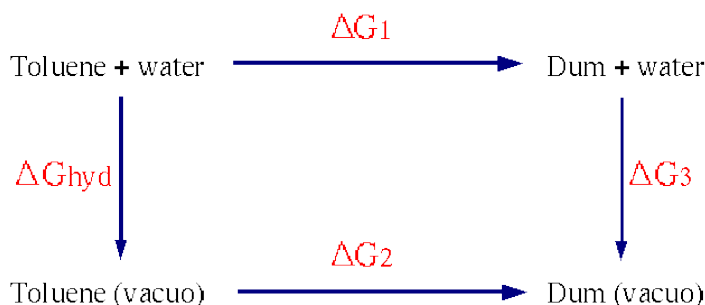# Exercise 9

In this exercise you are to calculate the hydration free energy of a molecule of toluene (a commonly used solvent). In order to do this, the following thermodynamic cycle can be utilised:

In processes 1 and 2 the atoms of the toluene molecule are mutated into dummy atoms that do not have any non-bonded interactions. Process 3 can be seen as the hydration free energy of a molecule consisting of dummy atoms; this should be zero as dummy atoms do not interact with their environment. Therefore only processes 1 and 2 need to be modelled for the calculation of the hydration free energy of toluene.

The files needed for the simulations are to be found in the Ex9.tar.gz. Have a look at the `toluene.itp` file – it contains already the parameters necessary for the transformation of all atoms into dummy atoms:

- In the atom definition section an additional description with identical mass, but without charge and defined as atom type `DUM` has been added.

- All force field parameters are contained twice – once for the starting, and once for the final state. In our case both are identical.

For simulations of the system in vacuo, references to solvent molecules in the `.mdp` files need to be removed.

You should start with setting up a box (3 x 3 x 3 nm^3 is a good size) containing only the (single) toluene molecule. This can be done with either the `editconf` or `genbox` command. For simulations in water, the system needs to be solvated. This can be done using the `genbox` command with the `-cs` option (without additional argument). You might need to perform an energy minimisation on the hydrated system in order to get rid of bad contacts (you can use the `em.mdp` from exercise 7).

The following needs to be done for both the hydrated (process 1) and in vacuo (process 2) system:

- Do a initial equilibration of the model using the `EQ.mdp`.

- Choose a number ($n \geq 15$) of *lambda*-values to run the simulations at. It is highly recommendable to run each simulation in a separate directory.

- Adjust the `init_lambda` value in the `equi0.00.mdp` and `run0.00.mdp` (and possibly the file names) to the value for the actual calculation.

- Perform first an equilibration (`equi0.00.mdp`) and then a production run (`run0.00.mdp`) at each value for lambda.

- Each run should produce a file `dhdl.xvg` (name can be changed with the `-dhdl` option of `mdrun`) containing the $\frac{\partial \mathcal{H}}{\partial \lambda}$ values calculated at each step of the simulation. You can extract the average using the `g_analyze` tool.

Finally you can plot the $\frac{\partial \mathcal{H}}{\partial \lambda}$ as a function of λ separately for each process, and integrate over λ to obtain the change in free energy for the respective process (the integration can be done directly in `xmgrace`).

What method has been used in the determination of the change in free energy in this exercise?
What value do you get for the hydration free energy of toluene?
Is that value realistic?
Attach the $\frac{\partial \mathcal{H}}{\partial \lambda}$ curves and any other material you find illustrative!