Simulations of Self-Assembly of Polypeptide-Based Copolymers

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ECUST (華東理工大學) is a key research university featuring distinctive disciplines and a balanced curriculum of science, engineering, materials, computer, economics, management, arts and law.

Undergraduate Student: 15,462
Postgraduate Student: 8,674
Doctoral Candidate: 1,567
Faculty Member: 3,507
Self-Assembly of Polypeptide-based Copolymers

Background

Polypeptide systems can self-assemble into structures with rich morphologies

Hierarchical self-assembly become the development frontier of self-assembly

Recent Researches of Lin's Group

**Ex. 1**
Block Copolymers

**Ex. 2**
Graft Copolymers

**Ex. 3**
Polymer Mixtures

Assemble

Assemble

Assemble

5°C  20°C  40°C
Ex.1

Self-Assembly of Polypeptide-Based Block Copolymers
Self-Assembly of Diblock Copolymers

PEG-\textit{b}-PBLG

PBLG: \textit{poly}(\gamma\text{-}benzyl-L\text{-}glutamate)  
PEG: \textit{poly}ethylene glycol

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Add Tetrafluoroacetic acid}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{CD spectra for the PBLG-\textit{b}-PEG micelle solutions with various TFA mol fractions}
\end{figure}

\begin{itemize}
  \item S. Lin*, J. Lin et al. \textit{Macromolecules} 40, 1684 (2007)
\end{itemize}
Brownian Dynamics Simulation

- Rapidly increasing computational power
- Coarse-grained approach

BD simulation becomes a powerful tool for studying biological molecules, drug design, and self-assembly, etc.

Brownian Dynamics Model

Total Potentials

\[ F = U_{ij} + U_{\text{mol}} \]

\[ U_{\text{bond}}(r) = \frac{1}{2} k_b (r - r_0)^2 \]

\[ U_{\text{angle}}(\phi) = \frac{1}{2} k_a (\cos \phi - \cos \phi_0)^2 \]

\[ U_{ij} = \begin{cases} 
4 \varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 + \left( \frac{\sigma_{ij}}{r_{ij}^c} \right)^6, & r \leq r_{ij}^c \\
0, & r > r_{ij}^c 
\end{cases} \]

Equations of Motion

\[ m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i - \Gamma_0 \frac{d\vec{r}_i}{dt} + \vec{W}_i(t) \]

\[ \langle \vec{W}_i(t) \cdot \vec{W}_j(t') \rangle = 6 k_B T_0 \Gamma_0 \delta_{ij} \delta(t - t') \]
Typical snapshots of AB copolymer with various percents of the rigid conformation of A-block: (a) $f_R = 100\%$; (b) $f_R = 71.4\%$; (c) $f_R = 42.9\%$.

As the rigid chain conformation of the A-block decreases, the rod-like micelle is broken into small aggregates coexisting with some single copolymers (unimers).

Plot of the largest aggregation number versus the percent of flexible chain conformation of the A-block.
Mechanism

Proposed Mechanism

- Polypeptides favor ordered parallel packing with the long axis aligning in an orientation vector. The vectors gradually change along the long-center-axis of the micelle in a cholesteric liquid crystal manner.

- When the acid content is increased, the α-helix conformation transforms to random coil, spherical micelles with coiled polypeptides randomly packing inside the cores are formed.

Scheme of the structure change of PBLG-b-PEG micelle from (a) rod to (b) sphere induced by the helix-to-coil conformation transition.
Self-Assembly of Triblock Copolymers (1)

PLGA -b -PPO -b -PLGA

PLGA: poly(L-glutamic acid)
PPO: poly(propylene oxide)

SCFT is powerful for the study of equilibrium thermodynamic feature of polymeric systems, capable of capturing the characteristic of polymeric systems found in experiments.

**SCFT Model**

Experiment:
1) pH changes; 2) PLGA length changes

SCFT: 1) $a_A/a_B$ changes; 2) $f_A$ changes

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**Free Energy**

\[
\frac{NF}{\rho_0 k_B T} = -c_p \ln \frac{Q_p}{V} - c_s N \ln \frac{Q_s}{V} - \frac{1}{V} \int dr [\omega_A(r)\varphi_A(r) + \omega_B(r)\varphi_B(r) + \omega_S(r)\varphi_S(r) - \chi_{AB}N\varphi_A(r)\varphi_B(r) - \chi_{AS}N\varphi_A(r)\varphi_S(r) - \chi_{BS}N\varphi_B(r)\varphi_S(r) + \xi(r)(1 - \varphi_A(r) - \varphi_B(r) - \varphi_S(r))]
\]

**Chemical Potential Field**

\[
\begin{align*}
\omega_A(r) &= \chi_{AB}N\varphi_B(r) + \chi_{AS}N\varphi_S(r) + \xi(r) \\
\omega_B(r) &= \chi_{AB}N\varphi_A(r) + \chi_{BS}N\varphi_S(r) + \xi(r) \\
\omega_S(r) &= \chi_{AS}N\varphi_A(r) + \chi_{BS}N\varphi_B(r) + \xi(r) \\
\varphi_A(r) + \varphi_B(r) + \varphi_S(r) &= 1
\end{align*}
\]
SCFT Results

Morphologies

\( f_A = 0.111 \)  \( f_A = 0.158 \)

\( f_A = 0.256 \)  \( f_A = 0.396 \)

Aggregate morphologies of amphiphilic ABA triblock copolymers in dilute solution

Density distributions of the blocks on a cross section of the spherical micelle and vesicle marked with an arrow in the inset
Mechanism

Scheme of Structure Change

- When the PLGA are longer or in basic surroundings where PLGA takes a flexible extended chain form, spherical micelles are formed.
- When the PLGA becomes shorter or PLGA tends to shrink in acidic condition, vesicles are formed.
Self-Assembly of Triblock Copolymers (2)

PBLG block in vesicle wall are aligned parallel with each other to form monolayer vesicle wall.

Effect of PBLG length on the aggregates.

DPD, proposed by Hoogerbrugge and Koelman, is a mesoscopic simulation technique suitable for complex fluids.

**Forces**

**Conservative Force**
\[ F_{ij}^C = a_{ij} \sqrt{\omega(r_{ij})} \hat{r}_{ij} \]

**Harmonic Spring Force**
\[ F_{ij}^S = C(1 - r_{ij} / r_{eq}) \hat{r}_{ij} \]

**Angle Force**
\[ F_{ij}^A = -\nabla[k_\theta (\theta - \pi)^2] \]

**Dissipative Force**
\[ F_{ij}^D = -\gamma \omega^D (r_{ij})(\hat{r}_{ij} \cdot \mathbf{v}_{ij}) \hat{r}_{ij} \]

**Random Force**
\[ F_{ij}^R = \sigma \omega^R (r_{ij}) \theta_{ij} \hat{r}_{ij} \]

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Rigid rod blocks are aligned parallel with each other to form the vesicle wall, which validates the formation of experimentally observed monolayer vesicle
Ex.2
Self-Assembly of Polypeptide-Based Graft Copolymers
Self-Assembly of Graft Copolymers

Polymer: PBLG-g-PEG

Solvent: THF/DMF

Self-Assembly of Graft Copolymers

**Polymer:** PBLG-g-PEG
**Solvent:** Ethanol/Denaturant acid (TFA)

TEM photographs of the PBLG-g-PEG aggregates formed in ethanol solutions with TFA mol fractions

CD spectra for the PBLG-g-PEG aggregate solutions with various TFA mol fractions

DPD Models

Angle Force

$$F^A = -\nabla[k_\theta (\cos \theta - \cos 180^\circ)^2] \quad k_\theta = 20$$

Harmonic Spring Force

**Bond1:**
$$F_{ij}^S = C\left(1 - \frac{r_{ij}}{r_{eq}}\right)\hat{r}_{ij} \quad r_{eq} = 0.7$$

**Bond2:**
$$F_{ij}^1 = C\left(1 - \frac{r_{ij}}{r_{eq}}\right)\hat{r}_{ij} \quad r_{eq} = 1.4$$

**Bond3:**
$$F_{ij}^2 = C\left(1 - \frac{r_{ij}}{r_{eq}}\right)\hat{r}_{ij} \quad r_{eq} = 5.6 \quad C = 5.6$$
Packing of graft copolymers in the spindle-like micelles by dissipative particle dynamics simulation

The rod-like backbones of the graft copolymers are aligned along the long axis of spindle-like micelles.
Mechanism

Scheme of Structure Transformation

- In spindle-like micelles, a bundle of helices aggregates in a nematic liquid crystal manner to form the core.
- As the denaturant acid is added, the polypeptide becomes flexible and tends to be randomly packed within the aggregate core.
Ex.3
Self-Assembly of Polymer Mixtures into Helical Structures
Self-Assembly of Polymer Blends

Polymers:

- PBLG_{31000} - b - PEG_{2000}
- PBLG_{X}

Solvents:

- THF/DMF

Effect of the PBLG length (X)

(a) X = 40000

(b) X = 110000

(c) X = 520000

Characterization of the Super-Helices

Chirality:
- PBLG backbone: Right-handed
- Super-helix: Right-handed

Scale bars: 500 nm
Effect of Fraction of Peptide Copolymers

Effect of the PBLG-\textit{b}-PEG Weight Fraction (SEM)

The samples were prepared at \textit{room temperature}. Scale bar: 500 nm.
Effect of Self-Assembling Temperature

Super-helices prepared at room temperature:
- Decreasing temp: Plain fibers
- Increasing temp: Abacus-like structures

Preparing temperature increases

(a) 5 °C   (b) 10 °C   (c) 20 °C   (d) 40 °C

Scale bars: 200 nm
Brownian Dynamics Model

Equations of Motion

\[ F = U_{ij} + U_{\text{angle}} + U_{\text{bond}} \]

\[ m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i - \Gamma_0 \frac{d\vec{r}_i}{dt} + \vec{W}_i(t) \]

<table>
<thead>
<tr>
<th>Interaction</th>
<th>(\sigma_{ij})</th>
<th>(\varepsilon_{ij})</th>
<th>(r_{ij}^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\varepsilon_{RR})</td>
<td>1.0</td>
<td>1.3 – 2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>(\varepsilon_{RC})</td>
<td>1.0</td>
<td>1.0</td>
<td>(2^{1/6})</td>
</tr>
<tr>
<td>(\varepsilon_{CC})</td>
<td>1.0</td>
<td>1.0</td>
<td>(2^{1/6})</td>
</tr>
</tbody>
</table>
Brownian Dynamics Simulation

Rod/Rod-Coil, $\varepsilon_{RR} = 2.5$

Rod/Rod-Coil, $\varepsilon_{RR} = 2.2$

Rod/Rod-Coil, $\varepsilon_{RR} = 1.8$

Rod/Coil-Coil, $\varepsilon_{RR} = 2.2$

S > 0.7 in the abacus region when $\varepsilon_{RR} \geq 2.5$ and then sharply decreases to about 0.2 with decreasing $\varepsilon_{RR}$. With further decreasing $\varepsilon_{RR}$, S is very low, implying the packing of rod blocks is disordered in fiber and unimer regions.
Global helical distribution of block copolymers is in a large length scale

Local twisting packing of rod blocks is in a small length scale

- Homopolymer bundles form the inner axis, and block copolymers form the screw through ordered packing of the rod blocks
- Rod blocks tend to align in an orientation vector, and such a vector is gradually changed along the axis of the bundle
As $\varepsilon_{RR}$ decreases: abacus-like structure transform to helix, then to plain fiber, and finally to unimer

As rod block length $L_R$ increases: the region of helix becomes wider, while the region width of plain fiber keeps unchanged roughly

As coil block length $L_C$ increases: the boundaries move to higher $\varepsilon_{RR}$, which is opposite to the effect of $L_R$
Efffect of Block Length on Pitch of Super-helices

- Helical wrapping of block copolymers on homopolymer bundles is in a more extended manner for longer rod block, and the local twisting of rod blocks is easier to occur for shorter rod block.
- Structure diversity of helices for various $L_c$ is not obvious relative to the helices formed by mixtures with different $L_R$. 

![Graphs showing the effect of block length on pitch of super-helices](image)
Conclusions

1. The polypeptide-based diblock and triblock copolymers are able to self-assemble into various nanostructures such as vesicles. DPD, BD, and SCFT are capable of providing insight into the details of the structures. The is helpful for the explanation of the mechanism behind the self-assembly.

2. The polypeptide-based graft copolymers can self-assemble into spindle-like micelles. DPD revealed the structures and the packing manners of polypeptides.

3. Mixtures of peptide-based polymers can generate various hierarchical structures such as helical structures. The structures depend on various impact factors such as temperature. Computer simulations revealed the details of the self-assembled structures.
More Information

http://jlinlab.ecust.edu.cn/
Thanks !