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Generalized ensembles Monte Carlo methods in chemical physics

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Abstract

In this review we present the expanded ensemble method for calculation of free energy and related properties in computer simulations. The basis of the method, its methodological aspects and facilities are discussed. We trace the relationship of this method to other relevant approaches for free energy computations unified under the name "generalized ensemles". Finally, we consider the most important applications of the generalized ensemble techniques to problems of physical, chemical and biological interest.

1. Introduction

Calculation of free energy and other related quantities (chemical potential, entropy) in computer simulations is a much more difficult computational problem than that of the structural properties. The

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basic problem is that the free energy and other quantities involving contribution from entropy, cannot be obtained by a simple (direct) averaging of an appropriate function of particles coordinates and velocities. Meanwhile knowledge of free energy and related quantities is extremely important for understanding of many processes and phenomena in physics, chemistry and biology. Free energy plays the key role in determining directions and trends of molecular phenomena such as phase transitions, solvation, conformational transitions in macromolecules, chemical equilibria, to mention a few.

During the last decades several schemes have been suggested in literature to calculate free energies using computer simulations [1, 2, 3, 4, 5, 6]. Most of these methods require a considerable number of repeated computer runs and face difficulties or even fail for systems with strong coupling parameters or at high densities.

About ten years ago the authors of this review suggested an approach called the expanded ensemble Monte Carlo (EEMC) method [7] which soon proved to be an efficient and precise instrument in computing free energies. The method turned out to be promising in treatment of systems at high density, low temperature, with rough multiminima potential landscape, in presence of complicated molecular components.

Besides the free energy computation, the EE method turned out to be a very efficient tool to treat the 'multiple minima', or 'metastable states' problem. Such problems typically arise in studies of systems near phase transition point or other kinds of structural transitions, for example in protein folding. A comprehensive review of the applications of the generalized ensemble methods to treat these kinds of problems has been recently given by Iba [8]. In our review, we shall concentrate on applications of the expanded ensemble method to compute free energy and related quantities. We review the basis of the method, its most important applications and facilities. We shall try also to trace the relationship of the EE method to relevant approaches developed in other simulation groups.

2. Generalized ensemble methods

2.1 Expanded ensemble method

Consider a canonical (*NVT*) ensemble with the configurational part of the Hamiltonian $h(q)$ and introduce a "reduced" Hamiltonian $H = -\beta h$. Let H_0 – be the Hamiltonian of the system for which the partition function is known exactly (e.g. of the ideal gas). We introduce a set of Hamiltonians $H_0, H_1, \ldots, H_M$ so that, with the increase of the index m, $0 \le m \le M$, the Hamiltonian H_m is gradually transfered from H_0 into $H_M = H$ (so called "mutation"). One can use for instance a linear function:

$$H_m = (1 - \lambda_m)H_0 + \lambda_m H_m \tag{1}$$

with $0 = \lambda_0 < \lambda_1 < \ldots < \lambda_M = 1$, or other dependence of the same kind.

For each m consider a canonical ensemble with the configurational partition function

$$Z_m = \int_V dq \exp(H_m(q)) \tag{2}$$

Now we introduce an ”expanded” ensemble with the partition function:

$$Z = \sum_{m=0}^{M} Z_m \exp(\eta_m) \tag{3}$$

where η_m are modification (also called balancing, or preweighting) factors. The optimal choice of η_m will be discussed below. Each of the canonical ensembles with the index m now becomes a subensemble of the generalized, or expanded (augmented), ensemble.

The MC random walk in the expanded ensemble is being carried out according to a conventional Metropolis procedure with two kind of steps: 1) usual configurational shifts within a certain subensemble (change of a microstate), yielding a purely Boltzmann sampling, and 2) change of the parameter λ_m to the neighbouring one with $m \to m \pm 1$ at fixed configuration (i.e. change of a macrostate). In both cases the acceptance probability is determined as: $min(1, \exp(\Delta(H_m + \eta_m))$.

In the course of MC run the number of visits to the m-th subensemble, n_m, is determined and the related probability (the weight of the macrostate, the “histogram”) is then estimated as: $p_m = n_m/n$, n being the total number of MC steps. On the other hand it is clear that

$$p_m = \frac{Z_m}{Z} \exp(\eta_m) \tag{4}$$

and hence it follows:

$$\frac{p_m}{p_k} = \frac{Z_m}{Z_k} \exp(\eta_m - \eta_k) = \exp(\beta_k F_k - \beta_m F_m) \exp(\eta_m - \eta_k). \tag{5}$$

Thus we can obtain free energy differences for any pair of subensembles. As far as the free energy of the subensemble "0" is considered to be known we can get the absolute value of the free energy, i.e. for $m = M$ and $k = 0$ we get:

$$\beta F = -\ln Z_M = -\ln Z_0 + \eta_M - \eta_0 - \ln(p_M/p_0) \tag{6}$$

By properly adjusting values of η_m (η_0 is usually chosen equal to zero) we can attain nearly flat distribution in p_m so that the value of η_M yields the main contribution to free energy, βF.

By choosing the specific kind of expansion parameter we arrive at different types of expanded ensembles. If ”mutation” corresponds to change of temperature with the Hamiltonian being fixed we get the β-expanded ensemble or ”simulated tempering” of Marinari and Parisi [9]. An example of this type is given in the original work [7]. If the

extreme Hamiltonians, H_0 and H_M, differ by additional presence of an extra particle then this is the method of gradual insertion of a particle proposed by Nezbeda and Kolafa in [10]. Later, this version of EE has been employed by Wilding and Müller for insertion of a polymer chain into a polymer melt [11]. Another example of EE, expansion over the number of particles or *N*-expansion, is given in ref. [7] as well as in earlier [12, 13] works (see also recent paper [14]). Pressure expanded NpT -ensemble was used in [15] for calculating the equilibrium lattice constant in a hexagonally arranged pattern of DNA-molecules. In work [16], fourth space coordinate was introduced and treated within expanded ensemble formalism in which one subemsemble with all fourth coordinates equal to zero was the physical system. Different variations of the expanded ensemble will be discussed in more details in this review below.

Optimal choice of the total number of subensembles (M + 1) and of specific dependence of λ_m on m is the item of methodological concern.

2.2 Optimization of parameters of the expanded ensemble

It is evident that for the EE method to be successful, two conditions must be satisfied. The first one is that probabilities p_m should not be too small (one must be able to evaluate them in a finite simulation run). The second is that the transition rate between subensembles should be high enough to provide a fast exploration of the expanded configurational space. The first condition may be achieved by a proper choice of the balancing factors η_m, while the second one by a proper choice of amount and distribution of subensembles, i.e., by the set of λ_m.

It is clear from (5) that a flat distribution of probabilities p_m is obtained if balancing factors η_m are equal (or differ by a constant) to free energies of the subensembles, i.e. to quantities which we want to calculate. That is why one have to use a special procedure to optimize the balancing factors. The simplest way to do this is to use an iterative procedure with short trial runs. One starts from some (e.g. zero) initial values of η_m, make a short EE simulation run and evaluate probabilities p_m in some (usually narrow) interval of subensembles. Then one corrects balancing factors for the next iteration by:

$$\eta_m^{(i)} - \eta_k^{(i)} = \eta_m^{(i-1)} - \eta_k^{(i-1)} - ln\frac{p_m^i}{p_k^i} \qquad (7)$$

In this relation p_m^i and p_k^i are visiting probabilities for boxes m and k at i-th iteration. If some boxes were not visited at all, one can set probabilities for them at the "lowest detectable" level, $p_m = 1/N_{steps}$ where N_{steps} is the number of MC steps in the simulation. This way of optimization of balancing factors was used in our original work [7] and in a number of subsequent EE simulations [17, 18]

The described above simple way to optimize balancing factors works well if parameters η_m are already more or less close to the optimal values. If we have no idea

what the optimal values of η_m are, the primitive iterative procedure starting from zero η_m values may take too long time. A procedure for initial choice of the balancing factors was introduced in work [19]. According to this work, separate short preliminary MC runs are arranged in each subensemble and average energies $< U_m >$ in each of them are evaluated. Then initial values of $\eta_m^{(0)}$ are calculated by

$$\eta_m^{(0)} - \eta_{m-1}^{(0)} = \frac{1}{2}(\beta_m - \beta_{m-1})(< U_m > + < U_{m-1} >) \tag{8}$$

This relation directly follows from the general Gibbs-Helmholtz equation between internal energy $U(\beta)$ and free energy $F(\beta)$:

$$U(\beta) = \frac{d}{d\beta}(\beta F(\beta)) \tag{9}$$

After initial estimation of η_m, a few iterations within the EE scheme are made during which the balancing factors are further optimized according to (7). Then the production run follows, typically when deviations in p_k do not exceed 10 % from the ideal value

$$p_{id} = \frac{1}{M+1}.$$

Another methodological concern is to choose optimally the number of subensembles (boxes), $M+1$, and the specific (optimal) dependence of the expansion parameter on m. The number of boxes is chosen so as to provide, for the established pair of boundary states H_0 and H_M, sufficiently high probability of transitions between neighbouring boxes, $m \rightarrow m \pm 1$. Also, the dependence of the expansion parameter on m should serve to optimize transition rates in the whole range of m. A smaller number of subensembles leads to a fast decay in the acceptance ratio of transitions and to a larger statistical error. A very large number of subensembles means a longer path between the ends, that also results in a higher statistical errors despite of more frequent transitions between the neighboring subensembles. A study of optimal choice of the number of subensembles has been made in work [20] for the Lennard-Jones fluid as an example. It was shown that the best results were obtained when the acceptance ratios for the transitions between the subensembles was about 30%, though this number is not crucial. Good estimations of free energies with only slightly higher statistical error were obtained when the acceptance ratio varied between 15 and 70 %.

We should stress that the choice of parameters of the expanded ensemble (both η_m and λ_m) do not influence the final output result but of course may strongly influence the efficiency of the calculations.

2.3 Multicanonical or Entropuic sampling

Methods which are quite close to the EEMC are the multicanonical sampling (MS) suggested by Berg and Neuhaus in 1992 [21] and entropic sampling (ES) introduced by Lee in 1993 [22]. Both of these methods proved to be completely equivalent to each other, see e.g. [23]; so both terms, MS and ES, to our point of view, can be treated as synonyms.

While in EEMC one aims at attaining flat distribution in temperature, volume or other expansion parameter, in the case of MS or ES the aim is to obtain flat distribution in energy. Hence we can treat them as an Energy-expanded microcanonical ensemble

Consider the canonical configurational partition function in the form:

$$Z = \int dE\Omega(E)exp(-\beta E); \quad \Omega(E) = \int dq\delta(E - H(q)) \tag{10}$$

where $\Omega(E)$ is the density of energy states.

The conventional canonical Metropolis MC procedure of obtaining the trial state includes a homogeneous choice of microstate in coordinate space (q) (that yields distribution in energy $\Omega(E)$) with addition of the canonical distribution factor, $exp(-\beta H(q))$. Finally it results in canonical distribution in energy: $p(E) = Const\Omega(E)exp(-\beta E)$

On the other hand if we arrange a MC random walk in the configurational space (q) so that the additional probability function (instead of the canonical factor $exp(-\beta H(q))$) is chosen to be the inverse of $\Omega(E)$, i.e. $w(E(q)) = |\Omega(E(q))]^{-1}$, then the "natural" factor $\Omega(E)$ is completely compensated and the distribution over E, $p(E)$, becomes flat.

This approach appears to be extremely important for simulation of complex systems with rough potential landscapes such as polypeptides and proteins, spin glasses and also cases of first order phase transitions (see e.g. papers of Janke [24] and of Smith and Bruce [23]).

As long as densities $\Omega(E)$ are initially unknown or are known approximately, an iterative procedure for obtaining flat $p(E)$ distributions is necessary.

Hansmann and Okamoto [25] pointed to an important fact that distributions $w(E)$ in multicanonical sampling and balancing factors of the temperature expanded MC method (simulated tempering) yielding in each case flat distributions $p(E)$ or $p(\beta)$ are related by a Laplace transform:

$$exp(-\eta) = \int dEw^{-1}(E)exp(-\beta E) \tag{11}$$

It follows that weight factors for the two algorithms can be calculated from each other. Comparative calculations carried out in [25, 26] for a peptide Met-enkefalin with

the aid of both methods have shown that both of them being closely related are equally effective in the numerical work.

Yan *et al*[27] have implemented "two-dimensional" density of state calculation by organizing random walk in two-dimensional space of particle number and energy. Other recent developments in multicanonical sampling algorithms is given in work [28].

Still in a number of papers (see e.g. the review [29]) it is pointed out that the procedure of adjustment of $w(E)$ (or η_m in the EE method) "can be tedious and time-consuming". The way to alleviate this drawback of both lies in application of the Replica exchange method developed in 1996-1997 which will be discussed further in a separate section. Another way to overcome this problem in ES method was suggested recently by Wang and Landau in works [30, 31]

2.4 Wang-Landau algorithm in ES method

The Wang-Landau (WL) -algorithm can be considered as self- (or auto-) adjusting procedure for obtaining $w(E(q)) = |\Omega(E(q))]^{-1}$ in multicanonical or entropy sampling simulations. The energy range of interest, $E_{min} < E < E_{max}$, is being divided into a finite number, N_b, of equal intervals ("boxes"), $\Delta E = \frac{(E_{max} - E_{min})}{N_b}$. All the initial values of $\Omega(E_i)$ corresponding to these boxes are taken to be equal (e.g. in [30] they were all taken equal to 1). In order to avoid processing with large numbers it is convenient to introduce entropy distribution $S(E_i) = \ln \Omega(E_i)$ (in [30] the initial values of $S(E_i)$ are zeros). Two sets of counters are introduced in the procedure, both of the length N_b: one is for $S(E_i)$ and another is for visits of energy states to calculate the relevant probability distribution (a histogram) $p(E_i)$. Each state (configuration) of the simulated system corresponds to a definite value of energy and hence it belongs to one of N_b energy intervals (boxes) introduced in the range $E_{min} < E < E_{max}$. A MC step includes a standard trial change of the state with a uniform coordinate distribution and further applying the following transition probability condition:

$p(i \to i')=min[1, \exp[S(E_i) - S(E_{i'})]]$. If this condition is fulfilled the trial state (i') is accepted, in the opposite case the accepted state is the the initial configuration (i). Finally the entropy of the accepted state ($S(E_i)$ or $S(E_{i'})$) is augmented by ΔS and the corresponding counter of visits is augmented by 1.

A certain number of such elementary steps, m, constitute a sweep. At the end of the current sweep the value of ΔS is changed according to the relation: $\Delta S \to a\Delta S$ where $0 < a < 1$ is an increment (in [30] a=0.5 though other values could also be used).

After several sweeps the $S(E_i)$ dependence is formed and fine tuned in the whole range of E. Further continuing of the procedure results only in addition of a constant to the $S(E_i)$-dependence. It corresponds to the flat character of the histogram $p(E_i)$ which is

reached simultaneously. This way the density of states $\Omega(E_i) = \exp(S(E_i))$ can be calculated rather accurately in a very large range of orders of magnitude, e.g. from 10^{-1} to 10^{-30} or even to lower orders. It provides calculation of canonical partition function and averages, such as energy and heat capacity in a wide temperature range by numerical integration of the appropriate function with the the canonical distribution of energy $p(E) = Const\,\Omega(E)exp(-\beta E)$

Wang-Landau algorithm, first implemented for a lattice spin system, was promptly generelized to lattice polymers [32], off-lattice simulations [33], path-integral Monte Carlo [34].

2.5 Replica exchange method

"Replica exchange method" (REM) or "Parallel tempering"(PT) were suggested recently in a number of papers (e.g. [35] and a review [29]). It appears to be very suitable for parallelization.

Suppose we have M+1 subensembles in the EE method. In conventional EE procedure a *single* system is walking freely in the space of expansion parameter, e.g. temperature, jumping from one subensemble to another. In the case of the replica exchange method *each* of $M + 1$ subensembles is inhabited by an independent system (a "copy", a "replica") so that the total number of replicas is also $M + 1$. If the expansion parameter is the inverse temperature, β_m, then the procedure is usually called "Parallel tempering". Thus the latter term can be considered as a designation of a specific case of the general approach "Replica exchange method" (the relation of terms is the same as between "Expanded ensemble method" and "Simulated tempering"). The procedure of REM includes:

(1) Conventional MC steps with changes of configurations (microstates) in each of independent replicas. For these steps both MC and MD procedures can be used.

(2) Simultaneous exchange of macrostates (e.g. values of temperatures in PT) between pairs of replicas occurring in the adjacent subensembles, i and $i + 1$ (e.g. $i = 1, 3, 5, \ldots$ or $i = 2, 4, 6, \ldots$, see [36]). The acceptance of exchange is decided according to the Metropolis rule. Suppose we try to transpose the replica i occupying the position m with the replica j occupying the position n (usually $n = m + 1$). The acceptance of such a trial move is decided according to the following rule [29]:

$$p[i,m;j,n \rightarrow j,m;i,n] = min[1,\Delta] \tag{12}$$

where $\Delta = (\beta_n - \beta_m)(E(q^{[i]}) - E(q^{[j]}))$ and $E(q^{[i]})$ is the potential energy of the i-th copy.

This way each replica can visit all the subensembles. This is very important for investigating systems with rough potential landscapes, e.g. polypeptides, and also supercooled liquids (see for instance [36]).

An attractive feature of replica exchange method is that it does not require a preliminary adjustment of balancing factors or other parameters which is necessary in

EE or ES methods. At the same time it should be pointed out that free energy cannot be evaluated within REM approach in the same straightforward way as it can be done via EE procedure. Other methodological issues of the parallel tempering are discussed in work [37].

2.6 Other generalized ensembles

In a series of papers Hansmann, Okamoto and coworkers developed a generalized ensemble method which allows better to sample multicanonical distributions and they carried out calculations for small peptides within both MC and MD numerical procedure [38, 39, 40, 41, 42, 43, 44]. They also implemented a new parallel tempering technique to solution of the same problem [40, 41, 42, 43, 44, 45]. Among other techniques related to generalized ensembles (many of which are in fact equivalent to the discussed above) we can name bicanonical ensemble [46], multiensemble sampling [47], adaptive umbrella sampling [48], Hamilton scaling Monte Carlo [49], hyperparallel tempering [50], histogram-reweighting Monte Carlo [51] and multicanonical replica exchange [52].

3. Applications

3.1 Free energy calculations for some model systems

In the first applications of the expanded ensembles [7, 53], the expansion parameter was determined as $\lambda_m = \beta_m/\beta$, where $\beta = 1/kT$ and Hamiltonian of the reference system was set to zero: $H_0 = 0$. This case corresponds to the temperature expanded canonical ensemble, since a change of the parameter λ_m may be interpreted as a change of temperature: $T_m = 1/(k\beta_m)$. Case $\beta_m = 0$, or $T_m = \infty$, corresponds to the absence of interactions, or to the ideal gas system with the known free energy. That is why, in the temperature expanded canonical ensemble one can calculate absolute values of free energies in the whole temperature interval from the given temperature to infinity.

In this formulation the EE method was applied to calculation of free energy for the restricted primitive model of an electrolyte at a very low temperature ($\beta = 20$, in natural units). The same scheme was suggested independently by Marinari and Parisi in [9] who called their method ”simulated tempering”. They have applied their scheme to investigate a random field Ising model. Temperature expanded canonical ensemble was also used in subsequent paper of our group [54] for calculating free energy of a quantum two-dimensional Hiesenberg ferromagnet within Handscomb MC procedure.

The molecular dynamics version of the temperature expanded ensemble was first tested in work [17] for a Lennard-Jones system and for water represented by rigid and flexible simple point charge (SPC) models. A good agreement was found between molecular dynamics and Monte Carlo simulations for the same systems. Molecular dynamics simulations, however, turned out to be more efficient for molecular liquids like water.

3.2 Chemical potential

If H differs from H_0 by presence of an extra single particle and the process of mutation of the Hamiltonian from H_0 to H consists of gradual insertion of this particle

then we get another example of the EE MC method. Such a scheme was suggested for instance by Nezbeda and Kolafa [10] who applied it to calculations of the chemical potential in a hard sphere fluid at high packing fractions within canonical ensemble MC procedure. The idea of gradual insertion of a particle stems to the earlier paper of Mon and Grifiths [55]. The particle insertion method with balancing factors in *NPT*-ensemble was suggested in earlier works of our group [12, 13]. An analogous scheme within canonical and grand canonical ensembles was suggested by Kaminsky in [56] who implemented his scheme of "augmented" ensembles to chemical potential – density calculations for hard sphere and LJ fluids. Free energy of cavity formation in a dense hard sphere fluid was carried out by Attard [57] within his "force balance" MC scheme which actually also appears to be a variant of the EE method. Application of the multicanonical sampling in Wang-Landau formulation to compute chemical potential is described in [58].

Wilding and Müller [11] were the first who applied the gradual particle insertion EE MC procedure for calculating chemical potential in a polymer system. For polymers other methods (e.g. Widom's method [1]) become practically inapplicable since probability of direct insertion of a chain into a dense polymer system is vanishingly small. In paper [11] this probability was estimated indirectly and appeared to be $p \sim 10^{-10} - 10^{-80}$ depending on density and other input parameters. Instead, one can introduce a penetrable "ghost" chain, with excluded volume and thermal interactions changing as parameters of the expanded ensemble.

Another version of chemical potential calculations for a dense polymer system was suggested by Escobedo and Pablo [59]. In this approach, a monomer was added or deleted from a chosen polymer according to the EE algorithm. In this way, a whole polymer chain may be smoothly converted to nothing and back. Later they developed this approach further to include also case of Gibbs ensemble simulations and hyperparallel tempering [50,60, 61, 62, 63, 64].

In our papers [19], [65] the EEMC method was used in free energy calculations for lattice and off-lattice models of free polymer chains with a phantom chains used for the reference systems. Lattice phantom chain (a free random walk) was gradually transferred into a selfavoiding walk by increasing the energy parameter attributed to each overlap of monomers. In work [66] an analogous EEMC procedure was applied for calculating free energy (entropy) of closed and stretched athermal lattice polymers.

A direct comparison of the EE method with a widespread method of free energy calculation, thermodynamic integration(TI), has been made in the work of van der Vegt and Briels [67] who calculated chemical potential of chloroform in a swollen polymer. EE method was found to probe the simulation box much more efficiently than TI. Other comparisons of different methods (including EE-method) for evaluating chemical potential of a hard sphere, Lennard-Jones and some other simple models are presented in works [68, 69].

In another application, the EE method was used for computations of chemical potential of nanoparticles in a hard-sphere polymer [70].

3.3 Solvation free energies

The solvation free energy is determined as the Gibbs free energy change in a process of transfer a solute molecule from ideal gas phase into a solvent. Knowledge of this

quantity is very important in many industrial and pharmaceutical application, because the solvation free energy determines solubility and association of solutes, partitioning, phase equilibria, nucleation processes to mention a few.

The solvation free energy is closely related to the chemical potential of the solute molecule, and its computation can be carried out by the same techniques as for the chemical potential. Different techniques to compute solvation free energy existed from a long time ago starting from the Widom's particle insertion method [1] and its improvements [71, 72, 73]. Expanded ensemble method with gradual particle insertion turned out to be a very efficient way to compute solvation free energies even for large and strongly charged solutes.

The application of the EE method for computations of solvation free energies is rather straightforward (see e.g ref. [18].) In this work, two cases were considered: a hydrophobic methane-like molecule and alkali halides ion pairs in water. In the later case, the efficiency of the EE method was especially impressive: the solvation free energies of ion pairs were determined with precision less that 0.5% and turned out to be in very good agreement with experimental data. In work [74], solvation free energy and entropy during a process of "charging" of a fictitious ion have been determined. Hernandez-Cobos *et al* have implemented histogram reweighting Monte Carlo method to compute solvation free energy of methane or other hydrophobic solutes [75].

In the last few years the EE method has been applied for computation of solvation free energies of many complex organic molecules. Khare and Rutledge applied EE procedure for obtaining chemical potential of a model benzene fluid at a set of different temperatures [76] and of aromatic compounds in n-alkane solutions [77]. They considered the λ parameter as a continuous variable. Errington and Panagiotopolous [78] have used the EE method for calculation of solvation free energies of benzene and cyclohexane in water. These calculations were used for tuning force field parameters describing these molecules.

Computations of solvation free energies may be used for evaluation of the so called $logP$ parameters defining partitioning of some solute molecules between two non-mixing solvents in equilibrium. Knowledge of $logP$ parameters is especially important in the pharmacology industry as they define general properties of permeability of different substancies in the living organisms. In work [79], the EE method was used to compute octanol/water $logP$ parameters of rather big, up to 50 atoms, organic drug-like compounds. The solvation free energies were determined both in water and in octanol solution and then the corresponding $logP$ parameters were evaluated.

3.4 Osmotic pressure

Osmotic pressure may be defined as a volume-derivative of the free energy of solute particles (for example, ions). Application of the EE method to compute the free energy difference as a function of distance between DNA rods in a system of oriented and hexagonally ordered DNA molecules has been described in work [15]. In this case, the expansion parameter of EE was the distance between DNA, which was proportional to the volume of the system. This implementation of the EE is referred to as volume-expanded NVT ensemble. The resulting dependence of free energy on volume allows

one to determine osmotic pressure dependence on separation parameter in the ordered system of DNA molecules. In the case of divalent counterions this dependence has a minimum corresponding to the stable equilibrium ordered phase of the system.

The same approach was used in papers [30, 31] for studying of electrostatically induced association of rodlike virus particles. Such association may happen if concentration of divalent ions in solution exceed some threshold value which depends on the type of added ions. By calculating the osmotic pressure in an ordered polyelectrolyte system at different conditions, one can compute effective electrostatic force between the charged rods and thus define conditions necessary for association of virus particles. Computations using the volume-expanded NVT ensemble [80] yielded results in a quantitative agreement with the experiment.

Authors of a recent paper [82] implemented volume-expanded isotension (NPT) ensemble for calculating properties of a polymer solution confined to a planar slit. The slit is in equilibrium with a surrounding bulk solution and the method allows variation of the slit width while the polymer chemical potential is being maintained constant. By computing the free energy change due to change of the slit width, the osmotic pressure and so the force between the two surfaces was evaluated. This approach was later used in paper [83] to compute polyampholyte-induced repulsion between charged surfaces.

3.5 Phase equilibria

One of the most widespread approaches to study phase equilibria is to use Gibbs ensemble technique [84]. This technique is based on performing a simulation in two regions, with particle exchange and volume transfer between them so that the total number of particle and volume are constant. One of the regions may represent for example the liquid phase and another the gas phase, but the algorithm provides equal temperature, pressure and chemical potential in both phases. While this technique has proved to be very efficient in studies of phase transitions for simple molecular models, it turned out to be impractical for more complex, branched or polymer-like molecules, since particle transfer between the two phases has in this case very low acceptance probability. Even simple models with strong electrostatic interactions (like primitive electrolyte model) may pose a problem. The underlying reason is the same as in computation of chemical potential by particle insertion: it is very difficult to install a big molecule in a liquid.

In a series of works Panagiotopoulos and coworkers [49, 78, 85, 86] have developed a number of generalized ensembles techniques for investigation of phase equilibria both in simple models and complex systems. In work [49] they introduced “Hamiltonian scaling” grand canonical Monte Carlo approach which allow one to evaluate grand canonical partition function over a range of chemical potentials and applied it to a fluid described by the Buckingam exponential-6 potential [49] and primitive electroyte model [78, 87]. The formulation of the method followed most closely the multicanonical Monte Carlo approach [21] and histogram reweighting method. In work [51] this methodology was used to compute the surface tension of the Lennard-Jones fluid within the grand-canonical ensemble simulations. The generalized ensemble technique helped in this case to facilitate transitions between the liquid and gas phases.

Multicanonical and histogram reweighting method were used by Smith and Bruce [0] for studies of solid-solid phase transitions in a system with hard spheres or square-

well potential. Multiple histogram method was also used by Ferreira and Barroso [89] for determination of the phase diagram and phase coexistence of the Lennard-Jones fluid. In work [85], the expanded ensemble method with gradual particle insertions, was used to study phase equilibria of water with two higher hydrocarbons, *n*-butane and *n*-hexane. The computational problem of the latter study is closely related to the calculation of solvation free energies which was discussed above.

A review on application of different versions of generalized ensemble methods to simulation of phase transition in fluids is given by de Pablo *et al* [64].

3.6 Protein folding

The problem of "protein folding" has received much attention in the last decades and by now is one of the most challenging problems in structural biology. The general question is, what will be the tertiary (globular) structure of a protein having a given amino-acid sequence? Finding answer to the question is of vital importance for understanding of how the life is functioning.

From the statistical-mechanical point of view, the problem may be solved by finding a protein configuration having minimal energy, or more exactly, finding a local minima of the configurational surface having minimal free energy. Taking in mind that configurational surface of, even not very big, protein may have a very big number of local minima separated by high - and unknown - potential barriers, it became clear that the problem can not be solved by traditional simulational techniques. This is even confirmed by the fact that *in vivo* protein synthesis takes time of the order of seconds or longer, that is many orders more than the modern molecular dynamics simulations can afford.

The generalized ensemble methods turned out to be very suitable to treat the situation with rough configurational surface with multiple energy minima. By linking "high" and "low"-temperature states, the generalized ensemble methods may generate random walk which does not stack in local energy minima and allow to sample efficiently all relevant points of the configurational space.

In series of works [25, 38, 40, 42, 43, 90, 91] Hansmann, Okamoto and co-workers explored applicability of different versions of generalized ensembles to the protein folding problem. In papers [25, 38] they applied multicanonical ensemble and simulated tempering (equivalent to the expanded ensemble technique) to study conformational transitions between the right- and left-hand forms of one of simple peptides – Met-enkephalin, consisting of five aminoacids. They found that the rate of transitions between the two forms is in fact the same for both approaches. In work [40], parallel tempering algorithm has been applied for conformational studies of the same protein. Helix-coil transition of Met-enkephalin was studied in [41]. More complex peptides (for example, two forms of C-peptide of ribonuclease A, consisting of 13 aminoacids) were simulated in [43, 90]. Bartels *et al* have used the "adaptive umbrella sampling" technique (which is in practice a version of multicanonical algorithm) for conformational analysis of RN24 protein (13 residues) [92]. Irbäck and Sandelin [93] have implemented simulated and parallel tempering to study folding of a model lattice polymer. Conformational properties of a similar simple polymer model (helix-coil and random coil – beta sheet transitions) were studied by entropy sampling approach within the Wang-Landau algorithm in work [94]. More details on recent advances in this area is given in reviews [29, 95]

Most of mentioned above "protein folding" simulations were carried out without water molecules for mainly methodological purposes. Since natural proteins exist in aqueous environment, inclusion of water molecules in simulations is necessary for correct prediction of protein properties. Only recently such simulations became possible for small peptides. RGDW peptide consisting of four aminoacids has been studied in work [48]. Another four-residues peptide (glycine dimer) in water was considered in work [96]. Mitsutake *et al* reported results on conformational study of Met-enkephalin in presence of TIP3P water molecules using the generalized ensemble technique [29].

4. Conclusion

In this review we have considered the expanded ensemble computer simulation method and related approaches with the common name generalized ensembles. This methodology turned out to be very fruitful in solving many important problems in computer simulations of complex molecular systems and for computations of thermodynamical quantities. In considering the applications of the generalized ensembles techniques, the main attention has been paid to systems of chemical and biophysical interest. We should also mention that there exist numerous applications of the generalized ensembles methods in other areas. A very important application area is lattice spin systems (Ising model [9, 97, 98], Potts model [21], spin glases [24, 97, 99], other spin lattice models [54]). Other systems of interest are crystals [100], nucleation and cluster formation [14, 101, 102], image restoration problem [103], path integrals in quantum statistics [7, 34, 104] and even quantum chromodynamics [105, 106, 107], too wide range of systems and models to be included into this review.

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References

1. B. Widom, J. Chem. Phys. **39**, 2808 (1963).
2. G. M. Torrie and J. P. Valleau, J. Comput. Phys. **23**, 187 (1977).
3. T. P. Straatsma, H. J. C. Berendsen, and J. P. M. Postma, J. Chem. Phys. **85**, 6720 (1986).
4. D. Frenkel, in *Proceedings of the International School "Enrico Fermi"* (North-Holland, Amsterdam, 1986), pp. 151–188.
5. D. E. Pearlman and P. A. Koolman, J. Chem. Phys. **91**, 7831 (1989).
6. D. L. Beveridge and F. M. DiCapua, Annu. Rev. Biophys. Biophys. Chem. **18**, 431 (1989).
7. A. P. Lyubartsev, A. A. Martsinovskii, S. V. Shevkunov, and P. N. Vorontsov-Velyaminov, J.Chem.Phys. **96**, 1776 (1992).
8. Y. Iba, Int. J. Modern Physics C **12**, 623 (2001).
9. E. Marinari and G. Parisi, Europhys. Lett. **19**, 451 (1992).
10. I. Nezbeda and J. A. Kolafa, Mol. Simulations **5**, 391 (1991).
11. N. B. Wilding and M. J. Muller, J. Chem. Phys. **101**, 4324 (1994).
12. S. V. Shevkunov, A. A. Martsinovski, and P. N. Vorontsov-Velyaminov, High Temp. Phys. (USSR) **26**, 246 (1988).
13. S. V. Shevkunov, P. N. Vorontsov-Velyaminov, and A. A. Martsinovskii, Mol. Simulations **5**, 119 (1991).
14. I. Kusaka and D. W. Oxtoby, J. Chem. Phys. **113**, 10100 (2000).
15. A. P. Lyubartsev and L. Nordenskiöld, J. Phys. Chem. **99**, 10373 (1995).
16. W. Paul and M. Müller, J. Chem. Phys. **115**, 630 (2001).

17. A. P. Lyubartsev, A. Laaksonen, and P. N. Vorontsov-Velyaminov, Mol. Phys. **82**, 455 (1994).
18. A. P. Lyubartsev, O. K. Forrisdahl, and A. Laaksonen, J. Chem. Phys. **108**, 227 (1998).
19. P. N. Vorontsov-Velyaminov, A. V. Broukhno, T. V. Kuznetsova, and A. P. Lyubartsev, J. Phys. Chem **100**, 1153 (1996).
20. A. P. Lyubartsev, A. Laaksonen, and P. N. Vorontsov-Velyaminov, Mol. Simul. **18**, 43 (1996).
21. B. A. Berg and T. Neuhaus, Phys. Rev. Lett. **68**, 9 (1992).
22. J. Lee, Phys. Rev. Lett. **71**, 211 (1993).
23. G. R. Smith and A. D. Bruce, J. Phys. A **28**, 6623 (1995).
24. W. Janke, Physica A **254**, 164 (1998).
25. U. H. E. Hansmann and Y. Okamoto, Phys. Rev. E **54**, 5863 (1996).
26. U. H. E. Hansman and Y. Okamoto, J. Comput. Chem. **18**, 920 (1997).
27. Q. L. Yan, R. Faller, and J. J. de Pablo, J. Chem. Phys. **116**, 8745 (2002).
28. B. A. Berg, Comp. Phys. Comm. **147**, 77 (2002).
29. A. Mitsutake, Y. Sugita, and Y. Okamoto, Biopolymers **60**, 96 (2001).
30. F. Wang and D. P. Landau, Phys. Rev. Lett. **86**, 2050 (2001).
31. F. Wang and D. P. Landau, Phys. Rev. E **64**, 056101 (2001).
32. T. S. Jain and J. J. de Pablo, J. Chem. Phys. **116**, 7238 (2002).
33. M. S. Shell, P. G. Debenedetti, and A. Z. Panagiotopoulos, Phys. Rev. E **66**, 056703 (2002).
34. P. N. Vorontsov-Velyaminov and A. P. Lyubartsev, J. Phys. A **36**, 685 (2003).
35. K. Hukushima and K. Nemoto, J. Phys. Soc. Japan **65**, 1604 (1996).
36. R. Yamamoto and W. Kob, Phys. Rev. E **61**, 5473 (2000).
37. S. B. Opps and J. Schofield, Phys. Rev. E **63**, 056701 (2001).
38. U. H. E. Hansmann and Y. Okamoto, Phys. Rev. E **56**, 2228 (1997).
39. U. H. E. Hansmann and Y. Okamoto, Proc. Natl. Acad. Sci. USA **94**, 10652 (1997).
40. U. H. E. Hansmann, Chem. Phys. Lett **281**, 140 (1997).
41. U. H. E. Hansmann, Physica A **254**, 15 (1998).
42. U. H. E. Hansmann, F. Eisenmenger, and Y. Okamoto, Chem. Phys. Lett **297**, 374 (1998).
43. U. H. E. Hansmann, Eur. Phys. J. B **12**, 607 (1999).
44. Y. Sugita and Y. Okamoto, Chem. Phys. Lett **314**, 141 (1999).
45. Y. Sugita and Y. Okamoto, J. Chem. Phys. **113**, 6042 (2000).
46. W. C. Swope and H. C. Andersen, J. Chem. Phys. **102**, 2851 (1995).
47. K. K. Han, Phys. Rev. E **Phys. Rev. E**, 6906 (1996).
48. C. Bartels and M. Karplus, J. Phys. Chem. B **102**, 865 (1998).
49. J. R. Errington and A. Z. Panagiotopoulos, J. Chem. Phys. **109**, 1093 (1998).
50. Q. Y. Yan and J. J. de Pablo, J. Chem. Phys. **111**, 9505 (1999).
51. J. J. Potoff and A. Z. Panagiotopoulos, J. Chem. Phys. **112**, 6411 (2000).
52. Y. Sugita and Y. Okamoto, Chem. Phys. Lett. **329**, 261 (2000).
53. A. P. Lyubartsev, A. A. Martsinovskii, P. N. Vorontsov-Velyaminov, and T. V. Kuznetsova, Rus. J. Phys. Chem. **67**, 230 (1993).
54. T. V. Kuznetsova and P. N. Vorontsov-Velyaminov, J. Phys.: Condens. Matter **5**, 717 (1993).
55. K. K. Mon and R. B. Griffiths, Phys. Rev. A **31**, 956 (1985).
56. R. D. Kaminsky, J. Chem. Phys. **101**, 4986 (1994).
57. P. Attard, J. Chem. Phys. **98**, 2225 (1993).
58. T. J. H. Vlugt, Molecular Physics **100**, 2763 (2002).
59. F. A. Escobedo and J. J. dePablo, J. Chem. Phys. **103**, 2703 (1995).
60. F. A. Escobedo and J. J. de Pablo, Fluid Phase Equilibria **116**, 312 (1996).
61. F. A. Escobedo and J. J. de Pablo, J. Chem. Phys. **105**, 4391 (1996).
62. F. A. Escobedo and J. J. de Pablo, J. Chem. Phys. **106**, 2911 (1997).

63. F. A. Escobedo and J. J. de Pablo, J. Chem. Phys. **108**, 8761 (1998).
64. J. J. de Pablo, Q. L. Yan, and F. A. Escobedo, Ann. Rev. Phys. Chem. **50**, 377 (1999).
65. A. V. Broukhno, T. V. Kuznetsova, A. P. Lyubartsev, and P. N. Vorontsov-Velyaminov, Vysokomolekulyarnye Soedineniya **A38**, 77 (1996).
66. P. N. Vorontsov-Velyaminov, D. A. Ivanov, S. D. Ivanov, and A. V. Broukhno, Colloids and Surfaces **A148**, 171 (1999).
67. N. F. A. van der Vegt and W. J. Briels, J. Chem. Phys. **109**, 7578 (1998).
68. D. A. Kofke and P. T. Cummings, Mol. Phys. **92**, 973 (1997).
69. M. Athens, Phys. Rev. E **66**, 046705 (2002).
70. M. K. Tej and J. C. Meredith, J. Chem. Phys. **117**, 5443 (2002).
71. K. E. Shing and K. E. Gubbins, Mol. Phys. **43**, 717 (1981).
72. D. Frenkel and B. Smit, Mol. Phys. **75**, 983 (1992).
73. K. Ding and J. P. Valleau, J. Chem. Phys. **98**, 3306 (1993).
74. D. L. Bergman, A. P. Lyubartsev, and A. Laaksonen, Phys. Rev. E **60**, 4482 (1999).
75. J. Hernandez-Cobos, A. D. Mackie, and L. F. Vega, J. Chem. Phys. **114**, 7527 (2001).
76. A. A. Khare and G. C. Rutledge, J. Chem. Phys. **110**, 3063 (1999).
77. A. A. Khare and G. C. Rutledge, J. Phys. Chem. B. **104**, 3639 (2000).
78. J. R. Errington and A. Z. Panagiotopoulos, J. Chem. Phys. **111**, 9731 (1999).
79. A. P. Lyubartsev, S. P. Jacobsson, G. Sundholm, and A. Laaksonen, J. Phys. Chem. B **105**, 7775 (2001).
80. A. P. Lyubartsev, J. X. Tang, P. A. Janmey, and L. Nordenskiöld, Phys. Rev. Lett. **81**, 5465 (1998).
81. J. X. Tang, P. A. Janmey, A. Lyubartsev, and L. Nordenskiöld, Biophys. J. **83**, 566 (2002).
82. A. Broukhno, B. Jönsson, T. Åkesson, and P. N. Vorontsov-Velyaminov, J. Chem. Phys. **113**, 5493 (2000).
83. A. Broukhno, M. O. Khan, T. Åkesson, and B. Jönsson, Langmuir **18**, 6429 (2002).
84. A. Z. Panagiotopoulos, Molec. Phys. **61**, 813 (1987).
85. G. C. Boulougouris, J. R. Errington, I. G. Economou, A. Z. Panagiotopoulos, and D. N. Theodorou, J. Phys. Chem. B. **104**, 4958 (2000).
86. A. Z. Panagiotopoulos, J. Phys. Condens. Matt. **12**, R25 (2000).
87. G. Orkoulas and A. Z. Panagiotopoulos, J. Chem. Phys. **110**, 1581 (1999).
88. G. R. Smith and A. D. Bruce, Phys. Rev. E **53**, 6530 (1996).
89. A. L. Ferreira and M. A. Barroso, Phys. Rev. E **61**, 1195 (2000).
90. U. H. E. Hansmann, Int. J. Mod. Phys. C **10**, 1521 (1999).
91. U. H. E. Hansmann and Y. Okamoto, Current Opinion in Structural Biology **9**, 177 (1999).
92. C. Bartels, M. Schaefer, and M. Karplus, J. Chem. Phys. **111**, 8048 (1999).
93. A. Irbäck and E. Sandelin, J. Chem. Phys. **110**, 12256 (1999).
94. N. Rathore and J. J. de Pablo, J. Chem. Phys. **116**, 7225 (2002).
95. U. H. E. Hansmann, Int. J. Quant. Chem. **90**, 1515 (2002).
96. N. Nakajama, Chem. Phys. Lett. **288**, 319 (1998).
97. F. M. Liang, Phys. Lett. A **252**, 275 (1999).
98. M. Fitzgerald, R. R. Picard, and R. N. Silver, Europhys. Lett. **46**, 282 (1999).
99. B. Hesselbo and R. B. Stinchcombe, Phys. Rev. Lett **74**, 2151 (1995).
100. A. D. Bruce, A. N. Jackson, G. J. Ackland, and N. B. Wilding, Phys. Rev. E **61**, 906 (2000).
101. S. V. Shevkunov, Zhurnal Exp. i Teor. Fiz. **108**, 1373 (1995).
102. I. Kusaka and D. W. Oxtoby, J. Chem. Phys. **115**, 4883 (2001).
103. J. M. Pryce and A. D. Bruce, J. Phys. A **28**, 511 (1995).
104. M. Kolar and S. F. O'Shea, J. Phys. A Math Gen. **29**, 3471 (1996).
105. B. Alles, G. Boyd, M. D'Elia, A. DiGiacomo, and E. Vicari, Phys. Lett. B **389**, 107 (1996).
106. G. Boyd, Nucl. Phys. B **53**, 544 (1997).
107. G. Boyd, Nucl. Phys. B **60**A, 341 (1998).