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MOLECULAR MECHANICS IN BIOLOGY: From Structure to Function, Taking Account of Solvation

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INTRODUCTION

In molecular biology it is attempted to obtain an understanding of biological function in terms of structure, interactions, and processes at the molecular or even atomic level. Experimental techniques, such as X-ray crystallography and NMR spectroscopy, are routinely used to provide an atomic picture of the structure and mobility of biomolecules, for example proteins and DNA fragments. More flexible molecules, such as lipids and sugars, are less accessible to structure determination by these methods. Information with respect to dynamics is even more difficult to obtain; only spectroscopic measuring techniques yield such information, but only for special groups of atoms, not for all atoms in a biomolecule. Generally, energetic information cannot be measured at the atomic level. Because of the limitations of experimental measuring techniques, the characterization of a biomolecular system at the atomic level in terms of structure, mobility, dynamics, and energetics is incomplete. These four types of information are listed in the order of decreasing knowledge about them. This incomplete molecular picture makes it difficult to establish the link between molecular structure, mobility, dynamics, and interactions on the one hand, and biological function on the other.

An alternative way to study biomolecular systems at the atomic level is simulation on a computer. It involves three basic choices.

1. A biomolecular system generally has too many degrees of freedom (electronic, atomic) to be simulated. However, the ones that are essential to a proper representation of the quantity or phenomenon

one is interested in, must be explicitly present in the molecular model.
2. An interaction function for these degrees of freedom must be defined, which contains the average effect of the degrees of freedom that have been omitted in the molecular model.
3. The motion of the molecular system is governed by equations of motion. Depending on the type of degrees of freedom in the model (quantum-mechanical, classical, or stochastic), this can be Schrödinger's, Newton's or Lagrange's, or Langevin's equation of motion. The length of the simulation must be sufficiently long to allow for an adequate sampling of essential degrees of freedom.

Whether a biomolecular system can be usefully simulated depends on three factors:

1. the time scale of the quantity or process of interest,
2. the required accuracy of the simulated property or process,
3. the available computing power.

In Figure 1 it is illustrated that the three basic choices of molecular simulation depend on the three factors listed above. One should choose as few degrees of freedom and as simple an interaction as possible in order to allow for as long as possible simulation, without throwing the

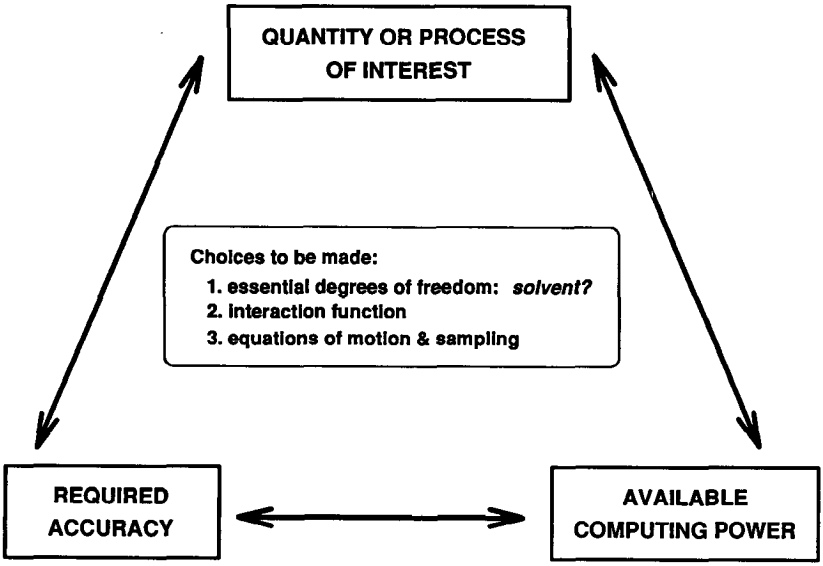

Figure 1

baby out with the bathwater: insufficient accuracy of the simulated quantity or process of interest.

An obvious way to limit the number of degrees of freedom in a biomolecular simulation is to omit all or almost all solvent degrees of freedom. Due to the abundance of solvent degrees of freedom for a biomolecule in solution, omission of these in a simulation easily reduces the required computing power by a factor of 10–50. In fact, the first protein simulations were carried out for a protein in vacuo (32). On the other hand, it is clear that the complete neglect of solvent effects will limit the accuracy of the biomolecular properties obtained from an in vacuo simulation. So, what is the role of solvent molecules in a biomolecular system? To answer this question we focus on proteins in aqueous solution, but corresponding considerations with respect to nucleic acids, sugars, lipids, or other solvents can be given.

Solvent molecules play different roles with respect to protein properties one is interested in, for example:

1. The structure and stability of a folded protein depends on the type of solvent. In aqueous solution a protein tends to minimize its apolar surface area: the hydrophobic effect.
2. Individual water molecules play a structural role in folded proteins, e.g. the four internally bound water molecules in bovine pancreatic trypsin inhibitor (BPTI).
3. Polar solvents exert a dielectric screening effect on interactions between protein charges.
4. The viscosity of the solvent will influence the dynamics of the protein atoms and may thereby influence the kinetics of processes.

In this paper we briefly review the treatment of solvent and solvent effects in biomolecular simulation. It is not meant to be a complete review of the relevant literature, only a discussion of the relevant issues, in which we draw examples mainly from our own work. Other reviews discuss specific aspects of solvent effects and treatment (1, 40, 41, 57).

STUDIES OF BIOMOLECULES USING EXPLICIT SOLVENT MOLECULES

When simulating a microscopic system of finite size, the boundary of the system should be treated such as to minimize edge effects. The standard procedure is to use periodic boundary conditions. The biomolecule and its surrounding solvent molecules are put into a periodic space-filling box, which is treated as if it is surrounded by identical

translated images of itself. In this way basically an infinite periodic system is simulated. The periodic box should be taken large enough to avoid interactions between molecules and their periodic images. This condition leads to sizeable amounts of solvent molecules, typically a few thousand, to solvate a protein. In an early protein simulation of this type, the protein BPTI could only be simulated over 20 ps (53), due to limited computing resources at the time. Presently, a state-of-the-art molecular dynamics (MD) simulation of a protein in solution covers at least an order of magnitude longer period (6–8, 11, 12, 29, 31, 60).

Since BPTI is a small, well-characterized protein, it is often used to test molecular models and simulation procedures. Levitt & Sharon (29) analyzed the solvent effect on some protein properties by a comparison of MD simulations in vacuo and in water, covering about 200 ps. The hydration behavior of water molecules in a 1.4-ns MD simulation of BPTI was analyzed and compared to NMR derived data recently (7). Ahlström et al (2) studied the properties of interfacial water molecules for different proteins in solution. The effect of various degrees of hydration upon the structural and dynamical properties of myoglobin was studied by Steinbach et al (48). Solvent viscosity effects (18) and dielectric screening effects (46) have also been analyzed. Structural, dynamical, and energetic effects of high-pressure solvation have been studied for BPTI (8, 24). Other studies concern the role of water molecules in DNA operator-repressor binding (14), α-helix bending (15), or unfolding (51). The studies show that the explicit inclusion of solvent molecules in a simulation significantly improves the description of the average structural and energetic protein properties. They also illustrate the necessity of explicit solvent treatment when studying properties such as protein stability or complexation.

EXPLICIT TREATMENT OF SOLVENT IN THE SIMULATION

Roles of Solvent Molecules

Solvent molecules play different roles in a protein simulation. First, they may serve to improve the packing in the interior of the protein or in the interface of a protein complex. Surface tension effects generally reduce the likelihood of occurrence of sizeable cavities inside a protein, since they tend to minimize the free surface area. If a cavity in a protein in a simulation is not filled with solvent molecules, it is likely to collapse, thereby inducing distortions in the protein structure.

When the solvent molecules possess hydrogen-bonding capacity, they may also play a role in satisfying unmatched hydrogen bond–donor or –acceptor groups of the protein. For example, one of the four internal water molecules in BPTI makes four hydrogen bonds to the protein.

When the solvent molecules possess a sizeable dipole moment, they exert a shielding effect on the electric interaction between charges or dipoles in the protein. As a consequence, the protein structure and stability may change depending on the polarity of the solvent.

Finally, the viscosity of the solvent may influence the dynamics of protein atoms or segments near the surface. This effect may even be transmitted through the protein matrix to affect the dynamical properties of the protein interior.

The model for the solvent molecules that is used in biomolecular simulations should possess the properties that allow it to play the roles discussed here.

Types of Solvent

Solvents that are used to dissolve proteins or polypeptides are water, dimethylsulfoxide (DMSO), chloroform ($CHCl_3$), and carbontetrachloride (CCl_4), to mention the most important ones. Good-quality molecular models for these solvents are available in the literature (4, 5, 16, 22, 34, 39).

Solvent Models

An important aspect of choosing an interatomic interaction function for a biomolecular system including explicit solvent molecules is the consistency between different parts of the interaction function, for example the protein-protein, protein-solvent, and solvent-solvent terms (57). When combining a solvent model with a protein force field, the definition of the protein-solvent interaction requires special attention. In most cases this interaction is defined using so-called combination rules. In most biomolecular force fields, the r_{ij}^{-12} repulsive only r_{ij}^{-6} attractive van der Waals interaction parameters $C_{12}(i,j)$ and $C_6(i,j)$ for a pair of atoms are given in terms of one-atom parameters $C_{12}(i)$ and $C_6(i)$, from which the pair interaction parameters are obtained by the application of a combination rule such as

$$C_{12}(i,j) = \sqrt{C_{12}(i)C_{12}(j)} \qquad 1a.$$

and

$$C_6(i,j) = \sqrt{C_6(i)C_6(j)} \qquad 1b.$$

When the van der Waals interaction is expressed in terms of an energy ϵ_{ij} and a distance σ_{ij} with

$$C_{12}(i,j) = 4\epsilon_{ij}\sigma_{ij}^{12} \quad 2a.$$

and

$$C_6(i,j) = 4\epsilon_{ij}\sigma_{ij}^{6}, \quad 2b.$$

a different combination rule is sometimes used, e.g.

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad 3a.$$

and

$$\epsilon_{ij} = (\epsilon_i + \epsilon_j)/2. \quad 3b.$$

From Equations 1–3 it is clear that combination rule 1 defines a different protein-solvent interaction than combination rule 3. If protein and solvent force fields are of different types, the application of combination rules like 1 and 3 may lead to an imbalance between protein-protein, protein-solvent, and solvent-solvent interactions.

Treatment of Boundaries

Application of periodic boundary conditions is the best way to avoid distortions due to the presence of boundaries in a finite size system. Yet, one should keep in mind that the periodicity generally is an artifact, which may affect the simulated properties, unless the periodic box is chosen sufficiently large to avoid these. Since the simulation of a protein in a periodic box containing many solvent molecules is computationally expensive, the explicit treatment of solvent molecules is often limited to the first solvation shell. Although such a treatment is more realistic than a complete omission of solvent molecules, it still suffers from surface tension distortions of the solvent layer and lack of dielectric screening due to the vacuum outside the solvation shell.

Treatment of Long-Range Electrostatic Effects

The electrostatic interaction between (partial) charges on atoms is inversely proportional to r_{ij}, the distance between atoms i and j. This distance dependence gives the electrostatic interaction a very long range. In a polar solvent, however, the full charge-charge interaction will be screened by the solvent molecules that orient themselves to reduce the total (free) energy of the system. In order to properly account for the solvent screening, the computational box should be chosen sufficiently large, and long-range electrostatic interaction should be included, at least in an approximate, average manner. A variety of

methods for the treatment of long-range electrostatic interactions in molecular systems have been reviewed earlier (13, 55). Two techniques that are most useful in the simulation of solvated biomolecules using periodic boundary conditions are the so-called twin-range method (55) and the reaction field approach including ionic effects. In the twin-range method, two interaction ranges are distinguished and treated differently. The short-range interactions are exactly calculated, whereas for the longer-ranged interactions, say beyond 8–10 Å, the high-frequency components are neglected. In the second mentioned approach, the reaction field from the charges inside the cut-off sphere due to an electrostatic continuum, with given dielectric permittivity ϵ and ionic strength I outside the cut-off sphere, is calculated using the linearized Poisson-Boltzmann equation. The use of these reaction-field forces in a MD simulation avoids the concentration of ions just outside the cut-off sphere.

Although the long-ranged interactions between ions in aqueous solution can be adequately approximated in a simulation, the inclusion of ions in a simulation of a protein in aqueous solution may not yield reliable results, since the relaxation time of an ionic distribution is likely to be longer than the simulation period. This slow relaxation is caused by the slow diffusion of hydrated ions in solution. In a biomolecular simulation including water and counterions, the simulation averages may be easily based on nonequilibrated ion distributions, causing sizeable deviations from the mean effect of the ions. Therefore, the mean influence of the ionic solution might be better approximated by a simulation, which only includes solvating water molecules.

COMPARISON OF SIMULATED WITH EXPERIMENTAL DATA

The quality of the model for the solvent and the solvent-protein interaction should be assessed by a comparison of simulated with experimental data with respect to solvation properties or behavior of solvent molecules in the solvation layer. Below, we give a number of examples of such a comparison, all taken from the literature. They concern MD simulations of proteins, peptides, or sugars in which the GROMOS force field (54) is used in conjunction with the SPC (5) and SPC/E (4) water models.

X-Ray and Neutron Diffraction Data

X-ray and neutron diffraction studies of biomolecular crystals may yield information on the behavior of solvent molecules, usually in the

form of occupancy factors for solvent sites in the crystal. For cyclodextrins, both X-ray and neutron diffraction data are available, which indicate a partially mobile network of cyclodextrin-water and water-water hydrogen bonds. A number of the hydrogen bonds show so-called flip-flop behavior, in which donor and acceptor exchange their roles (42). Such a system is ideal to test the relative strength of solute-water and water-water hydrogen-bond interactions. In a number of MD simulation studies, Koehler et al (25–28) found that the flip-flop phenomenon was observed in the simulations, and that the relative occupancy of the water and hydroxyl hydrogen (deuterium) atom sites was reproduced too. Almost all experimentally observed three-center hydrogen bonds were found in the simulations, even with respect to the asymmetry of the three-center geometry. This example shows the usefulness of a comparison of simulated solvation behavior with experimentally observed data.

NMR Spectroscopic Data

Using new NMR techniques, the residence times of water molecules in the surface hydration shell of polypeptides and proteins can be studied, and very rough estimates can be obtained (36). These have been compared to residence times calculated from a long MD simulation of BPTI in aqueous solution (7). The simulated results are in good agreement with the experimental data. The residence times of individual water molecules coming near a given BPTI atom, as obtained from the simulation, vary greatly and range between 10 and 500 ps.

Dielectric Permittivity Data

Experimental determination of the dielectric permittivity of proteins shows that the dielectric dispersion curves generally contain two distinct regions (20). The dielectric response is constant up to frequencies of the order of 1 MHz, at which point the response decreases significantly. The lower dielectric response is then constant within the 1–100 MHz range. At approximately 100 MHz it drops again to that of pure water. The response observed at 100 MHz has been attributed to the slower orientational relaxation of protein-bound water molecules compared with bulk water molecules (20). Smith et al (46) have analyzed the dielectric response of the proteins BPTI and lysozyme using 1-ns MD simulations of these proteins in aqueous solution and found that the calculated frequency-dependent dielectric constant was consistent with known experimental dielectric dispersion curves for proteins in aqueous solution. This example shows the importance of explicit inclusion of water molecules, both in the hydration shell and in the bulk, in the simulation when studying dielectric relaxation effects.

Fluorescence Decay Data

Fluorescence anisotropy decay measurements can be used to probe the interaction between tryptophan-containing peptides and the surrounding solvent molecules. Chen et al (9) have determined the orientational correlation decay times of the transition moment of the Trp side chain in a number of Trp-containing mono- and dipeptides in aqueous solution at different pH and temperature values. They found values ranging from 19 to 43 ps for the monopeptides. MD simulation of a Trp residue in water, using the GROMOS force field and SPC water, resulted in a too short decay time of about 8 ps (9). The origins of this discrepancy are not yet known. Further investigations are required to determine whether it is due to a too-weak peptide-water interaction or to technical aspects of the simulation with respect to the chosen values of the time step Δt, the application of bond-length constraints, and the coupling time constant τ_T of the coupling to the heat bath. We standardly use constraints for all bond lengths, $\Delta t = 2$ fs and $\tau_T = 0.1$ ps, (14, 25, 46, 54, 55). Chen et al (9) only constrained bonds involving hydrogen atoms and used $\Delta t = 2$ fs and $\tau_T = 0.5$ ps, which will lead to more noise in the simulation and a higher mean temperature than when the standard parameter settings are used. However, it is clear that studies such as Chen et al's (9) are very useful to evaluate protein-solvent interactions.

APPROXIMATE TREATMENT OF SOLVENT EFFECTS

Mean Force and Dynamic Effects

An alternative to the explicit treatment of solvent molecules in a biomolecular simulation is an implicit one: the influence of the solvent on the solute degrees of freedom is incorporated in the interaction function and equations of motion of the latter in an average manner. The solvent effect upon the structure and dynamics of a solute can be divided into different types.

1. The average or mean interaction between solute atoms is affected by the presence of solvent. When the solvent is omitted from the simulation, the solute force field should be changed to incorporate the mean solvent effect, that is, a potential of mean force should be used for the solute.
2. The solvent exerts a dynamical effect on the solute, which can be mimicked by the introduction of a frictional force representing sol-

vent drag, and of a randomly fluctuating force representing collisions with solvent molecules, into the equations of motion. In the simplest case the frictional force is taken proportional to the velocity of the solute atom to which it applies, and the random force is of white noise character, uncorrelated between the different degrees of freedom:

$$m_i \mathrm{d}v_i(t)/\mathrm{d}t = F_i^{\mathrm{mean}}(t) - m_i\gamma_i v_i(t) + R_i(t). \quad 4.$$

This is the Langevin equation in which the (solute) atomic mass, friction coefficient, and velocity are denoted by m_i, γ_i, and v_i. The mean force is F_i^{mean} and the random force is R_i (45).

Local vs Long-Range Mean Forces

A potential of mean force that describes the average solvent effect upon the solute degrees of freedom can be derived along different lines of approach.

1. The mean force on the solute atoms can be determined from a full MD simulation including explicit solvent molecules (52). This is a very costly procedure.
2. Integral equation theories, such as the reference interaction site model (RISM), can be used to define potentials of mean force. Examples are given in (37) for ion-water mixtures, and in (30) for hydrocarbon-water systems.
3. A third possibility is to make an educated guess with respect to the functional form of the dependence of the potential of mean force on the solute atomic coordinates, and to adjust the model parameters such that specific experimental data, like vapor-to-water transfer energies, are reproduced by the model.

The latter type of mean force potential is mostly used when studying biomolecular systems. Two different types of contribution to the mean force of solvation are generally distinguished (3, 49).

1. The first one represents local solute-solvent interactions and is often assumed to be proportional to the solvent-accessible surface area of a solute atom, or to another measure of the local solute-solvent contacts. It should account for the energy of cavity formation, solute-solvent dispersion interactions, etc.
2. The second contribution represents long-range solute-solvent interactions due to dielectric screening and polarization effects.

Although this distinction is conceptually and practically useful, it bears the danger of incorporating specific solvent effects twice, especially

when the mean force parameters are obtained by fitting to experimental data.

Accessible Surface Area Type Models

In this type of mean solvation model the local solvent contribution to the potential of mean force for solute atoms is taken proportional to the area of the solute atom or group of atoms that is accessible to solvent molecules (17, 21, 35, 43, 49, 59). Other local quantities, such as the hydration volume (23, 58) or the number of solute-solvent contacts (10, 50), can be used too. The detailed implementation of such models allows much room for variation of model features and calibration of parameters. We only mention a number of important aspects:

1. Is the solvation energy split into terms representing solute atoms or groups of atoms?
2. How is the accessible surface area or hydration volume defined, and is it calculated exactly (analytically or numerically) or using an approximate expression?
3. Which are the solute molecules and solvents that are used to calibrate the model parameters?
4. Which conformations of the solute molecules are used in the parameter calibration procedure?
5. Which experimental data are used for the calibration, e.g. vapor-to-water transfer (free) energies, or apolar solvent–to-water transfer (free) energies?
6. Which force field is used in conjunction with the accessible surface area mean force term when calibrating the mean force parameters?

Currently, it is not clear whether accessible surface area solvation models are an efficient way to account for solvent effects. The calculation of the surface area of an atom generally involves nonnegligible computational effort. When simulating larger molecules it is more efficient to incorporate a (thick) layer of solvation molecules than to evaluate the accessible surface area for all solute atoms.

Simple Pairwise Solvation-Force Models

The expression for the accessible surface area of a solute atom generally depends on the coordinates of the solute atom itself and those of its nearest-neighbor solute atoms. Thus, a mean force potential based on an accessible-area model becomes a many-body interaction. The computation of the mean force of solvation would be considerably simplified and sped up, if the mean force could be formulated as a sum of pairwise (two-body) interactions. In fact, the mean force potential in

the solvent-contact or occupancy model (50) can be expressed as a sum of two-body terms, which are proportional to $\exp(-r_{ij}^2/2\sigma^2)$. We have tried a slightly different functional form (WF van Gunsteren, FJ Luque, D Timms & AE Torda, unpublished work):

$$V^{\text{mean}}(r_{ij}) = \begin{cases} V_{\text{des}}^{ij} & r_{ij} < R_1^{ij} \\ V_{\text{des}}^{ij}\left\{1 - \left[\dfrac{(r_{ij} - R_1^{ij})}{(R_2^{ij} - R_1^{ij})}\right]^2\right\}^2 & R_1^{ij} \le r_{ij} \le R_2^{ij}, \\ 0 & r_{ij} > R_2^{ij} \end{cases} \quad 5.$$

in which r_{ij} is the distance between atoms i and j. The model parameters are R_1^{ij}, an inner distance at which desolvation is complete, R_2^{ij}, an outer solvent-separated distance at which solvation is complete, and V_{des}^{ij}, the energetic cost of desolvation. The distance range over which the desolvation force derived from Equation 5 is nonzero is governed by the van der Waals radii of the various types of solute atoms and the size of a solvent (water) molecule. The parameters in Equation 5 were determined from experimental aqueous second virial coefficients for small molecules.

Although a simple pairwise solvation force induces only a minor increase of the required computing effort, it remains to be investigated whether its accuracy is comparable to that of a simulation including a (thick) layer of solvent molecules.

Dielectric Screening Models

Different approximate models for treating the long-range solute-solvent interactions due to dielectric screening and polarization effects are available too (19, 33, 38, 44, 47, 49). Still et al (49) use an expression involving only one-body and two-body terms, which is based on the continuum approximation of a dielectric medium. A simpler approach is to make the relative dielectric permittivity, ϵ, distance dependent. Pickersgill (38) proposes $\epsilon = 4.5 r_{ij}$ Å, based on a calculation of shifts in pK_a values in the protein papain. Mehler (33, 47) proposes to use a sigmoidal function of the distance:

$$\epsilon(r_{ij}) = A + B/[1 + k \exp(-\lambda B r_{ij})], \quad 6.$$

where $B = \epsilon_0 - A$, ϵ_0 is the dielectric constant of water, and A, λ, and k are model parameters.

A much more complicated way to incorporate long-range electrostatic effects using a continuum representation of the solvent is based on solving the Poisson-Boltzmann equation on a three-dimensional grid

(19, 44). A simple two-body interaction term is proposed that accounts for charge-solvent interactions in an average way (19).

The dielectric solvation models discussed so far all assume an instantaneous dielectric response of the solvent surrounding a solute molecule. The time lag of the reaction field, corresponding to the frequency dispersion of the dielectric constant, has been neglected. For a proper mean representation of the dynamic properties of the solute, the treatment of the long-range electrostatic forces should be based on the expressions for the delayed reaction field (56) in conjunction with a randomly fluctuating electric field term representing solvent fluctuations.

Stochastic Dynamics Simulation

The influence of the solvent on the dynamics of a solute molecule can be mimicked by the inclusion of a frictional force and a random force in Newton's equations of motion (see Equation 4). The width of the Gaussian distribution of the random force $R_i(t)$ is related to the friction coefficient γ_i by the second fluctuation-dissipation theorem

$$\langle R_i(o) \cdot R_j(t) \rangle = 6 m_i \gamma_i k_B T_{ref} \delta_{ij} \delta(t), \qquad 7.$$

where k_B is Boltzmann's constant and T_{ref} is the reference temperature of the solvent bath (45). The choice of appropriate atomic friction coefficients γ_i will in general depend on the type of system that is considered. It may be derived from the solvent viscosity η and the atomic radius R and mass M of a solvent molecule via Stokes' law

$$\gamma_i = (6\pi R \eta / \mathrm{M}) w_i, \qquad 8.$$

in which the parameter w_i represents the degree of solvent exposure of solute atom i (45). A comparison of the dynamic properties of an undecapeptide, cyclosporin A, in water and in CCl_4 as obtained from a stochastic dynamics (SD) simulation with those obtained from MD simulations with explicit treatment of these solvent molecules, shows that the SD simulation technique offers a good approximation of the mean dynamic solvent effect (45).

OUTLOOK

For an accurate description of the structure, mobility, dynamics, and energetics of a biomolecule in solution, a simulation including explicit treatment of solvent molecules and periodic boundary conditions to minimize edge effects is generally necessary. When choosing an atomic interaction function, the solute-solvent terms should be balanced with

respect to the solute-solute and solvent-solvent terms to ensure proper solvation behavior. For systems containing charged atoms, the long-range electrostatic interaction should be included, at least in an average manner. The inclusion of counterions in a simulation is only recommended when a well-equilibrated initial ion distribution is available and the simulation period is longer than the relaxation time of the ion distribution. Simulations including explicit solvent molecules may be made more accurate by the inclusion of polarizability into the biomolecular and solvent force fields.

The approximate treatment of solvent effects in the form of mean solvation models works well for apolar solvents but poses considerable difficulties to the definition of a simple, efficient, and yet accurate potential of mean force to be used for large biomolecules. SD simulation yields a good approximation of the mean dynamic effects of a solvent on a solute.

Finally, we note that the lack of detailed experimental data with respect to solute-solvent interactions at the atomic level is hampering both the testing of atomic force fields, which include explicit solute-solvent interaction terms, and the calibration of the parameters of the empirical mean-solvation-force models against experiment. Once the reliability of simulation models is well established, computer simulation provides a basis upon which to build the connection between biomolecular structure, dynamics, and energetics on the one hand and biomolecular function on the other.

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