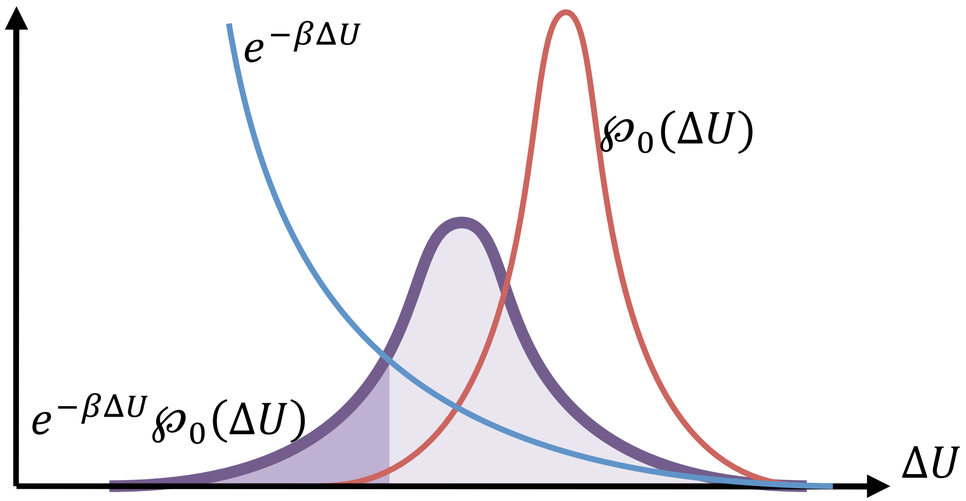
The Zwanzig Relation: Limitations

- In terms of an integral over the distribution of ΔU (instead of over $\rho_o(r^N)$) the Zwanzig relation is,

$$\beta(A_1 - A_0) = -\ln \int e^{-\beta \Delta U} \rho_0(\Delta U) d\Delta U.$$

- Sampling is from the red curve
- Accurate estimation requires the purple curve
- The calculation will not be accurate if U_0 and U_1 are very different!



(from [1])

Other ways to calculate ΔG

- The Bennett Acceptance Ratio (BAR) [3] uses data from two states
- The Multistate Bennett Acceptance Ratio (MBAR) [4] uses data from a series of states
- BAR/MBAR are proven to be statistically optimal
- Thermodynamic integration is based on the fundamental theorem of calculus, integrating one the derivative of the free energy with respect to a parameter
- All of the methods require thermodynamic states with configuration space overlap, meaning that
  - similar configurations have similar energies
  - the most relevant configuration space is similar