Improved Lennard-Jones Parameters for Accurate Molecular Dynamics Simulations

Eliot Boulanger[¶,*], *Lei Huang*[¶], *Alexander D. MacKerell Jr.*[†], *and Benoît Roux*[¶]

[¶]*Department of Biochemistry and Molecular Biology, The University of Chicago, Chicago, IL*
[*]*Department of Chemistry, KU Leuven, Leuven, Belgium*
[†]*Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD*

The outcome of classical molecular dynamics simulations highly depends on the accuracy of the force field. While bonded and electrostatic parameters can be determined from quantum mechanical computations, the Lennard-Jones parameters associated with the core repulsion and van der Waals dispersive attraction often need to be empirically adjusted in order to match experimental liquid phase data. Predictive models require a global optimization of the Lennard-Jones parameters for a large training set of molecules.

We compiled a database of enthalpy of vaporization, density and free energy of solvation for 531 molecules encompassing all kind of atom types which are liquid at reasonable temperatures. Our starting point was GAFF[1] Lennard-Jones parameters and we refined charges and dihedral parameters using GAAMP.[2] The optimization was made for molecular volume and enthalpy of vaporization using the least square method and the free energy of solvation was used for validation. We build pure liquid boxes of around 20x20x20 $Å^3$ and equilibrated them. Gradients for the objective function were obtained in a perturbative manner using short molecular dynamics (0.5 – 2ns).

Comparing our results to the original GAFF parameters, we could maintain a very good molecular volume and significantly improve the prediction of the heat of vaporization. Our parameters systematically underestimate the free energy of solvation and we proposed to rescale the water-compound interaction.

[1] *J. Wang, R.M. Wolf, J.W. Caldwell, P.A. Kollman, D.A. Case,* J. Comput. Chem. **2004**, 25 (9), 1157-1174
[2] *L. Huang, B. Roux,* J. Chem. Theory Comput., **2013**, 9, 3543-3556