On the faithfulness of molecular mechanics representations in multi-scale free energy simulations

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1 Introduction

Computer simulations are an indispensable tool in the drug development process to predict binding free energies, solubilities, and membrane permeability of drug candidates. Although the targets are very different, all free energy simulations share some common features and challenges. The two fundamental prerequisites for the determination of free energies are the *accurate description of inter- and intramolecular interactions*, and the *adequate sampling of all relevant microstates*. These two requirements are in conflict with each other, since a more sophisticated description of molecular interactions entails an increase of the computational costs, which inhibits the capability to search through a multitude of different possible conformations. In terms of the balance between those two requirements, one can distinguish two major classes of computational methods: a) classical force fields based on molecular mechanics (MM), which are fast and well suited for sampling, but involve approximations that limit their reliability b) quantum-mechanical methods (QM), which are based on molecular orbital calculations and combine a heavy computational burden with highly accurate interaction strengths.

To reconcile the conflict between the computational costs of sampling on the one hand and physical faithfulness on the other hand, it is possible to resort to a multi-scale approach that employs an MM representation to perform the sampling, followed by post-processing of the MM trajectory with a QM Hamiltonian to obtain the correct ensemble. This approach has led to significantly improved results in the recent past,(1–3) however there are several cases where the multi-scale approach fails to converge. This can be explained by the disparity of the respective energy surfaces. If the MM energy surface is not representative for the QM energy surface, most samples will lie in high energy areas of phase space, and, therefore, only marginally contribute to the free energy result.

Since there is a connection between the phase space overlap and the associated entropy difference, it is difficult to predict problematic cases *a priori*. However, by using

linear response theory and taking loans from Marcus theory, it is possible to roughly estimate the expected phase space overlap via the reorganization energy (ΔU_{reorg}, c.f. Figure 1). Thus, the expected variance of a free energy estimate with the Zwanzig equation (in reduced units of $k_B T$) is given by

$$\sigma^2_{Zwanzig} \approx \frac{e^{2\Delta U_{reorg}} - 1}{n}, \tag{1}$$

where n represents the number of independent potential energy difference samples.(4)

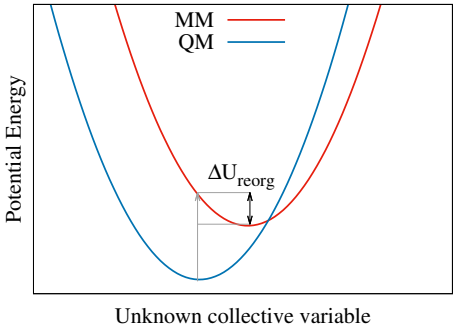

Figure 1: A simple metric for the convergence of a multi-scale free energy calculation between a molecular-mechanical representation (MM) and a (real) quantum-mechanical system (QM) is the reorganization energy based on Marcus Theory (ΔU_{reorg}). It is characterized by the potential energy difference within the MM potential energy surface between the QM-optimized structure and the MM-optimized structure.

Vice versa, reorganization energies can also be employed to assess the quality of MM force fields for solubility and binding calculations. We illustrate this for N-acteyl-alanine-methylamide, and N-acteyl-serine-methylamide, using the CHARMM36 force field as the MM representation, and BLYP/6-31G(d), as well as M06-2X/6-31G(d), as the QM target Hamiltonians.

2 Methods

All MM calculations were carried out with CHARMM, and QM/MM calculations were conducted with Q-Chem, using the CHARMM/Q-Chem interface. The initial backbone coformations of N-acteyl-alanine-methylamide, and N-acteyl-serine-methylamide were generated by using harmonic restraints with a force constant of 100 kcal$\mathring{A}^{-2}$, with equilibrium torsion angles of $\phi = -135°$,$\psi = 135°$ for the β-sheet structure, $\phi = -60°$,$\psi = 150°$ for the $PP2$-helix, $\phi = -60°$,$\psi = -40°$ for the α-helix, and $\phi = 60°$,$\psi = 40°$ for the left-handed-helix with 150 steps of Adopted Basis Newton-Raphson energy minimization. The QM-optimized structures were then generated with 500 steps of Adopted Basis Newton-Raphson energy minimization. For the determination of the MM-optimized structure, the QM-optimized structures were minimized again

for 500 steps with the CHARMM36 force field. For the structures in aqueous solution, 1683 TIP3P water molecules were added and simulated for 0.1 ns with constant pressure and a time step of 1 fs. The simulations in aqueous were repeated eight times with different initial conditions to generate different solvent structures. The reorganization energies for aqueous solution in Table 1 are averages of energy minimizations based on those eight different solvent structures.

3 Results and Discussion

Table 1: Reorganization energies between MM and QM (ΔU_{reorg}) for the CHARMM36 force field, including the contributions from different energy terms. Two target QM Hamiltonians are used (BLYP/6-31G(d) and M06-2X/6-31G(d)), and each comparison was performed once the in the gas phase and once in aqueous solution using QM/MM with TIP3P water. Four different backbone conformations are considered: β sheet, $PP2$ helix, α helix and left-handed helix (left-h. helix). Due to the omission of some energy terms (e.g., dihedral and CMAP terms), the contributions do not necessarily add up to 100%. All data in kcal/mol.

		Alanine					**Serine**			
Structure	ΔU_{reorg}	Bond[a]	Angle[b]	Elec[c]	vdW[d]	ΔU_{reorg}	Bond	Angle	Elec	vdW
Gas phase BLYP/6-31G(d)										
β sheet	10.0	44%	16%	7%	12%	8.6	48%	15%	7%	6%
$PP2$ helix	7.5	63%	15%	1%	13%	6.0	75%	18%	-2%	0%
α helix	10.0	48%	11%	11%	9%	6.0	76%	18%	-2%	-2%
left-h. helix	14.2	33%	-13%	3%	56%	9.0	50%	5%	6%	2%
Gas phase M06-2X/6-31G(d)										
β sheet	4.1	44%	6%	18%	15%	6.6	25%	12%	29%	4%
$PP2$ helix	4.4	46%	-6%	17%	22%	3.9	42%	2%	29%	12%
α helix	4.7	44%	-3%	14%	21%	3.9	42%	0%	32%	12%
left-h. helix	3.7	54%	0%	31%	5%	8.6	20%	-5%	42%	3%
Aqueous phase BLYP/6-31G(d)										
β sheet	5.4	74%	-5%	22%	-1%	6.4	67%	8%	22%	0%
$PP2$ helix	6.0	64%	-13%	38%	-5%	6.7	61%	0%	38%	-14%
α helix	5.9	67%	-5%	27%	-14%	6.7	64%	8%	27%	-18%
left-h. helix	6.0	73%	-20%	39%	-6%	6.2	73%	-9%	39%	-12%
Aqueous phase M06-2X/6-31G(d)										
β sheet	4.1	46%	-12%	42%	10%	8.7	19%	-4%	2%	126%
$PP2$ helix	5.6	32%	-19%	62%	8%	5.4	27%	-11%	17%	134%
α helix	5.3	34%	-12%	54%	-1%	3.0	49%	-13%	57%	113%
left-h. helix	6.2	33%	-26%	72%	7%	6.6	26%	-17%	9%	136%

[a] Contribution to ΔU_{reorg} based on mismatches of the bond lengths in % [b] Contribution to ΔU_{reorg} based on mismatches of the bond angles in % [c] Contributions to ΔU_{reorg} based on electrostatic interactions in % [d] Contributions to ΔU_{reorg} based on Lennard-Jones interactions in %

The high reorganization energies for alanine and serine (on average 6.4 kcal/mol, see second and seventh column in Table 1) show that use of MM trajectories for reweighting to QM energy surfaces is likely to yield high variances and low precision here. A surprising result in both gas phase and aqueous solution is the dominance of discrepancies due to the bonded structure of the MM force field (on average 49%), rather than differences that arise from non-bonded interactions (on average 25% for electrostatics and 20% for

van der Waals interactions). On average, each bond length of the MM-optimized structure deviates by about 0.018 Å from the QM-optimized structure, which adds up to the observed discrepancies. This holds true for several backbone conformations and both evaluated QM methods. Notably, the optimal bond length depends on the exact details of the QM method, such as the amount of Hartree-Fock exchange in Density Functional Theory (e.g., the average ΔU_{reorg} for the pure functional BLYP is 7.5 kcal/mol, while for the hybrid functional M06-2X it is 5.3 kcal/mol).

This is a clear indicator that the currently employed "one-size-fits-all" approach of bond length parametrization is inadequate for multi-scale free energy calculations. The changes of the bonded structure due to the response to the electrostatic environment between the different phases is most likely not adequately described in this formalism. Such deviations of the MM force field from the target QM function should be corrected by adjusting the bonded parameters based on the target QM function and the phase under consideration in a custom-fit approach for each individual bond.(5) This would entail that currently employed thermodynamic cycles have to be complemented with legs that consider the changes of the bonded structure between the phases, but this can be straightforwardly implemented by employing a free energy calculation between the dummy end states of the different legs based on post-processing.

A striking result are also the high contributions of the van der Waals interactions to the ΔU_{reorg} of serine in aqueous solution with M06-2X (last section of Table 1) with more than 100%. Those steric clashes are counterbalanced by the grid-based CMAP potential (data not shown). For BLYP, the CHARMM36 van der Waals interactions stabilize the QM structure (indicated by the negative signs). This might be an indicator that the Lennard Jones parameters also should be adapted to the QM target.

4 Conclusions

The results show that the use of multi-scale free energy simulations requires a prior tuning of the bonded terms to the target QM Hamiltonian to improve convergence.

References

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