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PERSPECTIVE: FREE ENERGIES AND PHASE EQUILIBRIA

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Analysis of the free energy is required to understand and predict the equilibrium behavior of thermodynamic systems, which is to say, systems in which temperature has some influence on the equilibrium condition. In practice, all processes in the world around us proceed at a finite temperature, so any application of molecular simulation that aims to evaluate the equilibrium behavior must consider the free energy. There are many such phenomena to which simulation has been applied for this purpose. Examples include chemical-reaction equilibrium, protein-ligand affinity, solubility, melting and boiling. Some of these are examples of phase equilibria, which are an especially important and practical class of thermodynamic phenomena. Phase transformations are characterized by some macroscopically observable change signifying a wholesale rearrangement or restructuring occurring at the molecular level. Typically this change occurs at a specific value of some thermodynamic variable such as the temperature or pressure. At the exact point where the transition occurs, both phases are equally stable – have equal free energy – and we find a condition of phase equilibrium or coexistence [1].

1.   Free-Energy Measurement

Free-energy calculations are among the most difficult but most important encountered in molecular simulation. A key "feature" of these calculations is their tendency to be inaccurate, yielding highly reproducible results that are nevertheless wrong, despite the calculation being performed in a way that is technically correct. Often seemingly innocuous changes in the way the calculation is performed can introduce (or eliminate) significant inaccuracies. So it

is important when performing these calculations to have a strong sense of how they can go awry, and proceed in a way that avoids their pitfalls.

The aim of any free-energy calculation is to evaluate the *difference* in free energy between two systems. "System" is used here in a very general sense. The systems may differ in thermodynamic state (temperature, pressure, chemical composition), in the presence or absence of a constraint, or most generally in their Hamiltonian. Often the free energy of one system is known, either because it is sufficiently simple to permit evaluation analytically (e.g., an ideal gas or a harmonic crystal), or because its free energy was established by a separate calculation. In many cases the free-energy difference is itself the principal quantity of interest. The important point here is that free-energy calculations always involve two (or more) systems. We will label these systems A and B in our subsequent discussion, and their free energy difference will be defined $\Delta F = F_B - F_A$.

Once the systems of interest have been identified, a large variety of methods are available to evaluate ΔF. At first glance the methods seem to be very diverse and unrelated, but they nevertheless can be grouped into two broad categories: (a) methods based on measurement of density of states and (b) methods based on work calculations. Implicit in both approaches is the idea of a path joining the two systems, and one way that specific methods differ is in how this path is defined. As free energy is a state function, the free-energy difference of course does not depend on the path, but the performance of a method can depend greatly on this choice (and other details). It is always possible to define a parameter λ that locates a position on the path, such that one value λ_A corresponds to system A and another value λ_B indicates system B. The parameter λ may be continuous or discrete (in fact, it is not uncommon that it have only two values, λ_A and λ_B), and may represent a single variable or a set of variables, depending on the choice of the path. Moreover, for a given path, the parameter λ can be viewed as a state variable, such that a free energy $F(\lambda)$ can be associated with each value of λ. Thus $\Delta F = F(\lambda_B) - F(\lambda_A)$. The term "Landau free energy" is sometimes used in connection with this dependence.

1.1. Density-of-States Methods

If a system is given complete freedom to move back and forth across the path joining A and B, it will explore all possible values of the path variable λ, but it will (in general) not spend equal time at each value. The probability $p(\lambda)$ that the system is observed to be at a particular point λ on the path is related to the value of the free energy there

$$p(\lambda) \propto \exp\left(-F(\lambda)/kT\right),\tag{1}$$

where T is the absolute temperature and k is Boltzmann's constant. This relation is the basic idea behind the density-of-states methods. The specific way in which λ samples values depends on how the simulation is implemented. Typically density-of-states calculations are performed as part of Monte Carlo (MC) simulations. In this case sampling includes trial moves in which λ is perturbed to a new value, and a decision to accept the trial is taken in the usual MC fashion. It is possible also to have λ vary as part of a molecular dynamics (MD) simulation. In such a situation λ must couple to the equations of motion of the system, usually via an extended-Lagrangian formalism [2]. Then λ follows a deterministic dynamical trajectory akin to the way that the particles' coordinates do.

In almost all cases of practical interest, conventional Boltzmann sampling will probe only a small fraction of all possible λ-values. The variation of the free energy $F(\lambda)$ can be many times kT when considered over all λ values of interest, and consequently the probability $p(\lambda)$ can vary over many orders of magnitude. Extra measures must therefore be taken to ensure that sufficient information is gathered over all λ to evaluate the desired free-energy difference, and one of the features distinguishing different density-of-states methods is the way that they take these measures. Almost always an artificial bias $\phi(\lambda)$ must be imposed to force the system to examine values of λ where the free energy is unfavorable, Usually the aim is to formulate the bias to lead to a uniform sampling over λ, which is achieved if $\phi(\lambda) = -F(\lambda)$. Of course, inasmuch as the aim is to evaluate $F(\lambda)$ it is necessary to set up a scheme in which the free energy can be estimated either through preliminary simulations or as part of a systematic process of iteration. The greatest difficulty is found if the free energy change is extensive, meaning that λ affects the entire system and not just a small part of it (e.g., a path that results in a change in the thermodynamic phase, versus a path in which a single molecule is added to the system). In such cases $F(\lambda)$ scales with the system size and is likely to vary by very large amounts with λ. The practical consequence is that the bias must be tuned very precisely to ensure that good sampling over all λ is accomplished. A robust solution to the problem is the use of windowing, in which the problem of evaluating the full free energy profile $F(\lambda)$ is broken into smaller problems, each involving only a small range of all λ of interest. Separate simulations are performed over each λ range, and the composite data are assembled to yield the full profile. Even here there are different ways that one can proceed, and a popular approach to this end uses the histogram-reweighting method, which optimally combines the data in a way that accounts for their relative precision. Histogram reweighting is discussed in another chapter of this volume.

Within the framework outlined above, the most obvious way to measure the probability distribution $p(\lambda)$ is to use a visited-states approach: MC or MD sampling of λ values is performed, perhaps in the presence of the bias ϕ, and

a histogram is recorded of the frequency with which each value (or bin of values) of λ is occupied. The Wang-Landau method [3, 4] (and its extensions) is the most prominent such technique today. Another approach of this type applies a history-dependent bias using a Gaussian basis [5]. An alternative to visited-states has recently emerged in the form of transition-matrix methods [6–10]. In such an approach one does not tabulate the occupancy of each λ value; rather one tallies statistics about the attempts to transition from one λ to another in a MC simulation. The movement among different λs forms a Markov process, and knowledge of the transition probabilities is sufficient to derive the limiting distribution $p(\lambda)$. Interestingly, even rejected MC trials contribute information to the transition matrix, so it seems that this approach is gathering information that is discarded in visited-states methods. The transition-matrix approach has several other appealing features. The method can accommodate the use of a bias to flatten the sampling, but the bias does not enter into the transition matrix, so if the bias is updated as part of a scheme to achieve a flat distribution the previously recorded transition probabilities do not have to be discarded, as they must be in visited-states methods (at least in its simpler formulations). Moreover, if windowing is applied to obtain uniform samples across λ, it is easy to join data from different windows. It is not even required that adjacent windows overlap, just that they attempt trials (without necessarily accepting) into each other's domain. Details of the transition-matrix methods are still being refined, and the versatility of the approach is currently being explored through its application to different problems. Additionally, there are efforts now to combine visited-states and transition-matrix approaches, exploiting the relatively fast (but rough) convergence of the former while relying on the more complete data collection abilities of the latter to obtain the best precision [11].

1.2.   Work-Based Methods

Classical thermodynamics relates the difference in free energy between two systems to the work associated with a reversible process that takes one into the other. A straightforward application of this idea leads to the thermodynamic integration (TI) free-energy method, which has a long history and has seen widespread application. The TI method is but one of several approaches in a class based on the connection between ΔF and the work involved in transforming a system from A to B. A very important development in this area occurred recently, when Jarzynski showed that ΔF could be related to work associated with *any* such process, not just a reversible one [12–15]. Jarzynski's non-equilibrium work (NEW) approach requires evaluation of an ensemble of

work values, and thus involves repeated transformation from A to B, evaluating the work each time. The connection to the free energy is then

$$\exp(-\Delta F/kT) = \overline{\exp(-W/kT)}, \tag{2}$$

where W is the total work, and the overbar on the right-hand side indicates an average taken over many realizations of the path from A to B, always starting from an equilibrium A condition. For an equilibrium (reversible) path, the repeated work measurements will each yield exactly the same value (within the precision of the calculations), while for an arbitrary non-equilibrium transformation a distribution of work values will be observed. It is remarkable that these non-equilibrium transformations can be analyzed to yield a quantity related to the equilibrium states.

The instantaneous work w involved in the transformation $\lambda \rightarrow \lambda + \Delta\lambda$ will in general depend upon the detailed molecular configuration of the system at the instant of the change. Assuming that there is no process of heat transfer accompanying the transformation, this work is given simply by the change in the total energy of the system

$$w = E(\mathbf{r}^N; \lambda + \Delta\lambda) - E(\mathbf{r}^N; \lambda). \tag{3}$$

For sufficiently small $\Delta\lambda$, this difference can be given in terms of the derivative

$$w = \left(\frac{dE(\lambda)}{d\lambda}\right)_{\mathbf{r}^N} \Delta\lambda, \tag{4}$$

which can be interpreted in terms of a force acting on the parameter λ. The derivative relation is the natural formulation for use in MD simulations, in which the work is evaluated by integrating the product of this force times the displacement in λ over the complete path. The former expression (Eq. (3)) is more appropriate for MC simulation, in which larger steps in λ are typically taken across the path from A to B.

Thermodynamic integration is perhaps the first method by which free energies were calculated by molecular simulation. Thermodynamic integration methods are usually derived from classical thermodynamics [1], with molecular simulation appearing simply to measure the integrand. As indicated above, TI also derives as a special (reversible) case of Jarzynski's NEW formalism, whereby $\Delta F = W^{\text{rev}}$ for the reversible path. The total work W^{rev} is in turn given by integration of Eq. (4), leading to:

$$\Delta F = \int_{\lambda_A}^{\lambda_B} w(\lambda)\, d\lambda. \tag{5}$$

Equilibrium values of w are measured in separate simulations at a few discrete λ points along the path. It is then assumed that w is a smooth function

of λ, and simple quadrature formulas (e.g., trapezoid rule) can be applied. The primary mechanism for the failure of TI is the occurrence of a phase transition, and therefore a discontinuity in w, along the path. Otherwise TI has been successfully applied to a very wide variety of systems, dating to the earliest simulations. Its primary disadvantage is that it does not provide direct measurement of the free energy, and if one is not interested in behavior for points along the integration path then another approach might be preferred.

TI approximates a reversible path by smoothing equilibrium, ensemble-averaged, "forces" measured discretely along the path. Alternatively, one can access a reversible path by mimicking a truly reversible process, i.e., by attempting to traverse the path via a slow, continuous transition. In this manner the simulation constantly evolves from system A to system B, such that every MC or MD move is accompanied by a tiny step in λ (or some variation of this protocol). The differential work associated with these changes is accumulated to yield the total work W, which then approximates the free-energy difference. The process may proceed isothermally or adiabatically, the latter being the so-called *adiabatic-switch* method (and which instead yields the entropy difference between A and B) [16]. The weakness of these methods is in the uncertainty on whether the evolution of the system is sufficiently slow to be considered reversible. Such concerns can be allayed by implementing the calculation using the Jarzynski free-energy formula, Eq. (9); however this remedy then requires averaging of repeated realizations of the transition. One is then led to ask whether it is better to average, say, ten NEW passes, or to perform a single switch ten times more slowly.

Free-energy perturbation (FEP) is obtained as the special case of the NEW method in which the transformation from A to B is taken in a single step. Free-energy perturbation is a well established and widely used method. Its principal advantage is that it permits ΔF to be given as an ensemble average over configurations of the A system, removing the complication and expense of defining and traversing a path. The working formula emphasizes this feature

$$\exp(-\beta \Delta F) = \langle \exp[-\beta(E_B - E_A)]\rangle_A .\tag{6}$$

A given NEW calculation can in principle be performed in either direction, starting from A and transforming to B, or vice versa. In practice the calculation will give different results when applied in one or the other direction; moreover these results will bracket the correct value of ΔF. The results differ because they are inaccurate, and the fact that they bracket the correct value makes it tempting to take their average as the "best" result. But this practice is not a good idea, because the magnitude of the inaccuracies is in general not the same for the two directions [17,18]. In fact, it is not uncommon for one direction to provide the right result while the other yields an inaccurate one. But it is also not uncommon in other cases for the average to give a better estimate than either direction individually. The point is that one often does not know what

is the best way to interpret the results. The more careful practitioners will apply sufficient calculation (and perhaps use sufficient stages) until a point is reached in which the results from each direction match each other. However, this practice can be wasteful. To understand the problem and its remedy it is helpful to consider the systems A and B from the perspective of configuration space.

1.3.   Configuration Space

Configuration space is a high-dimensional space of all molecular configurations, such that any particular arrangement of the N atoms in real space is represented by a single point in $3N$-dimensional configuration space (more generally we may consider $6N$-dimensional *phase space*, which includes also the momenta) [19]. An arbitrary point in configuration space will typically describe a configuration that is unrealistic and unimportant, in the sense that one would not expect ever to observe the configuration to arise spontaneously in course of the system's natural dynamics. For example, it might be a configuration in which two atoms occupy overlapping positions. Configuration space will of course contain points that do represent realistic, or important configurations, ones that are in fact observed in the system. It is helpful to consider the set Γ^* of all such configurations, as we do schematically in Fig. 1. The enclosing square represents the high-dimensional configuration space, and the ovals drawn within it represent (in a highly simplified manner) the set of all important configurations for the systems.

The concept of "important configurations" is relevant to free-energy calculations because the ease with which a reliable (accurate) free-energy difference can be measured depends largely on the relation between the Γ^* regions of the two systems defining the free-energy difference. There are five general possibilities [20], summarized in Fig. 1. In a FEP calculation perturbing from A to B, the simulation samples the region labeled Γ_A^* and at intervals it examines its present configuration and gauges its importance to the B system. Three general outcomes are possible for the difference $E_B - E_A$ seen in Eq. (6): (a) it is a large positive number and the contribution to the FEP average is small; this occurs if the point is in Γ_A^* but not in Γ_B^*; (b) it is a number of order unity, and a significant contribution is made to the FEP average; this occurs if the point is in Γ_A^* and in Γ_B^*; or (c) it is a large negative number, and an enormous contribution is made to the FEP average; this occurs if the point is *not* in Γ_A^* but is in Γ_B^*. The third case will arise rarely if ever, because the sampling is by definition largely confined to the region Γ_A^*. This contradiction (a large contribution made by a configuration that is never sampled) is the source of the inaccuracy in FEP calculation, and it arises if any part of Γ_B^* lies outside of Γ_A^*.
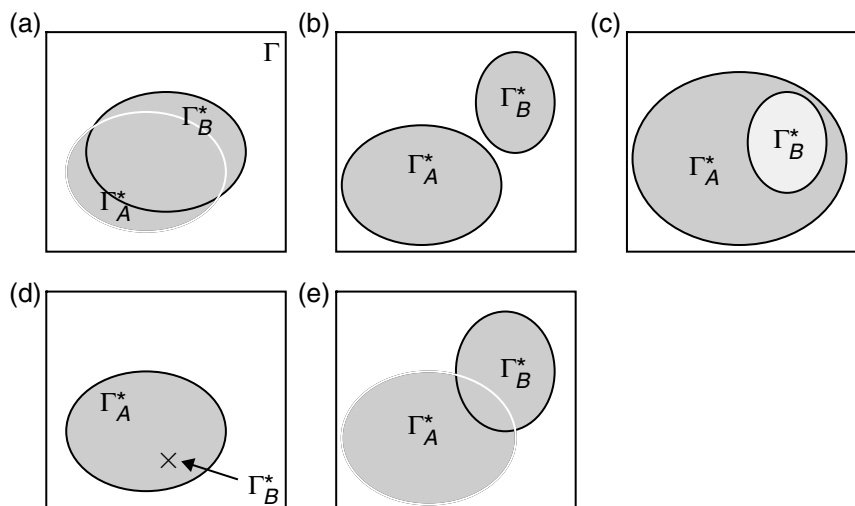
Figure 1. Schematic depiction of types of structures that can occur for the region of important configurations involving two systems. The square region represents all of phase space, and the filled regions are the important configurations Γ_A^* and Γ_B^* for the systems "*A*" and "*B*", as indicated. (a) simple case in which Γ_A^* and Γ_B^* are roughly coincident, and there is no signifi- cant region of one that lies outside the other; (b) case in which the important configurations of *A* and *B* have no overlap, and energetic barriers prevent each from sampling the other; (c) case in which one system's important configurations are a wholly contained, not-very-small subset of the others; (d) case in which Γ_B^* is a very small subset of Γ_A^*; (e) case in which Γ_A^* and Γ_B^* overlap, but neither wholly contains the other.

This observation leads us to the most important rule for the reliable applica- tion of FEP: the reference and target systems must obey a *configuration-space subset relation*. That is, the important configuration space of the target system (*B*) must be wholly contained within the important configuration space of the system governing the sampling (*A*). Failure to adhere to this requirement will lead to an inaccurate result. Note the asymmetry of the relation "is a subset of" is directly related to the asymmetry of the FEP calculation. Exchange of the roles of *A* and *B* as target or reference can make or break the accuracy of the calculation.

For example, consider the free energy change associated with the addi- tion of a molecule to the system. In this case, ΔF equals the excess chemical potential. The *A* system is one in which the "test" molecule has no interaction with the others, and the *B* system is one in which it interacts as all the other molecules do. Any configuration in which the test molecule overlaps another molecule is not important to *B* but is (potentially) important to *A* – the *B* sys- tem may be a subset of *A*, while *A* is most certainly not a subset of *B*. Whether all of Γ_B^* is within Γ_A^* cannot be stated for the general case. In more complex

systems (e.g., water) it is likely that there are configurations sampled by *B* that would not be important to *A*, while in simpler systems (a Lennard–Jones fluid at moderate density) the subset relation is satisfied.

This black-and-white picture, in which the Γ* regions are well defined with crisp boundaries, presents only a conceptual illustration of the nature of the calculations. In reality the "importance" of a given configuration (point in Γ) is not so clear-cut, and the Γ* regions for the *A* and *B* systems may overlap in shades of gray (i.e., degrees of importance).

The discussion here is given in the context of a FEP calculation, but the same ideas are relevant to the more general NEW calculation. Each increment of work performed in a NEW calculation must adhere to the subset relation too. The difference with NEW is that if the change is made sufficiently slowly (approaching reversibility), then the important phase spaces at each step will differ by only small amounts (cf. Fig. 1(a)), and the subset relation will be satisfied. To the extent that a NEW calculation is performed irreversibly, the issue of inaccuracy and asymmetry becomes increasingly important.

1.4. Staging Strategies

In practice one is confronted with pair of systems for which ΔF is desired, and there is no control over whether their Γ* regions satisfy a subset relation. Yet FEP and NEW cannot be safely applied unless this condition is met. Two remedies are possible. Phase space can be redefined, such that a given point in it can represent different configurations for the *A* and *B* systems [21–23]. This approach has been applied to evaluate free energy differences between crystal structures (e.g., fcc vs. bcc) of a given model system. The phase-space points are defined to represent deviations from a perfect-crystal configuration, and the reference crystal is defined differently for the two systems. The switch from *A* to *B* entails swapping the definition of the reference crystal while keeping the deviations (i.e., the redefined phase-space point) fixed. With this transformation, two systems having disjoint Γ* regions are redefined such that their Γ* at least have significant overlap, and perhaps obey the subset requirement.

Multiple staging is a more general approach to deal with systems that do not satisfy the subset relation [24–26]. Here the desired free energy difference is expressed in terms of the free energy of one or more intermediate systems, typically defined only to facilitate the free-energy calculation. Thus,

$$\Delta F = (F_B - F_M) + (F_M - F_A), \tag{7}$$

where *M* indicates the intermediate. Free-energy methods are then brought to evaluate separately the two differences, between the *M* and *B* and *M* and *A* systems, respectively. The *M* system should be defined such that a subset relation can be formed between it and both the *A* and *B* systems. There are

several options to this end, depending on the Γ^* relation in place for the A and B systems. Figure 2 summarizes the possibilities, and the cases are named as follows:

- *Umbrella sampling*. Here M is formulated to contain both A and B, and sampling is performed from it into each [27].
- *Funnel sampling*. This is possible only if B is already a subset of A. Then M is defined as a subset of A and superset of B, and each perturbation stage is performed accordingly [20, 25, 28].
- *Overlap sampling*. Here M is formulated to be a subset of both A and B, and sampling is performed on each with pesrturbation into M [29].

General ways to define M to satisfy these requirements are summarized in Table 1, which also lists the general working equations for each multi-stage scheme. Umbrella sampling is a well-established method but is has only recently been viewed from the perspective given here. Bennett's acceptance-ratio method is a particular type of overlap sampling in which an optimal
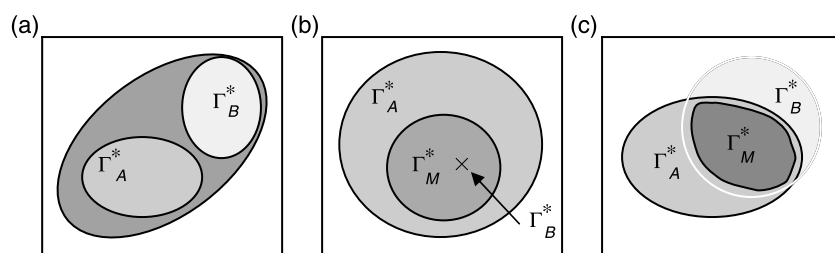

Figure 2. Schematic depiction of types of structures that can occur for the region of important configurations involving two systems and a weight system formulated for multistage sampling. The square region represents all of phase space, and the filled regions are the important configurations Γ_A^*, Γ_B^*, and Γ_M^* for the systems A and B, and M as indicated. (a) well formulated umbrella potential defines important configuration that have both Γ_A^* and Γ_B^* as subsets; (b) safely formulated funnel potential needed to focus sampling on tiny set of configurations Γ_B^* while still representing all configurations important to A; (c) well formulated overlap potential, with important configurations formed as a subset of both the A and B systems.

Table 1. Summary of staging methods for free-energy perturbation calculations

Method	Formula for $e^{-\beta(F_B - F_A)}$	Preferred staging potential, $e^{-\beta E_M}$
Umbrella sampling	$\dfrac{\left\langle e^{-\beta(E_B - E_M)} \right\rangle_M}{\left\langle e^{-\beta(E_A - E_M)} \right\rangle_M}$	$\left(e^{-\beta(E_A - F_A)} + e^{-\beta(E_B - F_B)} \right)$
Overlap sampling	$\dfrac{\left\langle e^{-\beta(E_M - E_A)} \right\rangle_A}{\left\langle e^{-\beta(E_M - E_B)} \right\rangle_B}$	$\left(e^{+\beta(E_A - F_A)} + e^{+\beta(E_B - F_B)} \right)^{-1}$
Funnel sampling	$\left\langle e^{-\beta(E_M - E_A)} \right\rangle_A \left\langle e^{-\beta(E_B - E_M)} \right\rangle_M$	No general formulation

M is selected to minimize the variance of ΔF; it is a highly effective and underappreciated method. The funnel-sampling multistage scheme is new, and a general, effective formulation for an M system appropriate to it has not yet been identified. Overlap sampling and umbrella sampling are not particularly helpful if A and B already satisfy the subset relation – they do not give much better precision than a simple single-stage FEP calculation taken in the appropriate direction. However, if implemented correctly they do provide some measure of safety against problems of inaccuracy, which is useful because in most cases one usually does not know clearly the nature of the phase-space relation for the A and B systems, and whether (and which way) a single-stage calculation is safe to perform between them.

2.   Methods for Evaluation of Phase Coexistence

Our perspective now shifts to the calculation of phase coexistence by molecular simulation, for which free-energy methods play a major role. Applications in this area have exploded over the past decade or so, owing to fundamental advances in algorithms, hardware, and molecular models. Some of the methods and concepts surveyed here have been discussed in more detail in recent reviews [30, 31].

2.1.   What is a Phase?

An *order parameter* is a statistic for a configuration. It is a number (or perhaps a vector, tensor, or some other set of numbers) that can be calculated or measured for a system in a particular configuration, and that in some sense quantifies the configuration. Examples include the density, the mole fraction in a mixture, the magnetic moment of a ferromagnet, and so on. Some molecular order parameters are formulated as expansion coefficients of an appropriate distribution function rendered in a suitable basis set. For example, a natural choice for crystalline translation order parameters is the value of the structure factor for an appropriate wave vector $\mathbf{k}$. Orientational order parameters are widely used in the field of liquid crystals, and a common choice is based on expansion of the orientation distribution in Legendre polynomials. Usually an order parameter is defined such that it has a physical manifestation that can be observed experimentally.

A thermodynamic phase is the set of all configurations that have (or are near) a given value of an order parameter. Phases are important because a system will spontaneously change its phase in response to some external perturbation.

In doing so, the configurations exhibited by the system change from those associated with one value of the order parameter to those of another. Usually such a large shift in the predominant configurations will cause the system's physical properties (mechanical, electrical, optical, etc.) to change in ways that might be very useful. A well known example is the boiling of a liquid to form a vapor. In response to a small change in temperature, the observed configurations of the system go from those corresponding to a large density to those for a much smaller density. In both cases the system (being at fixed pressure) is free to adopt any desired density. In changing phase it overwhelmingly selects configurations for one density over another. This phenomenon, and its many variants, has a multitude of practical applications.

Clearly, there is a close connection between this molecular picture of a phase transformation, and the ideas presented above about the important phase space for a system. When a system changes phase, it is actually changing its important phase space, and the Γ^* region for the system before and after the change can relate in any of the ways described in Fig. 1. Analysis of the free energy is required to identify the location of the phase change quantitatively. Often the order parameter describing the phase change serves as the path parameter λ when performing this analysis.

2.2.   Conditions for Phase Equilibria

In a typical phase-equilibrium problem one is interested in the two (or more) phases involved in the transformation. At the exact condition at which one becomes favored over the other, both are equally stable. Molecular simulation is applied to locate this point of phase equilibrium and to characterize the coexisting phases. Formally, the thermodynamic conditions of coexistence can be identified as those minimizing an appropriate free energy, or equivalently by finding the states in which the intensive "field" variables of temperature, pressure, and chemical potential (and perhaps others) are equal among the candidate phases. Most methods for evaluation of phase equilibria by molecular simulation are based on identifying the conditions that satisfy the thermodynamic phase-coexistence criteria, and consequently they require evaluation of free energies or a free-energy difference. Still there is a lot of variability in the approaches, because really there are two problems involved in the calculation. The first is the measurement of the thermodynamic properties, particularly the free energy, while the second is the numerical "root-finding" problem of locating the coexistence conditions. Methods differ largely in the way they combine these two numerical problems, and the most effective and popular methods synthesize these calculations in elegant ways.

2.3. Direct Contact of Phases, Spontaneous Transformations

Before turning to the free-energy based approaches for evaluating phase coexistence, it is worthwhile to consider the more intuitive approaches that mimic the way phase transitions are studied experimentally. By this we mean methods in which a system is simulated and the phase it spontaneously adopts is identified as the stable thermodynamic phase. Two general approaches can be taken, depending on the types of variables that are fixed in the simulation (i.e., the governing ensemble).

In the first case, only one size variable is imposed (typically the number of molecules), and the remaining variables are fields (temperature, pressure, chemical potential difference). Then a scan is made of one or more of the fields (e.g., the temperature is increased), and one looks for the condition at which the phase changes spontaneously (e.g., the system undergoes a sudden expansion). For example, the temperature at which this happens, and the conditions of the phases before and after the transition, characterizes the coexistence point. In practice this method is effective only for producing a coarse description of the phase behavior. It is very easy for a system to remain in a metastable condition as the field variable moves through the transition point, and the spontaneous transformation may occur at a point well beyond the true value. The reverse process is susceptible to the same problem, so the transformation process exhibits hysteresis when the field is cycled back and forth through the transition value.

In the second case, two or more extensive variables are imposed (i.e., the number of molecules and the volume), and the system is simulated at a condition inside the two-phase region. A macroscopic system in this situation would separate into the two phases, and both would coexist in the given volume. In principle, this too happens in a molecular simulation, but usually the system size is not sufficiently large to wash out effects due to the presence of the interface. In effect, neither bulk phase is simulated. Nevertheless, the direct-contact method does work in some situations. Solid-fluid phase behavior has been studied this way. The interface is slow to equilibrate in this system, so one must be careful to ensure that the simulation begins with a well equilibrated solid. Vapor-liquid equilibria have also been examined using direct contact of the phases. Of course, this approach cannot be applied when too close to the critical point. Often such systems are examined because the interfacial properties are themselves of direct interest.

Spontaneous formation of phases has been used recently to examine the behaviors of models that exhibit complex morphologies. Glotzer *et al.* have examined the mesophases formed by a wide variety of model nanoparticles, including hard particles with tethers, and particles with sticky patches [32].

The systems have been observed to spontaneously form many complex structures, including columns, lamella, micelles, sheets, double layers, gyroid phases, and so on. The question remains of the absolute stability of the observed structures, but their spontaneous formation is a strong indicator that they are certainly relevant, and could likely be the most stable of all possible phases at the simulated conditions. The phase behaviors of other types of mesoscale models are also studied through the direct-observation methods. Systems modeled using dissipative particle dynamics [2, 33] are good candidates for this treatment, because they have a very soft repulsion and particles can in effect pass through each other; and as a consequence they equilibrate very quickly.

2.4.   Methods Based on Solution of Thermodynamic Equalities

A well worn approach to the free-energy based evaluation of phase equilibria focuses on satisfying the coexistence conditions given in terms of equality of the field parameters. In this approach each phase is studied separately, and state conditions are varied systematically until the coexistence conditions are met. An effective way to attack this problem is to combine the search for the coexistence point with the evaluation of the free energy through thermodynamic integration. For example, to evaluate a vapor-liquid coexistence point, one can start with a subcooled liquid of known chemical potential (evaluated using any of the methods reviewed above), and proceed with a series of isothermal-isobaric simulations following a line of decreasing pressure. At each point the chemical potential can be evaluated through the thermodynamic integration using the measured density

$$\mu(P) = \mu(P_0) + \int_{P_0}^{P} \mathrm{d}p / \rho(p). \tag{8}$$

A similar series of simulations can be performed in the vapor separately, at the same temperature as the liquid simulations, but increasing the pressure toward the point of saturation (alternatively, an equation of state might be applied to characterize the vapor). Once the liquid and vapor simulations reach an overlapping range of pressures, the chemical potentials computed according to Eq. (8) can be examined at each pressure, until the point is found at which chemical potential is equal across the two phases for a given pressure.

This general approach can be somewhat tedious to implement, but it is perhaps the most robust of all methods. It is likely to provide a good result for almost all types of coexistence. It has been applied to many types of phase equilibria, including those involving solids [34], liquid crystals [35], plastic

crystals, as well as fluids. The search for the coexistence condition can be applied using almost any order parameter (density was used in this example), although one must perhaps put some effort toward developing the appropriate formalism defining a field to couple to the parameter, and implementing a simulation in which this field is applied. Complications arise if many field parameters are relevant. For example, if one is studying a mixture, then a separate field parameter (chemical potential) is needed to couple to each mole-fraction variable. The problem can be simplified by fixing all but one of the field variables in the two phases, but often this leads to a statement of the coexistence problem that is at odds with the problem of real interest (e.g., one might want to know the composition of the incipient phase arising from another phase of given composition, which in the context of vapor-liquid equilibria is known as a bubble-point or a dew-point calculation). For mixtures, this formulation is expressed by the semigrand ensemble [36].

This method, like many others, will suffer when applied to characterize a weak phase transition, that is, one that is accompanied by only a small change in the relevant order parameter. The order parameter is related to the slope of the line that is being mapped in this calculation, and consequently for a weak transition the slopes of these lines for the two phases will not be very different from each other. It can be difficult to locate precisely the intersection of two nearly parallel lines – any errors in the position of the lines will have a greatly magnified effect on the error in the point of intersection. Therefore the application of this method to a weak transition can fail if the relevant ensemble averages and the free energies for the initial points of the integration are not measured with high precision and accuracy.

2.5. Gibbs Ensemble

A breakthrough in technique for the evaluation of phase coexistence by molecular simulation arrived in 1987 with the advent of the Gibbs ensemble [37]. This method presents a very clever synthesis of the problem of locating the conditions of coexistence and measuring the free energy in the candidate phases. It accomplishes this through the simulation of both phases simultaneously, each occupying its own simulation volume. Although the phases are not in "physical" contact, they are in contact thermodynamically. This means that they are capable of exchanging volume and mass in response to the thermodynamic driving forces of pressure and chemical potential difference, respectively. The systems evolve in this way, increasing or decreasing in density with the mass and volume exchanges, until the point of coexistence is found. Upon reaching this condition the systems will fluctuate in density about the values appropriate for the equilibrium state, which can then be measured as a simple

ensemble average. Details of the method are available in several reviews and texts [2, 37, 38].

The Gibbs ensemble is the method of choice for straightforward evaluation of vapor–liquid and liquid–liquid equilibria. It does not suffer any particular complications when applied to mixtures, and it has been applied with great success to many phase coexistence calculations. However, there are several ways in which it can fail. First, an essential element of the technique is the exchange of molecules at random between the coexisting phases. If trials of this type are not accepted with sufficient frequency, the systems will not equilibrate and a poor result is obtained. This problem arises in applications to large, complex molecules, and/or at low temperatures and high densities. It can be overcome to a useful degree through the application of special sampling techniques, such as configurational bias. Second, in its basic form the Gibbs ensemble is not applicable to equilibria involving solids, or to lattice models. The problem is only partially due to the difficulty of inserting a molecule into a solid. The "mass balance" is the more insidious obstacle. The number of molecules present in each phase at equilibrium is set by the initial number of molecules and the volume of the composite system of both phases (as well as the values of the coexistence densities). A defect-free crystal can be set up in a periodic system using only a particular number of molecules. For example an *fcc* lattice in cubic periodic boundaries can be set up using 32, 108, 256, 500, and so on molecules (i.e., $4n^3$ where n is an integer). When beginning a Gibbs ensemble calculation there is no simple way to ensure this condition will be met in the equilibrium system. Tilwani and Wu [39] have treated these problems with an alternative approach in which an atom is added to the unit box of the solid and this new unit box is used to fill up (tile) space. In this way, particles can be added or removed from the system, while the crystal structure is maintained.

The Gibbs ensemble fails also upon approach to the critical point. As this condition is reached, contributions to the averages increase for densities in the region between the two phases. It then becomes possible, even likely, that the simulated phases will swap their roles as the liquid and vapor phases. This is not a fatal flaw, but it presents a complication to the method, and it is an indicator that the general approach is beginning to fail. Thus the consensus today is that in this region of the phase envelope density-of-states methods are more suitable for characterizing the coexistence behavior. More generally, the Gibbs ensemble can encounter difficulty when applied to any weak phase transition, if only because it is necessary to configure the composite system so that it lies in the two phase region – this can be difficult to do if this region is very narrow. Interestingly enough, the Gibbs ensemble can fail also if it is applied using very large system sizes. In this situation an interface is increasingly likely to form in one or both phases, and the result is that a clean separation of phases between the volumes is no longer in place – instead both

simulation volumes each end up representing both phases. Typically the Gibbs ensemble is applied for its simplicity and ability to provide quick results, so the large systems needed to raise this problem are not usually encountered.

2.6. Gibbs–Duhem Integration

The Gibbs–Duhem integration (GDI) method [40] applies thermodynamic integration to both parts of the combined problem of evaluating the free energy and locating the point of transition. In particular, the path of integration is constructed to follow the line of coexistence. All of this is neatly packaged by the Clapeyron differential equation for the coexistence line, which in the pressure–temperature plane is [1]

$$\left(\frac{\mathrm{d}P}{\mathrm{d}T}\right)_{\sigma} = \frac{\Delta H}{T\,\Delta V},$$ (9)

where ΔH and ΔV are the differences in molar enthalpy and molar volume, respectively, between the two phases; the σ subscript indicates a path along the coexistence line. The GDI procedure treats Eq. (9) as a numerical problem of integrating an ordinary differential equation. The complication, of course, is that the right-hand side must be evaluated through molecular simulation at the temperature and pressure specified by the integration procedure, and moreover separate simulations are required to characterize both phases involved in the difference. A simple iterative process is applied to refine the pressure according to Eq. (9) after a step in temperature is taken, using preliminary results for the ensemble averages from the simulations. Predictor-corrector methods are effective in performing the integration, and inasmuch as the primary error in the calculation arises from the imprecision of the ensemble averages, a low-order integration scheme suffices for the purpose.

The GDI method applies much more broadly than indicated in this description. Any type of field variables can be used in the role held by pressure and temperature in Eq. (9), with appropriate modification to the right-hand side. For example, integrations have been performed along paths of varying composition, polydispersity, orientational order, and interparticle-potential softness, rigidity, or shape [36]. The method applies equally well to equilibria involving fluids or solids, or other types of phases. It has been used to follow three-phase coexistence lines too. In this application one must integrate two differential equations similar to Eq. (9), involving three field variables. In all cases there are a number of practical implementation issues to consider, such as how the integration is started, and the proper selection of the functional form of the field variables (e.g., integration in ln(P) vs. $1/T$ has advantages for tracing

vapor–liquid coexistence lines). These issues have been discussed in some detail in recent reviews [36, 41].

The GDI method has some limitations. It does require an initial point of coexistence in order to begin the integration procedure. Concerns are often expressed that errors in this initial point will propagate throughout the integration, but this problem is not as bad as one might think. A stability analysis shows that any such errors will be attenuated if the integration is performed in a direction from a weaker to a stronger transition (e.g., away from the liquid–vapor critical point toward lower temperatures). On the other hand, if the integration is performed in the opposite direction, initial and accumulated errors will be amplified. Regardless it seems that in practice any such problems do not arise. A related concern is the general difficulty in treating weak phase transitions. If the differences on the right-hand side of Eq. (9) are small, and thus may be formed using averages that have stochastic errors comparable to the differences themselves, then it is clear that the method will not work well. In such cases one might be better off employing a method that directly bridges the difference between the phases, such as by mapping the full density of states in this region.

The basic idea of tracing coexistence lines has been further generalized for mapping of other classes of phase equilibria, such as tracing of azeotropes [42], and dew/bubble-point lines [41]. Escobedo has developed and applied a general framework for these approaches [30, 43–47].

2.7.   Mapping the Density of States

Density of states methods evaluate coexisting phases by calculating the full free-energy profile across the range of values of the order parameter between and including the two phases. It is only in the past few years that this method has come to be viewed as generally viable, and even a good choice for evaluating phase coexistence. The effort involved in collecting information for the intermediate points seems wasteful, although with the approach these data are needed to obtain the relative free energies of the real states of interest (i.e., the coexisting phases). The methods reviewed above are popular because they avoid this complication and are more efficient because of it. However, there is some advantage in having the system cycle through the uninteresting states. It helps to move the sampling through phase space. Thus, a simulated system might go from a liquid configuration, then to a vapor, and back to the liquid but in a very different configuration from which it started. This is particularly important for complex fluids such as polymers (in the context of other phase equilibria), in which it is otherwise difficult to escape from ergodic traps. Second, the intermediate states may be of interest in themselves; they can be used, for example, to evaluate the surface tension associated with contacting the two

phases [10]. Third, it may be that the distance between the coexisting phases is not so large (i.e., the transition is weak), so covering the ground between them does not introduce so much expense; moreover in such a situation other methods do not work very well. Regardless, continuing improvements in computing hardware and algorithms (some reviewed above), particularly in parallel methods and architectures, have made the density-of-states strategy look much more appealing.

We describe the basic approach in the context of vapor–liquid equilibria. Simulation can be performed in the grand-canonical potential with a chemical potential selected to be in the vicinity of the coexistence value. The density of states is mapped as a function of number of molecules at fixed volume; the transition-matrix method with a biasing potential in N has been found to be convenient and effective in this application. The resulting density of states will most likely exhibit two unequal peaks, representing the two nearly coexisting phases. Histogram reweighting is then applied to the density of states to determine the value of the chemical potential that makes the peaks equal in size. This is taken to be the coexistence value of the chemical potential, and the positions of the peaks give the molecule numbers (densities) of the coexisting phases. The coexistence pressure can be determined from the grand potential, which is available from the density of states. Additional details are presented by Errington [9].

3. Outlook

The nature of the questions that we address with the help of computer simulations is changing. Increasingly, we wish to be able to predict the changes that will occur in a system when external conditions (e.g., temperature, pressure or the chemical potential of one or more species) are changed. In order to predict the stable phase of a many-body system, or the "native" conformation of a macromolecule, we need to know the accessible volume in phase space that corresponds to this state or, in other words, its free energy.

Both the MC and the MD methods were created in effectively the form in which we use them today. However, the techniques used to compute free energy differences have expanded tremendously and have become much more powerful and much more general than they were only a decade ago. Yet, the roots of some of these techniques go back a long way. For instance, the density-of-states method was already considered in the late 1950s [48] and was first implemented in the 1960s [49]. The aim of the present chapter is to provide a (very concise) review of some of the major developments. As the developments are in a state of flux, this review provides nothing more than a snapshot.

It is always risky to identify challenges for the future, but some seem clear. First of all, it would seem that there must be a quantum-mechanical counterpart to Jarzynski's NEW method. However, it is not at all obvious that this would lead to a tractable computational scheme. A second challenge has to do with the very nature of free energy. In its most general (Landau) form, the free energy of a system is a measure of the available phase space compatible with one or more constraints. In the case of the Helmholtz free energy, the quantities that we constrain are simply the volume V and the number of particles N. However, when we consider the pathway by which a system transforms from one state to another, the constraint may correspond to a non-thermodynamic order parameter. In simple cases, we know this order parameter, but often we do not. We know the initial and final states of the system and hopefully the transformation between the two can be characterized by one, or a few, order parameters. If such a low-dimensional picture is correct, it is meaningful to speak of the "free-energy landscape" of the system. However, although methods exist to find pathways that connect initial and final states in a barrier-crossing process [50], we still lack systematic ways to *construct* optimal low-dimensional order-parameters to characterize the transformation of the system. To date, most successful schemes to map free-energy landscapes *assume* that the true reaction coordinates are spanned by a relatively small set of supposedly relevant coordinates. However, is not obvious that it will always be possible to find such coordinates. Yet, without a physical picture of the constraint or reaction coordinate, free energy surfaces are hardly more informative than the high-dimensional potential-energy surface from which they are ultimately derived. Without this knowledge we can still compute the relative stability of initial and final state (provided we have a criterion to distinguish the two), but we will be unable to gain physical insight into the factors that affect the rate of transformation from the metastable to the stable state.

Acknowledgments

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