Computational and Theoretical Design of Micelle Formation and Coacervation in Polymeric Solutions

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OBJECTIVES AND DESIGN GOALS

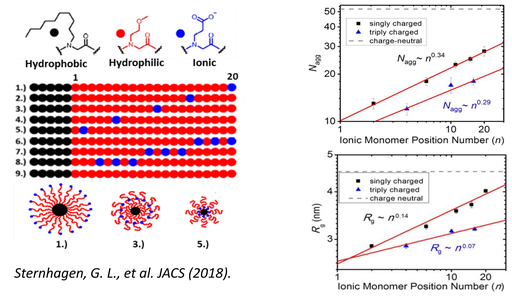
Computer simulations and theory are efficient tools for materials design which not only comprehend experimental data but also possess predictive capabilities. In our work, we consider the effects of monomer sequence on the properties of block-copolymer **micelles** and polyelectrolyte complex **coacervates**. Advanced simulation techniques are used to find equilibrium micelle properties and get insight into kinetics of their formation. We also study the effects of the stiffness and hydrophobicity of polyelectrolytes on coacervate structure and properties. Our predictions provide guidelines for tuning micelle dimensions and aggregation numbers as well as for the design of liquid crystalline complex coacervates and complex coacervates of enhanced salt-resistance.

DESIGN APPROACH

- **In simulations**, we are using techniques including molecular dynamics (MD), adaptive biasing force method, and Gibbs ensemble simulation to study the micelle formation and coacervation in polymeric solution.
- **In theory**, we primarily utilize the random phase approximation (RPA) to treat the correlation attraction between oppositely charged polyelectrolytes; it is combined with the Flory-Huggins theory, Onsager approach to nematic ordering, and, in some cases, informed by scaling analysis.

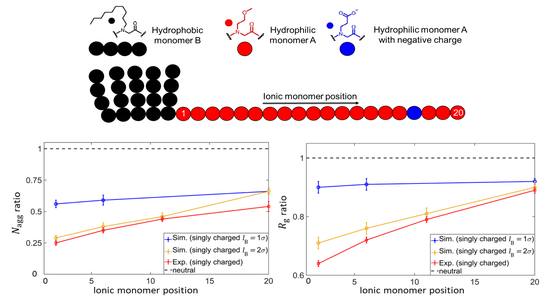
Sequence Effects on Polyelectrolyte (PE) Micelle Structures

Experimental observation: micelle size is determined by the position of ionic monomer.

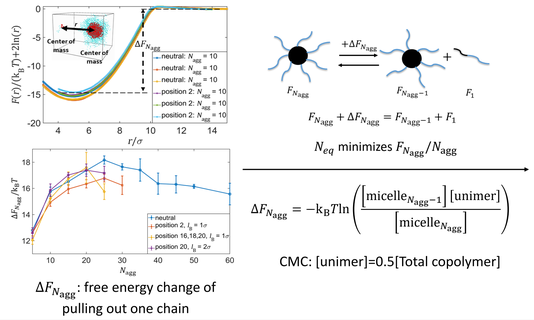


Sternhagen, G. L., et al. JACS (2018).

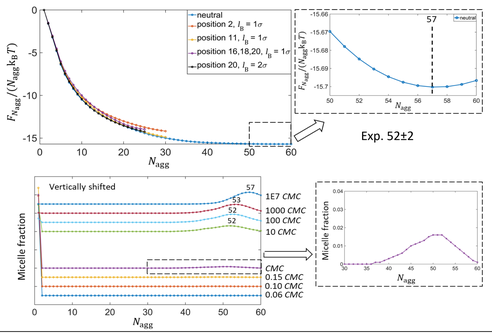
Simple MD simulation: qualitative agreement but cannot determine equilibrium state and free energy change.



Equilibrium micelle size and critical micelle concentration (CMC): the results show that the micelle stability is determined by ionic monomer position and simple MD simulation is far from equilibrium.

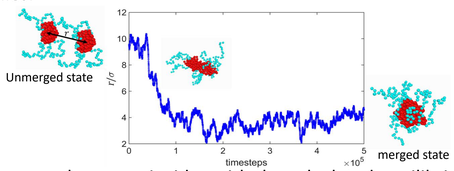


$\Delta F_{N_{agg}}$: free energy change of pulling out one chain

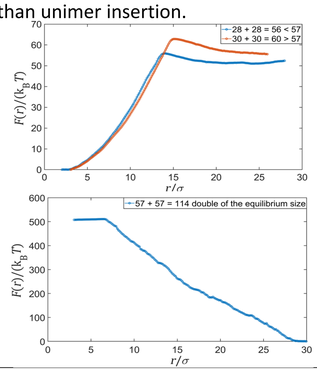


Free Energy Change of Micelle Fusion/Fission

Collective variable: distance between the center of mass of two micelles.



Free energy change: coincides with the calculated equilibrium size of neutral micelle (57). Free energy barrier for fusion is much higher than unimer insertion.



Sequence-Controlled Complex Coacervation: Random Polyelectrolytes

- Random polyelectrolytes are statistical copolymers of charged and uncharged monomers
- Primary sequence = first-order Markov process $P_+ = \begin{bmatrix} p_{++} & p_{+0} \\ p_{0+} & p_{00} \end{bmatrix}$

average degree of ionization $f = fp_{++} + (1-f)p_{+0}$ *degree of charge blockiness* $\lambda = p_{++} + p_{00} - 1$

- Structure factor contains usual Gaussian part and local sequence-dependent term

$$g_q^{++} = \frac{12f^2}{q^2} + f(1-f)\Lambda \qquad \Lambda = \frac{1+\lambda}{1-\lambda}$$

- The RPA correlation osmotic pressure due is calculated **analytically**

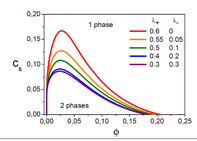
$$\Pi_{corr} = -\frac{1}{24\pi r_{sm}^3}\frac{1+\beta+\beta^2}{\sqrt{2+\beta}}$$

and β is the measure of *charge blockiness*

$$\beta = (1-f)\Lambda\sqrt{\frac{\pi u\phi}{3}}$$

- Generalization to **sequence-asymmetric case**

$$\Lambda = \frac{1+\lambda_+\lambda_-}{(1-\lambda_+)(1-\lambda_-)}$$



Effect of primary sequence on binodals

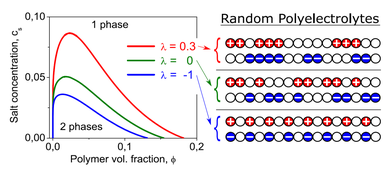
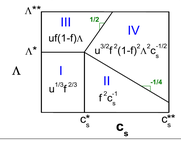


Diagram of scaling regimes (limiting laws for density)



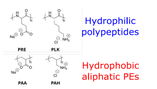
Artem Rumyantsev, Nicholas Jackson, Boyuan Yu, Jeffrey Ting, Wei Chen, Matthew Tirrell, and Juan de Pablo. *ACS Macro Letters* **2019**

Effect of Hydrophobicity in Complex Coacervation

Motivation: **experiment** by Lu Li (Tirrell Group)

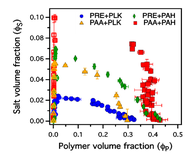
- PEs with identical ionic groups but *different backbones*

Complex density and stability



1. Hydrophobic aliphatic PEs
2. Mixed pair
3. Mixed pair
4. Hydrophilic polypeptides

Binodals



! Hydrophobic coacervate cannot be dissolved by the salt addition

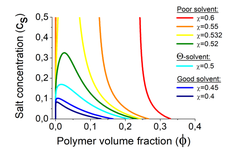
Theory: RPA combined with Flory-Huggins lattice approach

$$F_{corr} = \frac{1}{12\pi r_{sm}^3}(1-s)\sqrt{2+s} \qquad F_{FH} = \frac{\phi}{N}\ln\frac{\phi}{2} + (1-\phi)\ln(1-\phi) - \chi\phi^2$$

Effective solvent quality for coacervate $\chi = \frac{\chi_{+s} + \chi_{-s}}{2} - \frac{\chi_{+-}}{4}$

Interactions stabilizing complex coacervate

	Salt-free	Salt-added
Θ and good solvent	**Coulomb**	—
Poor solvent	**Coulomb + Hydrophobic**	**Hydrophobic**



L. Li, A. Rumyantsev, S. Srivastava, J. de Pablo, and M. Tirrell. *In preparation*

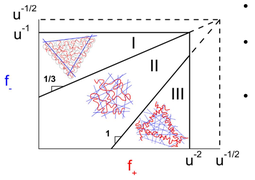
Liquid Crystalline Complex Coacervates

Coacervate of flexible and semiflexible polyelectrolytes

$l \simeq d$ $l \gg d$

1. Isotropic Coacervate

Diagram of scaling regimes



- Two unequal correlation lengths, $\xi_+ \neq \xi_-$
- Limiting laws for density and $\xi_\pm$ derived within the **RPA** and **scaling** coincides in all regimes
- This is possible due to scaling-informed application of the RPA in regime III: polycation = rod of electrostatic blobs

regime	ϕ	ξ_+	ξ_-
I	$u^{1/2}f_+^{1/2}f_-^{1/2}$	$u^{-1/2}f_+^{-1/2}f_-^{-1/2}$	$u^{-1/4}f_+^{-3/4}f_-^{1/4}$
II	$u^{1/3}f_+^{2/3}$	$u^{-1/3}f_+^{-2/3}$	$u^{-1/6}f_+^{-5/6}f_-^{1/2}$
III	$u^{1/3}f_+^{6/7}f_-^{1/2}$	$u^{-1/3}f_+^{1/7}f_-^{-3/4}$	$u^{-1/6}f_+^{-1/12}f_-^{-1/4}$

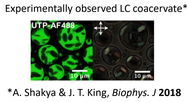
2. Liquid Crystalline Coacervate

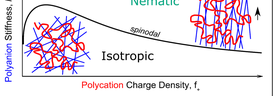
$$\mathcal{F}_{RPA} = \frac{1}{2}\int \ln\left(1 + \frac{4\pi^2 u f_+^2 \phi_- L_-}{q^2} t_{\mathbf{q}} + \frac{48\pi u f_+^2 \phi_+}{q^4}\right)\frac{d^3q}{(2\pi)^3}$$

account for anisotropy of Coulomb interactions

$$t_{\mathbf{q}} = \int \frac{\sin^2(\mathbf{q}\mathbf{n}L_-/2)}{(\mathbf{q}\mathbf{n}L_-/2)^2} f(\theta) d\mathbf{n}$$

Experimentally observed LC coacervate*





*A. Shakya & J. T. King, *Biophys. J* **2018**

Artem Rumyantsev and Juan de Pablo. *Macromolecules* **2019**

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