Derivations for Effective Free Energy Differences

Ian Kenney

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1 Maximum likelihood estimation of the free energies of states

We start with the likelihood function, which defines the likelihood of seeing our measured results given a set of free energy values for the states in our network:

$$L(\{\bar{\Delta}_{ij}\}|\{g_i\}) = \prod_{ij} \exp\left(\frac{-1}{2\sigma_{ij}^2}((g_j - g_i) - \bar{\Delta}_{ij})^2\right) \tag{1}$$

We want to use this function to find the most likely $\{g_i\}$ that fits our data. We can do this by taking the gradient in g-space, $\boldsymbol{\nabla}_g$, and setting it equal to the null vector. Since the likelihood function is monotonic, we can maximize the natural logarithm of (1), as this is will greatly simplify the mathematics. The log-likelihood is given by:

$$\ln L = \sum_{ij} \frac{-1}{2\sigma_{ij}^2}((g_j - g_i) - \bar{\Delta}_{ij})^2 \tag{2}$$

We define the gradient operator as:

$$\boldsymbol{\nabla}_g \equiv \sum_k \boldsymbol{\hat{g}_k} \frac{\partial}{\partial g_k} \tag{3}$$

Taking the gradient of (2) and setting equal to the null vector, we find:

$$\begin{aligned}
\mathbf{0} = \boldsymbol{\nabla}_g \ln L &= \sum_{ij} \frac{-1}{2\sigma_{ij}^2} \boldsymbol{\nabla}_g ((g_j - g_i) - \bar{\Delta}_{ij})^2 &(4)\\
&= \sum_{ij} \frac{-1}{\sigma_{ij}^2}((g_j - g_i) - \bar{\Delta}_{ij})\,[\boldsymbol{\hat{g}_j} - \boldsymbol{\hat{g}_i}] &(5)\\
&= \sum_{ij} \frac{1}{\sigma_{ij}^2}((g_j - g_i) - \bar{\Delta}_{ij})\,[\boldsymbol{\hat{g}_i} - \boldsymbol{\hat{g}_j}] &(6)
\end{aligned}$$

From here, we can compute $\{g_i\}$ numerically using `scipy.optimize.root`, which uses the hybrid Powell method to find the roots of $\boldsymbol{\nabla}_g \ln L$. We provide the root function the jacobian, whose elements are:

$$\begin{aligned}
J_{nm} = \frac{\partial}{\partial g_n} \left(\boldsymbol{\nabla}_g \ln L\right)_m = \frac{\partial}{\partial g_n} \sum_{ij} \frac{1}{\sigma_{ij}^2} \left[(g_j - g_i) - \boldsymbol{\bar{\Delta}_{ij}}\right] (\delta_{mi} - \delta_{mj}) &\quad(7)\\
= \sum_{ij} \frac{1}{\sigma_{ij}^2} (\delta_{nj} - \delta_{ni})(\delta_{mi} - \delta_{mj}) &\quad(8)\\
= \sum_{ij} \frac{1}{\sigma_{ij}^2} \left[\delta_{nj}\delta_{mi} - \delta_{nj}\delta_{mj} - \delta_{ni}\delta_{mi} + \delta_{ni}\delta_{mj}\right] &\quad(9)\\
&\quad(10)
\end{aligned}$$