新規粗視化分子動力学法による微小管核形成過程の包括的理解

EX25305

Elucidation of microtubule nucleation using novel coarse-grained molecular dynamics simulation

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Introduction

- Microtubules are indispensable cytoskeletal polymers that underpin numerous cellular activities. Each microtubule is assembled from α/β-tubulin heterodimers, whose exchangeable nucleotide-binding site carries either GTP or GDP.
- Microtubule is formed in two sequential steps—**nucleation followed by elongation**. Also, two mechanistically distinct nucleation modes have been identified.
- Because nucleation is thermodynamically unfavorable, it is the rate-limiting of microtubule formation; yet it remains less explored experimentally and computationally.
- Here, we employ a **newly developed coarse-grained molecular dynamics (MD)** framework that we created to enable long-timescale, many-molecule simulations that are inaccessible to conventional all-atom MD. Using this approach, we aim to achieve a unified mechanistic picture of both spontaneous and template-based nucleation.
- Elucidating the molecular details of microtubule nucleation will lay the groundwork for future investigations into how macromolecular crowding, cellular context, and disease-related mutations modulate nucleation efficiency.

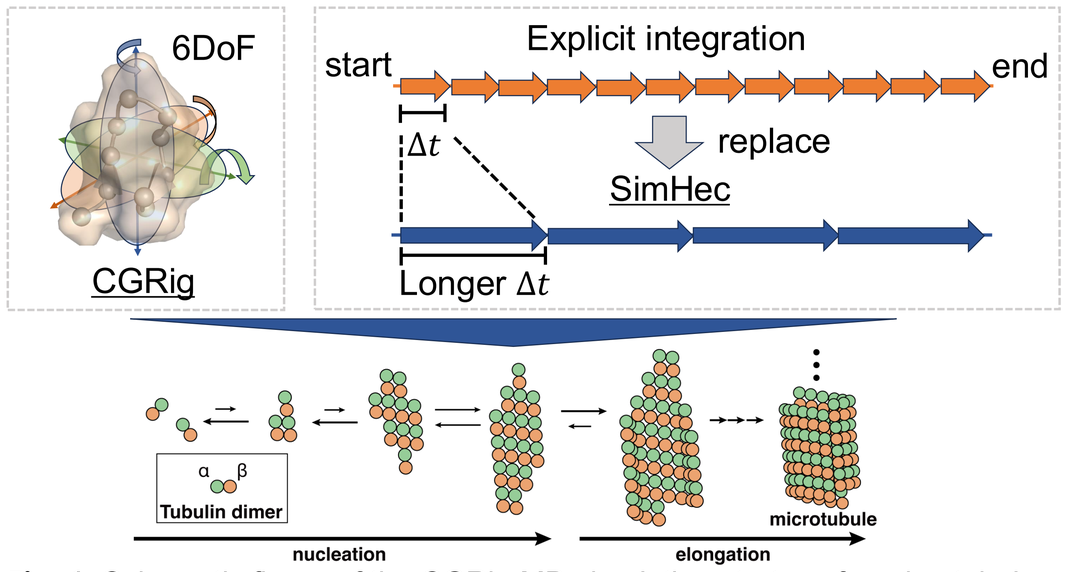


Fig. 1: Schematic figure of the CGRig MD simulation strategy for microtubule.

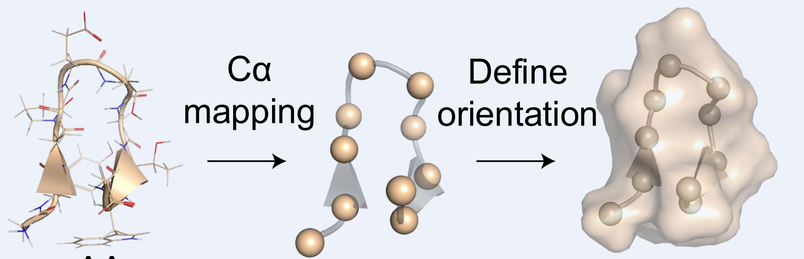
Methods

Modeling

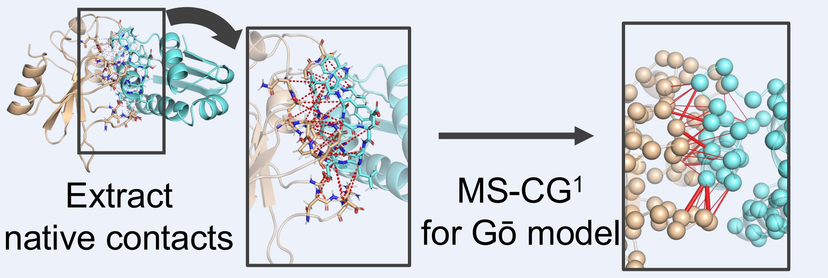
All-atom (AA) MD simulation

Time	500 ns
Force field	Amber ff19SB
Temperature	303.15 K

Hierarchical clustering



Interaction potential



$$U(\boldsymbol{r}) = \sum_{\text{native}} -\frac{\epsilon_{ij}}{2}\left(1+\cos\left(\frac{r_{ij}-r_0}{r_c-r_0}\pi\right)\right) + \sum_{\text{nonnative}} \frac{\varepsilon}{2}\left(1+\cos\left(\frac{r_{ij}}{\sigma_{ij}}\pi\right)\right)$$

r_0 : ref. distance

Optimized by MS-CG

Sum of the residue radius

[1]: Izvekov et al., 2005

SimHec

Solve overdamped Langevin equation:

$$\boldsymbol{A}\Delta\boldsymbol{R} = \boldsymbol{F}(\boldsymbol{R}(t)) + \boldsymbol{\Xi}(t)$$

$$\frac{1}{\Delta t}\boldsymbol{G} + \boldsymbol{P}(\boldsymbol{R}(t))$$

Corrected Hessian

$$\boldsymbol{P} = \sum_{e\in E_P} \boldsymbol{h}_e^+,$$

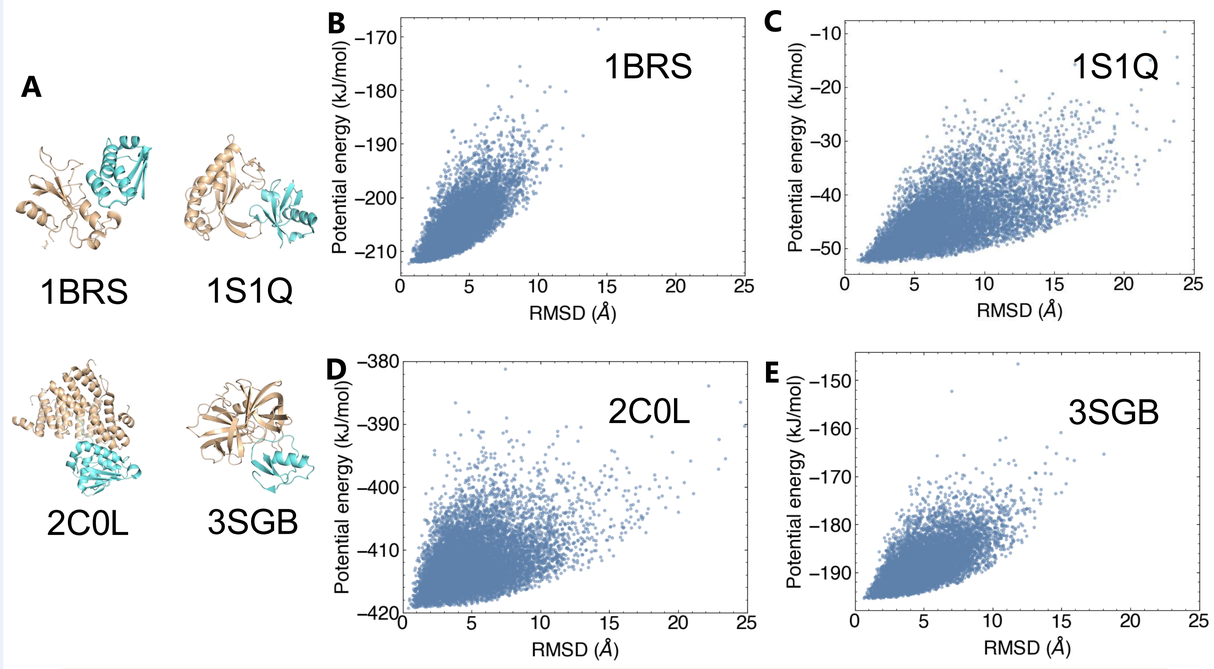
$$\boldsymbol{h}_e^+ = \max\left(\ddot{\varphi}_e\left(r_{ij}\right),0\right)\begin{bmatrix} \boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} & -\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} \\ -\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} & \boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij}\end{bmatrix} + \max\left(\frac{\dot{\varphi}_e\left(r_{ij}\right)}{r_{ij}},0\right)\begin{bmatrix} \boldsymbol{I}-\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} & -\boldsymbol{I}+\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} \\ -\boldsymbol{I}+\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij} & \boldsymbol{I}-\boldsymbol{e}_{ij}\otimes\boldsymbol{e}_{ij}\end{bmatrix}$$

Consider rotation:

$$\left(\frac{1}{\Delta t}\boldsymbol{G}_{\mathrm{r}} + \boldsymbol{P}(\boldsymbol{Q}(t))\right)\Delta\boldsymbol{Q} = \tau(\boldsymbol{Q}(t)) + \Xi_{\mathrm{r}}(t)$$

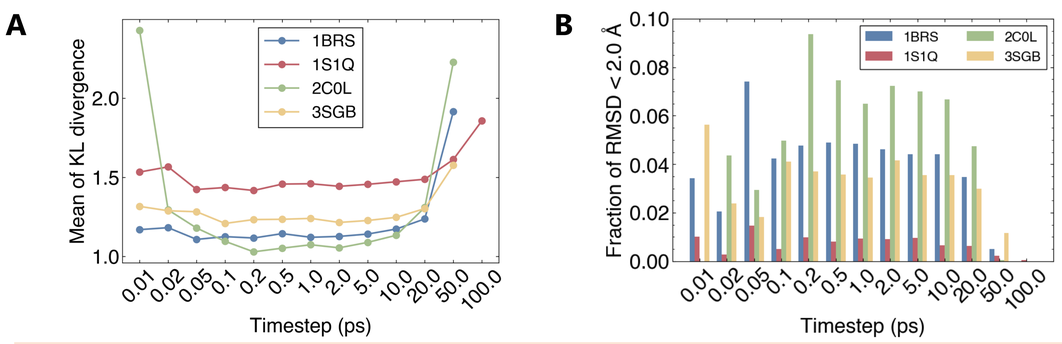
[2]: Washio et al., 2021

Results



Converged on the representative structure properly in all cases.

Fig. 2: Potential evaluation; (A) Tested complexes. (B)-(E) Potential energy distribution by center-of-mass (COM) distance and root mean squared deviation (RMSD). (B) refers to 1BRS, (C) refers to 1S1Q, (D) refers to 2C0L, and (E) refers to 3SGB. It also showed the minimum energy point in the sampled structural ensemble.



Timestep for explicit integration would be allowed $\Delta t \leq 2.0$ ps.

Fig. 3: Timestep evaluation for the explicit integration; (A) The Kullback-Leibler (KL) divergence change by timestep. (B) The structural deviation by timestep.

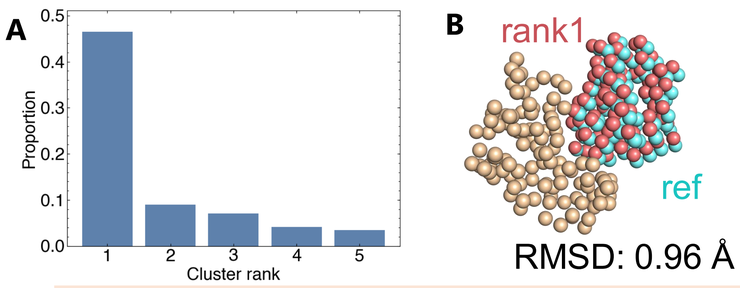


Fig. 4: Blind docking for 1BRS by implicit integration; (A) The proportion of the top 5 clusters for all snapshots by gromos clustering. (B) The representative structure of the rank1 cluster.

Implicit integration scheme could also converge on the reference pose.

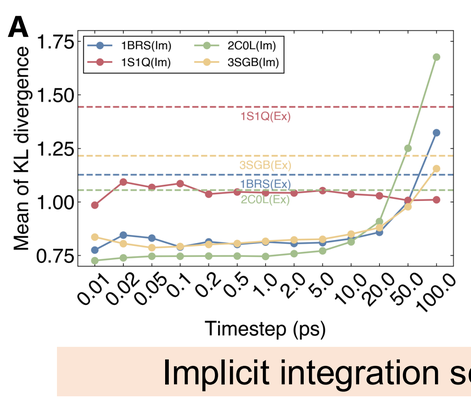
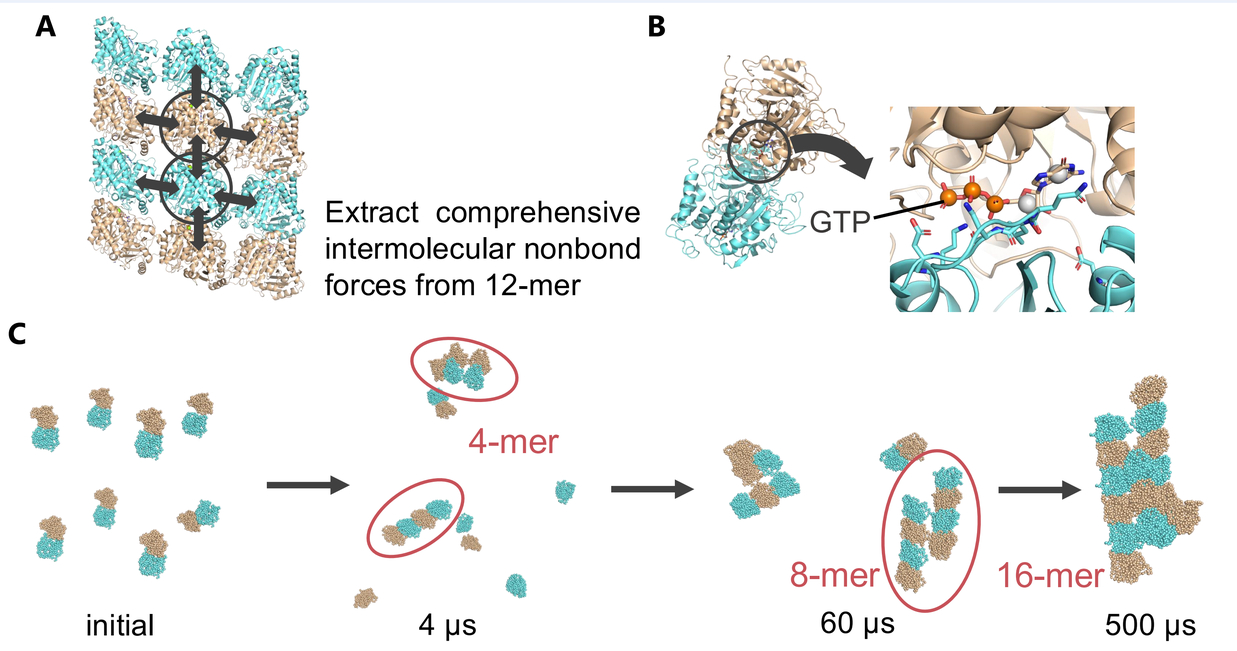


Table. 1: Performance evaluation for implicit integration

System	1BRS	1S1Q	2C0L	3SGB
Timestep	50 ps	100 ps	20 ps	100 ps
Relative calc. cost	9.0	11.0	12.3	7.8
Speedup	2.78	4.55	0.81	6.41

Implicit integration scheme enabled -6.4x faster simulation.

Fig. 5: Timestep evaluation for implicit integration; (A) The KL divergence change by timestep. The dashed line shows the value in explicit integration with 2.0 ps as timestep.



Our method could reproduce microtubule nucleation process.

Fig. 6: Application for tubulin nucleation process; (A) The system used in reference AA MD simulation. (B) Modeling scheme for GTP. GTP was represented by five beads. (C) MD simulation for 8 tubulin dimers. They formed characteristic intermediate oligomers.

Future work