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# From Microscopic Monte-Carlo Simulations to Macroscopic Solvation Models

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The hydration free energy of model ionic and hydrophobic solutes are studied. Based on Metropolis Monte-Carlo simulations in the extended NpT ensemble, the Landau free energy surfaces, dependent on solute parameters, were determined. In particular, the solute charge as well as the diameter and well depth of the Lennard-Jones potential were chosen as the order parameters.

Regarding the charge and the Lennard-Jones potential diameter, simulations confirmed and/or completed other results obtained so far. The role of the third parameter, the potential well-depth, was studied in a more detail. It modifies slightly the solvation radius of the solute, and therefore influences the solvation free energy.

## 1 Introduction

Solvation/hydration phenomena take place in biomolecular systems and play very important role in technological processes. Therefore, theoretical description of these phenomena are very important. First of all, one has to estimate the free energy of solvation in such processes, which is a difficult problem by itself, and until now not solved sufficiently accurately. Also theoretical description of "subprocesses", such as hydrophobic and hydrophilic solvation, is still a challenging task.

In this work we study the solvation free energy of model ionic and hydrophobic solutes. From the results of exhaustive series of Metropolis Monte-Carlo simulations we determined the free energy functions, which are dependent on solute "control parameters". Our main goal is interpretation of the simulation results based on implicit solvent models and description of the solvation processes and binding free energies of more complex systems in the space of control parameters.

## 2 Methodology

Sampling of the configuration space was carried out using Metropolis Monte-Carlo method. Each simulation was carried out in the extended isothermic-isobaric ensemble with additional degree of freedom, either the solute charge  $q$  or one of the solute Lennard-Jones interaction potential parameters,  $\varepsilon$  or  $\sigma$ . In each simulation only one solute parameter was varied with the other two being fixed. The multi-window umbrella sampling approach was

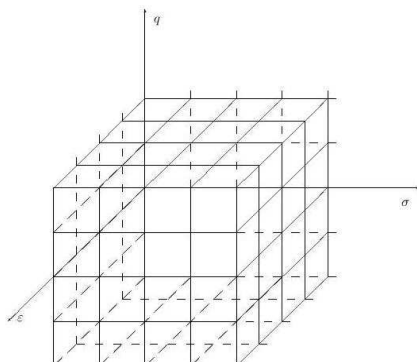


Figure 1. Simulation scheme. The axes represent 3 solute parameters under studies,  $\varepsilon$ ,  $\sigma$  and  $q$ . Each line corresponds to a set of simulations (in consecutive windows) with one parameter being a simulation degree of freedom and the other two being fixed. For practical reasons, only one parameter was changed during one simulation. The ranges of parameters covered in this work:  $\varepsilon \in [0.05; 12.8]kJ/mol$ ,  $\sigma \in [2; 5]\text{\AA}$ ,  $q \in [-1; 1]e$ .

used to assure effective sampling of the parameter space. The results from consecutive simulation windows were merged together based on the following formula:

$$\Delta G(\xi) = -k_B T \ln \frac{\rho_{bias}(\xi_j)}{\rho_{bias}(\xi_i)} - \Delta V_{bias,ij}(\xi) \quad (1)$$

where  $\xi$  is either  $q$ ,  $\varepsilon$  or  $\sigma$ ,  $\rho$  is the probability density in the extended ensemble and  $V_{bias}$  is the biasing potential. The indices  $i, j$  indicate that the  $\Delta G_{ij}$  is obtained from two consecutive and overlapping windows. Lynden-Bell et al.<sup>1</sup> applied this method earlier in the molecular dynamics simulations, sampling only  $q$  and  $\sigma$ .

### 3 Results

Results of our simulations with variable charge, are in good agreement with earlier work<sup>1</sup>, namely, we have observed similar asymmetry of the free energy of ionic solvation for positive and negative charges. The dependence of the the solvation free energy on  $\varepsilon$  has not been studied before. The selected results are shown in Figure 2 (left plot).

One may notice the difference between curves corresponding to the neutral solute, in comparison to the charged solutes. Also clear asymmetry between positive and negative ions is visible. Using the results of one-dimensional simulations we were able to represent the free energy of solvation as a function of single parameter, with two other parameters fixed. We also were able to develop two-dimensional free energy functions. The example of the free energy of solvation as a function of Lennard-Jones parameters -  $G(\varepsilon, \sigma)$  - is shown in Figure 2 (right plot). We failed to merge the  $G(\varepsilon)$  and  $G(\sigma)$  results of simulations with fixed negative solute charges.

The simulations yielded many structural data concerning the first solvation shell of water molecules. This information is very helpful in understanding the solvation process and also the shape of the free energy curves. These data are not presented here.

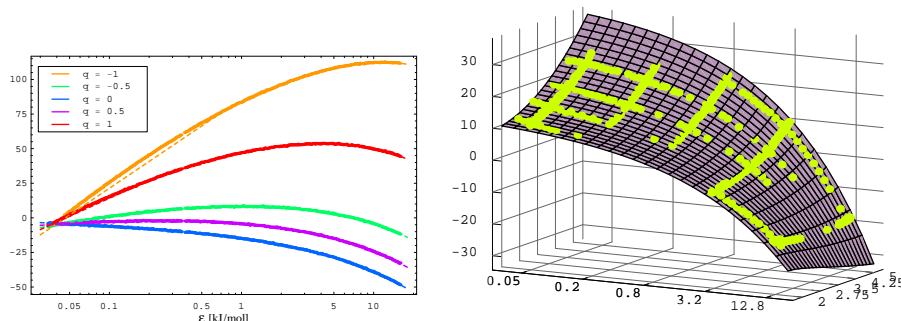


Figure 2. The solvation free energy curves with fitted functions. Left plot:  $\Delta G(\varepsilon)$  for five fixed values of the solute charge,  $q$  (curves were shifted for better view). In all presented cases  $\sigma$  was fixed at  $3.5\text{\AA}$ . Right plot:  $\Delta G(\varepsilon, \sigma)$ , the solute charge was fixed at  $q = 0$ ; vertical axis presents  $\Delta G[\text{kJ/mol}]$ , left horizontal axis shows the solute parameter  $\varepsilon[\text{kJ/mol}]$ , and right horizontal axis shows the solute parameter  $\sigma[\text{\AA}]$ . The bivariate free energy surface was calibrated with respect to experimental solvation free energies of methane<sup>2</sup>.

## 4 Concluding Remarks

The results from the series of Monte Carlo simulations allowed us to propose solvation free energy functions dependent on solute parameters:  $G(q)$ ,  $G(\varepsilon)$ ,  $G(\sigma)$  and some of  $G(\varepsilon, \sigma)$ . These solvation free energy functions may be further interpreted based on the mesoscopic solvation models, such as the one recently developed by Gallicchio et al.<sup>3</sup>.

The  $\varepsilon$  and  $\sigma$  sampling results from simulations with the fixed negative charge ( $q = -1$ ,  $q = -0.5$ ) did not merge, probably because the first solvation shell of water molecules did not maintain the tetrahedral structure around the small solute ( $\sigma = 2\text{\AA}$ ) during the  $\varepsilon$  sampling. However, such structure is present during the  $\sigma$  sampling simulations (in the region of small  $\sigma$  and fixed small  $\varepsilon$ ).

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