

Molecular Simulation Approaches to Solubility

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1 Introduction

Over the past fifty years, molecular simulation has emerged as a useful tool for providing microscopic insight into a variety of chemical systems and processes. There are two main particle-based simulation techniques – molecular dynamics, which uses deterministic equations of motion integrated over small time steps to evolve the system, and Monte Carlo sampling, which uses a Markov chain to construct a stochastic sequence of system configurations. Molecular dynamics can provide insight into time-dependent and time-averaged properties of the system, whereas Monte Carlo simulations provide ensemble-averaged properties. Both techniques have been extensively used to investigate solubility in different chemical systems.

2 Solubility

The solubility of a solute in a solvent, or more generally the transfer of a solute between two solvation environments, is usually expressed either in terms of the infinite-dilution limit or the solubility limit, where the latter often involves the mutual solubility limit in the sense that both “solute” and “solvent” can transfer between the two environments. Commonly, these environments are homogeneous bulk phases, but in principle one might also be interested in the transfer involving a micro-phase region, such as a surfactant micelle or an octadecyl-bonded phase in reversed-phase liquid chromatography. Most commonly studied are the transfer of the solute between the gas and liquid phases (free

energy of solvation), gas and water phases (free energy of hydration), or two liquid phases.

Phase coexistence for a system consisting of two phases α and β requires that

$$\begin{aligned}\mu_i^\alpha &= \mu_i^\beta \\ p^\alpha &= p^\beta \\ T^\alpha &= T^\beta\end{aligned}\tag{1}$$

where μ_i is chemical potential of species i (and the equality needs to be satisfied for all independent components), p is the pressure, and T is the absolute temperature of a given phase.¹⁻³ The solubility is often thought of in terms of the Gibbs free energy of transfer of solute i from phase α to phase β , and is defined by the following expression.^{4,5}

$$\Delta G_i^{\alpha \rightarrow \beta}(T, p, X^\alpha, X^\beta) = -RT \ln K_i^{\alpha \rightarrow \beta}(T, p, X^\alpha, X^\beta) = -RT \ln \left(\frac{\rho_i^\beta(T, p, X^\alpha, X^\beta)}{\rho_i^\alpha(T, p, X^\alpha, X^\beta)} \right)\tag{2}$$

where X denotes the equilibrium composition, R is the universal gas constant, and ρ is the number density of i in a given phase. For solute i , the partition coefficient K is defined by the ratio of the concentrations of i in the two phases. When evaluating solubility experimentally, K is the observable property of interest. The specific value of K depends on the concentration units with molarity (or number density) being preferred on statistical mechanical grounds (because the translational entropy depends on volume), but molality often used on practical grounds (because it avoids the need to measure the volume).

Because K depends on temperature, pressure, and concentration, it is useful to relate this property to the Gibbs free energy of the standard state, ΔG° . In the gas phase,

the standard state is defined as the pure gas at one atmosphere for a given temperature. The standard state can be defined in different ways for liquids and solutions. For a pure liquid, the standard state is the pure liquid at one atmosphere for a given temperature. In solution, it may be defined as a (hypothetical) ideal solution with unit molarity or molality, or with respect to infinite dilution properties.¹ It is naturally of great importance to clarify the definitions used for the standard states before comparing different experimental or simulation results.

The most direct comparison between experiment and simulation is the comparison of K under the same conditions. Until fairly recently, this was not possible, since there was no method to directly determine K from simulation. Therefore, techniques were developed to determine the solubility of a given species in terms of the standard Gibbs free energy of transfer. Defined for the transfer between phases,

$$\Delta G^\circ = G^{\circ,\beta} - G^{\circ,\alpha}. \quad (3)$$

This becomes equal to the difference in the standard chemical potential when phase α is the N particle system and β is the $N+1$ particle system (or the $N-1$ and N particle systems, respectively). The chemical potential of the solute, μ^s , is the partial derivative the Gibbs free energy with respect to the number of solute molecules present at constant temperature, T , and pressure, p . The standard chemical potential, μ_s° , is defined as

$$\mu_s^\circ(T, p) = \mu_s(T, p, x_s) - k_B T \ln a_s \quad (4)$$

where $a_s = x_s \gamma_s$ is the activity of the solute, x_s is the mole fraction of the solute, γ_s is the activity coefficient of the solute, and k_B is Boltzmann's constant. A key point here is that when using the standard state to determine solubility, one is evaluating the difference in the standard chemical potential between two phases while the actual chemical potential difference is zero (see equation 1). Because of this condition of phase coexistence, the difference in the standard chemical potential is related to the ratio of the activity of the solute in the two phases,

$$\Delta\mu_s^\circ = \mu_s^{\circ,\beta} - \mu_s^{\circ,\alpha} = -k_B T \ln(a_s^\beta / a_s^\alpha). \quad (5)$$

For infinitely dilute systems, the activity coefficient of each phase is assumed to be unity, and the ratio of activities is simply the ratio of the mole fraction of the solute between the phases. Most simulation techniques seek to determine the chemical potential at infinite dilution and relate this to the solubility coefficient. While this is a reasonable approach in many situations, it is important to keep the system size of the simulation and the properties of the solute in mind. Due to computational limits, many "infinitely dilute" simulation systems consist of only a few hundred solvent molecules. For many solutes, one solute molecule in the presence of a few hundred solvent molecules is already above the solubility limit.

More recently, the development of the Gibbs ensemble Monte Carlo technique^{6,7} has allowed for the direct determination of K by simulating two phases simultaneously. In the Gibbs ensemble, molecules can transfer directly between the phases over the course of a simulation and the system properties, such as the solute number densities, are

evaluated as ensemble averages. This does not pose a restriction on the number of solute molecules in a specific phase and together with the direct evaluation of solute number densities leads to very precise determinations of solubility coefficients.

3 Computing Solubility for the Infinite Dilution Limit

The infinitely dilute solution is of particular interest because it provides a means to examine solute-solvent interactions without the presence of solute-solute interactions.⁴ There are many different standards used to measure solubility based on different criteria.¹ The most common measure of the solubility of a gas in a liquid at infinite dilution is Henry's law constant,

$$H_s = \lim_{x \rightarrow \infty} \frac{p_s^{gas}}{x_s^{liq}}, \quad (6)$$

where p_s is the partial pressure of the solute in the gas and x_s is the concentration of the solute in the solvent. Henry's law states that at infinite dilution the partial pressure of a solute is directly proportional to the concentration of the solute in the solvent phase. H is related to the excess, or residual, chemical potential, μ^E , by⁹

$$\frac{\mu_s^E}{k_B T} = \ln \frac{H_s}{\rho k_B T} \quad (7)$$

where ρ is the density of the solvent. The excess chemical potential is the difference between the chemical potential of the real system and that of an ideal system at the same temperature and pressure. According to the potential distribution theorem,¹⁰ the change in free energy in the canonical ensemble (constant- N, V, T) upon the addition of a particle

(i.e. the chemical potential) can be calculated from an ensemble average over configurations of the original system (containing $N-1$ particles)

$$\mu_S^E = -k_B T \ln \left\langle \exp \left(\frac{U_{\text{test}}}{k_B T} \right) \right\rangle_{N-1, V, T} \quad (8)$$

where U_{test} is the interaction energy of a test particle (the N^{th} particle) with the system, i.e. $U_{\text{test}} = U_N - U_{N-1}$. Most simulation techniques seek to use this expression to determine the excess chemical potential of the system, and from there, determine Henry's law constant. It should be noted that equation 8 is only valid in the canonical ensemble and different expressions need to be used in the isobaric-isothermal and Gibbs ensembles.¹¹

Thermodynamic Integration

The most widespread methods used to calculate free energy differences are thermodynamic integration (TI) and free energy perturbation (FEP). Both methods can be applied equally well in the canonical and isobaric-isothermal ensembles to obtain Helmholtz and Gibbs free energies, respectively. TI seeks to determine the free energy of the system of interest by constructing a reversible pathway between a reference system of known free energy and the system of interest.¹¹ TI is based on the equation

$$\Delta F = F_1 - F_0 = \int_0^1 \frac{\partial F(\lambda)}{\partial \lambda} d\lambda = \int_0^1 \left\langle \frac{\partial H(\mathbf{q}, \mathbf{p}, \lambda)}{\partial \lambda} \right\rangle_{\lambda} d\lambda \quad (9)$$

where ΔF is the free energy difference between state 1 and state 0, $F(\lambda)$ is the free energy of the system as a function of the coupling parameter λ which can run from zero to unity, and $H(\mathbf{q}, \mathbf{p}, \lambda)$ is the Hamiltonian of the system as a function of λ and the set of

generalized coordinates and momenta.¹² $F(\lambda)$ is chosen such that when $\lambda = 0$, $F(\lambda) = F_0$, the free energy of the reference or initial system, and when $\lambda = 1$, $F(\lambda) = F_1$, the free energy of the target system. In contrast to experimental techniques, a simulation is not constrained to follow a physical thermodynamic integration pathway. For example, if the reference system is defined as the $N-1$ particle system and the N particle system is the target system, one technique is to use the strength of the interactions between the N^{th} particle and the rest of the system as the coupling parameter λ . A series of simulations, then, proceeds along this pathway, progressively inserting a particle into the system, by turning on its full interaction potential as λ moves from 0 to 1. Using a finite number of values for λ , the integration over λ is performed numerically to determine the free energy difference.¹¹

While reliable and applicable to a wide variety of systems, including difficult systems such as solids, TI is subject to some drawbacks. As summarized by Kofke and Cummings,¹³ one main drawback to TI is its “perceived inefficiency.” This perception arises primarily from the reliance of TI on sampling a series of intermediate and thermodynamically uninteresting states as the system moves from state 0 to state 1. Traversing these intermediate states is not inherently less efficient than other methods used in the calculation of the chemical potential, according to Kofke and Cummings. Additionally, care must be used when choosing an integration pathway so as not to cross a phase boundary.¹³

Thermodynamic integration has been used alone and in combination with other techniques to model the solubility properties of a variety of systems. These include non-polar solutes, such as n-alkanes in water, where differences in the solvation free energies between alkane species agreed with experimental results while the statistical error within the calculated values of $\langle \partial H(\lambda)/\partial \lambda \rangle$ for each value of λ was at most $\pm 5\%$, as estimated by block averaging.^{14,15} The free energies of hydration for *p*-substituted benzamidine derivatives were used to predict solvation order, with errors around 30% for the free energy values, based on standard deviations in the exponential term (eq. 8).¹⁶ In addition, the solubility of charged species in water has also been examined using TI.¹⁷ Straatsma and Berendsen provide many good points to be taken into consideration when modeling such systems, but conclude that TI is generally a reliable technique.¹⁷ In one novel application, TI was used to predict the solubility of atomic species such as silicon and sulphur in liquid and solid iron under conditions of extreme pressures and temperatures, with statistical errors around 5% in the free energy calculations.¹⁸

Free Energy Perturbation

The second common class of methods used to calculate chemical potential includes those based on free energy perturbation. These methods are primarily concerned with the relationship¹³

$$\Delta F = F_1 - F_0 = -k_B T \ln \left\langle \exp[\Delta H_{10}(\mathbf{q}, \mathbf{p})] \right\rangle_0. \quad (10)$$

The subscript 0 on the braces indicates an ensemble average at state 0. In most applications, state 0 is taken as the reference state and state 1 is the perturbed state,

although in principle these labels are interchangeable. FEP and TI, thus, are very similar in theory; both are primarily concerned with the construction of a thermodynamic pathway between two states of interest. The distinction is how this pathway is constructed. TI is concerned with the integral in equation 9. It is not necessary for intermediate states to overlap, but the accuracy of the calculation depends on the smoothness of a plot of $\partial H(\lambda)/\partial \lambda$ versus λ .¹⁴ In FEP, ΔF is determined by simulating one state and perturbing the interaction parameters at each point to sample the second state. This requires that the two states of interest be fairly close in energy so that they overlap substantially in phase space. The total free energy difference between the first state and the final state is the sum of the free energy differences between the intermediate pairs of states.¹⁴ A series of different FEP techniques have been proposed; these can be loosely arranged into single stage and multiple stage methods.

Single Stage Techniques

The most common single stage FEP method is that of Widom's test particle insertion.¹⁰ This method follows directly from equation 10. Choosing the reference system to have $N-1$ particles and the perturbed system as that with N particles, ΔF is equal to the excess chemical potential given by equation 8 (for the canonical ensemble). In practice, the ensemble average is measured by inserting the test particle into the system, calculating the potential energy of the test particle with the system, and removing the particle before continuing the simulation. This means that as the simulation progresses, the system itself

is not disturbed; in fact, the calculation of the residual chemical potential could be performed simply on the configuration file from a simulation of the $N-1$ particle system.

The primary drawback of this method is its increasing inability to adequately sample the N particle system as the density of the fluid increases, particularly as one moves beyond single atom insertions to insertions of whole molecules. Methods, such as configuration-biased insertions,¹⁹⁻²⁴ are available to overcome or lessen this restriction. In principle, it is possible to proceed in the opposite direction, i.e. from the N system to the $N-1$ system, through particle removal, but in practice this method is not as reliable or as straightforward and can suffer from inadequate sampling of the $N-1$ particle system.¹³

Widom's test particle insertion technique has been used to probe the solubility of small molecules in a variety of systems. The simulation results for the solubility of oxygen and carbon dioxide in fluorocarbons show good agreement with experimental results, and statistical errors of, at most, 7% in the calculation of μ^E .^{25,26} Others have used the technique to examine the solubility of alkanes in a rubber polymer; over the progression from methane to hexane, the uncertainty in the calculated solubility coefficient ranged from 10 to 69% based on data from eight different starting configurations.²⁷ Widom's insertion technique is also often used to compute Henry's law constant. Recently, Boutard, *et al.* calculated the Henry's law constants for carbon dioxide, methane, oxygen and nitrogen in ethanol with a statistical uncertainty of about 5%.²⁸ Widom's method may also be used to incrementally insert long chain molecules

into a fluid.²⁹ For a homopolymer of length l in the solvent system, the chemical potential of the $l+1$ chain is determined by inserting an additional bead at the end of the l chain. Kumar *et al.*²⁹ show that μ^E for each step along the growth of the chain may be computed and, through a building up process, used to determine the chemical potential of the whole chain. This provides a useful technique for inserting larger molecules into solutions.

Multiple Stage Techniques

FEP methods may also proceed through a series of stages, where intermediate states may be joined together in the course of calculating the chemical potential. It is possible to use multiple intermediates, but for the ease of discussion, the examples presented here will use only one, with M indicating the intermediate state. Just as before, the reference and perturbed states must be defined, and it is this definition that separates the available multistage FEP methods. Among the most common techniques are umbrella sampling and the overlapping distribution method. In umbrella sampling, the M state is defined as the reference state, with the $N-1$ and N states as perturbations.³⁰ In a single simulation, a sampling distribution is constructed to sample both inserting and removing a single particle. A bias is used in the selection of the sampling distribution to ensure that regions important to both the $N-1$ and N “perturbations” are sampled evenly. The excess chemical potential is then calculated according to

$$\mu^E = -k_B T \ln \left(\frac{\langle \exp(-U_N/k_B T) / \pi \rangle_\pi}{\langle \exp(-U_{N-1}/k_B T) / \pi \rangle_\pi} \right), \quad (11)$$

where U_m is the potential energy of the N or $N-1$ particle system and π is distribution weighting function.³⁰ Care must be taken when using this method to select an appropriate weighting function so as not to bias the system towards either perturbation. A variation of umbrella sampling known as “double-wide sampling”³¹ has been used to study the partition coefficients of small organic molecules in water and chloroform. The trends in solubility predicted by simulation followed those known from experiment, although the range of free energies was larger for the simulation results and the statistical error in the calculated free energies was on the order of 10%.³² This technique was recently used to examine solvent effects on partition coefficients for a wider range of solvents, including tetrahydrofuran and acetonitrile.³³

Alternatively, in the overlapping distribution method, both the $N-1$ and N states are considered reference states while M is a perturbation to each. As the name implies, the perturbation state is chosen so that the phase space of M overlaps that of both the $N-1$ and N systems. The calculation of the chemical potential requires two separate simulations, one for each reference system,³⁴

$$\mu^E = -k_B T \ln \left(\frac{\langle \exp(-U_{(N-1) \rightarrow M} / k_B T) \rangle}{\langle \exp(-U_{N \rightarrow M} / k_B T) \rangle} \right). \quad (12)$$

While this method has not been widely used, Kofke and coworkers have shown recently that it may be more efficient than some methods that are more popular.^{35,36} A separate study by Shirts and Pande³⁷ came to a similar conclusion, showing that Bennett's method,³⁸ a type of overlap sampling, is more efficient than TI in many situations. One

example of successful application is the chemical potential of flexible chain molecules of up to fourteen hard spheres, where the overlapping distribution method was shown to be as reliable as Widom's technique for certain systems with errors in the residual chemical potential on the order of a few percent.³⁹

Expanded Ensembles

The next two techniques used to determine excess chemical potential are also related. The first is the expanded ensemble method.⁴⁰⁻⁴² This method determines the free energy difference due to the insertion of a particle by constructing a series of intermediate states between the $N-1$ and N systems and tracking the frequency with which these subsystems are sampled. The initial subsystem is that of $N-1$ interacting particles and 1 non-interacting “solute” particle, which may or may not be of the same chemical species as the solvent molecules. A series of m intermediates is constructed with the interactions, α_m , between the solute and the solvent slowly increasing until the M^{th} subsystem, where the solute fully interacts with the solvent system ($\alpha_M = 1$), which corresponds to the true N particle ensemble. A Monte Carlo walk through the expanded system samples each state between $\alpha_0 = 0$ and $\alpha_M = 1$ to produce a probability distribution, p_m , over the subensembles. The excess chemical potential may be related to the ratio of the probability distributions of the two end states,

$$\mu^E = -\ln\left(\frac{p_M}{p_0}\right) + \pi_M - \pi_0, \quad (13)$$

where π_m is the weighting factor of the m^{th} state.⁴⁰ These weighting factors are necessary to ensure that all the subsystems are sampled with roughly equal probability; without the weighting factors, those subsystems with larger chemical potentials would be less frequently sampled, which introduces statistical errors. In general, π_m is chosen to be proportional to the relative free energy of the subsystem m , but this is the quantity of interest to be determined via simulation.⁴³ Therefore a trial run must be used to determine an approximate value for the free energy, and this initial weight can then be iteratively updated over the course of a simulation based on the sampling at the previous weight. One major drawback is that this iterative approach means that the data collected using previous weighting functions must be discarded because the excess chemical potential is dependent upon the weighting factor. This method has been used to determine solvation free energies for molecules from methane to benzylamine in water, and for aqueous ionic solutions with standard deviations of the residual chemical potential generally less than 5% of the value.⁴⁴ The solubility of a series of drug-related compounds has also been examined using expanded ensembles. Solvation free energies were calculated with a precision of about 2 kJ/mol (11%).⁴⁵

Transition Matrix Monte Carlo

The transition matrix Monte Carlo (TMMC) method used by Cichowski *et al.*⁴³ to determine Henry's law constants seeks to improve upon the expanded ensemble approach by integrating transition matrix techniques and the expanded ensemble technique. Beginning with the same expanded ensemble framework, Cichowski *et al.* use the

transition matrix approach to determine the weighting factors. Instead of tracking only the times each subsystem is visited and then discarding the accumulated statistics each time the weighting factor is updated, TMMC monitors the transition probabilities between the ensembles. For each attempt to transition between microstates of two subensembles, a collection matrix is updated regardless of whether or not the transition is completed. From this matrix, the transition probabilities between the subensembles are determined. The key is that although biasing is still used during sampling to ensure even sampling of all subsystems, the bias is removed before the collection matrix is updated. Thus the statistics accumulated over the whole simulation may be used, not only those of a given biasing factor. This makes the technique more efficient than the expanded ensemble approach. Cichowski *et al.* determined Henry's law constants for a few small solutes in ethanol with no more than 4% standard deviation as determined from four independent simulations.

Gibbs Ensemble

The methods described so far, all require the use of standard states to compute Gibbs free energies of transfer at infinite dilution via equation 3 from separate simulations for the two phases. Rather different in spirit, the Gibbs Ensemble Monte Carlo^{6,7} (GEMC) approach may also be used to explore infinitely dilute systems, but the calculation of Gibbs free energies proceeds analogously as experiments via equation 2. The Gibbs ensemble uses two (or more) separate simulation boxes representing distinct bulk phases. A series of specialized moves are used in addition to the standard translation, rotation,

and conformation moves to bring the bulk phases into equilibrium. At constant pressure and temperature, this includes volume exchange moves with a pressure bath and particle swap moves between the phases to equilibrate the pressure and the chemical potential of the phases, respectively.⁸ Due to the dependence on swapping particles, the original GEMC method is not very efficient for dense systems or articulated solutes where the acceptance rate for swap moves can become very small (i.e., similar problems are encountered as with Widom’s insertion method). For flexible molecules (and to a lesser extent for rigid molecules), the use of configurational-bias growth procedures can dramatically enhance the swap acceptance rates.^{24,46-49} In addition, expanded ensembles can also be used that allow for a gradual transfer of the solute^{50,51} and pre-weighting factors can be employed to improve the statistical precision by ensuring roughly equal number of solute molecules in both phases.⁵² For liquid-liquid equilibria, the transfer rate can be greatly enhanced by using one (or multiple) intermediate phase, such as a vapor phase.^{53,54}

The primary advantage of the Gibbs ensemble is that the Gibbs free energy of transfer for particles allowed to swap between the two phases may be calculated directly from the number densities of the particles in the two phases⁸

$$\Delta G_i = -k_B T \ln \left(\frac{\rho_i^\alpha}{\rho_i^\beta} \right). \quad (14)$$

The direct computation of a ratio of mechanical properties greatly improves the statistical precision compared to indirect methods, such as thermodynamic integration and free

energy perturbation, and it avoids the need to specify a standard state for the solution with the usual assumption of ideal solution behavior. Similarly, the Henry's law constant can be directly computed via equation 6, where the property x_s^{liq} is obtained from its ensemble average. Dalton's law of partial pressures may be used to determine p_s^{gas} from the mole fraction of the solute in the gas phase and the ensemble averaged saturation pressure. Using this technique, it is possible to determine Henry's law constant in a manner that more closely mimics experimental conditions. Another advantage of the Gibbs ensemble approach is that it avoids the systematic errors that can be encountered in FEP calculations depending on the phase space relationship between the reference and the perturbed system.^{13,55}

Recently, GEMC simulations were used to compute Henry's law constants for methane, carbon dioxide, nitrogen, and oxygen in ethanol with a precision of about 3% based on the standard error of the mean taken over four independent simulations.⁵⁶ GEMC has also been used to examine partitioning of alkanes and alcohols in neat and water-saturated 1-octanol as well as into water to examine the effects of multiple solvents on partitioning.^{52,54} In the field of chromatography, GEMC has been used to examine the partitioning of solutes between the stationary and mobile phases in both gas-liquid and liquid-liquid chromatography.⁵⁷⁻⁶² Using GEMC, it is possible to simulate systems with multiple organic solutes present and to calculate free energies of transfer and partition coefficients, K , for each solute. The K may be determined directly from the ensemble-averaged number densities with great precision (often less than 3% uncertainty) so that

differences between isomers, such as 2-methylpentane and 3-methylpentane, may be resolved.⁵⁷ Furthermore, GEMC allows investigations of systems where one or more solutes are present in larger concentration,^{58,60} where one or multiple interfaces are present, such as the liquid-air interface in gas-liquid chromatography⁵⁹ or the silica-bonded phase and bonded phase/mobile phase interfaces in reversed-phase liquid chromatography.⁶² Finally, the precision of GEMC simulations for Gibbs free energies of transfer is also sufficient to explore deviation from van't Hoff behavior caused by the heat capacity of transfer.⁶³

Continuum Solvation Models

Although not usually considered in the context of molecular simulation, continuum solvation models are discussed here briefly because these methods are very popular for the computation of solubilities. Instead of using explicit molecular models to examine the interactions of solute and solvent, as is done in particle-based simulations, continuum solvation models use a simplified representation of the solvent, such as a continuum characterized by properties of the bulk solvent.⁶⁴ The continuum models are generally parameterized for specific solvents to reproduce the interactions of these solvent with a variety of solutes. The continuum representation of the solvent results in significant gains in computational efficiency not only because one does not need to compute the interactions with a large number of solvent molecules but more so because continuum solvation models do not require sampling of the phase space of the solvent molecules, i.e. one does not need to move solvent molecules to obtain free energies. However, the

neglect of sampling the solvent degrees of freedom also implies that continuum solvation models cannot be simply applied over a range of state points (temperatures and pressures).

The free energy of solvation is determined by placing the solute into a cavity in the continuum solvent, which becomes polarized. The key concept in understanding the polarization effects on the solvent and solute is the reaction field.⁶⁵ The reaction field is the electric field exerted by the solvent on the solute once the solvent has been polarized. The reaction field polarizes the solute, which in turn changes the polarization of the solvent. Out of this process comes the self-consistent reaction field method.⁶⁶ The first continuum model is the Born-Kirkwood-Onsager approach,⁶⁷⁻⁶⁹ where the solvent is usually modeled as a homogeneous, isotropic continuum characterized by the dielectric constant.⁶⁶ While it is widely implemented, this method has two strict limitations. First, the solute must be nearly spherical and second, multipole effects, beyond monopole and dipole interactions, must be negligible.⁶⁶ A second approach is the polarizable continuum model⁷⁰ (PCM) which divides the surface of the solute into discrete elements each containing a point charge. The overall interaction of the solute and the continuum is then a summation of the point charge interactions. Thirdly, the conductor-like screening model⁷¹ (COSMO) uses a similar approach as PCM but instead of a dielectric outside of the solute cavity, a conductor is used with corrections added for dielectric behavior. Klamt and coworkers⁷²⁻⁷⁴ have used COSMO, and its statistical mechanical extension, COSMO-RS, to study the solubility of drugs, pesticides, and other molecules in water

and organic solvents, with results generally better for aqueous systems than nonaqueous systems. A final example of a popular continuum solvation models is the SMx family.⁷⁵ These models use a generalized Born approach where Born electrostatics are combined with a quantum mechanical description of the solute and the standard state free energy of solvation is calculated from the solvent free energy and the gas phase electronic energy contributions. The current model, SM6, was standardized using aqueous solvation free energy calculations for a range of 273 neutral solutes, as well as 112 ions.⁷⁶ The addition of one or more explicit water molecules showed significant improvement in free energy calculations for solutes that interact strongly with the solvent.

4 Computing the Solubility Limit

The second problem in solubility where simulation is used to probe behavior is that of the solubility limit. This is the maximum amount of a solute soluble in a given volume of solvent. It should be noted that in particular for cases where both the “solute” and the “solvent” exist in the liquid state, one should discuss the mutual solubility in the sense that both components have the ability to influence the solubility characteristics (and other properties) of the phase in which they are the minor component.

The solubility limit has been explicitly explored far less frequently than the infinite dilution limit and fewer simulation techniques have been used to probe this behavior. The most common is the use of GEMC simulations, particularly through modeling binary mixtures. By creating two bulk phases and propagating the system to

reach equilibrium, the solubility of molecule *A* in the bulk phase that is rich in molecule *B*, and vice versa, may be determined. Various research groups have simulated the binary vapor-liquid phase behavior of hydrocarbon mixtures using GEMC (for example, see references 77-82). The statistical uncertainty of the mole fraction of *A* in the bulk phase of *B* is usually less than 10%, often much less than this. Simulations of systems with supercritical carbon dioxide as one of the phases give similar uncertainties and provide insight into partitioning and fluid structure for these systems.^{80,82} GEMC has also been used to study the solubility of gas molecules in aqueous electrolyte solutions.⁸³ Additionally, systems with three or more components and more than two phases are accessible with GEMC.⁸⁴⁻⁸⁶ In one recent application, GEMC was used to examine *n*-decane/*n*-perfluoropentane/carbon dioxide and *n*-pentane/*n*-perfluorodecane/carbon dioxide systems.⁸⁶ The results show how an increase in pressure leads to a swelling of the two immiscible liquid phases and ultimately leads to an upper critical solution pressure (being the endpoint of the liquid-liquid-vapor three-phase region). These simulations closely followed experimental results and the phase compositions were calculated within a few percent of statistical uncertainty. The latter is one of the few examples of computational investigations of mutual solubilities involving two (condensed) liquid phases. Another example is a recent investigation of the mutual solubility of water and 1-butanol that also explored the surface tension behavior at the solubility limit.⁸⁷

Other Monte Carlo methods have also been used to examine binary phase behavior. One recent example uses TMMC to determine the phase behavior of monatomic systems.⁸⁸ Important features of the phase diagrams, such as triple points and azeotropes, were determined with less than 1% uncertainty based on four independent simulations. Monte Carlo simulations in the grand canonical ensemble (GCMC) have also been used extensively to study fluid phase behavior. The thermodynamic constraints for the grand canonical ensemble are fixed temperature, volume and chemical potential, i.e. the number of particles and energy can fluctuate.¹¹ Over the course of the simulation, the number of particles and energy of a given configuration may be stored and the probability distribution may be extracted after a simulation. Histogram-reweighting is often used to connect the different simulations. In order to allow for an exploration of the two-phase region throughout the course of a single simulation, the initial run is often carried out near the critical point with additional simulations and their histograms used to separately sample the liquid and vapor regions further away from the critical point.⁸⁹ Thus, although GCMC is an excellent method to map large regions in pressure-temperature space, it is less well suited to explore solubility at a single state point (in particular, if this state point is far away from the critical region). Potoff, *et al.* used GCMC to examine the phase behavior of a variety of non-polar and polar binary systems.⁸⁹ The average uncertainty in the pressures and compositions of the diagrams was a few percent.

Another method to probe the solubility limit was suggested by MacCullum and Tieleman.⁹⁰ In their study of water/1-octanol binary phase behavior, they simulated a series of systems with varying mole fractions of solute (in this case, water) and determined the excess chemical potential of water at each composition using a variant of Widom's particle insertion technique. Using the relationship that the chemical potential of a given molecular species must be equal between two phases that are in contact and at equilibrium, they determined the solubility limit of water in 1-octanol by comparing the chemical potential of water/octanol systems to that of pure water. Similarly, Ferrario *et al.*⁹¹ used TI to determine the solubility limit of potassium fluoride in water by simulating a series of different systems with increasing potassium fluoride concentrations. This technique, while more intensive than GEMC for many systems, has potential applications for systems for which GEMC is untenable.

Phase behavior may also be probed with continuum solvation models. Thompson, *et al.* used SM5.42 to predict solubility based on solvation free energy calculations.⁹² Using a series of liquid and solid solutes (90 total solutes), the mean unsigned error of the logarithm of the solubility was about 0.4 compared to experimental solubility. For these calculations, the activity coefficient is unity for the saturated system. Based on the results for these 90 solutes, spanning seven orders of magnitude in solubility, this solvation model parameterized for infinite dilution can be used to predict saturated solubility as well. The authors postulate that these findings may be extended to the validity of other implicit and explicit solvation models.⁹²

5 Finite Size Effects

One concern for all particle-based simulations is the necessary system size limitation due to computational efficiency and memory constraints. This restricts most simulations to no more than a few thousand molecules, often much less. In order to determine bulk properties, larger systems are necessary. The use of periodic boundaries to replicate the system in each dimension is the most common means to simulate bulk properties using a finite system.¹⁵ Nevertheless, the finite size of the system can introduce systematic errors for computations of the solubility and, in particular, for calculations of the chemical potential.^{8,93} It is always best to perform test simulations with systems of varying size to estimate the finite size corrections for the system of interest. It should be noted here that an expression for this correction has been derived for chemical potential calculations.⁹³

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