# Hydration free energy of calcium

## Introduction

In this exercise Q and Qgui will be used to calculate the hydration free energy of an ion in water. The practical is based on the free energy perturbation (FEP) method. The simulation setup uses a spherical boundary condition, that is, a droplet of water with the ion in the simulation centre. The exercise consists of four parts: building the model of a ion in a droplet in water, generation of the parameters and topology for the system, running the actual FEP simulation and lastly, analysis of the output.

## Procedure

### Building ion and creating parameters and topology

We will use Qgui to build the ion:

1. Start Qgui by writing **Qgui -p**
2. First you need to specify the force field parameter file (Qoplsaa.prm) and the library file (Qoplsaa.lib) by clicking on Setting in the File menu. You will find the files under /$HOME/QGUI/FF/OPLS. Secondly, you need click on Edit where it says Use submission script and click on save. Thirdly, all executables should version 6 and not 5 (Qpre6, Qdyn6, Qfep6 and Qcalc6). Once all these three steps are completed you click on save.
3. Click on View in PyMOL
4. Select atom in Atoms and then click Add.
5. Click on Save as and give a name for the pdb file (for example ca.pdb).
6. Quit PyMOL
7. Once back in the main Qgui window, you can now load the file you created
8. Now you go to Prepare Topology
9. Edit the pdb: change the atom name and residue name to CA and CA and save.
10. Change the size of the simulation sphere to 12 Å.
11. Click Run.

### Setting up the FEP simulations

1. First you need to load the topology (something.top) you made in the previous step in the Main window.
2. From the Setup menu in Qgui select FEP
3. Add the ion as Q-atom
4. In setup select section select Charges
5. Click on the ion and change j1 to 0, and click on change charges
6. To configure the MD simulation, click on Configure MD.
7. Here we only need to add an Atom restraint on the ion: select the ion, click on Add restraint and then save.
8. Click on write
9. Normally, you could have clicked on Run, but this does not work, so you click on Write.

10. You will need to go into a terminal and cd to the directory 300.00/1/ and chmod +x on run.sh. Then execute the run.sh. This script will take around 10 minutes to finish.

## Analyzing the output

Once the simulations are done, you analyze them in Qgui:

1. Click on FEP under Analzye
2. Add a title
3. Add runs (just select the 300 folder)
4. Click on FEP summary

## Correcting for system size

We are using as spherical model and need to correct for using a finite system, that is, we are not simulating an infinite system. This can be done by using the Born fomula:

$$\Delta G_{Born} = -166 \frac{Q_i^2}{R_{Born}} \left(1 - \frac{1}{\varepsilon(T)}\right)$$

Here, Qi refers to the charge in the cavity with radius $R_{Born}$ embedded in a medium with dielectric constant $\varepsilon(T)$.

Your value should be about -44 kcal/mol.
The experimental value ranges from -360 ot -380 kcal/mol.

## Radial distribution functions

We will use the software vmd to examine the trajectories.

1. Make sure that you are in the directory where you have your output files and start vmd by typing vmd.
2. Load the structures by clicking on New molecule under File, and load the topology pdb file (ca_top.pdb). Then you can load the md_0000_1000.dcd file into the same object as your pdb file (i.e select the name of the pdb file in the Load files for: dropdown menu). Click on load and close the window.
3. In order to make it easier to visualize the molecular system, go to Representations under Graphics.
4. Here you should first change the Drawing Method to CPK. Next, create a new representation, and select Drawing Method VDW and in the Selected Atoms box write name Ca2. Now you should see your ion in the center of the window.
5. Examine the structures by playing with the control panel.
6. To calculate the radial distribution function, go to Extensions->Analysis->Radial pair distribution function. Here you first need to choose the choose the correct molecule (name of your object). Selection 1 should be name Ca2, Selection 2 should be name O. Untick the box Use pbc, tick the box Display Int(g(r)). Click Compute g(r).
7. What is the average ion – oxygen distance in for the water molecules in the first solvation shell?
8. How many water molecules are in the first solvation shell?

## Questions for reflection

1. How well does your value compare with the experimental?
2. Are there any contributions that is missing?
3. How could you use FEP for changing larger molecules than an ion? (Assume that you are using Qgui)

## Reference

Duarte, F., Bauer, P., Barrozo, A., Amrein, B. A., Purg, M., Åqvist, J., & Kamerlin, S. C. L. (2014). Force Field Independent Metal Parameters Using a Nonbonded Dummy Model. *The Journal of Physical Chemistry. B*, *118*(16), 4351–4362. http://doi.org/10.1021/jp501737x