Pressure Correction for Solvation Theories

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Liquid state theories such as integral equations and classical density functional theory often overestimate the bulk pressure of fluids because they require closure relations or truncations of functionals. Consequently, the cost to create a molecular cavity in the fluid is no longer negligible and those theories predict wrong solvation free energies. We show how to correct them simply by computing an optimized Van der Walls volume of the solute and removing the undue free energy to create such volume in the fluid. Given this versatile correction, we demonstrate that state-of-the-art solvation theories can predict, within seconds, hydration free energies of a benchmark of small neutral drug-like molecules with the same accuracy as day-long molecular simulations.

The ability to predict accurately solvation free energies (SFEs) and solvent maps unlocks the access to several key thermodynamical observables of biomolecular systems [1] like relative solubilities, binding free energies [2, 3], transfer free energies [4] or partition coefficients [5]. SFEs can be rigorously computed with methods involving molecular simulations and free energy perturbation (FEP) techniques [6, 7]. Those are time and resource consuming: they require tens to thousands of CPU hours on high-performance computers. Implicit-solvent models [8] that ignore the molecular description of the solvent were designed in order to cope the expensive cost of FEP, but solving Poisson equation in a dielectric continuum often delivers inaccurate results [9–11] and/or require quantum mechanical calculations [12]. Recently, considering the necessity of evaluating precisely solvation free energies in the drug design process, major actors of the pharmaceutical drug discovery industry publicly called the academic world for alternatives, pointing out the lack of precision of current methods or their high numerical cost [13].

An alternative lies within liquid state theories [14]. Indeed, solvation theories like the molecular density functional theory (MDFT) [15] or the three-dimensional reference interaction site model (3D-RISM) integral equation [16], are now able to predict hydration free energies of complex solutes like proteins [17, 18] or aluminosilicate surfaces [19]. At their roots, they solve the molecular Ornstein-Zernike (MOZ) equation using two different approaches in order to compute estimations of SFEs in few minutes at most. MDFT, for instance, minimizes a free energy functional $F[\rho(r, \omega)]$ of a six-dimensional solvent molecular density $\rho(r, \omega)$, where $\omega = (\theta, \phi, \psi)$ are the three Euler angles of the rigid solvent molecule at position $r$ relative to a frozen three-dimensional solute. The free energy minimization happens in the external potential generated by each atom of the solute modeled, for instance, by the same Lennard-Jones potentials and point charges as in a molecular dynamics simulation. The minimum of the free energy functional is the solvation free energy of the given solute. The density that minimizes the functional is the equilibrium spatial and angular map of solvent molecules $\rho_{eq}(r, \omega)$, often described as the molecular solvent map. Since the functional is unknown, one most-often truncates it to a density expansion at second order, which can be shown to be equivalent to the well-known hyper-netted chain (HNC) approximation in the integral equation theory. A MDFT minimization in the HNC approximation is 3 to 5 orders of magnitude faster than FEP/algorithmic methods relying on molecular dynamics (MD) in predicting SFEs [17]. The speed-up increases with the size of the solute.

Liquid state theories in the HNC and other approximations overestimate the pressure of the bulk solvent [20–22]. The HNC bulk pressure of most common models of water like TIP3P [23] or SPCE [24] at 300K and 1 kg per liter is around 10000 atm instead of 1 atm. Since the free energy to create a molecular cavity within a fluid increases with its volume and the pressure in the fluid, those theories that overestimate the pressure also overestimate the SFE. For small molecules, SFEs predicted in the HNC approximation are not even in qualitative agreement with experiments, for which the precision is about half a kcal/mol on modern calorimetric apparatus.

To assess the accuracy of MDFT and elaborate the pressure correction (PC), we use the FreeSolv database [25]. It contains experimental and predicted [26] hydration free energies of 642 small neutral drug-like molecules. Since MDFT computes the SFE of rigid solutes [27], we did reference calculations for rigid solutes by using Hybrid-4D MC simulations [28]. Briefly summarized, Belloni’s Hybrid-4D computation of solvation free energy is based on two parallel out-of-equilibrium Monte Carlo (MC) simulations, one of bulk water and one of the solvated solute, and the Jarinsky equality [29]. In the bulk water (resp. solvated) simulation, the rigid solute is slowly inserted (resp. deleted) via a fictive 4th dimension every 100 iterations. The work of each insertion/deletion is calculated and the Bennett acceptance ration [30] is used to combine the insertion and deletion distributions to predict the SFE.

In Fig. 1.a, we compare SFEs approximated by MDFT-HNC [31] and calculated by the abovementioned
state-of-the-art reference MC calculations. The root mean squared error (RMSE) is 19.8 kcal/mol. Clearly, HNC SFEs must be corrected. In the case of MDFT-HNC with a pressure-based correction (PC), it reads

$$\Delta G_{\text{solv}} = \min_{\rho}(\mathcal{F}(\rho(r, \omega))) + \text{PC}. \quad (1)$$

Several paths have already been followed to pressure-correct SFEs: from empirical fits of the error on experimental values [33–36], to semi-empirical corrections without parameters like the partial molar volume correction proposed by Sergievskyi et al. [32, 37]. The latter correction is based on the idea that at the macroscopic scale, the free energy to create a cavity of volume $V$ in a fluid of pressure $P$ is $PV$. Thus, in the macroscopic limit, if the pressure is $P_{\text{HNC}} = 10000$ atm instead of $P_{\text{Exp}} = 1$ atm, the pressure correction (PC in Eq. 1) is $\text{PC} = -(P_{\text{HNC}} - P_{\text{Exp}}) V$. Even if this correction is justified in the macroscopic limit, it is not at the molecular scale. If one uses the unambiguous partial molar volume (PMV) noted $\Delta V$ as the molecular volume, one comes back to Sergievskyi’s proposition. The PMV can be derived rigorously in liquid state theories inherently in the grand canonical ensemble like MDFT from the variation $\Delta N$ in the number of solvent molecules in the MDFT supercell while inserting the solute at constant temperature, volume and solvent chemical potential. The PMV pressure correction is thus $\text{PC}_{\text{PMV}} = -\Delta P \Delta V = (P_{\text{HNC}} - P_{\text{Exp}}) \Delta N / n_b$ where $n_b$ is the bulk solvent density. As shown in Fig. 1b, the PMV pressure correction improves drastically the predicted solvation free energies [32, 37–39], yielding a root mean square error to reference simulations of 2.48 kcal/mol compared to 19.76 kcal/mol for the uncorrected ($\text{PC} = 0$ in Eq. 1) HNC results.

We now present the volume optimized pressure correction that uses a geometrical definition of the molecular volume, that is the volume of overlapping Van der Waals (VdW) spheres centered on every atom of the solute. The radii depend upon the chemical nature of each atom and were initially taken from [40] that gathers multiple experimental estimations. Since those 10 radii are not unambiguously defined and subject to large incertitude, we optimized them by about 6% in average around Bondi’s experimental values so that the $PV$ pressure correction minimizes the RMSE of MDFT compared to reference calculations. The VdW volumes were iteratively calculated and optimize via the Nelder-Mead algorithm [41, 42] using a bootstrap technique on a subset of 288 molecules from the FreeSolv database.

**MDFT vs MC** We first optimize the VdW radii on reference SFEs calculated by molecular simulations. In order to discard all possible error compensation effects due to force field and flexibility, we evaluated the performances of MDFT with respect to MC simulations on

![Figure 1. Comparison between the hydration free energies of the FreeSolv database (642 neutral drug-like molecules) of reference simulations on the horizontal axis and of MDFT-HNC (a) without correction, (b) with the $\text{PC}_{\text{PMV}}$ correction [32], and (c) the $\text{PC}_{\text{VdW}}$ correction of this work. The statistical error bars of the simulations (3 standard deviations) are smaller than the size of the dots. The statistical measures at the bottom-right corner refer to Pearson’s $R$, Spearman’s $\rho$ and Kendall’s $\tau$.](image)
rigid molecules. Thus, we first minimize the RMSE of MDFT with respect to the rigid MC simulations. The optimized radii are reported in Table I. The comparison between MDFT SFE predictions with PC\textsubscript{VdW} and MC on the whole FreeSolv database is shown in Fig. 1c. The proposed VdW pressure correction divides the average error by a factor of 5 with respect to the MC simulations: the RMSE is now 0.47 kcal/mol. Correlations are also improved with \( R = 0.99 \) and Kendall’s \( \tau = 0.93 \) with PC\textsubscript{VdW} compared to \( R = 0.95 \) and \( \tau = 0.79 \) with PC\textsubscript{PMV}. Although the optimization of the 10 radii was conducted on less than half the molecules in the database, those results obtained on the whole database show a high transferability to the other molecules.

**MDFT vs Experiment** We now turn to optimizing the VdW radii on experimental SFEs. Since MDFT computes the SFE of rigid solutes, we restrict ourselves to rigid molecules. To this purpose, we compute the deviation between SFEs we obtained with single conformer MC simulations and SFEs values computed via alchemical transformation from flexible solute MD simulation given in the FreeSolv database. If the difference in SFE of the rigid conformer and of the flexible molecule is below 0.1 kcal/mol, the molecule is considered rigid. That is the case of 288 molecules among the 642 of the FreeSolv database, those used in the paragraph above for consistency. Then, we optimize the VdW radii with respect to the experimental SFE of those 288 “rigid” molecules. The final VdW radii are reported in Table I. In Fig. 2b, we show the comparison between PC\textsubscript{VdW}-corrected MDFT-HNC SFEs and the experimental SFEs for the whole dataset of molecules, including those that are flexible. The RMSE of MDFT compared to the experiment is 1.36 kcal/mol, thus reaching the same accuracy as reference FEP simulations with respect to experiments: the RMSE between FEP SFEs and experiments is 1.40 kcal/mol (see Fig. 2a). Note that each MDFT’s SFE prediction takes few seconds to compute on a 8 cores-laptop [17].

The pressure correction we introduced in this paper is simple, versatile and efficient. Using this correction, we have compared MDFT, a state-of-the-art solvation theory, with experimental and simulation results to assess its capability to predict solvation free energies. In order to discard all possible error compensation effects due to force field and flexibility, for instance, we evaluated the performances of MDFT with respect to MC simulations. MDFT can predict SFEs of small drug-like molecules with the same accuracy as MC simulations (RMSE of 0.47 kcal/mol for MDFT vs MC), in few seconds on a laptop. Optimizing the pressure correction on experimentally measured SFE of rigid molecules, we reached the same accuracy as flexible MD state-of-the-art simulations coupled with FEP (RMSE of 1.36 kcal/mol for MDFT vs Exp). This Van der Waals pressure correction can be applied to any liquid state theory that overestimates the pressure of the bulk fluid, like 3D-RISM for instance.

This paper shows that solvation free energies and thus affinities (or binding free energies) can be predicted four orders of magnitude faster with the molecular density functional theory than with state-of-the-art molecular simulations methods, without trading off accuracy. In the context of *in silico* drug discovery, this means that screening accurately chemical libraries containing millions of molecules is now possible in the time scale of days.
| VdW radius (Å) | C | N | O | H | F | Cl | Br | I | P | S |
|---------------|---|---|---|---|---|----|----|---|---|---|
| Initial values | 1.70 | 1.55 | 1.52 | 1.20 | 1.47 | 1.75 | 1.85 | 1.98 | 1.80 | 1.80 |
| Optimized vs. Sim. | 1.711 | 1.734 | 1.588 | 1.318 | 1.59 | 1.815 | 1.872 | 1.982 | 1.458 | 1.721 |
| Optimized vs. Exp. | 1.682 | 1.893 | 1.430 | 1.353 | 1.510 | 1.887 | 1.984 | 1.960 | 1.426 | 1.804 |

Table I. Van der Walls radii used for the optimized pressure-correction PC$_{V}$. First row: initial values as taken for experiments. Second and third raw: optimized versus reference FEP SFE calculations or experimental SFEs.

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[1] Klimovitch, P. V.; Mobley, D. L. Predicting hydration free energies using all-atom molecular dynamics simulations and multiple starting conformations. *Journal of Computer-Aided Molecular Design* **2010**, *24*, 307–316.

[2] Snyder, P. W.; Meinicke, J.; Moustakas, D. T.; Thomas, S. W.; Harder, M.; Mack, E. T.; Lockett, M. R.; Heroux, A.; Sherman, W.; Whitesides, G. M. Mechanism of the hydrophobic effect in the biomolecular recognition of arylsulfonamides by carbonic anhydrase. *Proceedings of the National Academy of Sciences* **2011**, *108*, 17889–17894.

[3] Wang, L.; Berne, B. J.; Friesner, R. A. Ligand binding to protein-binding pockets with wet and dry regions. *Proceedings of the National Academy of Sciences* **2011**, *108*, 1326–1330.

[4] Moeser, B.; Horinek, D. The role of the concentration scale in the definition of transfer free energies. *Biophysical Chemistry* **2015**, *196*, 68–76.

[5] Bannan, C. C.; Calabrò, G.; Kyu, D. Y.; Mobley, D. L. Calculating Partition Coefficients of Small Molecules in Octanol/Water and Cyclohexane/Water. *Journal of Chemical Theory and Computation* **2016**, *12*, 4015–4024.

[6] Zwanzig, R. W. High Temperature Equation of State by a Perturbation Method. I. Nonpolar Gases. *The Journal of Chemical Physics* **1954**, *22*, 1420–1426.

[7] Shirts, M. R.; Chodera, J. D. Statistically optimal analysis of samples from multiple equilibrium states. *The Journal of Chemical Physics* **2008**, *129*, 124105.

[8] Tomasi, J.; Cammi, R.; Mennucci, B. Medium effects on the properties of chemical systems: An overview of recent formulations in the polarizable continuum model (PCM). *International Journal of Quantum Chemistry* **75**, 21.

[9] Moberly, D. L.; Bayly, C. I.; Cooper, M. D.; Shirts, M. R.; Dill, K. A. Small Molecule Hydration Free Energies in Explicit Solvent: An Extensive Test of Fixed-Charge Atomistic Simulations. *Journal of Chemical Theory and Computation* **2009**, *5*, 350–358.

[10] Fennell, C. J.; Kehoe, C.; Dill, K. A. Oil/Water Transfer Is Partly Driven by Molecular Shape, Not Just Size. *Journal of the American Chemical Society* **2010**, *132*, 234–240.

[11] Wagoner, J.; Baker, N. A. Solvation forces on biomolecular structures: A comparison of explicit solvent and Poisson-Boltzmann models. *Journal of Computational Chemistry* **2004**, *25*, 1623–1629.

[12] Klamt, A. COSMO-RS for aqueous solvation and interfaces. *Fluid Phase Equilibria* **2016**, *407*, 152–158.

[13] Sherborne, B. Collaborating to improve the use of free-energy and other quantitative methods in drug discovery. *J Comput Aided Mol Des* **2016**, *3*, 94107.

[14] Hansen, J.-P.; McDonald, I. R. *Theory of Simple Liquids: With Applications to Soft Matter*, 4th ed.; Academic Press: Amstersdam, 2013.

[15] Jeannairet, G.; Levesque, M.; Vuilleumier, R.; Borgis, D. Molecular Density Functional Theory of Water. *The Journal of Physical Chemistry Letters* **2013**, *6*.

[16] Beglov, D.; Roux, B. An Integral Equation to Describe the Solvation of Polar Molecules in Liquid Water. *The Journal of Physical Chemistry B* **1997**, *101*, 7821.

[17] Ding, L.; Levesque, M.; Borgis, D.; Belloni, L. Efficient molecular density functional theory using generalized spherical harmonics expansions. *The Journal of Chemical Physics* **2017**, *147*, 094107.

[18] Imai, T.; Kovalenko, A.; Hirata, F. Solvation thermodynamics of protein studied by the 3D-RISM theory. *Chemical Physics Letters* **2004**, *395*, 1–6.

[19] Levesque, M.; Marvy, V.; Rotenberg, B.; Jeannairet, G.; Vuilleumier, R.; Borgis, D. Solvation of complex surfaces via molecular density functional theory. *The Journal of Chemical Physics* **2012**, *137*, 224107–224107–8.

[20] Evans, R.; Tarazona, P.; Marconi, U. M. B. On the failure of certain integral equation theories to account for complete wetting at solid-fluid interfaces. *Molecular Physics* **1983**, *50*, 993–1011.

[21] Rickayzen, G.; Augousti, A. Integral equations and the pressure at the liquid-solid interface. *Molecular Physics* **1984**, *52*, 1355–1366.

[22] Powles, J.; Rickayzen, G.; Williams, M. The density profile of a fluid confined to a slit. *Molecular Physics* **1988**, *64*, 33–41.

[23] Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Klein, M. Comparison of simple potential functions for simulating liquid water. *The Journal of Chemical Physics* **1983**, *79*, 926–935.

[24] Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. The missing term in effective pair potentials. *The Journal of Physical Chemistry* **1989**, *91*, 6269–6271.

[25] Duarte Ramos Matos, G.; Kyu, D. Y.; Loefller, H. H.; Chodera, J. D.; Shirts, M. R.; Mobley, D. L. Approaches for Calculating Solvation Free Energies and Enthalpies Demonstrated with an Update of the FreeSolv Database. *Journal of Chemical & Engineering Data* **2017**, *62*, 1559–1569.

[26] Predictions were computed with computational thermodynamics from free energy calculations with TIP3P [23] parameters for the solvent and GAFF (v.1.7) [43] parameters with AM1-BCC partial charges [44, 45] for the solutes. The same force field parameters were used for MDFT and MC calculation in this paper.

[27] The effect of a molecule flexibility is in principle not an obstacle for MDFT. Several conformers can be identified.
and their SFEs contribute to a weighted average. This work is ongoing.

[28] Belloni, L. Non-equilibrium hybrid insertion/extraction through the 4th dimension in grand-canonical simulation. *The Journal of Chemical Physics* 2019, 151, 021101.

[29] Jarzynski, C. Nonequilibrium Equality for Free Energy Differences. *Physical Review Letters* 1997, 78, 2690–2693.

[30] Bennett, C. H. Efficient estimation of free energy differences from Monte Carlo data. *Journal of Computational Physics* 1976, 22, 245–268.

[31] Sergievskyi, V. P.; Jeanmairet, G.; Levesque, M.; Borgis, D. Pressure Correction in Classical Density Functional Theory: Hyper Netted Chain and Hard Sphere Bridge Functionals. arXiv:1509.01409 [cond-mat] 2015.

[32] Roy, D.; Kovalenko, A. Performance of 3D-RISM-KH in Predicting Hydration Free Energy: Effect of Solute Parameters. *The Journal of Physical Chemistry A* 2019, 123, 4087–4093.

[33] Sergievskyi, V.; Jeanmairet, G.; Levesque, M.; Borgis, D. Non-equilibrium hybrid insertion/extraction through the 4th dimension in grand-canonical simulation. *The Journal of Chemical Physics* 2019, 151, 021101.

[34] Bondi, A. van der Waals Volumes and Radii. *The Journal of Physical Chemistry* 1964, 68, 441–451.

[35] Gao, F.; Han, L. Implementing the Nelder-Mead simplex algorithm with adaptive parameters. *Computational Optimization and Applications* 2012, 51, 259–277.

[36] ajd98, Utilities for molecular volume calculation. Contribute to ajd98/molecularvolume development by creating an account on GitHub. 2019; https://github.com/ajd98/molecularvolume.