# Comparison of Approximate Methods for Calculating the Friction Coefficient and Intrinsic Viscosity of Nanoparticles and Macromolecules

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ABSTRACT: A number of methods for estimating the translational friction coefficient *f* and the intrinsic viscosity  $[\eta]$  of polymers and nanoparticles have been proposed. These methods range from first-principles "boundaryelement" or "bead-model" solutions of the Stokes equation employing a precise description of particle shape, to coarse-grained descriptions of polymer structures and approximate computational methods at an intermediate level of description, and finally to phenomenological estimates that relate *f* to the surface area of the particle. Analytic treatments normally involve slender-body and various "preaveraging" approximations, etc., that render the calculation analytically tractable, but numerically uncertain. Powerful numerical path-integral methods have become available in recent years that allow the assessment of the accuracy of the various approximate methods. We compare several methods of computing *f* and  $[\eta]$  to determine their applicability to various classes of particle shapes.

#### 1. Introduction

The translational diffusion coefficient D of a dilute solution of Brownian particles of arbitrary size and shape is related to the Stokes friction coefficient f through the Einstein relation<sup>1,2</sup>

$$D = \frac{k_{\rm B}T}{f} \tag{1}$$

where  $k_{\rm B}$  is Boltzmann's constant and *T* is the temperature. This relationship indicates that diffusion is governed by competition between thermal energy and viscous forces, which respectively excite and dampen particle motions. Dimensional analysis implies that we can write *f* in three dimensions *formally* as

$$f = 6\pi\eta R_{\rm h} \tag{2}$$

where the "hydrodynamic radius"  $R_h$  has the units of length in three dimensions and where  $\eta$  is the solvent shear viscosity. Stokes' original calculation<sup>3</sup> of *f* indicates that  $R_h$  of a spherical particle equals its radius, while for other shapes  $R_h$  provides a useful measure of particle size and shape.

A second dynamical measure of particle size is the "intrinsic viscosity",  $[\eta]$ , or, more formally, the "virial coefficient" for the solution viscosity. The product

$$J = M[\eta] \tag{3}$$

where M is the molar mass of the particle, has units of molar volume. Einstein's calculation of the viscosity of a dilute suspension of spheres<sup>1,2</sup> indicates that the "hydrodynamic volume" can be defined as

$$V_{\rm h} = \frac{2J}{5N_{\rm A}} \tag{4}$$

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where  $N_A$  is Avogadro's number.  $V_h$  is the volume of a sphere having an equivalent intrinsic viscosity and provides another basic measure of particle size and shape.

There is obvious value in predicting the diffusivity of Brownian particles in a processing or a biological context. Furthermore, the hydrodynamic radius and hydrodynamic volume are important in macromolecular characterization by dynamic light scattering, gel permeation chromatography, sedimentation measurements, and other characterization measurements.<sup>1,4</sup> It is standard practice to validate models of molecular size or shape by measuring these shape functionals and their ratios.<sup>4</sup> The general problem has been brought into renewed focus recently in connection with the characterization of nanoparticle dispersions, such as nanocomposites of exfoliated clay, carbon nanotubes, and other complex-shaped "nanoparticles".

Numerous methods have been introduced to estimate  $R_h$  and  $[\eta]$ . Douglas and Freed review some of the history of this problem leading up to recent renormalization group (RG) calculations of these properties for polymers in solution.<sup>5</sup> Unfortunately, the available analytic methods of computing these properties often involve uncontrolled approximations, such as the configurational preaveraging approximation (defined below) or the truncation of the  $\epsilon$ -expansion in RG calculations. The accuracy, therefore, of these computations is uncertain.<sup>5</sup> The difficulties are so severe that there is no known analytic method for accurately calculating the friction coefficient of a single ideal random walk chain. The difficulty of this problem is comparable to solving the  $\phi^4$  field theory in three dimensions.<sup>5</sup> In other words, an exact analytic solution for even this special class of objects (flexible polymer chains without excluded volume interactions) is apparently unattainable, and numerical approaches or approximation schemes must be used.

Numerical methods that consider complex-shaped objects to be built up formally by a superposition of idealized hydrodynamic point sources ("beads") have been very useful in obtaining reliable information about these transport properties. In principle,

10.1021/ma061069f CCC: \$37.00 © 2007 American Chemical Society Published on Web 03/13/2007 bead-model computations allow for the essentially exact computation of hydrodynamic properties of complex-shaped particles, as long as the particles are described by a large number of beads. However, computational expediency often makes such an "exact" approach unfeasible, and approximate bead-model computations such as Hydro have been introduced for the purpose of routine estimates of hydrodynamic properties<sup>6–14</sup> by scientists involved in structural studies of complex-shaped macromolecules and particles. Below, we compare our new computational method for calculating transport properties to the valuable working tool (Hydro) to understand the relative advantages of each method. In our personal view, the description of complex-shaped objects in terms of hydrodynamic beads is somewhat cumbersome, requiring a large number of beads when we want to describe fine structural details. We feel that the need exists for more physically natural and computationally efficient approaches to calculating the hydrodynamic properties of complex-shaped particles. This led us to develop and validate a numerical path-integration (PI) method that has proven quite accurate in estimating  $R_{\rm h}$  or  $[\eta]$  for arbitrarily shaped objects. Our PI method is not exact (see below), but the uncertainties are well prescribed by our former studies. This tool provides a reliable standard for testing the performance of other approximate computational methods.

Of course, it is always possible to solve Stokes' equation directly by boundary-element techniques, in which the surface of the macromolecule is tiled with a discrete set of polygons. Applications of such techniques to the transport properties of macromolecules include the work of Youngren and Acrivos,15 Brune and Kim,<sup>16</sup> Allison,<sup>17</sup> Zhao and Pearlstein<sup>18</sup> and Aragon.<sup>19</sup> Such calculations are also formally exact in the small-element limit, but computation times are  $O(N^3)$  where N is the number of boundary elements. Obviously, such calculations, as well as high-resolution bead-model calculations involving a large number of beads, would be an appropriate standard for judging other approximation schemes. (Indeed, most of our confidence in the approximations stated in eq 7 below is founded on just such calculations and a limited number of results for which exact analytic computations are possible.<sup>20,21</sup>) The path-integration technique can also be applied to any collection of N polygonal boundary elements, but with computation times of only O(N).<sup>22–24</sup> Admittedly, the front factor is generally larger for the pathintegration technique so that it is expected to be slower for small N, but for large enough N, the path-integration method will always be faster. (The computational time of bead-model calculations also scales as  $O(N^3)$ , so the efficiency of this method is comparable to the boundary-element method.) For reasons of speed and flexibility, we have chosen to use the pathintegration technique as the standard against which to judge other approximate techniques.

### 2. Hydrodynamic-Electrostatic Interrelations

Our path-integration approach for calculating the transport properties of complex-shaped particles relies on an analogy between hydrodynamics and electrostatics that is based on the simple observation that an angular preaveraging of the Green's function for the Stokes equation (the Oseen tensor) is exactly the Green's function for Laplace's equation, or the Newtonian potential,<sup>25–27</sup> 1/r. (In fact, such preaveraging of the Oseen tensor is a relatively standard approximation in the theory of the transport properties. In other words, many authors have applied the hydrodynamic—electrostatic analogy, often without knowing it.) There are many interrelations between electrostatic, hydrodynamic, and elastostatic properties, some exact and others approximate, that derive from this simple observation. These are discussed at length by Douglas and Garboczi28 and by Mansfield and Douglas.<sup>24</sup> In particular, we are generally concerned with the energies of fields associated with the presence of particles. These energies may either be the selfenergies of the particle generated by the particle itself, as in the electrostatic field energy of a charged conducting sphere in space, or they are reaction field energies caused by the presence of a particle in an applied external field, as in the case of a charged conductor placed within an applied electric field. In a hydrodynamic context, the translational friction coefficient of a Brownian particle is a particle self-field energy, while the intrinsic viscosity corresponds to a reaction-field energy functional.<sup>28</sup> The interrelations between these fundamental hydrodynamic, elastic, and electrostatic "shape functionals" ultimately derive from a common formulation of these boundary value problems in a continuum mechanics description that involves the Laplacian operator, which in turn engenders a general connection with Brownian motion that we exploit below.

The hydrodynamic–electrostatic property interrelations just mentioned imply, among other things, the following simple direct relations for the hydrodynamic radius  $R_h$  and intrinsic viscosity  $[\eta]^{25-27}$ 

$$R_{\rm h} = q_{\rm h}C \tag{5}$$

$$J = M[\eta] = q_{\eta} N_{\rm A} \langle \alpha \rangle \tag{6}$$

where C and  $\langle \alpha \rangle$  are the electrostatic capacity and the mean electrostatic polarizability (1/3 the trace of the electrical polarizability tensor  $\alpha$ ) of a conducting object. The capacity C also governs the rate at which heat diffuses from a body at fixed temperature into the surrounding medium and other transport properties relating to shape (e.g., the Smoluchowki rate constant governing the steady-state diffusive flux of chemical species to or from a source having the shape of the particle in question).<sup>24,28</sup> By direct analogy,  $R_{\rm h}$  governs the rate of momentum diffusion away from a particle under Brownian motion, which accounts for dissipation (friction). The average polarizability  $\langle \alpha \rangle$  likewise has many physical applications such as the leading virial coefficient describing the electrical conductivity and thermal conductivity of a suspension of arbitrarily shaped objects having high electrical or thermal conductivity compared to the suspending medium.<sup>24,28</sup> The relation eq 6 arises because the application of shear to a fluid with suspended particles of general shape creates a stress dipole ("stresslet") that reacts upon the applied field in much the same way that a conducting particle perturbs an electric field. There are well-known, rigorously proven, variational inequalities or "isoperimetric relations" that imply, for all objects of a given volume, that C and  $\langle \alpha \rangle$  are minimized for a sphere.<sup>20</sup> The electrostatic-hydrodynamic analogy implies that  $R_h$  and  $[\eta]$  are also minimal for spheres, at least to within the accuracy of the analogy, and on the basis of our experience, we conjecture that this is in fact the case. Therefore, these functionals are suitable for shape classification, measuring departures from sphericity. in addition to their applications relating to the characterization of particle structure.

While  $q_h$  and  $q_\eta$  are not universal constants for all objects, eqs 5 and 6 have been shown to hold to a high degree of approximation for the range of particle shapes for which exact or accurate numerical results exist:<sup>20,21,26,28</sup>

$$q_{\rm h} = 1.00 \pm 0.01$$
 and  $q_{\eta} = 0.79 \pm 0.04$  (7)

The uncertainty in eqs 5–7 is usually comparable to experimental uncertainty, so that reliable estimates of  $R_h$  and  $[\eta]$  can be obtained on the basis of these relations.

These electrostatic—hydrodynamic property interrelations are also important because *C* and  $\langle \alpha \rangle$  can be simultaneously calculated to high accuracy for arbitrarily shaped objects using a numerical path-integration method that exploits a fundamental connection between Brownian motion and Laplace's equation.<sup>22,23,27,29,30</sup> In particular, this procedure involves launching random walks from a sphere enclosing the "probed" body and collecting statistics on the fraction of trajectories that hit the body as a function of the position from which they are initiated on the launch sphere. This Monte Carlo sampling method is exact for *C* and  $\langle \alpha \rangle$  in the limit of an infinite number of random walk trajectories, and finite-sampling uncertainties can be estimated from the variance in the results of several independent integrations. We are thus in a position to estimate *C*,  $\langle \alpha \rangle$ , *R*<sub>h</sub>, and [ $\eta$ ] for arbitrarily shaped objects via eqs 5–7.

Because  $q_{\eta}$  is given in eq 7 only to within 5%, our approach engenders a comparable uncertainty in [ $\eta$ ]. This variation in  $q_{\eta}$ arises entirely from its dependence on particle shape (e.g.,  $q_{\eta}$ = 0.833 for single spheres, but only 0.75 for elongated ellipsoids).<sup>20</sup> The value 0.79 represents a compromise over all classes of shapes, and the uncertainty ±0.04 has been set large enough to cover practically all possible cases.<sup>20</sup> The pathintegration technique actually gives us all nine components of the polarizability tensor, and we are currently investigating the degree to which the shape dependence of  $q_{\eta}$  can be determined from the components of  $\alpha$ . If it can, then we should be able in the future to give estimates of [ $\eta$ ] with even less uncertainty.

A further description of the path-integration technique, its validation through comparison to shapes where exact results are known, and its application to the calculation of the transport properties of proteins and other particle shapes of practical interest may be found in our previous work.<sup>22–24</sup> In the present work, we assess the accuracy of other approximate methods of estimating  $R_h$  or  $[\eta]$  and use the path-integration technique as the standard against which to judge these other methods.

## **3.** Some Approximate Methods for Calculating $R_h$ or $[\eta]$

A. Numerical "Bead-Model" Calculations. A standard approach in the computation of dynamical properties of polymers, employed, for example, in the well-known Rouse-Zimm formalism,<sup>1,2</sup> is to model individual segments as "beads" and to treat each bead as a point source of hydrodynamic interaction, the strength of the interaction being controlled by the size of the bead. The hydrodynamic interaction is transmitted through space via the Oseen tensor describing a point hydrodynamic source. (Taking the angular average of this tensor gives a Newtonian potential, 1/r, which is the Green's function for the Laplacian, as mentioned above.) By placing many of these point sources over the surface of a rigid body, the friction coefficient and the intrinsic viscosity can be accurately estimated. The rigid-body assumption implies that we are not concerned with particles exploring conformational degrees of freedom as they diffuse. A more rigorous treatment of flexible particles would require the time-dependent analogue of the Oseen tensor as well as other complications. Zimm<sup>31</sup> has forcefully argued that the rigid-body approximation is sufficient for the accurate computation of  $R_h$  or  $[\eta]$  (low-frequency transport properties) of flexible polymers. He recommends computing  $R_h$  or  $[\eta]$  independently for an ensemble of conformations, treating each as a rigid body, and taking ensemble averages. Although this approach has been challenged,<sup>32,33</sup> its

ability to rationalize observations on the properties of flexible polymers is perhaps the strongest argument in its favor, and we also adopt this assumption below.

Bead-model calculations of  $R_h$ ,  $[\eta]$ , and other polymer properties are widely utilized and are generally considered to give accurate estimates.<sup>6–13</sup> The widespread use of this computational method is due, in part, to the availability of software.<sup>14</sup> In this work, we compare one of the most widely utilized and respected bead-model programs, HYDRO,<sup>14</sup> with our pathintegration calculations. In the interest of making direct comparisons, we apply both HYDRO and the path-integrations to the same bead structures. However, as already mentioned, the path-integral technique is not limited to bead configurations. We can also treat surfaces modeled by a collection of boundaryelement polygons.

We also consider several more approximate computational methods that are in widespread use. Our goal in these comparisons is to understand the physical nature of the errors involved in these approximations and to clarify the type of particle surfaces to which the approximate methods can be applied with confidence.

**B. The Kirkwood Double-Sum Formula.** Perhaps the most widely utilized analytic approximation of the friction coefficient of polymer chains is the "double-sum formula" first derived by Kirkwood for flexible and rodlike polymers<sup>1,2</sup>

$$D \approx \frac{k_{\rm B}T}{Nf_0} + \frac{k_{\rm B}T}{6\pi\eta N^2} \sum_{i=1}^{N} \sum_{j\neq i}^{N} \frac{1}{r_{ij}}$$
(8)

where N,  $f_0$ , and  $r_{ij}$  represent respectively, the total number of segments, the friction coefficient of an isolated segment, and the displacement between two segments. (Freire and Garcia de la Torre<sup>34</sup> also present a useful discussion of double-sum formulas in transport theory.) The "Coulombic" interaction term  $1/r_{ij}$  (the result of an angular averaging of the Oseen tensor in the approximate computations leading to eq 8) results from the solvent-mediated hydrodynamic interaction between segments *i* and *j*, and we therefore construe the sum as extending only over segments at the surface for cases other than flexible polymers, when the whole chain is a "surface". In the limit of large *N*, we can disregard the first term and replace the sums with surface integrals to obtain

$$D \approx \frac{k_{\rm B}T}{6\pi\eta R_{\rm K}} \tag{9}$$

with

$$\frac{1}{R_{\rm K}} = \frac{1}{A^2} \int_{\mathcal{S}} \mathrm{d}\mathbf{r}_1 \int_{\mathcal{S}} \mathrm{d}\mathbf{r}_2 \frac{1}{|\mathbf{r}_{12}|} \tag{10}$$

Here, *A* is the surface area of the body, and  $\int_S d\mathbf{r}$  represents a surface integral. We will refer to  $R_K$  as the "Kirkwood radius". According to eq 10, the classic Kirkwood approximation of the polymer hydrodynamic radius  $R_K$  is simply the harmonic mean distance between arbitrary pairs of points on the surface. Comparison of eqs 1, 2, and 9 indicates that  $R_K$  directly approximates  $R_h$  within the KR double-sum approximation:

$$R_{\rm h} \approx R_{\rm K}$$
 (11)

The derivation of eq 8 requires several approximations that make its accuracy uncertain. Previous investigations of the accuracy of eq 11 for random coils have been performed by Zimm<sup>31</sup> and by Garcia de la Torre et al.,<sup>35</sup> but we are unaware of appraisals for particles of other shapes. The double-sum formalism is still often invoked to describe the transport properties of complexshaped particle clusters such as DL aggregates.<sup>36</sup> Here we examine the approximation for a wide class of particle shapes to determine the classes of particles for which the approximation applies. We also address the physical reasons for which this classical mean-field approximation breaks down, since this problem is essential to developing a more accurate analytic theory of polymer transport properties. The errors of the doublesum formula can be avoided in the numerical bead model calculations, but we are not aware of any analytic expressions that go beyond the double-sum formula. It is this analytic tractability that accounts for the continued use of the KR doublesum approximation.

The double-sum KR approximation, when applied to flexible polymers, is written

$$D \approx \frac{k_{\rm B}T}{Nf_0} + \frac{k_{\rm B}T}{6\pi\eta N^2} \sum_{i=1}^N \sum_{j\neq i}^N \left\langle \frac{1}{r_{ij}} \right\rangle \tag{12}$$

In this form, it involves a configurational preaveraging approximation (see below),<sup>5</sup> which effectively replaces the ensemble of conformations with its mean average (a mean-field approximation as in critical phenomena). This is not the same approximation as the rigid-body approximation mentioned above or the angular preaveraging approximation involved in eqs 5-7. In the rigid-body approximation, we solve Stokes' or Laplace's equation independently for each conformation and average over all such solutions. In the configurational preaveraging approximation, we first average over conformations and then solve some form of Stokes' equation only once for the mean-field configuration. Configurational preaveraging can be a serious approximation. Large errors can arise for random-coil polymers and other complex-shaped, statistically defined objects. These errors result from "rare" configurations that make a disproportionate contribution to the ensemble average so this is a problem of "large deviation theory".<sup>24</sup> In the case of random coil polymers, the "rare" configurations are extended chain conformations with very large friction coefficients. These configurational preaveraging errors are particularly annoying from the standpoint of analytic computation since chain flexibility or excluded volume interaction influences these conformational fluctuations and thus can lead to substantial variations in the magnitude of configurational preaveraging errors resulting from the Kirkwood formula.<sup>5</sup> The good news is that these errors are expected to become very small when the chains become highly extended and shape or friction fluctuations are more limited. Below, we test the validity of eq 8 or eq 12 for a number of polymer shapes, both rigid particles and flexible random coils, to better establish the uncertainties of the Kirkwood approximation and the appropriate class of bodies to which this approximation should be applied.

The derivation of the KR double-sum formula employs the replacement of the Oseen tensor with 1/r, but it also requires further approximations. Therefore, it is less accurate than predictions based solely on the electrostatic—hydrodynamic analogy, but it still has an interesting electrostatic interpretation. A charge Q distributed uniformly over a surface has self-energy  $Q^2/2R_K$ , while the self-energy of a perfect conductor of the same shape is  $Q^2/2C$ . Since the perfect conductor possesses the charge distribution of minimum energy, we obtain immediately the

following inequality, which has already been demonstrated for random  $\operatorname{coils}^{35}$ 

$$R_{\rm K} \le C \tag{13}$$

and which implies that the double sum always underestimates the friction coefficient and always overestimates the diffusion coefficient. Furthermore, just as *C* represents the proportionality between *Q* and *V* for a perfect conductor,  $R_{\rm K}$  gives the proportionality between *Q* and  $\langle V \rangle$  for a uniform charge distribution.

This connection between *C* and the chain friction coefficient *f* can be understood more precisely from a direct computation of the capacity of a polymer chain of conducting particles using a direct extension of the KR theory to the corresponding electrostatic problem.<sup>21</sup> The average capacity *C* of a polymeric chain can be exactly described as a superposition of point sources described by Coulomb's law so that the average capacity of an ensemble tethered polymer chain of conducting beads each of capacity *c* formally equals

$$\langle C \rangle = c \int_0^N \langle \psi(\tau) \rangle \,\mathrm{d}\tau$$
 (14a)

$$\langle \psi(\tau) \rangle = 1 - c \int_0^N \left\langle \frac{\psi(\tau)}{|R(\tau) - R(\tau')|} \right\rangle d\tau' \qquad (14b)$$

where  $\langle \cdots \rangle$  represents an averaging of the polymer chain ensemble. The "configuration preaveraging approximation" in this notation equals

$$\left\langle \frac{\psi(\tau)}{|R(\tau) - R(\tau')|} \right\rangle \approx \left\langle \psi(\tau) \right\rangle \left\langle \frac{1}{|R(\tau) - R(\tau')|} \right\rangle \quad (14c)$$

where the average of a product is taken to be the product of the averages. Introducing this mean-field approximation into eq 14 makes it reduce exactly to the KR double-sum formula for  $R_h$ , defined by eq 12, where *c* is replaced by the bead friction coefficient,  $f_0$ . More generally, eq 14 describes the KR integral equation for the friction coefficient of a polymer chain where the Oseen interaction has been angularly averaged so that it replaced by the Newtonian potential for a point charge in three dimensions, 1/r. The recognition of the relation between eq 14 and the KR equation is the origin of the electrostatic analogy between *C* and *f* and forms the basis of our computational method.<sup>21</sup>

**C. Russell and Rayleigh Approximations.** Other approximations for  $R_h$  are available when the particle or polymer is either spheriodal or disklike. Such surfaces can naturally be approximated by a spherical harmonic expansion about either the sphere or the disk, and it is possible to calculate f, C, and other transport properties in a formally exact, but laborious, perturbation expansion.<sup>37–43</sup> Douglas and Freed<sup>5</sup> have noted that combining the Fourier expansions for f and C to leading order in such a perturbation expansion gives the result that both  $R_h$  and C can be approximately related to the particle's surface area A as

$$R_{\rm h} \approx C \approx R_{\rm Russell} = \left(\frac{A}{4\pi}\right)^{1/2}$$
 (15)

This approximation for *C* was introduced long ago by Russell, and we therefore refer to it as the Russell approximation and to  $R_{\text{Russell}}$  as the "Russell radius".<sup>44,45</sup> Pastor and Karplus<sup>46,47</sup> have advocated eq 15 on empirical grounds to estimate the friction coefficient of molecular segments in Brownian and Langevin

dynamics simulations of proteins and other complex polymers, despite its uncertain basis, and the method is frequently utilized in recent scientific literature relating to the molecular dynamics of proteins. It would clearly be valuable to assess the uncertainty of this relation and to determine the class of bodies to which it applies.

We can similarly develop a spherical harmonic expansion about the disk limit, as first considered by Rayleigh<sup>39</sup> in the case of *C*. This leads to the corresponding approximation suitable for "flat", membrane-like, bodies

$$R_{\rm h} \approx C \approx R_{\rm Rayleigh} = 2\pi^{-3/2} A^{1/2} \tag{16}$$

where *A* represents the area of the body in two dimensions. We will also assess the numerical validity of this relation.

Before moving to other matters, we note that the approximations eqs 15 and 16 become exact for the sphere and disk, respectively, so that

$$R_{\rm K} = R_{\rm Russell} = C = R_{\rm h} = R$$
 (spheres) (17)

and

$$R_{\text{Rayleigh}} = C = \frac{2R}{\pi}$$
 (circular disks) (18)

where *R* represents the radius of either the sphere or disk. The equality between  $R_h$  and *C* applies also to general triaxial ellipsoids of revolution, of which the sphere and disk are special cases.<sup>25</sup>

# **4.** Path-Integral Techniques for Computing *C* and $[\eta]$ ; Monte Carlo Techniques for Computing $R_{\rm K}$ and *A*

The path-integral technique, or "Zeno algorithm", for simultaneously estimating both f and  $[\eta]$  involves enclosing the surface in question inside a sphere, L; initiating  $N_W$  random walks at arbitrary points on the surface of L; and following their trajectories until they either move to within a small distance  $\epsilon$ of the surface or wander off to infinity.<sup>22,23,30,48</sup> The values of C and  $\langle \alpha \rangle$  are determined from the statistics of these walks. The technique is numerically exact for both *C* and  $\langle \alpha \rangle$  in the limit  $N_W \rightarrow \infty$  and  $\epsilon \rightarrow 0$ ; at finite  $N_W$  and  $\epsilon$  we expect relative errors of magnitude  $N_{\rm W}^{-1/2}$  and  $\epsilon/C$ , respectively. Then,  $R_{\rm h}$  and  $[\eta]$  are determined using eqs 5–7. In the calculations reported here, we typically use  $N_{\rm W} \approx 10^6 - 10^8$  and  $\epsilon/C \approx 10^{-6} - 10^{-5}$ . Uncertainties in our calculations are given in the tables but are not generally included in the text for reasons of space and readability. All uncertainties arise from two sources. The first is sampling error, which is estimated by performing 20 independent integrations, taking the mean of these 20 values as the final result and taking  $(20)^{-1/2}$  times the standard deviation of these 20 values as the uncertainty in the final result. The second source of uncertainty arises from eq 7.

The Zeno algorithm requires us to compute the minimum distance between arbitrary points outside the surface and the surface itself.<sup>22</sup> We generally examine bodies that are constructed as unions of some number N of simple component objects such as boundary eleents or beads. In every case, therefore, the minimum distance to the surface is determined by computing the minimum distance to each component and taking the minimum over all components. Computation times, therefore, are O(N). Boundary-element solutions<sup>15–19</sup> of Stokes' or Laplace's equation as well as the bead-model calculations<sup>6–13</sup> are  $O(N^3)$  for N the number of boundary elements or beads, so that the path-integration technique is inherently faster when N

is large. All additional details on the technique are given in the literature.  $^{22,23}$ 

We calculate  $R_{\rm K}$  by generating  $N_{\rm S}$  points distributed randomly and uniformly over the surface and computing the harmonic mean by averaging over successive pairs of points. Provided we can sample all regions of the surface without bias, we expect good accuracy, with relative errors on the order of  $N_{\rm S}^{-1/2}$ . Uncertainties are again estimated by taking 20 independent integrations. The same integration also permits determination of *A*. In the Supporting Information accompanying this paper, we describe the techniques followed to take unbiased samples over complex surfaces.

# 5. Comparative Calculations for Random Coils and Other Special Structures

We have considered three different random-coil polymers models. The first is a pearl-necklace model without excluded volume, discussed in more detail elsewhere.<sup>24</sup> We have also assembled ensembles of simple-cubic lattice self-avoiding walks and self-avoiding rings. The self-avoiding walks were generated by the pivot algorithm. The self-avoiding rings were generated concurrently, taking each instance of a self-avoiding walk returning to a site adjacent to the origin as one instance of a self-avoiding ring. (Obviously, this approach for generating rings becomes inefficient at large N; nevertheless, we were able to generate adequate ensembles of about 50 000 members for Nas large as 1200 as well as one of about 4500 members at N =5000.) The Kirkwood radius for self-avoiding walks and rings was calculated via eq 12. To form a space-filling body for the path-integration calculation, each walk or ring was modeled as an array of unit cubes, one cube per lattice site. Because the path-integration is more computationally intensive than eq 12, it was limited to only 1000 walks or rings at each value of Nselected randomly from the larger ensemble. The ensemble averages for C and  $\langle \alpha \rangle$  were then used to determine  $R_{\rm h}$  and  $[\eta]$ as in eqs 5-7. A number of interesting results concerning the transport properties of self-avoiding walks have emerged in these calculations and will be reported elsewhere.49 In this paper, we concentrate on the validity of the Kirkwood double-sum formula.

*Random Coils in the*  $\theta$ *-State.* When both static and dynamic light scattering studies began to appear for random coil polymers, it was immediately noticed that theoretical predictions for  $R_{\rm g}/R_{\rm h}$  were inconsistent with experiment.<sup>50–53</sup> This inconsistency is attributed to approximation errors in the double-sum formula or other computations based on the configurationally preaveraging approximation.<sup>31,35</sup> For  $\theta$ -state polymers (approximated by random walk chains), the Kirkwood double-sum formula predicts  $R_{\rm g}/R_{\rm K} = 8/(3\sqrt{\pi}) \simeq 1.50$ , while experiments yield  $R_{\rm g}/R_{\rm h} \simeq 1.27$ . Calculations based on bead models with non-preaveraged Oseen tensor give  $R_g/R_h = 1.28 \pm 0.02$ ,<sup>31,34,35</sup> in much better agreement with experiment. Application of the path-integration technique to a pearl-necklace model without excluded volume yields  $R_g/R_h = 1.253 \pm 0.003$ ,<sup>24</sup> in qualitative accord with an earlier, but less precise, numerical study utilizing path-integration,<sup>27</sup> and it yields  $C/R_{\rm K} = 1.201 \pm 0.003$ .<sup>24</sup> These calculations all indicate, therefore, that the double-sum formula is in error by about 20%. Renormalization group theory estimates of the error due to the configurational preaveraging approximation, although highly uncertain, are also consistent with these calculations.<sup>4</sup> The fractal mass scaling characteristics of  $R_h$  and  $[\eta]$  for flexible polymer chains and other fractal objects are reported elsewhere.<sup>22</sup> The scaling law for  $R_{\rm h}$  has also been recently examined by Tseng et al.54 for a variety of model fractal aggregates based on the Zimm bead model method

Table 1. Values of the Ratio C/R<sub>K</sub> for Various Objects

particle shape	$C/R_{\rm K}$
miscellaneous bodies	
sphere	$1.0000(2)^{a}$
closed cylinder $(L/D = 1)$	1.0121(6)
tight torus	1.0135(6)
ellipsoid (1:2:3)	1.014(3)
open cylinder $(L/D = 1)$	1.0436(6)
DLA cluster $(d = 3)$	1.204(6)
platonic solids	
icosahedron	1.004(1)
dodecahedron	1.0061(6)
octahedron	1.0172(6)
cube	1.019(1)
tetrahedron	1.039(2)
proteins	
2hft	1.040(7)
1qgv	1.043(5)
la6m	1.048(6)
1qub	1.048(7)
laxj	1.053(6)
1cvl	1.057(6)
1mml	1.060(6)
1gof	1.061(4)
1tl2	1.074(6)
1cf9	1.098(5)
1bp7	1.105(7)
1aoi	1.175(8)
two-dimensional objects	
circular disk	1.079(3)
regular hexagon	1.081(3)
regular pentagon	1.086(2)
square	1.10(1)
equilateral triangle	1.103(3)
right triangle	1.108(3)
DLA cluster ( $d = 2$ )	1.092(8)
lumpy spheres, hemispherical protrusions	
a/R = 0.100, C/R = 1.0728(5)	1.022(5)
a/R = 0.0667, C/R = 1.0497(4)	1.009(1)
a/R = 0.0500, C/R = 1.0370(4)	1.007(2)
lumpy spheres, fcc protrusions	
a/R = 0.0707, C/R = 1.0170(1)	1.002(2)
a/R = 0.0589, C/R = 1.0112(2)	0.999(1)
a/R = 0.0505, C/R = 1.0134(2)	1.004(2)
a/R = 0.0442, C/R = 1.0115(2)	1.005(2)
a/R = 0.0393, C/R = 1.0085(2)	1.000(2)
a/R = 0.0353, C/R = 1.0092(2)	1.003(2)

<sup>a</sup> The digit in parentheses gives the uncertainty in the last decimal place.

of calculation. (See also ref 4 for a discussion of this mass scaling of  $R_h$  and the scaling variables that govern the rate of approach of these scaling relations to their asymptotic long chain limits.)

Random Coils, Good Solvent Conditions. For both selfavoiding walks and rings, we find that  $C/R_{\rm K}$  depends only weakly on N and extrapolates to about 1.10 in the limit of infinite N; i.e., the double-sum formula is in error by about 10%. This is consistent with our arguments above where we noted that weaker shape fluctuations should render the double-sum formula more accurate. Experimental values of  $R_{\rm g}$  / $R_{\rm h}$  cluster around 1.5, but values as low as 1.3 and as high as 1.7 are also reported.<sup>54</sup> The so-called "draining effect", i.e., the sensitivity of  $R_{\rm h}$  and  $[\eta]$  to monomer size and shape and the associated slow convergence of  $R_g/R_h$  to its infinite N value, appears to be responsible for this commonly reported experimental disparity. (In a separate work, we will focus on quantifying this draining effect.) Here we state our basic finding that the ratio  $R_g/R_h$  for self-avoiding walks and rings approaches 1.46 and 1.20, respectively, as  $N \rightarrow \infty$ .<sup>49</sup>

*Regular Polyhedra*. Results for the five Platonic solids appear in Tables 1 and 2. Note that  $C/R_{\rm K}$  obtains its largest value of Table 2. Values of the Ratio R<sub>Russell</sub>/C for Various Objects

Table 2. Values of the Ratio R <sub>Russell</sub> /C for	various Objects
particle shape	$R_{\rm Russell}/C$
miscellaneous bodies	
open cylinder $(L/D = 1)$	$0.8693(1)^a$
sphere	1.00000(0)
ellipsoid (1:2:3)	1.0038(6)
tight torus	1.0178(1)
closed cylinder $(L/D = 1)$	1.0278(1)
DLA cluster ( $d = 3$ )	1.435(4)
platonic solids	
icosahedron	1.0176(5)
dodecahedron	1.02819(9)
octahedron	1.0304(2)
tetrahedron	1.0398(7)
cube	1.0460(4)
proteins	
1qub	0.988(6)
2hft	1.111(7)
1axj	1.127(3)
1qgv	1.144(3)
1a6m	1.152(4)
lcvl	1.186(4)
1mml	1.192(6)
1bp7	1.210(7)
1gof	1.225(3)
1aoi	1.228(7)
1tl2	1.231(6)
1cf9	1.443(3)
lumpy spheres, hemispherical protrusions	
a/R = 0.100, C/R = 1.0728(5)	1.2762(7)
a/R = 0.0667, C/R = 1.0497(4)	1.2955(6)
a/R = 0.0500, C/R = 1.0370(4)	1.3046(6)
lumpy spheres, fcc protrusions	
a/R = 0.0707, C/R = 1.0170(1)	1.0679(3)
a/R = 0.0589, C/R = 1.0112(2)	1.0560(4)
a/R = 0.0505, C/R = 1.0134(2)	1.0759(3)
a/R = 0.0442, C/R = 1.0115(2)	1.0766(4)
a/R = 0.0393, C/R = 1.0085(2)	1.0619(3)
a/R = 0.0353, C/R = 1.0092(2)	1.0797(3)

Table 3. Values of the Ratio R<sub>Rayleigh</sub>/C for Various Two-Dimensional Objects

	-		
body	$R_{\text{Rayleigh}}/C$	body	$R_{\text{Rayleigh}}/C$
DLA cluster ( $d = 2$ ) right triangle equilateral triangle square	0.550(2) <sup>a</sup> 0.922(2) 0.9409(9) 0.9808(9)	pentagon hexagon circular disk	0.9906(7) 0.9939(7) 0.9990(6)

1.04 for the regular tetrahedron and decreases toward unity for all the higher polyhedra. The ratio  $R_{\text{Russell}}/C$  is less than about 1.05 for these five solids and tends toward unity for the higher polyhedra (although this trend is reversed for the cube and the tetrahedron—presumably because cubes and tetrahedra represent significant perturbations away from the sphere).

*Regular Polygons.* As displayed in Table 1,  $C/R_{\rm K}$  is largest at about 1.10 for equilateral triangles and tends to the circular disk value of 1.08 for higher polygons. Table 3 indicates that  $R_{\rm Rayleigh}/C$  is about 0.94 for the equilateral triangle and tends to 1 for higher polygons. Therefore,  $R_{\rm Rayleigh}$  is a better approximation than  $R_{\rm K}$  for these shapes.

*Rectangles.* Figure 1 shows that  $R_{\rm K}$  and *C* differ by about 9% for squares but that their ratio apparently converges to unity for rectangles of high aspect ratio. On the other hand,  $R_{\rm Rayleigh}$  gives a superior approximation only for aspect ratios near unity, and the quality of the approximation deteriorates rapidly with increasing aspect ratio.

*Cylinders.* Figures 2 and 3 show that  $C/R_{\rm K}$  for both open and closed cylinders having large length to diameter ratio (rod limit) tends asymptotically to unity.  $C/R_{\rm K}$  for closed cylinders of small length to diameter ratio tend asymptotically to the circular disk value, 1.08, while  $C/R_{\rm K}$  for open cylinders of small length to diameter ratio (ring limit) tends asymptotically to 1.



**Figure 1.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Ray}/C$  for rectangles of base *a* and height *b*.



**Figure 2.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Russ}/C$  for open cylinders of the indicated length to diameter ratio. Open cylinders have no ends, so small L/D corresponds to ringlike structures while large L/D corresponds to rodlike structures.

While  $R_{\text{Russell}}/C$  for both types of cylinders is near unity for aspect ratios near 1,  $R_{\text{Russell}}/C$  for closed cylinders tends to the circular disk value, 1.10 for small length to diameter ratios, and it decreases rapidly for both open and closed cylinders as the length-to-diameter ratio increases.

*Ellipsoids.* Tables 1 and 2 contain entries for the ellipsoid whose axes are in the ratio 1:2:3, while Figure 4 displays results for ellipsoids of revolution over a broad range of aspect ratios. Both  $R_{\rm K}$  and  $R_{\rm Russell}$  are excellent approximations for the 1:2:3 ellipsoid, and apparently the approximations apply well to ellipsoids in general, unless they have extreme aspect ratios. Oblate ellipsoids of revolution approach the circular disk values  $(C/R_{\rm K} = 1.08, R_{\rm Russell}/C = 1.11)$  asymptotically;  $C/R_{\rm K}$  for prolate ellipsoids of revolution tends to a value around 1.06 at aspect ratios of  $10^{+3}$ . It is impossible to tell from the data whether  $C/R_{\rm K}$  for prolate ellipsoids increases without bound or tends to an asymptote;  $R_{\rm Russell}/C$  decreases rapidly for prolate ellipsoids.



**Figure 3.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Russ}/C$  for closed cylinders of the indicated length to diameter ratio. Small L/D corresponds to the circular disk or plate limit while large L/D corresponds to rodlike structures.



**Figure 4.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Russ}/C$  for ellipsoids of revolution, where *a* and *c* represent semiaxes.

*Tori.* Data for tori appear in Tables 1 and 2 and in Figure 5. The "tight torus" or the torus for which  $r_1/r_2 = 1$  exhibits  $C/R_K = 1.018$ . The ratio  $C/R_K$  increases to a maximum of about 1.03 when  $r_1/r_2$  is about 1.7, and then tends to unity asymptotically.  $R_{\text{Russell}}/C$  passes through a maximum of about 1.04, before decreasing rapidly.

*"Lumpy" Spheres.* We now consider spheres covered with small protrusions. This is an important problem because the surfaces of large biomolecules are rough. As we will see, this roughness implies that the Russell approximation is not very good. Consider a large sphere of radius *R*, with small hemispherical protrusions of radius *a* on its surface. Figure 6 displays a two-dimensional analogue of this construction. The surface area can be written as  $A = 4\pi R^2 + n\Delta$ , where *n* is the number of protrusions and  $\Delta$  is the difference in area between a hemisphere and a circle, both of radius *a*:  $\Delta = \pi a^2$ . Furthermore, neglecting curvature of the large sphere and assuming 2-d close-packing of the protrusions implies  $n = 2\pi R^2/\sqrt{3}a^2$ 



**Figure 5.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Russ}/C$  for tori, where a torus is the body generated by revolving a circle of radius  $r_2$  around an external axis a distance  $r_1$  from the center of the circle.



Figure 6. "Lumpy" spheres have small protrusions that significantly increase their total surface area. In the hemispherical model (a and b), hemispherical protrusions are packed densely over the surface of a larger sphere. In the fcc model (c and d), the sphere is overlaid with an array of smaller close-packed spheres, and all of the smaller spheres with centers inside the larger sphere but which protrude from it are included in the final model. The actual constructions were three-dimensional, and these are two-dimensional schematics.

and  $A \cong (1.91)4\pi R^2$ , independent of *a*. So each protrusion makes a smaller contribution to *A* as *a* decreases, but the total number of protrusions grows in inverse proportion. The surface area is almost twice that of the sphere without protrusions, even when  $a \ll R$ . We note that the capacity (friction coefficient in the hydrodynamic-electrostatic analogy) of any object is bounded below and above by the radii of the largest inscribed sphere and the smallest circumscribing sphere, respectively, so that  $R \le C \le R + a$ .<sup>55</sup> Therefore, it follows for the lumpy sphere model that  $R_{\text{Russell}}/C \rightarrow \sqrt{1.91} = 1.38$  in the limit of protrusions small relative to the sphere size,  $a/R \rightarrow 0$ . Several model calculations of this effect, for a/R = 1/10, 1/15, and 1/20, are summarized in Tables 1 and 2, under the heading "lumpy spheres, hemispherical protrusions". Approximate close packing of the protrusions was achieved by first placing a single protrusion of radius 1 at spherical polar coordinates  $(R,\theta,\varphi) = (R,\pi,0)$  on the larger sphere of radius *R* and then placing each subsequent protrusion at the point  $(R,\theta,\varphi)$  which maximizes  $\theta$  subject to the constraint that there is no overlap with previously placed protrusions, identifying such maxima with grid searches of resolution  $\pi/1000$  in  $\theta$  and  $2\pi/1000$  in  $\varphi$ . This continued until no more protrusions could be added. Because the lumpy sphere model tends to a uniform spherical charge distribution in the limit  $a/R \rightarrow 0$ , we also find good agreement between  $R_{\rm K}$  and *C*.

A second, related lumpy sphere model is also summarized in Tables 1 and 2 under the heading "lumpy spheres, facecentered cubic (fcc) protrusions". For this model, we take a sphere of radius *R* and form protrusions by overlaying a closepacked fcc lattice of smaller spheres, again of radius *a*. All lattice spheres whose centers lie inside the large sphere and also protrude from it are included in the final model. Figure 6 displays a two-dimensional analogue of this construction. In this case,  $R_{\text{Russell}}/C$  is smaller than the 1.38 prediction because, on average, both *n* and  $\Delta$  are smaller, but again, it is independent of the ratio *a*/*R*. We again note good agreement between  $R_{\text{K}}$ and *C*.

Model Proteins. The so-called solvent-accessible surface<sup>56</sup> of typical globular proteins is sometimes used to determine, via the Russell approximation, the hydrodynamic radius of segments of proteins.<sup>46</sup> The solvent-accessible surface has a structure similar to the "lumpy" spheres discussed above, and so our results for those models call this practice into question. To examine this more closely,  $C/R_{\rm K}$  and  $R_{\rm Russell}/C$  were determined for a few protein structures obtained from the Protein Data Bank.<sup>57</sup> Surfaces were represented by placing a sphere of radius 5 Å at each  $C_{\alpha}$ . For most of the proteins studied,  $C/R_{\rm K}$  lies in the range 1.04-1.10. The one exception, 1aoi, has a long pendant chain.  $R_{\text{Russell}}/C$  is found in the range 1.1–1.4 for all but one of these proteins, 1qub, for which it is close to 1. The protein 1qub has the gross structure of a curved sausage, with contour-length-to-diameter ratio of around 10. We note from Figures 3 and 4 that smooth cylinders and ellipsoids of comparable aspect ratios display  $R_{\text{Russell}}/C$  values of around 0.8-0.9. But ours is a "lumpy" sausage, for which the arguments above must also apply. Apparently, the lumpiness brings  $R_{\text{Russell}}/C$  back to near 1. However, all the other proteins are not elongated, but nevertheless lumpy, so  $R_{\text{Russell}}/C$  is greater than unity.

Nested Spheres. Conducting surfaces with highly nonuniform charge distributions are expected to show the largest discrepancies between RK and C. A pair of concentric, or nested, conducting spheres provides one example of a nonuniform charge distribution, since, if two concentric spheres are held at the same potential, all the charge accumulates on the outer sphere. This is a relevant question because it can be taken as a model of a macromolecule with a cavity. Let  $r_1$  and  $r_2$  represent respectively the radii of the inner and outer spheres. The inner sphere can be considered part of the exterior surface if we imagine that a hole is drilled through this spherical shell (see the inset in Figure 7). For mathematical tractability, the diameter of this hole is assumed to be vanishingly small. In the electrostatic analogy, the hole represents a thin wire that keeps both spheres at the same potential. Both the capacity and the hydrodynamic radius are obviously equal to the radius of the outer sphere. However, in calculating  $R_{\rm K}$  and  $R_{\rm Russell}$ , we take the surface to be both spheres. In the limit  $r_1 \rightarrow r_2$ , the two charge distributions approach one another, and we expect



**Figure 7.** Two concentric spheres, of radius  $\beta$  and 1, respectively, with  $\beta < 1$ , are used to model a macromolecule with a cavity. The inner cavity belongs to the exterior of the body because we assume they are connected by a small hole, as in the inset.

 $C/R_{\rm K} \rightarrow 1$ . In the other limit,  $r_1 \rightarrow 0$ , the contribution from the inner sphere becomes negligible since it carries a charge proportional to its surface area, and so again we expect  $C/R_{\rm K} \rightarrow 1$ . Therefore, we can expect  $C/R_{\rm K}$  to attain some maximum as  $r_1/r_2$  varies between 0 and 1. In fact, we have

$$\frac{C}{R_{\rm K}} = \frac{\beta^3 + 2\beta^2 + 1}{(\beta^2 + 1)^2}, \quad \beta = r_1/r_2 \tag{19}$$

The curve for  $C/R_{\rm K}$  appears in Figure 7. The value of the maximum is 1.04751 at  $\beta = r_1/r_2 = 0.645$  75. Therefore, even in this situation, the error in  $R_{\rm K}$  is less than 5%. For the same model, we can take  $A = 4\pi(r_1^2 + r_2^2)$ , obtaining

$$\frac{R_{\text{Russell}}}{C} = (1 + \beta^2)^{1/2}$$
(20)

so  $R_{\text{Russell}}/C$  increases monotonically from 1 to  $\sqrt{2}$ . This function also appears in Figure 7.

*Isoceles Triangles.* Surfaces with sharp points are also known to have very nonuniform charge distributions. Therefore, we examined isosceles triangles of a wide range of altitude to base ratio, with results shown in Figure 8. The ratio  $C/R_{\rm K}$  exceeds 1.2 when the aspect ratio approaches  $10^{\pm3}$ , defining the aspect ratio as the ratio of altitude to base, and achieves a minimum of about 1.10, the value for equilateral triangles. Thus,  $C/R_{\rm K}$  seems to increase without limit as a/b becomes very large or very small, although at best, very slowly. In contrast, the ratio  $R_{\rm Rayleigh}/C$  achieves a maximum of 0.94 for equilateral triangles but degrades rapidly from there.

*Trigonal Bipyramids.* These shapes were also considered as objects possessing sharp points. These are formed by placing an equilateral triangle of side 1 in the x-y plane, centering the triangle at the origin, and by placing apices at the two points  $(0, 0, \pm h)$ . Results appear in Figure 9. Small *h* produces values expected of the equilateral triangle,  $C/R_{\rm K} \rightarrow 1.10$ ,  $R_{\rm Russell}/C \rightarrow 1.05$ . Large *h* again produces  $C/R_{\rm K}$  values that seem to increase without limit. Interestingly,  $R_{\rm Russell}/C$  appears always to give an error less than about 5% for *h* less than about 1.

![](_page_8_Figure_11.jpeg)

**Figure 8.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Ray}/C$  for isosceles triangles of the indicated altitude-to-base ratios.

![](_page_8_Figure_13.jpeg)

**Figure 9.** Ratios  $C/R_{\rm K}$  and  $R_{\rm Russ}/C$  for trigonal bipyramids. The base of each pyramid is an equilateral triangle of side 1, and *h* is the height of each pyramid. At small *h*, therefore, the object resembles a flat triangle, while at large *h* it resembles a double-pointed needle.

Diffusion-Limited Aggregate Clusters. DLA clusters in dimensions d = 2 and d = 3 were constructing on either the simple square or the simple cubic lattices, each consisting of 1000 cells. The ensuing surfaces were then represented as a mesh of triangles (d = 2) or assembly of cubes (d = 3). The d = 2cluster is shown in Figure 10. The gyration radii,  $R_{\rm g}$ , were also determined for these clusters:  $C/R_g = 0.788(3)$  in two dimensions and 1.096(4) in three dimensions. (Our estimate in three dimensions is compared to the estimates 0.97 and 0.97 of Chen and co-workers58 for diffusion-limited cluster-cluster and reaction-limited aggregates based on the bead model and the Zimm algorithm for calculating the polymer hydrodynamic radius.) Only a single cluster was generated in our computation; no attempt has been made to perform ensemble averaging. This ensemble averaging has been suggested to decrease the value of  $R_{\rm h}/R_{\rm g}$  in branched polymers<sup>58,59</sup> so that further ensemble calculations are required.

![](_page_9_Figure_1.jpeg)

Figure 10. A two-dimensional DLA cluster, consisting of 1000 cells of the simple cubic lattice.

Interestingly,  $C/R_{\rm K} = 1.09$  for the d = 2 DLA cluster is indistinguishable from the value for a circular disk to within numerical error. By contrast, the d = 3 DLA cluster gave the value  $C/R_{\rm K} = 1.20$  and thus  $R_{\rm K}/R_{\rm g} = 0.91$ . This result is contrasted with recent estimates of Lattuada et al.,<sup>36</sup> who suggest the rather low value of  $R_{\rm K}/R_{\rm g} = 0.765$  for DLA aggregates in three dimensions. Other estimates for a variety of models are discussed by Lattuada et al.<sup>36</sup> The large dispersion of results illuminates the need for general algorithms like Zeno and HYDRO. Finally, we note that the Russell and Rayleigh approximations for DLA in both 3 and 2 dimensions are not particularly accurate, signaling that such approximations should generally be avoided for fractal objects.

# 6. Comparison to Representative HYDRO Computations for $R_h$ and $[\eta]$

We now report computations comparing the path-integral results of Zeno with the predictions of the popular HYDRO program of Garcia de la Torre and co-workers, which is conveniently available on-line.<sup>6-14</sup> These computations represent the particle as an array of beads or spheres distributed over its surface and treat the center of each bead as a point source of hydrodynamic interaction. Since the path integrations can also be done for any body constructed as a union of spheres, overlapping or not, we can perform direct comparisons on identical models. (However, as mentioned before, the pathintegration method is not restricted to bead representations and thus physically more faithful shapes can be used.) Our comparisons indicate that the simplified bead-model computational program, HYDRO, can lead to inaccurate results if too few beads or overlapping beads are employed in the computations. These errors, which have been investigated previously by the developers of HYDRO, are not fundamental to the bead-model computational method, however, and more refined bead-model computations are possible which can reduce these errors to vanishingly small values. HYDRO predictions for  $[\eta]$  can be even more problematic than for  $R_{\rm h}$ , although these errors also seem to become small in the limit of a large number of beads. Garcia de la Torre and Carrasco<sup>60</sup> describe the origin of discrepancies in  $[\eta]$ , but the necessary corrections do not appear to have been implemented in the on-line version of HYDRO. There is no question that the general bead-model computational method is capable of obtaining highly accurate estimates of hydrodynamic properties, but we must distinguish this general method from the rather approximate, but relatively computationally efficient, HYDRO program, which is the working computational tool available for general use.

We first compare results for a single pair of beads. Exact results are available both for  $R_{\rm h}$  and  $[\eta]$ .<sup>20,21</sup> Let r be the radius of each of the two spheres, and let L be their separation. Consider first the simple case a sphere dumbbell where the spheres are just touching. In this case we find the bead-model calculation to be in error by -4% and +19%, respectively. (See Table 4 for a tabulation of  $R_h$  and  $[\eta]$ .) The path-integration error for  $R_{\rm h}$  is small (below 1%) and usually about 5% for  $[\eta]$ , consistent with the uncertainty in eq 7. At large enough L/2r, the HYDRO results become very accurate, as expected. The intrinsic viscosity data of Table 4 are also summarized in Figure 11, which plots ratios of the approximate path-integral or HYDRO results to the exact values. Notice the trend in the path integration results: The prediction is about 4% too low at L/2r= 1 and increases to nearly 7% too high at L/2r = 50 before decreasing. This trend can be attributed to the shape dependence of  $q_n$ , as mentioned above. The error bars in Figure 11 are generated primarily by the uncertainty in  $q_{\eta}$  (only secondarily by sampling error) and so are always broad enough to include the exact result, except in the vicinity of L/2r = 50. For that particular range of shapes,  $q_{\eta}$  falls slightly outside the range of eq 7. As already mentioned, in the future we hope to be able to predict the shape dependence of  $q_{\eta}$  directly from the components of the polarizability tensor, in which case our predictions for  $[\eta]$  should improve.

These illustrative computations demonstrate that the beadmodel calculations must be performed judiciously. Improved accuracy could be obtained by covering both spheres with many small beads. However, the computational cost increases accordingly. Not all practitioners of the HYDRO program are aware of these limitations.

Figures 12 and 13 compare predictions for an overlapping pair of beads ( $L/2r \leq 1$ ). This is known to be a particularly problematic situation for numerical bead-model computations, and in practice, beads should be chosen without overlap. The path-integration approach, however, is not similarly restricted. The error bars in Figures 12 and 13 are estimated from the upper and lower bounds cited in eq 7. The exact hydrodynamic results, when available, always fall within the uncertainty intervals of the path-integration calculations. The two-bead HYDRO results, on the other hand, remain about 4% or 5% too low for  $R_h$  until L/2r gets close to 0, at which point the error disappears. Furthermore, the HYDRO results for [ $\eta$ ] become progressively worse as L/2r approaches 0.

Next, we consider a  $3 \times 3 \times 3$  array of 27 spheres on the simple cubic lattice. Each sphere is one unit away from its nearest neighbors and has radius *r*. The ranges r < 0.5 and r > 0.5 correspond to separated and overlapping spheres, respectively. Results for  $R_h$  and  $[\eta]$  appear in Figures 14 and 15. Good agreement is not seen until *r* decreases to about 0.2. When the spheres are just touching,  $R_h$  is 4% too low and  $[\eta]$  is 46% too high. Again we expect that these errors of the bead model can be overcome by covering all the beads with numerous beads, but the computation time again becomes appreciable.

In the next case study, we consider a hollow block of beads, formed by constructing an array of dimensions  $n \times n \times n$  on the simple cubic lattice, but retaining only those beads on the surface. With this model, we attempt to follow the spirit of the bead-model approach: using many small beads to cover the surface of a cube. The total number of beads is  $N = n^3 - (n - 2)^3$ , and since HYDRO is limited to structures of 2000 beads

Table 4. Predictions for Dumbbells and Comparisons with Numerically Exact Results<sup>a</sup>

Hydrodynamic Radius					
L/2r	$L/2r$ $R_{\rm h}/r$ , exact $R_{\rm h}/r$ , path-integral results		$R_{\rm h}/r$ , results of HYDRO program		
1	1.3922	$1.39 \pm 0.01; (-0.1 \pm 0.7)\%$	1.334; -4%		
2	1.6054	$1.60 \pm 0.02; (-0.3 \pm 1.2)\%$	1.601; -0.3%		
3	1.7156	$1.71 \pm 0.02; (-0.3 \pm 1.2)\%$	1.715; -0.03%		
5	1.8184	$1.82 \pm 0.02; (+0.09 \pm 1.1)\%$	1.819; +0.03%		
Intrinsic Viscosity, Arbitrary Units					
L/2r	$[\eta]$ , exact	$[\eta]$ , path-integral results	$[\eta]$ , results for HYDRO program		
1	8.702	$8.4 \pm 0.4; (-3.5 \pm 4.6)\%$	10.34; +19%		
1.0201	8.824	$8.5 \pm 0.4; (-3.7 \pm 4.5)\%$	10.43; +18%		
1.1276	9.271	$9.2 \pm 0.5; (-0.7 \pm 5.4)\%$	10.90; +18%		
1.5431	12.34	$12.1 \pm 0.6; (-1.9 \pm 4.9)\%$	13.25; +7%		
3.7622	37.22	$38 \pm 2; (+2.1 \pm 5.4)\%$	37.52; +0.8%		
6.1323	84.02	$88 \pm 4; (+4.7 \pm 4.8)\%$	84.20; +0.2%		
10.0677	208.6	$220 \pm 10; (+5.5 \pm 4.8)\%$	208.7; +0.05%		
20	783.7	$830 \pm 40; (+5.9 \pm 5.1)\%$	783.7;0%		
50	4787	$5100 \pm 300; (+6.5 \pm 6.3)\%$	4787; 0%		
100	19030	$20000 \pm 1000; (+5.1 \pm 5.2)\%$	19030; 0%		
200	75890	$79000 \pm 5000; (+4.1 \pm 6.5)\%$	75890; 0%		

 $^{a}L =$  bead separation, r = bead radius. The path-integral results are displayed with uncertainty estimates, and with percent error relative to the exact results. HYDRO results are shown with percent error relative to exact results.

![](_page_10_Figure_5.jpeg)

**Figure 11.** Comparison of predictions for the intrinsic viscosity of a pair of nonoverlapping beads, each of radius r = 1 and separation *L*. Solid circles are the results of HYDRO, and open circles with error bars are the path-integration results.

total, we have only considered values of *n* between 3 and 19, inclusive. Individual beads have radius 0.5. Figure 16 compares the results for the two techniques. The same discrepancies mentioned above, -4% in  $R_h$  and +45% in  $[\eta]$ , are seen at N = 26, but the discrepancies decrease with increasing *N*. The discrepancies in  $R_h$  eventually drop below the inherent error of the path-integration method, but discrepancies in  $[\eta]$  never fall below 17%.

These comparisons imply that while the bead-model computations allow, in principle, for the accurate computation of  $R_h$ , errors arise from modeling spatially extended structures by point-source hydrodynamic interactions transmitted through space by the Oseen tensor. (Both the Oseen tensor and its Rotne–Prager<sup>61</sup> modification only provide correct descriptions of the interaction between two spherical beads at infinite bead separations.) HYDRO's results consistently improve when an increasing number of beads is employed, but the errors can remain large even for a large number of beads, especially for

![](_page_10_Figure_9.jpeg)

Figure 12. Comparison of predictions for the hydrodynamic radius of two overlapping beads, each of radius r = 1 and separation *L*.

the intrinsic viscosity. Particular problems with HYDRO can also arise if the beads are allowed to overlap. The recognition of these problems is not new, but many of the researchers who use the HYDRO program are apparently unaware of them. The path-integral method has the advantage that bead overlap has essentially no effect on the results of the method (the method is more "foolproof" ), and it is possible to make computations of reasonable accuracy in a relative short computational time. HYDRO determines  $R_h$  to an accuracy of 4% or better for the models considered, with accuracy improving with the size (N)of the model, as long as the beads do not overlap. However, to obtain accurate determinations of  $[\eta]$  would require using considerably more than 2000 beads, and with computation time varying as  $N^3$ , we can expect such computations to be rather time-consuming if not prohibitive. The path-integration has times of O(N), and it therefore permits the consideration of much larger and complex structures than the HYDRO method currently allows.

As a final comparison between the HYDRO program and path-integral approaches, we consider several biological macromolecules and self-assembled macromolecular complexes of

![](_page_11_Figure_1.jpeg)

Figure 13. Comparison of predictions for the intrinsic viscosity of two overlapping beads, each of radius r = 1 and separation L.

![](_page_11_Figure_3.jpeg)

**Figure 14.** Hydrodynamic radius of a cubic array of 27 beads of various radii, computed both by the HYDRO program and by the path-integration technique.

particular current experimental interest. The reliable computation of  $R_h$  and  $[\eta]$  for protein complexes and synthetic self-assembled structures such as nanotubes is important for characterizing these structures, and the consideration of test cases involving such structures is informative. We consider, therefore, the proteins myoglobin and immunoglobulin G, several ring forms of tubulin, and the icosahedral cage structure clathrin which have recently been considered in recent experimental investigations. Results for these model biological macromolecular structures are summarized in Table 5. In a separate paper, we have calculated  $R_h$  and  $[\eta]$  for a representative subset of the Protein Data Bank (about a thousand molecules), and we are continuing our tabulation to encompass the entire database.<sup>23,48,57</sup>

We constructed the myoglobin model using the X-ray crystal structure 1a6m from the Protein Data Bank,<sup>57</sup> representing each amino acid with a 5 Å radius bead centered at each  $C_{\alpha}$ .<sup>23</sup> We also consider the bead model of immunoglobulin G, available directly from the HYDRO Web site,<sup>14</sup> where it appears as a test case.

![](_page_11_Figure_8.jpeg)

Figure 15. Intrinsic viscosity of a cubic array of 27 beads of various radii, computed both by the HYDRO program and by the path-integration technique.

![](_page_11_Figure_10.jpeg)

**Figure 16.** Comparison of predictions by the HYDRO program and the path-integration technique for a hollow block of beads. The ratios of the predictions by HYDRO to those by the path-integration are displayed.

Tubulin is a structural protein that forms  $\alpha\beta$  dimers, which in turn normally self-assemble into hollow "nanotube" structures composed of rolled up sheets of proteins that play a fundamental role in cell mitosis. However, when codissolved with various toxins, viral agents, or chemotherapy drugs, tubulin selfassembles instead into closed rings, thereby interrupting cell division. We calculate  $R_h$  and  $[\eta]$  of two ring structures, of 8 and 14 dimers, respectively, induced by the cyanobacterial derivative cryptophycin. The rings are modeled by a set of overlapping beads, 21 beads per monomer,<sup>62-65</sup> as prescribed by Diaz et al.<sup>64</sup> The overlapping bead model for the 28-mer ring is shown in Figure 17 using coordinates provided by Boukari.65 Finally, we consider literature models of clathrin, a biologically crucial protein complex involved in particle transport through the cell membrane during endocytosis.<sup>66</sup> The complete clathrin cage is a self-assembled icosahedral complex of 36 triskelion moieties. Dynamic light scattering measurements

Table 5. Comparison between Path-Integration and HYDRO Computations for Several Biological Molecules; HYDRO Results Are Displayed with Percent Error Relative to the Path-Integral Results

		R	$R_{\rm h}$ , nm $M[\eta]$ , nm <sup>3</sup>		CPU time, <sup>f</sup> s		
model	Ν	path- integration	HYDRO	path- integration	HYDRO	path- integration	HYDRO
immunoglobulin G [14]	15	5.84	5.711; -2%	$2.3(2) \times 10^{3}$	$2.577 \times 10^3$ ; +12%	1	<1
tubulin dimer [65]	42	4.28	4.077; -5%	$8.0(3) \times 10^2$	$1.660 \times 10^3$ ; +108%	2	<1
myoglobin <sup>a</sup>	151	2.06	1.988; -3.5%	89(5)	279.2; +214%	7	5
triskelion [68]	192	14.5	14.38; -0.8%	$3.7(1) \times 10^4$	$4.02 \times 10^4$ ; +9%	15	8
tubulin ring, 16-mer [65]	336	11.3	11.09; -2%	$1.51(8) \times 10^4$	$2.24 \times 10^4$ ; +48%	27	26
tubulin ring, 28-mer <sup>b</sup> [65]	588	16.3	16.19; -0.7%	$5.0(3) \times 10^4$	$6.20 \times 10^4$ ; +24%	44	97
clathrin <sup>c</sup> [68]	6804	33.3		$3.7(2) \times 10^5$		620	$\approx 1400^{\circ}$
clathrin plus vesicle <sup>c-e</sup> [68]	6805	33.7		$3.8(2) \times 10^5$		620	$\approx 1400^{\circ}$

<sup>*a*</sup> Myoglobin model: one 5 Å bead per amino acid centered at each  $C_{\alpha}$ , PDB code 1a6m. <sup>*b*</sup> The overlapping bead model of the 28-mer tubulin ring is depicted in Figure 17. <sup>*c*</sup> The current version of HYDRO is limited to 2000 beads, which precludes computations on the two clathrin models. Computation time is estimated by logarithmic extrapolation. <sup>*d*</sup> The internal vesicle of the clathrin complex was modeled as a single, large, interior sphere. <sup>*e*</sup> The overlapping bead model of the clathrin complex is depicted in Figure 18. <sup>*f*</sup> Running on a 1 GHz Pentium III processor.

![](_page_12_Figure_5.jpeg)

Figure 17. Overlapping-spheres model of a 28-mer tubulin ring.

![](_page_12_Figure_7.jpeg)

Figure 18. Overlapping-spheres model of a clathrin cage with an internal vesicle.

have been reported by Ferguson et al.<sup>67</sup> The bead coordinates and sphere diameters of clathrin are prescribed by Kirchhausen,<sup>66</sup> with the resulting model appearing in Figure 18. We also consider two other examples, one, of a clathrin cage containing a spherical inclusion (also shown in Figure 18), based on the suggestion of Ferguson,<sup>68</sup> to see how it affects the  $R_h$  of the clathrin. Finally, we consider a single triskelion moiety from which the clathrin cage is assembled. Consistent with our previous results, the largest discrepancies between our pathintegration and HYDRO calculations occur for the model with the smallest number of beads (N = 42). The current version of HYDRO sets a limit of 2000 beads and therefore does not allow computations for the two largest molecular models. The experimental estimate of  $R_h$  for the 16-mer tubulin ring is reported as the ratio of  $R_h$  for the ring to that of the tubulin dimer and has been determined from fluorescence correlation spectroscopy and sedimentation velocity measurements to be 2.75, compared to our simulated estimate, 2.64 and the HYDRO ratio of 2.72. (The HYDRO estimate agrees better with experiment, but because of uncertainties in the geometry of the molecule, it is not clear that this can be attributed to the relative performance of the two computational methods.) Recent measurements by Ferguson et al. were restricted to the triskelion moieties that comprise the clathrin cage and dynamic light scattering estimates for  $R_h$  are not yet available. Note also that because of hydrodynamic screening, inclusion of a particle inside the clathrin cage has only a small effect on  $R_{\rm h}$ . Intrinsic viscosity measurements for clathrin are not available, but note the large discrepancy between Zeno and HYDRO.

Table 5 also gives actual computation times for the two approaches. The times displayed for the path-integration are for integrations comprised of  $10^4$  Brownian trajectories, which have better than 1% accuracy in *C* and about 1-2% accuracy in  $\langle \alpha \rangle$ . Since these are smaller than the uncertainties in  $q_h$  and  $q_\eta$ , respectively, and also comparable to experimental uncertainties,  $10^4$  trajectories are usually adequate.

### 7. Conclusions

We have appraised several approximation schemes for transport properties of macromolecules having a wide variety of shapes, using a recently developed path-integration technique. The Kirkwood double-sum formula underestimates the hydrodynamic radius and hence underestimates the friction coefficient and overestimates the diffusion coefficient, for all bodies except the sphere. Errors for  $\theta$ -state random coils are about 20% and about 10% for coils with strong excluded volume. Errors for smooth globular shapes are less than 3-4%, while for globular proteins, errors are usually less than 10%. Errors for very flat objects such as regular polygons or disks also fall in the range of about 8-10%. Errors for uniformly slender bodies also become small in the limit of high aspect ratio; this is observed either for rodlike objects (highly prolate cylinders or rectangles of high aspect ratio) or slender rings (tori and open cylinders). However, tapered slender bodies, e.g., ellipsoids of revolution, isosceles triangles, or trigonal bipyramids, exhibit larger errors than uniformly slender bodies. The isosceles triangles and trigonal bipyramids exhibit errors of 20% or larger at aspect ratios around  $10^3$ , and the data suggest that the errors might increase without limit. For ellipsoids, on the other hand, the errors tend to an asymptotic value of around 6%.

The Russell approximation, applicable to three-dimensional objects, is valid to about 5% or better for smooth globular shapes. The best agreement is obtained, obviously, for globular ellipsoids, i.e., neither too oblate nor too prolate. But it is not particularly good in any other case. Likewise, the Rayleigh approximation, for two-dimensional objects, is reasonably accurate only for approximately circular shapes.

Approximate bead-model calculations, such as the HYDRO program, also provide a useful means of estimating the transport properties of polymer solutions. Good accuracy for the intrinsic viscosity requires many beads and bead overlap must also be avoided. The ZENO method is not sensitive to bead overlap and is a relatively efficient method for calculating polymer transport properties in comparison to HYDRO. The computational efficiency of the Zeno method makes it particularly attractive, especially in computations of complex structures that become difficult by other methods of reliable accuracy.

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**Supporting Information Available:** Description of the surface integrations used to determine  $R_{\rm K}$  and A. This material is available free of charge via the Internet at http://pubs.acs.org.

#### **References and Notes**

- Yamakawa, H. Modern Theory of Polymer Solutions; Harper & Row: New York, 1971.
- (2) Doi, M.; Edwards, S. F. *The Theory of Polymer Dynamics*; Oxford University Press: Oxford, 1986.
- (3) Currie, I. G. Fundamental Mechanics of Fluids, 3rd ed.; Marcel Dekker: New York, 2003.
- (4) Douglas, J. F.; Roovers, J.; Freed, K. F. Macromolecules 1990, 23, 4168–4180.
- (5) Douglas, J. F.; Freed, K. F. Macromolecules 1994, 27, 6088-6099.
- (6) Garcia de la Torre, J.; Bloomfield, V. A. Q. Rev. Biophys. 1981, 14, 81–139.
- (7) Garcia de la Torre, J.; Navarro, S.; Lopez Martinez, M. C.; Diaz, F. G.; Lopez Cascales, J. J. *Biophys. J.* **1994**, 67, 530–531.
- (8) Garcia de la Torre, J.; Carrasco, B. Eur. Biophys. J. 1998, 27, 549– 557.
- (9) Carrasco, B.; Garcia de la Torre, J. Biophys. J. 1999, 75, 3044-3057.
- (10) Carrasco, B.; Garcia de la Torre, J. J. Chem. Phys. 1999, 111, 4317– 4826.
- (11) Garcia de la Torre, J.; Huertas, M. L.; Carrasco, B. *Biophys. J.* 2000, 78, 719–730.
- (12) Garcia de la Torre, J.; Llorca, O.; Carrascosa, J. L.; Valpuesta, J. M. *Eur. Biophys. J.* **2001**, *30*, 457–462.
- (13) Garcia de la Torre, J.; Carrasco, B. Biopolymers 2002, 63, 163-167.
- (14) http://leonardo.fcu.um.es/macromol/programs/hydro/hydro.htm.
- (15) Youngren, G. K.; Acrivos, A. J. Fluid Mech. 1975, 69, 377-403.
- (16) Brune, D.; Kim, S. Proc. Natl. Acad. Sci. U.S.A. 1993, 90, 3835-3839.
- (17) Allison, S. A. Macromolecules 1999, 32, 5304-5312.
- (18) Zhao, H.; Pearlstein, A. J. Phys. Fluids 2002, 14, 2376-2387.
- (19) Aragon, S. J. Comput. Chem. 2004, 25, 1191-1205.
- (20) Douglas, J. F.; Garboczi, E. J. Adv. Chem. Phys. 1995, 91, 85-153.
- (21) Douglas, J. F. Adv. Chem. Phys. 1997, 102, 121-191.
- (22) Mansfield, M. L.; Douglas, J. F.; Garboczi, E. J. Phys. Rev. E 2001, 64, 061401.
- (23) Kang, E.-H.; Mansfield, M. L.; Douglas, J. F. Phys. Rev. E 2004, 69, 031918.
- (24) Mansfield, M. L.; Douglas, J. F. Conden. Matter Phys. 2002, 2, 249–274.
- (25) Hubbard, J. B.; Douglas, J. F. Phys. Rev. E 1993, 47, 2983-2986.

- (26) Douglas, J. F.; Zhou, H.-X.; Hubbard, J. B. Phys. Rev. E 1994, 49, 5319-5331.
- (27) Zhou, H.-X.; Szabo, A.; Douglas, J. F.; Hubbard, J. B. J. Chem. Phys. 1994, 100, 3821–3826.
- (28) Garboczi, E. J.; Douglas, J. F. Phys. Rev. E 1996, 53, 6169-6180.
- (29) Luty, B. A.; McCammon, J. A.; Zhou, H.-X. J. Chem. Phys. 1992, 97, 5682–5686.
- (30) Given, J. A.; Hubbard, J. B.; Douglas, J. F. J. Chem. Phys. 1997, 106, 3761-3771.
- (31) Zimm, B. H. Macromolecules 1980, 13, 592-602.
- (32) Fixman, M. J. Chem. Phys. 1983, 78, 1588-1593.
- (33) Fixman, M. J. Chem. Phys. 1983, 78, 1594-1599.
- (34) Freire, J. J.; Garcia de la Torre, J. *Macromolecules* **1983**, *16*, 331–332.
- (35) Garcia de la Torre, J.; Lopez Martinez, M. C.; Tirado, M. M.; Freire, J. J. Macromolecules 1984, 17, 2715–2722.
- (36) Lattuada, M.; Wu, H.; Morbdelli, M. J. Colloid Interface Sci. 2003, 268, 96–105.
- (37) Aichi, K. Proc. Math.-Phys. Soc. Jpn. (Tokyo) 1908, 4, 243–246.
- (38) Rayleigh, J. W. *Philos. Mag.* **1916**, *31*, 177–186.
- (30) Rayleigh, J. W. 1 muos. Mug. 1910, 51, 177–180.
- (39) Rayleigh, J. W. S. *Theory of Sound;* Dover Press: New York, 1945; Vol. 2.
- (40) Erma, V. A. J. Math. Phys. 1963, 4, 1517-1526.
- (41) Edwards, S. F.; Papadopoulos, G. J. J. Phys. A 1968, 1, 173-187.
- (42) Brenner, J. Chem. Eng. Sci. 1964, 19, 519-539.
- (43) Ramkissoon, H. ZAMP 1986, 37, 859-866.
- (44) Russell, A. J. Inst. Electr. Eng. 1916, 55, 1-17.
- (45) Chow, Y. L.; Yovanovich, M. M. J. Appl. Phys. 1982, 53, 8470– 8475.
- (46) Pastor, R. W.; Karplus, M. J. Phys. Chem. 1988, 92, 2636-2641.
- (47) Venable, R. J.; Pastor, R. W. Biopolymers 1988, 27, 1001-1014.
- (48) Fortran code is available on the Internet at www.stevens.edu/zeno/ home.html.
- (49) Mansfield, M. L.; Douglas, J. F. Manuscript in preparation.
- (50) terMeer, H. U.; Burchard, W.; Wunderlich, W. Colloid Polym. Sci. 1980, 258, 675- 684.
  - (51) Schmidt, M.; Burchard, W. Macromolecules 1981, 14, 210-211.
  - (52) Tsunashima, Y.; Nemoto, N.; Kurata, M. Macromolecules 1983, 16, 1184–1188.
  - (53) Park, S.; Chang, T.; Park, I. H. Macromolecules 1991, 24, 5729– 5731.
  - (54) Tseng, C.; Tsao, H.; Chen, S. B. Phys. Rev. Lett. 2001, 86, 5494– 5497.
  - (55) Given any two bodies Ω₁ and Ω₂, with capacities C₁ and C₂, respectively, and with Ω₂ completely enclosing Ω₁, then it is a direct consequence of the path-integration formulation that C₁ ≤ C₂, with equality holding only when Ω₁ and Ω₂ are identical. There is also a demonstration in: Hill, R.; Power, G. Q. J. Appl. Mech. Appl. Math. 1956, 9, 313–319, which states that the hydrodynamic radius cannot exceed that of a sphere that entirely encloses the object.
  - (56) van Holde, K. E.; Johnson, W. C.; Ho, P. S. Principles of Physical Biochemistry; Prentice Hall: Upper Saddle River, NJ, 1998.
  - (57) Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. Nucl. Acids Res. 2000, 28, 235–242.
  - (58) Chen, Z.-Y.; Meaken, P.; Deutch, J. M. Phys. Rev. Lett. 1987, 59, 2121–2121. The estimate of the ratio  $R_{\rm h}/R_{\rm g}$  for fractal colloidal silica particles by Wiltzius [Wiltzius, P. Phys. Rev. Lett. 1987, 58, 710-713] indicates an experimental value near 0.72  $\pm$  0.02, which seems entirely out of line with estimates for DLA-type clusters. From this observation, we suggest that the clusters of Wilzius are actually equilibrium branched polymers consistent with lattice animals, which is plausible given the observations of Aubert and Cannell that similar aggregated silica particle clusters robustly relax to a structure with a fractal dimension near 2, the fractal dimension of lattice animals in three dimensions [Aubert, P.; Cannell, D. S. Phys. Rev. Lett. 1986, 56, 738-741. Ball, R. C.; Lee, J. R. J. Phys. I (France) 1996, 6, 357 371]. Lattice animals and other random fractals associated with equilibrium polymeric structures tend to be anisotropic [Family, F.; Vicsek, T.; Meakin, P. Phys. Rev. Lett. 1985, 55, 641-644], and this is probably the reason that  $R_{\rm h}/R_{\rm g}$  is so small for the silica particle aggregates studied by Wilzius and others. Random walk polymer chains share this anisotropy (in contrast to the relative isotropic shape of diffusion-limited aggregates), and these structures have a similar ratio  $R_{\rm h}/R_{\rm g}$  to the silica particle aggregates (see text).
  - (59) Adam, M.; Lairez, D.; Karpasas, M.; Gottlieb, M. *Macromolecules* 1997, 30, 5920–5929.
  - (60) Garcia de la Torre, J.; Carrasco, B. Eur. Polym. J. 1998, 27, 549– 557.
  - (61) Rotne, J.; Prager, S. J. Chem. Phys. 1969, 50, 4831-4837.

- (62) Boukari, H.; Nossal, R.; Sackett, D. L.; Schuck, P. Phys. Rev. Lett. 2004, 93, 098106.
- (63) Boukari, H.; Chernomordick, V.; Krueger, S.; Nossal, R.; Sackett, D. L. Physica B 2004, 350, E533-E535.
- (64) Diaz, J. F.; Pantos, E.; Bordas, J.; Andreu, J. M. J. Mol. Biol. 1994, 238, 214-225.
- (65) Boukari, H., personal communication.

- (66) Kirchhausen, T. Annu. Rev. Biochem. 2000, 69, 699-727. The coordinates for the clathrin cage that are utilized in our calculations are given in the Supporting Information.
- (67) Ferguson, M. L.; Prasad, K.; Sackett, D. L.; Boukari, H.; Lafer, E. M.; Nossal, R. *Biochemistry* 2006, 45, 5916–5922.
  (68) Ferguson, M. L., personal communication.

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