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Hamiltonian Replica Exchange Molecular Dynamics Using Soft-Core Interactions to Enhance Conformational Sampling

Jozef Hritz and Chris Oostenbrink

Leiden/Amsterdam Center for Drug Research (LACDR), Division of Molecular Toxicology,
Vrije Universiteit, Amsterdam NL-1081 HV, The Netherlands
E-mail: {hritz, c.oostenbrink}@few.vu.nl

We present a novel Hamiltonian replica exchange molecular dynamics (H-REMD) scheme that uses soft-core interactions between those parts of the system that contribute most to high energy barriers. The advantage of this approach over other REMD schemes is the possibility to use a relatively small number of replicas with locally larger differences between the individual Hamiltonians. Because soft-core potentials are almost the same as regular ones at longer distances, most of the interactions between atoms of perturbed parts will only be slightly changed. Rather, the strong repulsion between atoms that are close in space, which is in most cases resulting in high energy barriers, is weakened within higher replicas of our proposed scheme.

The presented approach leads to a significant enhancement of conformational sampling both for the smaller molecules GTP and 8-Br-GTP in explicit water and for residue Phe483 within the catalytic site of CYP2D6 in complex with its substrate MAMC.

1 Introduction

Replica exchange molecular dynamics (REMD) has shown a tremendous impact in the field of biomolecular simulation. While temperature REMD (T-REMD) is mostly used to enhance conformational sampling of larger systems in implicit solvent, Hamiltonian REMD (H-REMD) is also suitable for simulations in explicit solvent. However, it is not always trivial to find a perturbation of the Hamiltonian which leads to enhanced conformatioinal sampling.

Here we present a H-REMD scheme using soft-core interactions[1] which is particularly suitable for the enhanced sampling of selected flexible parts of systems in which the energy barrier between different conformations is high due to strong non-bonded repulsions. The barriers are lowered by weakening the interactions using soft-core interactions given by eq. (1):[2]

$$V_{LJ} = \left(\frac{C12}{\alpha C12/C6\lambda^2 + r^6} - C6 \right) \frac{1}{\alpha C12/C6\lambda^2 + r^6} \tag{1}$$

All simulations were performed using GROMOS05[3] and the GROMOS 53A6 force field.The REMD efficiency was significantly increased by allowing multiple replicas to run at the highest softness level. Values of other softness levels were optimized by mimicked REMD to maximize the number of global conformational transitions.[4]

2 REMD of GTP and 8-Br-GTP

We have tested the new protocol on the GTP and 8-Br-GTP molecules in explicit solvent, which are known to have high energy barriers between the anti and syn conformation of the

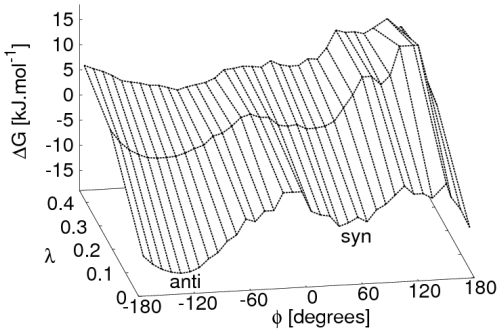

Figure 1. Potential of mean force along the glycosidic bond of GTP, as function of the softness parameter λ.

base with respect to the sugar moiety. During two 25 ns MD simulations of both systems the transition from the more stable to the less stable (but still experimentally observed) conformation is not seen at all. Also T-REMD over 50 replicas for 1 ns did not show any transition at room temperature. On the other hand, more than 20 of such transitions are observed in our new H-REMD scheme using 6 replicas (at 3 different Hamiltonians) during 6.8 ns per replica for GTP and 12 replicas (at 6 different Hamiltonians) during 7.7 ns per replica for 8-Br-GTP. The soft-core interactions were applied for the non-bonded base-sugar interactions in GTP and 8-Br-GTP.

The calculated population of GTP in the anti conformation was 95.6% $\pm$ 0.5% and 6.0% $\pm$ 1.8 % for 8-Br-GTP.[1] These values are in very good agreement with results coming from thermodynamic integration using a hidden dihedral angle restraint around the glycosidic bond. The observed inverse character for GTP and 8-Br-GTP is also in agreement with NMR estimates for anti/syn populations. Dihedral angle distributions around the glycosidic bond were also used to generate the potential of mean force (Fig. 1). From this figure it can be seen that the energy barrier as well as the free energy difference between the anti and syn conformation is decreasing with increasing softness. This leads to an increased number of conformational transitions at these levels of softness.

3 REMD of Phe483 within CYP2D6

Cytochromes P450 (CYPs) are heme-containing enzymes that can be found in virtually all organisms. CYP2D6 is one of the most crucial isoforms involved in the drug metabolism of humans. Mutagenesis experiments confirm importance of Phe483 in substrate binding. Its conformation is however quite unclear as it is positioned in a rather flexible loop region inside the catalytic site of CYP2D6. Several computational studies indicate that multiple Phe483 sidechain conformations are occuring. 10 ns of CYP2D6 MD simulations in complex with several ligands revealed only very few transitions for Phe483 between conformations corresponding to $\chi^1 = 70^\circ$ and $\chi^1 = 170^\circ$. Visual inspection indicates

that the corresponding energy barrier is mostly due to the repulsion between the Phe483 and Leu224 side-chains together with the dihedral angle term around χ^1. Therefore enhanced conformational sampling by H-REMD using soft-core interactions was performed for Phe483 within CYP2D6 in complex with the MAMC substrate in which the force constant for the χ^1 dihedral angle term was additionally decreased towards zero with increasing softness. When softness was applied only for the interactions between the sidechains of Phe483 and Leu224 no enhanced sampling was observed. Rather, the sidechains moved closer in space and a high energy barrier remained. On the other hand, when softness was applied for all interactions involving the Phe483 sidechain and the rest of the protein or MAMC, the barrier was significantly lowered. We observed 9 global conformational transitions within 1 ns of H-REMD using 8 replicas. These preliminary (not fully converged) simulations reveal that the conformation of Phe483 with $\chi^1 = 70^\circ$, as it is observed in the (apo) crystal structure is present for only 15% of the time when MAMC is bound in the active site. Interestingly, χ^1 had value $\sim 170^\circ$ in the homology model of CYP2D6 in complex with the codein, which was constructed in our group before crystal structure was released.

4 Concluding Remarks

We have developed a H-REMD scheme using soft-core interactions[1] and implemented it into the GROMOS05 package. Its high conformational sampling efficiency is shown for GTP and 8-Br-GTP as well as for Phe483 within the CYP2D6/MAMC complex. The high efficiency is obtained thanks to the fact that only those parts of the Hamiltonian are perturbed which contribute most to high energy barriers. Another efficiency gain was obtained by using a degenerate highest softness level and the optimal H-REMD settings obtained from optimization by REMD mimicking.[4]

Acknowledgments

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