European Journal of Medicinal Chemistry 91 (2015) 27–42

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Implicit solvent methods for free energy estimation

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ARTICLE INFO

Article history:
Received 19 June 2014
Received in revised form
21 August 2014
Accepted 23 August 2014
Available online 25 August 2014

Keywords:
Implicit solvent models
Poisson–Boltzmann equation
Generalized Born model
Continuum electrostatics
Molecular dynamics

ABSTRACT

Solvation is a fundamental contribution in many biological processes and especially in molecular binding. Its estimation can be performed by means of several computational approaches. The aim of this review is to give an overview of existing theories and methods to estimate solvent effects giving a specific focus on the category of implicit solvent models and their use in Molecular Dynamics. In many of these models, the solvent is considered as a continuum homogenous medium, while the solute can be represented at the atomic detail and at different levels of theory. Despite their degree of approximation, implicit methods are still widely employed due to their trade-off between accuracy and efficiency. Their derivation is rooted in the statistical mechanics and integral equations disciplines, some of the related details being provided here. Finally, methods that combine implicit solvent models and molecular dynamics simulation, are briefly described.

1. Introduction

It is well accepted that the role of solvent in biochemical processes is crucial. The estimation of hydration energy, binding energy, pKa of ligands or titratable protein residues heavily depends on a good description of the solvent behavior. The delicate balance between entropic desolvation penalty and enthalpic gain, that often characterize protein–protein and protein–ligand binding, is an example of a phenomenon extremely challenging to be quantitatively described [1]. In Molecular Dynamics, the calculation of the evolution and the equilibration of the solvent degrees of freedom often constitute the main sources of computational cost of the simulation. When performing a Monte Carlo move in a system composed by biomolecules surrounded by explicit solvent, the probability of randomly drawing a configuration where the solute and solvent displacements are compatible is practically negligible. Interestingly, one is not usually interested in knowing the solvent behavior per se, but rather its effects on the solute. In this context, implicit solvent methods find their application, aiming at reproducing the overall, thermally averaged, solvent effect at a lower computational cost.

This approach can be justified by a mean field approximation of the solvent in statistical mechanical terms [2]. Intuitively, one of the underlying assumptions that justify considering water molecules as a continuum medium is their relatively short relaxation time. The time typically needed by water molecules to react to a perturbation is much shorter than that corresponding to macromolecular conformational changes. In a pictorial view, and within the time frame of a typical water molecule displacement, the aqueous solvent 'sees' the protein in a fixed conformation, and, conversely, the protein cannot 'distinguish' among contributions of individual bulk water molecules. Of course, this kind of reasoning cannot be applied to water molecules that are undergoing a specific interaction and its validity can be also questioned in the case of water molecules located in deep pockets where the diffusion can be very different from that in the bulk solvent. However, implicit solvent models neglect the individual molecular behavior of the solvent with respect to explicit solvent simulations. As a consequence, some important phenomena that involve, for instance, hydrogen bonds, hydrophobic effects and, in general, a non-bulk solvent behavior can be missed [2]. Despite the mentioned approximations, implicit methods are still of wide interest because of their algorithmic efficiency, the much reduced number of degrees of freedom requiring simulation and equilibration, and the relatively good compromise between model accuracy and efficiency [3].

Implicit solvent methods can be used for several aims: fixed point calculations, polarizable solvent simulations and scoring docking poses [4–6]. They can be run in conjunction with either a classical atomistic treatment of the solute [7,8], or with quantomechanical calculations [9]. The physical phenomenon that is mostly, but not exclusively, represented in implicit solvent approaches is the linear response to the electric field generated by the

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http://dx.doi.org/10.1016/j.ejmech.2014.08.064
0223-5234/

solute. Usually, this response is originated by molecular polarization but also the salt effects can be, to some extent, accounted for.

Here, a general derivation of several implicit solvent models from statistical mechanical foundations is provided and then some specific approaches are described, grouped in: Semi-Heuristic, Poisson–Boltzmann (PB) based, Generalized Born (GB), Integral Equation based and combined methods, i.e. those that join PB or GB methods with atomistic simulations. Finally, other approaches are mentioned with their own peculiarities.

2. Implicit solvent description in the statistical mechanics framework

Let us distinguish the Cartesian coordinates of a system in those, **X**, describing the solute, and those, **Y**, describing the solvent, which can also possibly contain a dissociated salt. For a system at the thermodynamic equilibrium characterized by the temperature T, the joint probability of given configuration, that is of the (**X**,**Y**) pair, is given by Ref. [2]:

$$P(\mathbf{X},\mathbf{Y}) = \frac{\exp(-U(\mathbf{X},\mathbf{Y})/(k_BT))}{\int \exp(-U(\mathbf{X},\mathbf{Y})/(k_BT))\mathrm{d}\boldsymbol{X}\mathrm{d}\boldsymbol{Y}} \tag{1}$$

where $U(\mathbf{X},\mathbf{Y})$ is the total potential energy of the system, the denominator is a normalization coefficient called partition function and k_B is the Boltzmann constant. We assume that the potential energy can be written as the sum of intra-solute (SS), intra-solvent (WW), and solvent-solute (WS) interactions. This assumption, which is always verified in traditional pair-wise additive force fields, reads:

$$U(\mathbf{X},\mathbf{Y}) = U(\mathbf{X})_{SS} + U(\mathbf{Y})_{WW} + U(\mathbf{X},\mathbf{Y})_{WS} \tag{2}$$

Due to the fact that $P(\mathbf{X},\mathbf{Y})$ is the probability density of the system, any macroscopic quantity can be obtained by computing the corresponding statistical average, or expectation value. Henceforth, the expectation of the microscopic function $Q(\mathbf{X},\mathbf{Y})$ corresponding to the observable Q will be indicated as $\mathrm{E}_{\mathbf{X},\mathbf{Y}}\{Q(\mathbf{X},\mathbf{Y})\}$, where the subscript specifies on which variables the expectation operator acts, or, alternatively, by $<Q(\mathbf{X},\mathbf{Y})>$.

Let us now consider an observable Q corresponding to the average of a microscopic function of only the solute coordinates $\{\boldsymbol{X}\}$:

$$Q = E_{\mathbf{X},\mathbf{Y}}\{Q(\mathbf{X})\} = \int Q(\mathbf{X})P(\mathbf{X},\mathbf{Y})\mathrm{d}\boldsymbol{X}\mathrm{d}\boldsymbol{Y} \tag{3}$$

From this equation it is clear that in order to get the needed average, the knowledge of the possible solvent configurations, together with their statistical weights, is needed. The global probability distribution governing the thermodynamic equilibrium in the canonical ensemble is the Boltzmann distribution. An important question that may arise is whether we can still get an average value of a solute observable without having a specific knowledge of the configurations of the solvent.

To this aim, instead of considering the joint probability, one can consider the restriction of the probability to the solute, by integrating over the solvent space. Therefore one can write:

$$P(\mathbf{X}) = E_{\mathbf{Y}}\{1(\mathbf{X},\mathbf{Y})\} = \int 1(\mathbf{X},\mathbf{Y})P(\mathbf{X},\mathbf{Y})\mathrm{d}\boldsymbol{Y} = \int P(\mathbf{X},\mathbf{Y})\mathrm{d}\boldsymbol{Y} \tag{4}$$

This can be formally considered as the average value over **Y**, (expectation operator is over **Y**) of an observable always equal to 1 for each value of the pair $\mathbf{X},\mathbf{Y}$. Then, in a system at temperature T, the reduced probability is:

$$P(\mathbf{X}) = \frac{\int exp\left(-\left[U(\mathbf{X})_{SS}+U(\mathbf{Y})_{WW}+U(\mathbf{X},\mathbf{Y})_{WS}\right]\Big/(k_BT)\right)\mathrm{d}\boldsymbol{Y}}{\int exp\left(-\left[U(\mathbf{X})_{SS}+U(\mathbf{Y})_{WW}+U(\mathbf{X},\mathbf{Y})_{WS}\right]\Big/(k_BT)\right)\mathrm{d}\boldsymbol{X}\mathrm{d}\boldsymbol{Y}} \tag{5}$$

that we can more compactly rewrite as:

$$P(\mathbf{X}) = \frac{exp(-W(\mathbf{X})/(k_BT))}{\int exp(-W(\mathbf{X})/(k_BT))\mathrm{d}\boldsymbol{X}} \tag{6}$$

This last formula has a nice analogy with the general form of the joint distribution. This time, however, the joint probability is replaced by its solvent-averaged version $P(\mathbf{X})$ and for this reason the potential $W(\mathbf{X})$ is called Potential of Mean Force (PMF). It can be shown that in Cartesian coordinates if the chosen observable is the force then it holds:

$$E_{\mathbf{Y}}\{\boldsymbol{F_i}(\mathbf{X},\mathbf{Y})\} = -\frac{\partial \mathrm{W}(\mathbf{X})}{\partial \mathbf{x}_i} \tag{7}$$

From this fact derives the name potential of "mean force", where "mean" means, in this case, average with respect to the solvent degrees of freedom. As other potentials, its absolute value is up to a constant offset. It is usual to set the PMF reference as the value where there are no interactions between solvent and solute, that is $U(\mathbf{X},\mathbf{Y})_{WS} = 0$, in particular we can set this relation:

$$W(\mathbf{X}) = U(\mathbf{X})_{SS} + \Delta G_S(\mathbf{X}) \tag{8}$$

This relation is particularly interesting because it mixes the free energy $\Delta G_S(\mathbf{X})$ (solvent-solute related) to the intra-solute potential energy $U(\mathbf{X})_{SS}$; hence $W(\mathbf{X})$ is a free energy.

In this setting, we can observe that the following relation holds:

$$exp\left(-\frac{W(\mathbf{X})}{k_BT}\right) = \frac{\int exp\left(-\left[U(\mathbf{X})_{ss}+U(\mathbf{Y})_{ww}+U(\mathbf{X},\mathbf{Y})_{ws}\right]\Big/(k_BT)\right)d\boldsymbol{Y}}{\int exp\left(-U(\mathbf{Y})_{ww}/(k_BT)\right)d\boldsymbol{Y}} \tag{9}$$

In particular when $U(\mathbf{X},\mathbf{Y})_{WS} = 0$, then we must have $\Delta G_S(\mathbf{X}) = 0$. Consistently, the term ΔG_S is named solvation free energy and it is the energy needed to transfer the solute from vacuum to the solvent.

We can introduce now the concept of thermodynamic integration. We write the potential energy as: