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Reactive molecular dynamics models from *ab initio* molecular dynamics data using relative entropy minimization

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Abstract

We present two new multiscale molecular dynamics (MS-RMD) models for the hydrated excess proton in water developed directly from *ab initio* molecular dynamics (AIMD) simulation data of the same system. The potential of mean force along the proton transfer reaction coordinate and radial distribution functions for the MS-RMD models are shown faithfully reproduce those of AIMD. The models are developed using an algorithm based on relative entropy minimization, thus demonstrating the ability of the method to rapidly generate accurate and highly efficient reactive MD force fields.

Graphical abstract

Keywords

Reactive molecular dynamics; hydrated excess proton; relative entropy minimization; acids; multiscale modeling

I. Introduction

Proton transport is a fundamental process important to a variety of systems within the field of biology and materials science, relevant to systems ranging from membrane proteins[1,2]

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to fuel cells.[3,4] Proton transport is a unique process arising from both vehicular transport and proton Grotthuss hopping, which results from a rearrangement of covalent and hydrogen bonds.[5–9] Due to the importance of this process, it is necessary to have an accurate and physically realistic, yet efficient computational framework for simulating the process. While *ab initio* molecular dynamics (AIMD) would seem ideal, as it explicitly handles bond breaking and formation, the cost of such simulations prohibits their application to large biological or fuel cell systems. Similarly, classical molecular dynamics (MD) simulations can handle extremely large systems, but have fixed bonding topologies, precluding proton hopping and thereby ignoring the essential physics of the process.

Multiscale reactive molecular dynamics (MS-RMD),[10–12] and the earlier multistate empirical valence bond (MS-EVB) approach,[8,13,14] have emerged as efficient computational methods for studying proton transport in complex systems. They have both been shown to capture the solvation structure of a hydrated excess proton in water and the physics involved in proton transfer. Additionally, MS-RMD and MS-EVB offer the computational efficiency necessary for running simulations too large for AIMD, e.g., MS-RMD has been applied to study the proton transport mechanism in membrane proteins, [15,16] as well as to study and elucidate the proton transport mechanism in proton exchange membranes (PEMs).[4,17–19] However, development of accurate MS-RMD models can be nontrivial.[12]

Previous parameterization of MS-EVB models (as the precursor to MS-RMD) have been fit in part to the energetics as well as potential energy surfaces along the proton transfer reaction coordinate from *ab initio* calculations of small clusters of $[(\text{H}_2\text{O})_n\text{H}]^+$, where n is either 2 or 4.[8,13,14] While demonstrably successful in several ways, the approach relies in part on gas-phase protonated water clusters to parameterize a model meant for bulk phase simulations. To overcome this, force-matching has been utilized to parameterize an MS-RMD model to Car-Parrinello MD (CPMD) [10,11] data directly. (We shall consider this model to be MS-RMD version 1 for the hydrated excess proton in water.) In this latter approach, all classical force field parameters, i.e. pair potentials, bonds, angles, are first force-matched to minimize the force-matching variational residual from nonreactive configurations of the CPMD data; while the reactive configurations are then force-matched to include proton hopping. The method successfully generated an MS-RMD force field which very closely matches both the radial distribution functions (RDFs) and potential of mean force (PMF) for proton transfer in the CPMD data. Despite the success of this method, all pair potentials utilize a numerical b-spline functional form, which precludes its simple application to MD simulations of condensed phase systems as, e.g., simple mixing rules for the pair potentials cannot be used. (We note, however, that there is nothing that says force-matching cannot utilize predefined analytical forms, as has been done in Ref. [10]. Use of splines, however, improved the overlap of the model RDFs and PMF to those of the target.) The fitting MS-RMD models to CPMD data via force matching can be a challenging task, and the end result may not necessarily reproduce the desired pair distribution functions, although it will satisfy the Yvon-Born-Green equation connecting two- and three-body correlations.[20] As an alternative to force-matching, relative entropy minimization (REM) has been shown to effectively generate model coarse-grained force fields that can also reproduce the structure of a given target.[21–24]

In this Letter, we develop a REM approach to parameterize MS-RMD force fields for the hydrated excess proton in water, fitting to state-of-the-art *ab initio* MD (AIMD) data. While we acknowledge that AIMD water does have its well-documented shortcomings,[25,26] the fitting method described in this Letter are able to recapitulate the solvation structure and reactivity of hydrated excess protons without introducing the deficiencies seen in AIMD water. (This is discussed in more detail in the results section.) In that sense, the work is largely motivated by the fact that REM is agnostic to the target, and as more sophisticated quantum calculations become accessible for bulk phase calculations, REM would indeed be a powerful tool in reactive force field development. As such, the work herein is a demonstration of REM's ability to handle even highly dimensional, non-linear parameter space. We find that this approach can reproduce both the AIMD RDFs and proton transfer PMF. The MS-RMD models developed in this letter can also utilize standard Lennard-Jones (LJ) pair potentials (so that, e.g., standard mixing rules can be used with novel materials) and specific functional forms for the repulsive and off-diagonal MS-RMD potentials.

The remaining content of this Letter is organized as follows: in the Methodology section, we discuss the details of MS-RMD and the REM fitting scheme. In the Results section, we then discuss the derived models, termed MS-RMD versions 2 and 3, and compare the two models to the most recent reactive MS-EVB model, MS-EVB 3.2.[13] Finally, we conclude the Letter and discuss the outlook for the REM fitting scheme as applied to MS-RMD models, and outline desirable improvements in future models.

II. Methodology

Contrary to empirical classical MD, where the bonding topology is fixed, in MS-RMD (and MS-EVB before it), for a given nuclear configuration the ground state of a system $|\Psi\rangle$ is defined as a linear combination of unique bonding topologies (basis states):[8]

$$|\Psi\rangle = \sum_{i=1}^N c_i |i\rangle \quad (1)$$

where c_i is the coefficient of basis state i . The coefficients are determined by diagonalizing the Hamiltonian for each nuclear configuration such that:

$$\mathbf{H}\mathbf{c} = E_0\mathbf{c} \quad (2)$$

where E_0 is the ground state energy for that configuration. The diagonal matrix elements in the Hamiltonian are the diabatic energies of the basis states, defined by the classical force field energy of the basis state plus a repulsive term added to correct for an over-attraction between hydronium and water in the underlying classical force field. The off-diagonal elements, which introduce reactivity by allowing for “mixing” between basis states of different bonding topology, are a function of the distance between of hydronium and water. The functional forms of both the repulsive potentials and the off-diagonal coupling potential

are shown in the Supplemental Information, as well as all parameters used in the models described in this work. We note that variables fit using REM are shown in boldface, whereas those pertaining to the underlying classical force field or derived in previous models are shown regular typeface.

The MS-RMD models described below are parameterized using the REM scheme. The specific aim of REM is to find a model force field that generates a thermodynamic ensemble with maximal overlap to a target ensemble generated with a higher level of theory. In the present work, the target ensemble is AIMD and the model ensemble is the MS-RMD force field. The relative entropy of two ensembles is defined as:

$$S_{\text{rel}} = \sum_i p_T(i) \ln \frac{p_T(i)}{p_M(i)} \quad (3)$$

where $p(i)$ is the probability of configuration i in the target T and model M ensembles. In the constant NVT ensemble, the relative entropy is defined as

$$S_{\text{rel}} = \beta \langle U_M - U_T \rangle_T - \beta (A_M - A_T) + \langle S_{\text{map}} \rangle_T \quad (4)$$

where U is the potential energy, A is the configurational part of the Helmholtz free energy, and S_{map} is the entropy that results from degeneracies in the model.

The relative entropy is minimized on the condition that the average curvatures of the model potential energy with respect to the force field parameter λ_i over the model and target ensembles are equal:[21]

$$\left\langle \frac{\partial U_M}{\partial \lambda_i} \right\rangle_M = \left\langle \frac{\partial U_M}{\partial \lambda_i} \right\rangle_T \quad (5)$$

We therefore set out to minimize the difference between these two derivatives. The simplest numerical implementation for doing so uses the Newton-Raphson iteration scheme:[21]

$$\begin{aligned} \lambda_{i+1} &= \lambda_i - \frac{\left(\frac{\partial S_{\text{rel}}}{\partial \lambda} \right)}{\left(\frac{\partial^2 S_{\text{rel}}}{\partial \lambda^2} \right)} \\ &= \lambda_i - \chi \left[\left\langle \frac{\partial U}{\partial \lambda} \right\rangle_T - \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_M \right] \left[\left\langle \frac{\partial^2 U}{\partial \lambda^2} \right\rangle_T - \left\langle \frac{\partial^2 U}{\partial \lambda^2} \right\rangle_M + \beta \left\langle \left(\frac{\partial U}{\partial \lambda} \right)^2 \right\rangle_M - \beta \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_M^2 \right]^{-1} \end{aligned} \quad (6)$$

Here, we introduce a mixing parameter χ . Notice that upon satisfaction of the condition in Eq. 6, the derivative of the relative entropy with respect to λ is zero, and the first bracketed term in Eq. 6 is zero, and λ is unchanged. It should also be noted that in regions where the

second derivative of the relative entropy is negative, the optimization is far from the minimum, and the Newton-Raphson iteration scheme is inappropriate. The minimization procedure is performed iteratively, where the derivatives calculated in Eq. 6 are calculated over ensembles generated from updated parameters. As the minimization scheme utilized here requires the model to be somewhat close to the target ensemble, we began each minimization with the MS-EVB 3.2 parameters.[13] We should note that our implementation of the Newton-Raphson iteration scheme does not necessarily reach a global minimum, and may get trapped in a local minimum. Interestingly, we have found that all optimized parameter sets generate serviceable models, reproducing the target RDFs faithfully. This may be a result of the highly dimensional parameter space in which our minimization is performed (12 parameters are simultaneously optimized), which allows for greater flexibility – that is, certain parameters can compensate for deleterious effects of others.

The AIMD data to which the MS-RMD models in this paper were fit utilize the BLYP exchange-correlation functional with the D3 Grimme dispersion and the TZV2P basis set. The systems used in the fitting included 128 water molecules and a single excess proton.

III. Results

We present here the two new MS-RMD models (versions 2 and 3) fit using the relative entropy method (denoted as MS-RMD 2 and MS-RMD 3). While these models have entirely different RMD parameters, the primary difference between the two is the introduction of a Stillinger-Weber (SW) 3-body potential between hydronium oxygen and two water oxygens in the version MS-RMD 3 model. The SW potential is of the form:

$$\phi_3(r_{ij}, r_{ik}, \theta_{ijk}) = \varepsilon_{ijk} [\cos\theta_{ijk} - \cos\theta_{0ijk}]^2 \exp\left(\frac{\sigma_{ij}}{r_{ij} - \sigma_{ij}}\right) \exp\left(\frac{\sigma_{ik}}{r_{ik} - \sigma_{ik}}\right) \quad (7)$$

where ϕ_3 is the strength of the 3-body potential; r_{ij} is the distance between atoms i and j ; θ_{ijk} is the angle between atoms i , j , and k ; θ_{0ijk} is the equilibrium angle; the terms in the two exponentials on the right hand side of the equation dampen the SW potential at large atomic distances so that it only affects close neighbors.

To explain the introduction of the SW potential, consider the O*-Ow RDF in Fig. 1, where “*” denotes an atom on the most hydronium-like structure and “w” denotes an atom on a water molecule. This is perhaps the most illustrative metric for the success of the REM-generated models, and helps motivate our desire to fit the model to AIMD data. First, notice that the first solvation shell peak in AIMD is at 2.53 Å, whereas in MS-EVB it is located at 2.45 Å. Proton hopping in the AIMD simulation is larger than in MS-EVB 3.2, and so there is a desire to mimic this solvation structure. The first solvation shell peaks in MS-RMD 2 and 3 are located at 2.53 Å, demonstrating the success of REM.

The peak from the second solvation shell in AIMD is also at a shorter distance (4.26 Å) and is more pronounced than MS-EVB 3.2 and experiment (see again Fig. 1). This is not

surprising, given that AIMD water at the BLYP DFT level is well-known to be over-structured. There is also a deep valley in the RDF between the first and second solvation shell peaks. This valley is seen in experiment, but MS-EVB 3.2 has a small bulge in this region (at 3.18 Å), which is a result of additional water molecules “crowning” above the hydronium structure on its lone pair side. Previous studies have found that in both AIMD[27] and MS-EVB,[14] the presence of a water molecule (the 4th water) donating a weak hydrogen bond to the protonated oxygen (O*) on this side plays an important role in proton transport in aqueous solution. However, there are cases in MS-EVB 3.2 simulations that more than one water molecules occupy the region on top of O*, which is responsible for the small bulge. Similarly, this bulge is seen in MS-RMD 2 at the same location. To eliminate this crowning effect, we introduced the SW potential, which in fact has a beneficial effect on the solvation structure with respect to AIMD. The angular dependence diminishes the crowning effect by pushing out waters that are not hydrogen bonding with the hydronium oxygen linearly, very closely reproducing the valley seen between the first and second solvation shells. Introduction of the SW potential also increases the overlap of the second solvation shell peak of MS-RMD 3 and AIMD: MS-RMD 3 has a larger peak shifted to a shorter distance. In AIMD, this second solvation shell peak is centered at 4.26 Å, whereas in MS-RMD 2 it is centered at 4.48 Å, and 4.33 Å in MS-RMD 3. While there is a clear improvement in the location of this peak upon introduction of the SW potential, it is not enough to completely reproduce the shape and location of the second solvation shell peak. This largely has to do with the fact that we do not alter the interactions of the underlying water model (SPC/Fw), which almost entirely governs the interaction between the first and second solvation peaks. We note that given the formulation of MS-RMD, the parameters do indeed affect the interaction between the first and second solvation shells, as states in which the first shell have hydronium bonding topologies do contribute to the potential energy, just less, proportional to the c_i^2 value. While a refit water model would have improved the interaction between the first and second solvation shell waters, it is important to have a universal water model, since the objective is to be able to apply the excess proton model to diverse systems.

To further examine the solvation structure of the new MS-RMD models, we have decomposed the O*-O_w RDFs into the individual components, where O_{1x} is the nearest water oxygen, O_{1y} is the second closest, and O_{1z} is the third closest. To illustrate this, an example solvated hydronium is shown in the Fig. 1b inset. The decomposed RDFs are shown in Fig. 2, where the x, y, and z directions are plotted separately. We note that in addition to reproducing the peak position of the first solvation shell, MS-RMD 2 and 3 reproduce the peak positions of directionally specific nearest waters, thus generating models that very well match the solvation structure of the excess proton in AIMD. We find that MS-RMD 2 model does not improve the decomposed RDFs of the second solvation shell relative to MS-EVB 3.2, and that MS-RMD 3 provides a very small improvement.

The other relevant RDFs are also presented in Figure 1. In the H*-O_w RDF, both REM models improve the overlap with AIMD compared with MS-EVB 3.2: the first solvation shell peak is located at 1.51 Å in AIMD; 1.40 Å in MS-EVB 3.2; and 1.50 Å in MS-RMD 2 and 3. We also see a greater overlap of the second solvation shell peak in MS-RMD 2 and 3,

with a clear shift in the peak position to longer distances. The O*-H_w and H*-H_w RDFs in MS-RMD 2 and 3 offer more modest improvements relative to MS-EVB 3.2, but this is due to the fact that these species are in weaker contact with each other, and therefore the REM fitting is dominated by other pair interactions.

Since one primary objective of our model is to accurately simulate proton transfer, the PMF for that transfer is a useful metric for describing the system behavior. To describe proton transfer, we utilize here the proton transfer coordinate defined as δ , given by

$$\delta = \left| r_{\text{O}^*\text{H}^*} - r_{\text{O}_{1\text{x}}\text{H}^*} \right| \quad (8)$$

where $r_{\text{O}^*\text{H}^*}$ is the distance between the hydronium oxygen and hydronium hydrogen, and $r_{\text{O}_{1\text{x}}\text{H}^*}$ is the distance between the hydronium hydrogen and the nearest water oxygen. In Figure 3 we show the free energy profiles along this coordinate for AIMD, MS-EVB 3.2, MS-RMD 2, and MS-RMD 3. MS-EVB 3.2 clearly differs from the AIMD result, both in the location of the free energy minimum, and in the barrier height. MS-RMD 2 and MS-RMD 3 models both recover the free energy minimum and offer close approximations of the barrier height. The proton transfer barrier height is 0.58 kcal/mol for AIMD; 0.63 kcal/mol for MS-RMD 2; and 0.64 kcal/mol for MS-RMD 3. (We note that the differences in barrier height between the different models are a fraction of $k_B T$ at $T = 300$ K.) While the general shape of the PMF is retained for all values of δ , there are several regions in the PMF where MS-RMD 2 and MS-RMD 3 differ from AIMD. In particular, in regions where the free energy is higher the REM-generated models deviate most significantly from AIMD. Conversely, the two MS-RMD models match AIMD very closely in the region around the free energy well. While some of the deviations may be due to the restrictions of the underlying MS-RMD model functional form, or in the underlying classical model, the most likely cause of the discrepancy has to do with limited sampling used when fitting with the REM method. REM seeks to maximize the overlap of a model and target ensemble by matching state probabilities in either ensemble. Regions of the PMF with a higher free energy of course have a lower probability, and therefore are sampled less frequently while generating ensembles used in the fit. Therefore, these regions are less faithfully reproduced; the region directly around the free energy minimum in the free energy profile shows the greatest overlap between AIMD and MS-RMD models..

We also compared excess proton diffusion constants in the various models. The proton diffusion constant for AIMD is $0.78 \pm 0.24 \text{ \AA}^2/\text{ps}$, compared to the experimentally observed diffusion constant of $0.94 \pm 0.01 \text{ \AA}^2/\text{ps}$. [28] The calculated diffusion constants for MS-RMD 2 and 3 are $0.40 \pm 0.06 \text{ \AA}^2/\text{ps}$ and $0.41 \pm 0.05 \text{ \AA}^2/\text{ps}$. This is a modest improvement over the diffusion constant in MS-EVB 3.2, which is $0.37 \pm 0.01 \text{ \AA}^2/\text{ps}$.

As mentioned in the introduction, AIMD water does have its limitations. For example, AIMD water is quite over-structured. This effect is manifest most prominently in the O_w-O_w RDF, where the peaks in AIMD are substantially larger than in experiment, and the regions between solvation peaks are substantially shallower. [25,26] This might suggest that fitting

an RMD model to describe an excess proton in water to AIMD data could be problematic. This is not the case however: AIMD reproduces the solvation structure of a hydrated excess proton much more accurately. The O^*-O_w first solvation peak is located at 2.48 Å in experiment and 2.53 Å in AIMD; the second solvation peak is located at 4.47 Å in experiment and 4.26 Å in AIMD. The heights of the peaks differ slightly as well: $g(r)$ for the first solvation peak is 4.63 in experiment and 4.23 in AIMD; and for the second solvation peak 1.17 in experiment and 1.44 in AIMD. While the overlap between the RDFs is not perfect, and the second solvation shell of the hydronium ion in AIMD is indeed over-structured, there is not the severe deviation seen in the O_w-O_w RDFs for water. Other relevant RDFs shown in Figure 1 also show acceptable agreement between experiment and AIMD. Therefore, AIMD is an appropriate level of theory against which to fit RMD.

IV. Conclusions

We have shown that REM can be an effective tool for fitting MS-RMD models to condensed phase AIMD data. The models generated faithfully reproduce the solvation structure of a hydrated excess proton in water, and also reasonably match the free energy profile along the proton transfer coordinate. While force matching has previously been shown[11] to generate successful MS-RMD models based on condensed phase AIMD data, such models utilized tabulated pair potentials, which precludes the use of simple mixing rules in simulations with, for example, proteins described by the CHARMM force field. In addition, the reactive potentials employed splines rather than particular analytical functional forms, as were used in the models described in this Letter. Given the necessity for the system to be reasonably close to the free energy minimum for the REM scheme to excel, REM also offers an attractive companion to force matching, useful for additional refinement of force matched models, and vice-versa. We note that REM is also agnostic to the target AIMD ensemble used, so as higher level electronic structure methods such as MP2 become achievable for AIMD simulation, REM offers a promising option for the development of even more accurate MS-RMD models in the future.

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References

1. Wraight CA. Chance and design—proton transfer in water, channels and bioenergetic proteins. *Biochim Biophys Acta*. 2006; 1757:886–912. [PubMed: 16934216]
2. Decoursey TE. Voltage-gated proton channels and other proton transfer pathways. *Physiol Rev*. 2003; 83:475–579. [PubMed: 12663866]
3. Kreuer KD, Paddison SJ, Spohr E, Schuster M. Transport in proton conductors for fuel-cell applications: Simulations, elementary reactions, and phenomenology. *Chem Rev*. 2004; 104:4637–4678. [PubMed: 15669165]

4. Arntsen C, Savage J, Tse YLS, Voth GA. Simulation of proton transport in proton exchange membranes with reactive molecular dynamics. *Fuel Cells*. 2016; 16:695–703.
5. Agmon N. The Grotthuss mechanism. *Chem Phys Lett*. 1995; 244:456–462.
6. Tuckerman M, Laasonen K, Sprik M, Parrinello M. Ab initio molecular dynamics simulation of the solvation and transport of hydronium and hydroxyl ions in water. *J Chem Phys*. 1995; 103:150–161.
7. Lobaugh J, Voth GA. The quantum dynamics of an excess proton in water. *J Chem Phys*. 1996; 104:2056–2069.
8. Schmitt UW, Voth GA. The computer simulation of proton transport in water. *J Chem Phys*. 1999; 111:9361–9381.
9. Marx D, Tuckerman ME, Hutter J, Parrinello M. The nature of the hydrated excess proton in water. *Nature*. 1999; 397:601–604.
10. Knight C, Maupin CM, Izvekov S, Voth GA. Defining condensed phase reactive force fields from ab initio molecular dynamics simulations: The case of the hydrated excess proton. *J Chem Theory Comput*. 2010; 6:3223–3232. [PubMed: 26616784]
11. Knight C, Lindberg GE, Voth GA. Multiscale reactive molecular dynamics. *J Chem Phys*. 2012; 137:22A525.
12. Lee S, Liang R, Voth GA, Swanson JM. Computationally efficient multiscale reactive molecular dynamics to describe amino acid deprotonation in proteins. *J Chem Theory Comput*. 2016; 12:879–891. [PubMed: 26734942]
13. Wu Y, Chen H, Wang F, Paesani F, Voth GA. An improved multistate empirical valence bond model for aqueous proton solvation and transport. *J Phys Chem B*. 2008; 112:467–482. [PubMed: 17999484]
14. Biswas R, Tse YL, Tokmakoff A, Voth GA. Role of presolvation and anharmonicity in aqueous phase hydrated proton solvation and transport. *J Phys Chem B*. 2016; 120:1793–1804. [PubMed: 26575795]
15. Lee S, Swanson JM, Voth GA. Multiscale simulations reveal key aspects of the proton transport mechanism in the ClC-ec1 antiporter. *Biophys J*. 2016; 110:1334–1345. [PubMed: 27028643]
16. Lee S, Mayes HB, Swanson JM, Voth GA. The origin of coupled chloride and proton transport in a Cl⁻/H⁺ antiporter. *J Am Chem Soc*. 2016; 138:14923–14930. [PubMed: 27783900]
17. Tse YLS, Herring AM, Kim K, Voth GA. Molecular dynamics simulations of proton transport in 3M and Nafion perfluorosulfonic acid membranes. *J Phys Chem C*. 2013; 117:8079–8091.
18. Savage J, Tse YLS, Voth GA. Proton transport mechanism of perfluorosulfonic acid membranes. *J Phys Chem C*. 2014; 118:17436–17445.
19. Savage J, Voth GA. Proton solvation and transport in realistic proton exchange membrane morphologies. *J Phys Chem C*. 2016; 120:3176–3186.
20. Noid WG, Chu JW, Ayton GS, Voth GA. Multiscale coarse-graining and structural correlations: connections to liquid-state theory. *J Phys Chem B*. 2007; 111:4116–4127. [PubMed: 17394308]
21. Shell MS. The relative entropy is fundamental to multiscale and inverse thermodynamic problems. *J Chem Phys*. 2008; 129:144108. [PubMed: 19045135]
22. Chaimovich A, Shell MS. Anomalous waterlike behavior in spherically-symmetric water models optimized with the relative entropy. *Phys Chem Chem Phys*. 2009; 11:1901–1915. [PubMed: 19280001]
23. Chaimovich A, Shell MS. Relative entropy as a universal metric for multiscale errors. *Phys Rev E: Stat, Nonlinear, Soft Matter Phys*. 2010; 81:060104.
24. Chaimovich A, Shell MS. Coarse-graining errors and numerical optimization using a relative entropy framework. *J Chem Phys*. 2011; 134:094112. [PubMed: 21384955]
25. Cisneros GA, Wikfeldt KT, Ojamae L, Lu J, Xu Y, Torabifard H, Bartok AP, Csanyi G, Molinero V, Paesani F. Modeling molecular interactions in water: From pairwise to many-body potential energy functions. *Chem Rev*. 2016; 116:7501–7528. [PubMed: 27186804]
26. Gillan MJ, Alfe D, Michaelides A. Perspective: How good is DFT for water? *J Chem Phys*. 2016; 144:130901. [PubMed: 27059554]
27. Tse YL, Knight C, Voth GA. An analysis of hydrated proton diffusion in ab initio molecular dynamics. *J Chem Phys*. 2015; 142:014104. [PubMed: 25573550]

28. Roberts NK, Northey HL. Proton and deuteron mobility in normal and heavy water solutions of electrolytes. *J Chem Soc, Faraday Trans 1*. 1974; 70:253–262.

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Figure 1.

Comparisons of RDFs between atoms of the hydronium ion (*) and water molecules: (a) O^*-O_W ; (b) H^*-O_W ; (c) O^*-H_W ; (d) H^*-H_W .

Figure 2. Decomposed RDFs between the hydronium oxygen (O^*) and first solvation water oxygen atoms (O_{1x} , O_{1y} , O_{1z}) and second solvation water oxygen atoms (O_{2x} , O_{2y} , O_{2z}).

Figure 3.
Free energy profiles (PMFs) for proton transfer reaction from different models.