedicine.

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