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A Multiscale Simulation Approach to Modelling Drug-Protein Binding Kinetics

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Supporting Information

Set up for QM/MM to MM FEP simulation

In all our QM/MM to MM FEP simulation, we followed an approach similar to that presented in ref [1]. The method works within a framework called the “Multiscale Monte Carlo” approach which uses Monte Carlo (MC) sampling in combination with the Metropolis-Hasting algorithm. The algorithm approximates a “slow” Hamiltonian such as that employed in a QM/MM description with the simpler, faster Hamiltonian of MM. The fast Hamiltonian is used to guide sampling of the slow Hamiltonian.

In the “Multiscale Monte Carlo” approach, the MC move starts from a chosen reference state (A) and uses both the “slow” (QM/MM) and “fast” (MM) Hamiltonians to calculate the state total energy. MC moves are then repeated within the MM description until an alternative state (B) is reached. The energy of this state is again evaluated with both the QM/MM and MM Hamiltonians (see Fig. S1).

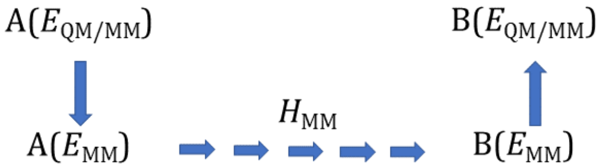

Figure S1: Schematic representation of the “Multiscale Monte Carlo” approach. The simulation starts with an exemplary reference state A whose energy is calculated in both the “slow” and “fast” Hamiltonians. Then the MC moves are carried out using only the “fast” Hamiltonian, and once an alternative state B is reached, its energy is again evaluated both in the QM/MM and in the MM frameworks. The “Multiscale Monte Carlo” simulation runs in several blocks and in each block, a new configurational state is sampled. Here we have shown only one representative step.

As a next step, the move to a new reference state B is accepted with probability

$$P = \min\left\{1, exp^{(\Delta\Delta \mathrm{E}/k_B T)}\right\} \tag{1}$$

Where $\Delta\Delta E = [\Delta E_{\mathrm{QM/MM}}(\mathrm{B}) - \Delta E_{\mathrm{MM}}(\mathrm{B})] - [\Delta E_{\mathrm{QM/MM}}(\mathrm{A}) - \Delta E_{\mathrm{MM}}(\mathrm{A})]$

Further, the correction on the free energy is calculated using the total Hamiltonian (H)

$$H(\lambda) = (1-\lambda)\, H_{\mathrm{QM/MM}} + \lambda H_{\mathrm{MM}} \tag{2}$$

Simulations with different values of λ are run and the correction on the free energies are evaluated with thermodynamic integration (TI) as shown in Eq. 3 and 4.

$$\Delta G_{\mathrm{QM/MM}\rightarrow\mathrm{MM}} = \int_0^1 \left(\frac{\delta G}{\delta\lambda}\right)\, \delta\lambda \tag{3}$$

$$\Delta G_{\mathrm{QM/MM}\rightarrow\mathrm{MM}} = \int_0^1 \langle H_{\mathrm{MM}} - H_{\mathrm{QM/MM}}\rangle_\lambda\, \delta\lambda \tag{4}$$

The λ coordinate is used to scale the QM/MM Hamiltonian to the MM Hamiltonian. The λ=0 state corresponds to a fully QM/MM Hamiltonian whereas λ=1 to a fully MM Hamiltonian. In our calculation, we used a total 8 λ values: 0.0, 0.142, 0.285, 0.429, 0.571, 0.714, 0.857 and 1.0.

Furthermore, to evaluate the final correction free energies, we incorporated the replica exchange scheme within the TI method.[2,3] The Replica Exchange acceptance test is used to make exchanges between the neighboring replicas according to Eq. 5.

$$exp\left[\frac{1}{kT}\left(E_B(j) - E_B(i) - E_A(j) + E_A(i)\right)\right] \geq rand(0,1) \qquad 5$$

Where i and j are the two replicas with energy E_{A} and E_{B}, respectively, and exchanges between these two replicas could only happen if they meet the above criteria. As the λ value increases, H gets closer to the H_{MM}, therefore the rates of the acceptance of the Replica Exchange Monte Carlo moves are also increased. Overall, the implementation of the replica exchange scheme in the TI method across all the λ coordinates enhances QM/MM sampling.

Finally, with this set up, we ran a total 50 Metropolis Hastings Multiscale Monte Carlo moves per lambda value, with a replica exchange test attempted between pairs of lambda values after every move. This corresponded to a total of 2.5 M MC moves in the MM Hamiltonian per lambda window, and 50 QM energies per lambda window. In total, over 8 lambda windows, this corresponded to 20 M MM MC moves, and 400 QM energy evaluations.

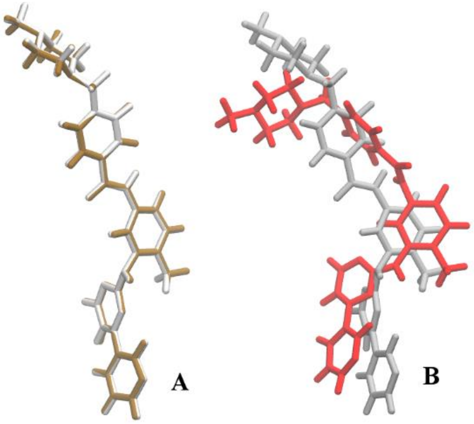

Figure S2: The ligand conformation sampled in the Monte Carlo simulation. On the left, the conformation sampled in both the QM/MM (light gray) and MM (brown) level in the bound state. On the right, the conformation sampled in the bound (light gray) and in the unbound solvent (red) state at the QM/MM level.

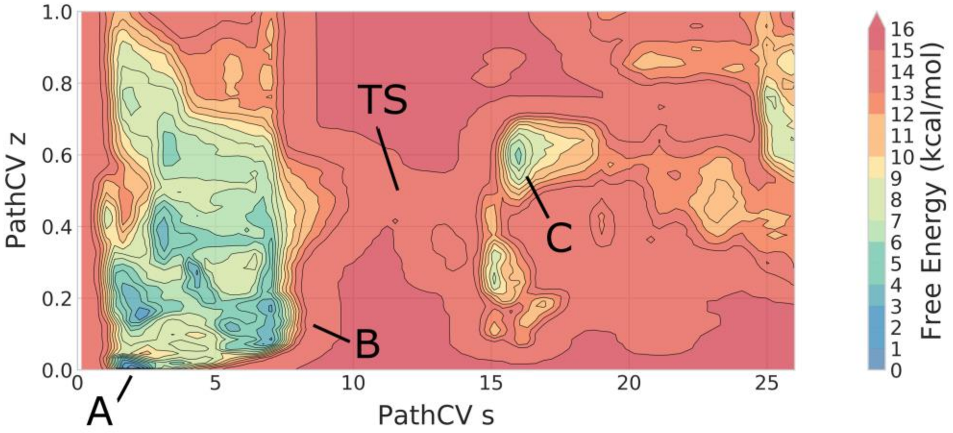

Figure S3: Two-dimensional binding free energy surface obtained with Metadynamics and the MM force-field. On the x-axis is the progression along the path as described by the first PathCV (s), while on the y-axis is the distance from the reference structures, the second PathCV (z). The relevant areas as discussed in the main manuscript are also labeled. Free energy isolines are shown every kcal/mol.

References

(1) Woods, C. J.; Manby, F. R.; Mulholland, A. J. An Efficient Method for the Calculation of Quantum Mechanics/molecular Mechanics Free Energies. *J. Chem. Phys.* **2008**, *128* (1).

(2) Woods, C. J.; Essex, J. W.; King, M. A. Enhanced Configurational Sampling in Binding Free-Energy Calculations. *J Phys Chem B* **2003**, *107*, 13711–13718.

(3) Woods, C. J.; Essex, J. W.; King, M. A. The Development of Replica-Exchange-Based Free-Energy Methods. *J. Phys. Chem. B* **2003**, *107* (49), 13703–13710.