



# Exploring Hamiltonian dielectric solvent molecular dynamics



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## ARTICLE INFO

### Article history:

Received 30 April 2014

In final form 28 July 2014

Available online 4 August 2014

## ABSTRACT

Hamiltonian dielectric solvent (HADES) is a recent method [7,25], which enables Hamiltonian molecular dynamics (MD) simulations of peptides and proteins in dielectric continua. Sample simulations of an  $\alpha$ -helical decapeptide with and without explicit solvent demonstrate the high efficiency of HADES-MD. Addressing the folding of this peptide by replica exchange MD we study the properties of HADES by comparing melting curves, secondary structure motifs and salt bridges with explicit solvent results. Despite the unoptimized *ad hoc* parametrization of HADES, calculated reaction field energies correlate well with numerical grid solutions of the dielectric Poisson equation.

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## 1. Introduction

A major factor, which limits the conformational sampling of peptides and proteins by molecular dynamics (MD) simulations, is the explicit inclusion of the structure determining aqueous solvent. If one describes such solute–solvent systems by standard all-atom molecular mechanics (MM) force fields [1–3], then the solvent atoms typically outnumber the solute atoms by at least an order of magnitude [4–6]. Therefore, instead of focusing on the solute–solute and solute–solvent interactions, one has to spend most of the computational effort on the calculation of the interactions between the water molecules.

A large part of this effort would be saved, if the surrounding water could be replaced by a continuum model that needs to be computationally inexpensive and physically correct. This task demands the solution of the dielectric Poisson equation (PE) on the fly with the numerical integration of the protein dynamics [7]. A corresponding approach neglects, of course, the dielectric relaxation [8] (femtoseconds to picoseconds) of the water and its structure near a protein surface. Whereas the former approximation may be of minor importance for proteins, because their conformational dynamics proceeds on much slower time scales (>nanoseconds), the significance of the latter is still unclear [9] and can be assessed only if a continuum approach, which meets the above criteria, is available. In this context, complementary information from hybrid approaches, which interpolate between an explicit and a continuum description by using a few layers of explicit solvent, may be helpful [10].

There have been many attempts to construct such a continuum approach for MD simulations. However, as demonstrated in Ref. [7], all these attempts essentially represent failures (see also corresponding discussions in Refs. [11–15]). Atomic forces derived from numerical solutions of the PE [16,17], for instance, do not comply with Newton's reaction principle, because they do not yield exact atomic reaction forces, and, therefore, violate energy conservation. On the other hand, a free energy functional approach [18], which actually yields a Hamiltonian dynamics, turned out to be slower [14] than explicit solvent simulations. Finally, the popular generalized Born methods (see e.g. Refs. [19–21]) do not solve the PE [7,20,22].

Starting with the reformulation of the PE [15,23,24], which replaces the polarization of the surrounding continuum by an anti-polarization within the solute protein, we recently succeeded [7,25] to construct a continuum approach for MM-MD simulations, which actually meets the above requirements and is called 'Hamiltonian dielectric solvent' (HADES).

Like all continuum methods also the HADES reaction field (RF) energies and forces, which summarize the interaction of the protein charges with the continuum, depend on the description of the effective atomic volumes  $v_i$  [9,26], which collectively define the space  $\mathfrak{R}_s$  occupied by the protein and, hence, separate the interior region characterized by a small dielectric constant  $\epsilon_s$  from the exterior region characterized by the large dielectric constant  $\epsilon_c$  of the solvent continuum. Therefore the parameters  $\sigma_i$ , which, in HADES, steer the atomic sizes [7], have to be carefully chosen, if one wants to achieve realistic descriptions. In the preceding works [7,25], however, only an *ad hoc* parametrization has been provided. Moreover, the contended computational efficiency has solely been demonstrated by HADES-MD simulations on a small dipeptide.

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With this contribution we want to demonstrate that the alleged computational efficiency pertains also to larger peptides. Furthermore, we want to check to what extent the preliminary *ad hoc* choice [7]  $\Lambda$  of the atomic size parameters  $\sigma_i$  affects the conformational landscape of such a model system.

As a sample system we chose the  $\alpha$ -helical decapeptide Ace-AAAKEAAAKK-NH<sub>2</sub>, which we call  $\mathcal{P}$  from now on, because the melting curve of its CHARMM22/CMAP [1,27] model has been previously studied [28] by replica exchange [29,30] (RE) and by replica exchange with solute tempering [31,32] (REST) MD simulations in explicit water, which was described by the ‘three point transferable intermolecular potential’ [33] (TIP3P). Note that the chosen sequence contains four charged residues that can form internal salt bridges, which may cause difficulties in continuum approaches featuring improper descriptions of atomic volumes [9]. Hence, comparisons of HADES-RE-MD on  $\mathcal{P}$  with the previous explicit solvent descriptions [28] can indicate to what extent our first choice  $\Lambda$  of the volume parameters  $\sigma_i$  was reasonable.

Whereas standard non-polarizable MM force fields are known to exhibit distinct conformational preferences [6,34], HADES should be impartial in this respect. Thus the choice of an  $\alpha$ -helical model peptide was solely dictated by the much larger computational effort required for a statistically meaningful explicit solvent sampling of  $\beta$ -hairpin folding-unfolding equilibria.

## 2. HADES continuum electrostatics

In HADES the protein volume  $\mathfrak{V}_s$  is described by the characteristic function

$$\Theta(\mathbf{r}) = \begin{cases} 1, & \text{if } \mathbf{r} \in \mathfrak{V}_s \\ 0, & \text{else} \end{cases} \quad (1)$$

and is decomposed [24] by local characteristic functions  $\vartheta_i(\mathbf{r})$  into atomic volumes  $v_i$ . The atomic functions  $\vartheta_i(\mathbf{r})$  are centered around the positions  $\mathbf{r}_i$  of the atoms  $i$  and obey  $\sum_i \vartheta_i(\mathbf{r}) = \Theta(\mathbf{r})$  for all  $\mathbf{r}$ . Using this partition, the PE has been exactly transformed [7] into the new representation

$$\Delta \Phi(\mathbf{r}) = -\frac{4\pi}{\varepsilon_s} \sum_i [q_i \delta(\mathbf{r} - \mathbf{r}_i) + \hat{\rho}_i(\mathbf{r}) - \nabla \cdot \hat{\mathbf{P}}_i(\mathbf{r})]. \quad (2)$$

Here, the atomic partial charges  $q_i$ , which generate the Coulomb potential  $\Phi^C(\mathbf{r})$ , are clearly separated from the sources  $\hat{\rho}_i(\mathbf{r})$  and  $\hat{\mathbf{P}}_i(\mathbf{r})$  of the RF potential  $\Phi^{\text{RF}}(\mathbf{r})$ , which is the difference between the solutions  $\Phi(\mathbf{r}|\varepsilon_s, \varepsilon_c)$  of the PE for  $\varepsilon_s \neq \varepsilon_c$  and  $\varepsilon_s = \varepsilon_c$ . The sources of  $\Phi^{\text{RF}}(\mathbf{r})$  are the atomic shielding charge distributions  $\hat{\rho}_i(\mathbf{r})$  and antipolarization densities  $\hat{\mathbf{P}}_i(\mathbf{r})$ , which are both confined to the atomic volumes  $v_i$ . In the representation (2) the usual boundary conditions imposed to  $\Phi(\mathbf{r})$  are replaced by the conditions

$$\hat{q}_i = -q_i(1 - \varepsilon_s/\varepsilon_c) \quad (3)$$

for the strengths (volume integrals)  $\hat{q}_i$  of the  $\hat{\rho}_i(\mathbf{r})$  and by the self-consistency conditions

$$\hat{\mathbf{p}}_i = -\frac{v_i \varepsilon_s}{4\pi} \left(1 - \frac{\varepsilon_s}{\varepsilon_c}\right) \langle \mathbf{E} \rangle_{v_i} \quad (4)$$

for the strengths  $\hat{\mathbf{p}}_i$  of the  $\hat{\mathbf{P}}_i(\mathbf{r})$ , where  $v_i = \int \vartheta_i(\mathbf{r}) d^3r$  denotes the atomic volumes and  $\langle \mathbf{E} \rangle_{v_i} = (1/v_i) \int \vartheta_i(\mathbf{r}) [-\nabla \Phi(\mathbf{r})] d^3r$  the atomic field averages.

The exact representation (2) of the PE is not very useful by itself for computations, because the exact characteristic functions  $\vartheta_i(\mathbf{r})$  are difficult to handle analytically or numerically. However, it provides an excellent starting point to derive simple and computationally tractable approximations. Following a previous suggestion [24] we introduced the Gaussian models  $\tilde{\vartheta}_i(\mathbf{r}|\mathbf{r}_i, \tilde{v}_i, \sigma_i)$  for the exact

atomic shape functions  $\vartheta_i(\mathbf{r})$ . These atomic models are specified by the approximate volumes  $\tilde{v}_i$  and by the Gaussian widths  $\sigma_i$ . Whereas the  $\tilde{v}_i$  are fixed by a self-consistency condition [24], the  $\sigma_i$  are the parameters of HADES. The introduction of the  $\tilde{\vartheta}_i(\mathbf{r}|\mathbf{r}_i, \tilde{v}_i, \sigma_i)$  immediately leads to Gaussian approximations  $\tilde{\rho}_i(\mathbf{r}|\mathbf{r}_i, \hat{q}_i, \hat{\sigma}_i)$  and  $\tilde{\mathbf{P}}_i(\mathbf{r}|\mathbf{r}_i, \hat{\mathbf{p}}_i, \sigma_i)$  also for the  $\hat{\rho}_i(\mathbf{r})$  and  $\hat{\mathbf{P}}_i(\mathbf{r})$ . Here, the strengths  $\hat{\mathbf{p}}_i$  of the Gaussian models  $\tilde{\mathbf{P}}_i(\mathbf{r}|\mathbf{r}_i, \hat{\mathbf{p}}_i, \sigma_i)$  have to fulfill a self-consistency condition analogous to Eq. (4), whereas the exact condition (3) identically applies to the strengths  $\hat{q}_i$  of the models  $\tilde{\rho}_i(\mathbf{r}|\mathbf{r}_i, \hat{q}_i, \hat{\sigma}_i)$ , whose widths  $\hat{\sigma}_i$  differ by a factor in the range  $1.2 \leq \zeta \leq 1.6$  from the  $\sigma_i$ . This factor is another HADES parameter [7].

As a result of the Gaussian approximations, the self-consistent HADES computation of the approximate RF potential  $\tilde{\Phi}^{\text{RF}}(\mathbf{r}_i)$  is essentially analogous to that of a potential, which is generated by induced dipoles of a polarizable force field [7]. One immediately obtains an analytically tractable approximation

$$\tilde{W}^{\text{RF}}(\mathbf{R}) = \sum_i (q_i/2) \tilde{\Phi}^{\text{RF}}(\mathbf{r}_i) \quad (5)$$

for the electrostatic contribution to the solvation free energy, which enables the derivation [25] of explicit expressions for the atomic RF forces. Note that these forces obey Newton’s third law and enable Hamiltonian MD simulations [25].

## 3. Simulation setups

Issues of computational efficiency were addressed by comparing for the  $\alpha$ -helical decapeptide  $\mathcal{P}$  introduced above the timings of five different MD simulation setups. Three of them employed our MD package IPHIGENIE [25,35–37]. The explicit solvent setup I consisted of the 150 atom peptide  $\mathcal{P}$  solvated by 1809 TIP3P water models adding up to a total of  $N=5577$  atoms enclosed in a periodic orthorhombic dodecahedron of inner radius  $R_i = 21.1$  Å. This carefully equilibrated system (temperature  $T=300$  K, volume  $V=53.1$  nm<sup>3</sup>) was adopted from Reichold [28] and is, together with his REST-MD and RE-MD simulations on explicitly solvated  $\mathcal{P}$ , described in Sections S1 and S2 of the Supporting Information (SI). The setups II and III applied HADES- and vacuum-MD, respectively, to the thermal motion of  $\mathcal{P}$ ’s 150 atoms. The setups IV and V used the NAMD program [38], which offers [39] a popular GB method [40,41]. They applied GB- (IV) and vacuum-MD (V) to  $\mathcal{P}$ . All timing simulations were carried out on a single core of a  $4 \times 16$  core 2.5 GHz AMD Opteron 6274 workstation.

In all simulations  $\mathcal{P}$  was described by the CHARMM22/CMAP force field [1,27]. Bond lengths involving hydrogen atoms were constrained by the MSHAKE algorithm [42]. In setup I the dynamics was integrated in the NVT ensemble by the velocity Verlet algorithm [43,44] with a time step  $\Delta t=1$  fs and the solvent was coupled to a Berendsen thermostat (coupling constant  $\tau=0.5$  ps, target temperature  $T_0=300$  K). The long-range electrostatic and dispersive interactions were treated by the combination of the fast structure-adapted multipole method with a RF correction, which is called SAMM<sub>4,1</sub>/RF [5,35,37]. In the continuum setups II and IV the dielectric constants were chosen as  $\varepsilon_c=80$  and  $\varepsilon_s=1$ . In the setups II and III a Langevin dynamics was applied using a second order integration algorithm [45] (with  $T_0=300$  K,  $\gamma=1/\text{ps}$ ,  $\Delta t=1$  fs). Related temperature control methods were applied in the NAMD setups IV and V.

HADES-MD simulations were carried out with the two *ad hoc* choices  $\Lambda$  and  $\Lambda'$  for the Gaussian atomic widths  $\sigma_i$  listed in Table S2 of the SI.  $\Lambda$  distinguishes [7] only the four atom types  $X \in \{\text{H}, \text{O}, \text{N}, \text{C}\}$ , to which it assigns values  $\sigma_X$  in the range 0.52–0.87 Å. In  $\Lambda'$  the widths  $\sigma_X$  of the carboxylate oxygens in E and of the amino hydrogens in K are reduced by the factor 0.8 to generate an enhanced solubility. All other HADES parameters and convergence criteria

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