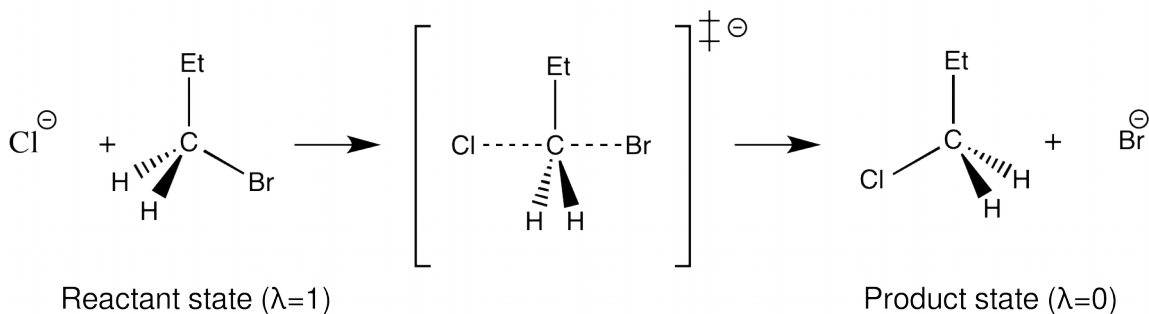


If you have a Windows system you should install an ssh client, we recommend MobaXterm (<http://mobaxterm.mobatek.net/>)
 For visualizing trajectories (if you have no idea what that means, please ask), we will be using VMD (<http://www.ks.uiuc.edu/Research/vmd/>)

EVB tutorial

In this tutorial we will cover the basic steps involved in preparing input files to be used with the Q computer simulation package. We will be analyzing a simple SN2 reaction between 1-bromopropane and a chloride anion in which 1-chloropropane and a bromine anion are formed. We will perform the calculation in the gas-phase as well as in an aqueous solution and analyze the effect of solvent on the reaction activation free energy (ΔG^\ddagger). The reaction scheme is shown below:



We will consider the reactants and products as two separate states, each with their own value of the mapping parameter(λ). In the reactant state the value of $\lambda = 1$ and in the product state $\lambda = 0$, the total energy of the subsystem is calculated with the equation written below where E_1 corresponds to the reactant state, and E_2 to the product state.

$$E = \lambda E_1 + (1 - \lambda)E_2$$

Each bin used in the simulation corresponds to decrease in λ , i.e. the number of bins (Usually 51) determines how many equal steps it will take for λ to go from 1 to 0. In each bin the phase space will be sampled using molecular dynamics, and the data used to determine the reaction energy profile.

For a successful EVB simulation a good reference reaction is essential, in our case we will calculate the corresponding reaction in the gas-

phase using DFT, more specifically the M06-2X functional with the 6-31+G(d,p) basis set. The calculation will be performed using the Gaussian 09 program package. We will then use the calculated reaction parameters, the reaction free energy (ΔG_0) and the ΔG^\ddagger , to determine the value of the coupling constant (H_{12}) and the gas shift (α) in the EVB gas-phase calculation. Those parameters will then be used to calculate the energetics of the reaction in the aqueous phase.

To begin the EVB calculation we first need the forcefield parameters, namely the partial charge for each EVB atom, for both the reactant and product states. Due to time limitations the force field parameters will be provided for you, they were obtained with Schrodinger Maestro (<http://www.schrodinger.com/freemaestro/>) and AmberTools Antechamber (<http://ambermd.org/#AmberTools>). Alternatively they can be calculated using quantum mechanical calculations.

The EVB simulation

We will be simulating the reaction using the Q molecular dynamics program (<http://xray.bmc.uu.se/~aqwww/q/>).

When accessing the cluster, load the necessary software modules:
module load q/5.06-20140814-intel
module load qscripts/20150811

Q consists of three main utilities:

- qprep5 (used to create the topology from pdb structure and library/parameter files)
- qdyn5 (used to run MD)
- qfep5 (used for free energy calculations)

Connect to the HPC main node computer and create a folder for your calculations. Enter the newly created directory and issue the command:

```
"cp -r /tmp/probr_cl ."
```

1. BUILD THE TOPOLOGY (qprep5)

Prepare the structure so that Q can read it, and determine force field parameters.

Enter the folder the folder *0-topol*

Visualize the structure (*probr_cl.pdb*) with a visualization program (VMD, Chimera)

Create qprep5 input with “*nano prep.inp*”

```
# read the library files
readlib ./0-ff/qoplsaa.lib
readlib ./0-ff/prb.lib
readlib ./0-ff/cl-.lib
# read the force field parameter file
readprm ./0-ff/qoplsaa_prb_cl-.prm
# read the structure
readpdb probr_cl.pdb
# create a spherical boundary of 20A around atom C1 on residue number 1
boundary sphere 1:C1 20
# solvate the system
#solvate 1:C1 20 1 HOH
# make and write the topology
maketop probr_cl.top
writetop probr_cl.top
# write the solvated structure
writepdb probr_cl_start.pdb y
quit
```

Figure 1. Qprep5 input for topology preparation

CTRL-X then press Y and Enter to save and exit.

Exit folder 0-topol

Enter folder 0-ff

The files found in this folder are :

.lib - library files

contain information about residues:

- pdb residue name
- pdb atom names
- ff atom types
- charges
- connect records
- improper dihedrals, charge groups)

Basically serves as a connection between the pdb structure and the force field parameters.

.prm - parameter files

contain force field parameters:

- atom types

- bond types
- angle types
- torsion types
- improper types

Exit folder 0-ff

Prepare the topology with:
“qprep5 < prep.inp > prep.log”

Enter folder 1-makeFEP

Open the fep file, it contains the changes in force fields, like charges and atom types, when moving from one EVB state (reactants) to the other (products).

Exit folder 1-makeFEP

With this the topology is prepared and we can move on to the relaxation

Exit folder 0-topol

2. SYSTEM RELAXATION (gdyn5)

Enter 1-relax

Create relaxation input with “nano relax_300K.inp”

```

[MD]
steps                100000
stepsize              1
temperature           300
random_seed           2156
initial_temperature   300

[intervals]
non_bond              30
output                5000
trajectory            5000

[files]
topology              probr_cl.top
final                 relax_300K.re
trajectory            relax_300K.dcd
fep                   probr_cl.fep

[sequence_restraints]
1 12 0.5 1 0 # solute

[distance_restraints]
1 11 0.0 3.5 3.0 2 # C-Br (leaving group)
1 12 0.0 3.5 3.0 1 # C-Cl (nucleophile)

[lambdas]
1.00 0.00

```

Figure 2. Qdyn5 input for the relaxation step

Copy the topology file (*probr_cl.top*) from *0-topol* and the fep file (*probr_cl.fep*) from *0-topol/1-makeFEP* to this directory (*1-relax*).

Create a script to submit the calculation to the HPC queue, with "*nano run_q_relax.sh*".

```
#$ -N SN2-gas_phase
#$ -pe mpi 1
#$ -cwd
#$ -j y
#$ -S /bin/bash

# Load modules:
module purge
module load q/5.06-20140814-intel

qdyn5p relax_300K.inp > relax_300K.log
```

Figure 3. Job submission script

Submit the job with “*qsub run_q_relax.sh*”.

Copy the trajectory file **relax_300K.dcd** and the structure file **probr_cl_start.pdb** to your computer and use VMD to visualize the it.

Exit folder 1-relax

3. FEP Calculation

Enter folder 2-fep

Three files have already been prepared for you:

- genfeps_eq.template (template for preFEP equilibration input)
- genfeps_fep.template (template for 51 FEP inputs)
- run_feps_q.sh (submission script)

These are input files for the script *q_genfeps.py* which is used to *qdyn5* inputs for each frame of the FEP simulation, as well as a pre-FEP equilibration input.

The replicas start of with the exact same coordinates, but their initial velocity distributions are different.

```
q_genfeps.py 51 ../1-relax/relax_300K.inp genfeps_fep.template \  
genfeps_eq.template --rs run_feps_q.sh --repeats 4
```

To submit all the calculations enter the command:

```
for i in rep_00*; do cd $i; qsub run_feps_q.sh; cd ../; done
```

To concatenate all trajectory files from different frames

trjcat.sh

Copy all.dcd to your computer along with probr_cl_start.pdb and view the trajectory.

4. The reaction in aqueous solution

Repeat all the steps but now for the aqueous solution, remove the comment from the solvate line in the prep.inp. The submission scripts are modified a bit, so that we can make use of parallelization.

Calibrate the gas phase simulation to QM activation and reaction free energies with the *q_automapper.py* script:

q_automapper.py X Y 80 10

Where X and Y are the ΔG^\ddagger and ΔG_0 , respectively.

The last line should look something like this:

q_mapper.py 83.5584816576 8.23512362102 --nt 1 --bin 51 --skip 50 --min 10 --temp 300.0

Now run this in wat/2-fep to map the water reaction to the obtained H_{12} and α parameters.

To view the energy profiles run the following commands :

q_analysemaps.py

and

./qa.ViewPlots.sh

to view the energy profiles

All energy files are contained in the file *q_mapper.log*

Using VMD, plot reactive distances (C-Cl, C-Br, Cl-Br) and angles (Cl-C-Br)