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Biophysical Chemistry 116 (2005) 121 – 128

Biophysical Chemistry

http://www.elsevier.com/locate/biophyschem

MULTIHYDRO and MONTEHYDRO: Conformational search and Monte Carlo calculation of solution properties of rigid or flexible bead models

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Received 1 December 2004; received in revised form 23 March 2005; accepted 31 March 2005
Available online 13 April 2005

Abstract

A computer program, MULTIHYDRO, has been constructed for the calculation of hydrodynamic coefficients and other solution properties of multiple possible conformations of a bead model. With minimal additional programming to describe the model under study, this program interfaces efficiently with HYDRO [J. García de la Torre, S. Navarro, M. López Martínez, F. Díaz, J. Cascales, HYDRO: a computer software for the prediction of hydrodynamic properties of macromolecules, Biophys. J. 67 (1994) 530–531] [3] for the calculation of solution properties, including hydrodynamic coefficients, radius of gyration, covolume, etc. A useful application is the conformation search of rigid macromolecules, because many possible conformations can be evaluated in a single run of the program. In this paper we also pay attention to the properties of flexible macromolecules, in the so-called Monte Carlo rigid-body approximation, which is virtually exact for the simpler solution properties. The theoretical aspects of the procedure are described, and we show how MULTIHYDRO can be employed for this calculation. However, for flexible molecules, a more general simulation scheme is importance-sampling Monte Carlo generation. We describe how this procedure is implemented in another computer program, MONTEHYDRO. Examples of the usage of these tools are provided.

Keywords: Monte Carlo simulation; Hydrodynamic properties; Bead models

1. Introduction

The calculation of solution properties (sedimentation, translational and rotational diffusion coefficients, intrinsic viscosity, radius of gyration, etc.) of rigid macromolecules or assemblies of arbitrary shape is facilitated by methodologies like the bead-model procedure [1,2]. For simple models, composed of spheres of various sizes, the HYDRO computer program [3] is a useful tool, and related programs are available for more specific purposes. These programs calculate hydrodynamic and related properties for the structure from the bead coordinates and radii provided by the user. Usually, the ultimate goal is to determine models consistent with experimental solution data. Determining a detailed three-dimensional structure in an ab initio manner, from just a few values of hydrodynamic coefficients or other simple solution properties, is obviously an impossible task. In a more feasible scenario, some hypothetical, approximated structure could be guessed, with details remaining to be refined. For instance, a general structure could be formulated containing a few adjustable parameters (some distances, angles, etc.). In this situation we could attempt to make a search for the best fitting structure, calculating the properties for a number (sufficiently large but still moderate) of possible conformations. The procedure could also be applied to systematic conformational searches or identification of coexisting conformers [4,5]. There have been some previous initiatives to interface conformational search with hydrodynamic calculations in interesting, and even complex situations [6,7]. Our purpose here is to provide a simple, modular and unified tool for this purpose.

We also consider the problem of calculating the solution properties of flexible macromolecules. This calculation can also be made using bead models; indeed, the bead-modeling methodology comes from the pioneering studies by Kirk-

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doi:10.1016/j.bpc.2005.03.005

wood and Riseman [8,9] on fully flexible random coil polymers. The hydrodynamics of flexible entities is a complex problem because the hydrodynamic aspects are interwoven with the statistical aspects arising from the conformational variability. A useful and practically feasible approach to this problem, based on the well-developed rigid-body hydrodynamics is the so-called rigid-body Monte Carlo (RBMC) treatment. Essentially, the RBMC calculation includes three stages:

(i) generation of a collection of conformations of the macromolecule;
(ii) for each conformation, the properties are calculated as if it were an instantaneously rigid particle, for bead models, HYDRO can be used at this stage;
(iii) the final results for the solution properties are the averages of the individual properties for each possible conformation.

Of course, either the generation of the Monte Carlo sample or the final averaging procedure should take into account the Maxwell-Boltzmann distribution associated to the internal, potential energy of the particle. The RBMC procedure, originally proposed by Zimm [10], and further developed by other workers [11–13], is fully rigorous for equilibrium properties (mean dimensions, scattering, etc.), and for hydrodynamic entities is a good approximation [14,15] that provides quite accurate predictions for translational (diffusion and sedimentation) coefficients and intrinsic viscosities. This procedure is not intended for the reorientational, internal dynamics of flexible macromolecules, but it can be still employed to estimate the longest relaxation time of some semi flexible structures, like weakly bending rods [12], or some stiff multisubunit macromolecules [16].

We note that stages (i) and (ii), in short the serial procedure of generation of conformations and the evaluation of properties–eventually using the HYDRO program–are common to the two different problems commented on above: conformational search for rigid structures and RBMC calculations of flexible macromolecules. Furthermore, in both situations a conveniently formatted output is needed for either optimization or averaging. Of course, the core of the calculation will be the formulation of the model itself, which has to be done for each specific case. However, it is clear that these works have in common some tasks. With this idea in mind, we have written a computer code, program MULTIHYDRO, which carries out these common, repetitive tasks, and when properly complemented with the part of the code that describes the model, constitutes a practical tool for conformational search and RBMC calculations.

For intensive or complex Monte Carlo calculations, the most efficient procedure is the importance-sampling algorithm, while the uniform sampling that would be feasible with MULTIHYDRO is not adequate. For such cases, we have developed a separate computer program, MONTEHYDRO, for importance-sampling Monte Carlo calculation for a rather general model of a flexible particle, including bond length restrictions, angular bending interaction, and non-bonded, excluded-volume potentials. The program can be used for a variety of cases, including segmentally flexible particles, semi flexible worm-like chains, etc.

A segmentally flexible structure, composed of two globular domains connected by a linker containing a flexible hinge, is the structure used to show the applicability of the MULTIHYDRO and MONTEHYDRO approaches.

2. The MULTIHYDRO program

MULTIHYDRO is a computer code, written in Fortran, intended to facilitate the generation of multiple possible conformations of a bead model. A scheme of its usage is presented in Fig. 1. MULTIHYDRO is written in a modular form, so that the user just has to insert two pieces of Fortran code: (1) one with some physical data of the macromolecular solution and simulation parameters (as described below), and (2) another that constructs the Cartesian

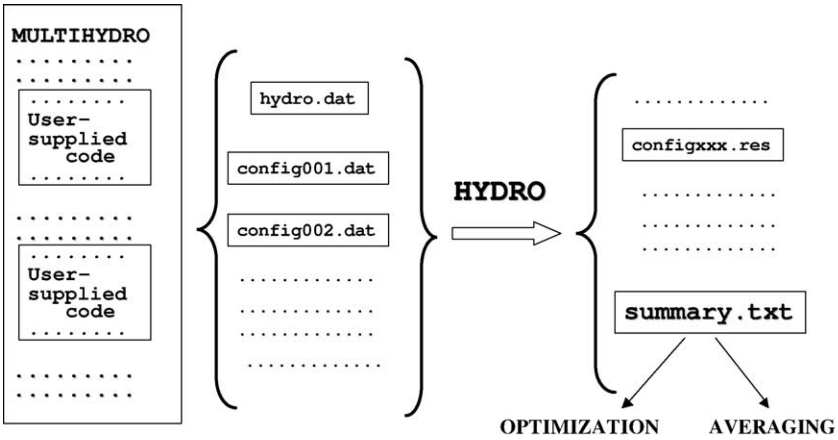

Fig. 1. Scheme of a MULTIHYDRO calculation. MULTIHYDRO generates the main input file hydro.dat and the structural files for the HYDRO calculation, which in turn gives the results file for each conformation, and the tabular file with the summary of results.

coordinates and radii of the beads. The code that we supply already includes subroutines for purposes like generation of random vectors, detection of overlaps, etc. Once the program is completed with the two user modules, its execution produces all the files needed for a multi-case run of HYDRO, which finally provides results for the properties of all the conformations, collected in a tabular file (summary.txt), which the user would finally employ for best-fitting search, Monte Carlo averaging, etc. A scheme of this process is presented in Fig. 1.

As an example of the use of MULTIHYDRO, we consider the hypothetical case of a structure composed of two identical globular, approximately spherical domains, joined by a connector that is supposed to be bent near its middle point. The aim is the determination of the bending angle, θ, as the value that best fits a set of solution properties of this macromolecule. For this purpose, we build a bead model consisting of two spheres of radius R_1 for the globular regions, and a string of N_c spheres of radius R_2 for the connector, whose length would be $L=2N_cR_2$. The model is depicted in Fig. 2. MULTIHYDRO can be employed to calculate the properties of this model as a function of θ.

Suppose that the radius of the globular domains, estimated from the hydrated volume is $R_1 \approx 25$ Å, while the connector has a length and thickness of about 50 and 10 Å, respectively, and is modeled with $N_c=5$ and $R_2=5$ Å. The θ angle is discretised in intervals of 5°. These data are supplied in the code block shown in Fig. 3A. The whole range from $\theta=0°$ to $\theta=180°$ would require 36 values of the angle. However, the range of θ is limited between $\theta=0$ and $\theta=\theta_0$, because of the overlap between the two globular domains (for simplicity we ignore the small overlap between the connector beads near the bend). With the dimensions given above, overlap between the two larger end beads occurs for $\theta_0=120°$. For the calculation of Cartesian coordinates, the central bead in the connector is placed at the origin. One of the arms (two connector beads plus the large sphere) lies in the negative part of the z-axis, with coordinates $z_i=-\rho_i$, ρ_i being the distance from bead i to the center of the central bead, and $x_i=y_i=0$. For the other arm, we have $z_i=\rho_i\cos\theta$, $x_i=\rho_i\sin\theta$, and $y_i=0$. The calculation of coordinates is programmed in the user-supplied block of code presented in Fig. 3B. Execution of the MULTIHYDRO program, including the two user modules, produces a list of values of all the solution properties. The results for the sedimentation coefficient, radius of gyration, and intrinsic viscosity, are plotted in Fig. 4. These computed values would then be compared with the experimental ones, to find the optimal value.

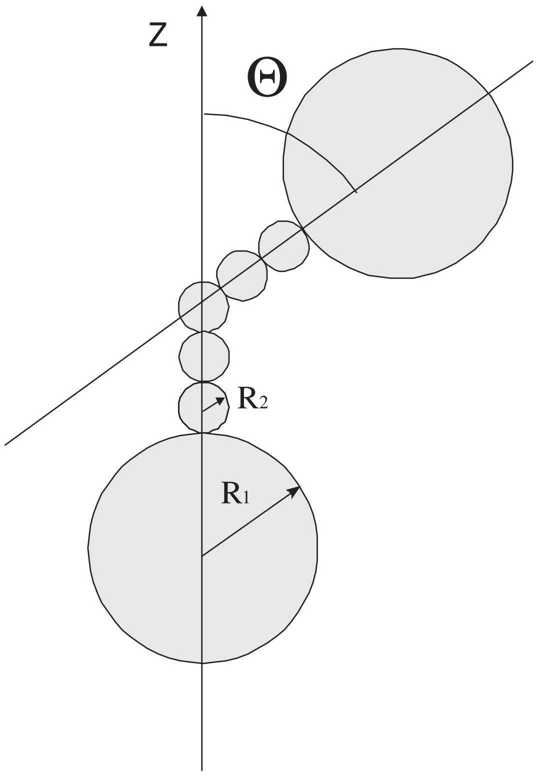

Fig. 2. Bent or broken dumbbell bead model.

The same procedure, illustrated for this deliberately simple (with a single internal variable) but illustrative case, can be followed for cases of arbitrary complexity.

3. Monte Carlo calculation of solution properties based on MULTIHYDRO

As indicated above, in the Monte Carlo calculation, the solution properties are evaluated as statistical averages over the possible conformations of the flexible particle. If the conformations are defined by a set of internal coordinates, **q**, then a general expression for the average of some general property, p, would be:

$$\langle p \rangle = \left(\int w(\mathbf{q})p(\mathbf{q})\mathrm{d}\mathbf{q} \right) \Big/ \left(\int w(\mathbf{q})\mathrm{d}\mathbf{q} \right) \tag{1}$$

$w(\mathbf{q})$ is the statistical weight corresponding to a set of **q** coordinates. In some practical instances the conformational space is discretized, and the integrals are evaluated as sums over a sample of conformations. Then Eq. (1) reduces to an average over a sample of N_{conf} uniformly distributed random conformations:

$$\langle p \rangle = \left(\sum_{i=1}^{N_{\mathrm{conf}}} w_i p_i \right) \Big/ \left(\sum_{i=1}^{N_{\mathrm{conf}}} w_i \right) \tag{2}$$

where p_i and w_i are the individual value and statistical weight for the ith conformation. The latter will contain the Boltzmann exponential of the potential energy, exp $(-V_i/k_BT)$, where k_BT is Boltzmann's factor, and eventually a geometrical weight, depending on the coordinates that define the internal degrees of freedom. In some simple representations of the internal potential, the beads composing the model are hard spheres which cannot penetrate each other. Then, some of the N_{conf} uniformly generated conformations

(A)

```
! Physical data
temp=293.      ! Temperature, Kelvin
eta0=0.010     ! Solvent viscosity
rm=110000.     ! Molecular weight
vbar=0.710     ! Partial specific volume
solden=1.0     ! Solution density
title='The bent dumb-bell'
filename='config'

! Model data (dimension is Angs.)
nconf=36
n1=3 ; n2=2 ; ntotal=n1+n2+2
r2=5. ; r1=25.
```

(B)

```
! Generate conformation number iconf
i=0
! First arm, n1 beads aligned with axis Z
DO i1=1,n1
  i=i+1 ; e(i)=r2 ;
  x(i,3)=-(i1-1)*2.*r2 ; x(i1,1)=0. ; x(i1,2)=0. ;
ENDDO

! One of the big spheres
i=i+1; e(i)=r1
x(i,3)=x(i-1,3)-r2-r1 ; x(i,1)=0. ; x(i,2)=0. ;

! Second arm, n2 beads making angle theta

theta=(3.1416/nconf)*(iconf-1)
u(1)=sin(theta) ; u(2)=0. ; u(3)=cos(theta)
DO i2=1,n2
  i=i+1 ; e(i)=r2 ; rad=i2*2.*r2
  x(i,1)=rad*u(1) ;x(i,2)=rad*u(2) ;x(i,3)=rad*u(3) ;
ENDDO

! Second big sphere
i=i+1 ;e(i)=r1 ;rad=rad+r2+r1
x(i,1)=rad*u(1) ;x(i,2)=rad*u(2) ;x(i,3)=rad*u(3) ;

!Check overlap between big spheres
CALL CHECK_OVERLAP(x,e,ntotal,n1+1,iflag)
if(iflag.eq.1) goto 222
n=i
```

Fig. 3. Parts of user-supplied code, to be inserted in MULTIHYDRO, for the calculations with the model in Fig. 2. (A) Physical data and model dimensions. (B) Code to set up coordinates and radii of beads, for varying θ.

would have $w_i = 0$, and do not contribute to the sums in Eq. (2). Still this equation would be valid replacing N_{conf} by the number of allowed conformations.

It is clear that MULTIHYDRO is a useful tool for Monte Carlo calculations, because it covers the more tedious task of generating conformations and evaluating properties. With the final results file, summary.txt, the user can easily carry out the averages in Eq. (2) easily, for instance importing that file into a spreadsheet where the calculations of the sums in this equation can be accomplished.

Some problems can be treated with a rather simple and efficient (although perhaps more conceptually complex) approach, based on the nature of the internal variables of the flexible particle. For instance, in the case of structures with two straight arms, like that considered in the previous section, if one of the arms is fixed (say, aligned with z, as in Fig. 2), the internal coordinates are the pair of polar angles (θ; ϕ) that define the spatial position of the second arm. The molecule could experience a bending potential, $V(\theta)$, to which the associated Boltzmann weight would be associated, $\exp[-V(\theta)/k_BT]$. The differential of internal coordinates is in this case the differential of solid angle, $d\mathbf{q} = \sin\theta d\theta d\phi$, and Eq. (1) gives

$$\langle p\rangle = \left(\int_\theta\int_\phi \exp[-V(\theta)/kT]\, p(\theta,\phi)\sin\theta d\theta d\phi\right) \Big/ \left(\int_\theta\int_\phi \exp[-V(\theta)/kT]\sin\theta d\theta d\phi\right). \tag{3}$$

This example is further simplified if we note that the longitudinal angle ϕ gives just an orientation; conformations with the same ϕ are structurally identical and have the same properties. Then the previous equation reduces to another with single integrals. For conformations with θ close to 180°, the arms are close to each other and bead overlap occurs beyond some angle θ_0. If an infinite potential and zero weight is associated to forbidden overlap, then, the expression is simply:

$$\langle p\rangle = \left(\int_0^{\theta_0} p(\theta)\exp[-V(\theta)/kT]\sin\theta d\theta\right) \Big/ \left(\int_0^{\theta_0} \exp[-V(\theta)/kT]\sin\theta d\theta\right). \tag{4}$$

Finally, Eq. (4) can be calculated as a discrete sum, for instance computing the integrals by Simpson's numerical integration. Thus we finally return to the evaluation of an expression like Eq. (2), with an statistical weight $w_i = \exp[-V(\theta_i)/kT]\sin\theta_i$, containing both a conformational contribution and a geometric one. Again, the sums can be easily evaluated from the output of MULTIHYDRO. In the case of a freely-hinged particle, there is no bending potential ($V(\theta_i) = 0$), so conformations just have the geometric weight ($w_i = \sin\theta_i$), and the result is extremely simple

$$\langle p\rangle = \left(\sum_{i=1}^{N_{\mathrm{conf}}} \sin\theta_i p_i\right) \Big/ \left(\sum_{i=1}^{N_{\mathrm{conf}}} \sin\theta_i\right). \tag{5}$$

For the dimensions of the particle considered in Figs. 2 and 3, with the data for the p_i's plotted in Fig. 4, in the freely-hinged case, the final results for the solution properties are those reported in Table 1.

Table 1
Properties of the broken-dumbbell structure shown in Fig. 2, with the dimensions and physical data given in the main text

	MULTIHYDRO	MONTEHYDRO
Translational diffusion, $D_t \times 10^7$, cm^2/s	5.66	5.79
Sedimentation coefficient, s, S	7.41	7.22
Intrinsic viscosity, $[\eta]$, cm^3/g	4.01	3.88
Radius of gyration, R_g, nm	4.30	4.15

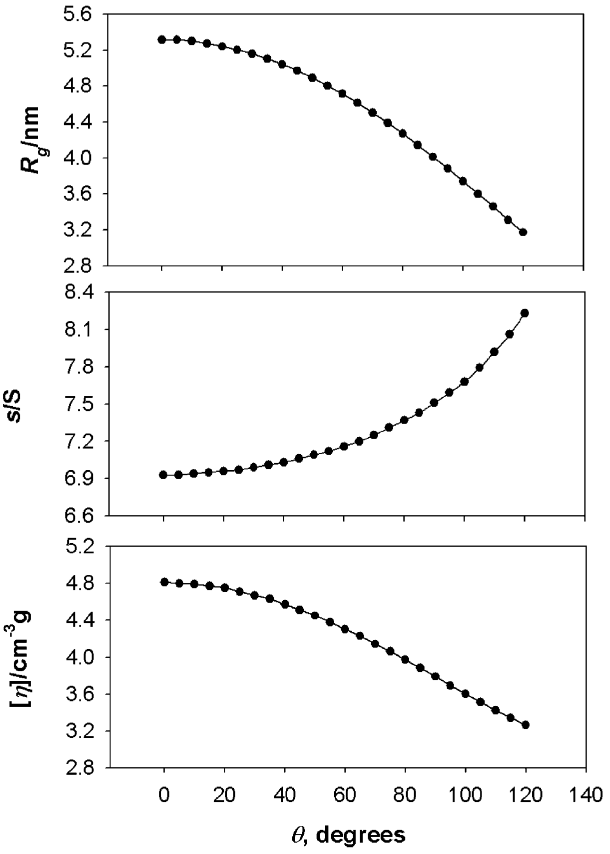

Fig. 4. Results for the θ-dependent solution properties calculated for the model in Fig. 3.

4. Importance-sampling Monte Carlo: the MONTEHYDRO program

The importance-sampling procedure [17] is a variant of the Monte Carlo method in which the conformations are not picked from a uniform sampling (as outlined in the preceeding section) but, instead, the generation of conformations is biased according to their different probabilities. This results in a gain in performance, since conformations with rather small statistical weight are very unlikely to be in the sample. The procedure is sequential: starting from some conformation, with potential energy V_{prev}, a new conformation is generated by introducing a small change in the internal coordinates, and the potential energy of the new conformation V_{new}, is compared with the previous one. If potential is decreased, with $V_{\mathrm{new}} < V_{\mathrm{prev}}$, the new conformation is accepted. Otherwise, when $V_{\mathrm{new}} > V_{\mathrm{prev}}$ then the following test is carried out: a uniform random number in the interval (0,1), u, is generated. If $u < \exp[-(V_{\mathrm{new}} - V_{\mathrm{prev}})/k_BT]$, the conformation is still accepted, and otherwise it is rejected, taking as the new conformation a copy of the previous one. As the generation of conformations in this method already considers the statistical weight, it has not to be employed in the calculation of averages, which will be unweighted means: $\langle p\rangle = (\Sigma p_i)/N_{\mathrm{conf}}$.

A general implementation of the importance-sampling Monte Carlo method is not feasible. However, for a model with a few (but frequent) types of interaction, a rather general program can be devised. We have constructed a Monte Carlo program, intended for RBMC calculation of solution properties, of a model composed of beads and connectors, having the following components in the interaction potential:

(1) “Bonds” or “connectors”, which are essentially distance restrictions, represented by continuous but stiff springs. If two beads, i and j are bonded or connected, they are joined in the model by a Hookean spring with potential $V = k_B TH(r_{ij} - d_{ij})^2$, where d_{ij} is the equilibrium length of the connector. Giving a sufficiently large value to the dimensionless constant H, then the fluctuation of r_{ij} around d_{ij} is rather small; we take $H = 100$, and then the variance of r_{ij} is just $0.05 d_{ij}$. Note that a rigid particle (or more practically, a rigid domain in a flexible particle), can be modeled placing one of these hard connectors between every pair of beads comprising that part of the molecule.

(2) Angular, bending interactions. The angle, θ, subtended by two contiguous connectors (i.e., which both act on a given bead) is similar to a bond angle. A simple quadratic potential is associated to this bending angle: $V = k_B TQ(\theta - \theta_e)^2$. The dimensionless constant gauges the strength of the angular interaction; it can be varied smoothly from 0 (free bending) to large values. A practically fixed angle, with $\theta \approx \theta_e$ can be obtained setting $Q = 100$. For a straight conformation (three colinear beads), $\theta_0 = 0$.

(3) Non-bonded interactions, representative of excluded-volume interaction between the beads. As for bond interactions, a pairwise potential is again employed, of the form $V(r_{ij})$. A frequent choice is the truncated Lennard-Jones parameter, $V(r_{ij}) = 4\epsilon[(\sigma/r_{ij})^6 - (\sigma/r_{ij})^{12}]$, with $V(r_{ij}) = 0$ if $r_{ij} > r_{\max}$. A simple case is the hard spheres potential, which just avoids bead overlapping: $V(r_{ij}) = 0$ if $r_{ij} > s_{ij}$ and $V(r_{ij}) = \infty$ if $r_{ij} < s_{ij}$, where s_{ij} is the smallest distance allowed between bead centers, usually taken as the sum of the

```
1000000 !Nsteps
100000  !Nconf
0.001   !Delta
6543231 !Iseed
7   !N, number of beads
2.5  0. 0. 0.  !radius and coords
0.5  3. 0. 0.
0.5  4. 0. 0.
0.5  5. 0. 0.
0.5  6. 0. 0.
0.5  7. 0. 0.
2.5 10. 0. 0.
6  !Nbonds
 1  2   3.  100. !i,j, d, H
 2  3   1.  100.
 3  4   1.  100.
 4  5   1.  100.
 5  6   1.  100.
 6  7   3.  100.
5  !Nangles
 1  2  3  0. 100. !i,j,k, alpha0, Q
 2  3  4  0. 100.
 3  4  5  0.   0.
 4  5  6  0. 100.
 5  6  7  0. 100.
10  !Nnonbon
 1  4  5  0.3   1.8   7.2 !i,j,itype,eps,sig,rmax
 1  5  5  0.3   1.8   7.2
 1  6  5  0.3   1.8   7.2
 1  7  5  0.5   4.0  16.0
 2  5  5  0.1   0.8   3.2
 2  6  5  0.1   0.8   3.2
 2  7  5  0.3   1.8   7.2
 3  6  5  0.1   0.8   3.2
 3  7  5  0.3   1.8   7.2
 4  7  5  0.3   1.8   7.2
```

Fig. 5. User-supplied data file for the MONTEHYDRO run. Units of length and energy are $u = 1$ nm and $k_B T = 4.04 \times 10^{-14}$ erg. Lennard-Jones parameter (itype=5).

radii of the two beads: $s_{ij}=\sigma_i+\sigma_j$. Alternatively, other, more detailed interaction potentials (like the Lennard-Jones function) can be employed.

MONTEHYDRO works internally with the Cartesian coordinates of the beads. In the importance-sampling algorithm, at each simulation step, the new conformation is obtained from the previous one changing all the bead coordinates by a small amount, δ, which is a uniform random number in the interval $(-\Delta,+\Delta)$, where Δ is known as the Monte Carlo size step (one random number for each bead coordinate). Once the preliminary coordinates of the new conformation have been calculated, the importance-sampling test is performed to calculate the new final coordinates, the components of the potential, and the total potential is employed in the importance-sampling test. In addition to generating the sample, MONTEHYDRO calculates also the individual properties and, as the final results, the Monte Carlo averaging. For this purpose, a HYDRO subroutine has been embodied in the program, which makes it possible to obtain hydrodynamic properties. The set of properties calculated by MONTEHYDRO includes the radius of gyration, R_g, the translational diffusion coefficient D_t (from which the sedimentation coefficient, s, can be evaluated), the intrinsic viscosity, $[\eta]$ and the longest rotational relaxationtime τ_1.

The program is simply controlled by a user data file. In Fig. 5 we present the data file corresponding to the same structure considered in the previous section. Nsteps is the number of Monte Carlo steps, and Nconf is the number of conformations selected for calculation of properties. Nconf is smaller than–indeed it should be an integer divisor of–Nsteps. The simulation steps are usually small and initial and final conformation at each step are rather similar; therefore, conformations are sampled after a series of Nsteps/Nconf consecutive steps. Iseed is a seed for random number generation. Delta is Δ (in nm), the maximum amplitude of the MonteCarlo displacement of coordinates. Next we have a list of the radii and initial coordinates of the N beads; in this case, the initial conformation is the fully straight one. This is followed by a list of the Nbond connectors, with a line for each one giving the indices of the connected beads, the equilibrium distance and the Hookean spring constant. Next we have the Nang angular, bending interactions, identifying the three beads involved, the equilibrium angle and the Q bending constant. Note that all the constants take the high value (100.), except that of the central angle, subtended by beads 3, 4 and 5 (4 is the hinge), where $Q=0$ for the fully flexible hinge. Finally, the data file includes lines for the Nnonbond excluded-volume interactions for pairs of beads not involved in bonds or angles, giving the interaction type, 0 in this case for hard-spheres interaction, and the overlap distance (the sum of the two radii). MONTEHYDRO only needs this simple data file to make the MCRB calculation for the specified structure, giving for the solution properties the results that are listed in Table 1. It is evident that the MONTEHYDRO and MULTIHYDRO calculations give results that are practically identical (within the statistical error), as they should.

The CPU time required by a MULTIHYDRO or MONTEHYDRO calculation is very small for small N. Thus, for the example presented above with $N=7$ beads, the generation of 1000 conformations and the calculation of properties took a CPU time of less than 1 s in a Pentium 3.0GHz with Visual Compaq Fortran. With a large number of N, the CPU time needed for the HYDRO calculation increases remarkably and will be the most time-consuming part of the procedure (being approximately $2\times10^8 N^3$ s for each conformation −22 s for $N=100$—in the mentioned platform).

5. Concluding remarks

We have attempted to provide two useful tools, having a similar basis and modular structure: MULTIHYDRO for conformational search of rigid structures, and MONTEHYDRO for Monte Carlo calculations for flexible particles. Our elementary procedure of conformational search, essentially based on single-valued hydrodynamic properties is related, and in some regards it complements the sophisticated conformational search based on small angle X-ray scattering measurements (SAXS) [18,19]. By the way, we note that HYDRO computes the angular dependence of scattering intensities and distribution of distances [20] so that MULTIHYDRO can be employed for simple search procedures including also scattering measurements, and MONTEHYDRO can be used to evaluate scattering intensities and distribution of distances for flexible entities.

The examples employed in this paper are deliberately simple because we try to emphasize the structure and modus operandi of our procedures (modularity of computer code, interfacing various programs, etc.) Of course, user-supplied program modules will have a complexity determined by the level of detail included in their model. The implementation of sophisticated models (perhaps with atomic level) in this scheme is feasible, although it may require some programming effort and, as indicate above, may be computationally intensive.

6. Computer programs

MULTIHYDRO and MONTEHYDRO will be available from our web site, http://leonardo.fcu.um.es/macromol.

Acknowledgements

This work was supported by a grant from Ministerio de Ciencia y Tecnología to J.G.T., and A.O. and H.E.P.S. are the recipients of predoctoral fellowships from the FPI and

FPU programs, respectively, of Ministerio de Educación y Ciencia. J.G.H.C. is the recipient of a Ramon y Cajal research contract from Ministerio de Educación y Ciencia.

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