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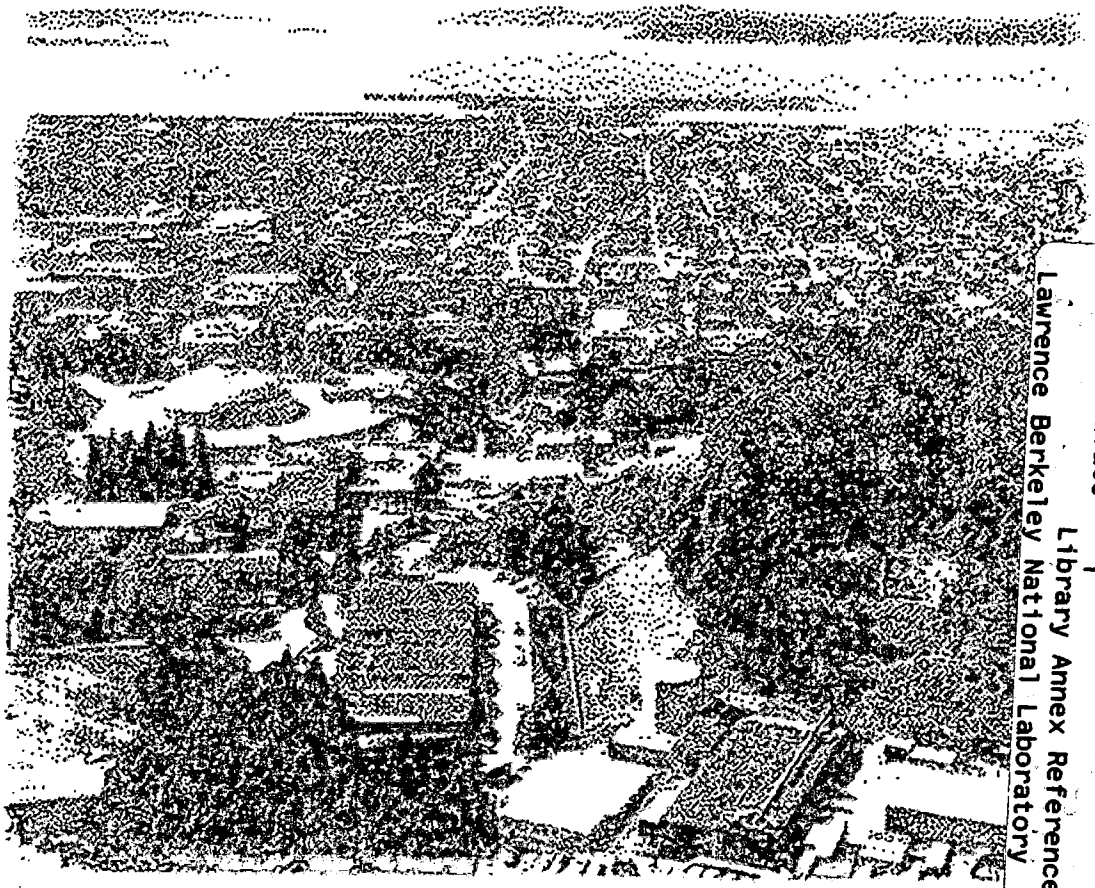

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Orientation-Averaged Pair Potentials between Dipolar Colloidal Particles

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Potentials of mean force between nonuniformly charged colloids or globular proteins are often estimated as a pairwise sum of distinct orientation averages for charge-dipole, and dipole-dipole interactions. In systems with dipole-related interactions comparable to or exceeding the thermal energy, however, correlations between charge-dipole and dipole-dipole terms can render the additivity assumption highly inaccurate. Based on the third-order cumulant expansion of intercolloidal interactions, we derive an asymptotically exact relation for the potential of mean force that includes the correlation between distinct contributions. Using a simple discrete-orientation model, we obtain an approximate expression for the nonadditivity correction that reproduces correct behavior in weak *and* strong coupling limits and is sufficiently accurate for practical calculations over a wide range of interaction strengths including those characteristic of aqueous protein solutions.

I. Introduction

Prediction of solution properties and phase behavior of ionic colloids depends on a reliable description of effective potentials between dispersed particles. These potentials comprise several distinct contributions, the most important being Van der Waals forces, Coulombic interactions, and forces from hydrophobic and osmotic effects[1-3]. In most theories, individual contributions are considered as pairwise additive potentials of mean force obtained upon integration over microscopic variables such as the translational and orientational degrees of freedom of solvent molecules and simple solutes surrounding the colloids. The Derjaguin-Verwey-Landau-Overbeek (DLVO) theory of colloid stability, arguably the most widely accepted theory of colloidal solutions, considers the intercolloidal potential between approximately spherical macroparticles as a sum of dispersion attraction and screened Coulomb repulsion described by the linearized Poisson-Boltzmann approximation[4]. Despite its many simplifications, the DLVO theory has provided qualitative explanations of a variety of observed phenomena such as the roles of pH, ion adsorption, and screening by simple salts, all controlling the stability of the dispersion[2,5,6]. Applications of DLVO theory have often been proposed for approximate descriptions of Coulombic effects in solutions of globular proteins. The usefulness of these applications is, however, limited by the nonuniform distribution of ionized groups on protein molecules resulting in strong dipole, quadrupole, and higher multipole interactions[7-21]. These interactions render pair potentials orientation-dependent and lead to notable deviations from the predictions of the Poisson-Boltzmann equation for spherically symmetric particles. Given a detailed charge distribution on the macroions, the electrostatic problem can be solved by numerical methods like finite difference[23], multipole expansion[8,15], or boundary element[10,17,21] solution of the Poisson and Poisson-Boltzmann equations for the interior of the particles, and for the surrounding liquid phase, respectively. In systems with moderate interaction strengths, the procedure can be facilitated by adopting the superposition approximation[20] that presumes additivity of field perturbations due to distinct macroparticles. A useful alternative avoiding approximations of the theory is provided by essentially exact computer simulations for models with realistic configuration of colloid or protein charges[24]. While detailed numerical calculations or computer simulations provide the most accurate description of intercolloidal electrostatics, for practical application, it is also desirable to examine approximate analytic methods that would provide semi-quantitative estimates of essential contributions in the form of compact analytic expressions. Besides the general insights they can provide, approximate analytic expressions for the potential of mean force are of interest as input information for various liquid-state theories such as integral equations[25,26], and for calculations of phase equilibria in protein or colloidal solutions[27]. Most often, approximate analytic methods for colloids with anisotropic charges consider only the leading contributions, i.e. the charge-charge, charge-dipole, and dipole-dipole interactions. Calculations of the potential of mean force between dipolar particles

requires orientation averaging that can be performed analytically only under simplifying assumptions. Typical simplifications include: a) the assumption of pairwise additivity of orientation-averaged charge-dipole and dipole-dipole terms, and b) truncated cumulant expansion of the Boltzmann factor associated with the angle-dependent interaction. Both simplifications restrict applicability of the model to interactions small in comparison to thermal energy, k_BT [8]. Because many ionized proteins carry charges, q, of the order of 10 e_0 (e_0 is the elementary charge), and dipole moments μ, reaching several hundred Debye (D), the charge-dipole and the dipole-dipole energies can be comparable to k_BT rendering the expansion method unreliable[8,13]. Further, the orientation probabilities of these terms can be strongly correlated with increasing strength of interactions. As a consequence, pairwise additivity of distinct angle-averaged terms remains limited to weak and moderate interaction strengths. In the present article, we describe a generalization of the cumulant-expansion method to the case of simultaneous charge-dipole and dipole-dipole interactions which takes into account correlations between the two coupled contributions. In addition, we propose an approximate, discrete-orientation analytic model that avoids the truncated expansion step and is applicable to systems with arbitrarily strong interactions. The model provides a reasonably accurate estimate of the nonadditivity correction when interactions are too strong for direct application of the third-order cumulant expansion. We test the approximate formulae by comparison with rigorous results for weak coupling (high temperature) and strong coupling (low T) limits, and with exact numerical results for the orientational part of the configuration integral for a pair of dipolar primitive-model colloids. Electrostatic screening due to the simple ions, typically present in biological systems and in many chemical processing environments, is described within the Debye-Hueckel approximation (characteristic of the DLVO theory) as adapted[8] to polar particles and dielectrically heterogeneous systems.

II.1 Analysis

The pair potential between nonuniformly charged colloidal particles, such as proteins includes interactions between net charges, charge-dipole, dipole-dipole and higher multipole contributions. In the first approximation, we consider only dominant terms arising from net charge and dipole interactions, while we ignore quadrupolar and higher order effects. When calculating thermodynamic properties of the solution, the orientation dependence of dipole energies prevents a direct application of standard liquid theories that are designed for fluids with isotropic interparticle forces[25,26]. The difficulty can be overcome by integrating-out the orientational degrees of freedom of interacting dipoles, a procedure leading to the potential of mean force which depends solely on interparticle separation[7,8,13,14]. Within the primitive model, whereby the solvent effects are considered only through the dielectric constant of the medium, the relevant interactions entering the problem are:

$$\beta u_{qq}(r_{ij}) = \frac{\beta q_i q_j}{4\pi\varepsilon\varepsilon_o r_{ij}} S_0(r_{ij},\kappa) \tag{1}$$

$$\beta v_{q\mu}(r_{ij},\theta_j) = -\frac{\beta q_i \mu_j \cos\theta_j}{4\pi\varepsilon\varepsilon_o r_{ij}^2} S_1(r_{ij},\kappa) \tag{2}$$

$$\beta v_{\mu\mu}(r_{ij},\theta_i,\theta_j,\phi) = \frac{-\beta\mu_i\mu_j\,(\,2\;\; S_2(r_{ij},\kappa)\cos\theta_i\cos\theta_j - S_3\,(r_{ij},\kappa)\sin\theta_i\sin\theta_j\cos\varphi)}{4\pi\varepsilon\varepsilon_o r_{ij}^3} \tag{3}$$

Here, $\beta=1/k_BT$, ε is the relative permittivity of the medium, and ε_o the permittivity of vacuum, q and μ denote the charge and dipole moment on interacting particles i and j, separated by the distance r_{ij}, θ_i is the angle between the directions of dipole i and vector r_{ij}, $\phi=(\phi_i-\phi_j)$, and ϕ_i describes the rotation of dipole i around r_{ij} (see Figure 1). Electrostatic screening due to the presence of a simple electrolyte is absorbed in functions $S_k(r_{ij},\kappa)$ which are, at the Debye-Hueckel level, approximately described[8] by the following expressions:

$$S_0(r_{ij},\kappa) = \frac{e^{-\kappa(r_{ij}-\sigma_{ij})}}{[1+(\frac{\kappa\sigma_{ij}}{2})]^2} \tag{4}$$

$$S_1(r_{ij},\kappa) = \frac{3\,e^{-\kappa(r_{ij}-\sigma_{ij})}\,(1+\kappa r_{ij})}{[1+\frac{(\kappa\sigma_{ij})}{2}][2+\kappa\sigma_{ij}+\frac{(\kappa\sigma_{ij})^2}{4}+(1+\frac{\kappa\sigma_{ij}}{2})\frac{\varepsilon_p}{\varepsilon}]} \tag{5}$$

$$S_2(r_{ij},\kappa) = \frac{9\, e^{-\kappa(r_{ij}-\sigma_{ij})}\,(1+\kappa r_{ij}+\frac{(\kappa r_{ij})^2}{2})}{[2+\kappa\sigma_{ij}+\frac{(\kappa\sigma_{ij})^2}{4}+(1+\frac{\kappa\sigma_{ij}}{2})\frac{\varepsilon_p}{\varepsilon}]^2} \tag{6}$$

$$S_3(r_{ij},\kappa) = \frac{9\, e^{-\kappa(r_{ij}-\sigma r_{ij})}\,(1+\kappa r_{ij})}{[2+\kappa\sigma_{ij}+\frac{(\kappa\sigma_{ij})^2}{4}+(1+\frac{\kappa\sigma_{ij}}{2})\frac{\varepsilon_p}{\varepsilon}]^2} \quad . \tag{7}$$

Above, $1/\kappa$ is the Debye screening length, ε_p the relative permittivity of the colloid particle's interior, and σ_{ij} the contact distance for particles i and j [8].

If we represent the Hamiltonian of the system, H, as a sum of two terms, $H=H_o+V$, with H_o comprising isotropic interactions, and perturbation V the dipole-related terms, the angle-averaged potential of mean force, $w(r_{ij})$, can be written as

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - ln\,\{\frac{1}{8\pi}\iiint_{\theta_i=0\ \theta_j=0\ \phi=0}^{\pi\ \pi\ 2\pi} e^{-\beta v(r_{ij},\theta_i,\theta_j,\phi)} sin\,\theta_i\, sin\,\theta_j\, d\theta_i\, d\theta_j\, d\phi\,\} =$$

$$= \beta u_{qq}(r_{ij}) - ln < e^{-\beta v(r_{ij},\theta_i,\theta_j,\phi)} >_{H_0} \tag{8}$$

with $\quad v(r_{ij},\theta_i,\theta_j,\phi) = v_{q\mu}(r_{ij},\theta_i)+v_{\mu q}(r_{ij},\theta_j)+v_{\mu\mu}(r_{ij},\theta_i,\theta_j,\phi)$.

Here, the angular brackets $< >_{H_o}$ denote the average with respect to the unperturbed Hamiltonian (devoid of angle-dependent interactions). The particular case of an interacting charge and dipole, eq 2, with $v_{q\mu}$ depending on a single angle, θ_j, results in an analytic solution[14] for the above integral:

$$\beta w_{q\mu}(r_{ij}) = -ln\,[\frac{1}{\alpha_1(r_{ij})}\, sinh\,\alpha_1(r_{ij})] \quad \text{with} \quad \alpha_1 = \frac{\beta q_i \mu_j}{4\pi\varepsilon\varepsilon_o r_{ij}^2} S_1(r_{ij},\kappa) \tag{9}$$

II.2 Truncated-expansion method

For systems with dipole-dipole interactions, the standard procedure, applicable at weak coupling energies ($v_{\mu\mu}$ small compared to $1/\beta$), requires expansion of the Boltzmann factor in eq 8 leading to

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - ln[1 - <\beta v(r_{ij},\theta_i,\theta_j,\phi)>_{H_o} + \frac{1}{2}<\beta^2 v^2(r_{ij},\theta_i,\theta_j,\phi)>_{H_o} - \frac{1}{6}<\beta^3 v^3(r_{ij},\theta_i,\theta_j,\phi)>_{H_o} + ...] \tag{10}$$

For particular interactions (charge-dipole, or dipole-dipole), it is easy to show that odd-order cumulants vanish; the series is usually truncated beyond the third-order term giving

$$\beta w_{q\mu}(r_{ij}) = -\frac{\alpha_1^{\,2}(r_{ij})}{6} \tag{11}$$

$$\beta w_{\mu\mu}(r_{ij}) = -\frac{2\alpha_2^{\,2}(r_{ij}) + \alpha_3^{\,2}(r_{ij})}{9} \quad \text{with} \quad \alpha_2 = \frac{\beta\mu_i\mu_j}{4\pi\varepsilon\varepsilon_o r_{ij}^{\,3}} S_2(r_{ij},\kappa), \quad \alpha_3 = \frac{\beta\mu_i\mu_j}{4\pi\varepsilon\varepsilon_o r_{ij}^{\,3}} S_3(r_{ij},\kappa) \tag{12}$$

Clearly, eq 11 captures the exact weak-coupling (high-temperature) limit of the rigorous result given by eq 9. In the weak-coupling regime, the potential of mean force behaves as a quadratic function of coefficients $\alpha_k(r)$. At increased interaction strengths where the two dipoles approach a nearly aligned configuration, however, there is a crossover from quadratic to linear dependence of the potential of mean force on $\alpha_k(r)$. Eq 11 fails to predict this saturation behavior. Applicability of the truncated cumulant expansion is therefore limited to small charges and dipoles, or strong electrostatic screening, and eq 9 must be used for accurate charge-dipole interactions between, for example charged proteins. The dipole-dipole term, on the other hand, is usually small in comparison with $1/\beta$. Hence, the interprotein potential can be reasonably approximated by combining the rigorous results for pure charge-charge and charge-dipole interactions with the approximate estimate, eq 12, for the dipole-dipole term. For two identical particles, this gives

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - 2\, ln\, [\frac{1}{\alpha_1(r_{ij})} sinh\, \alpha_1(r_{ij})] - \frac{2\alpha_2^{\,2}(r_{ij}) + \alpha_3^{\,2}(r_{ij})}{9} + ... \tag{13}$$

The weakness of this method, however, lies in its inability to capture adverse correlations between charge-dipole and dipole-dipole terms present when each of the particles carries both a net charge and a dipole. For equally charged particles, opposing orientations are favored by charge-dipole and dipole-dipole

interactions. Coupling between the two effects is illustrated in Figure 2 which presents the orientational correlation function, $< cos\ \theta_1\ cos\ \theta_2 >_H$, for a pair of colloidal particles with equal dipoles $\mu_1=\mu_2=400$ D as a function of the charge, $0 < q < 20\ e_o$, located at the centers of both particles, for three different center-to-center separations r_{12}=2, 3, or 4 nm. The variation of $< cos\ \theta_1\ cos\ \theta_2 >_H$, determined numerically as the weighted average

$$< cos\ \theta_i\ cos\ \theta_j >_H = \frac{\iiint_{\theta_i\ \theta_j\ \phi} cos\ \theta_i\ cos\ \theta_j\ e^{-\beta v(r_{ij},\theta_i,\theta_j,\phi)} sin\ \theta_i\ sin\ \theta_j\ d\theta_i\ d\theta_j\ d\phi}{\iiint_{\theta_i\ \theta_j\ \phi} e^{-\beta v(r_{ij},\theta_i,\theta_j,\phi)} sin\ \theta_i\ sin\ \theta_j\ d\theta_i\ d\theta_j\ d\phi} \quad . \qquad (14)$$

Eq 14 reveals a crossover from attractive dipole-dipole interactions (positive $< cos\ \theta_1\ cos\ \theta_2 >_H$) at weak charges q, to effective dipole-dipole repulsion (negative $< cos\ \theta_1\ cos\ \theta_2 >_H$) when strong charge-dipole forces impose an unfavorable (antiparallel) dipole-dipole orientation. The angle-averaged charge-dipole terms, $w_{q\mu}(r)$, and the dipole-dipole term, $w_{\mu\mu}(r)$, can therefore be strongly nonadditive and warrant simultaneous orientation/averaging of the complete potential $v_{ij}(r_{ij},\theta_i,\theta_j,\phi)= v_{q\mu}(r_{ij},\theta_j)+v_{\mu q}(r_{ji},\theta_i) +v_{\mu\mu}(r_{ij},\theta_i,\theta_j,\phi)$. For a pair of identical particles, $v_{ij}(r_{ij},\theta_i,\theta_j,\phi)$ is given by

$$\beta v_{ij}(r_{ij},\theta_i,\theta_i,\phi) = -\alpha_1(cos\ \theta_i - cos\ \theta_j) - 2\alpha_2\ cos\ \theta_i\ cos\ \theta_j + \alpha_3\ sin\ \theta_i\ sin\ \theta_j\ cos\ \varphi \quad . \qquad (15)$$

Coefficients $\alpha_k(r_{ij})$ are functions of interparticle separation given by eqs 9 and 12. Considering only the second cumulant, and for identical particles, the truncated expansion procedure applied to the potential of eq. 15 suggests the pairwise sum:

$$\beta w(r_{ij}) = -2\frac{\alpha_1^2(r_{ij})}{6} - \frac{2\alpha_2^2(r_{ij})+\alpha_3^2(r_{ij})}{9} \qquad (16)$$

however, the third cumulant corresponding to the potential of eq 15

$$<\beta v_{ij}^{3}(r_{ij},\theta_i,\theta_i,\phi)>_{H_o} = <[-\alpha_1(\cos\theta_i - \cos\theta_j) - 2\alpha_2 \cos\theta_i \cos\theta_j + \alpha_3 \sin\theta_i \sin\theta_j \cos\varphi]^3>_{H_o} \tag{17}$$

contains a nonvanishing term $<-\alpha_1^2\alpha_2 \cos^2\theta_i \cos^2\theta_j>_{H_o}$ associated with the coupling of charge-dipole and dipole-dipole interactions. Performing the integrations, the total potential of mean force is approximately described by:

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - 2\frac{\alpha_1^2(r_{ij})}{6} - \frac{2\alpha_2^2(r_{ij})+\alpha_3^2(r_{ij})}{9} + \frac{2\alpha_1^2(r_{ij})\alpha_2(r_{ij})}{9} + O\{[v_{q\mu}+v_{\mu\mu}]^4\}$$

with charge-dipole/dipole-dipole coupling term being (18)

$$\frac{2\alpha_1^2(r_{ij})\alpha_2(r_{ij})}{9} = \frac{2\beta^3 q^2\mu^4}{9(4\pi\varepsilon\varepsilon_o)^3 r_{ij}^7} S_1^2(r_{ij},\kappa)\, S_2(r_{ij},\kappa) \propto \frac{e^{-3\kappa(r_{ij}-\sigma_{ij})}}{r_{ij}^7} \quad .$$

In view of eq 9, a somewhat better approximation is

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - 2\ ln\ [\frac{1}{\alpha_1(r_{ij})} sinh\ \alpha_1(r_{ij})] - \frac{2\alpha_2^2(r_{ij})+\alpha_3^2(r_{ij})}{9} + \frac{2\alpha_1^2(r_{ij})\alpha_2(r_{ij})}{9} + \ldots \quad . \tag{19}$$

When the charge-dipole and dipole-dipole interactions (second and third terms on the r.h.s. of eq 19 are of comparable strength, the mixed charge-dipole/dipole-dipole contribution (the last term on the r.h.s. of eq 19) can be of similar magnitude (but with opposite sign and shorter range) as the two distinct charge-dipole and dipole-dipole terms. For oppositely charged dipolar particles, on the other hand, the mixed term represents an equally strong but attractive contribution. In typical colloidal or protein solutions, with particle charges of the order 10 e_o, and dipoles of several hundred D, the interactions are often too strong (compared to k_BT) to make the third-order expansion useful for quantitative estimates. Eq 19 is therefore mainly applicable at moderate interaction strength. In addition, by identifying the lowest-order coupling term, eq 18 establishes the correct high-temperature behavior needed for validating alternative approximations.

II.3 Discrete-orientation approximation

A rigorous calculation of the potential of mean force requires solving the configuration integral of eq 8, employing $v_{ij}(r_{ij},\theta_i,\theta_j,\phi)$ given in eq 15. In the absence of an exact analytic solution of this integral, and avoiding the expansion of the Boltzmann factor [questionable for $v_{ij}(r_{ij},\theta_i,\theta_j,\phi)$ close to (or exceeding) $1/\beta$], we proceed by presuming that the orientation space of the two dipoles can be discretized, with each dipole sampling only six principal directions: θ_i=0, π, ϕ_i=0, and $\theta_i=\pi/2$, ϕ_i=0, $\pi/2$, π, or $3\pi/2$, as illustrated in Figure 3 which shows an orientation with θ_1, θ_2 and ϕ_{12} all at $\pi/2$. The above discretization reduces the integral of eq 8 to a sum of 36 terms. All terms are of simple form because trigonometric functions for allowed orientations assume only values 0, 1 or -1. For symmetry reasons, the 36 orientations correspond to only eight different energy levels, hence the partition function contains only eight independent terms. After some algebra, we arrive at the following compact expression:

$$\beta w^d(r_{ij}) = \beta u_{qq}(r_{ij}) - \ln\{[8+8e^{\alpha_1}+8e^{-\alpha_1}+4e^{\alpha_3}+4e^{-\alpha_3}+2e^{2\alpha_2}+e^{-2\alpha_2+2\alpha_1}+e^{-2\alpha_2-2\alpha_1}]/36\} =$$

$$= \beta u_{qq}(r_{ij}) - \ln\{[4+4\cosh\alpha_3+e^{2\alpha_2}+8\cosh\alpha_1+e^{-2\alpha_2}\cosh 2\alpha_1]/18\} \qquad (20)$$

where $w^d(r_{ij})$ is the intercolloidal potential of mean force in the discrete-orientation approximation. eq 20 reduces to the exact weak-coupling form, eq 18, when all angle-dependent interactions are small compared to thermal energy, $1/\beta$. Similarly, it reproduces a correct strong-coupling limit of fully aligned dipoles when either the charge-dipole term, or the dipole-dipole term appreciably exceeds $1/\beta$. For intermediate interaction strengths, eq 20 constitutes an approximate interpolation formula between the two extreme regimes. At intermediate conditions (characteristic of aqueous protein solutions), however, a more accurate approximation can be obtained by exploiting the exact result for the orientation-averaged charge-dipole contribution given by eq 9. We use eq 20 to estimate the *perturbation* of $w(r)$ from a hypothetical reference state comprising uncoupled charge-dipole, and dipole-dipole interactions. At conditions typical of aqueous protein solutions, the two distinct types of interaction are adequately described by eq 13. We therefore augment eq 13 by including the perturbation term, $w_p(r)$, obtained as the difference between the approximate potential of mean force from eq 20 and the sum of corresponding charge-dipole and dipole-dipole terms:

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - 2 \ln [\frac{1}{\alpha_1(r_{ij})} \sinh \alpha_1(r_{ij})] - \frac{2\alpha_2^2(r_{ij}) + \alpha_3^2(r_{ij})}{9} + w_P(r_{ij})$$

$$w_P(r_{ij}) = w^d(\alpha_1,\alpha_2,\alpha_3) - w^d(\alpha_1,0,0) - w^d(0,\alpha_2,\alpha_3) =$$

$$= -\ln \frac{18(4+4\cosh \alpha_3 + e^{2\alpha_2} + 8\cosh \alpha_1 + e^{-2\alpha_2}\cosh 2\alpha_1)}{(9+8\cosh \alpha_1 + \cosh 2\alpha_1)(12+4\cosh \alpha_3 + 2\cosh 2\alpha_2)} \quad . \tag{21}$$

In the case of extremely strong dipole-dipole interactions (exceeding those observed in typical protein solutions), when orientational saturation gives rise to the crossover from quadratic to linear dependence of the dipole-dipole term on α_2, an analogous procedure can be used to avoid the truncated expansion estimate for the dipole-dipole interaction. Presuming that the reference state comprises only charge-charge and charge-dipole interactions we obtain:

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - 2 \ln [\frac{1}{\alpha_1(r_{ij})} \sinh \alpha_1(r_{ij})] + w_P(r_{ij}) \qquad \text{where}$$

$$w_P(r_{ij}) = w^d(\alpha_1,\alpha_2,\alpha_3) - w^d(\alpha_1,0,0) \quad \text{and} \tag{22}$$

$$\beta w(r_{ij}) = \beta u_{qq}(r_{ij}) - \ln \frac{(4+4\cosh \alpha_3 + e^{2\alpha_2} + 8\cosh \alpha_1 + e^{-2\alpha_2}\cosh 2\alpha_1)(\alpha_1^{-1}\sinh \alpha_1)^2}{2\,(2+\cosh \alpha_1)^2} \quad .$$

Eq 22 provides a fair description for strongly interacting dipoles, but is less accurate than eq 21 within the intermediate range of interaction strengths corresponding to dipolar proteins in dilute electrolyte solutions.

III. Results and Discussion

We assess the accuracies of the approximate expressions discussed above by comparison with 'exact' results obtained from numerical integration of eq 8 for a broad range of macroion charges and dipoles. Except for the simultaneous presence of charge-dipole and dipole-dipole interactions, the numerical solution of eq 8 is obtained following the procedure described earlie[13]. In Figure 4, we present the ratios $w_{ap}(\sigma)/w(\sigma)$ between the approximate potentials of mean force (excluding the charge-charge term u_{qq})

$w_{ap}(\sigma)$, obtained by eqs 13 or 21, and numerical results for $w(\sigma)$ from eq 8. We cover situations ranging from vanishingly small charges and dipole momenta to typical protein charges $q\sim 10\ e_0$ and dipole moments $\mu= 400$ D at aqueous-solution conditions, with ambient temperature, T=298 K, $\varepsilon=\varepsilon_p=78.5$, and at an ionic strength for a monovalent salt of I=0.1 mol dm^{-3} (close to physiological salt concentration). To include systems with relatively strong interactions, we consider two colloids at a center-to-center separation equal to their contact distance of σ=3.0 nm. Situations corresponding to other contact distances or screening strengths can be considered through implicit renormalization of dimensionless parameters, $\alpha_i(r)$ from eqs 9 and 12. We also note that, within given parameter range, eq 13 reproduces almost quantitatively the pairwise sum of charge-dipole and dipole-dipole terms determined by exact numerical integration. Its deviation from unity therefore directly measures the relative error associated with the additivity approximation. According to Figure 4, the assumption of pairwise additivity of charge-dipole and dipole-dipole terms) leads to small deviations from the exact result at moderate charges and dipoles (up to ~ 100 D for given σ and κ) where the net interaction remains below $1/\beta$. Further increases in colloid charges and dipoles can result in serious errors due to nonadditivity of the dipole forces. At q=10 e_0 and μ=400 D, the relative error exceeds 75%. To illustrate the effect of charge-dipole and dipole-dipole correlations in the weak-coupling regime, Figure 5 compares total potentials of mean force from various approximate expressions and the results of the pairwise-additivity assumption. We also include the exact results obtained by numerical integration of eq 8, and predictions of eqs 13, 19 and 21. In the weak-interaction regime, the predictions of the truncated-cumulant-expansion method, eq 19, as well as the discrete-orientation perturbation model, eq 21, agree quantitatively with exact numerical data. Both approximations correctly describe the deviations from pairwise additivity of charge-dipole and dipole-dipole terms which, in the given case, amount to up to 20% of the total interaction. The inclusion of the nonadditivity correction considered in eq 19 will, however, not prevent the breakdown of the the truncated expansion approach at conditions when interactions become comparable to $1/\beta$.

The results of the perturbation method, eq 21, on the other hand, remain close to the exact numerical results (the ratio $w_{ap}(\sigma)/w(\sigma)$ shown in Figure 4 remains relatively close to unity) at all practically relevant conditions. Unlike the truncated-cumulant-expansion given by eqs 13 or 19, this approximation remains applicable at strong-coupling regimes. Figure 6 further illustrates the performance of the perturbation method at relatively high dipole moments (μ=400 D, and charges, q=8e_0). The distance dependence of the approximate potential of mean force from eq 21 (dashed-dotted curve in Figure 6) is similar to that obtained from the exact numerical solution of eq 8 (thick solid curve in Figure 6). Truncated expansion approach, eq 19 (thin solid line in Figure 6), overestimates the nonadditivity correction. It is interesting to

note the strong deviations in the net potential of mean force from the pairwise sum of the angle-averaged charge-dipole and dipole-dipole terms (dashed cirves in Figure 6). This feature is captured by eq 21. In view of its accuracy for relatively strong interactions, eq 21 provides a useful approximation for analytic calculations of the phase behavior in systems containing strong dipoles and charges, e.g. solutions of ionized proteins[27,28].

A pertinent example demonstrates the importance of a self-consistent account of the various contributions to electrostatic interactions in protein solutions and related colloidal systems. In Figure 7, we present complete electrostatic potentials of mean force (including the monopole interaction) from eq 21 for a pair of identical model proteins with varying macroion charge q, and fixed dipole moment μ=380 D. The proteins are separated by the contact distance σ=3 nm. The relative permittivity of the macroions ε_p is 4, and the salt concentration is varied from zero to 0.5 mol dm^{-3} corresponding to a Debye screening parameter of $\kappa \sim 0.23$ A^{-1}. As implied in eqs 4-7, the screening of electrostatic interactions is strongest for monopole-monopole interaction and weakest for the dipole-dipole term. As a consequence, different contributions to the total interaction can dominate at different salt concentrations. Figure 7 shows an example where direct charge-charge repulsion represents the strongest term at high dilution, while attractive dipolar interactions prevail above a threshold salt concentration. Upon a further increase in the ionic strength, the attraction reaches an extremum and then gradually decreases. The minimum in the interprotein potential of mean force as a function of ionic strength is consistent with the nonmonotonic salt effects observed in measurements of cloud temperatures in lysozyme solutions[29-31], diffusion coefficients of lysozyme and concanavalin[31,32], activity of lactoglobulin[33], and association equilibria in insulin solutions[34]. Clearly, other important phenomena such as Van der Waals and hydrophobic interactions[1,19], and isotropic Coulombic effects[35-37] observed in multivalent salts, can contribute to interprotein attraction, shifting the observed[29-34] extrema towards higher salt concentrations. The solution behavior is determined by a delicate balance between Coulombic repulsion of protein charges and different attractive contributions; each of these should be included in accurate calculations.

Comparisons of the results from various approximate expressions with numerical solutions of eq 8, presented in Figures 4-6, provide an estimate of the numerical accuracy of the approximate methods introduced in Section II. In what follows, we evaluate the consequences of some of the model simplifications introduced in the above methods. These include the replacement of discrete charge distributions on the macroion by an idealized point-charge/point-dipole representation, the application of Debye-Hueckel screening of charges and dipoles, and the approximate account of dielectric inhomogeneities in the solution. While we defer permittivity effects[38] to future studies, we assess the effect of the first two

simplifications by a brief comparison of analytic predictions with the results of recent Monte Carlo simulations[24] for a model mimicking the charge distribution of a globular proteins in a simple electrolyte. Simulations considered[24] the average force for an isolated pair of macroions characterized by *small* contact distance $\sigma = 2$ nm, each macroion carrying ten ionic groups with net charge 8 e_0 and dipole μ=380 or 490 D. As shown in Figure 8, the discrete-orientation scheme leading to eq 22 provides a fair estimate of the magnitude and the range of the overall intercolloidal force despite the shortcomings of the theory. Clearly, due to the point-charge representation of small ions implied in the Debye-Hueckel approximation, the theory cannot capture the oscillations in the average force associated with the layering of simple ions between adjacent macroions. A more powerful liquid state theory that considers simple ions as an independent molecular species of finite size would be needed for further improvement. To illustrate, in Figure 8 we also include intercolloidal forces obtained from the Hypernetted-Chain (HNC) approximation[25,27,39,40] using the primitive model[25] of an asymmetric electrolyte augmented with the angle-averaged charge-dipole and dipole-dipole potentials between colloidal particles from eq 21. That model accounts for the finite size of simple ions, σ_i=0.4 nm. The calculated forces (dashed curves in Figure 8) reveal the onset of counterion layering between the two macroions. The effect is, however, weaker than that found by simulation because the preaveraged charge-dipole and dipole-dipole potentials retain the screening functions from the Debye-Hueckel approximation. Integral-equation theories for mixtures with strong angle-dependent interactions[41-45] appear promising for more rigorous descriptions of intercolloidal forces. Such descriptions should discriminate between different distributions of fixed macroion charges, going beyond simple dipole-dipole and charge dipole interactions, while also regarding the screening ions on an equal footing with the colloidal particles.

Acknowledgment

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Figure Captions

Figure 1. Schematic representation of interacting particles.

Figure 2. Orientation correlation functions, $< \cos\theta_1 \cos\theta_2 >_H$, for a pair of dipolar macroions with net dipoles μ=400 D at contact distances σ=2 (solid), 3 (dashed), or 4 nm (dotted curve), as functions of macroion charge q. Electrolyte concentration is 0.1 mol dm^{-3}.

Figure 3. Discrete-orientation model of interacting dipoles (showing orientation $\theta_1=\theta_2=\phi_{12}=\pi/2$).

Figure 4. Comparison at contact, between approximate intercolloidal potentials of mean force (excluding the charge-charge interaction), $w_{ap}(\sigma)$, obtained by assuming pairwise additivity of angle-averaged charge-dipole and dipole-dipole terms, eq 13 (upper surface), or by simultaneous orientation-averaging according to the perturbation method described by eq 21 (lower surface) as functions of macroion charges, q, and dipole moments, μ. The colloid diameter σ=3 nm and electrolyte concentration is 0.1 mol dm^{-3}. All results are divided by the exact numerical result of eq 8, such that deviations from unity measure the inaccuracies of the two approximations.

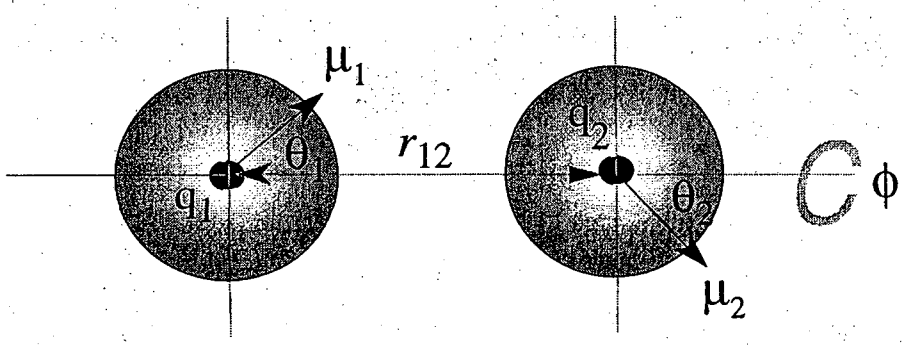
Figure 5. Distance dependence of the intercolloidal potentials of mean force for particles carrying charges q=2 e_0 and dipoles μ=200 D in 0.1 mol dm^{-3} univalent electrolyte solution. The macroion diameter σ=3 nm: exact numerical results, eq 8 (thick solid), truncated expansion, eq 19 (thin solid), perturbation approximation, eq 21 (thick dashed-dotted), additivity approximation based on exact numerical results for distinct charge-dipole and dipole-dipole terms (thick dashed), and additivity approximation based on the cumulant expansion method, eq 13 (thin dashed curve).

Figure 6. Distance dependence of the intercolloidal potentials of mean force for particles carrying charges q=8 e_0 and dipoles μ=400 D in 0.1 mol dm^{-3} univalent electrolyte solution. The macroion diameter σ=3

nm: exact numerical results, eq 8 (thick solid), truncated cumulant expansion, eq 19 (thin solid), perturbation approximation, eq 21 (thick dashed-dotted), additivity approximation based on exact numerical results for distinct charge-dipole and dipole-dipole terms (thick dashed), and additivity approximation based on cumulant expansion approach, eq 13 (thin dashed curve).

Figure 7. Potentials of mean force between identical colloidal particles of diameter σ=3 nm, each carrying a dipole μ=380 D, for several values of colloid charge q, as functions of the Debye-Hueckel screening parameter κ.

Figure 8. Comparison between simulated intercolloidal forces from reference 24 and predictions of the discrete-orientation model for colloidal particles of diameter σ=2 nm, charge q=8 e_0 and dipole μ=380 or 490 D in 0.125 mol dm^{-3} univalent electrolyte solution. Symbols denote simulation results at lower (diamonds) or higher (squares) dipole momenta. Solid curves correspond to the analytic estimates from eq 22. Dashed curves describe results from the HNC approximation for a colloid/electrolyte mixture with direct colloid-colloid potentials including the orientation-averaged charge-dipole and dipole-dipole contribution from eq 22. The units of force are k_BT/l_B, where l_B is the Bjerrum length (0.714 nm).



Bratko et al, Figure 1

Bratko et al, Fig. 2

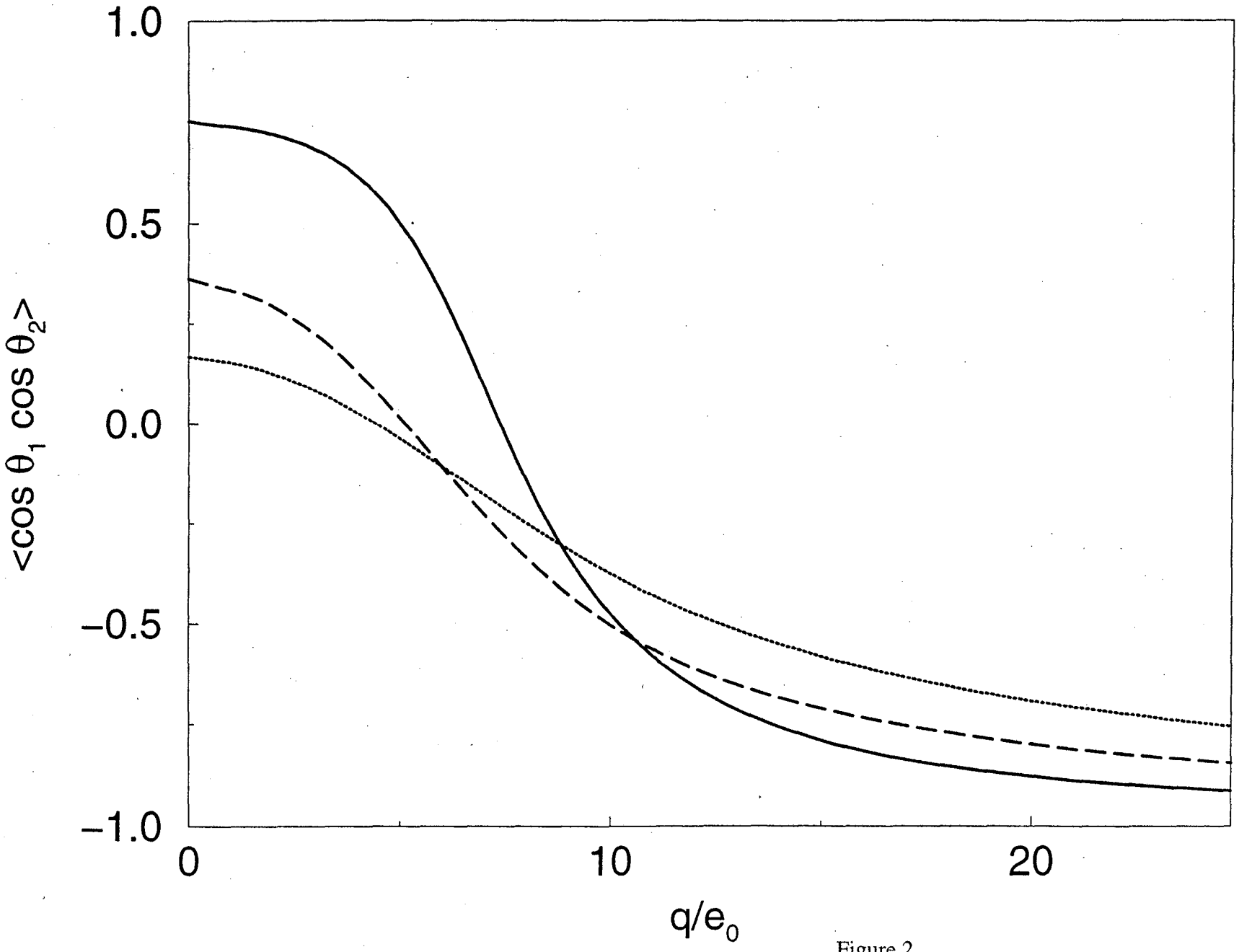
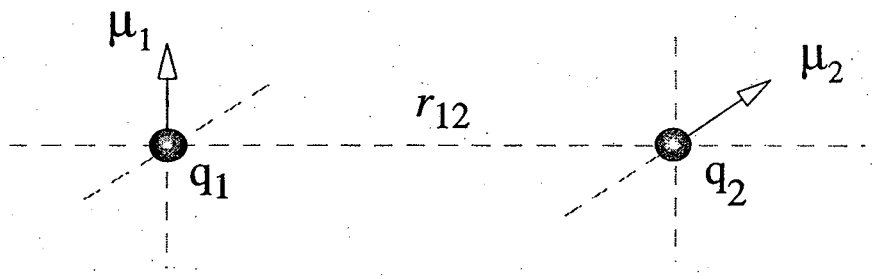


Figure 2



Bratko et al, Figure 3

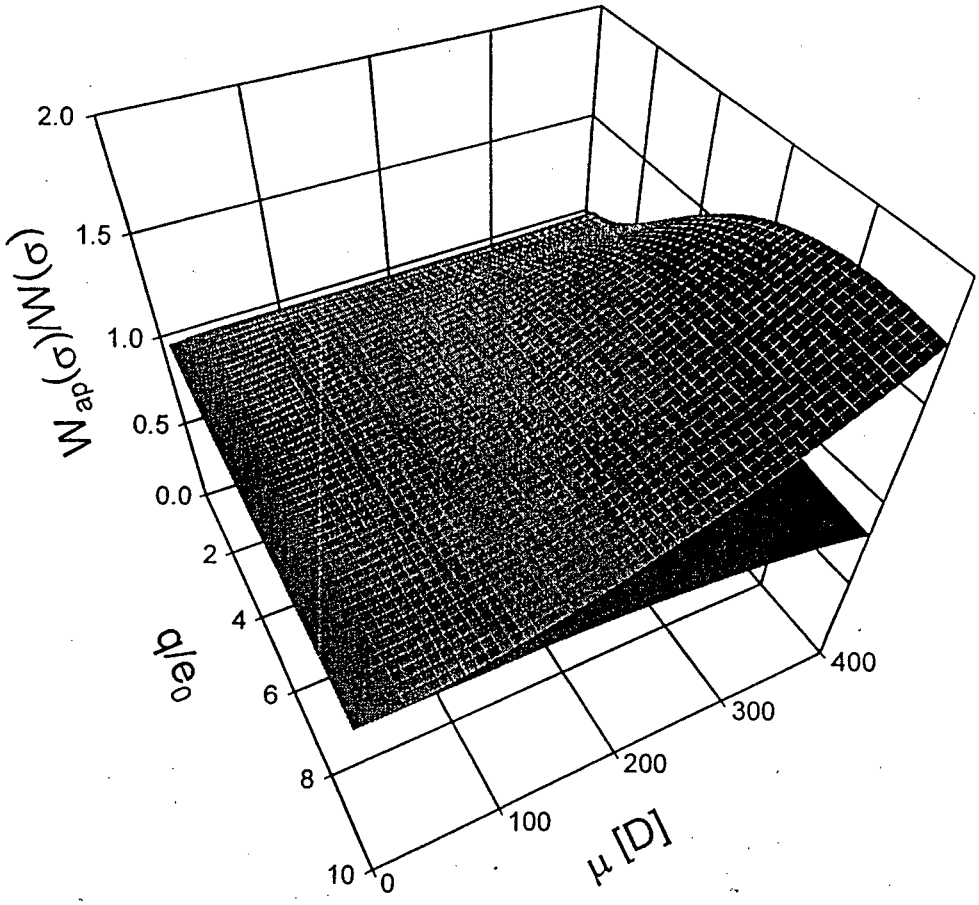


Figure 4

Bratko et al, Fig. 4

Bratko et al, Fig 5

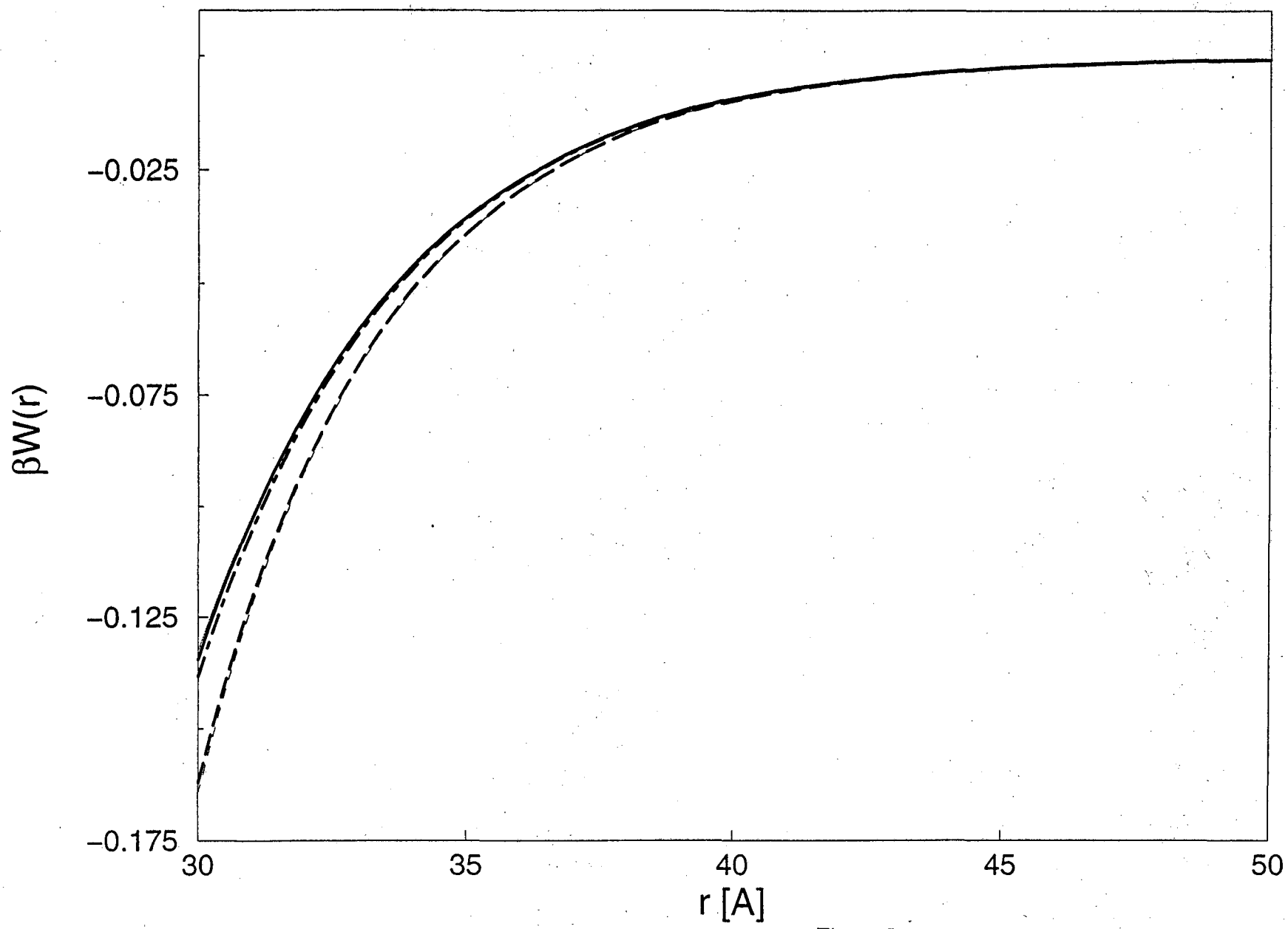


Figure 5

Bratko et al, Fig 6

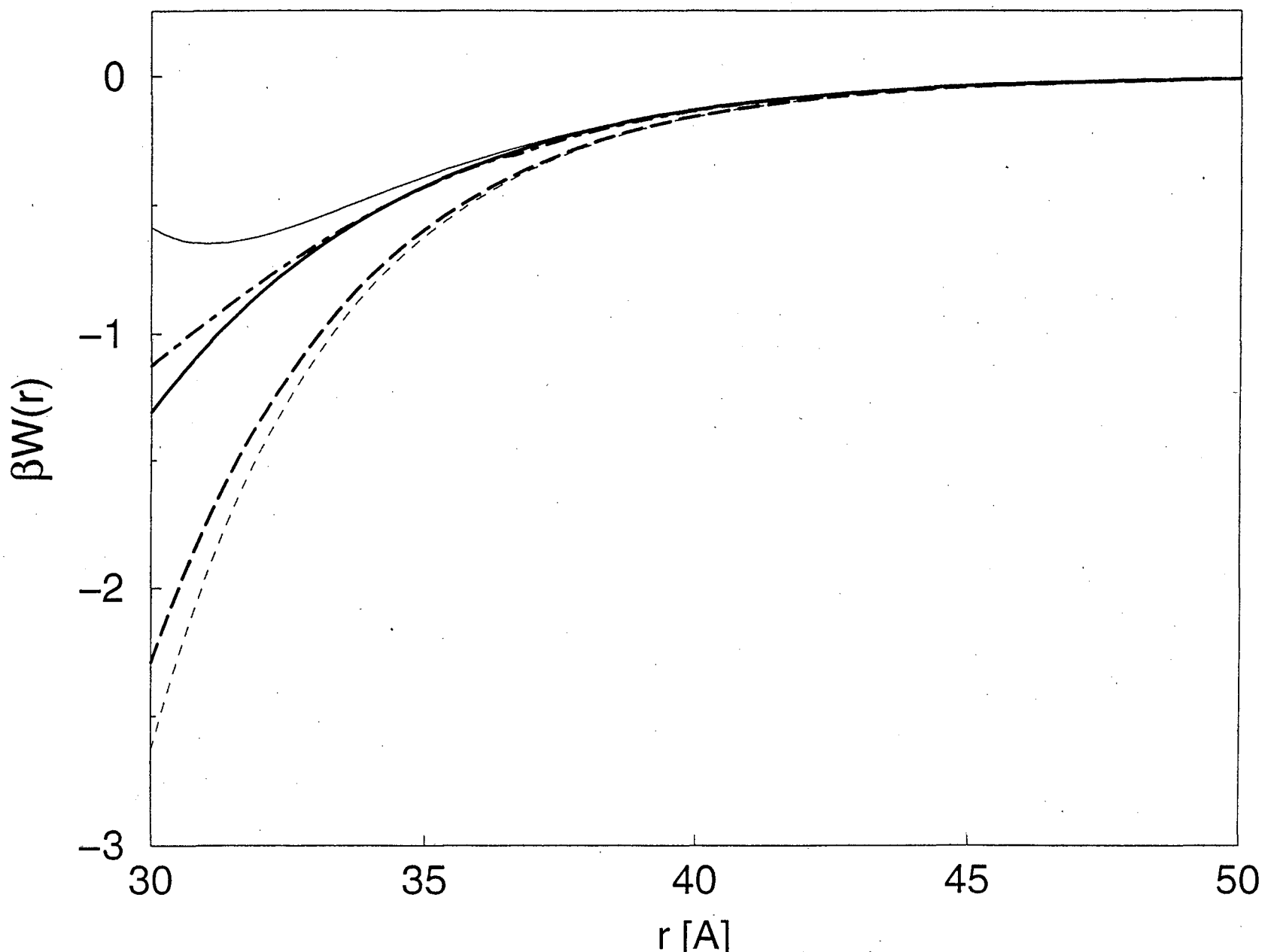


Figure 6

Bratko et al, Fig. 7

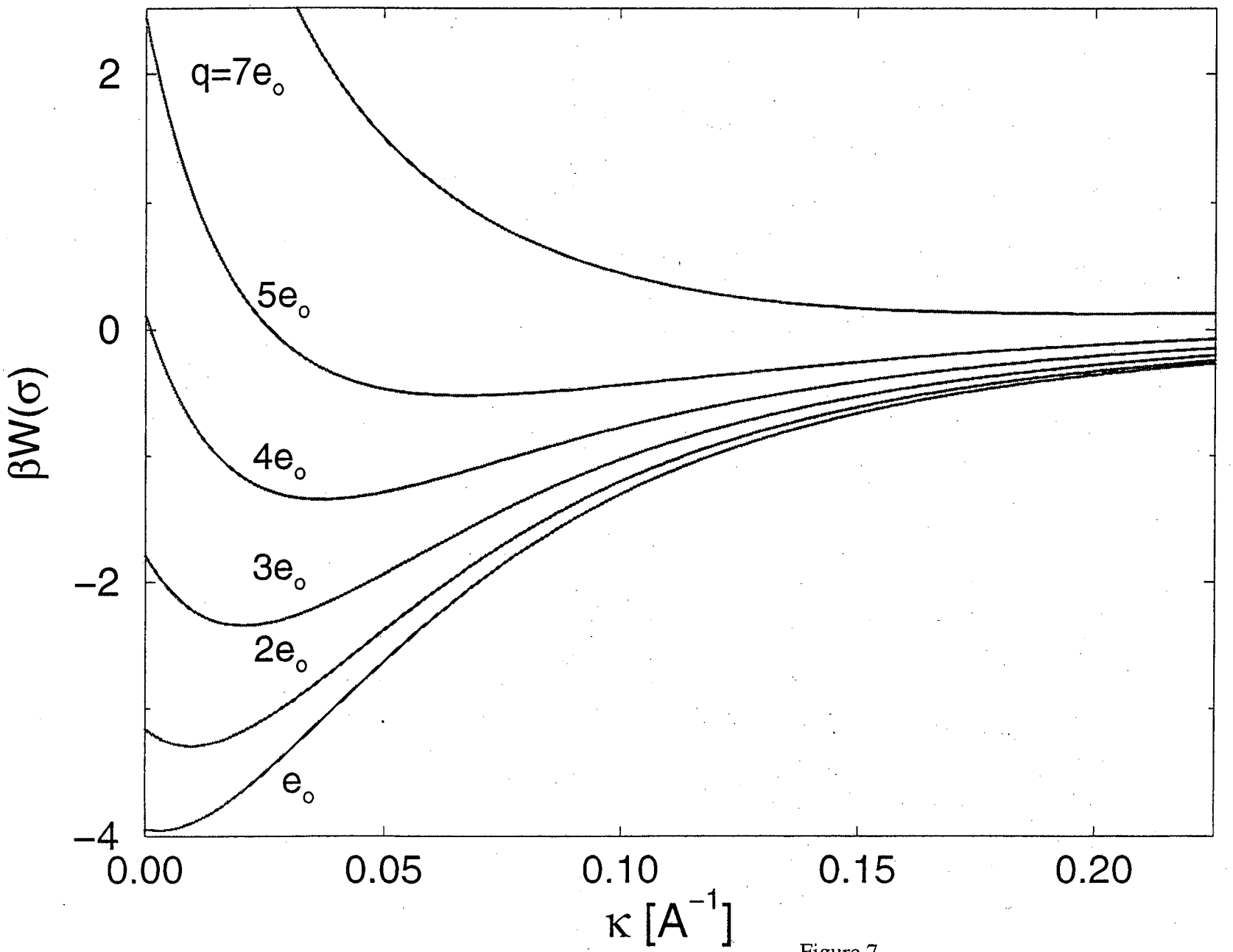


Figure 7

Bratko et al, Fig 8

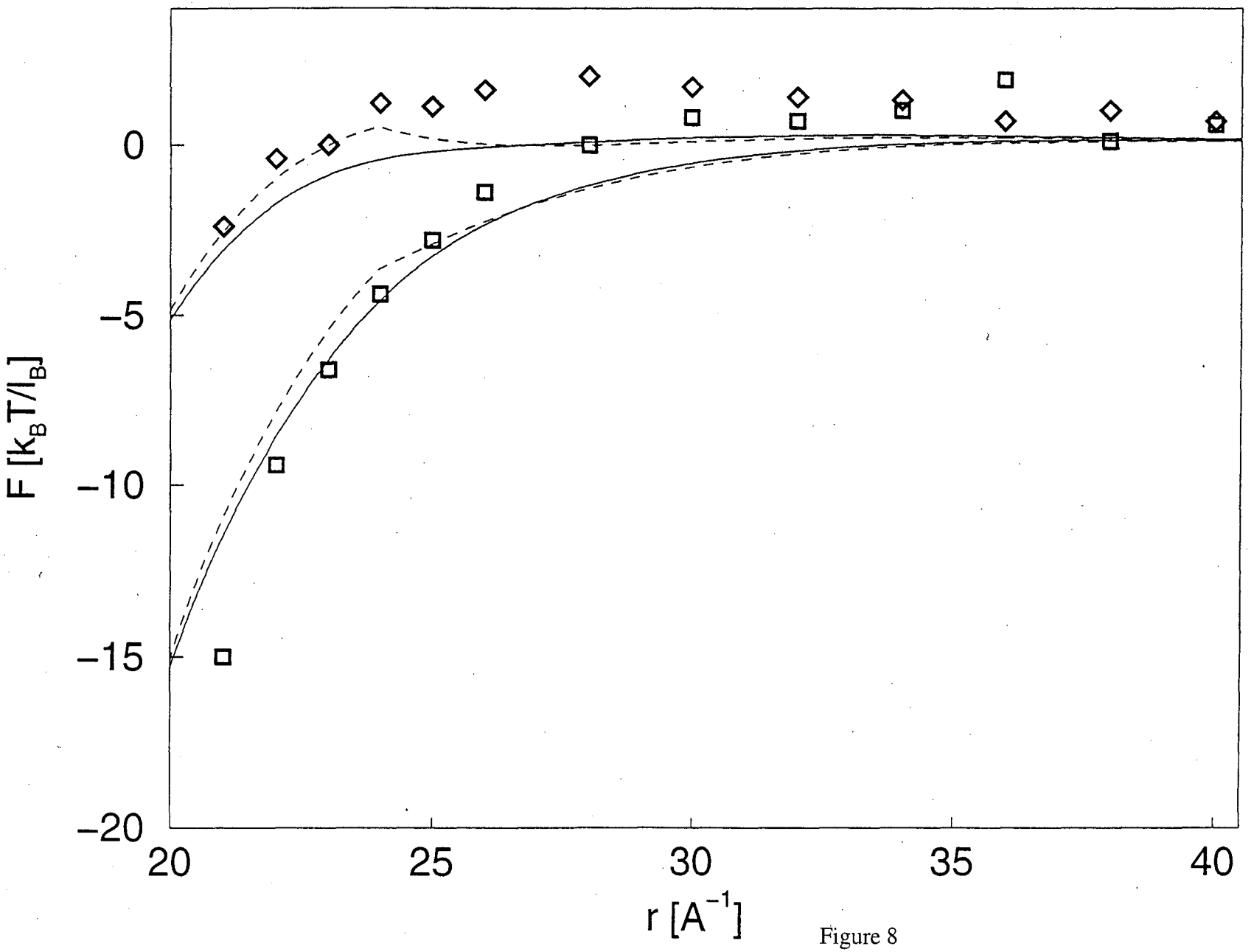


Figure 8

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