

1 Free Energy Calculation Using Qfep

Performing free energy perturbation (FEP) calculations with Q involves running a set of consecutive input files which have the mapping parameter λ ranging in a desired way (usually $[1, 0]$ to $[0, 1]$ for two states). Qfep is a program which reads the energy files generated by Qdyn and calculates the total change in free energy for the complete perturbation from state A (ε_1) to state B (ε_2). The difference in free energy between the two states is calculated by Zwanzig's formula:

$$\Delta G = \sum \Delta g = \sum -R \cdot T \cdot \ln \left\langle e^{-\left(\frac{\Delta V_{\text{eff}}}{R \cdot T}\right)} \right\rangle_A \quad (1)$$

Here, ΔV_{eff} is defined as the difference in V_{eff} between two adjacent perturbation steps.

The program returns a list containing average energies and λ values for each file. After that, the free energy change between each perturbation step (file) is summarized. The change is calculated relative to both the previous and the following perturbation step (dG_f and dG_r for forward and reverse directions, respectively). The accumulated sum of the energy changes between ε_1 to ε_2 is also given (sum(dG_f) and sum(dG_r)), as well as the average accumulated change calculated from the forward and reverse directions (hdG_i).

Qfep also calculates free energy functions, or potentials of mean force, using the perturbation formula. The reaction coordinate X is defined as the energy gap between the states $X = \Delta V = \varepsilon_1 - \varepsilon_2$ and is divided into intervals X_m (bins). The first term in the equation represents the free energy difference between the initial state ε_1 and the mapping potential V_i :

$$\Delta G(X_m) = \Delta G(\lambda_i) - R \cdot T \cdot \ln \left\langle e^{-\left(\frac{E_g(X_m) - V_i(X_m)}{R \cdot T}\right)} \right\rangle_i \quad (2)$$

The second term represents the free energy difference between the mapping potential V_i and the ground state potential E_g . The MD average in this term is only taken over those configurations where X belongs to X_m .

$$\Delta G(\lambda_i) = -R \cdot T \cdot \ln \sum_{n=0}^{i-1} \left\langle e^{-\left(\frac{V_{n+1} - V_n}{R \cdot T}\right)} \right\rangle_n \quad (3)$$

E_g is the solution to the secular determinant. The system is then represented by a $n \times n$ EVB Hamiltonian.

$$\begin{bmatrix} H_{11} & H_{12} \\ H_{21} & H_{22} \end{bmatrix}$$

Here, H_{11} and H_{22} are the energies of the two valence states which are calculated using classical force fields. For a two-state representation, the solution becomes:

$$E_g = \frac{1}{2} \cdot (\epsilon_1 + \epsilon_2) - \frac{1}{2} \sqrt{(\epsilon_1 - \epsilon_2)^2 + 4 \cdot H_{12}^2} \quad (4)$$

where H_{ij} or H_{12} is the off-diagonal matrix element representing the quantum mechanical coupling of the states. This coupling is zero for normal FEP calculations. $H_{ij} \neq 0$ results in the mixing of states i and j , which is desired when calculating reaction free energy profiles for reactions represented by the empirical valence bond (EVB) model. In Qfep, the off-diagonal element is a function of the form:

$$H_{ij} = A_{ij} \cdot (e^{-(\mu(r_{ij}-r_0)+\eta(r_{ij}-r_0)^2)}) \quad (5)$$

where r_{ij} is the measured distance between the reacting atoms. By choosing μ and η differently, H_{ij} can be either a constant, an exponential function, or a Gaussian function. The EVB method allows calibration of simulated reference reactions to experimental data obtained from gas-phase or solution experiments. The two EVB parameters H_{ij} (mostly A_{ij}) and $\Delta\alpha_{ij}$ are varied until the calculated profile and the experimental data coincide. $\Delta\alpha_{ij}$ is a constant energy shift between the states that represent their difference in heat of formation, which is not included in the force field. Generalized, the $\Delta\alpha_{ij}$ parameter determines the ΔG° level, and H_{ij} regulates the degree of mixing of the states at the transition state, i.e., the ΔG^\ddagger level.

The energies describing the FEP functions and the reaction free energy profile are summarized in the last table generated by Qfep. Note that each bin has contributions from several different values of λ . Likewise, each value of λ contributes to the sampling of several different bins.