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Phase transitions in hard-core Yukawa fluids: toward a theory of phase stability in protein solutions

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Abstract. Thermodynamically self-consistent integral equation theories (TC-IETs) supplemented by a one-phase freezing criterion, and Monte Carlo simulations, are used to investigate the thermodynamic and structural properties, as well as the phase diagram, of the hard-core Yukawa fluid (HCYF). The attention is focused on rapidly decaying Yukawa tails, a potential regime suited to model in an approximate manner the interaction between globular proteins in protein solutions. TC-IETs are found to give a reasonably accurate description of the physical properties of the HCYF in this limit. The position of the sublimation line relative to the liquid–vapour binodal line, known to play a crucial role in the onset of crystallization in protein solutions, seems qualitatively reproducible. We suggest on this basis the possibility of extending the use of TC-IET to more realistic models of protein solutions, so as to take into account the true multicomponent nature of these fluids, a physical situation whose description still challenges the currently available computer simulation capabilities.

In recent years a considerable number of papers have appeared reporting theoretical and simulation studies of model protein solutions (see [1–3] and references therein). The reason for such interest essentially stems from the problem of protein crystallization, a phenomenon whose predictability and control still seem far from being achieved [4].

Both theory and simulation rest however on a modelling of the system which is far from being trivial; in fact, the interparticle interactions strongly depend on the instantaneous configuration in which the macromolecules interact with the surrounding medium. It is commonly accepted, however, that at least for globular proteins the effective interaction can be roughly approximated as a strongly repulsive potential at short range plus a rapidly decaying and attractive tail [1, 3]. Simulations of such a system have recently been performed by various authors [3, 5, 6] and they have shown [3] that the most favourable conditions for crystal nucleation and growth should occur when the sublimation line of the fluid passes a few degrees above the (metastable) critical point [3, 7] of the liquid–vapour binodal line.

Now it is well known that the simulation of a system in which strong attractive forces are present may be affected by ergodicity problems. Moreover, an extension of the simulation approach to the more realistic case in which proteins, solute ions and water molecules are present does not seem easily feasible due to the strong size asymmetries of the particle species and to the (usually) high dilution of the macromolecules.

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Such a state of affairs makes desirable the availability of an accurate theoretical approach, able to predict, even roughly, the phase behaviour of the system under consideration.

We have recently undertaken an extensive investigation of the performances of a number of fluid-state theories for short-ranged potentials [8]. In this paper we report and discuss the predictions of these theories that can be relevant for the phase behaviour of protein solutions. In particular, we give results for the liquid–vapour binodal and for the freezing line of the system as obtained through the adoption of a one-phase freezing criterion due to other authors [9]. We also report the results of extensive Monte Carlo (MC) simulations which enable us to assess the performances of the theories in the estimation of various thermodynamic and structural quantities of interest.

We consider a fluid composed of hard-sphere particles of diameter σ , interacting through an attractive Yukawa tail; the interparticle potential is thus written as

$$v(r) = \begin{cases} \infty & r < \sigma \\ -\sigma\epsilon \exp[-\lambda(r - \sigma)]/r & r \geq \sigma. \end{cases} \quad (1)$$

The properties of this model fluid are calculated within the modified hypernetted-chain (MHNC) [10] approximation, and the generalized mean-spherical approximation (GMSA) [11, 12]. We refer the reader to references [10–13] for the details of these two theories. We merely recall that both the MHNC and the GMSA can be rendered thermodynamically self-consistent by means of some adjustable parameters. In the MHNC case, we use with this aim the hard-core diameter entering the Percus–Yevick bridge function (adopted as an approximate bridge function) in such a way as to satisfy the requirement of equality between the virial and fluctuation compressibility, namely

$$\left(\beta \frac{\partial P^{vir}}{\partial \rho} \right)_{T, \rho} = 1 - \rho \tilde{c}(q = 0). \quad (2)$$

Here $\tilde{c}(q = 0)$ is the $q = 0$ limit of the Fourier transform of $c(r)$.

In the GMSA the consistency parameters K and z , entering the Yukawa function in terms of which the GMSA closure for the direct correlation function

$$c(r) = -\beta v(r) + K \exp[-z(r - \sigma)]/r \quad r \geq \sigma \quad (3)$$

is written, are used so as to satisfy condition (2) and also

$$-\left(\frac{\partial F}{\partial V} \right)_T^U = P^{vir}. \quad (4)$$

The left-hand side of (4) is the pressure obtained from the energy route by differentiating the Helmholtz free energy F ; the latter is in turn obtained from the configurational energy U^{ex} through standard thermodynamic integration along an isochore path [14].

The solution of the GMSA under conditions (2) and (4) is obtained by us numerically. The same theory has however also been solved in a semianalytic manner by other authors [15].

Finally, we shall make a comparison with some recent results obtained elsewhere [8, 16, 17] in the self-consistent Ornstein–Zernike approximation (SCOZA) of Høye and Stell [18].

We shall measure the distance r in units of σ and the temperature T , the density ρ and the pressure P in units of ϵ/k_B , σ^{-3} and ϵ/σ^3 , respectively.

Theoretical results for the excess energy per particle, the equation of state and the isothermal compressibility are compared with the MC data at two different λ -values in figures 1 and 2.

The MHNC energies are quite accurate for both of the λ -values considered; the GMSA energies are reasonably good at $\lambda = 4$ and show a 10% maximum discrepancy from the MC

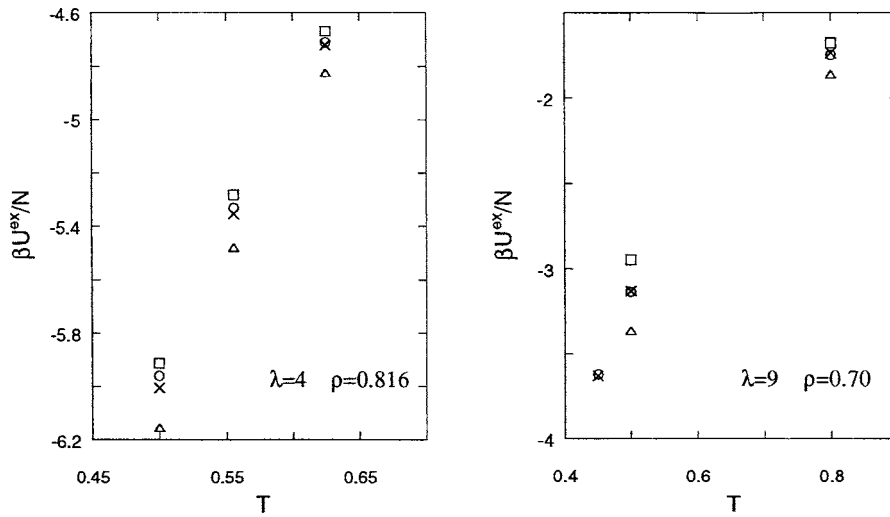


Figure 1. The excess internal energy per particle (in units of $k_B T$) versus the reduced temperature (note the different vertical scales in the two panels). Symbols: circles: MHNC; triangles: GMSA; squares: SCOZA; crosses: MC simulations.

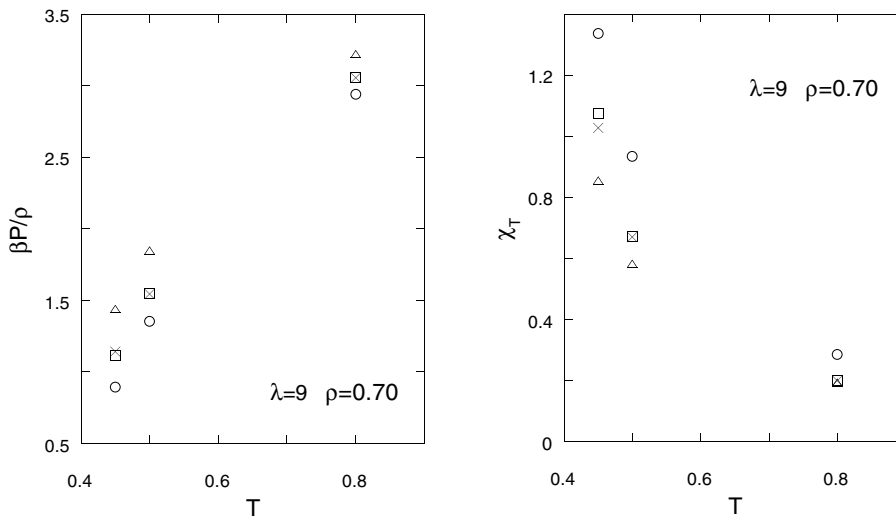


Figure 2. The equation of state (left) and compressibility (right) versus the reduced temperature. The key to the symbols is as for figure 1.

data at the highest λ . The MHNC and GMSA equations of state and compressibilities, here displayed for the most short-ranged potential case, are also within 10% of the MC result at temperatures that are not too low. The SCOZA results for the equation of state are quantitatively accurate at all temperatures considered. Other results, not reported here, show that at lower λ -values all of the theories become practically quantitative.

Results for the structural function are shown in figure 3. The MHNC radial distribution

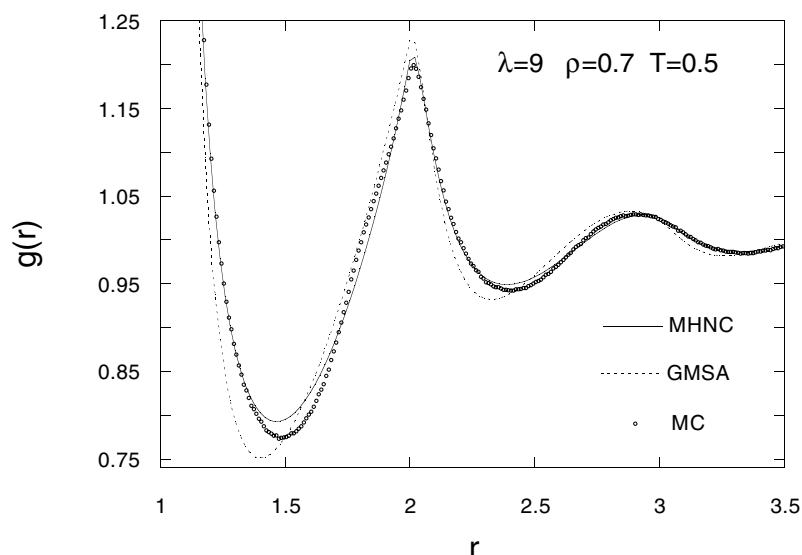


Figure 3. The radial distribution function for the HCYF at $\lambda = 9$. For the thermodynamic state point and symbols, see the body of the figure.

function compares quite well with the simulation result; the GMSA pattern somewhat underestimates the positions of the main features, with a trend towards losing the phase at large distances, but it appears on the whole qualitatively accurate. We have also calculated the GMSA structure factor and find that this compares quite well with the MHNC $S(q)$ except at very small wave vectors.

We then studied the phase diagram of the HCYF. The liquid–vapour binodal line has been determined by calculating the chemical potential at low and high density and by equating the two values at equal temperatures according to standard procedures. We have also monitored the behaviour of the multiparticle residual entropy [9], defined as

$$\Delta s \equiv s_{ex} - s_2 \quad (5)$$

where s_{ex} is the excess entropy per particle of the system, in units of the Boltzmann constant, and

$$s_2 = -\frac{1}{2}\rho \int \{g(r) \ln[g(r)] - g(r) + 1\} dr. \quad (6)$$

As originally found and discussed in reference [9], the vanishing of Δs can act as a quite sensitive indicator of the freezing transition, as we were able to specifically verify in our previous work [8] at $\lambda = 1.8$ and 4. Here we focus our attention on the $\Delta s = 0$ locus at higher λ -values, where the position and appearance of this line closely resembles those of the fluid–solid (sublimation) line obtained from simulation studies.

Results for the binodal line and the $\Delta s = 0$ loci are reported in figures 4 and 5. We see that at $\lambda = 7$ the GMSA binodal and the $\Delta s = 0$ locus do correctly reproduce the location of the Gibbs ensemble MC binodal relative to the sublimation line. The GMSA liquid–vapour coexistence line is however only qualitatively good; moreover, the numerical algorithm used for solution of this theory encounters some difficulties in the intermediate-density region where, in fact, we have to interpolate our results. SCOZA results for the binodal are however available [8] and look fairly good; such an accuracy seems useful for the investigation of the highest ($\lambda = 9$)

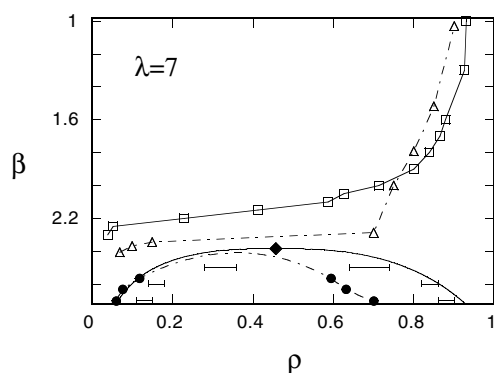


Figure 4. The phase diagram for the HCYF at $\lambda = 7$. Liquid–gas coexistence: horizontal bars: Gibbs ensemble MC results (reference [5]); continuous line: SCOZA; black circles: GMSA. $\Delta s = 0$ locus: triangles: GMSA; continuous line with squares: the sublimation line of reference [5]; the dashed lines in the figure are guides for the eye.

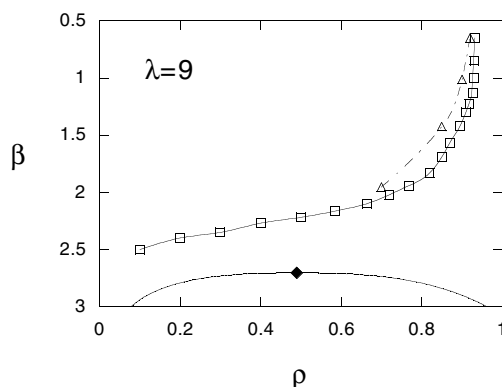


Figure 5. The phase diagram for the HCYF with $\lambda = 9$. Liquid–gas coexistence: continuous line: SCOZA (reference [16]). $\Delta s = 0$ locus: triangles, GMSA; continuous line with squares: the sublimation line of reference [5]. Dashed lines in the figure are guides for the eye.

case, where no simulation results are available. As can be seen in figure 5 (and similarly in figure 4), also at $\lambda = 9$, the SCOZA binodal [16] lies beneath the GMSA $\Delta s = 0$ locus; the latter, in turn, reproduces the sublimation–freezing line (obtained in reference [5] through the Kofke integration method) fairly well over the density range in which the theory could be solved numerically.

It appears from these results that the combination of information from the GMSA and the SCOZA might be able to provide a description of the relative position of the phase coexistence lines in the phase diagram of the HCYF in the regime of the very short-ranged potential. This might prove useful for extending the present investigation to two-component models of protein solutions, for which the theory should not encounter the difficulties typically met in the simulation of fluids containing highly diluted and strongly asymmetric particle species.

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