

Supporting Information

Challenges of the Use of Atomistic Simulations to Predict Solubilities of Drug-like Molecules

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I. SIMULATION DETAILS

The following are GROMACS 4.6.7 simulation input parameters, as are the MDP files with full details which are deposited in the Supporting Information.

General information

- Friction coefficient = $\text{mass}_{\text{particle}}/\tau_t$, $\tau_t = 2.0 \text{ ps}$.
- Parrinello-Rahman barostat (when applicable): $\tau_p = 10 \text{ ps}$ and compressibility = $4.5 \cdot 10^{-5} \text{ bar}^{-1}$.

Electrostatics (solid)

- PME cut-off: 1.0 nm.
- PME order: 4
- Fourier spacing = 0.10 nm
- we used the same parameters as the Aragonès et al in solid state simulations. Additional details can be found in the MDP files deposited with this paper.

Electrostatics (solution)

- PME cut-off: 1.2 nm.
- PME order: 6
- Fourier spacing = 0.10 nm
- we used the same parameters as the Aragonès et al. for solid state simulations. Additional details can be found in the MDP files deposited with this paper.

vdW interactions

- Cut-off: 1.0 nm
- Switch at 0.9 nm
- DispCorr = AllEnerPres
- additional details can be found in the MDP files deposited with this paper.

Solution simulation files were generated using the `SolvationToolkit` module found at <https://github.com/MobleyLab/SolvationToolkit>. `Solvation Toolkit` relies on `openmoltools`, `mdtraj`, `packmol`, `ParmEd`, and `OpenEye` tools. As noted in the main body of the text, AM1-BCC charges were assigned with `OpenEye`'s `quacpac` python module; we used `openmoltools` to drive this process. Specific source code used for charging is available at <https://github.com/choderalab/openmoltools/blob/v0.6.7/openmoltools/openeye.py#L13>. The code generates molecular conformations prior to charging, as was recommended at <http://docs.eyesopen.com/toolkits/cookbook/python/modeling/am1-bcc.html>.

We generated the simulation files for the acetylsalicylic solid simulations using the `pdb` file containing the crystal structure, `Antechamber` and `ParmEd`. We used the `Antechamber` AM1-BCC procedure to generate the charges for the solid state simulations.

Free energy estimation was done using the `alchemicalanalysis` script which can be found at <https://github.com/MobleyLab/alchemical-analysis>.

II. SUPPORTING DETAILS

The `DA_ideal_to_IEM.csv` file containing the elements of the phase space overlap matrix of a $\Delta A_{EM \rightarrow IEM}$ estimated from an alchemical path of 118 states can be found with this Supporting Information.

DISCLOSURE STATEMENT

DLM is a member of the Scientific Advisory Board for `OpenEye Scientific Software`. JDC is a member of the Scientific Advisory Board for `Schrödinger, LLC`.

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