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ARTICLE

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Calculation of hydrodynamic properties of macromolecular bead models with overlapping spheres

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Abstract For the calculation of hydrodynamic properties of rigid macromolecules using bead modelling, models with overlapping beads of different sizes are used in some applications. The hydrodynamic interaction tensor between unequal overlapping beads is unknown, and an oversimplified treatment with the Oseen tensor may introduce important errors. Here we discuss some aspects of the overlapping problem, and explore an ad hoc form of the interaction tensor, proposed by Zipper and Durchschlag. We carry out a systematic numerical study of the hydrodynamic properties of a two-spheres model, showing how the Zipper-Durchschlag correction removes efficiently the numerical instabilities, and predicts the correct limits.

Key words Bead model · Rigid macromolecules · Overlapping · Diffusion coefficients · Intrinsic viscosity

Introduction and theory

Summary of theory

Hydrodynamic properties of rigid macromolecules can be calculated with two different methodologies. One of them is the whole body approach, in which the shape of the particle is reduced to a biaxial or triaxial ellipsoid, for which quasi-analytical theoretical results (Harding 1995) and computer programs (Harding et al. 1997) are available. The other one consists of modelling the arbitrary shape of the rigid macromolecule, with any desired level of detail, using bead models in which a certain number of frictional elements (beads) are arranged in such a way that the size and shape of the particle is adequately reproduced (Bloomfield et al. 1967; García de la Torre and Bloomfield 1977, 1981; García de la Torre 1989; Carrasco and García de la Torre 1999). The bead modelling methodology, which is the one considered in this paper, is being used by some workers who build models in which beads overlap to a lesser or greater extent, and this is assumed to be the cause of numerical problems. Here, we discuss the physical origin of those problems and propose a way to avoid them.

The calculation of the properties requires the evaluation of the frictional forces, $\mathbf{F}_i$, at each bead. These forces contain, first, a contribution from the friction at the bead itself, determined by the friction coefficient of the sphere, which according to Stokes law is given by:

$$\zeta_i = 6\pi\eta_0\sigma_i \tag{1}$$

with σ_i being the radius of the spherical bead and η_0 the solvent viscosity. Furthermore, owing to the hydrodynamic interaction effect, $\mathbf{F}_i$ contains contributions arising from its interaction with all the other beads, and depends on the other forces, $\mathbf{F}_j$. Accordingly, the forces are linearly related, and have to be obtained as the solutions of a linear system of equations, given by

$$\sum_{j=1}^{N} \mathbf{B}_{ij} \cdot \mathbf{F}_j = \zeta_i(\mathbf{u}_i - \mathbf{v}_i^0) \tag{2}$$

where $\mathbf{u}_i$ and $\mathbf{v}_i^0$ are respectively the velocity of bead i and the solvent velocity at the point occupied by its center. This velocity depends on the type of dynamics (translational, rotational, shear flow, etc.) that is being considered. The matrices $\mathbf{B}_{ij}$ are given by:

$$\mathbf{B}_{ij} = \delta_{ij}\mathbf{I} + (1 - \delta_{ij})\zeta_i\mathbf{T}_{ij} \tag{3}$$

where $\mathbf{T}_{ij}$ is the so-called hydrodynamic interaction tensor, and δ_{ij} is Kronecker's delta. The system of equations can be written in a more compact form as

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$$\mathscr{B} \cdot \mathscr{F} = \mathscr{U} \tag{4}$$

where $\mathscr{F}$ and $\mathscr{U}$ are supervectors of dimension $3N$ containing respectively the forces $\mathbf{F}_i$ and the relative velocities $\mathbf{u}_i - \mathbf{v}_i^0$, and $\mathscr{B}$ is a matrix of dimension $3N \times 3N$ containing the 3×3 blocks, $\mathbf{B}_{ij}$. The solution of the system can be obtained from the inverse supermatrix:

$$\mathscr{C} = \mathscr{B}^{-1} \tag{5}$$

For the hydrodynamic interaction tensor, $\mathbf{T}_{ij}$ in Eq. (3), the primary and simplest choice is the Oseen tensor (Oseen 1927), given by:

$$\mathbf{T}_{ij} = (8\pi\eta_0 R_{ij})^{-1}(\mathbf{I} + \mathbf{R}_{ij}\mathbf{R}_{ij}/R_{ij}^2) \tag{6}$$

where $\mathbf{R}_{ij}$ is the distance vector from bead i to bead j. Equation (6) is strictly valid for widely separated beads, i.e. when $R_{ij} \gg \sigma_i + \sigma_j$. In addition to its approximate nature, its use in Eq. (3) may give rise to singularities in the matrix inversion, Eq. (5), that would yield quite erroneous results. This situation, which is more likely in models with tightly packed beads, was noted years ago (Zwanzig et al. 1968), and motivated the development of the modified interaction tensors of Rotne-Prager (Rotne and Prager 1969) and Yamakawa (Yamakawa 1970), for identical beads, that was later generalized to non-identical beads by García de la Torre and Bloomfield (1977). The modified interaction tensor reads:

$$\mathbf{T}_{ij} = (8\pi\eta_0 R_{ij})^{-1} \times \left(\mathbf{I} + \frac{\mathbf{R}_{ij}\mathbf{R}_{ij}}{R_{ij}^2} + \frac{\sigma_i^2 + \sigma_j^2}{R_{ij}^2}\left(\frac{1}{3}\mathbf{I} - \frac{\mathbf{R}_{ij}\mathbf{R}_{ij}}{R_{ij}^2}\right)\right) \tag{7}$$

(the original Rotne-Prager-Yamakawa expression contains $2\sigma^2$ in place of $\sigma_i^2 + \sigma_j^2$).

This summary of theory is valid for any hydrodynamic property: translational, rotational and viscosimetric. The differences from one to another are (1) the molecular and solvent velocities to be used in Eq. (2), and (2) the form in which the forces so obtained determine the specific property; more details on the procedures can be found elsewhere (García de la Torre and Bloomfield 1981; García de la Torre 1989; Carrasco and García de la Torre 1999). A convenient computational tool, in which all the existing bead-model theory is implemented, is the HYDRO computer program (García de la Torre et al. 1994).

The problem of bead overlapping

The above summarized theory is valid for non-overlapping beads ($R_{ij} > \sigma_i + \sigma_j$). If elements in the bead models overlap, several problems may arise. The forms of the hydrodynamic interaction tensors in Eqs. (6) or (7) are not strictly valid, but this is not the only difficulty; furthermore, the elements which overlap are not full spheres but truncated spheres, and therefore Eq. (1) for the element's friction coefficients is not correct.

Nonetheless, Rotne and Prager (1969) derived an interaction tensor for overlapping spheres of identical sizes that, when applied to a system of only two spheres, gives adequate results. Their expression is:

$$\mathbf{T}_{ij} = \frac{1}{6\pi\eta_0\sigma}\left(\left(1 - \frac{9}{32}\frac{R_{ij}}{\sigma}\right)\mathbf{I} + \frac{3}{32}\frac{\mathbf{R}_{ij}\mathbf{R}_{ij}}{R_{ij}\sigma}\right) \tag{8}$$

It has been proposed that this tensor may be used in cases when some overlap may eventually occur. An example of such situation would be the calculation of hydrodynamic properties of conformations of flexible polymers in the theta state (see, for instance García de la Torre et al. 1982), modelled as chains of identical beads. The "phantom" (not self-avoiding) nature of the chain model allows that two elements separated along the contour length may be superimposed on each other (Yamakawa 1971). In such situations, bead overlap is fortuitous and infrequent, and the use of the Rotne-Prager tensor avoids numerical difficulties. It was therefore included in the HYDRO computer program (García de la Torre et al. 1994) to handle adequately those situations.

Unfortunately, the hydrodynamic interaction tensor for unequal overlapping beads is unknown. In HYDRO, provision was made for this eventual possibility (in the assumption that it would be a rare situation, as described above), switching the interaction tensor to the simple Oseen form, Eq. (6).

In recent years, several authors have developed an interesting application of bead modelling in which the hydrodynamic properties of rigid biological macromolecules are predicted from the high-resolution structures obtained from X-ray diffraction, NMR, or similar atomic-level techniques. As kindly pointed out by a referee, one possibility in this line, based on the whole-body approach, consists of fitting the crystal structure to a triaxial ellipsoid following a published procedure (Taylor et al. 1983) and then calculate the hydrodynamics from the theory and computer programs for ellipsoids (Harding et al. 1997). On the other hand, other workers (Byron 1997; Hellweg et al. 1997; Zipper and Durchschlag 1997) have preferred a bead model approach, in which beads represent chemical groups (e.g., amino acid residues in proteins) or even atoms. It is amazing that the continuum hydrodynamics theory, on which bead model treatments are based, works fairly well when the suspended entities (frictional elements) have a size of the same order as the solvent molecules. However, this good performance has been proved, even for rather small molecules (Espinosa and García de la Torre 1987; Venable and Pastor 1988). With this idea in mind, some authors have developed models in which, owing to requirements or particularities of the specific modelling procedures, the beads have different sizes and show a remarkable amount of overlapping (Byron 1997; Hellweg et al. 1997; Zipper and Durchschlag 1997).

In one of such applications, Zipper and Durchschlag (1997) found that HYDRO could give erratic results (the computer program may even abort), and they correctly

associated this situation to the Oseen description of hydrodynamic interaction. From hydrodynamic theory we know, as commented above, that such singularities can be expected (Zwanzig et al. 1968), and are more likely when the degree of overlapping is important. Such deficiency is associated with the nearly singular behavior of supermatrix $\mathscr{B}$, which causes errors in its inversion [Eq. (5)].

Then, Zipper and Durchschlag (1997, 1998) proposed and implemented in HYDRO an ad hoc modification in the hydrodynamic interaction tensor (which is hereafter denoted as ZD-HI), in which the Rotne-Prager tensor for equal beads is also used for overlapping non-identical beads, just replacing the bead radius in Eq. (8) so that the radius used in that case is a value intermediate between the two bead radii:

$$\sigma_{\text{mean}} = \left[\left(\sigma_1^3 + \sigma_2^3\right)/2\right]^{1/3} \tag{9}$$

This choice is such that the volume of two beads of radius σ is the same as that of the pair of beads σ_1 and σ_2. Other choices of σ_{mean} were found to work nearly as well. In this work we have tested the choice consisting of taking just the arithmetic mean:

$$\sigma_{\text{mean}} = (\sigma_1 + \sigma_2)/2 \tag{10}$$

In either case, this is an empirical solution, not based on theoretical grounds, but Zipper and Durchschlag have found that it yields results that are at least acceptable, and removes the singularity in $\mathscr{B}$. In the present communication, we present an in-depth analysis of the performance of this procedure, carrying our a systematic study of a two-sphere hydrodynamic model.

In addition to the ZD-HI correction, we point out the need to account for bead overlapping in another aspect, related to the calculation of rotational quantities and intrinsic viscosity (García de la Torre and Carrasco 1998). An improved calculation of those properties may require the introduction of a correction that depends on the volume of the model. This improvement has been worked out for models with non-overlapping beads, for which the model volume is just the sum of the volumes of the beads:

$$V_{\text{m}} = (4\pi/3)\sum \sigma_i^3 \tag{11}$$

Although the volume corrections for rotation and intrinsic viscosity have not been theoretically derived for overlapping beads, it seems reasonable to still use them, taking a model volume in which overlapping has been adequately discounted.

If the extent of overlaps is moderate, it can be approximately assumed that all the overlaps are binary, i.e., any region of overlap belongs to two beads, but not to three or more. Thus, the volume of the model can be expressed as:

$$V_{\text{p}} = (4\pi/3)\sum_{i=1}^{N} \sigma_i^3 - \sum_{i=2}^{N}\sum_{j=1}^{i-1} V_{ij}^{\text{overl}} \tag{12}$$

where

$$V_{ij}^{\text{overl}} = 2\pi/3\Big(\sigma_i^3\left[1 - \cos\theta_i - \tfrac{1}{2}\cos\theta_i \sin^2\theta_i\right]. \\ +\sigma_j^3\left[1 - \cos\theta_j - \tfrac{1}{2}\cos\theta_j \sin^2\theta_j\right]\Big) \tag{13}$$

is the discount for binary overlaps.

Results and discussion

The model that we employ to test the treatment of overlapping beads consists of just two spheres with radii σ_1 and σ_2, separated by a center-to-center distance, d_{12}. Unfortunately, no exact theory is available for intermediate degrees of overlap; only the two limits (two touching spheres, and one sphere within the other one) have exactly known results. However, as described below, even this simple case shows clearly the strong numerical divergence that an inadequate use of overlapping may cause. For the presentation of results in a reduced form, the unit of length will be adequately chosen, and the dimensionless radii, reduced with that unit, are denoted as σ_1^* and σ_2^*. The properties that we calculate are the translational friction coefficient, the rotational friction coefficient, and the intrinsic viscosity, that will be presented in the reduced forms:

$$f_{\text{t}}^* = f_{\text{t}}/(6\pi\eta_0 u) \tag{14}$$

$$f_{\text{r}}^* = f_{\text{r}}/(6\pi\eta_0 u^3) \tag{15}$$

$$[\eta]^* = [\eta]M/N_{\text{A}}u^3 \tag{16}$$

where u is some adequately chosen unit of length. In Eq. (15), f_{r} is the mean rotational friction coefficient. For an axially symmetric particle, as in our example, $f_{\text{r}} = 3/(2/f_{\text{r}}^{\perp} + 1/f_{\text{r}}^{\parallel})$, where $f_{\text{r}}^{\perp}$ and $f_{\text{r}}^{\parallel}$ are the rotational friction coefficient for rotation around a perpendicular and parallel axis, respectively.

In the first example (case A in Fig. 1), we consider two spheres separated by a fixed distance between their centers, which is taken in this case as the unit of length, $u = d_{12}$. We vary the radii σ_1^* and σ_2^*, keeping constant their sum $\sigma_1^* + \sigma_2^* = 2$; the size difference is expressed by the ratio $C = \sigma_1^*/\sigma_2^*$. For the numerical calculations we vary the size ratio from $C = 1$ to the limiting situation in which the small bead is fully within the larger one, and the hydrodynamic model reduces to a single sphere of radius $\sigma^* = 1.5$, for which the hydrodynamic properties are $f_{\text{t}}^* = 3/2$, $f_{\text{r}}^* = (4/3)(3/2)^3 = 4.49$ and $[\eta]^* = (10\pi/3)(3/2)^3 = 35.3$. The performance of the various procedures should be judged in terms of their ability to converge to these limits when $C \to 1/3$. In Fig. 2 we present the results for the three properties as functions of C. We observe that, with the new treatment of overlapping spheres, as overlapping increases, the results converge to the single-sphere limits much better than the results with the old treatment. In the case of

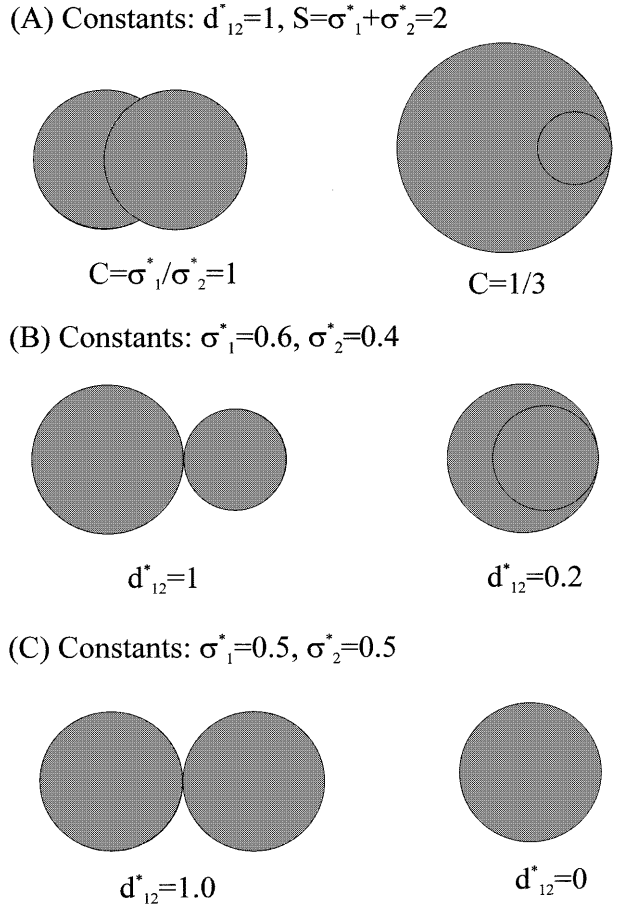

Fig. 1A–C Three cases for the two-sphere test problem

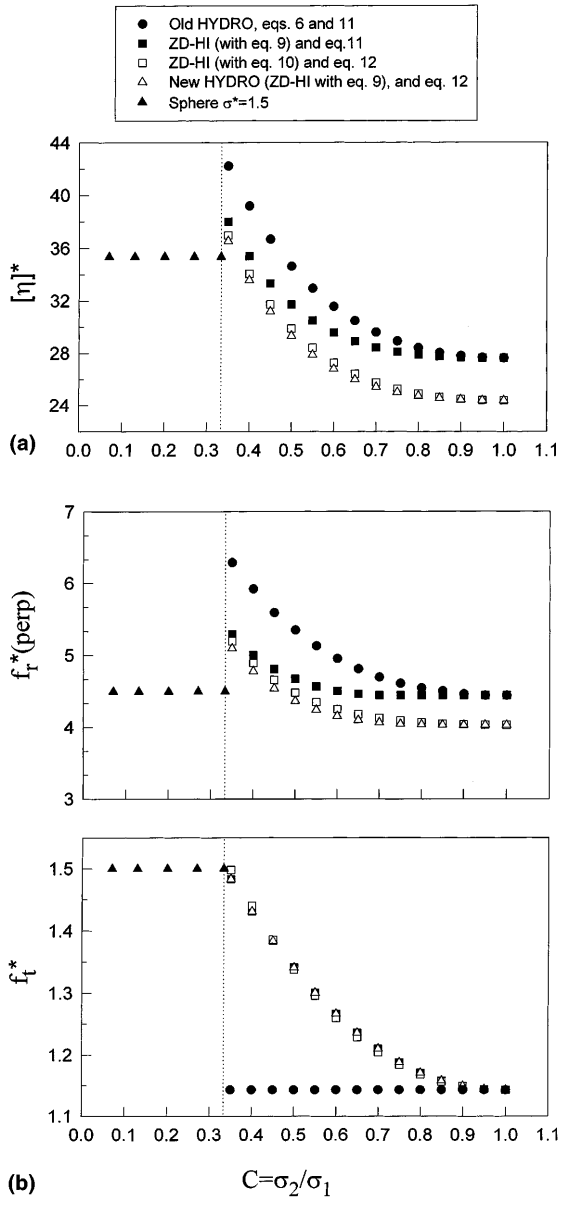

Fig. 2a, b Variation of hydrodynamic properties with the ratio of sizes (case A)

translational friction, the old treatment fails remarkably, as it predicts a constant f_t value, the same as for the pair of touching, non-overlapping spheres. For this property, the volume correction does not apply, and the alternative choices of σ_{mean} are equivalent. For rotation and viscosity, the limits found with the new methods are closer to the correct ones than those obtained with the old procedure. The ZD hydrodynamic interaction introduces a substantial improvement, with a minor difference between the results from Eqs. (9) and (10), and the discount for overlapping in the model volume brings the result even closer. However, the rotational coefficient and the viscosity still deviate from the correct limit, and they even still exhibit and unphysical dependence of properties with C below $C = 1/3$ (data not shown in Fig. 2), i.e., when the small sphere is fully inside the larger one. Obviously, this circumstance has to be avoided when building bead models.

The next example that we present is case B which is displayed in Fig. 1. Here we have a pair of unequal spheres with fixed radii, $\sigma_1^* = 0.6$ and $\sigma_2^* = 0.4$, whose center-to-center distance varies. Now we take for the unit of length the sum $u = \sigma_1 + \sigma_2$. Below $d_{12}^* = 1$, the spheres overlap, and below $d_{12}^* = 0.2$ the smaller one is fully inside the larger one, which is again the physically limiting situation, and the properties are those of a single sphere with radius $\sigma^* = 0.6$. The results obtained for this case are presented in Fig. 3. The most remarkable finding is for the old treatment (based on the Oseen tensor), and with intermediate overlaps ($d_{12}^* = 0.6$–0.7) the results show an unphysical discontinuity, diverging to infinity for $d_{12}^* = 0.6$. The diffusion matrix in this situation is singular, and this behavior is the same as the one that was already described for Oseen interaction between non-overlapping beads (Zwanzig et al. 1968). With the new treatment of hydrodynamic interactions, the abnormal behavior disappears; below $d_{12}^* = 1$ the properties vary smoothly and reach the correct value for the limit of $d_{12}^* = 0.2$. Therefore, the new treatment of hydrodynamic interaction removes efficiently the singu-

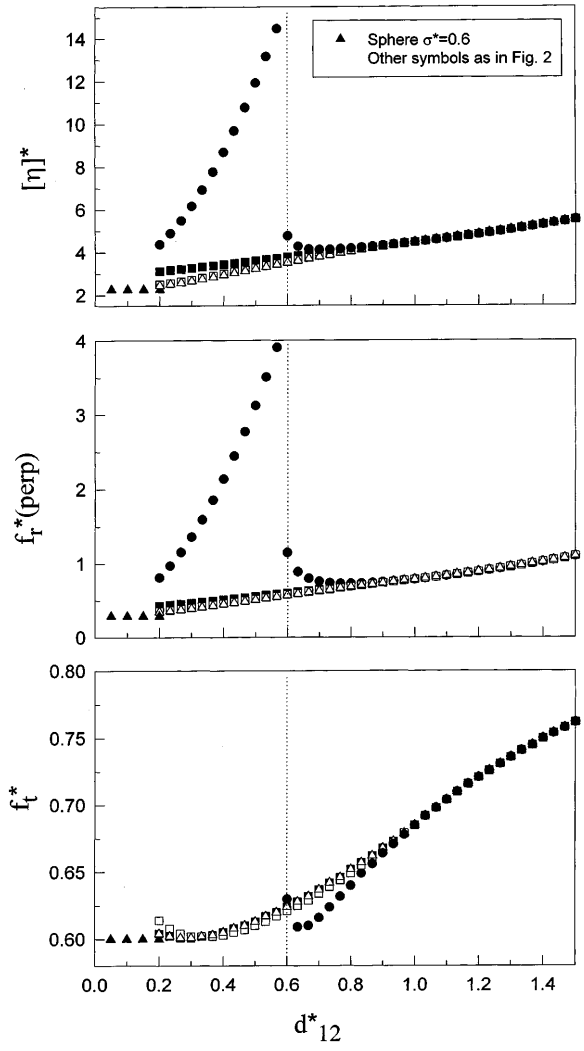

Fig. 3 Variation of hydrodynamic properties with the center-to-center distance between two unequal beads (case B)

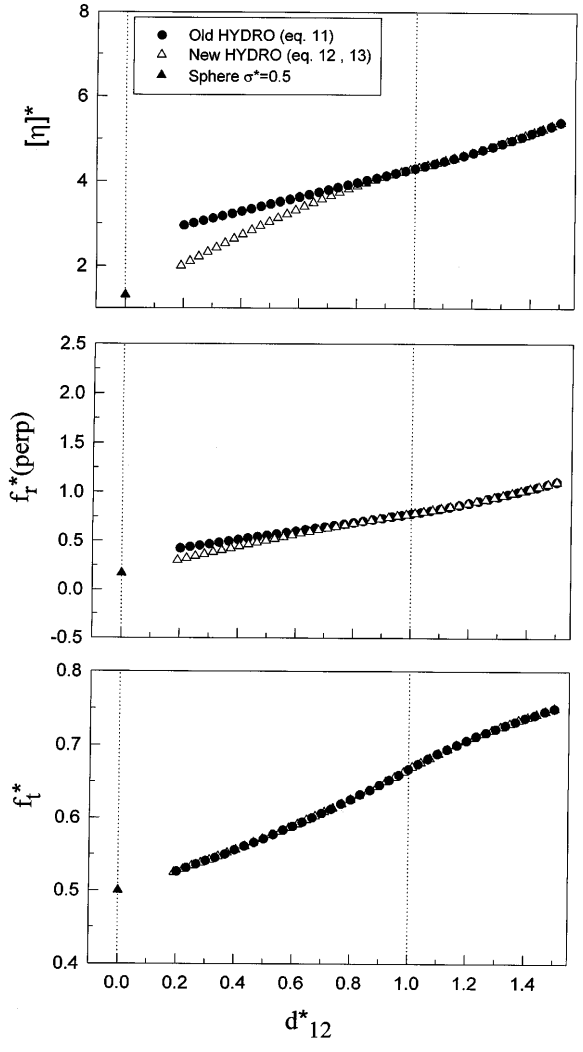

Fig. 4 Variation of hydrodynamic properties with the center-to-center distance between two identical beads (case C)

larities. The convergence to the correct limit is appreciably better with the volume from Eq. (12) than from Eq. (11); regarding the choice of σ_{mean}, Eq. 9 seems to perform slightly better than Eq. (10).

In the third example (case C in Fig. 1), we consider two identical overlapping beads, with variable center-to-center distance, d_{12}. In regard to the hydrodynamic interaction, this case was already well described in the old version of HYDRO, using the Rotne-Prager tensor, Eq. (7), but still the correct volume has to be introduced. The limit in which the model reduces to a single sphere is $d_{12}^{*} = 0$. In Fig. 4 we observe how there is a smooth transition from the non-overlapping region to the overlapping region, and a correct convergence to the single-sphere limit is achieved only when the volume is evaluated from Eq. (12).

Thus, according to all the evidence found in this systematic analysis of the two-sphere problem, we conclude that the treatment of overlapping spheres as proposed by Zipper and Durchschlag (1997, 1998) performs adequately, removing efficiently the singularities in the calculation and representing well the physical limits of the problem. We emphasize that, as discussed above, overlapping in bead models should be avoided when possible, but if it is required in some modelling procedures, the ad hoc expression of the interaction tensor proposed here for non-identical overlapping beads should be preferred to the simplistic representation based on the Oseen tensor.

The present version of the computer program HYDRO contains the new treatment. This program, along with the related computer program SOLPRO, can be freely downloaded from our web site, http://leonardo.fcu.um.es/macromol.

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