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Protein-Protein Association Free Energy From ReaDDY Simulation

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Abstract

Simulating the conditions and various processes occuring inside a biological cell is still a formidable task due to the high concentration of macromolecules present. In a systematic approach to study the Protein-Protein association reactions in cellular conditions, a particle based simulation strategy is used. A Reaction Diffusion Dynamics method is employed using ReaDDy to simulate the diffusive behaviour of the proteins and crowders taken as spherical beads with size equal to their hydrodynamic radii. Harmonic repulsive and Lennard-Jones interactions are given between the proteins and crowders to understand the effect of interactions on the free energy change of Protein-Protein associations in presence of crowders. Protein-Protein association reaction events can occur with certain rates, if they come within the reaction radius. Crowders are filled within the simulation box with different volume fractions upto 0.35 to simulate the physiologically relevent concentrations inside the cell. For a prolonged simulation of proteins and crowders, we observed many association and dissociation events. Free energy change of the association in presence of crowders is then obtained from the number of frames of the dimer state and the monomer state in presence and absence of crowders. Theoretical model such as Scaled particle theory is used to compare the results from the simulation. The observed simulation results for harmonic repulsive interaction agrees with the theoretical estimate.

Introduction

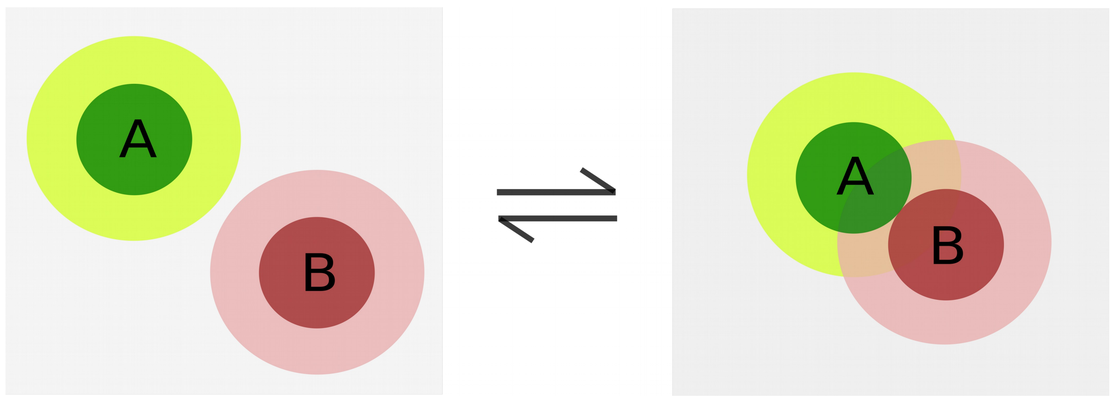

Figure 1. Dimerization reaction of Spherically modelled proteins A and B

Methods

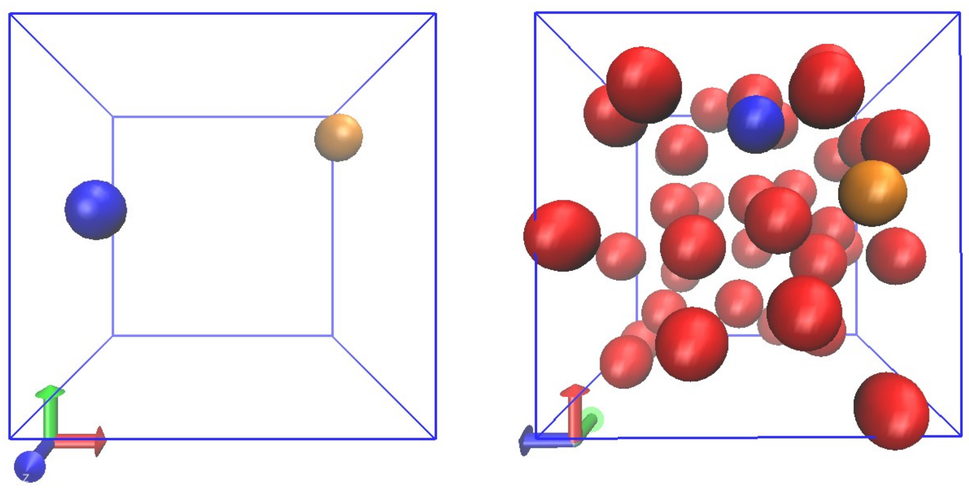

Figure 2. Visualization of ReaDDy simulation box containing two proteins and crowders at volume fraction Φ

Particle motion is governed by the stochastic differential equation,

$$\frac{\mathrm{d}\mathbf{x}_i(t)}{\mathrm{d}t} = -\frac{D_i(T)}{k_B T}\mathbf{f}_i(t) + \sqrt{2D_i(T)}\boldsymbol{\xi}_i(t)$$

Association and dissociation rates:

$$\lambda_{\mathrm{off}} = k_{\mathrm{off}} \qquad \lambda_{\mathrm{on}} = \frac{k_{\mathrm{on}}}{V_{\mathrm{eff}}} \qquad V_{\mathrm{eff}} = \int_0^R \exp(-\beta U) 4\pi r^2 \mathrm{d}r$$

Equilibrium constant K_a can be obtained from dimer and monomer state probabilities(P_1 and P_0 respectively) as,

$$K_a = \frac{P_1}{P_0} c^{\varnothing} N_{Av} v$$

Change in free energy change of association,

$$\Delta\Delta F_{2A} = \Delta F^{\varphi}_{2A} - \Delta F^{0}_{2A}$$

$$\Delta\Delta F_{2A} = -k_B T \ln(K_a^{\varphi}/K_a^{0})$$

Simulation details

Table 1. ReaDDy simulation details

Box Size (nm^3)	(15x15x15)
Temperature (K)	300
R_A (nm)	1.35
R_{2A} (nm)	1.70
Microscopic association rate (ns^{-1}), λ_{on}	0.1338
Microscopic dissociation rate (ns^{-1}), k_{off}	0.0003342

Results

From the number of dimer and monomer frames, we calculated the standard association free energy using ReaDDy

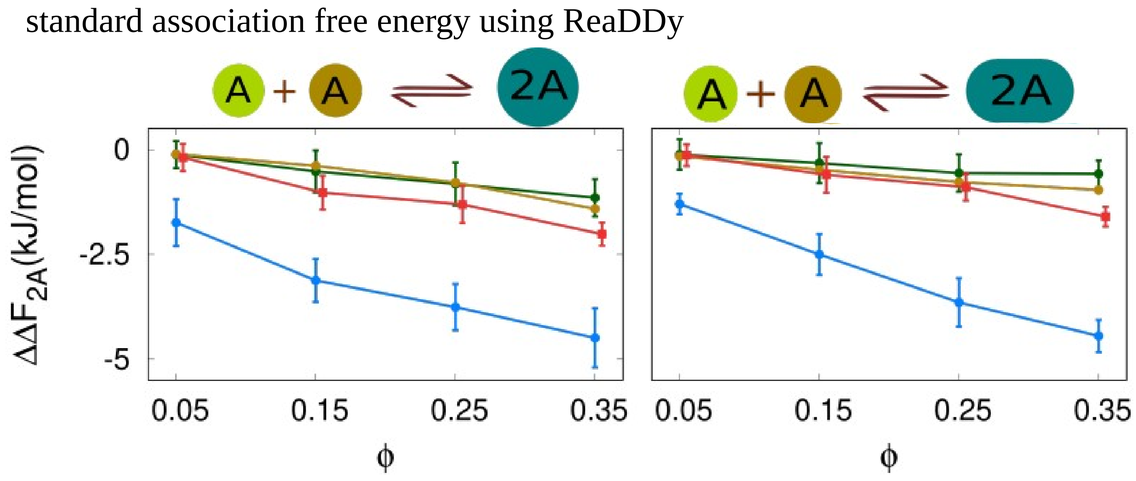

Figure 3. $\Delta\Delta F_{2A}$ (kJ/mol) vs. φ**.** Colors: HR (Harmonic repulsion (Green)), SPT (Scaled Particle Theory (Yellow)), LJ (Lennard-Jones (ε = 2.5k J/mol (Red) and ε = 5.2kJ/mol (Blue)).

Table 2. $\Delta\Delta F_{2A}$ (kJ/mol) vs. Φ with different interactions between proteins and crowders.

A + A ⇌ 2A

($\Delta\Delta F_{2A}$ (kJ/mol))				
φ	SPT	HR	LJ (ε = 2.5kJ/mol)	LJ (ε = 5.2kJ/mol)
0.05	-0.10	-0.12	-0.19	-1.74
0.15	-0.38	-0.51	-1.02	-3.12
0.25	-0.78	-0.81	-1.30	-3.75
0.35	-1.41	-1.14	-2.01	-4.48

A + A ⇌ 2A

0.05	-0.16	-0.11	-0.13	-1.29
0.15	-0.48	-0.32	-0.60	-2.50
0.25	-0.77	-0.55	-0.89	-3.64
0.35	-0.96	-0.57	-1.60	-4.44

Conclusion

- The $\Delta\Delta F_{2A}$ values from the simulation with harmonic repulsive potential agrees well with the theoretical SPT model.
- Stability increases with increase in volume fraction of crowders.

References

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[3] Hoffmannitz, et al. "ReaDDy 2: Fast and flexible software framework for interacting-particle reaction dynamics." PLoS computational biology 2019, 15