Applications of the TIGER2hs Replica Exchange Algorithm

Supramolecular host-guest recognition and binding free energy estimation of cyclodextrin inclusion complexes via enhanced sampling molecular dymanics

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In Short

- Host-guest recognition of cyclodextrin inclusion complexes with small organic molecules is vital in pharmaceutical sciences
- Enhanced sampling and binding free energy calculations will enable customization of inclusion complexes
- Comparison of molecular dynamics simulations and temperature replica exchange with TIGER2hs algorithm will be performed

Introduction Cyclodextrins (CDs) are cyclic oligosaccharides that can accommodate guest molecules such as poorly water-soluble drugs. While polar substances like glucose are highly soluble in water, they are unable to penetrate cell membranes by diffusion. Drug substances typically have to be more lipophilic in order to reach their target and thus tend to be less soluble in aqueous phases. This lack of solubility is a serious issue that can be addressed by CD inclusion complexes. For this reason, they are widely used and extensively studied in different areas like in food and pharmaceutical industries, as well as in analytical or polymer chemistry. The α-D-glucopyranose subunits are connected by 1,4 glycosidic bonds with ring sizes ranging from six (CD6) to 35 monomers in CD35. Depending on the number of chain links, the geometric shape of CD cavities is similar to a cavernous truncated cone (CD5-7) or torus (> 7) with varying degree of distortion.

Inclusion Complexes The hydrophobic cavity is suitable for the inclusion of small organic molecules. During the process of complexation in aqueous media, the less polar groups of the guest ligand displace the water molecules, which is mainly driven by van der Waals (vdW), hydrophobic interactions and to some extent (depending on the ligand) hydrogen bonding or steric effects (figure 1).

Cyclodextrin inclusion complexes are of high practical value and at the same time excellent models for molecular recognition. Due to their small size and restricted degrees of freedom through cyclization, convergence can be archieved fast and reliably. Because of their importance, especially in drug delivery systems, a vast number of cyclodextrins with various modifications, derivatizations and their corresponding host-guest complexes, are extensivly characterized by calorimetric and spectroscopic measurements.

Molecular Docking One method to study the interaction of ligand molecules and their host or receptor structure is molecular docking. It has been applied successfully in virtual screening or drug design projects. These calculations are fast and much easier to setup than atomistic physics-based simulations but have major disadvantages for understanding the physical driving force or the separation of enthalpic and entropic contributions. While incorporating conformational flexibility is possible in modern docking software packages, the sampling is based on statistical models and is not exhaustive

Molecular Dynamics Simulations Molecular dynamics simulations have been proven to be a useful technique to simulate biological processes and other dynamic systems. But due to sometimes large energy barriers between varying states, molecular dynamics simulations are easily trapped in local minima und do not converge even after micro- or milliseconds of simulation time. Especially in binding process of complex systems (e.g. protein-ligand interactions), large structural fluctuations in intermediate states of the binding path way are infeasible within the simulation time.

Enhanced Sampling Methods Various methods like replica exchange molecular dynamics (REMD), metadynamics or simulated annealing have been developed and extensively extended to overcome energy barriers and accelerate the simulation.

REMD One of the most used enhanced sampling methods are replica exchange simulations (also known as parallel tempering), especially with temperature exchange. The system of interest is simulated at different temperatures simultaneously and exchange attempts are performed after a defined number of time steps based on a Metropolis criterion. Depending on the force field used for simulation, they are very accurate and exhaustive but also

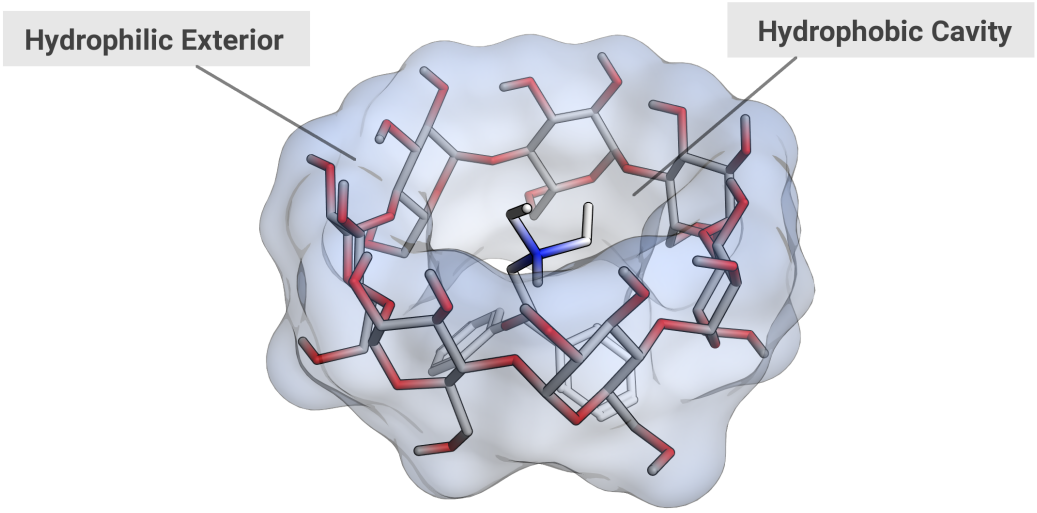

Figure 1: *Inclusion complex of β-Cyclodextin (CD7) and Diphenhydramine, an antihistamine drug.*

computationally demanding because a large number of replicas with small temperature differences are necessary for meaningful exchange rates and thus convergence if explicit solvation is used. Applying implicit solvation archieved great popularity but the results are often inaccurate due to the lack of explicit hydrogen bonds, viscosity and entropic effects (hydrophobic effect).

TIGER2hs We have developed TIGER2hs (Temperature intervals with global exchange of replicas and hybrid solvent) as an improved version of TIGER2A and TIGER2h. It combines the idea of global replica exchanges with a hybrid solvent approach to overcome costly averaging phases in TIGER2A. All replicas are cooled down to the baseline temperature after a sampling periode and the energy is calculated with the first two water shells around the solute in implicit solvent (hybrid solvent). Therefore only bulk properties of the solvent have to be described by the continuum model. The computational resources can be freely chosen because a fine grained temperature distribution like in REMD is not necessary. The method and related results have been submitted to Journal of Physical Chemistry B and are currently under review.

Objective As previously outlined, cyclodextrin inclusion complexes are excellent model systems for studying host-guest recognition processes with a massive amount of experimental data available. TIGER2hs was only successfully applied to protein folding till now and this project will be a proof of concept to investigate different application areas. The algorithm was adjusted to effectively sample more than one connected molecule. The effect of explicit solvation and reorganization will be part of our investigations. The results and approvements will be transferred to other systems in future projects.

More Information

[1] T. Loftsson et al., *J Pharm Pharmacol* **62**, 1607–1621 (2010). doi:10.1111/j.2042-7158.2010.01030.x

[2] S. Saha et al., *Scientific Reports* **6**, (2016). doi:10.1038/srep35764

[3] L. Wickstrom et al., *JCTC* **9**, 3136–3150 (2013). doi:10.1021/ct400003r

[4] M.V. Rekharsky et al., *Chemical Reviews* **98**, 1875–1918 (1998). doi:10.1021/cr970015o

[5] X. Li et al., *J Chem Phys* **143**, 144105 (2015). doi:10.1063/1.4932341

[6] D.J. Earl, M.W. Deem, *Phys Chem Chem Phys* **7**, 3910–3916 (2005). doi:10.1039/B509983H

[7] M. Kulke et al., *J Phys Chem B* **122**, 7295–7307 (2018). doi:10.1021/acs.jpcb.8b05178

[8] V. Salmaso et al., *Front Pharmacol* **9**, (2018). doi:10.3389/fphar.2018.00923

[9] J.C. Phillips et al., *J Comput Chem* **26**, (2005). doi:10.1002/jcc.20289