Simulations of Self-Assembly of Polypeptide-Based Copolymers

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2015. 09. 21

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

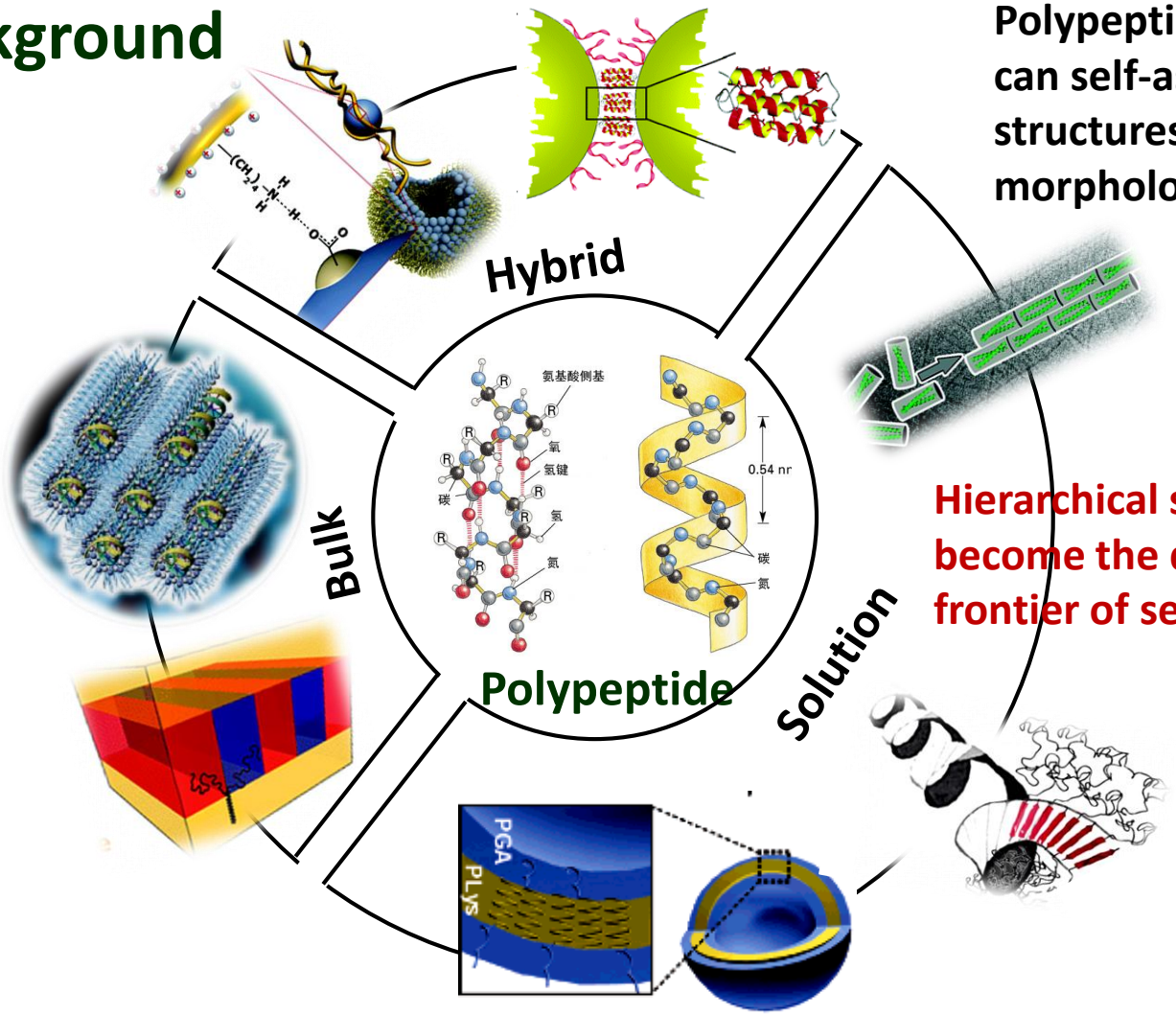
Postgraduate Student: 8,674

Doctoral Candidate: 1,567

Faculty Member: 3,507

Self-Assembly of Polypeptide-based Copolymers

Background



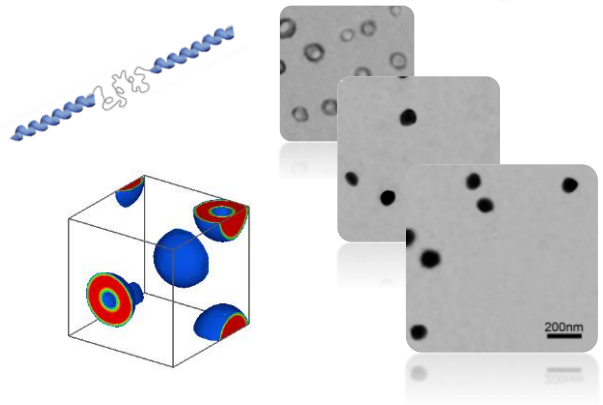
Polypeptide systems can self-assemble into structures with rich morphologies

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

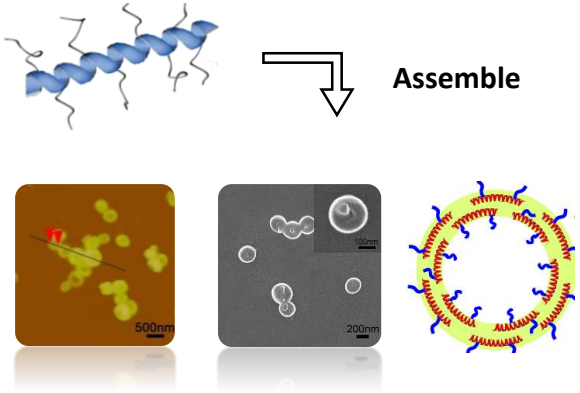
L Wang, J Lin*, X Zhang. ***Polymer*** 54, 3472 (2013) (Feature Article)
C. Cai, J. Lin*, Z. Zhuang. ***Adv. Polym. Sci.*** 259, 159 (2013) (Review)
C. Cai, L. Wang, J. Lin*. ***Chem. Commun.*** 47, 11189 (2011) (Feature Article)
C. Cai, J. Lin*. ***Nature Chem.*** 6, 857 (2014)

Recent Researches of Lin's Group

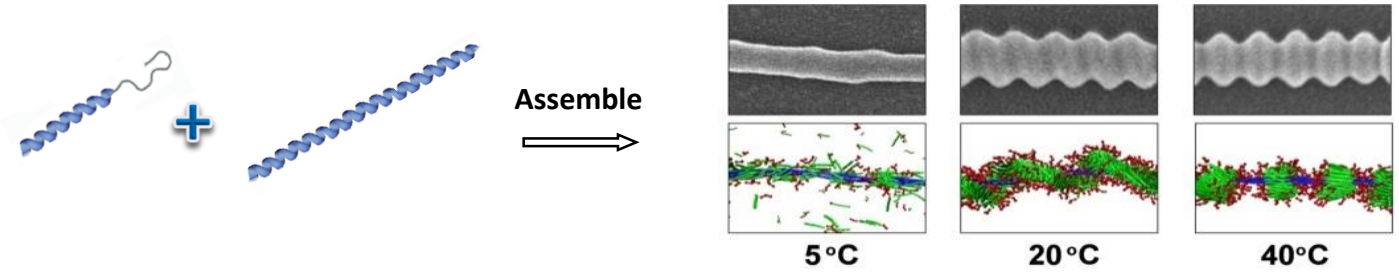
Ex.1 Block Copolymers



Ex.2 Graft Copolymers



Ex.3 Polymer Mixtures



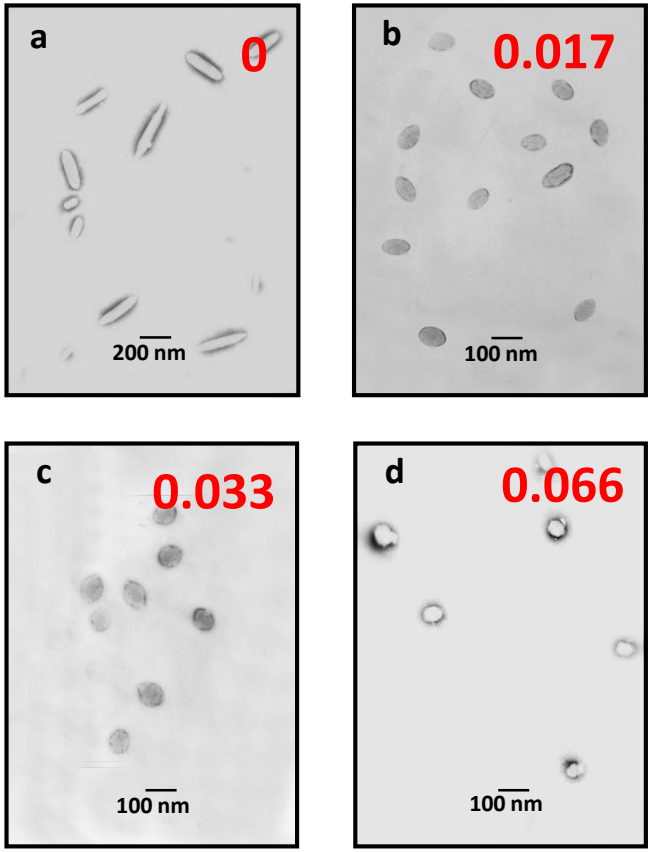
Ex.1

Self-Assembly of Polypeptide-Based Block Copolymers

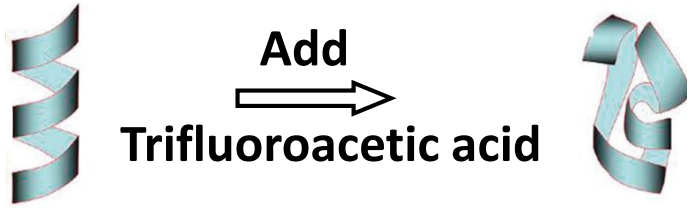
Self-Assembly of Diblock Copolymers

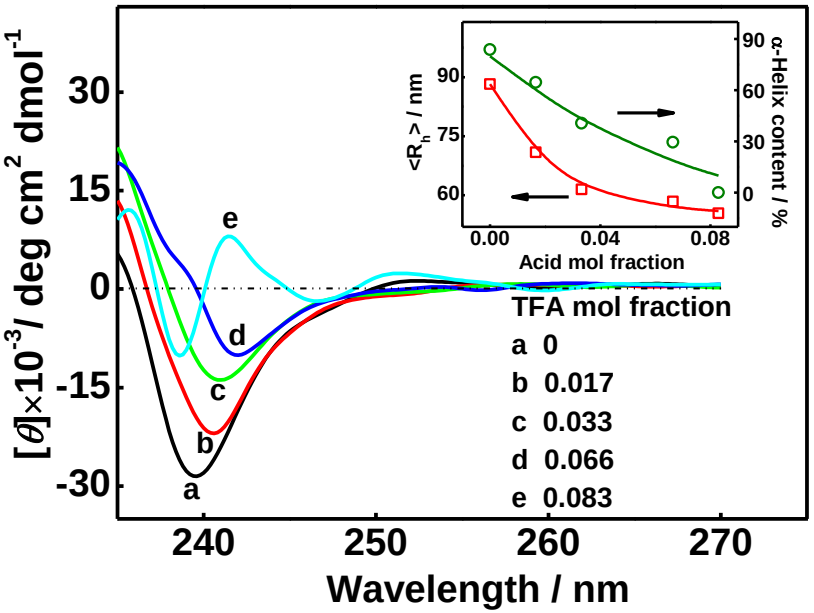
PEG-*b*-PBLG

PBLG: poly(γ-benzyl-L-glutamate)
PEG: polyethylene glycol



Effect of TFA Mol Fractions

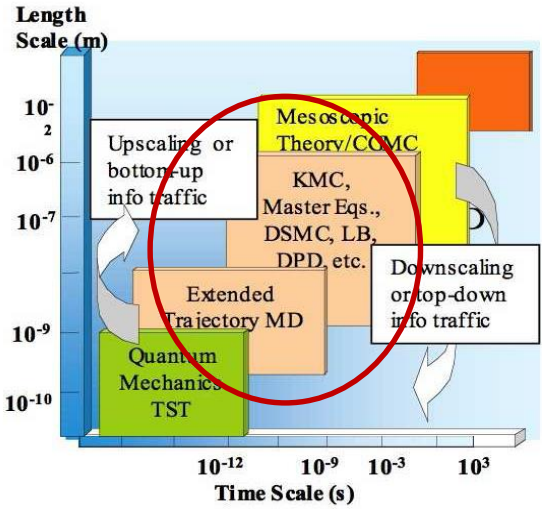




CD spectra for the PBLG-*b*-PEG micelle solutions with various TFA mol fractions

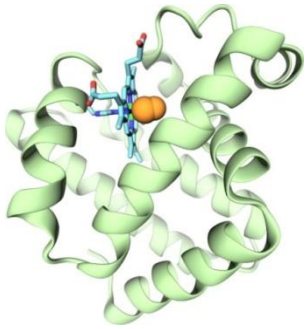
W. Ding, S. Lin, J. Lin* et al. ***J. Phys. Chem. B*** 112, 776 (2008)
S. Lin*, J. Lin et al. ***Macromolecules*** 40, 1684 (2007)
S. Lin, X. He, Y. Li, J. Lin* et al. ***J. Phys. Chem. B*** 113, 13926 (2009)

Brownian Dynamics Simulation

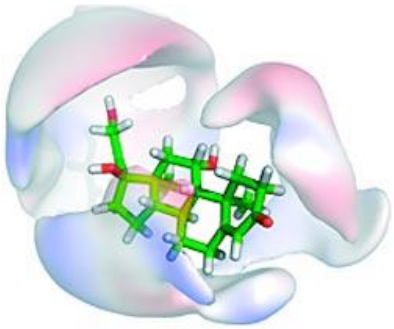


- Rapidly increasing computational power
- Coarse-grained approach

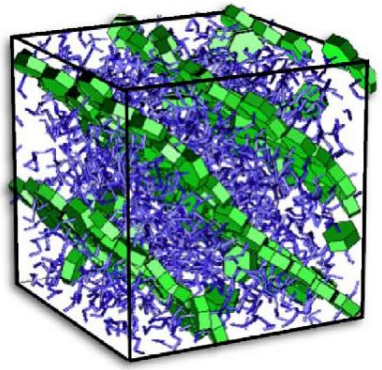
BD simulation becomes a *powerful tool* for studying biological molecules, drug design, and self-assembly, *etc*.



Biological Molecules



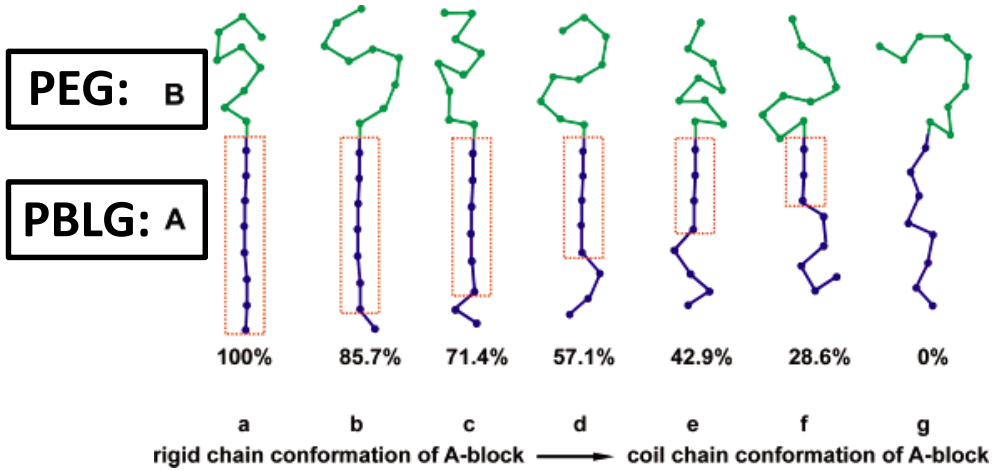
Drug Design



Self-Assembly

Y. Li, S. Lin, X. He, J. Lin, T. Jiang, ***J. Chem. Phys.*** 135, 014102 (2011)
W. M. Brown et al. ***J. Chem. Inf. Model.*** 48, 1626 (2008)
S. C. Glotzer, ***Curr. Opin. Colloid. In.*** 10, 287 (2005)

Brownian Dynamics Model



Equations of Motion

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

$$\langle \bar{W}_i(t) \cdot \bar{W}_j(t') \rangle = 6k_B T_0 \Gamma_0 \delta_{ij} \delta(t - t')$$

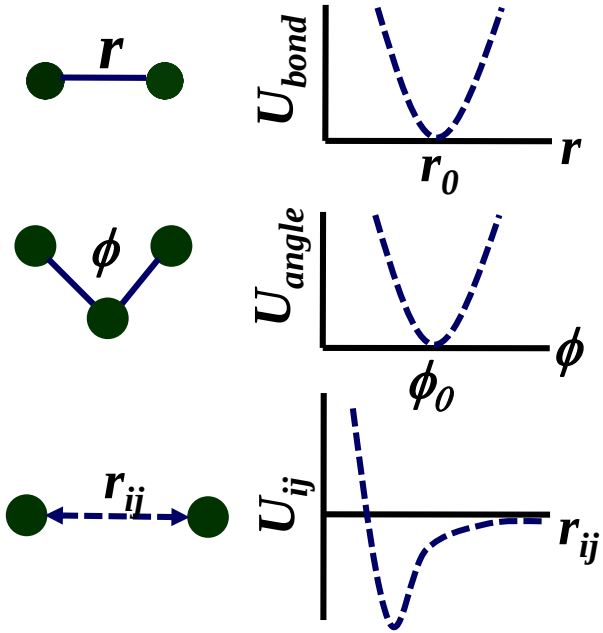
Total Potentials

$$F = U_{ij} + U_{mol}$$

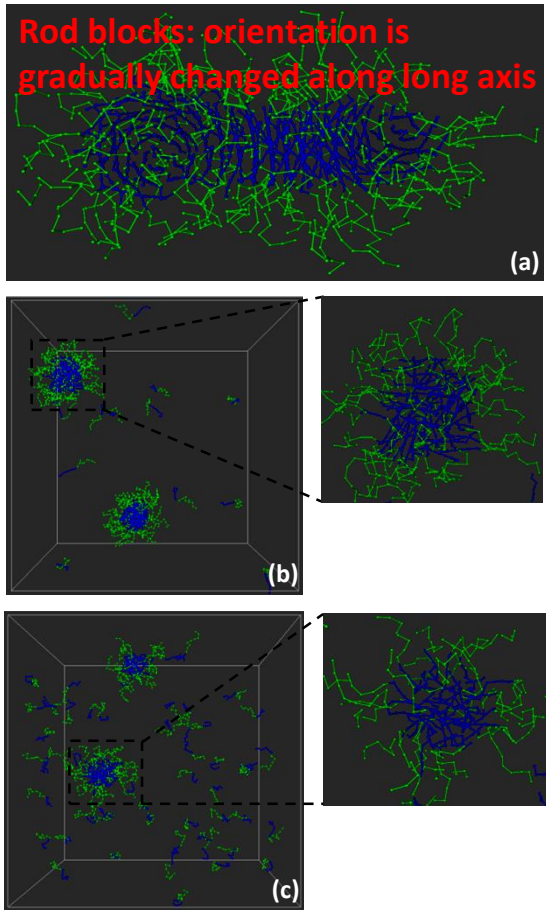
$$U_{bond}(r) = \frac{1}{2} k_b (r - r_0)^2$$

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

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

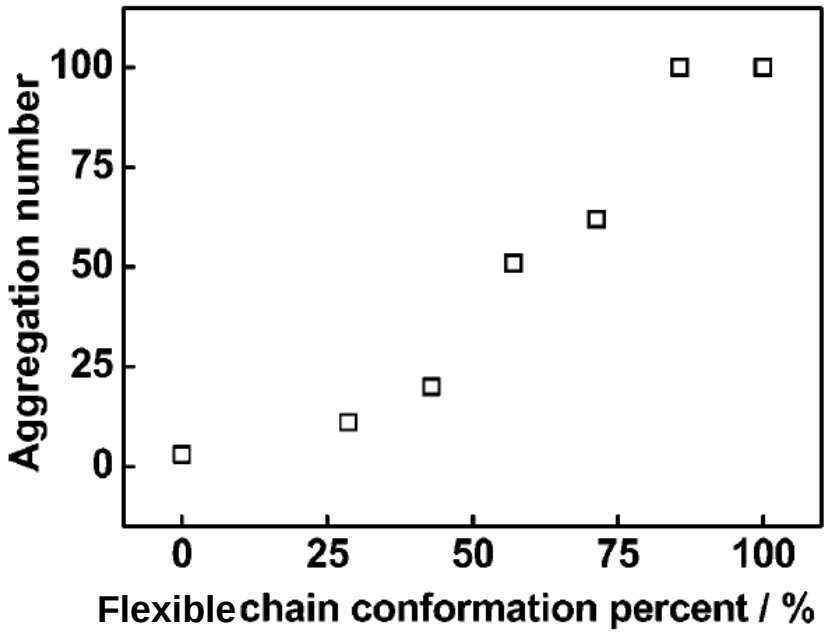


Simulation Results



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%.

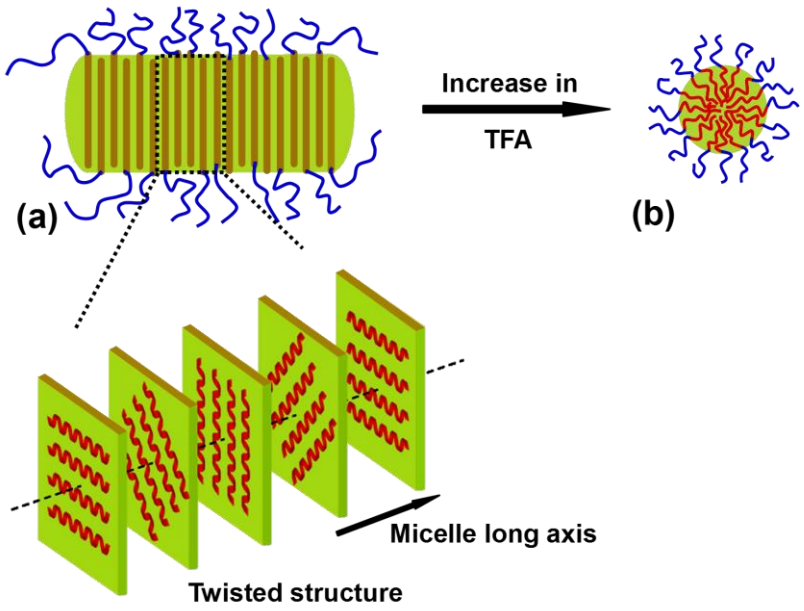
As the rigid chain conformation of the A-block decreases, the rod-like micelle is broken into small aggregates coexisting with some single copolymers (unimers)



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

Mechanism

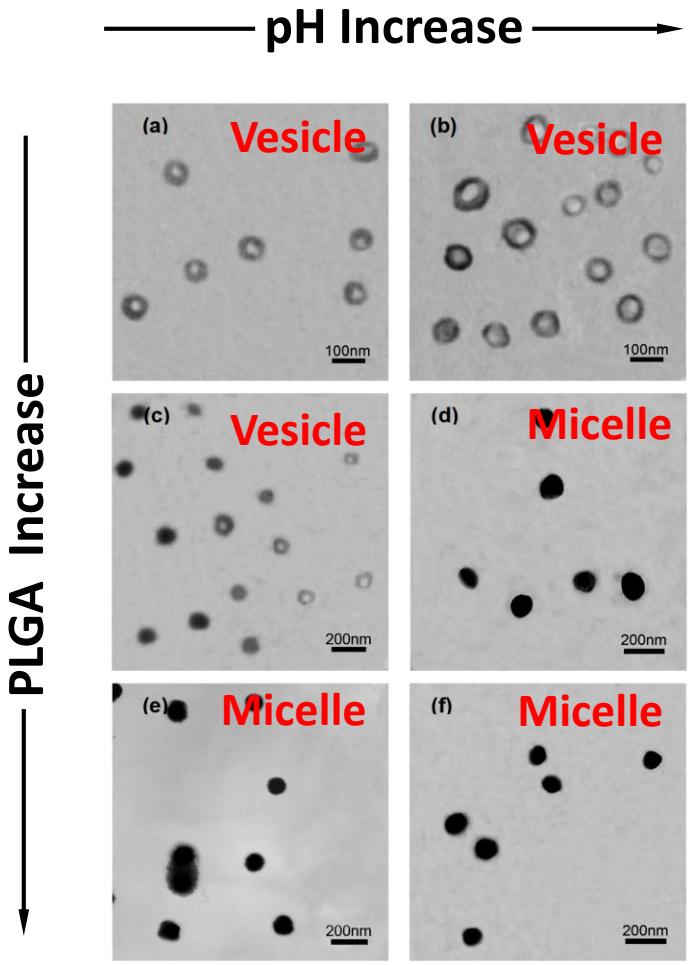
Proposed Mechanism



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

- 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.

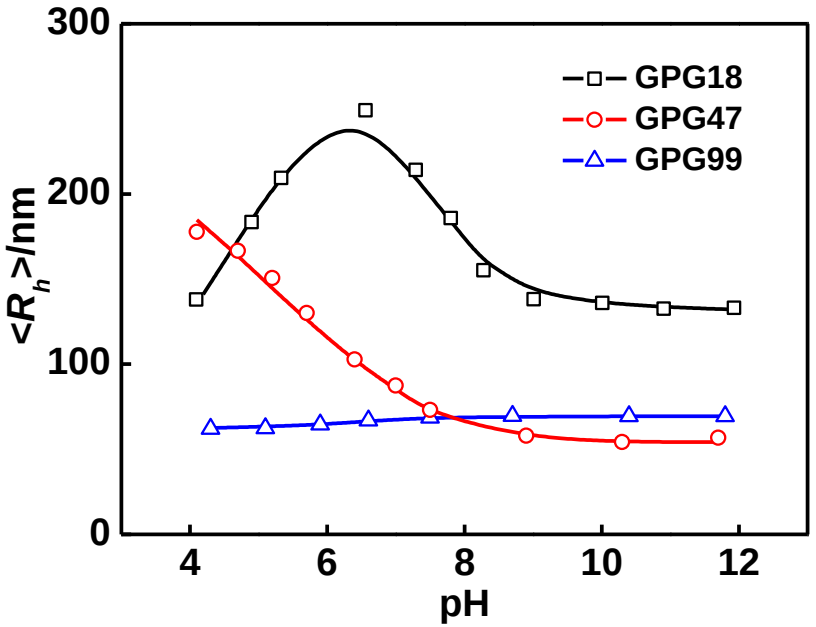
Self-Assembly of Triblock Copolymers (1)



PLGA -*b*- PPO -*b*- PLGA

PLGA: poly(L-glutamic acid)

PPO: poly(propylene oxide)

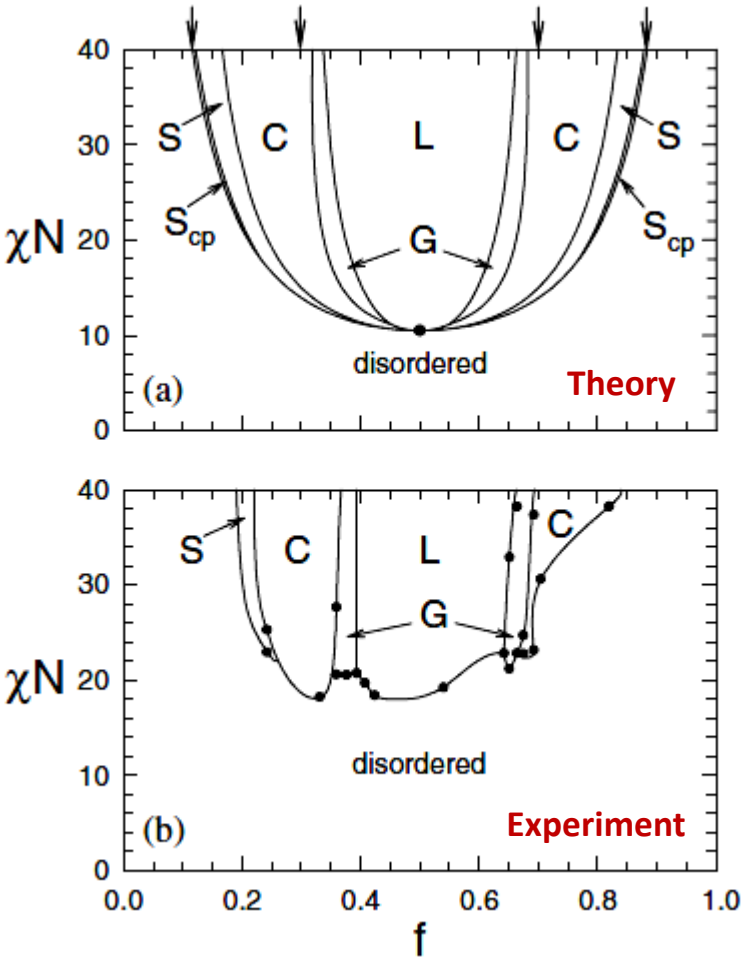


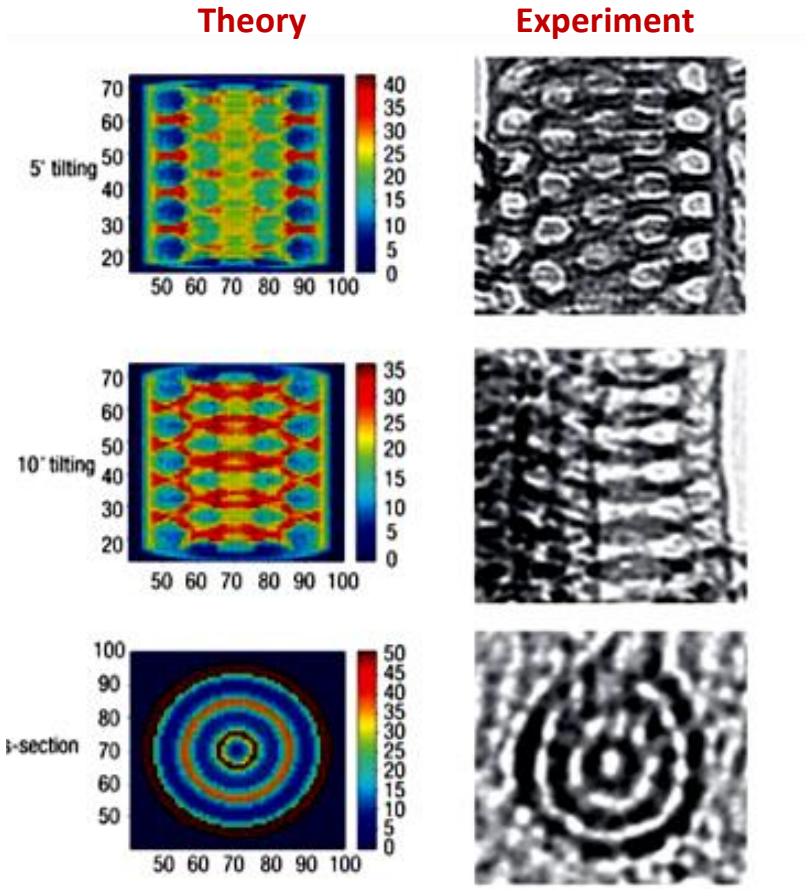
<R_h> of GPG aggregates as a function of pH value

C. Cai, L. Zhang, J. Lin* et al. ***J. Phys. Chem. B*** 112, 12666 (2008)

Self-Consistent Field Theory

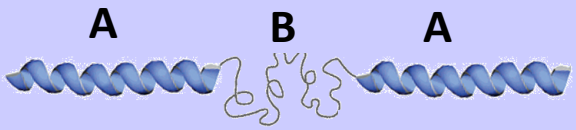
SCFT is powerful for the study of equilibrium thermodynamic feature of polymeric systems, capable of capturing the characteristic of polymeric systems found in experiments.





M. W. Matsen, ***J. Phys. Condens. Matter*** 14, R21 (2002)
Y. Wu, et al. ***Nat. Mater.*** 3, 816 (2004)

SCFT Model



a_A : a_B (Statistical Length)

Experiment:

1) pH changes; 2) PLGA length changes

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

$$\frac{\partial q(\mathbf{r},s)}{\partial s} = \frac{a_{\theta(s)}^2}{a_A^2}\nabla^2 q(\mathbf{r},s) - \omega_{\theta(s)}(\mathbf{r})q(\mathbf{r},s)$$

$$\theta(s) = \begin{cases} \text{A} & \text{if} \quad 0 < s < f_A/2 \\ \text{B} & \text{if} \quad f_A/2 < s < 1 - f_A/2 \\ \text{A} & \text{if} \quad 1 - f_A/2 < s < 1 \end{cases}$$

Free Energy

$$\frac{NF}{\rho_0 k_B T} = -c_P \ln \frac{Q_P}{V} - c_S N \ln \frac{Q_S}{V} - \frac{1}{V}\int d\mathbf{r}[\omega_A(\mathbf{r})\varphi_A(\mathbf{r}) + \omega_B(\mathbf{r})\varphi_B(\mathbf{r}) + \omega_S(\mathbf{r})\varphi_S(\mathbf{r}) - \chi_{AB}N\varphi_A(\mathbf{r})\varphi_B(\mathbf{r}) - \chi_{AS}N\varphi_A(\mathbf{r})\varphi_S(\mathbf{r}) - \chi_{BS}N\varphi_B(\mathbf{r})\varphi_S(\mathbf{r}) + \xi(\mathbf{r})(1 - \varphi_A(\mathbf{r}) - \varphi_B(\mathbf{r}) - \varphi_S(\mathbf{r}))]$$

Chemical Potential Field

$$\omega_A(\mathbf{r}) = \chi_{AB}N\varphi_B(\mathbf{r}) + \chi_{AS}N\varphi_S(\mathbf{r}) + \xi(\mathbf{r})$$

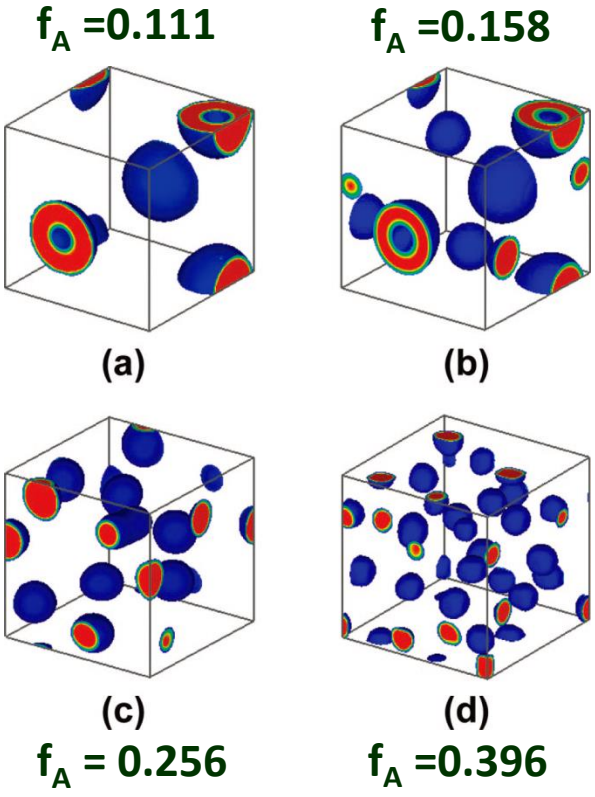
$$\omega_B(\mathbf{r}) = \chi_{AB}N\varphi_A(\mathbf{r}) + \chi_{BS}N\varphi_S(\mathbf{r}) + \xi(\mathbf{r})$$

$$\omega_S(\mathbf{r}) = \chi_{AS}N\varphi_A(\mathbf{r}) + \chi_{BS}N\varphi_B(\mathbf{r}) + \xi(\mathbf{r})$$

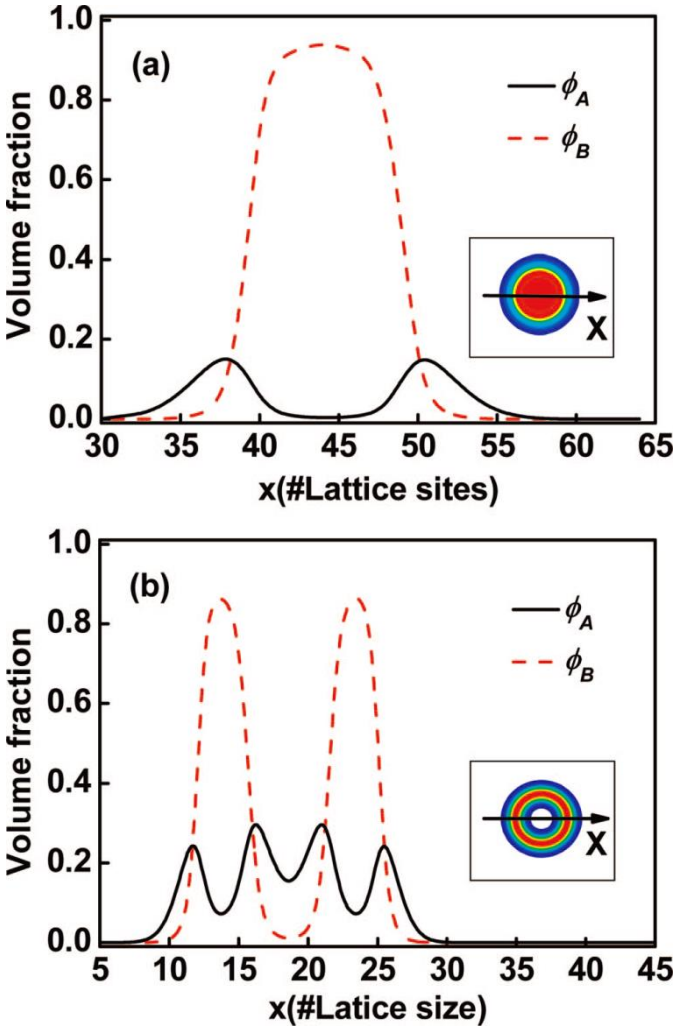
$$\varphi_A(\mathbf{r}) + \varphi_B(\mathbf{r}) + \varphi_S(\mathbf{r}) = 1$$

SCFT Results

Morphologies



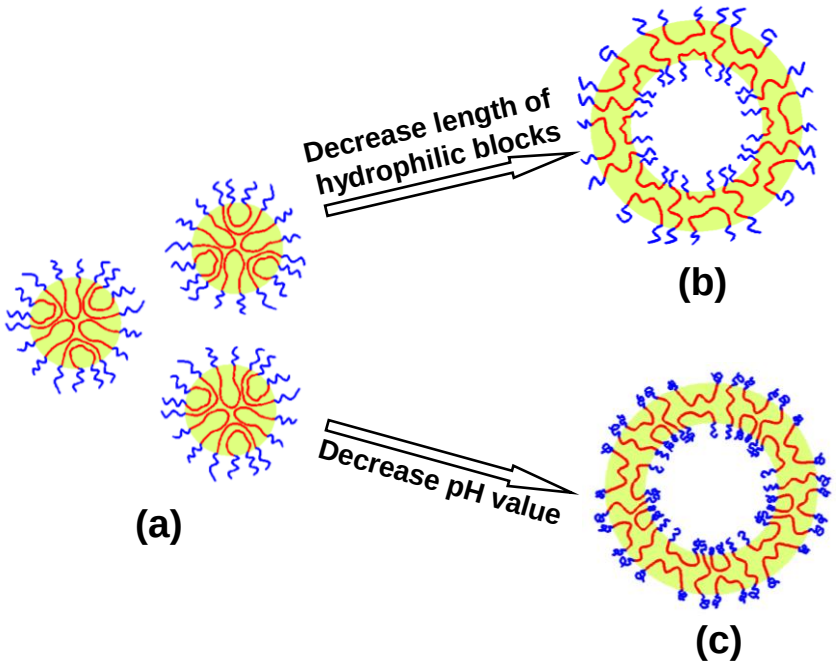
Aggregate morphologies of amphiphilic ABA triblock copolymers in dilute solution



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

Mechanism

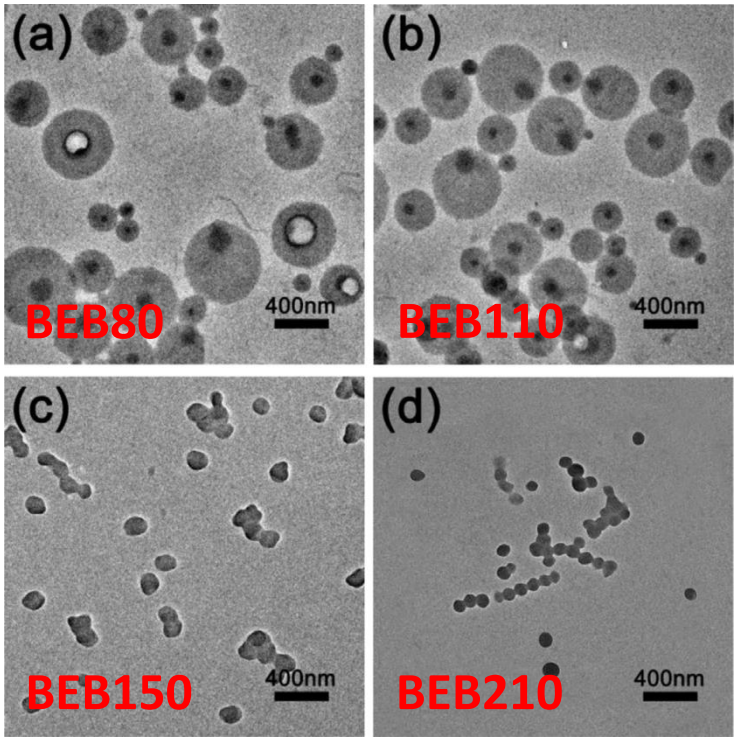
Scheme of Structure Change



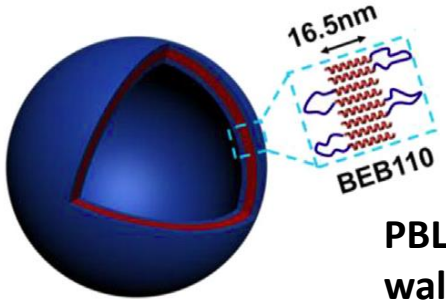
- When the PLGA are longer or in basic surroundings where PLGA takes a flexible extended chain form, spherical micelles are formed
- When the PLGA becomes shorter or PLGA tends to shrink in acidic condition, vesicles are formed

Self-Assembly of Triblock Copolymers (2)

PBLG -*b*- PEG -*b*- PBLG



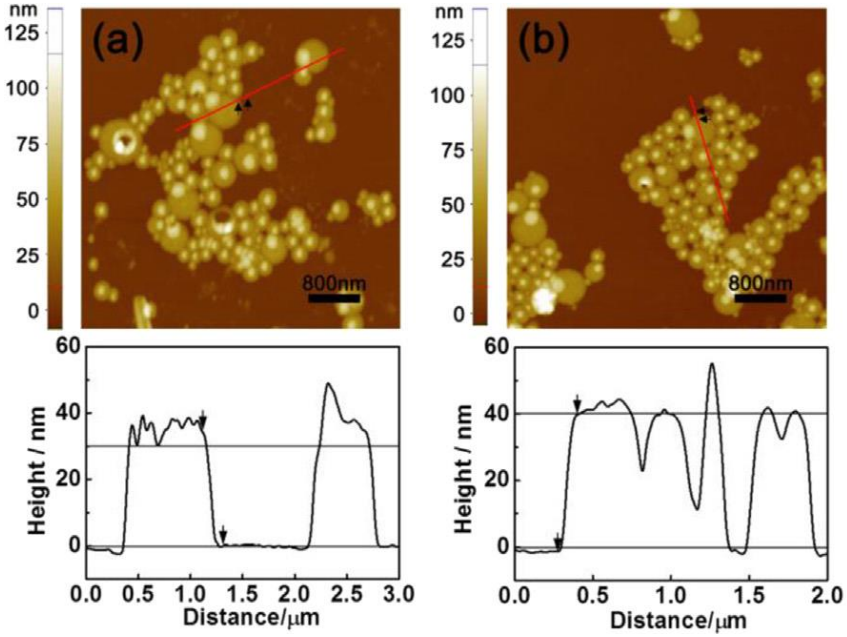
Effect of PBLG length on the aggregates



Vesicles

BEB110

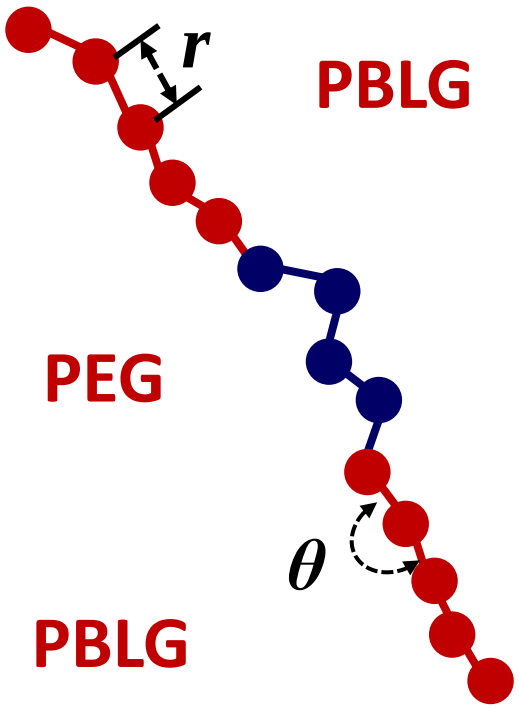
PBLG blocks in vesicle wall are aligned parallel with each other to form monolayer vesicle wall



Z. Zhuang, C. Cai, T. Jiang, J.Lin*, C. Yang. ***Polymer*** 55, 602 (2014)

Dissipative Particle Dynamics Method

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



Forces

Conservative Force

$$\mathbf{F}_{ij}^{\mathrm{C}} = a_{ij}\sqrt{\omega(r_{ij})}\hat{\mathbf{r}}_{ij}$$

Harmonic Spring Force

$$\mathbf{F}_{ij}^{\mathrm{S}} = C(1 - r_{ij}/r_{\mathrm{eq}})\hat{\mathbf{r}}_{ij}$$

Angle Force

$$\mathbf{F}^{\mathrm{A}} = -\nabla\left[k_{\theta}(\theta - \pi)^2\right]$$

Dissipative Force

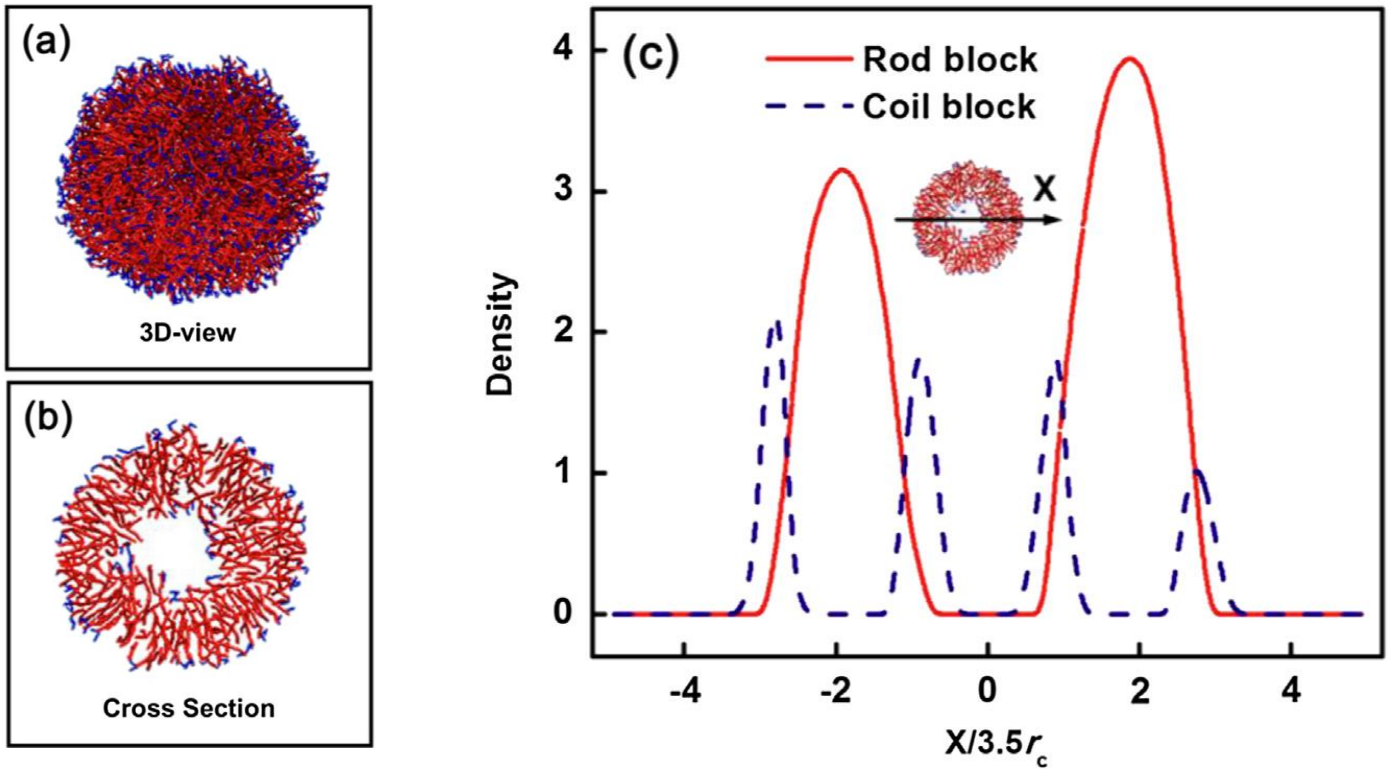
$$\mathbf{F}_{ij}^{\mathrm{D}} = -\gamma\,\omega^{\mathrm{D}}(r_{ij})(\hat{\mathbf{r}}_{ij}\cdot\mathbf{v}_{ij})\hat{\mathbf{r}}_{ij}$$

Random Force

$$\mathbf{F}_{ij}^{\mathrm{R}} = \sigma\,\omega^{\mathrm{R}}(r_{ij})\theta_{ij}\hat{\mathbf{r}}_{ij}$$

P. J. Hoogerbrugge, J. M. V. A. Koelman, ***Europhys. Lett.*** 19, 155 (1992)
J. M. V. A. Koelman, P. J. Hoogerbrugge, ***Europhys. Lett.*** 21, 363 (1993)
T. Jiang, L. Wang, S. Lin, J. Lin*, Y. Li, ***Langmuir*** 27, 6440 (2011)

DPD Simulation Results



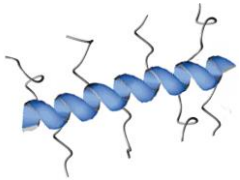
Rigid rod blocks are aligned parallel with each other to form the vesicle wall, which validates the formation of experimentally observed monolayer vesicle

Ex.2

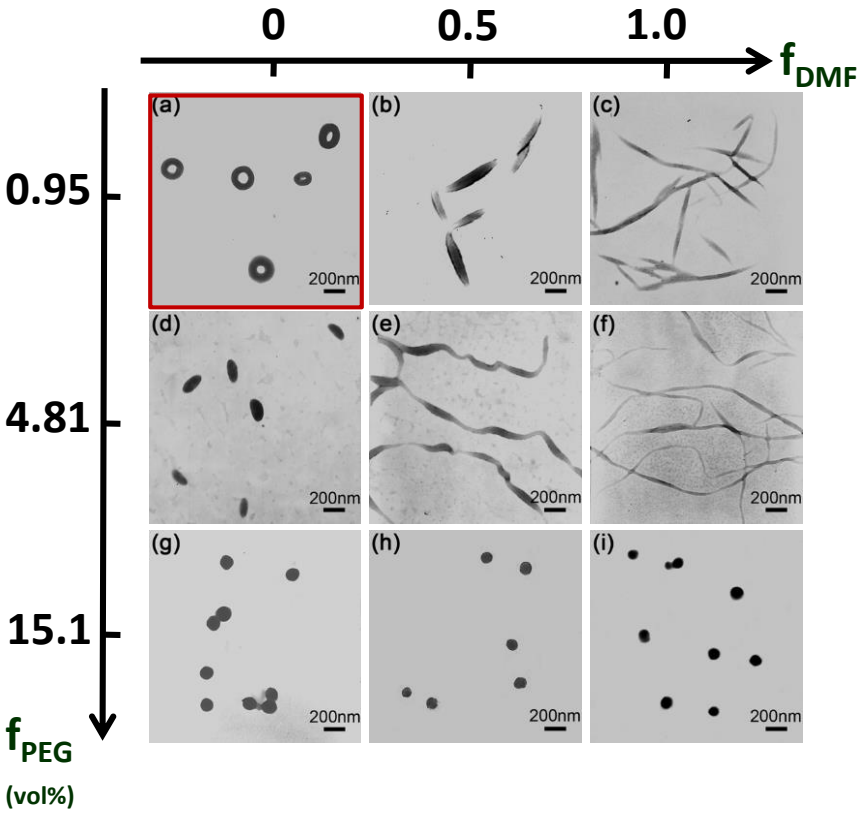
Self-Assembly of Polypeptide-Based Graft Copolymers

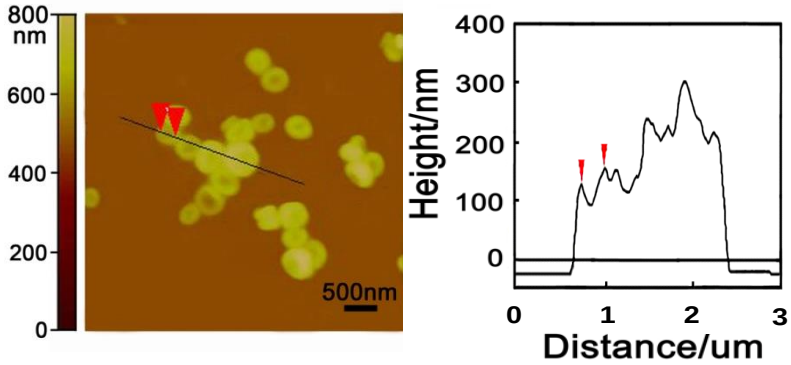
Self-Assembly of Graft Copolymers

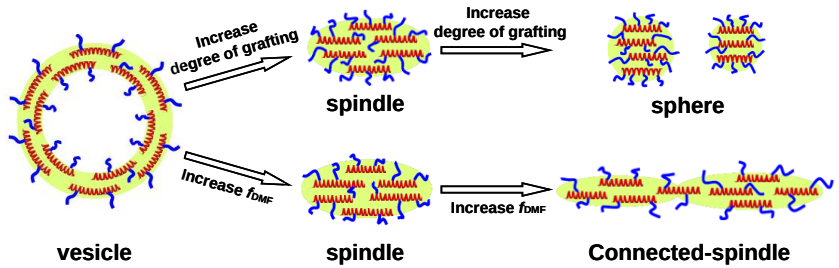
Polymer: PBLG-*g*-PEG



Solvent: THF/DMF





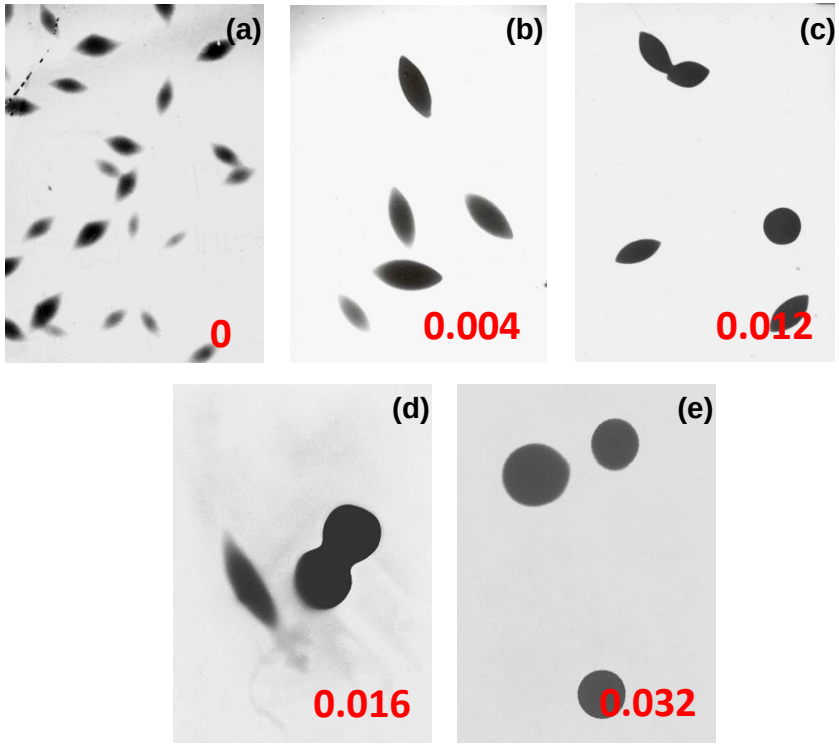


C. Cai, J. Lin* et al. ***Langmuir*** 26, 2791 (2010)
L. Chen, T. Jiang, J. Lin*, C. Cai, ***Langmuir*** 29, 8417 (2013)

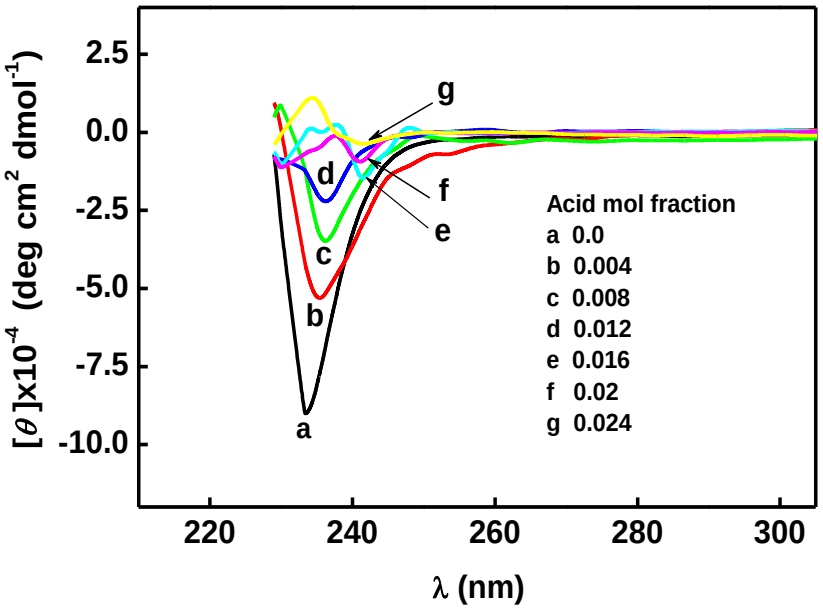
Self-Assembly of Graft Copolymers

Polymer: PBLG-*g*-PEG

Solvent: Ethanol/Denaturantacid (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

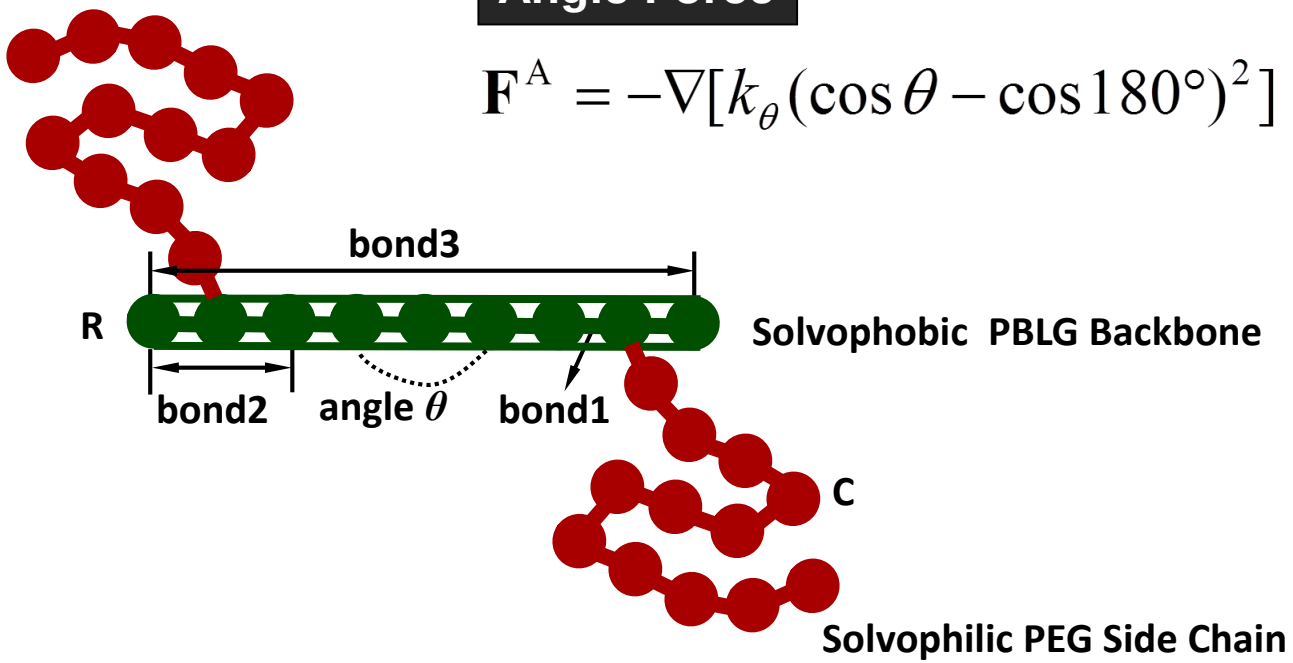
J. Lin* et al. ***Polymer*** 49, 1132 (2008)

J. Lin* S. Lin et al. ***Macromolecules*** 37, 5461 (2004)

DPD Models

Angle Force

$$\mathbf{F}^{A} = -\nabla[k_\theta(\cos\theta - \cos 180°)^2] \quad k_\theta = 20$$



Harmonic Spring Force

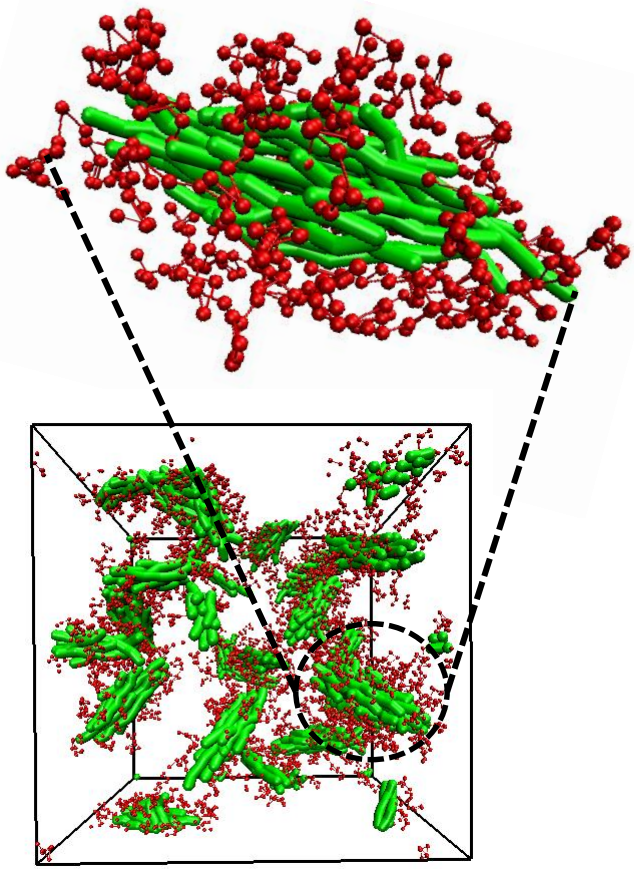
Bond1: $\mathbf{F}_{ij}^{S} = C(1 - r_{ij} / r_{eq})\hat{\mathbf{r}}_{ij} \qquad r_{eq} = 0.7$

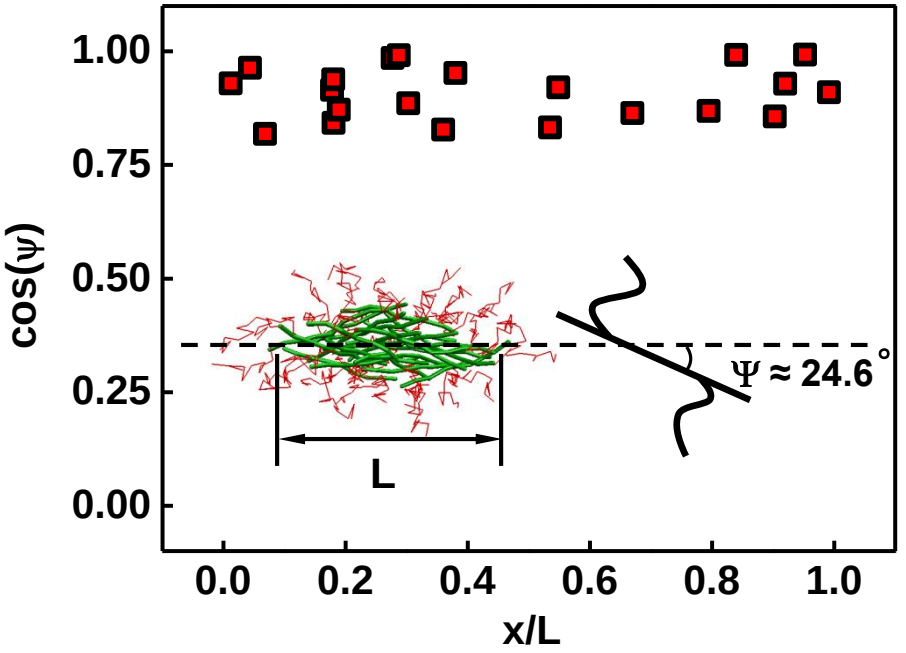
Bond2: $\mathbf{F}_{ij}^{1} = C(1 - r_{ij} / r_{eq})\hat{\mathbf{r}}_{ij} \qquad r_{eq} = 1.4$

Bond3: $\mathbf{F}_{ij}^{2} = C(1 - r_{ij} / r_{eq})\hat{\mathbf{r}}_{ij} \qquad r_{eq} = 5.6 \qquad C = 5.6$

DPD Simulation Results

Packing of graft copolymers in the spindle-like micelles by dissipative particle dynamics simulation

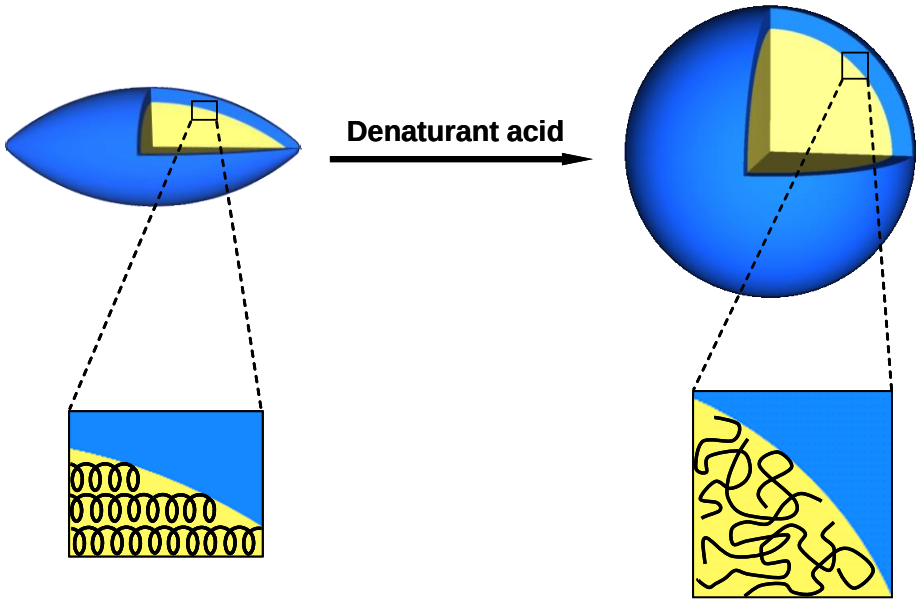




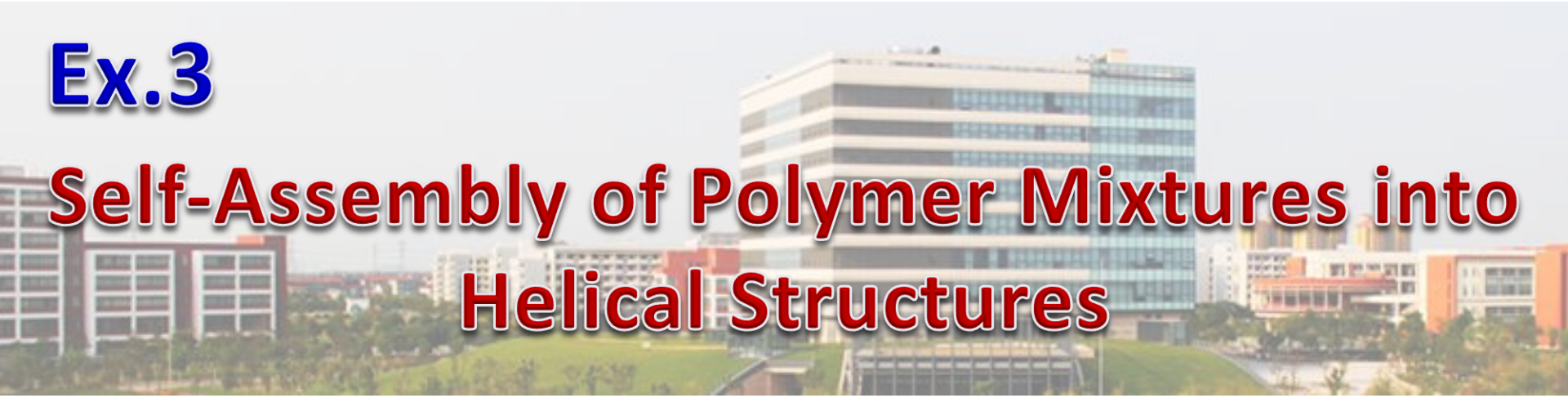
The rod-like backbones of the graft copolymers are aligned along the long axis of spindle-like micelles

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:

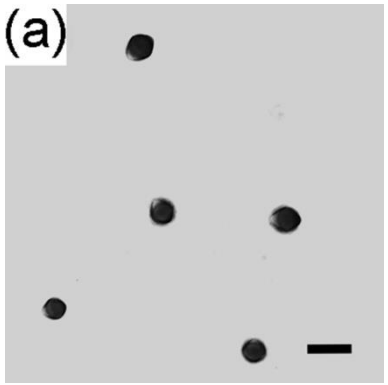
$PBLG_{31000}$-*b*-PEG_{2000}

$PBLG_X$

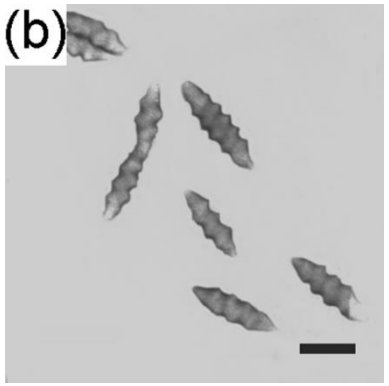
Solvents:

THF/DMF

Effect of the PBLG length (x)



X=40000



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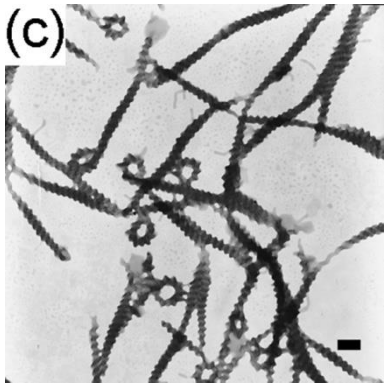
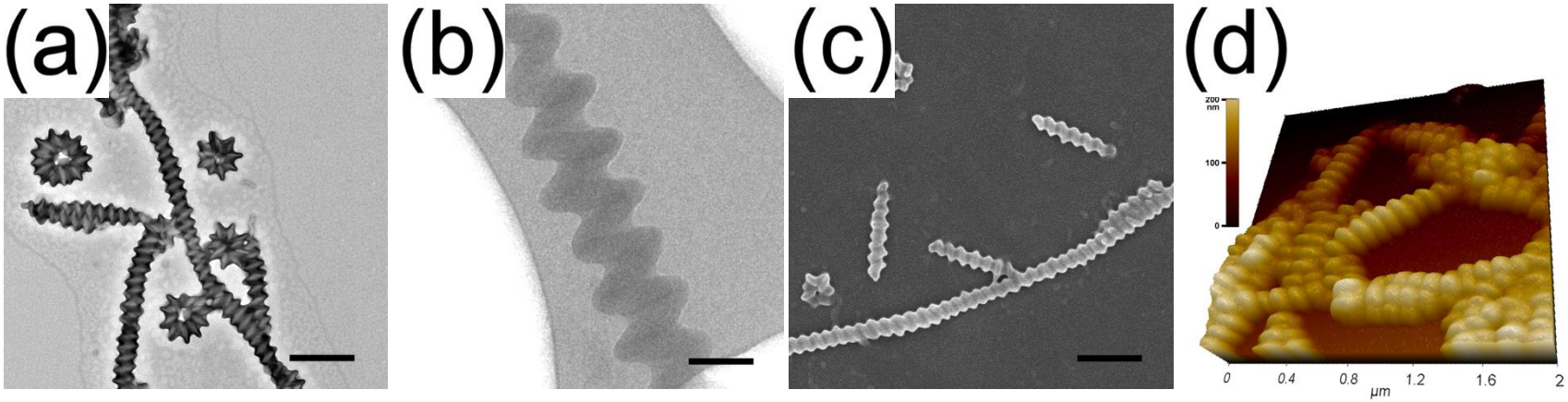


X=520000

C. Cai, J. Lin* et al. ***Chem. Commun.*** 2709 (2009)
C. Cai, J. Lin* et al. ***Angew. Chem. Int. Ed*** 52, 7732 (2013)

Characterization of the Super-Helices

Scale bars: 500 nm



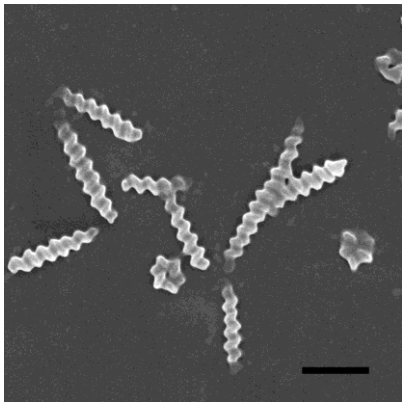
TEM Cryo-TEM SEM AFM

Chirality:

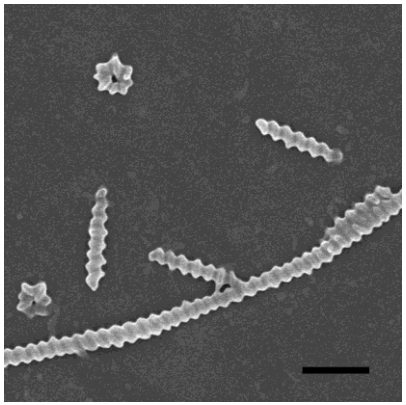
- PBLG backbone: Right-handed
- Super-helix: Right-handed

Effect of Fraction of Peptide Copolymers

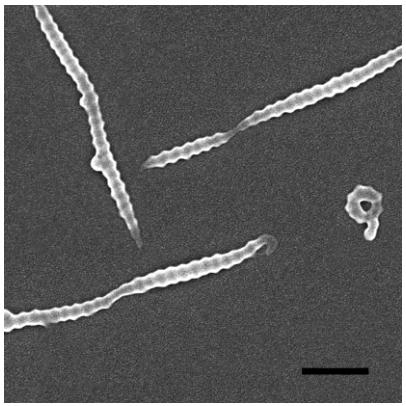
Effect of the PBLG-*b*-PEG Weight Fraction (SEM)



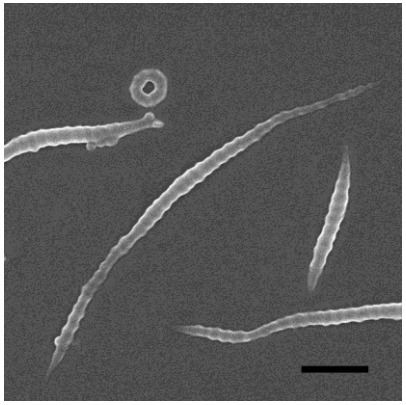
90 wt%



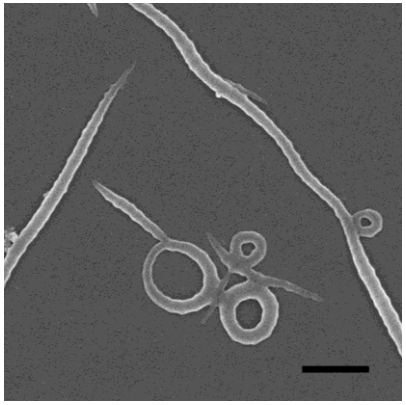
80 wt%



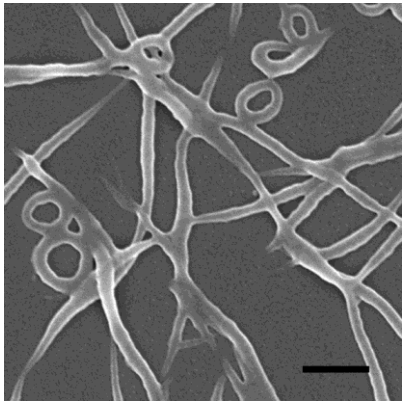
70 wt%



60 wt%



50 wt%

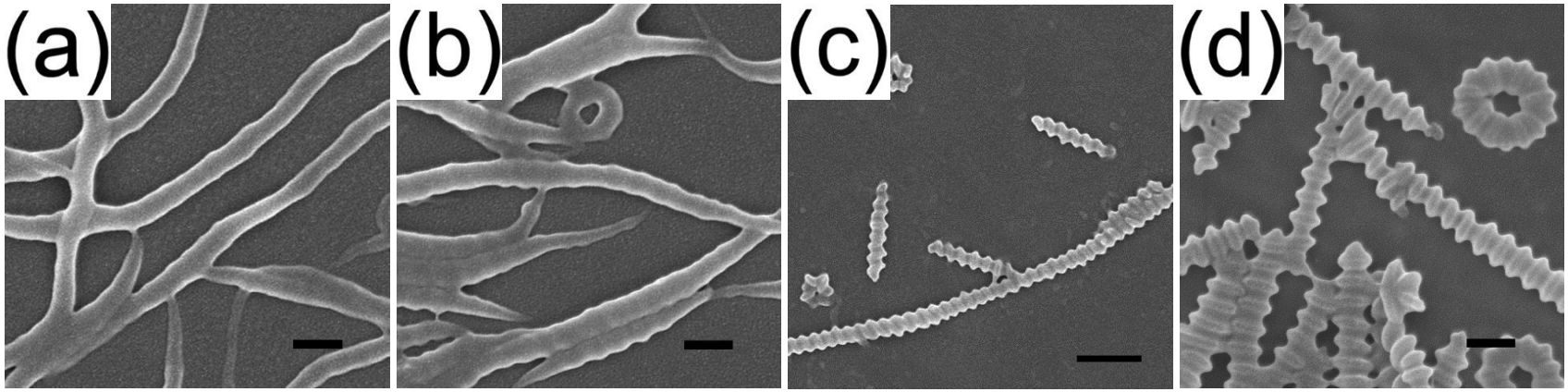


40 wt%

The samples were prepared at room temperature. Scale bar: 500 nm.

Effect of Self-Assembling Temperature

Scale bars: 200 nm

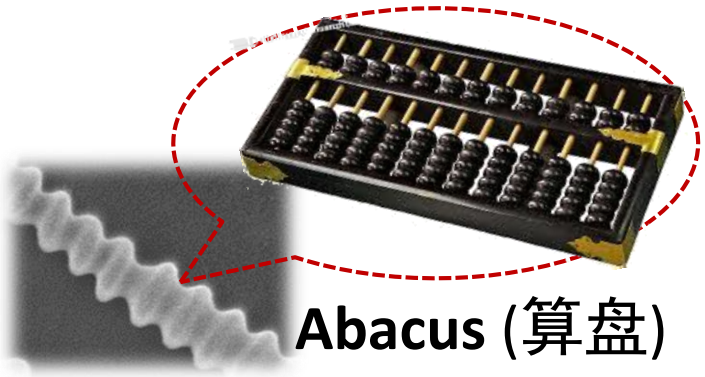


Preparing temperature increases

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

Super-helices prepared at room temperature:

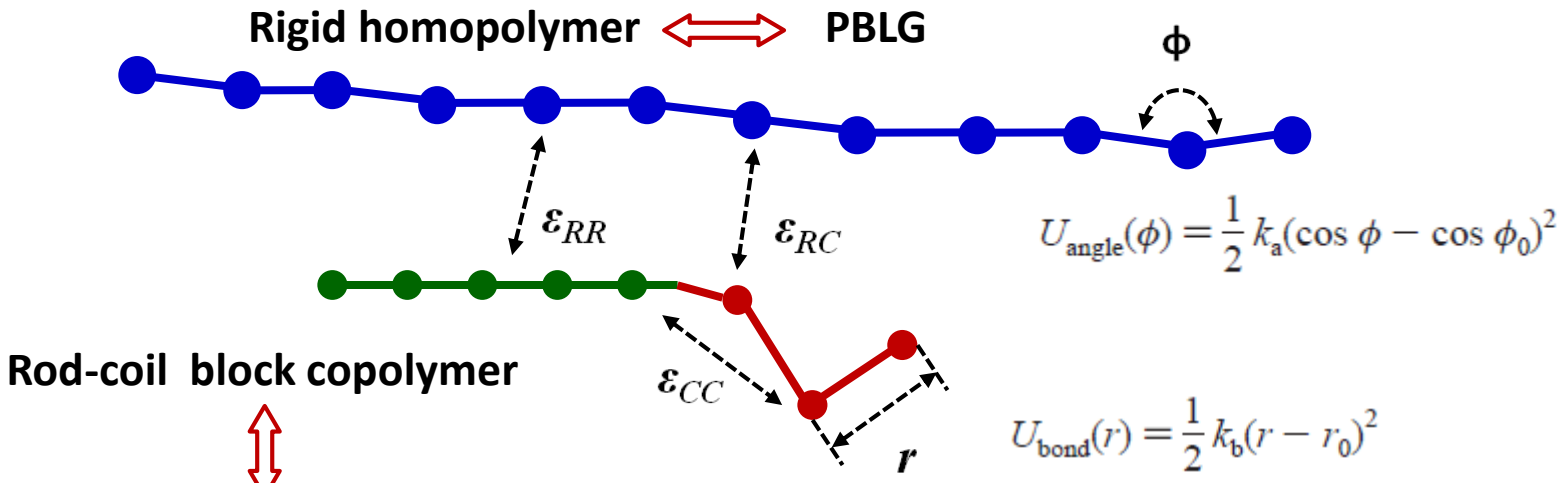
- Decreasing temp: Plain fibers
- Increasing temp: Abacus-like structures



Abacus (算盘)

A Chinese calculation tool

Brownian Dynamics Model



Equations of Motion

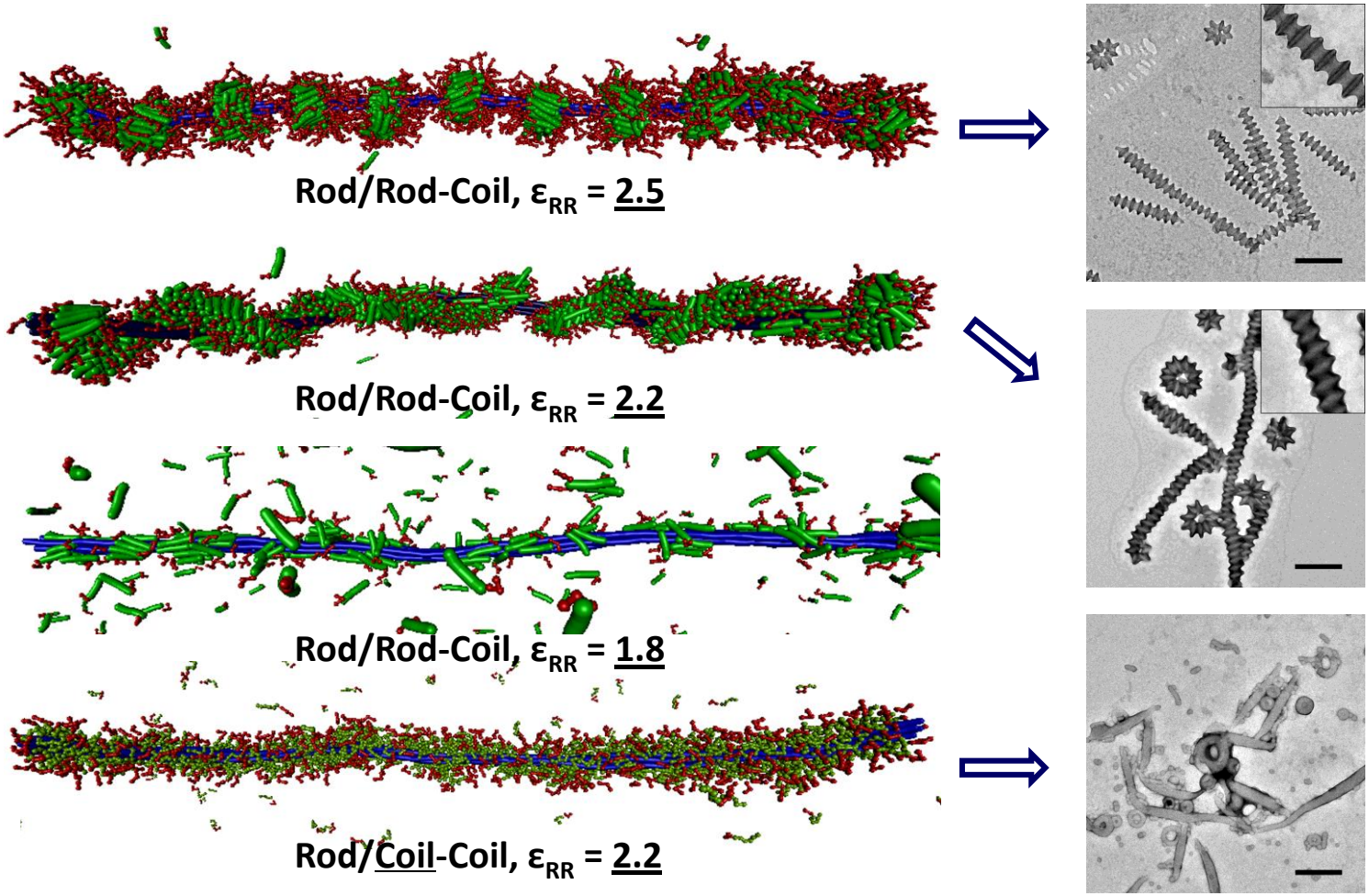
$$F = U_{ij} + U_{angle} + U_{bond}$$

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

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

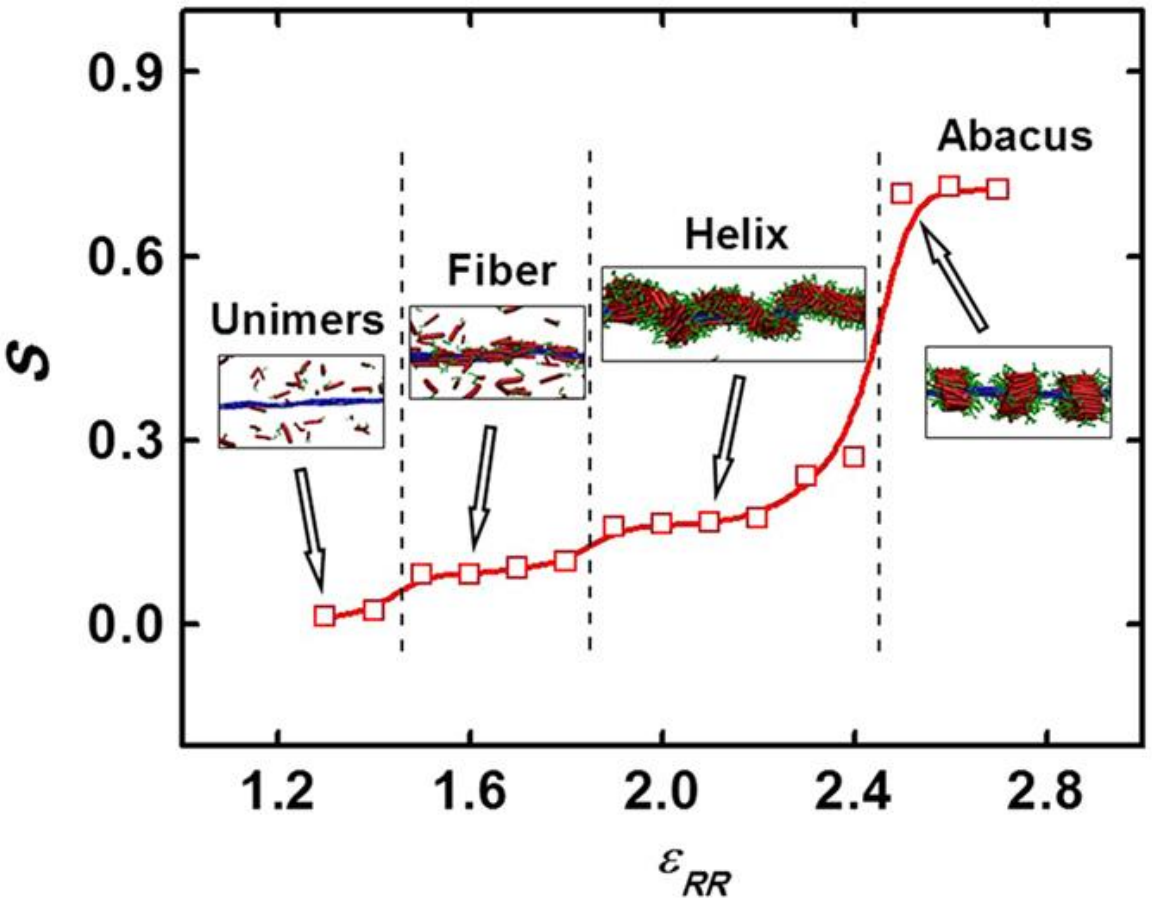
Interaction	σ_{ij}	ε_{ij}	r_{ij}^c
ε_{RR}	1.0	1.3 – 2.5	2.5
ε_{RC}	1.0	1.0	$2^{1/6}$
ε_{CC}	1.0	1.0	$2^{1/6}$

Brownian Dynamics Simulation



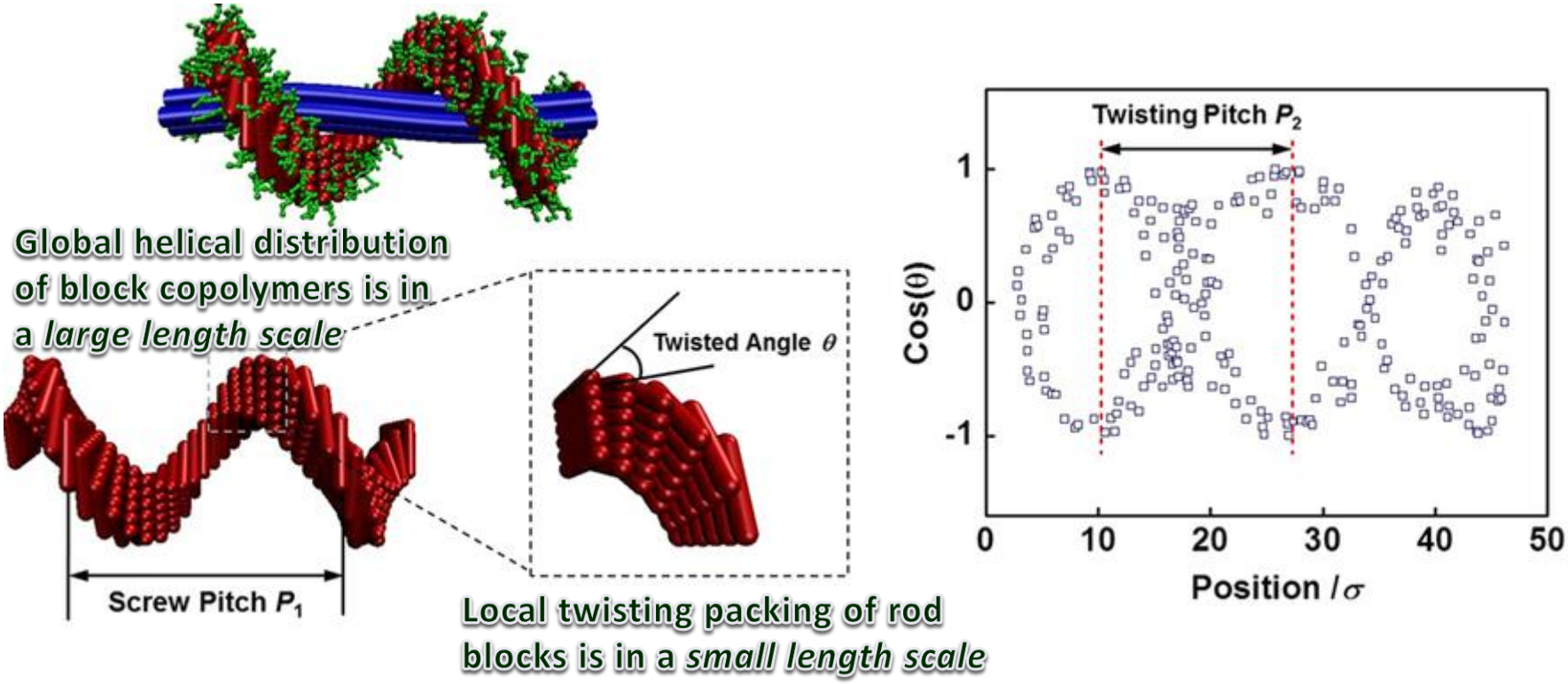
Y. Li, C. Cai, J Lin* et al. ***Sci. Rep.*** 5, 10137 (2015)

Order Parameters of Rod Blocks



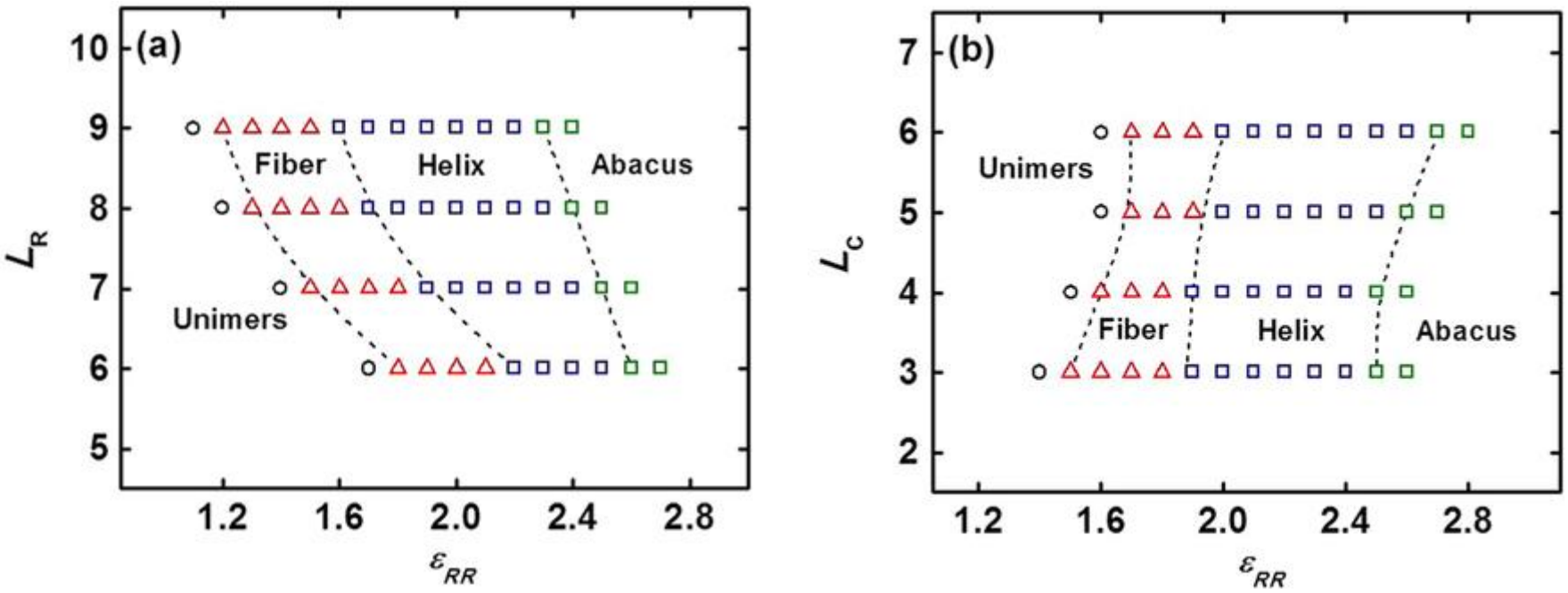
S > 0.7 in the abacus region when $\varepsilon_{RR} \geq 2.5$ and then sharply decreases to about 0.2 with decreasing ε_{RR}. With further decreasing ε_{RR}, S is very low, implying the packing of rod blocks is disordered in fiber and unimer regions.

Structural Details of Super-helices



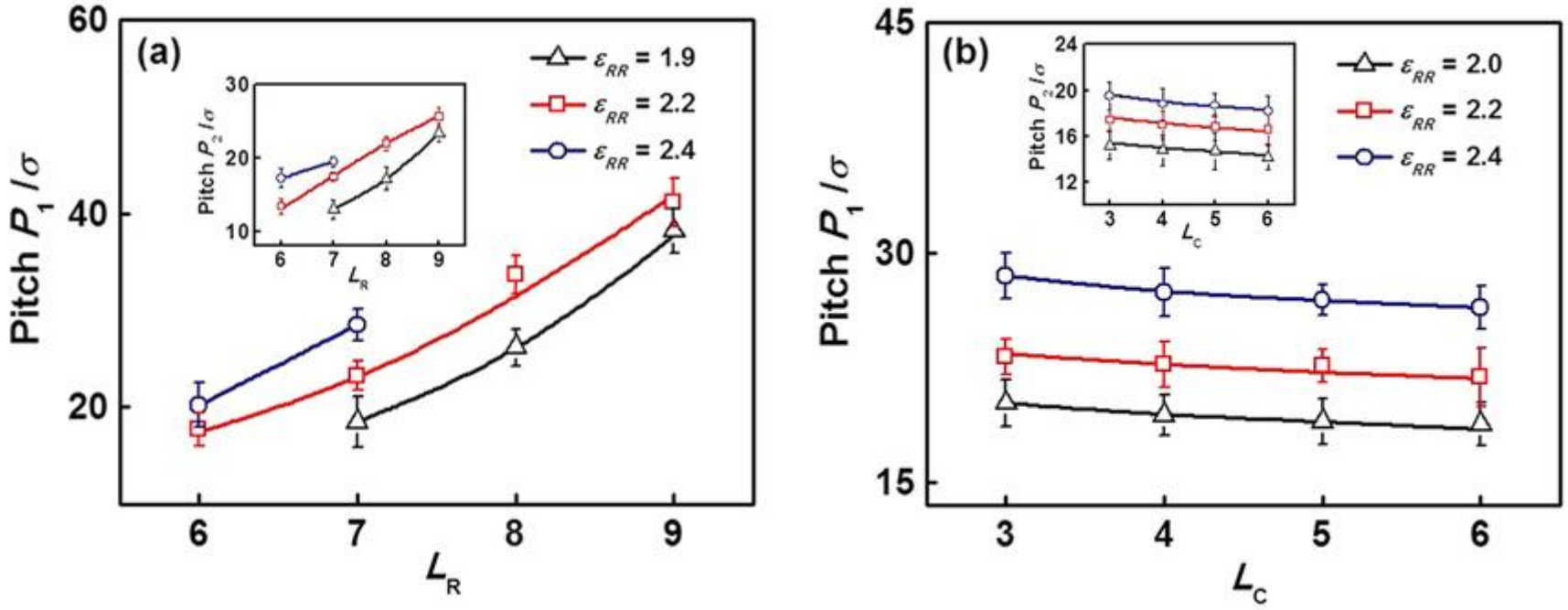
- Homopolymer bundles form the inner axis, and block copolymers form the screw through ordered packing of the rod blocks
- Rod blocks tend to align in an orientation vector, and such a vector is gradually changed along the axis of the bundle

Phase Diagrams



- As ε_{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 ε_{RR}, which is opposite to the effect of L_R

Effect of Block Length on Pitch of Super-helices

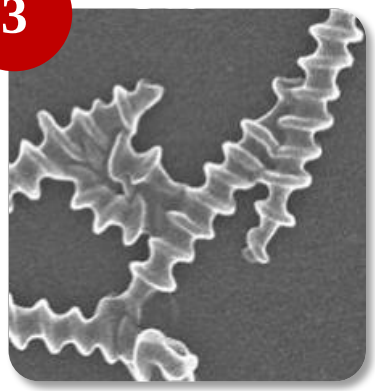


- Helical wrapping of block copolymers on homopolymer bundles is in a more extended manner for longer rod block, and the local twisting of rod blocks is easier to occur for shorter rod block
- Structure diversity of helices for various L_C is not obvious relative to the helices formed by mixtures with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

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 !