INTERACTION MODELS FOR WATER IN RELATION TO PROTEIN HYDRATION

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ABSTRACT

For molecular dynamics simulations of hydrated proteins a simple yet reliable model for the intermolecular potential for water is required. Such a model must be an effective pair potential valid for liquid densities that takes average many—body interactions into account. We have developed a three—point charge model (on hydrogen and oxygen positions) with a Lennard—Jones 6—12 potential on the oxygen positions only. Parameters for the model were determined from 12 molecular dynamics runs covering the two—dimensional parameter space of charge and oxygen repulsion. Both potential energy and pressure were required to coincide with experimental values. The model has very satisfactory properties, is easily incorporated into protein—water potentials, and requires only 0.25 sec computertime per dynamics step (for 216 molecules) on a CRAY—1 computer.

1. INTRODUCTION

The study of hydrated proteins by computer simulation methods such as Monte Carlo (MC) or Molecular Dynamics (MD) requires the use of a simple interaction model for water. The model must be suitable for a sufficiently accurate simulation of the liquid state of water, but must also be easily extendable to interaction of water with various molecular groups on the protein molecule.

The requirement of simplicity is related to the complexity of a simulation of a hydrated protein. The straightforward simulation of a small protein such as bovine pancreatic trypsin inhibitor (BPTI) with 58 amino acids in aqueous solution, using three—dimensional periodic boundary conditions, requires the inclusion of about 2000 water molecules if the protein is to be kept out of the interaction range of its own images. Representing all methyl and methylene groups as united atoms, the simulation comprises 458 non—hydrogen atoms of the protein, but about 6600 atoms in total including the water molecules. The MD simulation of such a system is a gigantic computing task, not only because of its size but also because water molecules tend to become trapped in favourable sites and long simulations are required to attain sufficient statistical accuracy.

Several approximations are possible that aim at considerable reduction of computer effort for the simulation of a hydrated macro— molecule. It is obvious that one should try to avoid the detailed simulation of water molecules far removed from the protein surface. The crudest approximation (next to simulations of a protein in vacuum[1—4]) is to replace the interaction with water molecules by potentials of mean force, representing the mean free energy of interaction between surface groups and water. The next approximation is the use of stochastic dynamics which, in addition to a mean force, mimics the dynamic character of the interaction with water by stochastic forces. Such methods are extendable to inclusion of a limited number of water molecules as required to simulate those water molecules that belong to the specific hydration[5] of the protein.

Although such approximate methods are under present development, they are not yet available in a reliable form and they will require extensive testing against more

fully detailed models. Therefore for some time to come reliable simulations of fully hydrated proteins incorporating several thousand water molecules will be required. In order to be feasible, even on a modern supercomputer, such simulations require a simple water model.

In the following sections we will consider various available models for water against the background of the philosophies on which these models are based. We then arrive at a new model for liquid water that is both simple and reliable for the purpose for which it is intended.

2. EFFECTIVE PAIR POTENTIALS

An ideal interaction potential should be derived from ab-initio quantum calculations and predict reliably all known experimental data for all phases of water. Such potentials do not exist because of two reasons: a) ab—initio methods are not accurate enough, b) the interaction potentials are not pairwise additive. The first reason is not serious because we can adjust parameters of the model according to empirical data (the model then becomes semi—empirical). If only ice and vapour data were used and liquid properties would then be well— predicted, we could speak of a satisfactory model. Unfortunately, such models cannot be devised. The deviation from pairwise additivity is quite strong[6,7] and can easily reach values of —5 to —8 kJ/mol. Thus any model that is expected to predict properties of liquid water correctly must be either a mom—pairadditive model or it must use am *effective pair potential* that includes the average non-additive character of the interaction.

Non-pairadditive potentials can best be realised by introducing polarisability into the model[7,8]. This, unfortunately, makes the use of such a model in MC or MD simulations quite expensive. Hence, and in view of our present aim, we will not consider polarisable models further. Thus restricting ourselves to effective pair potentials, we necessarily restrict the applicability of a given model to a certain range of density, temperature and external force fields. We choose the liquid density near zero pressure, around room temperature and without external fields. The model we propose in Section 4 has been tested for liquid water at a density of lg/cm^3 and a temperature of 300K. In a future publication we will also evaluate the model at conditions differing from those mentioned above.

3. SOME PROPERTIES OF AVAILABLE MODELS

Early empirical models made use of both solid and gas phase data. Parameters were adjusted to ice energy, ice lattice constants, gas phase dipole moment and gas phase second virial coefficients. The Rowlinson model[9] uses four point charges plus Lennard—Jones 6—12 interactions centered on the charges. The positive charge of 0.3278 e is situated on the proton positions while the negative charges are situated 0.025 mm above and below the oxygen positions, perpendicular to the molecular plane. Parameters were adjusted to ice data and to the dipole moment and second virial coefficient of the vapour. The BNS model[10] also uses four point charges (0.1956e), each in tetrahedral positions at 0.1mm from the oxygen. There is a single Lennard—Jones 6—12 potential centered on the oxygen nuclei, and the electrical potential is smoothly switched off at short range, depending on the oxygen—oxygen distance. Parameters were adjusted to ice data and the second virial coefficient.

When the BNS model was used for the first MD simulation on liquid water[11], it turned out not to be entirely satisfactory for the liquid state. An adjustment was made in the parameters equivalent to a scaling of temperature. This increases the binding-energy of a pair and causes a deviation of the second virial coefficient to larger (absolute) values[12]. Later it was found necessary to make further adjustments to the model on the basis of MD simulations. The well—known ST2 model was proposed[13] which has been quite successful for the simulation of liquid water. The negative charges were pushed towards the oxygen over 0.02 mm and the parameters were readjusted. The second virial coefficient now deviates quite considerably from the experimental value[7,12], being larger by almost a factor of two. Also the dipole moment of the model is considerably larger than the gas phase dipole moment (see Table 1).

TABLE 1   SOME PROPERTIES OF WATER MODELS

	Model	Ref	type	μ debye gas = 1.85	pair E kJ.mol^{-1}	minimum r nm
1.	Rowlinson	9	gas+solid	1.85	22.6	0.269
2.	BNS	10	eff.pair	2.11	27.2	0.276
3.	BNS scaled	11	eff. pair	2.17	28.8	0.276
4.	ST2	13	eff. pair	2.35	28.6	0.285
5.	MCY	14	pure pair	2.19	24.6	0.287
6.	MCY scaled	15	eff. pair	2.34	28.0	0.287
7.	PE	7	polarisable	1.85	20.9	0.300
8.	SPC(this work)	–	eff. pair	2.27	27.6	0.276

The configuration—interaction potential of Matsuoka, Clememti and Yoshimine[14] (MCY), although it has a higher dipole moment than the isolated water molecule, does not yield correct results if used with MC[16] or MD[15]. A reasonable first peak in the radial distribution function is obtained, but the second neighbour peak is at too short a distance, while the overall appearance resembles a higher temperature behaviour. The energy of the liquid is too low and the pressure is too high. Better results are obtained when the energy is scaled[15] by a factor of 1.14.

The adjustments necessary to obtain reasonable results for the liquid state clearly point to the inadequacy of a pure pair potential. The effective pair potential has as salient features:
a. the potential well between hydrogen-bonded pairs is about 25% deeper than for am isolated pair,
b. the dipole moment is about 25% larger than the dipole moment of the isolated molecule.
Introducing polarisability into a water model has revealed that similar average changes in energy and dipole moment indeed occur[7,8].

4. A SIMPLE POINT CHARGE MODEL

Based on the requirement of simplicity we have devised a new effective pair potential for liquid water. Molecular dynamics simulations are most economic if carried out on a rigid model (without internal degrees of freedom) using cartesian coordinates and employing a model consisting of the smallest possible number of point charges. The point charges should preferably coincide with the positions of the atomic masses, thus avoiding the reconstruction of charge centers and the redistribution of forces and torques. Efficient methods are available to carry out in cartesian coordinates on molecules with internal constraints[17~18].
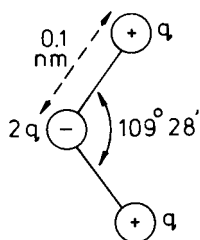

Fig. 1. Geometry and charges of the SPC model

We tried to parameterise a three—point charge model according to Fig.1, with a Lennard Jones interaction between oxygen centers

$$E_{LJ} = -(\frac{A}{r})^6 + (\frac{B}{r})^{12}; \ r = r_{OO}$$

If we fix the attractive r^6 term of the oxygen—oxygen interaction to the 'experimental" value derived from the London expression:

$$A = 0.37122 \text{ nm } (kJ.mol^{-1})^{1/6}$$

only two parameters remain to be adjusted: q and B. These should be derived from MC or MD simulations of liquid water. We chose to fit both the interaction energy and the pressure of the liquid to coincide with the experimental values at 300K, while the form of the radial distribution function g(r) was monitored as well.

The two—dimensional parameter space was sampled by 12 M.D. runs at 300K on 216 water molecules in a periodic box with density 1 g/cm^3. Each run was carried out, after equilibration, over a time of 2 ps, using a cut-off radius for the potential of .6 mm. The time step in the simulation was .002 ps. Both the potential energy F and the pressure turned out to be sufficiently linear in the parameters q and B. A plot of E and pV/NkT is given in Fig.2, as obtained from a least squares fit to the 12 sample data. It turned out that only in a certain region of this parameter space radial distribution functions with water—like structures can be obtained. Those points are indicated by + in Fig. 2, while the points marked - did not yield resolved second neighbour peaks.

The target point in parameter space is E = 41.8 kJ.mol^{-1} and p = 0. This value of the potential energy has been derived from the heat of vaporization at 25°C, making proper corrections for the work upon volume change and for intra— and intermolecular quantum vibrations.[20] For the final choice of parameters allowance was made for small corrections in E and p due to the finite cut-off radius used in the MD simulations. The final parameters are:

$$q = 0.41 \text{ e}$$
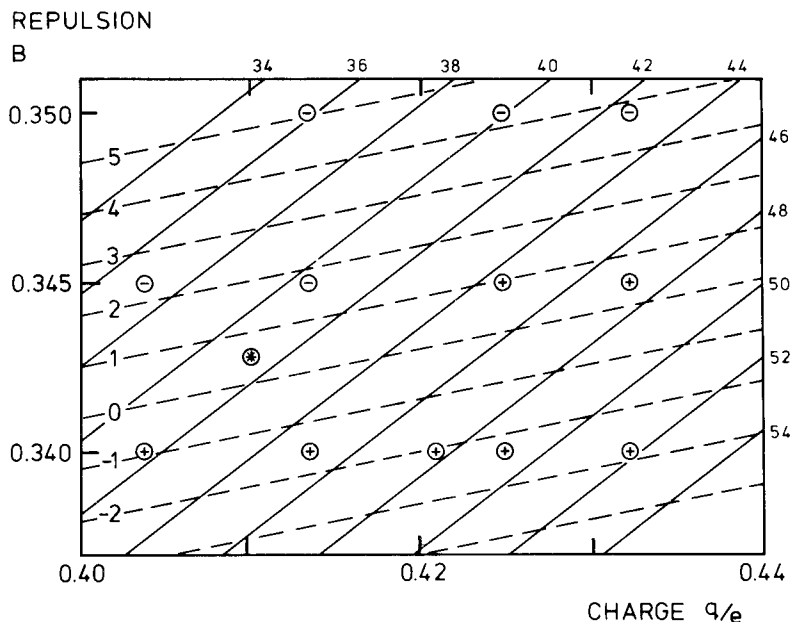$$B = 0.3428 \text{ mm } (kJ.mol^{-1})^{-12}$$

Fig.2. Potential energy and pressure of liquid water at 300 K in parameter space of charge on hydrogen q and oxygen—oxygen repulsion parameter B. B is expressed in units nm (kJ.mol^{-1})$^{1/12}$. Drawn limes: potential energy in kJ/mol; broken lines: pressure expressed as pV/NkT (one unit corresponds to 1385 bar). Circles represent MD simulations. + has a resolved second neighbour peak in the radial distribution curve; - has not. * : final parameters: q = 0.41 e and B = 0.3428

With these values the radial distribution curve still shows structure. We note, however, that particularly the value of the repulsion is critically close to the
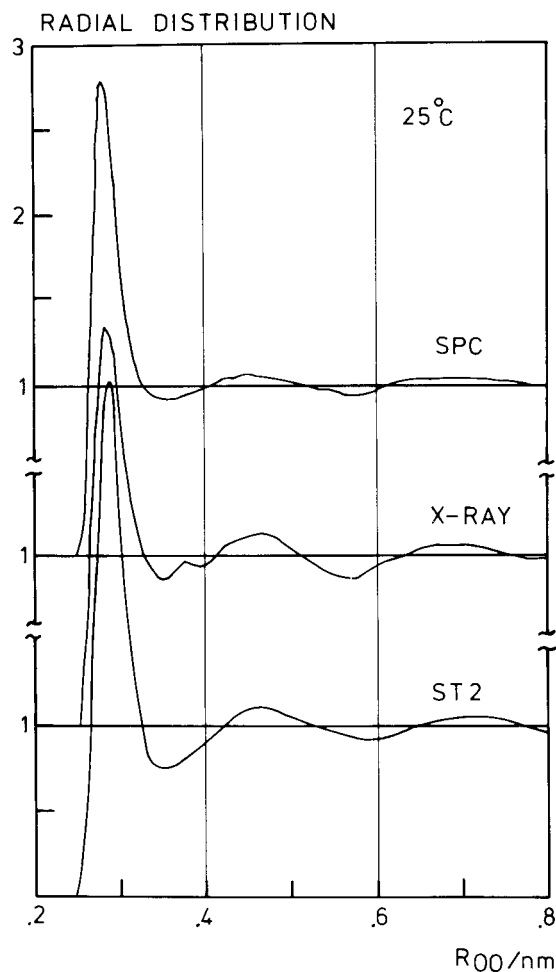
structureless region.

RADIAL DISTRIBUTION

Fig. 3. Radial distribution curve g(r) for the SPC model, compared with X—ray data of Narten (ref 21) . For comparison a g(r) of ST2 water at 300K is given.

Subsequently a full MD run was carried out on 216 molecules, with a small time step and a large cut—off radius. The results are summarised in Table 2.

TABLE 2. PROPERTIES OF SPC WATER

MD run characteristics:

density	$\rho = 1$ g cm^{-3}
temperature	$T = 300$ K
nr of mols	$N = 216$
time step	$\Delta t = 0.0005$ ps
time span	$t = 12.5$ ps
cut-off radius	$R = 0.85$ nm

MD run results:

potential energy	$-E = 42.2$ kJ.mol^{-1} (41.8*)
pressure	$pV/NkT = -0.36$ (0.0)
diffusion constant	$D = 3.6 \times 10^{-9}$ m^{2}s^{-1}(2.7)

Numbers in parentheses indicate experimental values
* including quantum corrections for intermolecular vibrations.

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The radial distribution function is given in Fig. 3, together with the experimental g(r) from X-ray diffraction[21] and the g(r) obtained from a MD run on ST2 water. The static and structural properties are quite well reproduced; the radial distribution is better than that of the ST2 model which overemphasises the tetrahedral structure of the liquid.

Dynamic properties studied thus far include the diffusion constant and the velocity correlation function of the centre of mass. The diffusion constant, obtained from the slope of the molecular squared displacement plotted against time, is somewhat larger than the experimental value[22] (see Table 2). The velocity correlation function(fig. 4) has an oscillatory character with negative tail indicative of rebounce against the molecular cage formed by neighbours. Its fourier$_1$ transform (fig. 4) reveals the experimental peaks at 60 and 175—200 cm^{-1} as observed by neutron scattering[23]. The oscillatory character is somewhat less pronounced than for the ST2 model[11].

Compared with the ST2 potential, the SPC potential has a very similar hydrogen-bonded pair energy curve.(fig.5). There is substantial difference when the second molecule is rotated about an axis perpendicular to the plane of the first molecule. No double minimum is observed, as it is for the rather tetrahedral ST2 model. It is likely that this feature of the ST2 model is unrealistic.

We conclude that the SPC model yields quite satisfactory results for liquid water, which are an improvement on the ST2 model. It is highly efficient for computer simulations. One dynamic step for 216 molecules requires 2.7 seconds CPU time on the CYBER 170/760 of the Computer Centre of the University of Gronimgen, about 0.25 seconds on a CRAY 1 computer at Daresbury, U.K. and about 0.2 seconds on a CYBER 205 (tested at CCC, Minneapolis).
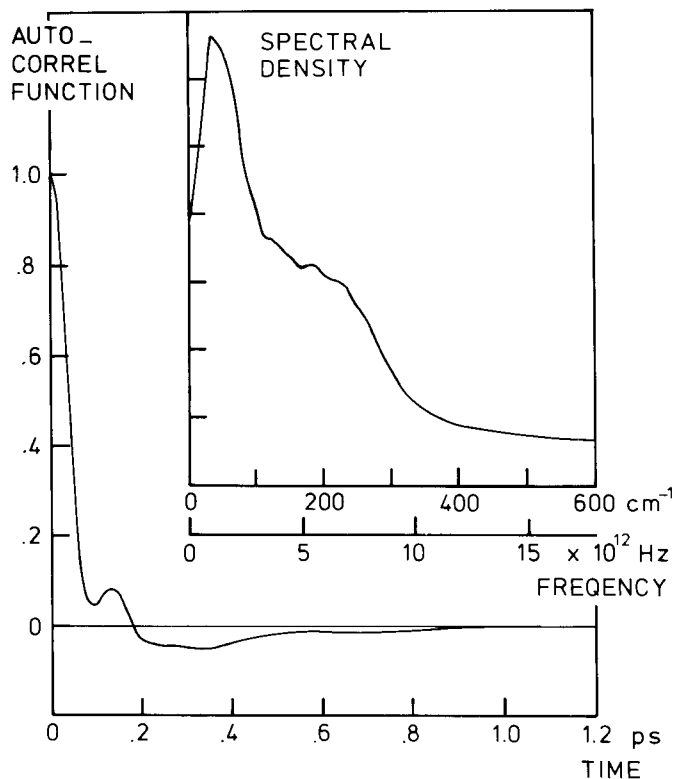
Fig. 4. Autocorrelation function of the center of mass velocity and its fourier transform.
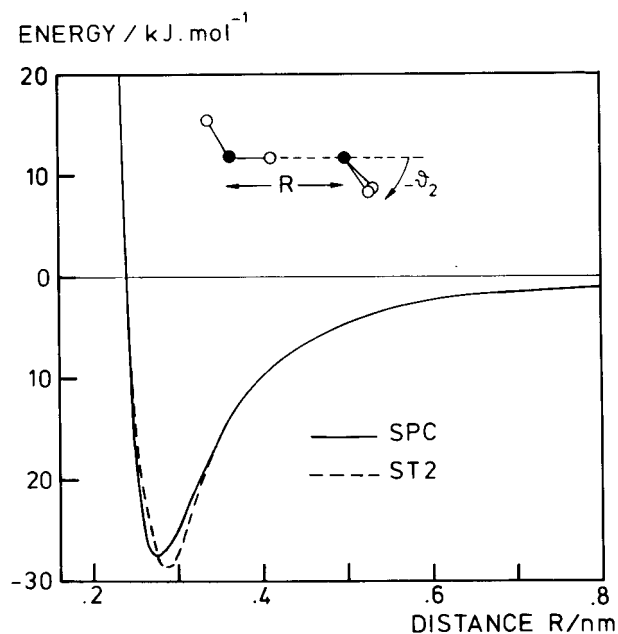
Fig. 5. Pair energy for the most favourable hydrogen—bonded pair for the SPC
and ST2 models, as a function of molecular separation. The rotation angle θ_2
of the second molecule is always such that the energy is minimal. For ST2 θ_2
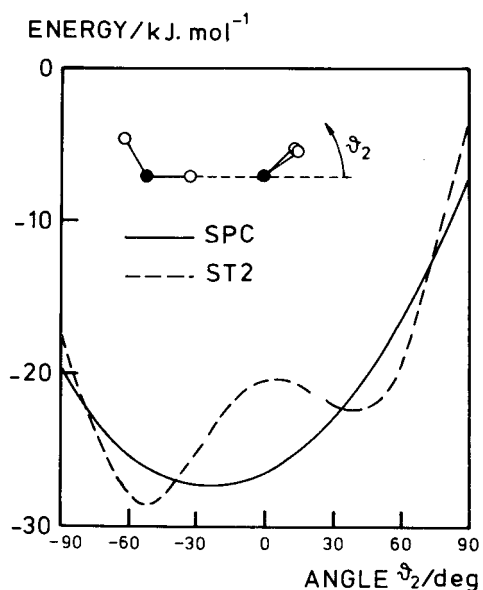is $-54°$; for SPC θ_2 is $-27°$.

Fig. 6. Pair energy for the most favourable hydrogen—bonded pair for the SPC
and ST2 models, as function of the rotation of the second molecule about am
axis perpendicular to the plane of the first molecule. The distance between
the molecules always corresponds to an energy minimum.

5. WATER-PROTEIN POTENTIALS

The SPC potential is quite suitable for interaction with molecular groups on
proteins when potentials of the 6-12-1 type are used. Since there are no virtual
charges on the water molecule, it is also not necessary to introduce virtual charges
on oxygen molecules of the hydrogen bond acceptors. Simple combination rules can be

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applied to obtain Lennard—Jones parameters for interactions between water and atoms of the protein. It is necessary to include those hydroqens on the protein that are involved in hydrogen bond donors; it is not necessary to include special hydrogen bonding potentials. Parameters can be chosen such that both the hydrogen—bonding energy and separation between donor and acceptor correspond to experimental data or to values obtained from calculations[24]. The sparseness of reliable data limits the reliability of the Lennard—Jones parameters on hydrogen—bond donors and acceptors.

We are presently engaged in molecular dynamics simulations of small hydrated proteins, using the SPC water model.

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