> **Today's lecture:** various other methods for computing free energies, including absolute free energies, beyond histogram techniques

Perturbation approaches to free energies

Perturbation techniques have a long history in statistical mechanics and were among the earliest methods used to compute free energy changes in molecular simulations. They were pioneered by Born and Kirkwood in theory in the 1920s and 1930s. In the 1950s, Zwanzig introduced the **free energy perturbation (FEP)** method in the context of Monte Carlo and molecular dynamics simulations.

The basic idea of the method is to compute the free energy between a reference state and some perturbed state. The perturbed state may include an additional particle, a slightly different potential energy function, or a small change in temperature, for example.

The FEP approach is highly general and can be applied to compute many kinds of free energies. Early implementations of the FEP method do not have as good statistical accuracy as multiple histogram reweighting techniques, although subsequent re-formulations have yielded approaches that are equally as accurate and, in some cases, identical to the Ferrenberg-Swendsen reweighting equations.

Basic formalism

In the following example, we will consider the free energy change as one perturbs the potential energy function in the canonical ensemble. Initially the energy function is $U_0(\mathbf{r}^N)$ and we perturb it to $U_1(\mathbf{r}^N)$. The earlier notes on histograms and free energies provided some examples of kinds of perturbations that might be considered. One could also derive an expression in which we perturbed the temperature rather than the potential.

The free energy difference between states 1 and 2 stems from a ratio of partition functions:

$$\beta A_1 - \beta A_0 = \ln \frac{Q_0}{Q_1}$$

$$= -\ln \frac{\left(\frac{Z_1}{\Lambda(T)^{3N} N!} \right)}{\left(\frac{Z_0}{\Lambda(T)^{3N} N!} \right)}$$

$$= -\ln \frac{\int e^{-\beta U_1(\mathbf{r}^N)} d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}$$

We can now re-express the top integral with the following identity:

$$\beta A_1 - \beta A_0 = -\ln \frac{\int e^{-\beta U_1(\mathbf{r}^N) + \beta U_0(\mathbf{r}^N) - \beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}$$

$$= -\ln \frac{\int e^{-\beta \Delta U(\mathbf{r}^N) - \beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}$$

Here, $\Delta U(\mathbf{r}^N) = U_1(\mathbf{r}^N) - U_0(\mathbf{r}^N)$. Notice that this expression is reminiscent of the configurational distribution in state 0:

$$\wp_0(\mathbf{r}^N) = \frac{e^{-\beta U_0(\mathbf{r}^N)}}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}$$

Making this substitution,

$$\beta A_1 - \beta A_0 = -\ln \int \wp_0(\mathbf{r}^N) e^{-\beta \Delta U(\mathbf{r}^N)} d\mathbf{r}^N$$

We can re-express this as an ensemble average in state 0:

$$\beta A_1 - \beta A_0 = -\ln \langle e^{-\beta \Delta U} \rangle_0$$

This important result shows that we can compute the free energy difference between the two states by performing an average over configurations in state 0. Practically, we can perform a simulation in state 0 in the canonical ensemble using, for example, a Monte Carlo simulation. We would then average over the trajectory of that simulation the term

$$e^{-\beta \Delta U}$$

which would require us to compute both the energies U_1 and U_0 in the ensemble. Keep in mind, however, that the trajectory itself would only be guided by U_0. In other words, our acceptance criterion would only entail energies computed from U_0.

The FEP equation is **asymmetric:** it gives the free energy difference based on an average in only one of the ensembles, here state 0. A similar derivation gives an expression if we use state 1 as the averaging ensemble:

$$\beta A_1 - \beta A_0 = \ln \langle e^{\beta \Delta U} \rangle_1$$

Statistical considerations

Even though the above equations appear straightforward, the calculated free energy differences can have substantial errors due to the averaging over an exponential term. To analyze this problem, let us rewrite the expression above in terms of the expected distribution $\wp_0(\Delta U)$ in state 0:

$$\beta A_1 - \beta A_0 = -\ln\langle e^{-\beta \Delta U}\rangle_0$$
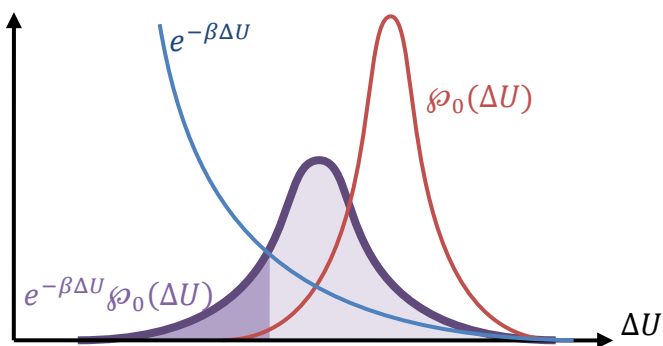$$= -\ln \int e^{-\beta \Delta U}\wp_0(\Delta U)d\Delta U$$

where

$$\wp_0(\Delta U) = \frac{\int \delta[U_1(\mathbf{r}^N) - U_0(\mathbf{r}^N) - \Delta U]\, e^{-\beta U_0(\mathbf{r}^N)}d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)}d\mathbf{r}^N}$$

Considering this form of the free energy difference equation, we see that there are two competing terms:

- $e^{-\beta \Delta U}$ grows very large for negative values of ΔU

- $\wp_0(\Delta U)$ is typically peaked at some intermediate value of ΔU, and tapers to zero away from this.

A typical graph of these functions might look like

Notice that the free energy difference is given by the entire area under the dark purple curve. However, part of this curve lies in a region very much in the tails of the distribution of $\wp_0(\Delta U)$. These energy differences would be sampled very rarely in the simulation, but make a large contribution to the integral due to the exponential. In other words, a substantial portion of the FEP average depends on the rare events in the simulation of state 0.

Practically, this limits the method to very small perturbations, i.e., where $\Delta U \approx 0$ for almost all configurations. Large perturbations result in a large statistical error in the computed free energy differences.

Bennett's method

One might perform an error propagation analysis on the FEP method to determine the expected error in the computed free energy difference as a function fo U_0 and U_1. This idea led Bennett to develop an approach for optimizing the FEP expression so as to minimize the error. This approach was originally called the acceptance ratio method, but is now often referred to as **Bennett's method** [Bennett, 1976].

Bennett started with the following modification of the free energy equation:

$$\beta A_1 - \beta A_0 = -\ln \frac{\int e^{-\beta U_1(\mathbf{r}^N)} d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N}$$

$$= -\ln \left(\frac{\int e^{-\beta U_1(\mathbf{r}^N)} d\mathbf{r}^N}{\int w(\mathbf{r}^N) e^{-\beta U_0(\mathbf{r}^N) - \beta U_1(\mathbf{r}^N)} d\mathbf{r}^N} \frac{\int w(\mathbf{r}^N) e^{-\beta U_0(\mathbf{r}^N) - \beta U_1(\mathbf{r}^N)} d\mathbf{r}^N}{\int e^{-\beta U_0(\mathbf{r}^N)} d\mathbf{r}^N} \right)$$

$$= -\ln \frac{\langle w e^{-\beta U_1} \rangle_0}{\langle w e^{-\beta U_0} \rangle_1}$$

Here, $w(\mathbf{r}^N)$ is an arbitrary weighting function. The averages here imply two simulations and two averages:

- A simulation in state 0 in which we find the average of the value $w e^{-\beta U_1}$ over all trajectory configurations.

- A simulation in state 1 in which we find the average of the value $w e^{-\beta U_2}$ over all trajectory configurations.

Notice that this expression is **symmetric**: both states 0 and 1 appear in equal roles.

Bennett's approach was to find an optimal value of the weighting function that minimizes the expected statistical error in the free energy difference. He used standard error propagation rules to determine $\sigma^2_{\beta(A_1 - A_0)}$ and then minimized this variationally with respect to the function $w(\mathbf{r}^N)$. The optimal weighting function, for minimum error, has the value:

$$w(\mathbf{r}^N) \propto \left(n_0^{-1} e^{-\beta A_0 - \beta U_1(\mathbf{r}^N)} + n_1^{-1} e^{-\beta A_1 - \beta U_0(\mathbf{r}^N)} \right)^{-1}$$

Frenkel and Smit give a detailed derivation of this result. Here, the constant of proportionality does not affect the statistical error. The variables n_0 and n_1 give the number of trajectory

configurations used in the free energy average for states 0 and 1. We will hereon out assume that this number is the same, so that:

$$w(\mathbf{r}^N) \propto \left(e^{-\beta A_0 - \beta U_1(\mathbf{r}^N)} + e^{-\beta A_1 - \beta U_0(\mathbf{r}^N)}\right)^{-1}$$

Plugging this expression into the symmetric FEP average, we arrive at the following relationship for the free energy difference:

$$\beta \Delta A = -\ln \frac{\left\langle \dfrac{1}{1 + e^{-\beta \Delta U + \beta \Delta A}} \right\rangle_0}{\left\langle \dfrac{1}{1 + e^{\beta \Delta U - \beta \Delta A}} \right\rangle_1}$$

Notice that the statistically optimal value for the free energy difference $\Delta A = A_1 - A_0$ depends on the difference itself! In practice, this equation is a self-consistent one: it can be solved or iterated until the free energy difference converges.

Here, the ΔU terms mean two different things, depending on the corresponding average. For the average in state 0, ΔU means the difference in energy $U_1 - U_0$ applied to configurations from the state 0 trajectory. Similarly, for the average in state 1, ΔU means the difference in energy $U_1 - U_0$ applied to configurations from the state 1 trajectory. In practice, one typically saves trajectories and re-processes them with different energy functions to determine the values in each state.

Importantly, notice that we now can no longer perform simple averages during our simulation runs to compute the quantities in brackets because we don't know what the value of ΔA will be. Instead, we must keep lists of the energies, or keep trajectories and re-compute the energies later, in order to evaluate the averages as we solve the equation for ΔA.

Keep in mind that we must be aware of issues with precision in evaluating the averages and exponentials in the computer.

Bennett's method provides a statistically optimal estimator of the free energy difference between two states. The equation above can be shown to be exactly identical to the Ferrenberg-Swendsen multiple histogram reweighting technique in the limit that the histogram bin size goes to zero.

Stratification

Even with Bennett's method, one can incur large errors in estimating free energy differences if the energy functions U_0 and U_1 are substantially dissimilar. This is because there will be little **overlap** in the regions of phase space that the two methods explore.

To overcome this problem, one can divide the total free energy difference into a series of small steps in which the system hops gradually from state 0 to state 1. Typically one introduces a **coupling parameter** λ:

$$U = (1 - \lambda)U_0 + \lambda U_1$$

For $\lambda = 0$, the system is governed by the potential in state 0. For $\lambda = 1$, the system is in state 1. For intermediate values of the coupling parameter, the energy function interpolates between the two.

The idea of stratification is to gradually change the potential using m intermediate values of λ:

$$\lambda_i = \frac{i}{m+1} \quad \text{where } i = 0,1,2\ldots,m+1$$

Then, the free energy change for each increment in λ can be computed using simulations with the potential for λ_i and λ_{i+1}:

$$\beta A(\lambda_{i+1}) - \beta A(\lambda_i)$$

The overall free energy difference is the sum of the m individual free energy differences:

$$\begin{aligned}
\beta A(\lambda = 1) - \beta A(\lambda = 0) &= \ln \frac{Z(\lambda = 0)}{Z(\lambda = 1)} \\
&= \ln \left(\frac{Z(\lambda_0 = 0)}{Z(\lambda_1)} \times \frac{Z(\lambda_1)}{Z(\lambda_2)} \times \frac{Z(\lambda_2)}{Z(\lambda_3)} \times \ldots \times \frac{Z(\lambda_m)}{Z(\lambda_{m+1} = 1)} \right) \\
&= \beta \sum_{i=0}^{m} A(\lambda_{i+1}) - A(\lambda_i)
\end{aligned}$$

By choosing a large number of intermediate states m, the statistical error can be reduced since the perturbations between each neighboring state are smaller. However, $m + 2$ simulations must be performed in order to compute the total free energy difference, so better accuracy comes at the expense of more simulations.

This approach is very similar to multiple histogram reweighting techniques in that we stitch data from a number of simulations together to produce a free energy difference, and that the simulations must have good "overlap" with each other in order for this to work. However, the stratification method here only considers pairs of states in building up a net free energy difference, while the multiple histogram reweighting equations consider all states at once. The latter are typically more accurate as a result, although the computations of the free energy differences can be more demanding.

Computing chemical potentials

The chemical potential of system in the canonical ensemble has the following relationship with the Helmholtz free energy:

$$\mu = \left(\frac{\partial A}{\partial N}\right)_{T,V}$$

However, the particle number is actually discrete, and thus we might write

$$\mu = A(T,V,N+1) - A(T,V,N)$$

Using the connection with the canonical partition function, we find

$$\beta\mu = \ln\frac{\left[\frac{Z(T,V,N)}{\Lambda(T)^{3N}N!}\right]}{\left[\frac{Z(T,V,N+1)}{\Lambda(T)^{3N+3}(N+1)!}\right]}$$

$$= \ln\frac{(N+1)\Lambda^3(T)}{V} + \ln\frac{V\int e^{-\beta U(\mathbf{r}^N)}d\mathbf{r}^N}{\int e^{-\beta U(\mathbf{r}^{N+1})}d\mathbf{r}^{N+1}}$$

$$= \mu_{ig} + \ln\frac{V\int e^{-\beta U(\mathbf{r}^N)}d\mathbf{r}^N}{\int e^{-\beta U(\mathbf{r}^{N+1})}d\mathbf{r}^{N+1}}$$

Here μ_{ig} is the ideal gas part of the chemical potential, known analytically. We are actually interested in computing the excess chemical potential:

$$\beta\mu_{ex} = \ln\frac{V\int e^{-\beta U(\mathbf{r}^N)}d\mathbf{r}^N}{\int e^{-\beta U(\mathbf{r}^{N+1})}d\mathbf{r}^{N+1}}$$

Another way to write this is to let the top integral contain a degree of freedom corresponding to an ideal gas particle that doesn't have any energetic contributions:

$$\beta\mu_{ex} = \ln\frac{\int e^{-\beta U(\mathbf{r}^N)}d\mathbf{r}^{N+1}}{\int e^{-\beta U(\mathbf{r}^{N+1})}d\mathbf{r}^{N+1}}$$

We can actually formulate this problem in terms of a free-energy perturbation to the system. The perturbation is to "turn on" the interactions of the $(N+1)$th particle with all of the other particles in the system.

$$U_0(\mathbf{r}^{N+1}) = U(\mathbf{r}^N)$$

$$U_1(\mathbf{r}^{N+1}) = U(\mathbf{r}^{N+1})$$

That is, we convert particle $N + 1$ from a noninteracting ideal gas particle (state 0) to an interacting particle of the same kind as all of the others (state 1). The excess chemical potential is the free energy associated with this change.

Applying the free energy perturbation approach, we find that

$$\beta \mu_{ex} = -\ln\langle e^{-\beta \Delta U} \rangle_0$$

Here, ΔU gives the energy of particle $N + 1$ interacting with all of the other particles. The average in state 0 takes place in the system of N interacting and 1 ideal gas particle.

Widom test particle insertion method

How can we compute the chemical potential using the equation above? Widom first proposed a method to do so that is known as the **test particle** approach. It involves the following steps:

- Perform a simulation with N particles in the canonical ensemble. This may be an MD or MC run.

- Periodically pause the simulation and insert a test particle at a random location in the simulation box. This procedure is equivalent to finding the location of the $(N + 1)$th ideal gas particle, since it would be present uniformly throughout the simulation box.

- Compute the change in energy due to the particle insertion, ΔU.

- Remove the test particle and continue the simulation run as if the test had never occurred.

- Find the average $\langle e^{-\beta \Delta U} \rangle$ over the course of the simulation run. This average provides the chemical potential,

$$\beta \mu_{ex} = -\ln\langle e^{-\beta \Delta U} \rangle$$

The particle insertion method can be applied to other ensembles beyond the canonical one, although the expression for the chemical potential is slightly different in each case. Frenkel and Smit have a detailed discussion of the correct implementation in other ensembles.

Statistical considerations

As with the other asymmetric FEP equations, the expression here is subject to statistical uncertainty if the inserted particle sufficiently perturbs the energy of the system. It is very difficult to compute the chemical potential using the particle insertion method for systems that are:

- very dense – in these cases an inserted particle almost always produces a core overlap, which results in a large change ΔU

- directional interactions – if the inserted particle is a rigid molecule, an orientation must be chosen. Systems that have highly-orientation dependent energies, like dipolar or hydrogen-bonded systems, will have large changes in ΔU depending on the orientation

Test particle deletion method

We could have also expressed the chemical potential using the expression:

$$\mu = A(T,V,N) - A(T,V,N-1)$$

and applying the other asymmetric FEP equation:

$$\beta \mu_{ex} = \ln\langle e^{\beta \Delta U}\rangle_1$$

Here, state 1 would correspond to N interacting particles and state 0 to $N-1$ interacting and one ideal gas particle. In a simulation, we could perform a random test *deletion* and compute the change in energy upon deleting a molecule ΔU. An average using this expression could also be used to compute the chemical potential.

In practice, this approach tends to fail because of a much higher statistical error. That is, the test deletion method has a much broader distribution of ΔU that makes states 0 and 1 have less overlap than would have been the case with an insertion. Therefore, test particle deletion is rarely used to compute the chemical potential.

Thermodynamic integration

Thermodynamic integration (TI) is an approach to free energy calculations that has a long history in statistical mechanics and goes back to the early work of Kirkwood. It is perhaps not quite as general as histogram-based techniques, since it requires one to compute derivatives of the Hamiltonian. Nor does it provide as statistically accurate estimates of free energy differences. However, often it is very straightforward to implement and can produce results quite fast.

The basic idea of thermodynamic integration is that it is often very easy to compute the derivative of a free energy function from a simulation average. Consider the Helmholtz free energy $A(T,V,N)$. It's derivative with respect to volume is:

$$\left(\frac{\partial A}{\partial V}\right)_{T,N} = -P$$

Thus, if we were able to compute the pressure as a function of V for fixed T, N we could integrate this expression to find the V-dependence of A:

$$A(T, V_1, N) - A(T, V_0, N) = \int_{V_0}^{V_1} P(V) dV$$

Numerically, we could do this by:

- Performing multiple simulations at different volumes V between V_0 and V_1 and finding the average pressure from each using the virial.

- Fitting the $P(V)$ curves to a suitable functional form.

- Integrating the expression to find the free energy difference between V_1 and V_0.

Similarly, we could compute the T-dependence of A using the thermodynamic identity:

$$\left(\frac{\partial (A/T)}{\partial (1/T)} \right)_{V,N} = E$$
$$= K + U$$
$$= \frac{3}{2} N k_B T + U$$

Integrating this expression,

$$\frac{A(T_1, V, N)}{T_1} - \frac{A(T_0, V, N)}{T_0} = -\int_{T_0}^{T_1} \frac{\frac{3}{2} N k_B T + U(T)}{T^2} dT$$
$$= -\frac{3}{2} N k_B \ln \left(\frac{T_1}{T_0} \right) - \int_{T_0}^{T_1} \frac{U(T)}{T^2} dT$$

In this case, we would perform simulations at different temperatures, and at each one we would compute the average potential energy for integrating this expression. This would enable us to compute the free energy difference between two temperatures of interest.

Formalism for changes in the energy function

In the above examples, we considered only the free energy changes along the macroscopic parameters T and V. One can also use FEP to compute free energy changes as the potential energy function itself changes. Consider the parameter λ to be a generic parameter of the potential energy function.

The free energy of the system is:

$$A = -k_B T \ln \frac{1}{N!\,\Lambda(T)^{3N}} \int e^{-\beta U(\mathbf{r}^N;\lambda)} d\mathbf{r}^N$$

To use TI, we need to find the derivative of this expression with respect to λ:

$$\frac{dA}{d\lambda} = -k_B T \frac{d}{d\lambda} \ln \int e^{-\beta U(\mathbf{r}^N;\lambda)} d\mathbf{r}^N$$

$$= -k_B T \frac{\int -\beta \left(\frac{dU}{d\lambda}\right) e^{-\beta U(\mathbf{r}^N;\lambda)} d\mathbf{r}^N}{\int e^{-\beta U(\mathbf{r}^N;\lambda)} d\mathbf{r}^N}$$

$$= \left\langle \frac{dU}{d\lambda} \right\rangle_\lambda$$

Here, the average gives the mean of the derivative of the potential energy function with respect to λ, performed in the ensemble of a given value of λ. This expression can now be integrated to find the free energy difference as a function of changes in λ, for fixed values of T, V, N:

$$A(\lambda_1) - A(\lambda_0) = \int_{\lambda_0}^{\lambda_1} \left\langle \frac{dU}{d\lambda} \right\rangle_\lambda d\lambda$$

Computation of the free energy difference then involves the following steps:

- Multiple simulations are performed for different values of λ spanning λ_0 to λ_1.

- For each simulation, the average $\left\langle \frac{dU}{d\lambda} \right\rangle_\lambda$ is computed over the course of the simulation.

- A curve is fitted to the derivative average as a function of λ and the integral is evaluated numerically.

In particular, this approach can be used to compute free energy changes of the type considered for FEP techniques, when the energy function is modified from U_0 to U_1. Here,

$$U = (1-\lambda)U_0 + \lambda U_1$$

And the TI approach takes the form,

$$A(\lambda = 1) - A(\lambda = 0) = \int_0^1 \langle U_1 - U_0 \rangle_\lambda d\lambda$$

Formalism for reaction coordinates

It is also possible to use TI to compute free energy changes along arbitrary microscopic reaction coordinates. Consider a generalized reaction coordinate

$$\xi(\mathbf{r}^N)$$

This function could return the distance between two atoms, the number of bonds, the radius of gyration… anything depending on the configurational coordinates alone. To perform thermodynamic integration, we need to find examine the Helmholtz free energy as a function of the reaction coordinate. This is simply the potential of mean force (PMF):

$$F(\xi) = A(T, V, N, \xi)$$

Implied in $F(\xi)$ are constant values of T, V, N. Per our earlier discussion of PMFs, its microscopic definition is

$$F(\xi) = -k_B T \ln \int e^{-\beta U(\mathbf{r}^N)} \delta[\xi - \hat{\xi}(\mathbf{r}^N)] d\mathbf{r}^N$$

To use thermodynamic integration, we need to find the derivative of $F(\xi)$. We previously showed that this relates to the average force along the direction ξ:

$$\frac{dF(\xi)}{d\xi} = -\langle f_\xi \rangle_\xi$$

with the definition

$$f_\xi = -\frac{d\mathbf{r}^N}{d\hat{\xi}} \cdot \nabla U$$

$$= \frac{d\mathbf{r}^N}{d\hat{\xi}} \cdot \mathbf{f}^N$$

Therefore, the free energy expression takes the form

$$F(\xi_1) - F(\xi_0) = -\int_{\xi_0}^{\xi_1} \langle f_\xi \rangle_\xi d\xi$$

This equation implies that we perform multiple simulations in which the system is constrained to a certain value of the reaction coordinate ξ. In each simulation, we compute the force along ξ.

Consider the example of a solute in solution interacting with a surface, where the distance z between the solute and surface is the reaction coordinate. Here, this expression would take the form:

$$F(z_1) - F(z_0) = -\int_{z_0}^{z_1} \langle f_{z,\text{solute}} \rangle_z dz$$

Here, $\langle f_{z,\text{solute}} \rangle_z$ is the average force acting on the solute in the z direction while the solute is constrained to sit at a fixed value of z from the surface. This net force extends from interactions with all of the other atoms in the system.

How can we constrain this distance in the simulations that compute this average? In a MC simulation, we never propose displacement moves in the z direction of the solute. In a MD simulation, we never update the z-component of the position of the solute when performing the integration step.

Absolute free energies and reference states

So far, we have only discussed methods for computing free energy changes. At a fundamental level, it is not possible to specify the absolute entropy or free energy of a classical system. Instead, we need to make contact with a quantum-mechanical model for which we know the quantum-mechanical, absolute entropy or free energy.

Our strategy will be to compute the free energy difference between our system and a reference state for which we know the absolute free energy. There are two models for which the absolute free energy is known analytically: the ideal gas and the ideal harmonic (Einstein) crystal.

For disordered phases like liquids and gases, we can compute the absolute free energy by connecting to an **ideal gas reference state**. That is, we find the difference in free energy between the current state of interest and one that is high-temperature and low-density. Typically, we choose two paths to do this:

- integration at constant density to high temperature

- integration at constant (high) temperature to low density

Any one of the free energy methods we have discussed can be used to perform these calculations, including flat histogram techniques, free energy perturbation (with stratification), and thermodynamic integration. If the latter is used, one must avoid passing through a phase transition as these methods fail for such cases.

For ordered phases like crystalline solids, one connects the system and current state to an **ideal harmonic crystal reference state.** This is a system in which each atom is non-interacting and constrained to its lattice site by a harmonic restraining potential. To find the free energy between the current system and the reference state, one computes the free energy change along the parameter λ:

$$U = (1 - \lambda)U_{\text{true}} + \lambda U_{\text{harmonic}}$$

In other words, the true system potential energy function is perturbed to the harmonic equivalent. Again, flat histogram techniques, free energy perturbation (with stratification), and thermodynamic integration can be used to compute this free energy change.