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Implementation of Steered Molecular Dynamics (SteeredMD) in the Schrodinger molecular dynamics software

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Motivation and Aim: The goal of this study was to develop a program called GuidedMD, which implements Steered Molecular Dynamics (SteeredMD) for the Schrödinger suite of programs (Schrödinger Inc., New York, NY, USA). This tool can be applied to explore conformational changes in proteins and protein-ligand interactions. The method was essential for studying allosteric modulation in the cannabinoid type 1 (CB1) G-protein-coupled receptor (GPCR) [1]. The standard biasing force plugin does not support the use of complex trajectories of atom displacements chosen for SteeredMD, therefore the main requirements for GuidedMD were flexibility (to perform simulations along complex trajectories and easily select steered atoms) and the capability to evaluate free energy changes.

Methods and Algorithms: GuidedMD utilizes Desmond [2] to conduct SteeredMD simulations. The biasing potential is implemented as a time-dependent moving harmonic spring. With this approach, an external steering force is applied to a set of selected atoms (F). A second selected set of atoms (Basis B) is used to restrain and retain the whole molecular system. The main routine involves a cyclic call of Desmond MD for each movement of the biasing potential (after each MD simulation output files are processed with a script to modify the coordinates of the restraining potentials for selection F). These modified files are then used as input for the subsequent iteration. The mean force of the system and the transformation of the system from state 1 to state 2 by pulling N atoms can be estimated as follows:

$$\langle \vec{F_i} \rangle = k \langle \Delta \vec{r_i} \rangle$$

$$\Delta G_{2,1} = -\sum_{i=1}^{N} \int_1^2 \langle \vec{F_i} \rangle d\vec{r}$$

To perform a SteeredMD simulation using GuidedMD, one must first prepare the input files for Desmond (e. g., via System Builder followed by Maestro's GUI, specifying the restrained atoms for both F and B selections). Secondary, trajectories for the restraining potential offsets should be generated (manually, or using a part of the GuidedMD TaskGen scripts). Thirdly, main routine script (CmsR) should be configured according to the short manual and executed. After simulation a BuildPlot script (part of GuidedMD) can be executed to get the results of SteeredMD: a PMF plot for all steered atoms and ΔG for the SteeredMD run. GuidedMD has been validated by several tests. In particular, a potential of mean force (PMF) for Cl^--Na^+ pair in vacuum was calculated. Chlorine ion (B) was restrained with the spring constant of 500 kcal/mol/Å^2, the moved

sodium ion (F) was restrained by 50 kcal/mol/Å^2. The system was built and equilibrated according to the protocol for CB1 receptor [1]. Number of MD steps (I) was 180, each MD run was for 10 ns at 300K in NVT ensemble (Nose-Hoover chain thermostat, relaxation 1 ps). For each iteration (i) coordinate of restraining potential ($\vec{r}$) for the sodium ion was set using equation:

$$(\vec{r}_{Na^+})_{new} = (\vec{r}_{Cl^-} - \vec{r}_{Na^+})/(I - i)$$

Also, the PMF for Na^+-Cl^- pair was conducted in SPC/E water. The protocol was similar with some modifications described below. Chlorine and sodium ions were placed in a box (70Å × 20Å × 20Å) so that they were equidistant from the box boundaries, and the distance between them was 20 Å in the x direction. Additionally, three oxygen atoms from the SPC/E water were restrained (for box alignment). The ensemble was NPT: using the Martyna-Tobias-Klein barostat, with a relaxation time of 2 ps and a pressure of 1.01325 MPa. The number of MD steps was 180.

Results: The accuracy of the test PMF computation in vacuum (in comparison with theoretical curve) was satisfactory: the relative accuracy was less than 0.1 %. As for simulation in SPC/E water, the shape of the computed curve is similar to published before [3]. The computed dielectric constant (Fig. 1) for SPC/E water (69) is close to published one (71.8) [4].

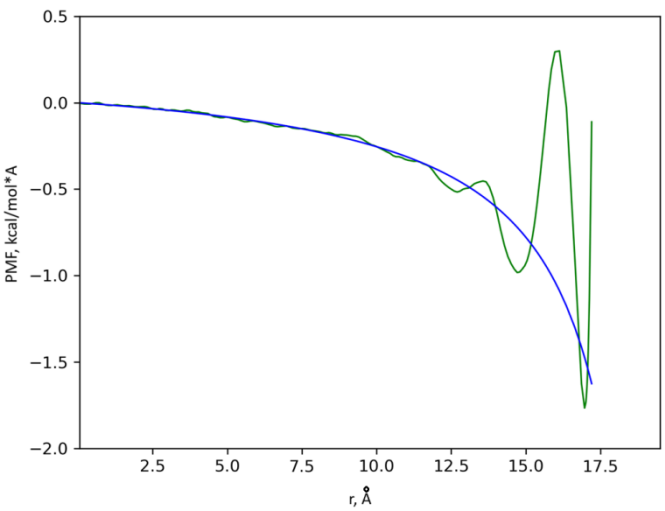

Fig. 1. PMF curve for sodium and chlorine ions in SPC/E water. Blue is theoretical PMF curve in vacuum normalized on $\varepsilon_r = 69$, green is result of computation via GuidedMD

An example of guided structure modification was previously described in detail by Gavryushov et al. [1]. Figure 2 describes the vectors of steering displacements at the structural transformation of the membrane domain of CB1 receptor from its inactive conformation to the active state. The steering forces are applied to a part of the transmembrane helix (TM7), with atoms shown as van der Waals (vdW) spheres, allowing the transformation of CB1 from the inactive to the active state *'in silico'*. The SteeredMD transformation of the CB1 domain immersed into membrane included 20 iterations, each for 10 ns. The energy of transformation in the presence of an agonist

ligand was approximately 0 kcal/mol, while without the ligand, it was above 20 kcal/mol. The latter value could estimate the transformation free energy difference.

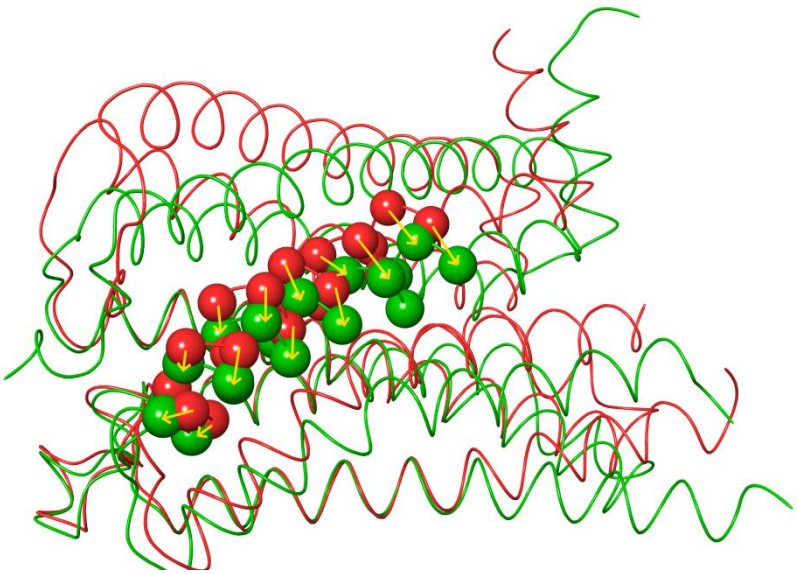

Fig. 2. Steering vectors for CB1 transformation. Red – inactive CB1 (from PDB code 5TGZ), green – active CB1 (relaxed structure from PDB code 5XRA). Yellow steering vectors show displacements of the alpha carbon atoms moved by the steering external forces

Conclusion: A GuidedMD is a flexible and user-friendly tool for performing SteeredMD using the Desmond software. With this developed software, it is possible to accomplish such tasks as: PMF calculations, guided structure transformations, rebuilding of missing chains in X-ray structures of proteins, and relative free energy calculations (using the equation above as well as the Jarzynski equation [5]).

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