Optimization of coarse-grained models: matching probability density in conformational space

Shijing Lu\textsuperscript{1,2} and Xin Zhou\textsuperscript{1,3}\textsuperscript{*}

\textsuperscript{1}Asia Pacific Center for Theoretical Physics, Pohang, Gyeongbuk 790-784, Korea
\textsuperscript{2}Institute of Modern Physics, Zhejiang University, Hangzhou 310027, China
\textsuperscript{3}Department of Physics, Pohang University of Science and Technology, Pohang, Gyeongbuk 790-784, Korea

(Dated: November 18, 2009)

Coarse-Graining (CG) models are low resolution approximation of high resolution models, such as all-atomic (AA) models. An effective CG model is expected to reproduce equilibrium values of sufficient physical quantities of its AA model, which requires to match the equilibrium probability density of the CG model to that of the AA model in conformational space. The present work proposes for constructing effective CG models a novel methodology that aims at minimizing the distance between CG model and AA model. The distance is defined as a functional of conformational probability densities in CG and AA models and further expanded by ensemble averages of a set of sufficient and independent basis functions. An orthogonalization strategy is adopted to get the independent basis functions from sufficiently preselected interesting physical quantities of the system. Two variational methods are developed to optimize parameters of effective CG force field by minimizing the functional of probability densities, are then generalized so that the CG model also reproduce the pressure of AA model. The general CG framework is verified in constructing one-site CG water from TIP3P water model.

I. INTRODUCTION

Two branches of computational physics, namely macro-scale continuous fluid dynamics and micro-scale molecular dynamics simulation, never stop efforts in extending their power to wider scales. For example, molecular dynamics simulation has been successfully applied to model mesoscopic three dimensional Rayleigh-Benard convection\textsuperscript{1} and by the same token fluid dynamics has been applied to simulate nano-scale convection behavior in electrochemical reactions\textsuperscript{2}. However, even though the proliferation of multiprocessor computers and parallel computation techniques have inspired the ambition of computer scientists, molecular dynamics simulation is still an torment for most large scale systems like macromolecules' self-assembling problem whose size is micrometer scale comprising of hundreds of millions of atoms and whose phase transition time is longer than 100 nanoseconds\textsuperscript{3}. In this circumstance coarse-grained (CG) method, as a promising way, and in some situations the only way\textsuperscript{4}, of bringing molecular dynamics simulation into large applications on multi-\textmu s time scale or multi-\textmu m length scale has therefore been discussed extensively recent years\textsuperscript{4,5,6}. Different from all-atom (AA) molecular dynamics, CG method usually subsumed high frequency intra-molecular vibrations into coarse grained sites. The low resolution model is then simulated in a carefully designed effective force field. This procedure has been proved available for protein dynamics\textsuperscript{7}, protein-membrane interaction simulation \textsuperscript{8} as well as protein folding\textsuperscript{9}.

Usually, the construction of a CG model includes three steps. The first one is to select the mapping from AA coordinates to CG coordinates, simply denoted as \( x = x(q) \). Here \( q \) and \( x \) represent the high-dimentional conformation vectors in AA and CG models, respectively. For example, while \( q \) is the position vector of all hydrogen and oxygen atoms of waters, \( x \) can be chosen as the position vector of the center of mass of water molecules, thus \( x(q) \) is a linear function of \( q \). It is also possible to design another mapping, for example, if selecting the spatial density of molecules, \( \rho(R) \), as the coarse-grained coordinates, \( x \), where \( R \) is the usual 3- \textit{dimensional spatial vector}, we may bridge molecular systems to macroscopic continuous field models. The second step is to presume a formula as effective force field of CG model with some free parameters, \( U(x; u_\gamma) \), e.g., a pair additive interaction in one-site CG water model, \( U(x; u_\gamma) = \sum_{ij} u(r_{ij}) \). Here values of the pairwise potential function \( u(r) \) at different pair distance \( r \) are free parameters, \( r_{ij} \) is the distance between the \( (i)th \) and \( (j)th \) CG sites. If \( \rho(R) \) is chosen as the \( x \) in continuous field model, \( U(x; u_\gamma) \) might be a density functional as \( U = \int \rho(R) w(R, R') \rho(R') dRdR' \) with the kernel \( w(R, R') \) as parameters. The final step of constructing CG models is to determine the free parameters \( u_\gamma \) by minimizing the difference between CG model and the referenced AA system. While the first two steps are usually set based on afore experience and knowledge of the studied systems, many different coarse-graining techniques have been developed to focus on optimizing \( U(x; u_\gamma) \) in the \( u_\gamma \) parameter space, based on different measurement of inter-model distance. A quite recent review is shown in reference \textsuperscript{11}. Among of them, the traditional coarse-graining methods calculate the distance based on equilibrium averages of some chosen physical quantities, such as the radius distribution function.

\*Electronic address: xzhou@apctp.org
where \( g_{cg/aa}(r) \) is the ensemble averaged RDF of CG sites in the CG/AA model, and \( \rho(r) \) is an optional weight function. The traditional CG method has already been widely applied in various systems \[13, 14, 15, 16\]. Two known algorithms, iterative inverse Boltzmann and reverse Monte Carlo \[17\] are applied in the traditional CG techniques to optimize CG force field. The iterative inverse Boltzmann method, introduced by Reith \textit{et al.} \[17\] iteratively adjust inter-particle interactions based on an idea gas assumption which declares the RDF of CG sites is equal to the exponential of the pairwise potential function, explicitly \( g(r) = \exp[-\beta u(r)] \) for the pairwise potential function \( u(r) \) and the equilibrium averaged RDF \( g(r) \) of CG sites. The assumption can be exact only in the low density limit. But fortunately the iterative inverse Boltzmann has been proved to be valid for dense systems like Lennard-Jones liquid \[17\], TIP3P water \[19\] and polymer systems \[17, 20\]. Similar to the iterative reverse Monte Carlo method, also consists of iterative adjustment of interactions, only that modification to potential function in each RMC iteration cycle is determined by the steepest descent algorithm, which calculates the derivatives of the equilibrium averages of the chosen physical properties to update the \( u(r) \). RMC has been used to determine ion-iron interaction in aqueous NaCl solutions \[15\], to study diffusive dynamics of liquid water \[21\], to model behavior of mesoscopic lipids and lipids assembly in water \[22\] and to study bilayer membrane \[23\].

Obviously, the optimized CG model based on the traditional CG method is dependent on the selection of physical quantities. To avoid (or depress) the dependence of estimating \( D_{trad} \) on the selection of physical quantities, an alternative CG method is to match the free energy surface of the AA model in the CG conformational space \[24\], which is defined as,

\[
F(x) = -k_B T \ln \int \exp[-\beta V(q)]\delta(x - x(q))dq, \tag{2}
\]

where \( k_B \) is the Boltzmann’s constant and \( T \) is temperature, \( \beta = 1/k_B T \). \( V(q) \) is the potential energy surface of the AA system, \( \delta() \) is the Dirac-\( \delta \) function. Thus the distance between the CG model and AA system could be defined as \( \beta F = \langle [\Delta U(x)]^2 \rangle \rho \), where \( \Delta U(x) \equiv U(x; u_\gamma) - F(x) \) and \( \rho(x) \) is an optional probability density. By calculating values of the free energy \( F(x) \) at many sampled CG conformations, \( \{x^i\}, i = 1, \cdots, M \), based on a jump-in-sample algorithm \[24\], we estimated the distance as \( \beta F = \frac{1}{M} \sum_{i=1}^{M} [\Delta U(x^i)]^2 \) and optimized effective CG force field of tetrahedral molecular liquids \[24\]. The free-energy matching method is expected to better take into account the overall characteristic of the AA system in comparison with the traditional CG method \[24\], however more computational costs are usually required in the free-energy matching method than the latter. Recently, by matching the total AA force on CG sites, a new CG method, force matching method \[23, 26\], has been presented and widely tested in various of systems (see \[11\] and references therein). The force matching method closely related to an improved variant of the free-energy matching CG method. Replacing to the very time-consuming calculation of \( \{F(x^i)\} \), we may calculate the gradients of free energies, \( \frac{\partial F}{\partial x_i} \big|_{x=x^i} \), for example, based on the blue-moon ensemble simulations \[27\], and define the distance between CG and AA models as \( D_{fog} = \frac{1}{M} \sum_{i=1}^{M} [\frac{\partial F}{\partial x_i} \big|_{x=x^i}]^2 \) to optimize CG force field. While the CG mapping function \( x = x(q) \) is linear, in principle, the force matching method can give the same results of the CG method by matching the gradients of free energy. The force matching CG method (or the more general free-energy-gradient matching method) significantly decreases the required computational costs in comparison with the free-energy matching method, but similarly keeps the accuracy of the latter.

In the work we present a new methodology to optimize effective CG force field based on matching the equilibrium probability density of AA system in the CG conformational space, named as distribution matching method. The ratio of the probability density function in CG model to that in AA model is expanded on a set of complete and linearly independent conformational functions (\textit{i.e.}, basis functions). We find the equilibrium fluctuation of the ratio of probability density functions accurately measures the distance between CG and AA models, since the fluctuation provides an upper limit of the error of reproducing AA equilibrium average of any conformational function in the CG model. The distribution matching CG technique has the almost similar computational cost as the traditional CG method but takes into account the overall characteristic of the free energy surface \( F(x) \) of AA systems, so it has the advantages of both the traditional CG method and the free-energy-based methods (matching free energy or its gradient or force).

This article is organized as follows, in Sec. \[II\] we first introduce the theories on definition of consistency between CG force field and AA force field, and then give the formulas of distribution matching inherited from consistency condition. After, details of an expansion of distribution function are outlined, two ways of applying the expansion to the distribution matching method are then present and compared in this section. Sec. \[III\] starts from an application of the distribution matching method for water model.

\section{II. THEORY AND METHODS}

While groups of atoms in a AA system are mapped as CG sites, \textit{i.e.}, \( x = x(q) \), the interaction among CG sites, \( U(x; u_\gamma) \), need to be optimized to minimize the difference between CG model and the AA system. It possibly
requires $U(x; u_s)$ matches the free energy surface $F(x)$ in whole the CG conformational space $x$, or more practice, in important (and interesting) CG conformational regions of $x$. We define a weight function as ratio of two probability density functions,

$$
\omega_{aa\rightarrow cg}(x) = \frac{P_{cg}(x)}{P_{aa}(x)},
$$

where $P_{cg/aa}(x)$ is the equilibrium probability density of the CG/AA model in the $x$ space, for example, $P_{cg}(x) \propto e^{-\beta U(x; u_s)}$ and $P_{aa} \propto e^{-\beta F(x)}$ in canonical ensemble. The weight function $\omega_{aa\rightarrow cg}(x) \propto \exp(-\beta[U(x; u_s) - F(x)])$ characterizes the difference of the CG model from the AA models. Considering the fact

$$
\langle \omega_{aa\rightarrow cg}(x)A(x) \rangle_{aa} = \langle A(x) \rangle_{cg},
$$

for any conformational function $A(x)$, the weight function can be expanded as a series of complete basis functions $A^\mu(x)$ [28],

$$
\omega_{aa\rightarrow cg}(x) = 1 + g_{\mu\nu}(aa) \langle \delta_{aa}A^\mu(x) \rangle_{cg} \delta_{aa}A^\nu(x).
$$

Here $\langle \cdot \cdot \cdot \rangle_{aa/cg}$ denotes the ensemble average in the AA/CG model, $\delta_{aa}A^\mu(x) = A^\mu(x) - \langle A^\mu(x) \rangle_{aa}$, $g_{\mu\nu}(aa)$ is the inverse covariance matrix of the basis functions which obey the equality, $g_{aa}(aa)g_{\mu\nu}(aa) = \delta^\mu_{\nu}$ while $g_{\mu\nu}(aa) \equiv \langle \delta_{aa}A^\mu(x) \delta_{aa}A^\nu(x) \rangle_{aa}$. We used Einstein summation notation for Greek superscript or subscript here and in the text below of the paper if without explicit expression. The fact $\langle \omega(x) \rangle_{aa} = 1$ is explicitly wrote out in Eq. 3. We can define the difference from the AA model to CG model as the equilibrium fluctuation of the weight function in the AA model,$

$$
\sigma_{aa\rightarrow cg}^2 = \langle \omega_{aa\rightarrow cg}(x) \rangle_{aa} - 1
\equiv g_{\mu\nu}(aa) \langle \delta_{aa}A^\mu(x) \rangle_{cg} \langle \delta_{aa}A^\nu(x) \rangle_{cg},
$$

because $s_{aa\rightarrow cg}$ gives the upper limit of the relative error of the ensemble means of any variable $A(x)$,

$$
\epsilon = \| \langle A(x) \rangle_{cg} - \langle A(x) \rangle_{aa} \| = \| \langle (\omega - 1)\delta_{aa}A \rangle_{aa} \|
\leq \sqrt{\langle \omega^2 \rangle_{aa} - 1} \sqrt{\langle (\delta_{aa}A^\mu)^2 \rangle_{aa}}
= s_{aa\rightarrow cg} \sigma(A^\mu),
$$

where $\sigma(A^\mu)$ is the fluctuation of $A^\mu(x)$ in the AA system. It is worth to mention that $s_{aa\rightarrow cg}$ is not a normal distance, since it is not symmetric about $aa$ and $cg$, i.e., $s_{cg\rightarrow aa} \neq s_{aa\rightarrow cg}$. It is not difficult to define a symmetric distance, such as, $D^2(aa, cg) = 4(\langle \omega_{aa\rightarrow cg}^2 \rangle_{P} - 1)$, where $P(x) = [P_{aa}(x) + P_{cg}(x)]/2$ is the average probability density and $\omega_{aa\rightarrow cg}(x) \equiv P_{aa}(x)$. For theoretical view points, it might be more robust to use the symmetric distance $D^2(aa, cg)$ in optimization of CG effective force field. However, the minimization of $D^2$ is similar to that of $s_{aa\rightarrow cg}^2$ except needing slightly more computational cost in comparison with the latter. In the current paper, we only use the $s_{aa\rightarrow cg}^2$ to illustrate the optimization of CG force field, it is direct to extend the method based on the symmetric distance. Actually, the only difference among the three distances is that the inverse covariance matrix $g_{\mu\nu}$ are estimated in different equilibrium conformational samples, such as $s_{aa\rightarrow cg}^2 = g_{\mu\nu}(aa)\delta_{aa}A^\mu A^\nu$, $s_{cg\rightarrow aa} = g_{\mu\nu}(cg)\delta_{aa}A^\mu A^\nu$ and $D^2(aa, cg) = D^2(cg, aa) = g_{\mu\nu}(P)\delta_{aa}A^\mu A^\nu$. Here $\alpha^\mu = \langle A^\mu \rangle_{cg} - \langle A^\mu \rangle_{aa}$.

While the basis set $A^\mu(x)$ is complete, Eq. 3 is exact and independent on the applied CG potential $U(x)$, thus we have an analyzed expansion of free energy surface in (any) high-dimensional $x$ space,

$$
F(x) = U(x) + k_BT \ln[1 + g_{\mu\nu}(aa)\delta_{aa}A^\mu A^\nu(x)]
= U(x) - k_BT \ln[1 - g_{\mu\nu}(cg)\delta_{aa}A^\mu A^\nu(x)].
$$

However, in practice, we only can use a finite-size basis set (and finite-size AA/CG equilibrium samples) in the expansion, thus the obtained $F(x)$ may have significant errors at somewhere of the $x$ space unless the dimension of $x$ is small and/or $U(x)$ very close to $F(x)$. Although the expansion can not be expected to be accurate in every where of $x$ space, $s^2$ is able to be estimated very well from Eq. 3, if many (but not very large number of) basis functions are applied in the expansion. We can chose interesting physical quantities of the system as much as possible to capture the difference between the AA to CG models. The linear correlated basis functions are automatically discarded by $g_{\mu\nu}(aa)$ in Eq. 3. In addition, since we estimate $g_{\mu\nu}(aa)$ in a finite-size conformational sample of the AA system, the number of independent basis functions is not more than the size of the sample. Actually, unless the difference between AA and CG models is very huge, the number of required basis functions is far smaller than the size of sample in estimate of $s^2$. More detailed discussion about the completeness of basis function in estimate of $s^2$ is discussed in the reference [29] where we applied the same expansion in structuring and sampling conformational space of complex systems.

Now the difference between two models (actually, two finite-size equilibrium conformational samples) is calculable, the only thing left for constructing CG models is to minimize $s^2$ by consecutively adjusting the CG force field $U(x; u_s)$. If any one of basis functions is linearly depend on other basis functions, the covariance matrix $g_{\mu\nu}$ will not have a full rank, then the inverse covariant matrix will be singular. In this situation, the basis functions can be rearranged so that linearly dependent functions can be eliminated. To do this we orthonormalize basis functions in the way that $A^\mu = C^\mu_\nu \delta_{aa}A^\nu$ where $\{A^\nu\}_{\nu=1,2,...}$ is a set of orthonormalized functions that have a diagonalized covariant matrix $\langle A^\mu A^\nu \rangle_{aa}$ whose diagonal elements is either zero (or very small) or unity. The orthonormal functions $\hat{A}^\mu$ with zero (or very small) eigenvalues can be safely cast away in that they are linearly dependent on the other basis functions. The distribution difference then becomes $s^2 = \sum_{\nu} \langle (\hat{A}^\nu)^2 \rangle_{cg}$. 
A. Fitting pairwise additive central potential

If the effective potential of CG model is pairwise additive and central, we have, \( U(x; u_{\gamma}) = \sum_{i<j} \varphi(r_{ij}) \). Here \( r_{ij} = |r_i - r_j| \) represents the distance between the \( i \)th and \( j \)th CG site. The pair-central force can be generally expressed in terms of a table of parameters, i.e., \( \varphi(r) = \sum_{N_i} \delta(r-r_i) u_{\gamma} \), in which \( N_i \) is the total number of tabular parameters, \( \delta(r) \) is a double-step function that \( \delta(r) = 1 \) when \( -\Delta r/2 < r \leq \Delta r/2 \) and 0 otherwise (in practice, we used a continuous version of the \( \delta(r) \) so that its first-order and second-order derivatives exist everywhere). The gradient of \( s^2 \) is given as following,

\[
\frac{\partial s^2}{\partial u_{\gamma}} = -2\beta \sum_\mu \langle \hat{A}^\mu \rangle_{cg} \langle \hat{A}^\mu \delta_{cg} f^\gamma \rangle_{cg}
\]

where \( f^\gamma(x) \) is defined as

\[
f^\gamma(x) \equiv \frac{\partial U(x)}{\partial u_{\gamma}} = \sum_{i<j} \delta(r-r^\gamma),
\]

and \( \delta_{cg} f^\gamma(x) \equiv f^\gamma(x) - \langle f^\gamma \rangle_{cg} \). The total energy in terms of potential parameters becomes \( U(x; u_{\gamma}) = u_{\gamma} f^\gamma(x) \), and \( f^\gamma(x) \) is actually the number of the CG-particle pairs with the pair distance in the interval \((r^\gamma - \Delta r) \leq r \leq (r^\gamma + \Delta r)\). There are lots of local optimization methods can be used to minimize \( s^2 \), such as the steepest descent method, the conjugate gradient method, etc. It is also possible to directly update \( U(x; u_{\gamma}) \) from Eq. (8). Specifically, the basis functions in the right side of Eq. (8) can be replaced by the orthonormalized basis \( \hat{A}^\mu \), the distribution difference in the left side can be re-expressed in terms of tabulated potential parameters \( u_{\gamma} \), further, by taking natural logarithm of both sides of Eq. (8), it yields

\[
-\beta \sum_\gamma \langle f^\gamma \rangle_x u_{\gamma} = \ln[\hat{\omega}(x)]
\]

where \( \hat{\omega}(x) = \omega(x) \), if \( \omega(x) \) which is estimated from Eq. (5) is larger than a presumed small positive value \( \omega_\epsilon \), but \( \hat{\omega}(x) = \omega_\epsilon \) if \( \omega(x) < \omega_\epsilon \). Here \( \omega_\epsilon \) is applied to make sure the left side of Eq. (11) be a real number. In this paper, we set \( \omega_\epsilon = 0.001 \). As we mentioned, due to the incomplete basis functions in Eq. (5), it is possible the estimated \( \omega(x) \) is very close to zero or even be negative at some \( x \), although the exact \( \omega(x) \) should be positive anywhere in principle. Therefore, we are able to correct the tabular potential parameters of \( U(x; u_{\gamma}) \) in an iteration process by estimating \( \Delta u_{\gamma} \) from the linear equation below,

\[
-\beta \sum_\gamma \langle f^\gamma \rangle_x \Delta u_{\gamma} = \langle f^\gamma \ln[\hat{\omega}(x)] \rangle_x.
\]

The angular bracket with subscript \( X \) means the ensemble average in an optional conformational sample, such as the equilibrium sample in t AA or CG model, or any hybrid sample which consisted of equilibrium conformations in both AA and CG models. Starts from Eq. (5) or Eq. (12), an effective CG potential can be obtained by following algorithms:

1. Choose an initial guess of potential function \( u_{\gamma}^{(0)} \). For many CG models the logarithmic RDF is a good start point,

\[
u_{\gamma}^{(0)} = -k_BT \ln g(r^\gamma),
\]

where \( g(r^\gamma) \) is RDF at the pair distance \( r^\gamma \) of CG sites in the AA system.

2. Run a MD simulation under the potential with the parameters formed in the \( \text{ith} \) iteration, \( u_{\gamma}^{(i)} \), calculate values of \( f^\gamma(x) \) and the orthonormalized basis functions \( \hat{A}^\mu \) at the sampled conformations, and estimate \( s^2 \) (and its gradient \( \nabla_{u_{\gamma}} s^2 \equiv \frac{\partial s^2}{\partial u_{\gamma}} \)).

3. Find the correction \( \Delta u_{\gamma}^{(i)} \) based on the direct iteration method described in Eq. (12), the conjugate gradient method or another local optimization methods, the parameters of CG potential for the next iteration is \( u_{\gamma}^{(i+1)} = u_{\gamma}^{(i)} + \Delta u_{\gamma}^{(i)} \).

4. Do aforementioned two steps until \( s^2 \) is smaller than a preselected threshold, which could be determined by analyzing statistic error of \( s^2 \).

B. Pressure Correction

However, while the ensemble average values of any conformation function \( A(x) \) in the AA model can be approximately obtained from \( \langle A(x) \rangle_{cg} \) with a relative error not more than \( s \), some interesting physical quantities, such as pressure, can not be written as the ensemble average of a common conformational function in the CG and AA models. Actually, the microscopic function of pressure

\[
\hat{P}(x) = \frac{NK_BT}{V} - \frac{1}{dV} L \frac{\partial W(x)}{\partial L}.
\]

has explicit dependence on potential energy surface \( W(x) \). Here \( V = L^d \) is the volume of the \( d \)-dimensional simulation box with length \( L \), and \( W(x) \) is dependent on \( L \) while scaling the real conformation \( x \) as the dimensionless one \( z = x/L \). For example, given the assumption that the force filed of CG model is pairwise central additive and \( d = 3 \), the pressure is thus able to be expressed as an integral over RDF [10] and further can be discretized in terms of potential parameters,

\[
\hat{P}_{cg}(x) = \frac{2\pi \rho N}{3V} \int_0^\infty [3r^2 g(r; x) + r^3 g'(r; x)] u(r) dr + \frac{p}{\beta} = \left[ \gamma^0 \right] u_{\gamma} + \rho k_BT,
\]
where $\rho = N/V$ is the number density of CG particles, $g(r; x)$ is value of RDF of special CG conformation $x$ at inter-particle distance $r$, $g'(r; x) = \frac{\partial g(r; x)}{\partial r}$, and

$$
\Upsilon^\gamma(x) = \frac{2\pi \rho N \Delta r}{3V} [3r_g^2 g(r_g; x) + r_g^2 g'(r_g; x)].
$$

Here we already suppose $r_g^2 g(r; x) u(r) = 0$ while $r = 0$ and $r \to \infty$. It is clearly, $\hat{P}_{cg}(x)$ is explicitly dependent on the parameters $u_\gamma$ of the CG force field, thus the macroscopic pressure, $P_{cg} = \langle \hat{P}_{cg}(x) \rangle_{cg}$, not only depends on the equilibrium distribution of CG, but also explicitly depends on the potential surface, $U(x; u_\gamma)$, itself. Thus, the error of the macroscopic pressure, $\varepsilon_P = |\langle \hat{P}_{aa}(q) \rangle_{aa} - \langle \hat{P}_{cg}(x) \rangle_{cg}|$, is

$$
\varepsilon_P = |\langle \hat{P}_{aa} - \hat{P}_{cg} \rangle_{aa} + \langle \hat{P}_{cg} \rangle_{aa} - \langle \hat{P}_{cg} \rangle_{cg}|.
$$

While the second term in the right side of Eq. (17) is limited by the $s_{aa-cg}$, the first term might be large since the microscopic pressure $\hat{P}$ has different dependence on $x$ in CG model from that in AA system. For reconstructing the pressure in CG model, extra efforts should be taken. One simple way is to directly use a penalty function to define a pseudo distance,

$$
s_p^2 \equiv s_{aa-cg}^2 + \alpha |\langle \hat{P}_{cg}(x) \rangle_{cg} - \langle \hat{P}_{aa}(q) \rangle_{aa}|^2,
$$

where $\alpha$ is a positive constant. The gradient of the pseudo distance now becomes

$$
\frac{\partial s_p^2}{\partial u_\gamma} = \frac{\partial s_{aa-cg}}{\partial u_\gamma} + 2\alpha |\langle \hat{P}_{cg} \rangle_{cg} - \langle \hat{P}_{aa} \rangle_{aa}| \frac{\partial}{\partial u_\gamma} \langle \hat{P}_{cg} \rangle_{cg},
$$

where

$$
\frac{\partial}{\partial u_\gamma} \langle \hat{P}_{cg} \rangle_{cg} = -\beta \langle \delta_{cg} f^\gamma(x) \hat{P}_{cg}(x) \rangle_{cg} + \langle \Upsilon^\gamma(x) \rangle_{cg}.
$$

With Eq. (13) and Eq. (17), we can minimize $s_p^2$ by using usual local minimization methods, such as the conjugate gradient method. In Eq. (15), the penalty coefficient $\alpha$ can be any positive number in principle. However, it is possible to make the pressure correction more consistent with the distribution matching scheme by defining the value of penalty coefficient in following way: First, recall the expansion expression given by Eq. (9), if $\delta_{aa} A^\mu$ are orthogonal to each other but not necessarily have been normalized, then Eq. (9) can be re-expressed as

$$
s^2 = \sum \mu \nu \gamma \delta_{aa} g_{\mu\nu} \langle (\delta_{aa} A^\nu) \hat{P}_{cg} \rangle_{cg}^2 \alpha^2 \gamma^2 \mu \nu \gamma ,
$$

where $g_{\mu\nu} = \langle (\delta_{aa} A^\nu) \rangle_{aa}^2$. Now if we add a hybrid basis function $\Delta_{aa} \hat{P}(x) = \hat{P}_{cg}(x) - \langle \hat{P}_{aa} \rangle_{aa}$ in the basis function set and neglect the correlation between the function and the rest of basis functions, we are able to give an appropriate value for the penalty coefficient, that is the reverse variance of $\hat{P}_{aa}$ in the AA system, i.e.,

$$
\alpha = \langle (\hat{P}_{aa}^2(q))_{aa} - \langle \hat{P}_{aa}(q) \rangle_{aa}^2 \rangle_{aa}^{-1}.
$$

It is possible to also consider the correlation of $\Delta_{aa} \hat{P}(x)$ with the other basis functions to further improve Eq. (13). In the paper, we only simply use Eq. (13) to illustrate the possibility of involving pressure matching in optimization of CG models, more discussions will appear elsewhere.

### III. TEST CASE: ONE SITE WATER MODEL

In this section, we use the distribution matching method to construct an effective (CG) force field for one site water model. We choose the TIP3P water model[30] as the AA model because of its simplicity. The illustration of applying the distribution matching method to optimize effective CG force field is not dependent on the selection of higher-resolution model, for example, we even can construct the one-site water from $ab$ initio simulations of water. The TIP3P water model treat water molecular as a rigid three sites model, and its force field involves only nonbounded interactions, i.e., the electrostatic interactions and the Lennard-Jones potential. The TIP3P simulation of water was carried out in the constant NVT condition, where the number of water molecules $N = 216$ in a cubic simulation box with the volume $6.4585 \text{ nm}^3$ (corresponding the density of water as $1.0 \text{ g cm}^{-3}$) at the temperature $300 \text{ K}$. In one site CG model, the water molecules are replaced by a spherically symmetrical site mapped by the center of mass of water molecules with the mass $2m_H + m_O$. Both the CG model and the TIP3P model are simulated by the MD package NAMD2.5 [31] with our modification for coarse-graining MD simulations. In all simulations, the Lennard-Jones potentials are gradually switched off from radius $r_{\text{switch}} = 0.8 \text{ nm}$ to $r_{\text{cutoff}} = 0.9 \text{ nm}$, the electrostatic force is calculated based on particle mesh Ewald method [31]. Langevin thermostat with the a damping coefficient of $5.0 \text{ ps}^{-1}$ is used; a length 20ns trajectory was generated from TIP3P simulation, and conformations are collected in a frequency of every 0.4 ps after the first 10 ps simulations for sake of thermal equilibrium. The CG simulations were performed in the same condition with the TIP3P simulation but the length of trajectory at each parameters $u_\gamma$ is as short as 800 ps with a sampling interval of 0.2 ps after dropping first 10 ps trajectory. The $g(r_{\mu\nu}; x)$ at $r_{\mu} = r_{\text{min}} + \mu \Delta r$, $\mu = 0, \ldots, 99$ are chosen as the basis functions for the expansion described in Eq. (9), $\Delta r = 0.008 \text{ nm}$ and $r_{\text{min}} = 0.1 \text{ nm}$. It is directly to use more basis function, such as multiple-body correlations, local orientational orders, in Eq. (9) to obtain more robust CG force field, the weights of all these preselected physical quantities in $s^2$ are automatically provided by estimating $g_{\mu\nu}$. As more and more physical quantities are applied, the $s^2$ will reachs saturation and does not change any more even more physical quantities are applied [22]. In the paper we only apply the RDFs to focus on illustrating the distribution matching CG method.
Without loss any generality, these values of RDF are first scaled then are applied as the basis functions, i.e.,

\[
\delta_{aa} A^\mu(x) = \frac{g(r_{\mu}; x) - \langle g(r_{\mu}; x) \rangle_{aa}}{\sigma_{aa}[g(r_{\mu}; x)] + \varepsilon_A}
\]  

(22)

where \(\sigma_{aa}[g(r_{\mu}; x)] = \sqrt{(g^2(r; x))_{aa} - (g(r; x))^2_{aa}}\) is fluctuation of \(g(r_{\mu}; x)\) in the TIP3P model, \(\varepsilon_A\) is a small positive value that makes sure the denominator is nonzero. The constant scaling factors, \(\sigma_{aa}[g(r_{\mu}; x)] + \varepsilon_A\) for different \(\mu\), makes all basis functions have the same order value so that the calculation of the corresponding matrix entries has better numerical stability. Inherit but different from the idea of orthogonalization protocol proposed in last section, which be also seen in the reference [28], we calculate the inverse covariance matrix by factorizing \(g^{\mu\nu}\). Because \(g^{\mu\nu}\) is positive definite and symmetric, it has all positive eigenvalues and can be decomposed to a form \(g^{\mu\nu} = V \Sigma V^T\) where \(V\) is a unitary matrix whose rows are orthonormal, \(\Sigma\) is diagonal matrix whose diagonal elements are eigenvalues of \(g^{\mu\nu}\). In practice, some of the basis functions can be linearly dependent on the others, therefore the covariance matrix \(g^{\mu\nu}\) has some zero eigenvalues and in that case \(\Sigma\) is irreversible. However if we choose row vectors of \(V\) as basis functions and desert those with zero length, we are able to build a non-degenerated functional space. Noticing that deserting eigenvectors are the same as truncating eigenvalues. We define the inverse matrix of \(\Sigma\) as:

\[
[D^{-1}]_{ii} = \begin{cases} \frac{1}{\sigma_{ii}} \text{ if } \sigma_{ii} \geq \varepsilon_D \\ 0 \text{ if } \sigma_{ii} < \varepsilon_D \end{cases}
\]  

(23)

Here \(\varepsilon_D\) is a threshold for truncating eigenvalues, in our case, \(\varepsilon_D\) is set to 0.001. Then, the inverse covariant matrix writes as \(g_{\mu\nu} = V^T\Sigma^{-1}V\). An alternative method to form \(g_{\mu\nu}\) is \(V^T[I + \varepsilon_D]\Sigma^{-1}V\), where \(I\) is the unit matrix. We starts from potential function defined in Eq. (13) and minimize the \(s^2\) with both the conjugate gradient method and the direct iteration method described by Eq. (12). Both of the methods work effectively except for the fact that the direct iteration method minimizes \(s^2\) slightly faster than the conjugate gradient method in the case. As demonstrates in Fig. I when using the direct iteration method \(s^2\) decrease from 12.0 to 0.01 within the first 10 iteration steps, on the other hand, the conjugate gradient method need more than 15 iteration steps to decrease \(s^2\) from 11.9 to 0.3. When the distance is smaller than 0.001, RDF, which we used to construct the basis functions, of referenced TIP3P model can be reproduce by CG model remarkably accurately, as demonstrated in Fig. 2.

Former researchers [17, 19] used to correct CG force field by adding a linear item to the effective pair potential to reproduce pressure of AA system in CG model. We declare that the linear correction is not the best compromise to revise pressure while having reasonably small effect on the accuracy of structure properties’ reconstruction. The effective pair potential of CG before and after the pressure correction described by Eq. (15) was shown in Fig. 3. Correspondingly, the evolution of \(s^2_{P}\) is shown in Fig. 4 RDF after the pressure correction is also shown in Fig. 2 as comparison. Fig. 3 clearly demonstrates that the pressure correction has change the pair potential more in the large \(r\) region, i.e., \(0.6 \sim 0.7\) nm, than in the small \(r\) region, i.e., \(0.2 \sim 0.5\) nm. In Fig. 2 \(s^2_{P} = 0.084\), but if take off the pressure penalty item the residue becomes \(s^2_{\Delta P} = s^2_{P} - \alpha(P_{cg} - P_{aa})^2 = 0.026\), which is insignificant comparing to \(s^2(20)\).

As for the one site water model, as shown in Fig. 3, the variance of pressure in the AA system, \(\sigma(\delta_{aa} P) = 818.1\) bar, which is equal to 0.012 kCal · mol\(^{-1}\)· Å\(^{-3}\), we use \(1/\sigma^2(\delta_{aa} P) \approx 7200\) mol\(^2\) · Å\(^6\) · kCal\(^{-2}\) as the value for \(\alpha\) in the pressure correction. We carried on the pressure correction after \(s^2\) had decreased to 0.014. The evolution of \(s^2_{P}\) is presented in Fig. 4. It is worth noticing that in the first four steps, minimization of \(s^2_{\Delta P}\) makes correction to that of \(s^2_{P}\) and increase from 0.014 to 0.3 due to the fact that pressure difference is too large. However, from the fifth step on, both of them can decrease smoothly. This is largely because pressure difference is numerically independent on RDF differences. Correction to the potential at this moment is roughly divided into two parts, one is the fine tune which add short wave length modification function \(\Delta\varphi(r)\) to pair interaction, say \(\varphi(r)\); the other part is the global shift which change the potential function significantly while holding the fine structure.

One of the well known dilemmas in CG techniques is that the pressure correction would lead to less accuracy in representing of other properties [10, 22, 32, 33] such as isothermal compressibility and conformance of RDF. This effect is shown in Fig. 5, when pressure consistency is taken into account, \(s^2\) increases from 0.001 to the value of 0.026. However on the other hand, CG with pressure correction shows greater extensibility than that without pressure correction at temperature \(T = 370\) K and \(T = 230\) K. It indicates the additional pressure correction makes the CG model be more consistent with the AA system. Another appealing feature Fig. 5 shows is that in the temperature region of \(T_{eff} = \{T|290 \leq T < 312\}\), \(s^2_{P} \leq 0.04\) and \(s^2 \leq 0.017\), both of which are very small value. Especially that in \(T_{eff}\), \(s^2\) is smaller that the best case of \(s^2_{P}\). Since the RDF corresponding to \(s^2_{P} = 0.026\) is almost indecipherable, we can safely declare that \(T_{eff}\) is the effective temperature region for the potential obtained from our method.

IV. CONCLUSION

The present work introduces a new methodology, the distribution matching method, to optimize CG force field effectively and efficiently. Consistency condition between CG and detailed atomistic model is given and reinterpreted as a requirement of matching of distributions thus equilibrium average of a set of sufficient and independent basis functions through the distribution expansion anal-
ysis. Based on the analysis, we proposed a two steps protocol to construct effective CG force field. The first step is to expand phase spaces differences between CG and AA model as linear combination of basis functions. In this part orthogonalization technique is suggested to avoid singularity led by linear dependencies among basis functions. The second step is to minimize the defined difference in whole the conformational space. Two different minimization approaches are introduced in this part, namely the conjugate gradient approach and the direct iteration approach. Both two approaches are demonstrated in the case of being applied to fit pairwise additive force field. With aforementioned two steps protocol we have been fully able to construct effective pair additive force field for CG models. We test this statement by applying the formulas to building one site model for TIP3P water model. Considering that pressure consistency is required in some situations we propose a method to correct pressure in accordance previous two steps protocol.

It is enlightened by constraint optimization techniques. By adding a penalty item to the definition of phase space difference we are able to limit the pressure deviance. The effectiveness of pressure correction method is also verified in one-site CG water model. The present methodology is encouraging, its capability to reverse distributions of arbitrary functions defined in CG coordinate space indicates a wide applications in multi-scale simulations.

Acknowledgments

Authors acknowledge the Max Planck Society (MPG) and the Korea Ministry of Education, Science and Technology (MEST) for the support of the Independent Junior Research Group at the Asia Pacific Center for Theoretical Physics (APCTP).

[1] D. C. Rapaport, Phys. Rev. E 73, 025301(R) (2006).
[2] S. Lu, Z. Su, J. Sha, and W. Zhou, Chem. Commun. 37, 5639 (2009).
[3] M. L. Klein and W. Shinoda, Science 321, 798 (2008).
[4] M. Praprotnik, K. Kremer, and L. Delle Site, Annu. Rev. Phys. Chem. 59, 545 (2008).
[5] S. A. Adcock and J. A. McCammon, Chem. Rev. 106, 1589 (2006).
[6] S. Izvekov and G. A. Voth, J. Phys. Chem. B 109, 2469 (2005).
[7] J. L. Klepeis, K. Lindorf-Larsen, R. O. Dror, and D. E. Shaw, Curr. Opin. Struct. Biol. 19, 120 (2009).
[8] E. Lindahl and M. S. Sansom, Curr. Opin. Struct. Biol. 18, 425 (2008).
[9] C. Clementi, Curr. Opin. Struct. Biol. 18, 10 (2008).
[10] J.-P. Hansen and I. R. Mcdonald, Theory of Simple Liquids (Academic Press, 2006).
[11] W. G. Noid, et al., J. Chem. Phys. 128, 244114 (2008).
[12] F. Müller-Plathe, Chem. Phys. Chem. 3, 754 (2002).
[13] P. Sherwood, B. R. Brooks, and M. S. Sansom, Curr. Opin. Struct. Biol. 18, 630 (2008).
[14] L. Delle Site, C. F. Abrams, A. Alavi, and K. Kremer, Phys. Rev. Lett. 89, 156103 (2002).
[15] X. Zhou, D. Andrienko, L. Delle Site, and K. Kremer, Europhys. Lett. 70, 264 (2005).
[16] X. Zhou, D. Andrienko, L. Delle Site, and K. Kremer, J. Chem. Phys. 123, 104904 (2005).
[17] D. Reith, M. Pütz, and F. Müller-Plathe, J. Comput. Chem. 24, 1624 (2003).
[18] A. P. Lyubartsev and A. Laaksonen, Phys. Rev. E 52, 3730 (1995).
[19] H. Wang, C. Junghans, and K. Kremer, Europhys. J. E 28, 221 (2009).
[20] R. Faller, Polymer 45, 3869 (2004).
[21] S. Matysiak, C. Clementi, M. Praprotnik, K. Kremer, and L. Delle Site, J. Chem. Phys. 128, 024503 (2008).
[22] A. P. Lyubartsev, Eur. Biophys. J. 35, 53 (2005).
[23] T. Murtola, E. Falck, M. Karttunen, and I. Vattulainen, J. Chem. Phys. 126, 075101 (2007).
[24] X. Zhou, Y. Jiang, S. Rasmussen, and H. Ziock, J. Chem. Phys. 128, 174107 (2008).
[25] F. Ercolessi and J. B. Adams, Europhys. Lett. 26, 583 (1994).
[26] S. Izvekov, M. Parrinello, C. J. Burnham, and G. A. Voth, J. Chem. Phys. 120, 10896 (2004).
[27] G. Ciccotti, R. Kapral, and E. Vanden-Eijnden, Chem. Phys. Chem. 6, 1809 (2002).
[28] L. Gong and X. Zhou, Phys. Rev. E 80, 026707 (2009).
[29] L. Gong and X. Zhou (2009), to be submitted.
[30] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. 79, 926 (1983).
[31] J. C. Phillips, et al., J. Comput. Chem. 26, 1781 (2005).
[32] M. E. Johnson, T. Head-Gordon, and A. A. Louis, J. Chem. Phys. 126, 144509 (2007).
[33] A. A. Louis, J. Phys. cond. matt. 14, 9187 (2002).
[34] M. A. van der Hoef and P. A. Madden, J. Chem. Phys. 111, 1520 (1999).
FIG. 1: Evolution of $s^2$ and $s^2_P$ in the first 20 iteration steps using different optimizing algorithm. In the figure, the subscript notion conj refers to the conjugate gradient method; direct means the direct iteration method (see text). At the 20th step, $s^2(20)$ is 0.3 with the conjugate gradient method, is 0.007 with the direct iteration method, meanwhile $s^2_P(20)$ is 1.4 and $s^2_{P,r} = 0.16$.

FIG. 2: Comparison between center of mass RDF of TIP3P water model and site-site RDF of one-site CG water model. Both simulations were performed under the constant NVT ensemble at temperature of 300 K and density of 1.0 g/cm$^3$. The inset shows an enlarged region of the first peak. The $s^2$ between the CG model without the pressure correction (CG-NPC) and the TIP3P model is 0.001, and $s^2_P$ between pressure corrected CG model (CG-PC) and TIP3P model is about 0.084.
FIG. 3: The effective pair potential for CG with and without pressure correction; the inset shows the difference between the two. $s^2$ and $s^2_P$ of the two potentials are the same with those of Fig. 2.

FIG. 4: This figure shows pressure distribution for, from left to right respectively, all-atom model (triangle line), coarse-grained models with (circle line) and without (square line) pressure correction. The average pressure of these distributions are, accordingly, $-184.3$ bar, $-64.5$ bar and $1.08 \times 10^4$ bar, respectively.
FIG. 5: Comparison of extensibility of pair potentials on different temperatures. The initial potentials is obtained in $T = 300$ K from different methods, using versus not using pressure correction in particular, and then is tested in other temperatures from 230 K to 370 K. The results are then compared to TIP3P simulations at the same temperature so as to calculate the free energy distances ($s^2$). The circle line shows the dependence of $s^2$ on temperature for non-pressure correction pair potential, its value at $T = 300$ K is 0.001; the triangle line show the results of the potential with pressure correction, its minimum value is 0.026.