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Phase behavior of colloids and proteins in aqueous suspensions: Theory and computer simulations

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The fluid phase behavior of colloidal suspensions with short-range attractive interactions is studied by means of Monte Carlo computer simulations and two theoretical approximations, namely, the discrete perturbation theory and the so-called self-consistent Ornstein-Zernike approximation. The suspensions are modeled as hard-core attractive Yukawa (HCAY) and Asakura-Oosawa (AO) fluids. A detailed comparison of the liquid-vapor phase diagrams obtained through different routes is presented. We confirm Noro-Frenkel's extended law of scaling according to which the properties of a short-ranged fluid at a given temperature and density are independent of the detailed form of the interaction, but just depend on the value of the second virial coefficient. By mapping the HCAY and AO fluids onto an equivalent square-well fluid of appropriate range at the critical point we show that the critical temperature as a function of the effective range is independent of the interaction potential, i.e., all curves fall in a master curve. Our findings are corroborated with recent experimental data for lysozyme proteins. © 2012 American Institute of Physics. [http://dx.doi.org/10.1063/1.4747193]

I. INTRODUCTION

The study of the phase equilibrium in colloidal suspensions is of particular relevance in physics, biology, materials science, and several other branches of science.^{1–4} This growing interest resides in the fact that, on one hand, colloidal suspensions are ubiquitous in nature comprising among others milk, paints, additives, etc. Additionally, they are simple model systems that allow us to obtain a better comprehension of the phase behavior of more complex fluids, such as protein suspensions.^{5–13}

Colloids are typically used as model systems mainly because of the following interesting common features: (1) colloids and other macromolecules share similar time (1 μ s -1 s) and length (10 nm -1μ m) scales, (2) the forces between colloidal particles also describe the interaction between macromolecules in aqueous environment, (3) from an experimental point of view the interaction between colloids can be tuned,^{14–18} and (4) colloidal suspensions can be studied by means of different complementary techniques, i.e., experiments,^{19–21} computer simulations^{22–24} and theoretical approximations.^{25–29} Hence, the understanding of the physical properties of colloidal suspensions allows us to give a qualitative (and sometimes quantitative) description of a large variety of complex fluids.³⁰

Protein phase separation is typically of interest in the production of protein crystals which are used both in pharmaceutical industry and protein crystallography.¹⁷ Recently, it has been shown that protein phase separation in organic tissues is related with diseases such as cataract,^{31–33} sickle cell anemia,^{34,35} Alzheimer disease,³⁶ cryoimmunoglobulinemia,³⁷ among others. Therefore, a complete knowledge of the phase transitions of proteins in suspension may help to develop therapies against such diseases. Additionally, proteins exhibit interesting structural and dynamical properties, such as cluster formation^{38–43} and intermediate order.^{44,45} In particular, lysozyme (a globular protein) has been used as model protein to understand the phase behavior of biomolecules in aqueous solutions.^{11,12,16,17,46–51} During the last few years, patchy-based models have also been used to explain the rich phase behavior of lysozyme and other proteins, see, e.g., Refs. 52–54.

Colloidal and protein suspensions show phase separations analogous to the transitions observed in simple liquids. In the fluid-solid transition the colloidal particles form regular structures (crystals) or amorphous structures (aggregates).^{55,56} In the coacervation or liquid-liquid transition (analogous to the vapor-liquid transition) of the colloidal suspensions two-liquid phases with different colloidal concentrations coexist.^{12,15,25,56} When the range of the attractive interparticle interaction is short-ranged (a few percent of the particle diameter), the liquid-liquid transition is buried inside the liquid-solid transition and, therefore, it is termed a metastable transition.⁵⁷ Recently, the research of the liquidliquid transition in systems with short-range attractive interactions has been motivated by the aim of finding the optimum conditions for nucleation, that occurs near to the metastable binodal,^{17,58} and of understanding the physical mechanisms behind the dynamical arrest transition in adhesive-like colloidal systems.41,59,60

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The phase behavior of both colloidal and protein suspensions can be changed by the addition of either salt or nonadsorbent particles.^{12,61} In particular, when an electrolyte is added the pH of the suspension is modified.^{12, 17, 18, 62–65} In this case, it is well-known that the microions form a heterogeneous cloud around the colloids, i.e., the so-called double layer,^{66–68} that is responsible for the screening of the electrostatic interactions. The colloidal screening can be quantified by the Debye length,^{18,69} κ^{-1} . In contrast, the addition of non-adsorbent polymers can cause a phase separation due to the (attractive) depletion forces.¹⁵ An uncharged substance induces an effective attraction between colloids which is responsible (under specific conditions) for particle aggregation; this effect is entropy driven. Such an attraction depends on the molecular mass and concentration of the added substance.¹⁷ In the case of mixtures of colloids and polymers, it depends both on the degree of polymerization and on the polymer concentration.^{16–18,55,70} Therefore, although it is well-known that the equilibrium state of a suspension is described by the minimization of the Helmholtz free energy, one typically chooses one route to induce changes in the phase, i.e., we usually construct either energy-driven or entropy-driven phase separation mechanisms. Interestingly, both routes allow us to obtain similar physical properties in the coexistence region.41,59

In theoretical approximations as well as simulations, one models the effective interaction between proteins as a hard core repulsion plus a short-range attractive tail and a long-range repulsion that includes information of the medium through some fit parameters, see, e.g., Ref. 5. The most extensively studied models are the hard-core attractive Yukawa (HCAY) that represents the screened electric potential and the Asakura-Oosawa (AO) that takes into account the effect of the depletion forces.⁷¹⁻⁷⁴ Both potentials can be crudely represented by the so-called squarewell (SW) potential.^{23,75} The HCAY potential has been studied within the context of proteins by Foffi et al.²⁶ by using both the self-consistent Ornstein-Zernike approximation (SCOZA) and a first-order perturbation theory for $\kappa\sigma \geq 5$, with σ being the particle diameter. Additionally, Li et al.13 obtained the binodal curve by means of Monte Carlo (MC) computer simulations for $\kappa \sigma \geq 3.9$. The phase behavior of systems driven by depletion mechanisms was investigated many years ago by Gast et al.⁷⁶ They localized both liquid-vapor and liquid-solid regions of coexistence by means of a thermodynamic perturbation theory. Recently, Germain and Amokrane re-investigated the mechanisms of gelation and phase coexistence in binary mixtures of hard spheres through the use of the AO potential model.^{77,78} Within the AO approximation, the phase behavior of either colloidal or protein suspensions has been studied in two limiting cases: the colloidal limit ($\sigma_c / \sigma_p \gg 1$) and the protein limit $(\sigma_c/\sigma_p \ll 1)$,^{24,61,76,79} where σ_c is the diameter of the colloid or protein and σ_p is the radius of the depletant agent or polymer, respectively.

The SW potential is one of the simplest and most studied potentials that mimics the properties of a variety of potentials like the HCAY and AO.^{80–82} Unfortunately, there is not a direct way to relate parameters like the Debye length or polymer concentration to the SW parameters. Thus, the SW potential does not provide a clear evidence of the thermodynamic mechanism that drives the phase transition, i.e., it is unclear whether the transition is either energy-driven or entropy-driven. However, according to the extended law of corresponding states proposed by Noro and Frenkel,⁷⁵ it is possible to find for an arbitrary potential an equivalent SW potential of width $(\lambda - 1)\sigma$, where $\lambda\sigma$ is the range of the attraction, through a direct comparison of the second virial coefficient (B_2) at the critical temperature, providing the range of the attraction is sufficiently short (a few percent of the particle diameter). In the context of proteins, Lomakin et al.83 compared the phase diagram of some kinds of crystalline proteins with simulation data of the SW fluid of variable range. They concluded that the mapping between the SW and the protein system is possible if the interaction range is lower than 1.25σ . Furthermore, Duda¹⁰ found that the SW suitable to describe the phase separation in lysozyme solutions must be very short-ranged with a width around 0.1σ .

The aim of this work is to study the phase separation in a protein suspension by modeling it as a colloidal suspension. We restrict our study to systems where the range of the attraction, in terms of $\lambda\sigma$, lies within the interval $1.05\sigma < \lambda$ $\leq 1.25\sigma$. Hence, in order to explore the phase behavior of a suspension of particles of the same interaction range, we limit our study to the parameter space ($\kappa\sigma$, η) shown in Figure 1, where η is the size ratio, $\eta \equiv \sigma_c / \sigma_p$, between the colloid and the polymer. The curves in Figure 1 show the correspondence of the potential parameters of the different model potentials obtained by considering that the reduced second virial coefficient, $B_2^* \equiv B_2/B_2^{HS}$, at the critical point is the same for both HCAY and AO fluids with a value of -1.5,^{75,84} with $B_2^{HS} = 2\pi\sigma^3/3$ being the second virial coefficient of a suspension of hard-spheres. The fact that $B_2^* \approx -1.5$ at the critical point has been explicitly discussed by Noro and Frenkel,⁷⁵ but it is still under debate since there is evidence of slight deviations,^{23,85} however, in our case, this kind of mapping just represents a guide to the parameters space of the potential.



FIG. 1. Potential parameters space (κ^* , η) as a function of λ determined by using the mapping proposed by Noro and Frenkel⁷⁵ where $B_2^* = -1.5$ at the critical point, and $\kappa^* \equiv \kappa \sigma$ and η is the colloid-polymer size ratio (see text for further details). The shaded area is the region of our interest.

In the particular case of the AO potential, we also study the phase diagram for $\eta = 5$ and 10. According to Figure 1 both potential parameters have the same λ -dependence; this point will be discussed in more detail below. Systems whose interaction range is lower than 1.05σ can be accurately represented by the Baxter potential⁸² and are out of the scope of this article. Particularly, we put emphasis on the use of the discrete perturbation theory (DPT) (Ref. 86) and the self-consistent Ornstein-Zernike approximation⁸⁷ to fully investigate the phase behavior of complex fluids where particles interact with either HCAY or AO potentials.

The DPT has originally been introduced to predict the thermodynamics of non-polar fluids and their mixtures^{86,88} and has also been extended recently to polar fluids.⁸⁹ It is a second-order perturbation theory that provides a simple analytical expression for the Helmholtz free-energy in terms of the density, temperature, and the interaction potential parameters. It has been successfully applied to different potentials and was able to predict interesting phenomena, such as the multiple fluid-fluid phase coexistence in monodisperse fluids and some anomalies of water.^{90–92} Here, we extend its applicability to the context of colloidal suspensions. SCOZA,⁸⁷ on the other hand, is an advanced liquid-state theory that enforces thermodynamic consistency between different routes to the thermodynamic properties and has proven to give reliable predictions even in the critical region where conventional liquidstate theories usually cease to be predictive. In Ref. 87 the SW fluid was investigated and the results were in excellent agreement with computer simulations for long and intermediate ranges of the interaction. However, the reliability of SCOZA predictions turned out to decrease for the short-ranged SW potential—a fact that was confirmed recently⁹³ with a refined numerical solution procedure. In both studies, it was seen that the solution of the SCOZA partial differential equation (PDE) for narrow SW fluids turned out to be sensitive to the boundary condition of the PDE at high density. In this work we will gain some insight whether SCOZA is more reliable for very short-ranged interactions when one turns to other forms of the interaction than the SW one. It seems that for the AO as well as the HCAY potential this feature of SCOZA, although still present, is much less pronounced, i.e., the predictions are reliable up to the smallest ranges considered here.

Our theoretical results are compared with Monte Carlo computer simulations using both the Gibbs ensemble⁹⁴ and the replica exchange method^{95–99} combined with the scheme proposed by Chapela *et al.*¹⁰⁰ The latter has been successfully used to determine the phase-coexistence of the HCAY fluid of very short-range, i.e., $9 < \kappa \sigma < 15$.¹⁰¹ It is a simple *NVT* ensemble technique that leads to the evolution of the two co-existence phases and, therefore, it permits a quick evaluation of the coexistence densities. Further details of the technique are discussed below.

The paper is organized as follows. In Sec. II we discuss the model potentials typically used to represent proteinprotein interactions. We furthermore briefly review the Monte Carlo simulation details for the study of the phase coexistence and we outline the main ideas of the DPT and SCOZA frameworks. Results are presented in Sec. III: the phase behavior of the fluids considered in this work is presented and analyzed and we also discuss the critical properties and present a comparison with experimental data for lysozyme proteins. Finally, in Sec. IV we provide the main conclusions of this work.

II. METHODS

A. Interaction potential

Lysozyme is one the more studied proteins, see, e.g., Refs. 51, 102, and 103. It is a quasi-spherical molecule with a diameter of approximately 3.4 nm, carrying $+11e_0$ electronic charges;¹⁸ which, in general, depends on the *p*H, and e_0 being the charge of the electron. Experiments performed with lysozyme proteins have shown that the interaction between two proteins could be taken as the combination of a short-ranged attractive tail and a long-ranged repulsive contribution.^{11,12,18} The former comes from the van der Waals contribution, while the repulsion is due to the electrostatic screening caused by the added electrolyte.¹⁰³ In those cases where the attraction is the dominant contribution, it is common practice to model the protein-protein interaction using the so-called HCAY potential.^{5, 13,22, 104–106} This potential can be written as follows,

$$u_{\rm HCAY}(r) = \begin{cases} \infty & r < \sigma \\ -\epsilon \sigma \frac{\exp\left[-\kappa(r-\sigma)\right]}{r} & r \ge \sigma \end{cases}, \tag{1}$$

where *r* is the relative distance between particles, ϵ is the depth of the potential well, and κ is the Debye screening parameter,

$$\kappa^{-1} = \sqrt{\frac{\varepsilon_0 \varepsilon_r k_B T}{N_A e_0^2} \left(\sum_i c_i z_i^2\right)^{-1}},\tag{2}$$

where c_i and z_i are the concentration and valence of the electrolyte, respectively, ε_0 and ε_r are the dielectric constants of the vacuum and medium, respectively, k_B is the Boltzmann constant, *T* the temperature, and N_A the Avogadro's constant. The screening parameter is usually expressed in reduced units, i.e., $\kappa^* \equiv \kappa \sigma$. To simplify the notation, from now on, we omit the star.

The phase behavior of the HCAY has been extensively studied, see, e.g., Refs. 27, 90, 92, 101, 107, and 108 and references therein. It is also known that the HCAY fluid exhibits a liquid-liquid transition that is metastable with respect to the liquid-solid transition for $\kappa \ge 6.05$.^{23,109} Here, we study its phase coexistence in the interval $4 \le \kappa \le 9$; in this regime the HCAY is considered to be a short-ranged potential and the coacervation becomes metastable.¹⁰³

As we mentioned previously, the liquid-liquid phase separation in proteins can be induced by adding a non-absorbent polymer into the solution. In the simplest level of description, the protein-polymer system can be modeled as a binary mixture of hard spheres with diameters σ and σ_p , respectively. However, especially regarding simulations, the study of the phase behavior of such a two-component system is still a challenge due to the large asymmetry in size between the components. Therefore, one typically maps the complete system onto a one-component model, where the proteins interact through an effective pair potential.^{110,111} Although such depletion potential is very complex in form, i.e., it shows a successive combination of attractions and repulsions, it is usually described, for simplicity, by the AO potential,⁷¹

$$u_{AO}(r) = -k_B T \phi_p \left[(\eta + 1)^3 - \frac{3}{2} \eta (\eta + 1)^2 \frac{r}{\sigma} + \frac{1}{2} \eta^3 \frac{r^3}{\sigma^3} \right],$$
(3)

for $\sigma < r < \sigma + \sigma_p$, and 0 for larger distances. Here, $\phi_p = \frac{\pi}{6}\rho\sigma_p^3$ is the total polymer packing fraction and $\eta = \sigma/\sigma_p$ the size ratio. The magnitude of the potential depth is $\epsilon = |u_{AO}(\sigma^+)| = k_B T \phi_p (1 + 3\eta/2)$; the depletion attraction increases either with ϕ_p or η . It has been reported that for $\eta > 3.3$ the vapor-liquid transition of the AO fluid becomes metastable,⁷⁶ but for $\eta > 12.5$ seems to disappear.¹⁵ Within the AO picture, the interaction between lysozyme proteins immersed in a polyethylene glycol (PEG) solution can be described by Eq. (3) with $\eta < 1.8$. Kulkarni *et al.* investigated the phase diagram in mixtures of proteins and polymers with $\eta = 1.19, 0.48$, and 0.32.¹¹²

The aforementioned HCAY and AO interaction potentials are used as model potentials to investigate energy-driven and entropy-driven phase separation mechanisms, respectively, in colloidal or protein suspensions where the interaction range is smaller than the particle size. Recently, Noro and Frenkel demonstrated that the details of the short-ranged potentials are not significant in determining the structure and thermodynamics of such fluids.⁷⁵ Consequently, they suggested that all features of each short-ranged potential could be condensed into only three quantities ($\sigma_{\rm eff}, \epsilon, B_2^*$) easily calculated from the potential; $\sigma_{\rm eff}$ is an effective diameter that accounts for the repulsion contribution of the potential at short-distances and ε is the depth of the potential well. They also defined the range of an arbitrary attractive potential to be equal to the range of the equivalent SW fluid that yields the same B_2^* at the same reduced temperature $T^* = k_B T/\epsilon$.⁷⁵ Therefore, the HCAY and AO can crudely be represented by the well-known square-well potential,⁸⁷

$$u_{SW}(r) = \begin{cases} \infty & r < \sigma \\ -\epsilon & \sigma \le r \le \lambda\sigma \\ 0 & r > \lambda\sigma \end{cases}$$
(4)

where ϵ is the strength of the attraction. This is a potential with a simple mathematical structure, however, it does not provide physical information about the mechanism that leads to the phase separation of matter.

Noro and Frenkel also showed that the knowledge of the potential alone should then be sufficient to predict the topology of the phase diagram. Thus, the so-called Noro-Frenkel's extended law of corresponding states mentions that all fluids with short-ranged spherically symmetric attractive interactions should exhibit the same properties when compared at the same values of (ρ^*, T^*, B_2^*) ,⁷⁵ where $\rho^* \equiv \rho \sigma^3$ is the reduced density. However, Gazzillo has recently proven that the Noro-Frenkel's extended law cannot be applied to vanishing attraction range for the HCAY, since its exact second virial coefficient diverges in such a limit,¹⁰⁴ see also references therein. A similar conclusion has been drawn recently by Mier y Terán and Alejandre.¹¹³

Despite the fact that, according to Gazzillo,¹⁰⁴ the HCAY potential, given by Eq. (1), does not reduce to the adhesive hard-sphere potential in the limit $\kappa \to \infty$ and, furthermore it cannot be mapped to a SW of finite range, it has been shown that the Noro-Frenkel's scaling through the equality of B_2 meets the requirements of the extended law of corresponding states for ranges out of the sticky limit. Therefore, such a scaling is here applied to obtain the potential parameters of both HCAY and AO fluids (see Figure 1) by assuming that $B_2^* = -1.5$ at the critical point.⁷⁵ As becomes evident from Figure 1, the functional dependence of κ and η versus λ is the same. This fact is of crucial importance for the understanding of the similarities in the phase behavior of the different fluids investigated here. This point, a scaling analysis of both the phase diagram and the critical points, and explicit comparison with experimental data of lysozyme proteins are provided further below.

B. Monte Carlo computer simulation techniques

We study the phase coexistence by means of Monte Carlo computer simulations. In particular, we use the so-called Gibbs ensemble technique originally proposed by Panagiotopoulos⁹⁴ and the canonical ensemble method developed by Chapela *et al.*¹⁰⁰ together with the replica exchange method.^{95,96,99}

In our Gibbs ensemble simulations, we initially place 1720 particles uniformly distributed in a cubic box that is divided into two equal volumes. Then, we perform the following operations: displacement of particles, exchange of volume and particle exchange between the boxes. One Monte Carlo cycle consists of performing randomly the aforementioned operations at the ratio of 200:1:800. We use 5×10^5 Monte Carlo cycles to equilibrate the system and 5×10^5 production cycles. The acceptance ratio for both particle displacement and volume changes was fixed to 50%.

To apply the canonical ensemble method, we construct a parallelepiped whose dimensions are $L_x = L_y$ and $L_z = 10L_x$, where L_i with i = x, y, z is the edge in the *i*-direction. In the center of the box, we place particles in a dense phase (phase I), surrounded by a more diluted phase (phase II). We then distribute 2500 particles in the box in such a way that the reduced total bulk density is always $\rho^* > 0.4$ to obtain a smoother density profile. The densities in the dense and diluted phases are $\rho_I^* > 0.8$ and $\rho_{II}^* < 0.1$, respectively. To accelerate the equilibration process, we execute the following two steps: (i) The dense phase is artificially separated from the dilute phase by imposing separating hardwalls that avoid the interaction with particles in the dilute phase and equilibrated as a fluid of hard-spheres. (ii) We then switch on the interaction potential and remove the artificial walls that separate both phases. Then, we choose a particle: it can be either displaced in the standard way or placed at a random position; this kind of operation was proposed by Lomakin et al.⁸³ The acceptance ratio of standard particle displacement is fixed to 30%. One cycle consists of 2500 attempts of particle displacements and 1000 attempts of particle deletion and subsequent insertion. Our equilibration process consists of 400 MC cycles of the first step and



FIG. 2. Density profile and the corresponding snapshot for a HCAY fluid with $\kappa = 4$ and $T^* = 0.49$ obtained by applying the canonical method,¹⁰⁰ which is discussed explicitly in Sec. III.

30 000 MC cycles of the second one. Averages are obtained through 40 000 MC cycles. The density profile, $\rho(z)$, is measured every 5 cycles in the center of mass of the system. Coexistence densities are estimated by fitting the density profile to a tanh function.¹⁰¹ To illustrate this simple method, Figure 2 shows a density profile and a snapshot of the HCAY fluid at $T^* = 0.49$ for $\kappa = 4$.

The replica exchange method is implemented as follows. Given our system of interest S_1 at a reduced temperature T_1^* , we construct a set of non-interacting replicas $\{S_i\}$ with the same properties as the original system, but at different temperatures. Temperatures of each replica are chosen in such a way that $T_1^* < T_2^* < \cdots < T_n^*$. In each system, we move the particles according to the conventional Monte Carlo scheme and eventually attempt to interchange the particle configurations between replicas. The acceptance probability of a configuration swap between systems S_1 and S_2 is given by¹¹⁴

$$p = \min\left(1, \exp\left[(\beta_i - \beta_{i+1})\left(U\left(\mathbf{r}_i^N\right) - U\left(\mathbf{r}_{i+1}^N\right)\right)\right]\right), \quad (5)$$

where $\beta_i = 1/(k_B T_i)$ and $U(\mathbf{r}_i^N)$ is the total potential energy of system S_i . The choice of the temperature range must ensure that the system at the highest temperature is out of the region of local minima or metastable states, i.e., the highest temperature must lie in the regime where no liquid-vapor transition is expected. The number of replicas is chosen so that the value of the acceptance ratio of configuration swaps is around to 20%.¹¹⁵ The implementation of the replica exchange method is straightforward. We construct 30 replicas of our system and modify our initial definition of a Monte Carlo cycle by including configuration swaps; in each cycle we attempt 20 system swaps. We choose the temperatures of the systems in such a way that the temperature difference between adjacent systems is constant.

To estimate the critical point, we use a scaling type law and the law of rectilinear diameters. According to this procedure the critical point parameters ρ_c and T_c are fitted to the following equations:¹¹⁶

$$\rho_l^* - \rho_v^* = C_1 \big(T_c^* - T^* \big)^{\beta}, \tag{6}$$

$$\frac{\rho_l^* + \rho_v^*}{2} = \rho_c^* + C_2 \big(T_c^* - T^* \big), \tag{7}$$



FIG. 3. Schematic representation of a hard-core attractive potential (solid line). It can be approximated by a sequence of square-wells and square-shoulders. The details of the discretization are discussed explicitly in the text.

where ρ_l^* and ρ_v^* are the coexisting liquid and vapor densities, respectively, at given temperature T^* , the critical exponent $\beta = 0.325$, and C_1 and C_2 are two further fit parameters.

C. Discrete perturbation theory

In the DPT (Ref. 86) a given potential u(r) is approximated through its discrete version, $u^{\text{DIS}}(r)$, given by a sequence of SW and square-shoulders (SS). Mathematically, the discrete potential can be written as follows:⁸⁶

$$u^{\text{DIS}}(r) = u^{\text{HS}}(r) + \sum_{i=1}^{n} u_i^S(r),$$
(8)

where $u^{\text{HS}}(r)$ is the hard-sphere potential, *n* is the number of steps forming the discrete potential, and

$$u_i^{S}(r) = \begin{cases} \epsilon_i & \lambda_{i-1}\sigma \le r < \lambda_i\sigma \\ 0 & \text{otherwise} \end{cases},$$
(9)

is the potential in each step *i*, with i = 1, ..., n. A schematic representation of the discrete potential is displayed in Figure 3.

The reduced excess Helmholtz free-energy, $a = A/Nk_BT$, for a system of spherical particles interacting via a discrete potential is given by,⁸⁶

$$a = a^{HS}(\phi) + \beta \sum_{i=1}^{n} \left[a_{1}^{S}(\epsilon_{i}, \lambda_{i}; \phi) - a_{1}^{S}(\epsilon_{i}, \lambda_{i-1}; \phi) \right] + \beta^{2} \sum_{i=1}^{n} \left[a_{2}^{S}(\epsilon_{i}, \lambda_{i}; \phi) - a_{2}^{S}(\epsilon_{i}, \lambda_{i-1}; \phi) \right],$$
(10)

where A is the total free energy, N is the number of particles, ϕ is the packing fraction, $\beta = 1/k_BT$; $a^{HS}(\phi)$ is the reduced Helmholtz free-energy of the reference system; which is given by the Carnahan-Starling equation of state,¹¹⁷

$$a^{\text{HS}}(\phi) = \frac{\phi(4-3\phi)}{(1-\phi)^2}.$$
 (11)

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The terms a_1^S and a_2^S are the first and second-order perturbation terms, respectively, for a SW ($\epsilon_i < 0$) or SS ($\epsilon_i > 0$), see Refs. 118 and 119. The perturbation terms are closely linked to simple relations,⁸⁶

$$a_1^{SW}(\epsilon,\lambda;\phi) = -a_1^{SS}(\epsilon,\lambda;\phi), \qquad (12)$$

$$a_2^{SW}(\epsilon,\lambda;\phi) = a_2^{SS}(\epsilon,\lambda;\phi).$$
(13)

From the reduced Helmholtz free energy expression, all thermodynamic properties can be straightforwardly obtained, such as the reduced pressure $P^* \equiv P\sigma^3/\epsilon$ and the reduced chemical potential $\mu^* \equiv \mu/k_B T$,¹²⁰

$$P^* = \rho^* T^* Z, \tag{14}$$

$$\mu^* = a + Z, \tag{15}$$

where the compressibility factor, Z, is defined as,

$$Z = \phi \left(\frac{\partial a}{\partial \phi}\right)_{T,V}.$$
 (16)

The equilibrium coexistence between two phases, I and II, is established by solving the following simultaneous equations:

$$P^*(\rho_I^*, T^*) = P^*(\rho_{II}^*, T^*), \tag{17}$$

$$\mu^*(\rho_I^*, T^*) = \mu^*(\rho_{II}^*, T^*).$$
(18)

Furthermore, in order to apply the DPT to an arbitrary potential it is necessary to use an accurate expression for the Helmholtz free energy SW first and second-order perturbation terms. In this work, we restrict our attention to short-ranged potentials, so we use expressions from the square-well equation of state (SWEOS) proposed by Espíndola *et al.*¹²¹ We denote in this work by ESPSW the second-order version of this SWEOS. We should point out that the use of ESPSW in the DPT approach imposes a natural restriction to the grid size employed in the discretization procedure of the interaction potential.

1. DPT for the hard-core Yukawa potential

Recently, the DPT has been applied to the study of thermodynamic properties of both hard-core repulsive Yukawa (HCRY) and HCAY fluids, respectively.^{90,92} In particular, authors focused on both the case of long-ranged interactions, i.e., $0.1 < \kappa < 4$, and the discretization details of the continuous part of the potential. They concluded that the DPT works well for the considered regime of κ , but its performance improves as κ decreases, i.e., for long-ranged interactions. In this work we extend the applicability of this approach by considering short-range attractions, i.e., $\kappa > 4$.

The inclusion of continuous potentials into the DPT for colloidal suspensions is the same as the one used in the context of simple liquids.⁹⁰ As we observe directly from Eq. (1),

the HCAY potential is radially symmetric, i.e., it is only a function of the particle separation *r*. The potential parameters are κ and ϵ . The former is directly related to the range of the potential and the latter corresponds to the well depth. In order to discretize the HCAY potential, we construct a succession of steps *i* of width 0.1 σ and depth $\epsilon_i < 1$; the depth is chosen as the potential at the middle point of the step (see Figure 3). We truncate the potential at a distance where the potential is smaller or equal to 10^{-6} according to the rules given explicitly by Torres *et al.*⁹⁰ After this, one can proceed to calculate the phase coexistence as explained above.

2. DPT for the Asakura-Oosawa potential

The AO interaction potential possesses also spherical symmetry. This allows us its natural inclusion within the DPT formalism. In particular, the attraction strength of the AO potential is a function of both the polymer concentration, ϕ_p , and the size ratio, η (see Eq. (3)). For the sake of the discussion, we define here the magnitude of the well depth as $\epsilon \equiv k_B T \phi_p (1 + 3\eta/2)$, which corresponds to $\epsilon = -u_{AO}(r = \sigma^+)$. Then, within the AO fluid, the reduced temperature is $T^* \equiv k_B T \epsilon = (\phi_p (1 + 3\eta/2))^{-1}$.

To obtain a discrete version of the AO potential, we divide the interval $[1, (1 + 1/\eta)]$ into *n* segments of length 0.1. Values of ϵ_i are also chosen as in the HCAY (Refs. 90 and 92) case.

D. SCOZA

The SCOZA, is a microscopic liquid-state theory that has proven to yield very accurate predictions for the thermodynamics, the structural properties and the liquid-vapor coexistence curve for various systems throughout the whole temperature-density plane.^{122, 123} Comparison with computer simulations has shown, in an impressive way, that SCOZA remains successful even in the critical region and exhibits some form of scaling with non-classical, i.e., non mean-field critical exponents.¹²⁴ The main ingredient of SCOZA is the self-consistency requirement between different statistical mechanical routes from the structural to the thermodynamic properties. A detailed description of SCOZA can be found in Ref. 87, 122 and 125, so we limit our presentation here to the essential ideas.

Like all integral equation theories SCOZA is based on the Ornstein-Zernike (OZ) relation,¹²⁶

$$h(r) = c(r) + \rho c \otimes h(r), \tag{19}$$

that defines the direct correlation function c(r) in terms of the total correlation function h(r) (\otimes denotes a convolution integral). Equation (19) is supplemented with a mean spherical approximation (MSA)-type closure relation,¹²⁶

$$g(r) = 0 \qquad \text{for} \quad r < \sigma,$$

$$c(r) = A(\rho, \beta)u(r) + c_{\text{HS}}(r) \qquad r > \sigma;$$
(20)

where g(r) = h(r) - 1 is the pair distribution function, $c_{\text{HS}}(r)$ is direct correlation function of the hard-core reference system and $A(\rho, \beta)$ is a function of the thermodynamic state (ρ, β)

 β). In contrast to the MSA, where $A(\rho, \beta) = -\beta$, here $A(\rho, \beta)$ is not fixed a priori but is instead determined so that thermodynamic consistency is ensured between the compressibility and the energy route. The consistency relation is expressed as a partial differential equation (PDE),

$$\frac{\partial}{\partial\beta} \left(\frac{1}{\chi^{red}} \right) = \rho \frac{\partial^2 u^{ex}}{\partial\rho^2}.$$
 (21)

 $\chi^{red} = \rho k_B T \chi_T$ is the reduced isothermal compressibility given by the compressibility route $\frac{1}{\chi^{red}} = 1 - \rho \tilde{c}(k = 0)$, where $\tilde{c}(k)$ denotes the Fourier transform of c(r), and $u^{ex} \equiv \frac{U^{ex}}{V}$ is the excess (over ideal) internal energy per volume given by the energy equation $u^{ex} = 2\pi \rho^2 \int g(r)\phi(r)r^2 dr$. Equation (21) supplemented by the OZ relation (19), the closure relation (20), and the expressions of the compressibility and the energy route yields a PDE for $A(\rho, \beta)$ that can be re-expressed as a PDE of diffusion type for u^{ex} ,

$$B(\rho, u^{ex})\frac{\partial u^{ex}}{\partial \beta} = \rho \frac{\partial^2 u^{ex}}{\partial \rho^2},$$
(22)

with a diffusion coefficient $B(\rho, u^{ex})$. The numerical solution procedure of SCOZA used in this work is described in detail in Ref. 87.

For a long time, applications of SCOZA were rather scarce due to historical and technical reasons, the complexity of the SCOZA formalism and the heavy numerical solution algorithm, i.e., for the case of continuum fluids, applications were initially restricted to the one-component HCAY fluid. This restriction can be traced back to the fact that SCOZA originally grew out of the semi-analytic solution of the MSA for such systems. These semi-analytic expressions lead to simplifications of the numerical solution of SCOZA and a considerable reduction of computational cost. However, these restrictions are purely technical ones and not part of the concept of SCOZA. The success of SCOZA for these few model systems was the motivation for broadening its applicability.^{87,105,125,127-129} Nowadays, SCOZA is solvable for arbitrary spherically symmetric hard-core potentials, such as the AO or the SW potential. However, in these cases the determination of the diffusion coefficient $B(\rho, u)$ must be done fully numerically and comes, of course, at a substantial computational cost.

III. RESULTS

A. Phase coexistence

We now turn to the liquid-vapor phase diagram of the HCAY, AO, and SW fluids as a function of the attractive range. As expected, the phase coexistence curve is shifted to lower temperatures as the interaction range decreases. This well-known effect can be understood naively by considering that less thermal energy is required to break short-ranged forces and, then, to induce a liquid-vapor phase separation.

For the sake of simplicity, we use identical notation in all figures. Our theoretical results are displayed by solid lines (DPT) and dotted lines (SCOZA), whereas our simulation data are represented by open squares (Gibbs ensemble) and circles (canonical ensemble). We also include the results from



FIG. 4. Phase diagram of the HCAY fluid for $\kappa = 4$ and $\kappa = 6$ obtained by the DPT (solid lines), SCOZA (dotted lines and critical point denoted by a star), and computer simulations using the Gibbs (squares) and canonical (circles) ensemble techniques. We have included Barker and Henderson perturbation-type results of Tavares and Prausnitz¹⁰⁶ (dash-dotted line) and Robles and de Haro¹³⁰ (dashed line). We also show simulation results of Duda *et al.*²² (triangles) and Lomba and Almarza¹³¹ (crosses).

other authors. Then, the corresponding symbols are explained in the figure caption.

1. HCAY fluid

We show the results for $4 \le \kappa \le 9$ in Figures 4–6. As can be seen, the perturbation-like approximations reproduce qualitatively the vapor-liquid phase diagram. They predict reasonably well the critical densities and overestimate the critical temperature. SCOZA results give, in general, better predictions compared to simulations, especially regarding the critical region. In order to quantize the discrepancies of the DPT, we have calculated the relative standard deviation of each phase diagram calculated through DPT with respect to our canonical simulation data and found that for all cases this deviation is at most 15% and almost independent of κ . Additionally, it is important to mention that the DPT could be improved if better expressions for the first and second-order free-energy perturbation terms for the SW potential were provided for very short-ranges, which are currently not available. SCOZA predicts accurately the critical points up to the highest κ value considered. However, the deviations of the liquid branch increase with decreasing interaction range. This feature of SCOZA is already known from previous studies of other potentials,⁸⁷ and was found to be more or less pronounced depending on the potential under study.

Regarding our simulation data, we see that they agree with other simulation results, however, the ones obtained with the Gibbs ensemble technique show a larger deviation at the liquid branch when $\kappa = 9$, see Figure 6; it is known that this technique cannot reproduce correctly the phase coexistence for short-ranged attractive potentials, see, e.g., Ref. 101 and references therein. In addition, the estimates of the critical points by means of the canonical ensemble technique are very close to those predicted by SCOZA. It seems that such



FIG. 5. Phase diagram of the HCAY fluid for $\kappa = 5$ and $\kappa = 7$ obtained by the DPT (solid lines), SCOZA (dotted lines and critical point denoted by a star), and computer simulations using the Gibbs (squares) and canonical (circles) ensemble techniques. We have included Barker and Henderson perturbation-type results of Tuinier and Fleer¹³² (dash double dotted line), Zhou¹³³ (dash-dotted line) and Fu¹³⁴ (long dotted line). We also show simulation results of Duda *et al.*²² (triangles) and thermodynamic integration from Dijkstra²³ (long dashed line).

a technique together with the replica exchange method is an appropriate route to deal with the determination of the phase diagram of short-ranged attractive fluids.¹⁰¹

2. AO fluid

The other short-ranged potential we have considered in this work is the AO potential (see Eq. (3)). We present its liquid-vapor phase diagram (see Figures 7–11) using both DPT and SCOZA as theoretical frameworks, as well as the Gibbs ensemble and the canonical simulation schemes. As far



FIG. 6. Phase diagram of the HCAY fluid for $\kappa = 9$ obtained by the DPT (solid lines), SCOZA (dotted lines and critical point denoted by a star), and computer simulations using the Gibbs (squares) and canonical (circles) ensemble techniques. We have included Barker and Henderson perturbation-type results of Tavares and Prausnitz¹⁰⁶ (dash line) and Zhou¹³³ (dash double dotted line). We also show simulation results of Orea *et al.*¹⁰¹ (pentagons).



FIG. 7. Phase diagram of the AO potential for $\eta = 1.25$. We show theoretical predictions obtained from DPT (solid line), SCOZA (dotted line and critical point denoted by a star), and simulation results obtained from canonical (circles) and Gibbs (squares) ensembles. We compare our results with the perturbation theory (dashed-dotted line) and computer simulations (triangles) of Dijkstra *et al.*²⁴

as we know, this is the first time that AO binodal curves are obtained through the aforementioned methods. Our control parameter is the size ratio, η . In some cases, we compare our results with available data from perturbation theory,^{15,24,135} and other computer simulations.^{24,79}

For the longer ranges, $\eta = 1.25$ and 1.67 (Figures 7 and 8), the perturbation-based approximations give similar results, i.e., they reproduce the phase diagram, outside the critical region. Our simulation data (canonical and Gibbs ensemble techniques) agree with those reported by Dijkstra *et al.*,²⁴ which were obtained via thermodynamic integration, however, they predict a coexistence curve shifted to slightly lower temperatures. In both figures, we observe that our canonical simulation results are in excellent agreement with SCOZA predictions even for the critical point.

The case $\eta = 2.5$ is shown in Figure 9. Here, we observe that perturbation-like approximations reproduce the dilute phase, whereas DPT gives better predictions for the liquid branch than the other two perturbation approaches. Regarding the simulation results, as in the previous figures, all methods predict similar curves, although the route via thermodynamic integration shifts the coexistence curve to lower temperatures and the critical point to higher densities. Again, SCOZA predictions are closer to the canonical simulation results. Compared to the two previous cases $\eta = 1.25$ and $\eta = 1.67$, where the agreement of SCOZA with simulations was excellent, now small discrepancies on the liquid side become visible. Such a deviation is pronounced when the range of the attraction becomes shorter. In particular, it happens in the same region as for the HCAY fluid, see Figure 5 for $\kappa = 7$, which corresponds, approximately, to $\eta = 2.5$ according to Figure 1.

We now focus on the case $\eta = 3$ shown in Figure 10. The liquid-vapor diagram obtained by means of the DPT agrees well with the predictions of the Gibbs ensemble for the vapor branch, whereas it agrees with the liquid branch far away



FIG. 8. Phase diagram of the AO potential for $\eta = 1.67$. We show theoretical predictions obtained from DPT (solid line), SCOZA (dotted line and critical point denoted by a star), and simulation results obtained from canonical (circles) and Gibbs (squares) ensembles. We compare our results with the perturbation theory of Dijkstra *et al.*²⁴ (dashed-dotted line), Tavares and Sandler¹³⁵ (dashed-line), and computer simulations of Dijkstra²⁴ (triangles).

from the critical point obtained by the canonical ensemble simulations. As observed in the previous cases, SCOZA gives a better estimate of the coexistence region compared with the canonical method, especially the critical point is well reproduced. However, at this point we start to appreciate differences between the two simulation techniques, which are expected since in the previous case, i.e., for the attractive Yukawa fluid, deviations between both schemes become evident at $\kappa > 8$, which corresponds to $\eta > 3$ according to Figure 1. We have also included data from Ilett *et al.*¹⁵ and Bolhouis *et al.*⁷⁹ The former data are obtained with a perturbation theory that predicts a gas branch consistent with



FIG. 9. Phase diagram of the AO potential for $\eta = 2.5$. We show theoretical predictions obtained from DPT (solid line), SCOZA (dotted line and critical point denoted by a star), and simulation results obtained from canonical (circles) and Gibbs (squares) ensembles. We compare our results with the perturbation theory of Dijkstra *et al.*²⁴ (dashed-dotted line), Tavares and Sandler¹³⁵ (dashed line), and thermodynamic integration results of Dijkstra²⁴ (triangles).



FIG. 10. Phase diagram of the AO potential for $\eta = 3$. We show theoretical predictions obtained from DPT (solid line), SCOZA (dotted line and critical point denoted by a star), and simulation results obtained from canonical (circles) ensemble and the Gibbs ensemble (squares). We compare our results with the perturbation theory of Ilett *et al.*¹⁵ (dashed-double dotted line), and computer simulations of Bolhuis *et al.*⁷⁹ (diamons).

our DPT calculations, nonetheless, both the critical point and the liquid branch are shifted to larger densities, and the latter study with computer simulations also shows differences with respect to our data: the critical density is shifted to smaller densities, the critical temperature is found at lower temperatures and the coexistence curve is narrower. Such differences might be associated to the fact that the authors in Ref. 79 used a few number of particles (108) in their Gibbs ensemble simulations, i.e., due to finite-size effects. Furthermore, the predictions of the liquid branch found with the Gibbs ensemble technique start to deviate strongly from all the other calculations that independently almost agree each other and, as we already mentioned above, $\eta = 3$ almost corresponds to $\kappa \approx 8$ (see Figure 1). In addition, if both potentials share the same second virial coefficient, then one should expect the same physical properties according to the extended law of corresponding states.⁷⁵ Thus, the Gibbs ensemble seems not to provide reliable results for AO fluids with size ratios $\eta > 3$.

The phase coexistence for $\eta = 5$ and $\eta = 10$ is depicted in Figure 11. In both cases the Gibbs ensemble technique did not equilibrate. Hence, the liquid-vapor coexistence was not obtained with this method. Since for these cases the AO range is very small, the DPT is no longer used because, as it has been mentioned before, better expressions are required for the first and second-order terms for $\lambda < 1.1$. Unfortunately, up to now, such terms are not available.

For $\eta = 5$ SCOZA still provides a good estimate of the liquid-vapor transition according to our canonical simulation data, in particular, it gives a quantitative resolution of the gas branch. In the special case of $\eta = 10$, strong differences among all the theoretical and simulation results can be observed. For instance, the data reported by Dijkstra²⁴ obtained by means of perturbation theory strongly differ from the ones calculated with thermodynamic integration. However, SCOZA predictions nicely lie in the same temperature range as those of our canonical simulations. The critical



FIG. 11. Phase diagram of the AO potential for $\eta = 5$ and $\eta = 10$. We show SCOZA (dotted line and critical point denoted by a star) and simulation results obtained from canonical ensemble (circles). For $\eta = 10$, we also compare our results with the perturbation theory (dashed line) and thermodynamic integration (triangles) of Dijkstra *et al.*²⁴

temperature predicted by the different schemes is the physical quantity that shows a stronger dispersion, but the predictions for the critical density seem to agree, except that of the perturbation theory of Dijkstra.²⁴ Clearly, further refinements of the theoretical approaches are necessary to correctly calculate the phase coexistence of the AO fluid for size ratios $\eta \geq 5$.

3. SW fluid

So far we have discussed the phase behavior of systems with short-range attractions, whose driving mechanism (energetic or entropic) can be explicitly modeled by the HCAY and AO potentials, see Eqs. (1) and (3), respectively. As we stressed in the Introduction, both potentials depend on physical properties of the host medium, for example, the pH or the polymer concentration, and can be crudely represented by a simple SW. The latter one mimics the main features of the HCAY and AO potentials: a hard-core that forbids particle overlap and an attractive tail that accounts for the physical mechanism that leads to the phase separation. However, there exists no general rule to map any attractive potential onto a SW potential. This issue has been extensively discussed since the work of Noro and Frenkel.⁷⁵ Nonetheless, the simple mathematical structure of the SW potential, see Eq. (4), permits to include it in different theoretical approximations, see, e.g., Refs. 87 and 136 and references therein, to study the phase behavior of both simple and complex fluids.

Recently, we have studied the phase behavior of the SW fluid by means of different perturbation theory based on the SWEOS and SCOZA within the framework of simple liquids.⁸⁷ We demonstrated that both schemes are accurate for ranges $\lambda > 1.5$,⁸⁷ but the regime of interest in the protein domain (see Figure 1) was not studied in detail. Thus, we here analyze and, for the sake of completeness, explore the feasibility of the ESPSW and SCOZA within the context of complex fluids. We show the liquid-vapor curves of the SW fluid for interaction ranges in the interval $1.05 \le \lambda \le 1.25$ in



FIG. 12. Phase diagram of the SW potential. Solid lines correspond to ESPSW (Ref. 121) and dotted lines to SCOZA, circles and squares to simulation data in the canonical and Gibbs ensembles, respectively. We also show simulation results of Pagan and Gunton¹³⁷ (diamonds), Duda¹⁰ (triangles), Lomakin *et al.*⁸³ (inverted triangles), Largo *et al.*¹³⁸ (pentagons), and theoretical results of Rosenbaum *et al.*⁸⁵ (dashed line).

Figure 12. As can be seen, our NVT results agree with previous simulation data obtained by different methodologies.^{10, 83, 137, 138}

The ESPSW overestimates the critical point parameters, especially the temperatures, but provides a good estimate for the critical densities. Besides, the observed deviations become more important as the attractive range decreases, however, for all ranges considered we find that relative standard deviation is less than 10% (data not shown), i.e., the deviation does not depend on the range.

Finally, SCOZA describes correctly the phase behavior down to $\lambda = 1.15$, including the critical point and the gas branch, but it fails for shorter ranges. This feature of SCOZA, which does not occur to this extent for the other potentials studied with SCOZA up to now was discussed in more detail in Ref. 93. Whether this is related to the fact that the SW potential is in contrast to all the other potentials studied with SCOZA—including the Yukawa,^{27, 101, 122, 127} the Sogami-Ise,¹²⁵ the triangular¹²⁹ and the AO potential—the only discontinuous function is still unclear.

B. Critical points and extended law of corresponding states

The thermodynamic properties for some real substances can be described by a set of universal equations; this was pointed out by Pitzer¹³⁹ and Guggenheim¹⁴⁰ in the so-called law of corresponding states. Physical quantities, such as vapor pressure, Boyle point, liquid-vapor coexistence curve, among others, take a constant value or fall onto one master curve when they are expressed in terms of the critical values of temperature, density, and pressure. By means of molecular simulations, Noro and Frenkel⁷⁵ have recently shown that the critical temperature, expressed in terms of the sticky parameter, τ , which was introduced by Baxter,¹⁴¹ takes a constant



FIG. 13. Binodal curves expressed in terms of B_2^* (left-axis) or τ (right-axis) obtained from the canonical simulations for the HCAY fluid; $\kappa = 4$ (solid squares), 5 (solid circles), 6 (solid triangles), 7 (solid inverted triangles), 9 (solid diamonds), the AO fluid; $\eta = 1.25$ (left triangles), 1.67 (right triangles), 2.5 (hexagons), 3 (stars), 5 (pentagons), 10 (asterisks), and the SW fluid; $\lambda = 1.25$ (empty squares), 1.20 (empty circles), 1.15 (empty triangles), 1.10 (empty inverted triangles), 1.05 (empty diamonds). Dashed lines are a guide to the eye.

value for several short-ranged attractive systems. This means that the critical point does not depend on the specific form of the interaction potential, but only on the strength of the attraction, which can be measured through the second virial coefficient, B_2 .

The reduced second virial coefficient or sticky parameter as a function of ρ/ρ_c at the liquid-vapor coexistence obtained from the canonical simulations for all fluids studied here is shown in Figure 13. One should note that the representation of the phase diagram in terms of either B_2^* or τ seems to follow a universal behavior regardless of both the functional form and the range of the potential. Taking into account that the functional form of the interaction potential (either AO or HCAY) is related to the physical mechanism, i.e., entropic or energetic, that drives the phase separation one comes to the conclusion that the topology of the equilibrium coexistence of colloidal suspensions with short-ranged attractive interactions does depend neither on the physical mechanism nor the attractive range. In particular, from the figure it becomes visible that $B_2^*(T_c^*)$ and $\tau(T_c^*)$ show a slight variation as the critical temperature is reached; $-1.6 < B_2^*(T_c^*) < -1$ or $0.096 < \tau(T_c^*) < 0.116$. Therefore, the extended law of corresponding states can be used as a simple predictor for the critical temperature for a variety of short-ranged potentials by solving the following equation:

$$\tau(T_c^*) \approx 0.1. \tag{23}$$

One of the corollaries deduced from the extended law is the possibility of mapping among different potentials by matching their corresponding second virial coefficients, see, e.g., Ref. 75. This possibility is displayed in Figure 14, which shows the reduced critical temperature of both HCAY and AO potentials as a function of the corresponding attraction range if we use the correspondence of the potential parameters η and κ according to Figure 1. We can observe that the simu-



FIG. 14. Critical temperature as a function of the interaction range for the HCAY and AO fluids. Open and closed symbols are simulation data obtained from the canonical method, respectively, whereas dotted and solid lines are results of SCOZA and ESPSW, respectively.

lation data predict the same linear relationship, regardless of the kind of interaction potential, which is also predicted by SCOZA. DPT also predicts a linear dependence for both potentials down to the interaction range where the discretization of the potential leads to a single-well. Therefore, for shorter interaction ranges ESPSW deviates from the linear dependence and lower critical temperatures are predicted (data not shown) because, as we explicitly mentioned, ESPSW has not been extended to ranges $\lambda < 1.1$. However, above such a point, it predicts the same physical properties for both potentials, i.e., ESPSW satisfies the extended law although its predictions for the critical temperature are shifted to higher temperatures compared to simulation data and SCOZA results. From practical point of view, it is useful to have some empirical relationships to determine the critical temperature from the potential parameters. Thus, by fitting all the available simulation data, the range-dependence of the critical temperature for the HCAY fluid is $T_c^* = 0.190(5) + 1.586(26)\kappa^{-1}$, and for the AO fluid is $T_c^* = 0.201(3) + 0.656(6)\eta^{-1}$.

In the previous paragraph, we noticed that canonical simulations and SCOZA predict the same linear relationship for the critical temperature for both the AO and Yukawa fluid as a function of the interaction range if we use the mapping of Figure 1 for the correspondence of the parameters η and κ , i.e., our results validate the corollary of the extended law of corresponding states. Thus, we can look for an equivalent SW potential, since it allows us to define quantitatively an effective attraction range. For this purpose, it is necessary to solve the following equation:

$$\lambda^{3} = 1 - 3 \frac{\int_{0}^{\infty} [1 - e^{-u(r^{*})/k_{B}T_{c}}]r^{*2}dr^{*}}{1 - e^{\varepsilon/k_{B}T_{c}}},$$
(24)

where $r^* \equiv r/\sigma$ and T_c can be estimated with Eq. (23).



FIG. 15. Critical temperature as function of the effective interaction range λ obtained from Eq. (24) for the HCAY, AO, and SW potentials. The critical temperature has a quasi-linear dependence on λ for all types of fluids here studied.

The critical temperature as a function of the effective attraction range calculated by means of Eq. (24) is displayed in Figure 15. We compare our calculations for all the data available for the HCAY, AO, and SW potentials. As one can notice, all the data fall more or less onto one line independent of the functional form of the interaction potential. The range-dependence of the critical temperature is $T_c^* = 0.289(1) + 1.961(59)(\lambda - 1)$. Hence, Eqs. (23) and (24) provide a good estimate of the critical temperature and the range of the effective attraction of a fluid where the attractive contribution dominates and leads to a phase separation.

C. Comparison with experimental data for lysozyme

One of the more used potentials for describing the phase behavior of a protein in suspension is the Derjaguin, Landau, Verwey, and Overbeek (DLVO) potential; this potential includes three kinds of interaction between particles: hard-core repulsion, due to the excluded volume; a short-ranged attraction, given by the London forces, i.e., van der Waals interactions, and a long-ranged interaction, which results of the repulsion between the charged components of the system. Clearly, the resulting potential is a complicated relation between the properties of the protein and its medium. However, despite the complexity of the protein-protein potential, it is possible to find a qualitative description of it. In fact, when the repulsion is weak and the attraction dominates, it is possible to represent crudely the interaction potential in terms of a HCAY fluid, see, e.g., Ref. 103.

Recently, Gögelein *et al.*¹⁰³ studied, by means of both static light scattering and a second-order thermodynamic perturbation theory of Barker and Henderon, the liquid-vapor and liquid-solid transitions of lysozyme in aqueous environments as function of salt, dimethyl sulfoxide (DMSO) and glycerol. Authors found the following simple, but important, relations for the protein-protein potential: the potential is attractive for interparticle separations greater than the mean diameter, the



FIG. 16. Vapor-liquid coexistence expressed in terms of B_2^* for lysozyme¹⁰³ for different salt concentrations (filled symbols) and Monte Carlo simulations (open symbols) for the HCAY fluid with variable range, κ . Solid lines are a fit for the liquid and gas branches based on the Eqs. (6) and (7). For clarity, the experimental curve for $\kappa = 6$ is shifted 0.45 units in the vertical direction upwards.

salt concentration (c_s) controls the width and depth of the potential (see Figure 3 of Ref. 103), and the glycerol concentration (c_g) determines the potential width (see Figure 5 of Ref. 103).

Gögelein *et al.*¹⁰³ reported the phase diagram in terms of the reduced second virial coefficient (see Figure 10(a) in Ref. 103), which was obtained by using static light scattering. In the vapor-liquid coexistence, they found a curve with the same characteristics that we observed in Figure 13, i.e., B_2^* does not depend strongly on the attractive range and $B_2^*(T_c^*) \approx -1.8$ in almost all the cases. This value is slightly greater than the one predicted by Noro and Frenkel⁷⁵ ($B_2^*(T_c^*) \approx -1.5$). Then, the experimental data will be shifted to compare with our predictions, but this does not affect the main conclusions of our work. Furthermore, authors¹⁰³ showed that the protein-protein potential can be mapped onto a HCAY fluid in the interval $4 \le \kappa \le 9$ (see Figure 8 of Ref. 103). Thus, for a direct comparison between experimental data and simulation results we use the same strategy.

A comparison of the lysozyme phase diagram for $c_s = 0.7$ and 0.9, no additive is added, with the one obtained for the HCAY fluid with $\kappa = 6$ and 9, respectively, is shown in Figure 16. For the sake of the comparison, the experimental curve for $\kappa = 6$ is shifted 0.45 units in the vertical direction upwards. We can immediately observe a quantitative agreement between experiments and simulations. Besides, it becomes clear that the effect of salt is to screen the interaction, i.e., an increase in the parameter κ . In addition, the vapor phase does not modify considerably with the change in the salt concentration, however, an increase of salt shifts the liquid boundary to higher densities. Both effects are also captured by our computer simulations.

To compare our predictions with the experimental data that include explicitly glycerol, we ignore the shape of the potential and only take into account the attraction range replacing the full potential (see Ref. 103) by a simple SW potential.



FIG. 17. Vapor-liquid coexistence expressed in terms of B_2^* for lysozyme at 0.7 M of salt and different concentrations of glycerol (filled symbols) and Monte Carlo simulations for the SW fluid with variable range, λ . Solid lines are a fit for the liquid and gas branches based on the Eqs. (6) and (7). For clarity, experimental curves are also shifted 0.3 ($c_g = 0\%$), 0.45 ($c_g = 10\%$), and 0.6 ($c_g = 20\%$) units in the vertical direction upwards.

As we stated previously, the SW can reproduce some of the properties of complex fluids and allows us to manipulate the effective range and strength. The comparison of the binodal of the SW of variable range with the experimental data for the cases $c_s = 0.7$ and variable glycerol concentration (c_g) is provided in Figure 17; experimental curves are also shifted 0.3 $(c_g = 0\%)$, 0.45 $(c_g = 10\%)$ and 0.6 $(c_g = 20\%)$ units in the vertical direction upwards. Again, a good agreement between experiments and simulation predictions is observed, including the critical point. The figure shows that the effect of glycerol is to decrease the potential range among the proteins. This affects particularly the extension of the liquid branch.

Hence, we here put of manifest that even for complex systems, such as the solution of lysozyme proteins, the particular functional form of the potential is not important to determine the liquid-vapor phase diagram, i.e., driving forces lead to the same phase coexistence. Furthermore, the second virial coefficient is a good indicator of the equilibrium coexistence and Figure 15 is one of the more important results of this work, since whether the critical temperature is known, it provides straightforwardly information of both the well depth and the effective range of the attraction.

IV. CONCLUSIONS

We have studied theoretically the phase behavior of colloidal systems. In particular, we investigated the gas-liquid coexistence in the short-range regime. As model systems we considered the hard-core attractive Yukawa and Asakura-Oosawa fluids, which were mapped onto equivalent SW fluids of appropriate range λ , within the regime 1.05 < λ < 1.25. We have confirmed that the coexistence curve is more or less independent of the detailed functional form of the interaction, but just depends on the value of the second virial coefficient, B_2 . Thus, interestingly, both driving forces, i.e., energy and entropy, lead to the same phase behavior. We have also compared our theoretical results with experimental data for lysozyme proteins and obtained excellent agreement. This indicates that although a protein solution is a very complex system, some of its thermodynamic properties can be quantitatively understood in terms of the physics of colloids. This is of scientific and technological importance, since predictions based on simple physical models are beneficial for the design, synthesis and control of processes involving proteins.

Our calculations were based on both computer simulations and theoretical approximations. We have found that the Gibbs ensemble does not provide reliable results for simulating short-range fluids. In particular, we observed strong deviations with respect to other simulation data in the interval κ > 9 or η > 3, which, in terms of the equivalent SW fluid, corresponds to attractions of range $\lambda < 1.1$. However, the canonical ensemble method provided us a powerful and simple route to evaluate the vapor-liquid coexistence without encountering the problems associated with the range of the attraction. We have also found that the theoretical approaches, i.e., the DPT and SCOZA, work well in the colloidal domain; in particular, SCOZA was able to predict—compared to simulation dataaccurate phase diagrams even in the critical region and it allowed us to evaluate correctly the λ -dependence of the critical temperature. In contrast to the SW fluid, where the SCOZA predictions turned out to deteriorate for shorter ranges of the interaction, SCOZA remained accurate for the AO and the HCAY fluid down to the smallest ranges considered. In addition, we observed that the DPT is only limited by the use of the chosen equation of state, since it is related to the grid size employed to resolve the phase coexistence. As we stated in the Introduction, the DPT is a second-order perturbation theory that was originally proposed to study the phase behavior of simple liquids. Despite its simplicity, we have shown here that it can also be extended straightforwardly to the domain of complex fluids. Furthermore, it has been recently generalized to take into account explicitly polar interactions.⁸⁹ Hence, it is an ideal candidate to investigate the liquid-solid transition in both colloidal and protein systems. Work along this direction is currently in progress.

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