生体高分子の粗視化分子シミュレーションで何を見る？

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バイオスーパーコンピューティング研究会(BSCRC)
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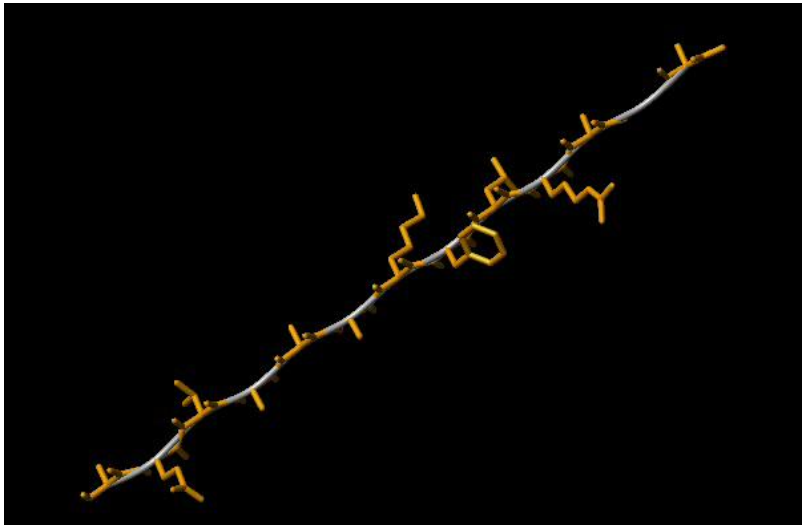
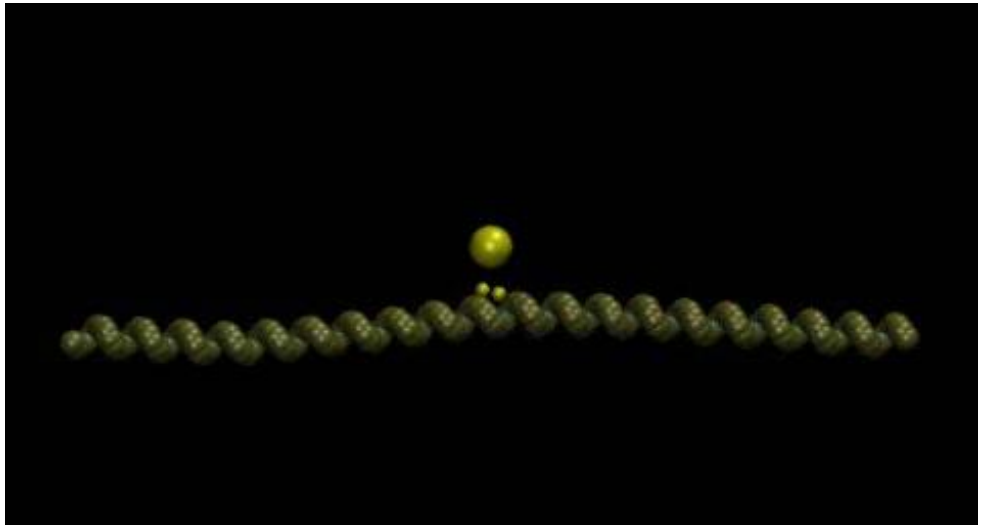
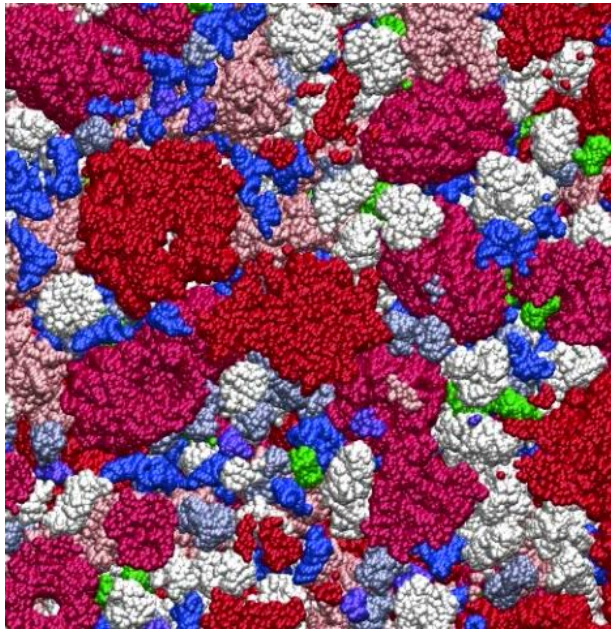
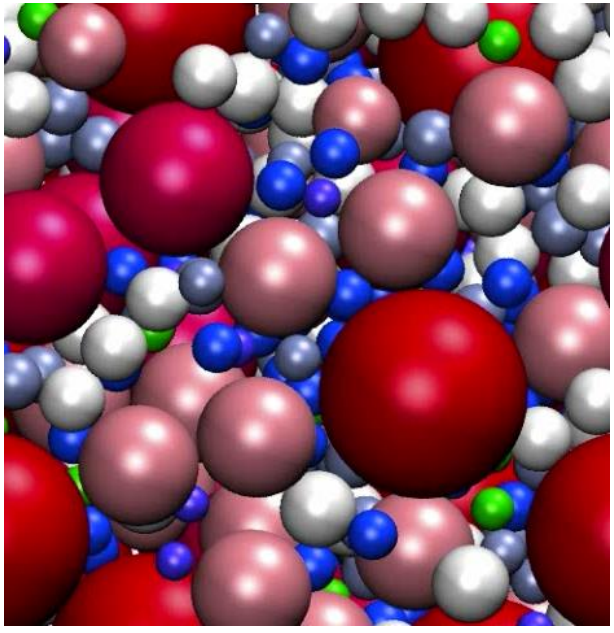
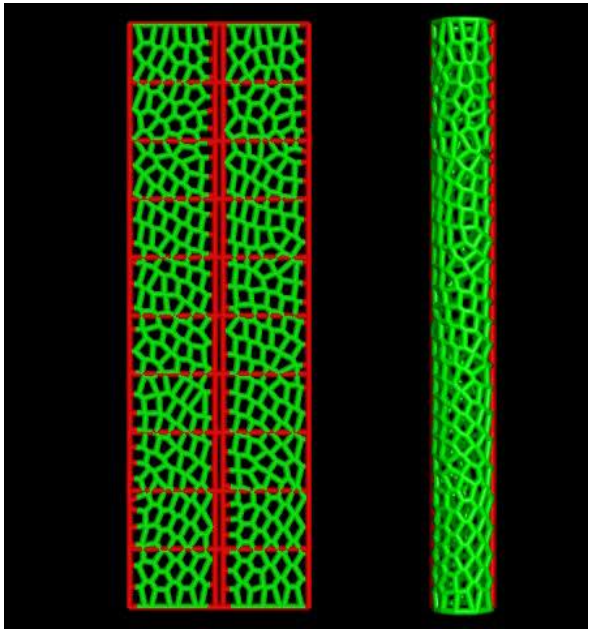










自己紹介

- 大学では分子生物学、生化学等、を学びました。修士課程（Y研究室）までは、大腸菌での遺伝子操作、タンパク質の発現、精製を行い分光学的手法（CD，NMR）でタンパク質の安定性を調べていました。私のバックグラウンドは生化学、分子生物学です。

- 博士課程（Y研究室）では、ブラウン動力学法を用いたタンパク質の折り畳みシミュレーションを行っていました。

- アメリカに留学（Skolnick Lab.）し、細胞内環境下でのシミュレーション等を行いました。

- 日本に帰国後、理研（S研究室）で生体高分子のシミュレーションに関わる仕事をしています。

- 物理化学・理論、そして数学には弱いですが、とても憧れがあります。 曖昧模糊で、結果の記述が多い、複雑な生物学の分野で、何か単純な物理化学的な原理を見つけ出し、予測可能な理論的なものを見つけ出せないかなー、と考えています。

今回の発表

- 今回は非常にリラックスした環境で発表ができるということで、あまり注目されませんでしたが、私的には気に入っている研究についてお話をさせていただきます。そして、最後に分子シミュレーション、特に粗視化分子シミュレーションに対する個人的な考えを少しだけ（2スライド）述べさせていただきます。

Force-field for two-points lipid model

- Bonding term

$$V^{\text{bond}} = \frac{1}{2} k_{\text{bond}} \left(r - r_0\right)^2$$

In the simulations, k_{bond} of $1000 k_B T / r_0^2$ and r_0 of 13 Å were used.

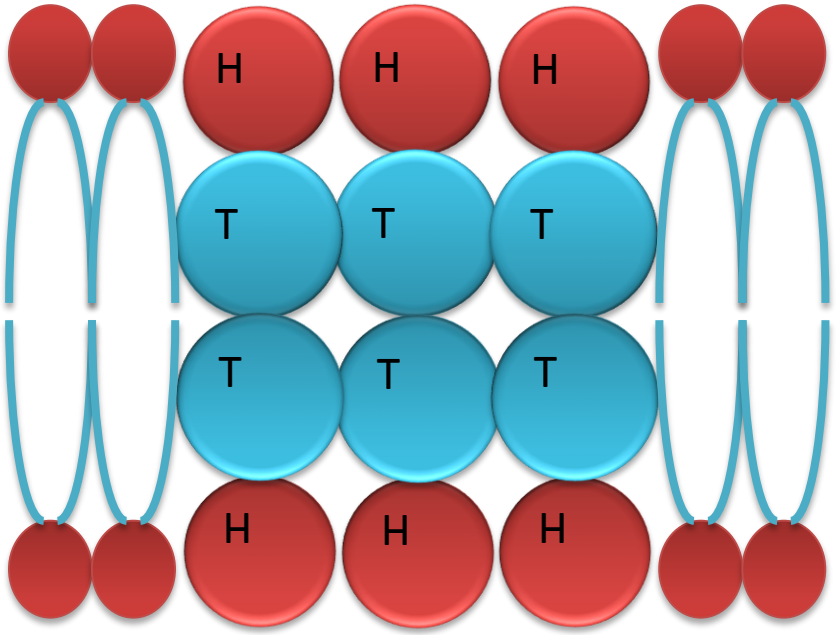
- Non-bonding term

$$V^{\text{inter}} = \sum_{\text{inter-lipid T-T pairs}} V_{\text{atr}} + \sum_{\text{all inter-lipid pairs}} V_{\text{rep}}$$

$$V_{\text{atr}} = \begin{cases} -\varepsilon_{\text{L}} & \text{if } r \le r_{\text{c}} \\ -\varepsilon_{\text{L}} \cos^2\left(\dfrac{\pi\left(r - r_{\text{c}}\right)}{2 w_{\text{c}}}\right) & \text{if } r_{\text{c}} < r \le r_{\text{c}} + w_{\text{c}} \\ 0 & \text{if } r > r_{\text{c}} + w_{\text{c}} \end{cases}$$

$$V_{\text{rep}} = \frac{1}{2} k_{\text{rep}} \left(r - r_{\text{c}}\right)^2 \qquad \text{if } r \le r_{\text{c}}$$

In the simulations, ε_{L} of $1.9 k_B T$, w_{c} of 19.5 Å, k_{rep} of $10 k_B T$ were used.



Equilibrium distances (Å) between inter-monomer particles, r_{c}

Particle #	H	T
H	11.70	12.35
T	12.35	13.00

ブラウン動力学(BD)

- Effects of solvent on solute molecules are implicitly considered. (Coarse-graining!!)

  ⇒It makes possible to examine long-time dynamics. (In principle, water molecules should be explicitly present in MD simulation systems.)

- Stochastic simulation based on the Langevin equation.

- Hydrodynamic interactions (HI) can be taken into account.

BD algorithm

- BD algorithm considering HI

$$\mathbf{r}(t+\Delta t)=\mathbf{r}(t)+\frac{\mathbf{DF}}{k_B T}\Delta t+\sqrt{2\Delta t}\mathbf{Bz}$$

with $\mathbf{D}=\mathbf{B}\mathbf{B}^T$

r is a 3*N* vector representing the spatial coordinates of all the particles in the simulation box. **D** is the diffusion tensor with size of 3*N* x 3*N*. **F** is a 3*N* vector of force. ***z*** is a 3*N* vector with zero mean and variance of 1.

- Rotne-Prager-Yamakawa tensor

$$\mathbf{D}_{ij}=\begin{cases}\dfrac{k_B T}{6\pi\eta a}\mathbf{I} & i=j,\\ \dfrac{k_B T}{8\pi\eta r_{ij}}\left[\left(\mathbf{I}+\hat{\mathbf{r}}_{ij}\hat{\mathbf{r}}_{ij}\right)+\dfrac{2a^2}{r_{ij}^{\,2}}\left(\dfrac{1}{3}\mathbf{I}-\hat{\mathbf{r}}_{ij}\hat{\mathbf{r}}_{ij}\right)\right] & i\neq j \text{ and } r_{ij}\geq 2a,\\ \dfrac{k_B T}{6\pi\eta a}\left[\left(1-\dfrac{9}{32}\dfrac{r_{ij}}{a}\right)\mathbf{I}+\dfrac{3}{32}\dfrac{r_{ij}}{a}\hat{\mathbf{r}}_{ij}\hat{\mathbf{r}}_{ij}\right] & i\neq j \text{ and } r_{ij}<2a.\end{cases}$$

粒子間の流体力学的相互作用を考慮しない場合

拡散行列Dは対角行列

$$D=\frac{k_B T}{6\pi\eta a}$$

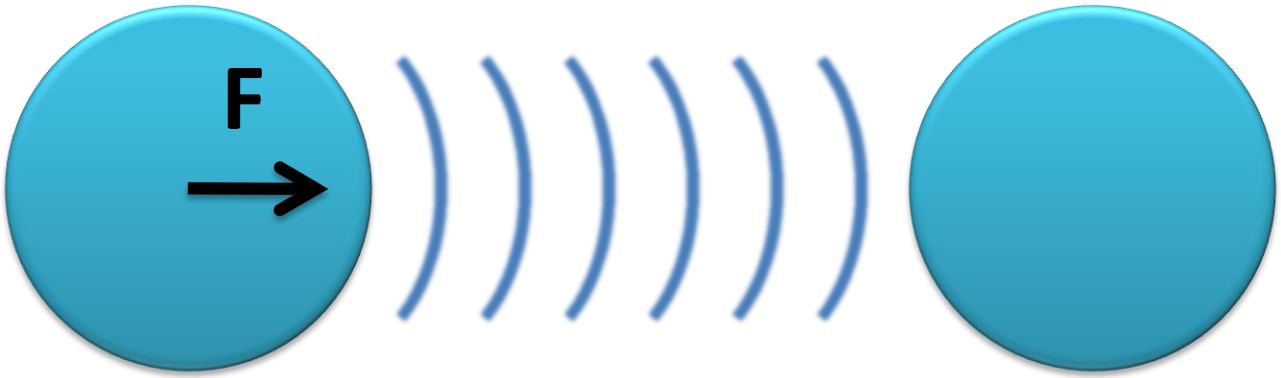
ストークス - アインシュタインの式

BD法では流体力学的相互作用を自在にON/OFFできます！

- MDではできない。
- 生体高分子のMDを行っている研究者のほとんどは、流体力学的相互作用に注目していない。

What are hydrodynamic interactions?

Each particle's force changes the solvent flow, and this in turn affects forces on other particles through the frictional forces affecting them.



Systems for membrane assembly

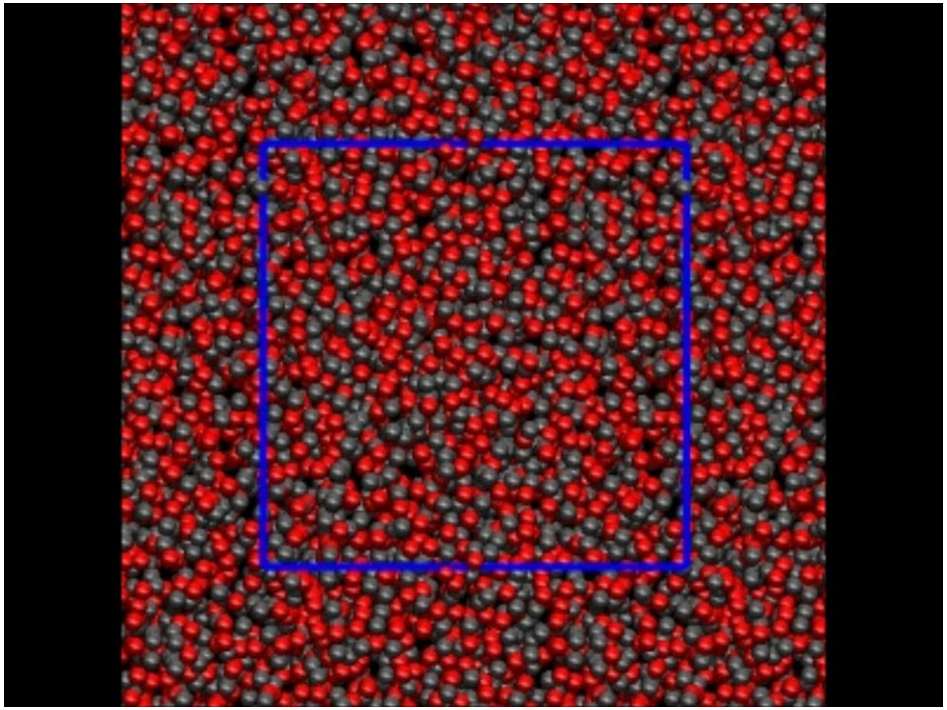
- 1000 coarse-grained lipid molecules were placed randomly in a 28 × 28 × 28 nm^3 periodic box without significant overlaps between particles.
- Ten independent initial configurations were generated.
- Simulation temperature was set to 298 K.
- Stokes radii of particles, a, were set to 6.5 Å.
- Time step was 2.24 ps, which corresponds to 0.5 × 10^{-3} a^2/D_0 with $D_0 = k_B T/6\pi\eta a$.
- HIs were considered by two different ways:
  - **BD simulation with full HIs. That is, HIs within each lipid molecule as well as between lipid molecules (With inter-HIs)**
  - **BD simulation with only intramolecular HIs, where intermolecular HIs are neglected (Without inter-HIs)**

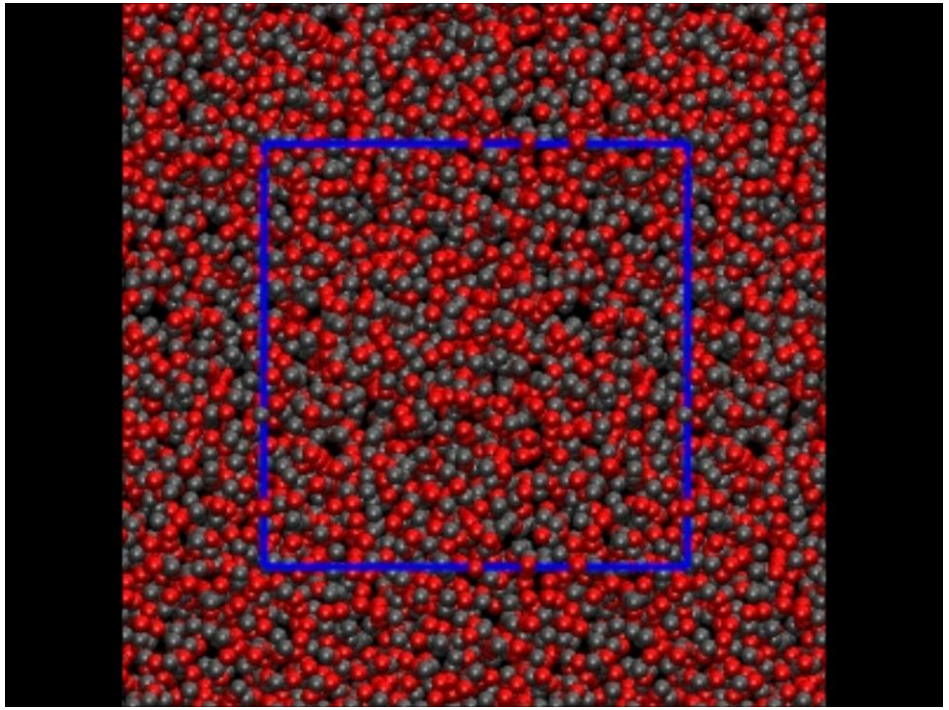
二つの条件の違いは、分子間の流体相互作用がある（with inter-HIs），なし（without inter-HI）のみ。 → 2つの結果の差から分子間流体力学の影響を見ることができる。

Representative simulation results

With inter-HIs

Without inter-HIs

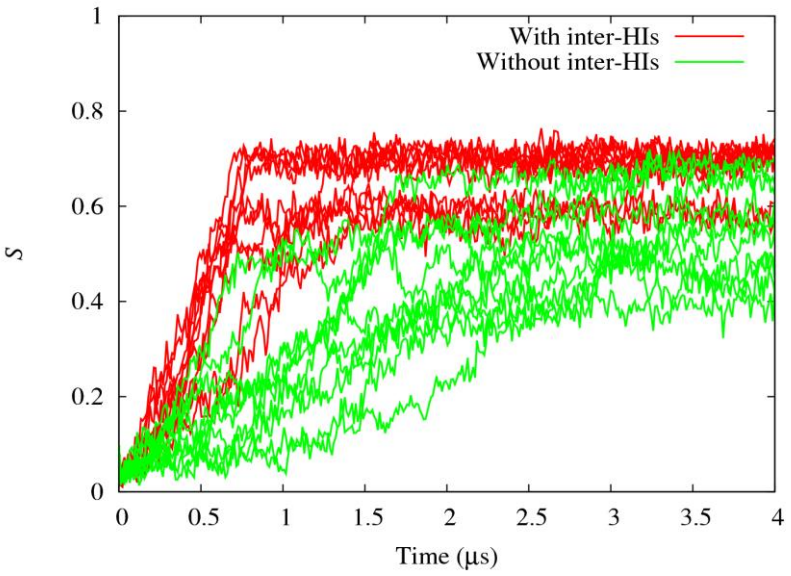




3.5 μs BD simulations

HI accelerate membrane self-assembly

Time evolution of nematic order parameter *S*

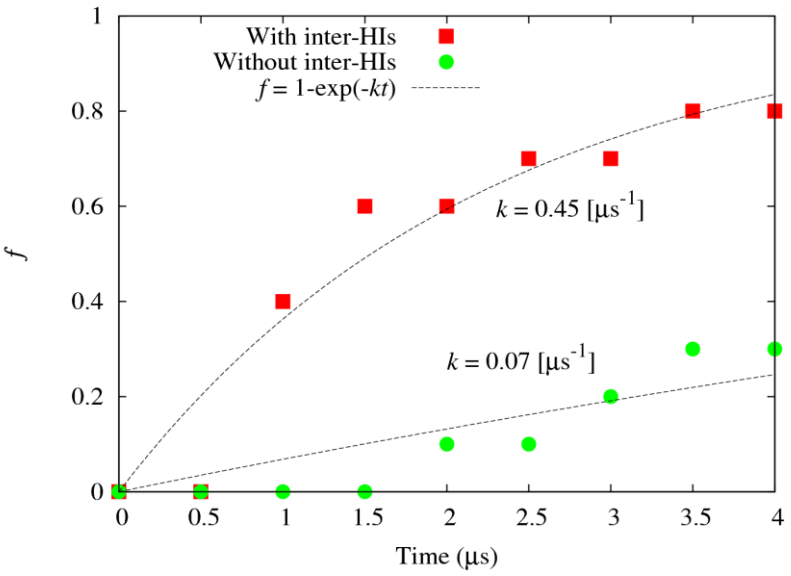


To measure order of lipid membrane, we evaluated the nematic order parameter *S* of the system which is given by the largest eigenvalue of an order parameter defined by 3 × 3 matrix

$$Q_{\alpha\beta} = \frac{1}{2}\left\langle 3\cos\theta_\alpha \cos\theta_\beta - \delta_{\alpha\beta} \right\rangle \text{ with } \alpha, \beta = x, y, z$$

Here, ϑ_α is the angle between a lipid molecule axis and α axis, $\delta_{\alpha\beta}$ is the Kronecker delta function, and represents the average over all molecules in the system. *S* equals 1 for perfectly aligned molecules and 0 for a random configuration.

Overall kinetics of membrane self-assembly



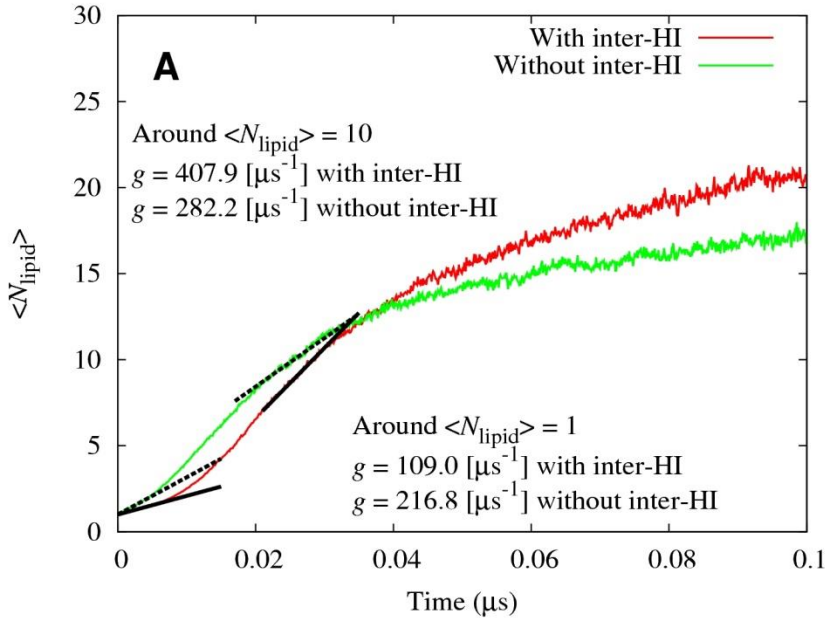
f is the fraction of systems that reach *S* > 0.7 within given time periods.

***k*(with HI)/*k*(without HI) = 6.4**

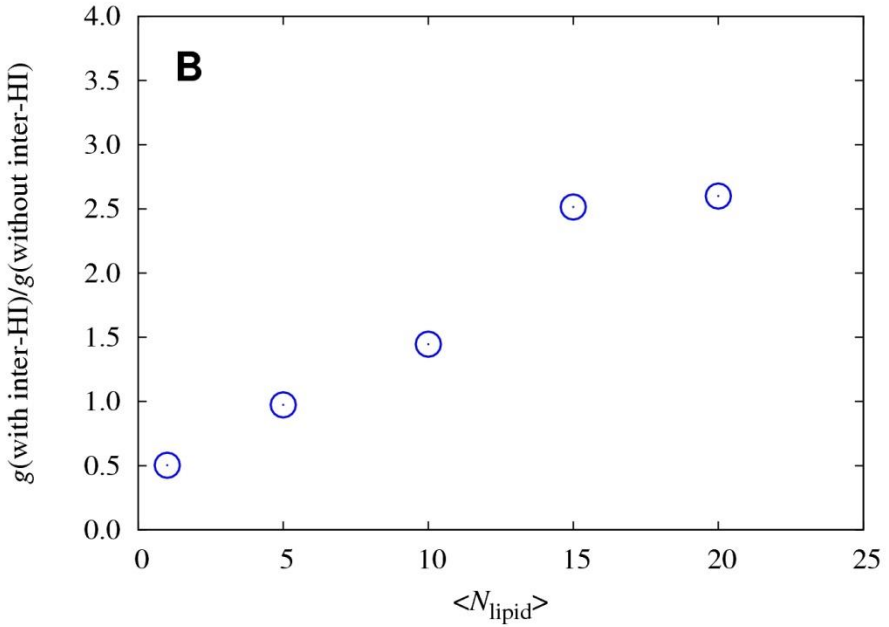
分子間HIは、膜形成速度を約6倍加速させている。

HI decelerate initial monomer-monomer association

Growth of average lipid-cluster size $\langle N_{lipid} \rangle$ up to 0.1 μs



The ratios of the slopes of the growth curves in the presence and absence of inter-HI for various $\langle N_{lipid} \rangle$

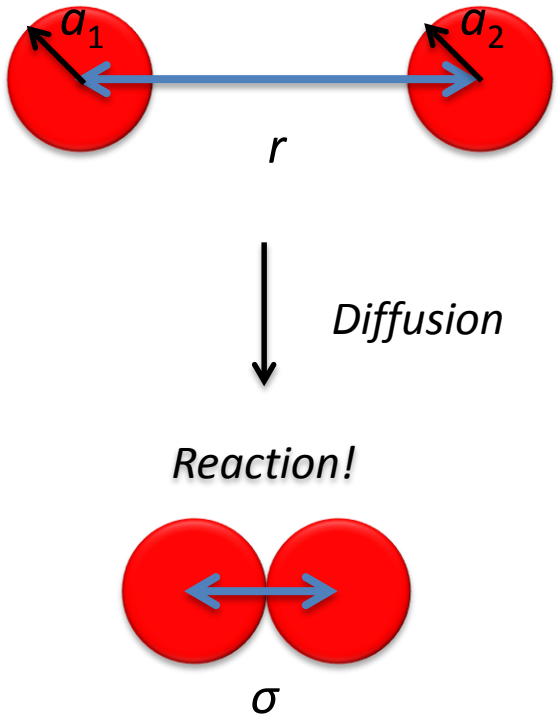


- $\langle N_{lipid} \rangle$ = 1 では, g(with inter-HI)/g(without inter-HI) = 0.50.
  => 分子間HIは、モノマー・モノマーの結合速度を遅くしている。
- しかし、$\langle N_{lipid} \rangle$ が 5以上になると、分子間HIを考慮した方が、脂質クラスターの融合速度が速い。

How can we explain this size dependent HI effects?

In a diffusion controlled kinetic, the diffusive encounter rate, k_D, can be described by

$$k_D = 4\pi \left[\int_{\sigma}^{\infty} \frac{\exp\left[W(r)/k_B T\right]}{D(r) r^2} dr \right]^{-1}$$



where $W(r)$ is the potential mean force between the reactants at center-to-center distance r, σ is the encounter distance, and $D(r)$ is the distance-dependent relative translational diffusion coefficient. When each reactant is represented by a sphere, $D(r)$ at diluted condition can be written by

$$D(r) = D_1 + D_2 - 2\hat{\mathbf{r}}_{12} \cdot \mathbf{D}_{12} \cdot \hat{\mathbf{r}}_{12}$$

Here, $\mathbf{D}_{12}$ is diffusion tensor between particles 1 and 2, $\hat{\mathbf{r}}_{12}$ is the unit vector between reactants, and D_i is the diffusion coefficient of particle i given by

$$D_i = \frac{k_B T}{6\pi\eta a_i}$$

How can we explain this size dependent HI effects?

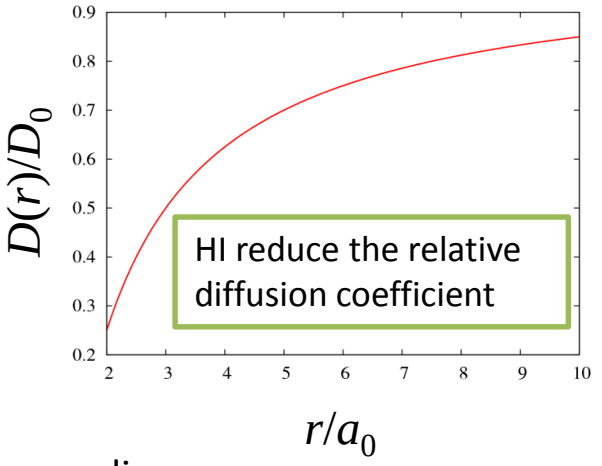
Let us assume $W(r) = 0$, the reactants have a same radius a_0, and σ is the sum of a_0. In the absence of HI, that is "free-draining (FD) limit", the relative diffusion coefficient is a constant and sum of the diffusion coefficients of the reactants, that is $D(r) = 2D_0$. Therefore, the rate constant in FD limit, k_D^{FD}, is given by

$$k_D^{FD} = 16\pi D_0 a_0$$

This is the **Smoluchowski expression**.

In the presence of HI at Oseen tensor level, $D(r)$ is given by

$$D(r) = 2D_0 - \frac{k_B T}{2\pi\eta r}$$



Then, the encounter rate , k_D^{Oseen}, is expressed as

$$k_D^{Oseen} = \frac{12\pi D_0 a_0}{\ln 4}$$

When the reactants are represented by single particles having the same radius,

$$\frac{k_D^{Oseen}}{k_D^{FD}} \approx 0.54$$

This means **HI reduce the diffusive encounter rate by 46% (Deutch and Felderhof, 1976).**

How can we explain this size dependent HI effects?

Next, we consider the diffusive encounter rate of objects consisting of *N* beads, like polymers. The diffusion coefficient of a random polymer connecting *N* identical beads in the presence of HI shows the following scaling property:

$$D^{\mathrm{Oseen}} \approx D_0 N^{-\nu} \qquad (0 < \nu < 1)$$

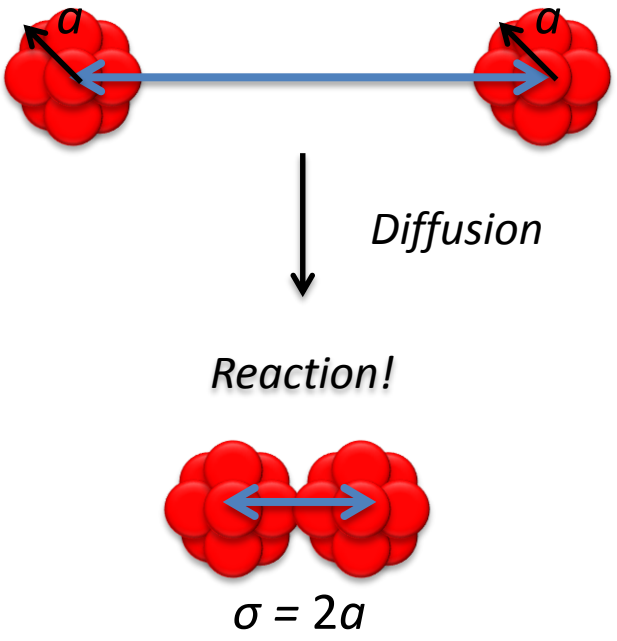
Here, D^{Oseen} is the diffusion coefficient of the polymer. The hydrodynamic radius of the polymer a is related to its D^{Oseen} by

$$a = \frac{k_{\mathrm{B}}T}{6\pi\eta D^{\mathrm{Oseen}}} = a_0 N^{\nu}$$

Thus, the radius of polymer has N^{ν} scaling. Therefore, the diffusive encounter rate in the presence of HI is given by

$$k_{\mathrm{D}}^{\mathrm{Oseen}} = \frac{12\pi D^{\mathrm{Oseen}} a}{\ln 4} = \frac{2k_{\mathrm{B}}T}{\eta \ln 4}$$

The rate does not show any *N* dependence for the reactant pair consisting of the same number of beads.



How can we explain this size dependent HI effects?

In the FD limit, the diffusion coefficient D^{FD} is given by Rouse theory, which is

$$D^{\mathrm{FD}} = D_0 N^{-1}$$

Because HI only affects kinetics and not thermodynamics, polymers have the same radius in the presence and absence of HI, which scales with N^{ν}. Therefore, we obtain the following scaling properties for the encounter rate in the FD limit:

$$k_{\mathrm{D}}^{\mathrm{FD}} = 16\pi D^{\mathrm{FD}} a = \frac{8k_B T}{3\eta} N^{\nu-1}$$

which **shows *N*-dependence**.

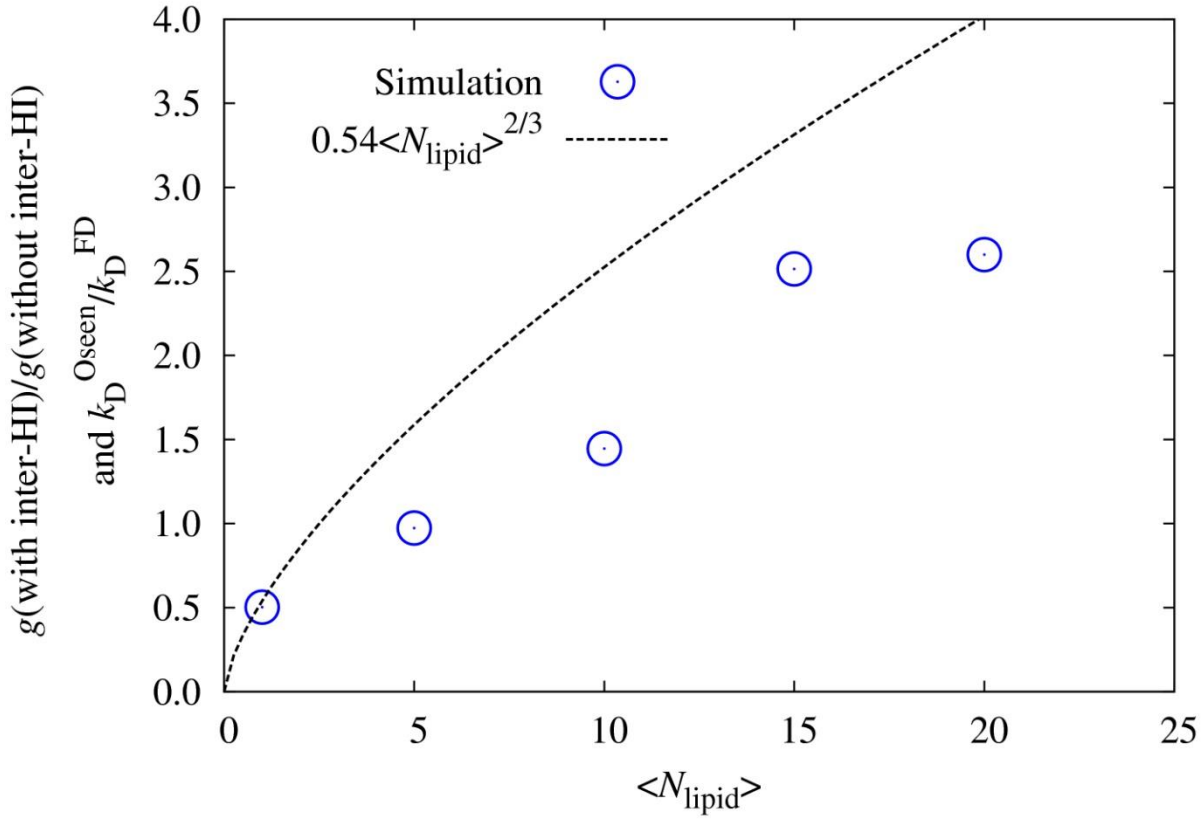
The ratio of the diffusive encounter rate k_D^{Oseen}/k_D^{FD} is given by

$$\frac{k_{\mathrm{D}}^{\mathrm{Oseen}}}{k_{\mathrm{D}}^{\mathrm{FD}}} = 0.54 N^{1-\nu}$$

Zimm theory predicts that $\nu = 1/3$ in poor solvent where polymers collapse into compact conformations. Therefore,

$$\frac{k_{\mathrm{D}}^{\mathrm{Oseen}}}{k_{\mathrm{D}}^{\mathrm{FD}}} = 0.54 N^{2/3}$$

Comparison between theory and simulation



- Note: the units of g and k_D are different. The former has the units of s^{-1} and the latter has units of $mol^{-1}m^3s^{-1}$. Therefore, direct comparison is difficult.
- However, we believe that **our theoretical model can capture an essence of HI effects on membrane self-assembly**.

まとめ

- 複雑な膜形成プロセスの、ほんの一部分だけかもしれませんが、その背景にある物理化学的なエッセンスを理論的に記述することができたので、個人的に気に入っている仕事です。（既にある理論を組み合わせただけですが、、、）

- このような解析は、モデルを“粗視化”しないとできない！

最後に

粗視化モデリング・シミュレーションの個人的な考え

- 最近、生命系シミュレーションの分野では、“粗視化”という言葉をよく聞くようになりました。

- そして、ほとんどの論文で、“粗視化　＝　自由度を低くし、長時間シミュレーションを可能にする”、としているようです。

- 確かにそうですが、私の中では、“粗視化　＝　複雑な現象から本質的な部分を抜き出す作業”と考えて、日々研究をしています。

良い言葉が出てこないので、偉い方のお言葉をお借りしました。

Tarmer Schlick著　Molecular Modeling and Simulation: An Interdisciplinary Guide（Springer）からの文章

I often remind my students of Pablo Picasso's statement on art: "*Art is the lie that helps tell the truth*". This view applies aptly to biomolecular modeling.

<途中省略>

The key in modeling is to develop and apply models that are appropriate for the questions being examined with them.

Make everything as simple as possible, but not simpler.
Albert Einstein

しかし、これが一番難しい。。。

ありがとうございました。