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# A first-passage algorithm for the hydrodynamic friction and diffusion-limited reaction rate of macromolecules

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Many important properties of a macromolecule can be expressed in terms of averages over the trajectories of diffusing particles that begin in the medium surrounding the molecule and terminate at its surface. These properties include its translational hydrodynamic friction coefficient and the Smoluchowski rate constant for diffusion-limited reactions. In this paper we introduce a first-passage algorithm (FPA) for calculating such quantities. This algorithm uses certain exact Green's functions, or propagators, for the Laplace equation to eliminate the need to construct explicitly those portions of a diffusing particle's trajectory that are not near an absorbing object. The algorithm is especially efficient for studying objects that contain large voids or have very irregular surfaces, such as macromolecules. Diffusion algorithms were previously shown to give accurate results for the quantities we study. In this paper, we show that first-passage methods make these algorithms more accurate and efficient. In future work, we expect to present systematic results for the properties of globular proteins. © 1997 American Institute of Physics.

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## I. INTRODUCTION

This paper initiates a project of calculating the bulk properties of disordered media by the use of a novel class of diffusion techniques. Disordered media<sup>1-3</sup> are systems belonging to the liquid state of matter,<sup>1</sup> i.e., those lacking long-range positional order, but possessing substantial organization, as measured by more complicated order parameters. Many such systems are two-phase materials in which one phase is dispersed throughout the other in an irregular manner. Examples of disordered media abound in physical chemistry (electrolytes or complex fluids undergoing phase separation), polymer chemistry (polymer or diblock copolymer blends), and biophysics (self-organizing lipid-membrane or polypeptide structures).

Bulk properties can be defined as large-scale averages<sup>2,3</sup> over the microstructure of a disordered system; frequently these are volume averages and/or ensemble averages over the solutions of Laplace equations or wave equations with source terms and/or boundary conditions prescribed on very complicated boundaries. These include the calculation of electrical and thermal conductivity (in the case that both phases are solid), and diffusion-limited reaction rate and fluid permeability (in the case that one phase is solid and the other is liquid).

By the term "diffusion techniques," we denote the general class of methods of solving partial differential equations that are based on mapping these equations onto generalized diffusion equations;<sup>4</sup> these are often called Monte Carlo diffusion algorithms. The theory behind this type of mapping is probabilistic potential theory.

In this series of papers, we develop a novel class of algorithms, which we call "first-passage algorithms," for efficiently solving a large class of parabolic and elliptic differential equations. These algorithms involve three steps.

- (1) We rewrite the differential equation as a Poisson equation, by putting all the non-Laplacian terms on the right-hand side of the equation.
- (2) We interpret this equation as a diffusion equation for freely diffusing particles, with the right-hand side terms interpreted as source terms, to be determined self-consistently. Precisely how this is done is the subject of a later paper in this series.<sup>5</sup> Here we simply note that this step allows us to solve, using random diffusion methods, a large class of differential equations, including the type of Smoluchowski equation that governs both the Brownian dynamics<sup>6</sup> and the solvation free energy<sup>7</sup> of a macromolecule.<sup>6,36</sup>
- (3) We perform efficient simulation of free diffusion near irregular surfaces using the basic first-passage concept; each diffusing particle performs a series of propagating events or "jumps" that allow it to traverse quickly domains of the system that contain no reactive surfaces. At present, propagators for these events are taken from a library of Green's functions that can be sampled by performing a single numerical integration. We are presently relaxing this restriction by calculating some other Green's functions using grid tabulation and higher-order interpolation.

The first-passage concept allows rapid simulation of diffusion near a great variety of reactive surfaces, including

those present in macromolecular models. This allows simulation of diffusion-limited reactions<sup>8(a),8(b)</sup> with or without force fields, between a small ligand molecule and a macromolecule containing one or more binding sites.

First-passage algorithms can also be used to determine a large number of macromolecular bulk properties by exploiting the mappings of potential theory. The capacitance<sup>9</sup>  $C$  of a macromolecule, defined as the electrostatic capacitance of a perfect conductor with size and shape identical to the macromolecule, determines,<sup>10</sup> either exactly or approximately, a number of bulk properties of a macromolecule. An example is the diffusion-limited reaction rate  $k$  using Smoluchowski boundary conditions of a small ligand diffusing near a macromolecule,<sup>6</sup>

$$k = 4\pi CD, \quad (1.1)$$

where  $D$  is the diffusion constant of the diffusing ligands. Certain bulk properties, for example, the hydrodynamic friction and intrinsic viscosity, are given accurately by a class of ‘‘angle averaged approximations’’<sup>11</sup> that reduce their calculation to the solution of a scalar wave equation. These give for the isotropically averaged translational hydrodynamic friction<sup>12</sup>  $\xi$  the relation<sup>11</sup>

$$\xi = 6\pi\eta C, \quad (1.2)$$

where  $\eta$  is the shear viscosity, and for the intrinsic viscosity  $\eta_0$  the formula,

$$\eta_0 = \frac{5}{6} \alpha, \quad (1.3)$$

where  $\alpha$  is the electrical polarization of a conductor shaped like the macromolecule. This approximation is accurate for a wide variety of molecular shapes.<sup>15</sup> We do not yet have an accurate formula of this type for the rotational friction coefficient.<sup>16</sup> The rotational friction coefficient of an axisymmetric molecule about its symmetry axis can be expressed<sup>17(a)</sup> in terms of the virtual mass<sup>17(b)</sup> of the object; the latter quantity is readily calculated using first-passage diffusion algorithms.<sup>5,18</sup> The hydrodynamic friction of flow through a packed bed<sup>14</sup> can be calculated using formula (1.2) by treating the particle bed as a large ‘‘molecule’’; this is a simple case of the general problem of suspension viscosity.<sup>13</sup>

The first passage algorithm constructs a random diffusion path as a series of first-passage propagation events (see Fig. 1) or ‘‘jumps.’’ To construct one of these ‘‘jumps’’ for a diffusing particle at position  $\mathbf{x}_0$ , one constructs a first-passage volume that surrounds it. Such a volume is the intersection of a sphere with a portion of the absorbing target surface sufficiently simple, geometrically, to allow construction of an analytic Green’s function for the Laplacian inside its surface. Here by an ‘‘analytic’’ Green’s function, we mean one whose values are determined by at most a single numerical quadrature. The surrounding first-passage sphere divides the trajectory into manageable portions; we absorb the diffusing particle at its surface in order to terminate it there, thus making its behavior inside the first-passage surface independent of the geometry of the absorbing target surface outside. As explained in Sec. III, the Green’s func-

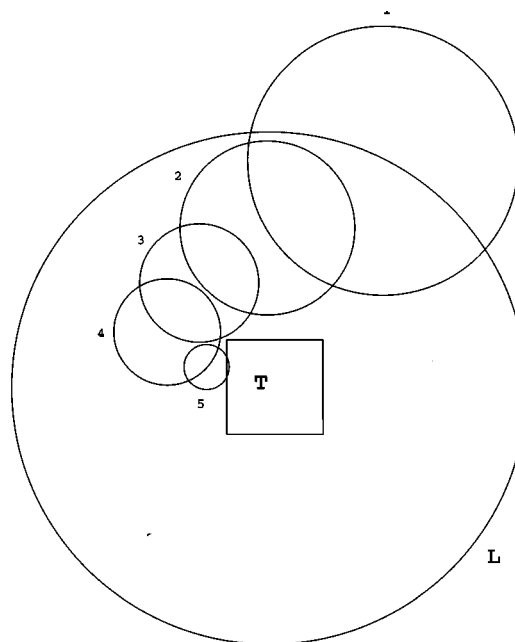


FIG. 1. A sample trajectory of the first-passage algorithm (FPA), simulating a particle diffusing near an absorbing cube. Here the symbol  $L$  denotes the launch sphere, and  $T$  denotes the target. The trajectory shown goes through five first passage events before hitting the target.

tion gives the probability density associated with the diffusing particle at position  $\mathbf{x}_0$  first contacting the first passage sphere (and thus being terminated) at the point  $\mathbf{x}_1$  on its surface. This termination site then becomes the center of the next first-passage surface.

Our present algorithm allows several possibilities for the first-passage surface: it may be a sphere<sup>19</sup> that does not intersect an absorbing target surface at all. (When a diffusing particle is far from the absorbing target surface, this is advantageous; we explain this in Sec. III.) It may be a sphere that intersects a spherical<sup>20,21</sup> or cylindrical patch of absorbing target surface. We have not exhausted the possibilities. The set of Green’s functions presented in Sec. III (see Fig. 2) is sufficient for calculating the geometrical, and thus the bulk, properties of a macromolecule, as represented in standard molecular mechanics packages.

First passage algorithms are free of three limitations that plagued earlier Monte Carlo diffusion methods. These are

- (1) We need not discretize<sup>22</sup> either absorbing medium or diffusing particle trajectory, either in space or in time. We do not approximate an absorbing target surface as a discrete set of periodically-spaced lattice points.<sup>24</sup> Nor do we approximate a diffusion path, which is a continuum Brownian motion, by a discrete-time random walk. Such an approximation (see Fig. 3) is fraught with difficulties when modeling a diffusing particle very near an absorbing surface.<sup>22</sup> Finally, we do not discretize the source.<sup>23</sup>
- (2) We need not approximate absorbing boundary conditions at a surface by defining an ‘‘absorption length,’’ and specifying that any random walker that steps closer to the surface than this length is absorbed. This concept

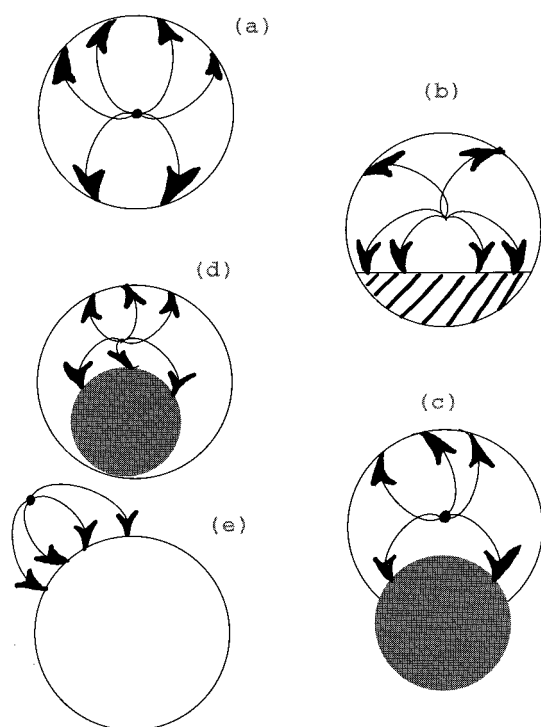


FIG. 2. Schematic of the five electrostatic Green's functions, or propagators, for the Laplacian that we use in this paper.

may be useful for some practical problems, but it yields an "absorption rate" that depends essentially upon the absorption length. (One could, alternatively, model absorbing boundary conditions by specifying that any walker stepping over the surface of the absorbing target object is absorbed. This method, however, requires that one use very small random walk step size when diffusing near an absorbing object.)

- (3) We need not require a diffusing particle to take small steps in both space and time when it diffuses in a strong force field,<sup>6</sup> because, even when forces are present, we need consider only force-free diffusion. As mentioned above, we do this by moving the non-Laplacian terms in a differential equation to the right-hand side of the equation, and treat them as "source terms" to be determined self-consistently.

One final advantage; our statistics are not degraded near a point of surface discontinuity even though solutions to the Laplace equation tend to have singularities at such points; first-passage algorithms already perform importance sampling, by definition of this term.

In this paper, we develop and test a first-passage algorithm for the capacitance of an object with the geometry of a macromolecule. In future publications, we intend to discuss first-passage algorithms<sup>5</sup> for the other bulk quantities mentioned in this Introduction. In addition, we will present a first-passage algorithm for Brownian dynamics and solvation free energy.

This paper is organized as follows: Section II describes the electrostatic analogies that we find useful for relating the

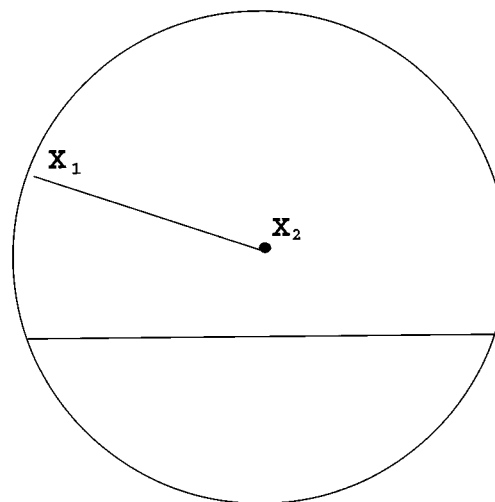


FIG. 3. Discrete random walk as an approximation to continuum Brownian motion. As shown here, a diffusing particle, exhibiting continuum Brownian motion may contact the absorbing set in between the discrete moments in this motion that are chosen by the random walk.

statistics of diffusing particles to the physical properties of macromolecules. Section III develops the set of Laplacian Green's functions that are the basis for the present class of algorithms. Section IV describes some exacting numerical tests that show first-passage methods, to be free of limitations present in other methods. Section V gives our conclusions and implications for further research. Five technical appendices are provided, in which we present explicitly the five exact Green's functions that are incorporated in the current version of our algorithm. A sixth technical appendix shows how to use them to obtain the explicit surface density of absorbed particles as a function of position on the target surface.

## II. ELECTROSTATIC ANALOGY FOR CALCULATING DIFFUSION-LIMITED QUANTITIES

In this section, we develop briefly the isomorphism between the electrostatic properties of an object that is an ideal conductor, and the statistical properties of particles diffusing near a geometrically identical object that is a perfect absorber.

The class of first-passage algorithms studied in this work are based on the mathematical study<sup>4</sup> termed "probabilistic potential theory." This study develops a detailed isomorphism, or mapping, between the calculation of electrostatic quantities<sup>9</sup> and the calculation of the average properties of diffusion paths. We first develop this mapping. Consider a system of particles undergoing diffusive motion near an absorbing object. The particles diffuse independently of one another and are absorbed upon contact with the object. The density  $p(x)$  of diffusing particles near an absorbing target surface at position  $x$  obeys the Laplace equation, the same equation obeyed by the electrostatic potential  $\phi(x)$  near an identically shaped conducting surface. In fact, the correspondence

$$p(x)/p(\infty) \equiv \phi(x)/\phi(\infty) \quad (2.1)$$

results from the fact that these two quantities obey Laplace's equation with identical boundary conditions. Here  $\phi(\infty)$  is the (constant) value of the electrical potential at infinity, and  $p(\infty)$  is the density of diffusing particles at infinity, i.e., far from the absorbing object. The gradient of this density gives the flux of diffusing particles, a quantity analogous to the electric field. The divergence of this flux gives the rate at which diffusing particles are absorbed or created at a surface, a quantity analogous to the density of electric charge on that surface. In fact, the time derivative of the diffusive particle density is related to the flux  $J$  of random walkers by the equation

$$\frac{\partial}{\partial t} p + \nabla \cdot J = 0 \quad (2.2)$$

just as the charge density  $\rho$  is related to the electric field  $E$  by the equation

$$4\pi\rho + \nabla \cdot E = 0. \quad (2.3)$$

The absorbing (resp., reflecting) boundary condition for diffusion problems corresponds to Dirichlet or conducting (resp., Neumann, or insulating), boundary condition for electrostatic problems.

Applications of this analogy are applied to problems in chemical physics in Ref. 8, to which the reader is referred. We will generalize this analogy substantially in Ref. 5.

### III. CALCULATION OF DIFFUSION-LIMITED QUANTITIES TO USING THE FIRST-PASSAGE ALGORITHM (FPA)

In this section, we develop in detail the first-passage algorithm (FPA) for simulating diffusive motion. We define a set of five Green's functions that completely characterize interaction of a diffusing particle with a general class of surfaces adequate to model macromolecular surfaces.

We can efficiently model diffusion-limited processes if we can determine the first-passage probability density on an absorbing first-passage surface surrounding a diffusing particle. In the diffusion problem shown in Fig. 2, absorbing boundary conditions must be imposed on both the absorbing target surface and the first-passage sphere; on the former because it reacts with diffusing particles, and on the latter because the contacts made with it by diffusing particles would otherwise not be "first-passages." The probability density associated with a diffusing particle originating at a point source at  $\mathbf{x}_0$  and being absorbed at point  $\mathbf{x}_1$  is given by

$$\sigma_1(x_1) = \mathbf{n}(x_1) \cdot \frac{d}{dx_1} G(x_0, x_1). \quad (3.1)$$

Here  $\mathbf{n}(x_1)$  is the unit normal vector to the absorbing surface at point  $\mathbf{x}_1$ ;  $G(x_0, x_1)$  is the Green's function for the Laplace equation associated with a unit source at point  $\mathbf{x}_0$  and absorbing boundaries at the target surface. If the portion of boundary of the absorbing object included in the first-passage sphere is not too irregular, the calculation of this Green's function reduces to a single one-dimensional integral, which

can be performed numerically for any specific value of  $\mathbf{x}_1$ . In particular, if the included patch of boundary is either flat or spherical<sup>20,21</sup> this can be done with Green's functions provided in this paper.

We first indicate how to use the solution for  $\sigma_1(x_1)$  to generate points on the first-passage surface having the correct distribution. If the absorbing target were not present, each point  $x_1$  on the first-passage sphere would be reached by the diffusing particle with uniform probability

$$\sigma_0(x_1) = 1/(4\pi d^2), \quad (3.2)$$

where  $d$  is the radius of the first-passage sphere. We choose a point on the first-passage sphere using this distribution. If the point lies inside the target, the diffusing particle has been absorbed. If this point lies outside the target, the diffusing particle may nevertheless have contacted the target before reaching this point. We correct for this possibility by generating points on the first-passage sphere with uniform probability density  $\sigma_0(x_1)$ , then rejecting them with probability

$$P = \frac{\sigma_0(x_1) - \sigma_1(x_1)}{\sigma_0(x_1)}. \quad (3.3)$$

Again, the diffusing particles that are rejected are taken to have been absorbed.

Capacitance calculations do not require the charge distribution on the target, but only the total charge. However, many applications of first-passage algorithms do require the charge distribution, i.e., they require determination of the specific point on the target at which absorption took place. We give an algorithm for the density of absorbed particles, as a function of position on the target surface, in Appendix F.

The five Green's functions used in the present first-passage algorithm are shown in Fig. 2. Complete formulas for these are given in the appendices to this paper. This set of Green's functions allows us to simulate, in an exact and efficient manner, diffusion near absorbing boundaries that, locally, are composed of either planar or spherical sections. As discussed in the Introduction, this class of surfaces includes that encountered in basic molecular mechanics modeling of macromolecules.

The present algorithm can be extended to provide first-passage probabilities near more complicated absorbing sets; this requires the inclusion of more Laplacian Green's functions or propagators. In particular, the study of fibrous media<sup>14</sup> suggests the inclusion of the Green's function for first passage near a cylindrical absorbing object. The small library of Green's functions chosen here seems to us to offer a good compromise between simplicity and flexibility.

The strategy adopted for our initial computations might be termed the "greedy" algorithm. It consists of choosing at each step the largest possible first-passage sphere for which the Green's function is available. The major computational expense of our algorithm lies in evaluating the Green's functions required in nontrivial first-passage calculations. If a first-passage sphere is very large in relation to the natural length scale of the target, the probability of starting at its center and making a first-passage contact with the target is very small. In such cases it is best to use instead a first-

passage sphere which is as large as possible without intersecting the target. This maximizes the probability of either getting closer to the target or of diffusing to infinity. We implement this idea as follows: no first-passage sphere may intersect the target unless its center lies closer to the target than a distance  $\delta$ . For each absorbing object one can study using this algorithm, there is an optimal choice of  $\delta$  in terms of minimizing the computer time used. We get good results for the problems studied here using  $\delta=(0.1)*b$ , with  $b$  the radius of the launch sphere. However, we have no general results on the optimal value of this quantity.

#### IV. TESTS OF THE FIRST-PASSAGE ALGORITHM

In this section we apply a number of exacting tests to the FPA in order to test its ability to treat absorbing targets with irregular surfaces. We show that, although edges and cusps in the definition of macromolecular accessible surface<sup>7</sup> pose problems for boundary element methods, first-passage algorithms have no such problems. We also show that, although local correlations in random number generators pose a serious potential problem for Brownian motion studies, our capacitance algorithm is free of such problems.

We test the FPA by calculating the capacitance of a number of sets for which exact results are available. We perform high-accuracy simulations to search for systematic errors in our method, i.e., surface irregularities that are treated incorrectly. Also, because the FPA replaces the generation of a very large number of random steps with the generation of a very small number of first-passage moves, it is a statistical process with strong local correlations, i.e., correlations between consecutive moves. Thus, the FPA should be sensitive to additional local correlations in random number generators, of just the type that have been detected recently.<sup>25</sup>

Our result for the capacitance of a unit sphere is

$$C(\text{unit sphere})=1.000\ 01\pm 0.000\ 1 \quad (4.1)$$

after simulating 40 million diffusing particles. We also calculate the capacitance of a pair of unit spheres<sup>26</sup> whose centers have variable separation  $l$ . For  $l=2$  and  $l=4$  we obtain, respectively,  $C=1.3863\pm 0.000\ 1$  and  $C=1.6052\pm 0.000\ 1$  after simulating at least 50 million diffusing particles near each set. Here the quoted uncertainty in the last decimal place corresponds to one standard deviation. (According to the law of large numbers, the fractional error  $\epsilon$  corresponding to one standard deviation, in any of the simulations described here, is given by

$$\epsilon = \sqrt{\frac{1-p}{p}} \frac{1}{\sqrt{N}}, \quad (4.2)$$

where  $p$  is the probability that a single diffusing particle contacts the target, and  $N$  is the number of diffusing particles.) These numerical results agree with exact analytic results to the available accuracy. We also simulated the case  $l=2$  in greater detail, using extremely long runs of 200 million walks each. After a total of 1.2 billion walks we get

$C=1.386\ 30\pm 0.000\ 025$ , which agrees with the exact result to one part in 40 thousand. This is consistent with formula (4.2).

Next, we use these test cases to search for any dependence of our results on the radius of the launch sphere  $b$ . We obtained statistically indistinguishable results when using  $b=2a$ ,  $b=4a$ , and  $b=10a$ .

Next, we calculate the capacitance of a symmetrical lens, which is defined to be the intersection of a pair of equal-sized spheres. This test allows us to check for inaccuracies in the method when applied to shapes that have sharp edges and corners. This is important for the study of macromolecules, because classical models for solvent-accessible surface frequently have cusps and other surface singularities. For such surfaces one finds<sup>27</sup> a very slow (logarithmic) rate of convergence of the boundary element result as the finite elements are made progressively smaller. (The physical basis for this is clear; charge tends to concentrate at the edges and corners of a surface, the natural places to piece together the boundary elements.) We study the symmetric lens formed by the intersection of two identical spheres whose centers have variable separation. For lenses with aspect ratio between one and 2000, we calculate the exact capacitance,<sup>28</sup> after simulating 100 million diffusing particles, to at least one part in twenty thousand.

Finally, we give our result for the capacitance of a unit cube. Boundary-element estimates of this quantity differ substantially.<sup>27,29-31</sup> Our result for this quantity is

$$C(\text{unit cube})=0.660\ 675\pm 0.000\ 01 \quad (4.3)$$

after simulating 4.7 billion diffusing particles. Again, Eq. (4.2) is used for the error bar. Note that we have done highly accurate simulations in order to eliminate random error, and identify any sources of systematic error. This result is consistent with, but more accurate than, the result obtained from periodically sampled diffusion paths by Zhou *et al.*<sup>8</sup> This result agrees with the most recent boundary-element calculations,<sup>29,30</sup> to the accuracy available with those methods.<sup>24</sup> However, our approach is exact in principle for the class of absorbing surfaces we treat, in the sense that no systematic error is present.

There is a natural approximation,<sup>32</sup> which we call the ‘‘simplex approximation’’ for the capacitance of any geometrical set that tiles a periodic lattice. For the capacitance of a cube, it gives  $C=0.6594$ . This is accurate to half a percent.

#### V. DISCUSSION OF RESULTS AND DIRECTIONS FOR FUTURE RESEARCH

This paper is the first in a series of papers devoted to calculating the bulk properties of macromolecules using a very efficient class of continuum diffusion algorithms, which we call first-passage algorithms. We provide an overview of our research program. We review and develop the relations between bulk properties, solutions of Laplace equations, and properties of diffusion paths.

In this paper, we provide an efficient algorithm for the capacitance of objects with the geometry of macromolecules.<sup>33</sup> In future papers,<sup>5</sup> we expect to provide first-

passage algorithms for the other basic geometrical quantities described in the Introduction (and thus the bulk properties one can determine from them). Also, we plan to offer efficient algorithms for Brownian dynamics and other problems involving diffusion in the presence of forces.

We anticipate the following fact: the Green's functions needed to calculate the solutions to all the problems discussed in this paper can be constructed rather easily out of those developed in detail in this paper. This will emerge in future work.

First-passage algorithms can be extended to provide the entire distribution of first-passage times for a diffusion process. To do this, we use a natural approximation for the average first-passage time associated with any Brownian path, that is with any sequence of first passages. It requires that one use a fairly small value of the  $\delta$ -parameter described at the end of Sec. IV. This implies that all large first-passage spheres do not intersect the target set. The average first-passage time to reach the surface of such a sphere, starting at the center, is given by

$$t_{\text{av}} = \frac{d^2}{6D}, \quad (5.1)$$

where  $d$  is the radius of the sphere and  $D$  is the diffusion constant. Most of the time required to trace out a trajectory will be spent in these large first-passage spheres. The contribution to the diffusion time from small first-passage spheres, i.e., from the ones that intersect the target set, can be approximated in several ways [the easiest is to pretend that they do not intersect the target set and use the result (5.1)].

A different extension of diffusion Monte Carlo methods to the calculation of rate constants is provided in Ref. 34.

## ACKNOWLEDGMENTS

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## APPENDIX A: GREEN'S FUNCTION NO. 1: FIRST PASSAGE TO THE BOUNDARY OF A SPHERE LOCATED TOTALLY IN THE VOID

First passage to a sphere located in the void, i.e., not intersecting any part of the absorbing target set, must be homogeneous, that is, the diffusing particle will first make contact with any point on the first-passage sphere with equal probability [see Fig. 2(a)].

## APPENDIX B: GREEN'S FUNCTION NO. 2: FIRST PASSAGE TO A SPHERE THAT INTERSECTS A FLAT ABSORBING BOUNDARY

In this Appendix, we present an algorithm for computing the fate of a particle diffusing near a flat, absorbing surface [see Fig. 2(b)].

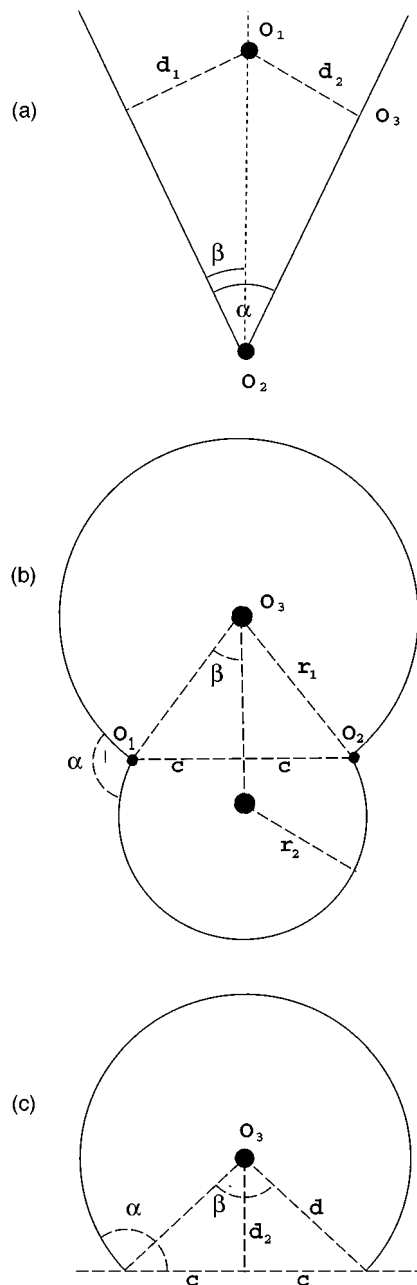


FIG. 4. The sequence of transformations used to calculate the Green's function for a point source of diffusing particles near a flat, absorbing surface. (a) A point source at position  $O_1$  between two flat intersecting absorbing surfaces is inverted about point  $O_1$  with a radius  $d = O_1O_2$  to yield (b) two intersecting absorbing spheres with a source at infinity. (c) This problem is again inverted through center  $O_3$  with radius  $r = O_3O_2$ . (c) This yields a point source inside an absorbing sphere truncated by an absorbing plane.

In the first-passage an algorithm developed in this paper, we simulate a diffusing particle near a flat surface, e.g. a face of a cube, as follows: we draw as large a first-passage sphere as possible, without that sphere intersecting the edges of the cube. The resulting first-passage sphere intersects the face of the cube to form a disk. The particle, beginning at the center of this sphere, must then make a first passage to some point on the union of the sphere and the disk. Both boundaries

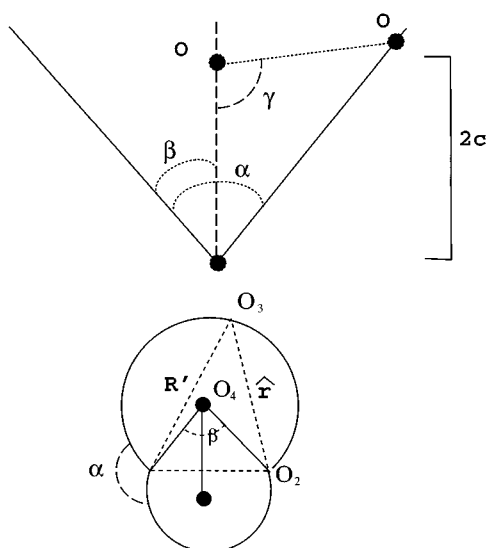


FIG. 5. Definition of coordinates for the point at which we want to know the first-passage probability.

satisfy absorbing boundary conditions. If the particle first contacts a point on the disk it is considered to have hit the target set, and that random walk then terminates. If the particle first contacts a point on the first-passage sphere, that point becomes the center of the next first-passage sphere to be drawn.

This problem is isomorphic to a standard electrostatic problem, namely that of calculating the surface charge density on a conducting sphere truncated by a conducting plane, as induced by a unit charge at the center of the sphere. We present the solution to this problem here.<sup>20,21</sup>

The surface charge density is most naturally calculated by the method of inversion; using the notation of Fig. 4(c), we invert this problem through a sphere of radius  $d$  centered on the charge at point  $O$ . We set the value of the electric charge  $q$  equal to  $-V_0d$ . The resulting inverted problem [see Fig. 4(b)] consists of a pair of intersecting spheres having (in general) different radii  $r_1$  and  $r_2$ , with the pair of spheres being held at a finite potential difference  $V_0$  with respect to infinity. The two spheres have in general different surface charge distributions.

This problem can be further simplified by again using the method of inversion. This time, we invert about one of the points  $O_1, O_2$ , in which the two spheres meet with a radius of inversion  $2c$  equal to the distance between these points. The result is Fig. 4(a). The potential difference  $V_0$  with respect to infinity inverts into a charge of magnitude  $-V_0a$  located at point  $O_1$ , with two infinite conducting planes at distances  $d_1$  and  $d_2$ . These planes intersect in an angle  $\alpha$ . The charge induced on these two planes by the point charge gives, via the chain of isomorphisms just described, the probability density associated with a random walker making a first passage at a particular point  $x$  in the original problem.

Maxwell<sup>20</sup> first computed the charge densities induced on a pair of infinite conducting intersecting planes by a

charge located between them. The isomorphism between this problem and that of two conducting intersecting spheres was exploited by MacDonald<sup>21</sup> in 1895 to give a solution for the latter. Thus if we perform the final inversion, relating Figs. 4(b) and 4(c), we get an analytic solution to the problem discussed here. We discuss this solution, using the notation of MacDonald when possible.

We first define the geometric parameters that characterize the pair of conducting surfaces in Fig. 4(b). Define  $r_1$  and  $r_2$  to be the greater, resp., the lesser of the two sphere radii. These quantities must be equal to  $d$  and  $(d^2/2d_2)$  in order to give Fig. 4(c) on inversion. Define

$$\alpha \equiv \sin^{-1} \left( \frac{d_2}{d} \right) + \frac{\pi}{2}, \quad (\text{B1})$$

$$\beta \equiv \sin^{-1} \left( \frac{c}{r_1} \right). \quad (\text{B2})$$

Now define quantities that characterize the point on the surface at which we want to know the density of random walkers. For brevity, we call this the "first-passage point." This is point  $O_3$  in Fig. 5(b). Give this point the cylindrical coordinates  $(\rho, z)$  with respect to the center of the sphere. The density of random walkers will then be given as a function of the parameters  $(\eta, \xi)$ , where

$$\eta \equiv \left| \log \left( \frac{r}{2c} \right) \right|, \quad (\text{B3})$$

$$\xi \equiv \theta - \beta. \quad (\text{B4})$$

These variables are used because the Maxwell solution is cast in terms of them. The intermediates  $r$  and  $\theta$  are polar coordinates, in the geometry of two intersecting spheres, of the first-passage point. Similarly,  $R'$  and  $\hat{r}$  are bipolar coordinates, and  $z$  and  $\rho$  are cylindrical coordinates for the same point. To obtain the quantities  $\eta$  and  $\xi$ , we begin with the quantities  $z$  and  $\rho$  [calculated directly from the displacement  $(\mathbf{x}_{\text{new}} - \mathbf{x}_{\text{old}})$ ], calculate the corresponding bipolar coordinates from

$$R'^2 = (\rho + c)^2 + z^2, \quad (\text{B5})$$

$$\hat{r}^2 = (\rho - c)^2 + z^2, \quad (\text{B6})$$

and finally derive  $r$  and  $\theta$  from

$$r^2 = 4c^2 + R'^2 - 4cR' \cos \gamma. \quad (\text{B7})$$

Also

$$\theta = \begin{cases} 0, & \text{if } r_1 = d \\ \alpha, & \text{if } r_2 = d' \end{cases} \quad (\text{B8})$$

Here

$$R \equiv 4c^2/R', \quad (\text{B9})$$

$$\cos \gamma \equiv \frac{(4c^2 + R'^2 - \hat{r}^2)}{4cR'}. \quad (\text{B10})$$

Again,  $(\rho, z)$  is the position in cylindrical coordinates of the first-passage point with respect to the starting point.

Finally, the random walker density  $\sigma(\eta, \xi)$  is given by



$$\sigma(\eta, \xi) = \frac{F}{4\pi c d \alpha} \int_{\eta}^{\infty} f(\zeta) d\zeta, \quad (\text{B11})$$

where the integrand  $f(\zeta)$  is

$$f(\zeta) = \frac{\sinh\left(\frac{\pi}{\alpha} \zeta\right)}{[\cosh(\zeta) - \cosh(\eta)]^{1/2}} \frac{1}{\left[\cosh\left(\frac{\pi}{\alpha} \zeta\right) - \cos\left(\frac{\pi}{\alpha} \xi\right)\right]^2} \quad (\text{B12})$$

and the prefactor  $F$  is

$$F \equiv -\frac{2\pi}{\alpha} [\cosh(\eta) - \cos(\xi)]^{3/2} \cdot \sin\left(\frac{\pi}{\alpha} \xi\right). \quad (\text{B13})$$

Here the geometric parameters  $c, d, \alpha$  are defined in Fig. 4(c). The charge density, or equivalently the diffusing-particle first-passage probability is being specified by a point with coordinates  $(\xi, \eta)$ ; those quantities are defined in Eqs. (B3) and (B4).

We note that the integrand defined in Eq. (B12) is singular at the point  $\zeta = \eta$ . The integral in Eq. (B11) is still well-defined; however, this singularity may slow the convergence of certain numerical integration procedures. Thus, we find it advisable to remove the singularity using integration by parts. To do this, we rewrite the integrand as follows:

$$f(\zeta) = \frac{\sinh(\zeta)}{[\cosh(\zeta) - \cosh(\eta)]^{1/2}} \cdot \frac{\sinh\left(\frac{\pi}{\alpha} \zeta\right)}{\sinh(\zeta)} \cdot \frac{1}{\left[\cosh\left(\frac{\pi}{\alpha} \zeta\right) - \cos\left(\frac{\pi}{\alpha} \xi\right)\right]^2}. \quad (\text{B14})$$

The first factor is easily seen to be an exact derivative. Thus integration by parts can be applied directly.

### APPENDIX C: GREEN'S FUNCTION NO. 3: FIRST PASSAGE TO A SPHERE THAT INTERSECTS AN ABSORBING SPHERICAL BOUNDARY

In this Appendix, we compute the fate of a particle diffusing near an absorbing spherical boundary [see Fig. 2(c)].

In the first-passage algorithm developed in this paper, we deal with absorbing sets composed of a number of spherical particles. In order to model the diffusive behavior of a particle moving near a set of absorbing spherical particles, one draws as large a first-passage sphere as possible such that it intersects only one absorbing particle. The diffusing particle is then contained in a domain bounded partly by the first-passage sphere and partly by the absorbing particle. The diffusing particle will first exit this domain at some point on its periphery, with transition probability given by the solution of a basic diffusion problem. These transition probabilities are most directly provided as discrete values of the Green's functions corresponding to the solution of this diffusion problem. There are three possible geometries for which we calculate Green's functions; we give these separate

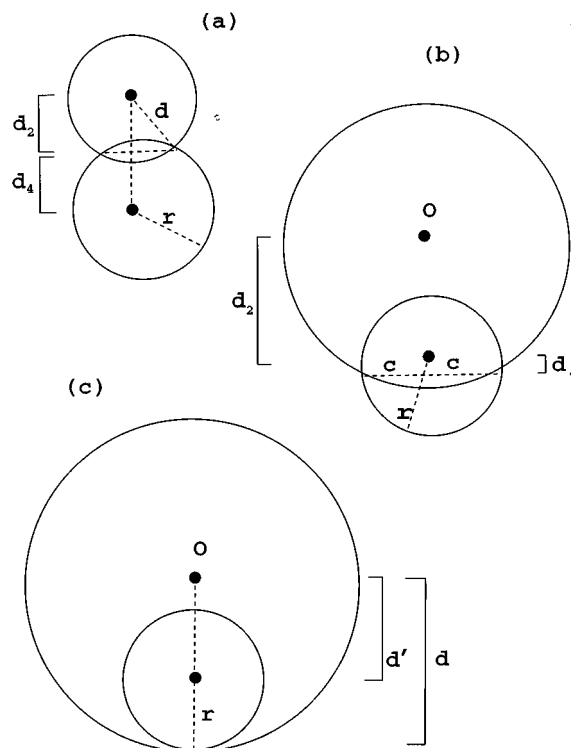


FIG. 6. Geometry for the first-passage sphere intersecting an absorbing sphere. (a), (b), and (c) are, resp., Case 1 and Case 2 (treated in Appendix C) and Case 3 (treated in Appendix D).

treatments. These are depicted in Fig. 6. The first two of these will be described in detail in this Appendix. The third is a singular limit of the second; it is sufficiently different from the second, and also sufficiently important, that it is given a separate discussion, presented as Appendix D.

The sequence of steps followed in the solution of the first-passage problems presented here is the same as that presented in Appendix B. The only change is that we begin, not with Fig. 4(c), but with the appropriate case of Fig. 6. We invert through the point labeled 0 to give the potential problem shown in Fig. 4(b), and from that point solve as in Appendix B. The only difference between the problem discussed in Appendix B and that discussed here is the value of the geometric parameters used to characterize the problem shown in Fig. 4(b). We present expressions for those parameters here, in terms of three basic quantities;  $r$ , the radius of the closest particle,  $d'$ , the distance from the random walker to the center of that particle, and  $d$ , the radius of the first-passage sphere. In terms of these, we define auxiliary quantities  $d_2$  and  $d_4$ . These are, in Case I,

$$d_4 = \frac{(d'^2 + r^2 - d^2)}{2d'}, \quad (\text{C1})$$

$$d_2 = d' - d_4, \quad (\text{C2})$$

$$c = \sqrt{r^2 - d_4^2}. \quad (\text{C3})$$

In Case II, we have

$$d4 = \frac{(d^2 - r^2 - d'^2)}{2d'}, \quad (\text{C4})$$

$$d2 = d' + d4, \quad (\text{C5})$$

$$c = \sqrt{r^2 - d4^2}. \quad (\text{C6})$$

In both cases, we have

$$\alpha = \sin^{-1}\left(\frac{d2}{d}\right) \pm \sin^{-1}\left(\frac{d4}{r}\right), \quad (\text{C7})$$

where the plus sign applies in Case I and the minus sign in Case II. Also, the radii  $r_1$  and  $r_2$  of the two intersecting spheres in Fig. 4(b) are given by

$$r_1 = \max\left[d, \frac{d^2 r}{(d'^2 - r^2)}\right], \quad (\text{C8})$$

$$r_2 = \min\left[d, \frac{d^2 r}{(d'^2 - r^2)}\right], \quad (\text{C9})$$

where  $r_1$  is chosen to be the larger of these two quantities and  $r_2$  is the smaller. The angle  $\beta$  is given by

$$\beta = \sin^{-1}\left(\frac{c}{r_1}\right). \quad (\text{C10})$$

The formulas of Appendix B, beginning with Eq. (B3), can now be used without change.

#### APPENDIX D: GREEN'S FUNCTION NO. 4: FIRST PASSAGE TO A SPHERE THAT COMPLETELY ENGULFS AN ABSORBING SPHERICAL BOUNDARY

In this Appendix, we compute the fate of a particle diffusing near a spherical absorbing object. We treat here the special case of a first-passage sphere precisely big enough to engulf the absorbing object [see Fig. 2(d)]. This is a special case of the Green's function computed in Appendix C. We compute this Green's function explicitly for two reasons; first, if the terminology of Appendix C be retained, the special case studied here is apparently singular. Thus, we must use a renormalized set of geometric parameters to get a finite result. Second, the Green's function corresponding to this special case is used by the algorithm a finite fraction of the time, namely, every time the diffusing particle is sufficiently closer to one absorbing sphere than it is to all the others. Thus, we have implemented it as a separate subroutine in our computer code.

The geometry of this problem is shown in Fig. 6(c), it is the limit of Fig. 6(b) as the first-passage sphere gets larger. Examination shows that the geometrical parameters  $\alpha$ ,  $\beta$ , and  $c$  are zero in this case;  $\alpha \rightarrow 0$  because  $d2 \rightarrow d$  and  $d4 \rightarrow r$ ;  $\beta \rightarrow 0$  because  $c \rightarrow 0$ . We then see from the definition (B4) of  $\xi$ , one of the two parameters that identifies the position of the first passage, that this quantity is zero in this case, because  $\beta \rightarrow 0$  and  $\theta \rightarrow 0$  [the latter is implied by Eq. (B8)]. The other such parameter,  $\eta$ , is also zero. To see this, we note from Fig. 5(b), that the auxiliary quantities  $\hat{r}$  and  $R'$  are identical (because the angle  $\alpha$  is zero). From Eq. (B9) and the fact that  $R'$  is in general nonzero,  $R \sim \epsilon^2$ . Thus, according to Eq. (B7),

$r^2 \sim \epsilon^2$ . Finally, Eq. (B3) implies that  $\eta \rightarrow 0$ . Reference to the general formula (B11) for the probability  $\sigma(x)$  of making the first passage at a point  $x$  shows that this formula is quite useless as it stands.

We obtain finite results for this case as follows: we set  $c = \epsilon$ , with  $\epsilon$  a small quantity. All of the geometric quantities mentioned above, which go to zero when  $c \rightarrow 0$ , are then calculated to first order in  $\epsilon$ . This gives

$$\eta = \frac{-2\epsilon\rho}{(\rho^2 + z^2)}, \quad (\text{D1})$$

$$\alpha = \epsilon\left(\frac{1}{r} - \frac{1}{d}\right), \quad (\text{D2})$$

$$\beta = \epsilon/r_1, \quad (\text{D3})$$

$$\xi = \begin{cases} \alpha - \beta & \text{if } r_1 = d \\ 0 - \beta & \text{if } r_2 = d \end{cases} \quad (\text{D4})$$

We reformulate the solution for the first-passage probability  $\sigma(x)$  in terms of the parameters

$$\eta' \equiv \eta/\alpha, \quad (\text{D5})$$

$$\xi' \equiv \xi/\alpha, \quad (\text{D5})$$

$$\alpha' \equiv \alpha/c, \quad (\text{D6})$$

all of which are finite as  $c \rightarrow 0$ . Also, we change the integration variable in Eq. (B11) to  $x$ , where

$$x \equiv \zeta/\alpha. \quad (\text{D7})$$

The first-passage probability is then

$$\sigma(\xi', \eta') = \bar{F} \int_{\eta'}^{\infty} \bar{f}(x) dx, \quad (\text{D8})$$

where

$$\bar{f}(x) = \frac{2 \sinh(\pi x)}{[\cosh(\pi x) - \cos(\pi \xi')]^2} \cdot \frac{\sqrt{2}}{(x^2 - \eta'^2)^{1/2}} \quad (\text{D9})$$

and

$$\bar{F} \equiv \frac{-\sqrt{2}}{16d} \cdot \sin(\pi \xi') \cdot \alpha' \cdot (\eta'^2 + \xi'^2)^{3/2}. \quad (\text{D10})$$

#### APPENDIX E: GREEN'S FUNCTION NO. 5: RETURN TO THE LAUNCH SPHERE

In this Appendix, we discuss a Green's function needed in the first-passage algorithm to place a diffusing particle back on the launch sphere after it has diffused outside that sphere.

First one determines whether the particle diffuses to infinity without returning. This is Eq. (27) of Ref. 19. If the diffusing particle does return to the surface, its probability density of first reaching a particular point on the surface is given by Eq. (30) of Ref. 19. An algorithm for efficiently choosing points with this distribution is given in Eq. (12) of Ref. 8. To make use of this formula, one must rotate coordinates so that the diffusing particle is on the polar axis, i.e. the  $z$ -axis of Cartesian coordinates, choose the site of return in

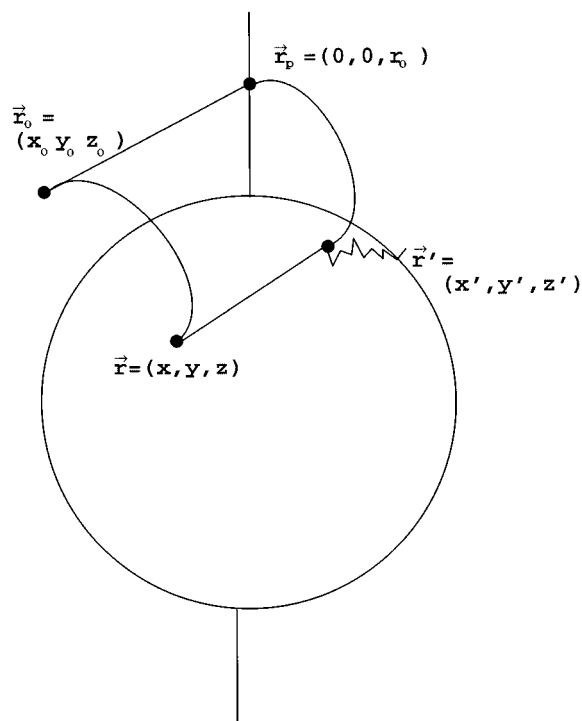


FIG. 7. Schematic of the calculation used to return diffusing particles to the launch sphere once they have left it. The particle is discovered at position  $(x_0, y_0, z_0)$ . We use rotation  $R^{-1}$  to move it onto the polar axis, and use the solution of an electrostatics problem (in spherical coordinates to place the particle back on the sphere, then use rotation  $R$  to return to the original coordinate system).

this transformed system, then perform the inverse rotation. This is discussed in Ref. 35, and illustrated in Fig. 7.

## APPENDIX F: CALCULATION OF THE DISTRIBUTION OF ABSORBED PARTICLES ON THE TARGET SURFACE

In this Appendix, we give an algorithm for determining the surface charge distribution (in an electrostatics problem) or the distribution of particle absorption events (in a diffusion problem).

The discussion above Eq. (3.2) gives a method for determining when a diffusing particle is taken to have been absorbed during a first-passage simulation. We now offer a method which can be applied after such an absorption event to determine the explicit point at which that absorption took place. To do this, we follow a process similar to that employed in Sec. III. We choose a candidate absorbing point by sampling from a distribution  $\sigma(r, \theta, \phi)$  which is both invertible (to give  $r$  as a function of  $\sigma$ ) and also is known to be an upper bound for the exact absorption probability  $\sigma_1(r, \theta, \phi)$ .

We first determine the absorption point for a first passage sphere that intersects a spherical target section with radius  $a$ , including a sector of polar angle  $\theta_0$ . To determine the distribution  $\sigma(r, \theta, \phi)$ , we assume the absorbing first-passage sphere is not present. The distribution  $\sigma(r, \theta, \phi)$  is then given by the surface charge distribution induced on a conducting spherical surface by an external point charge. This quantity

is given by Eq. (3), but with the quantity  $\alpha$  now given by  $\alpha = (a/r_0)$ . Here  $(r, \theta, \phi)$  are spherical coordinates of the candidate absorption point defined with the origin at the center of the absorbing target sphere and polar axis  $\theta=0$  normal to the target surface.

In order to sample from this distribution, we normalize it by its integral over the sector  $\cos(\theta) \leq \theta_0$ , set it equal to a random number  $s$ , and solve for  $\theta$ . The result is

$$\cos(\theta) = \frac{1 + \alpha^2 - C^{-2}}{2\alpha}, \quad (\text{F1})$$

with

$$C \equiv \frac{s}{[1 - 2\alpha \cos(\theta_0) + \alpha^2]^{1/2}} + \left( \frac{1-s}{1-\alpha} \right). \quad (\text{F2})$$

Here the sector angle  $\theta_0$  is given by (see Fig. 6)

$$\theta_0 = \tan^{-1} \frac{c}{d4}. \quad (\text{F3})$$

In Case 6a,

$$\theta_0 = \frac{\pi}{2} \tan^{-1} \frac{c}{d4}. \quad (\text{F4})$$

in Case 6b, and by  $\theta_0 = \pi$  in Case 6c. The candidate absorption point is then given by polar coordinates  $(a, \theta, \phi)$ .

We then reject this candidate absorption site with a probability given by

$$P = \frac{\sigma(x_1) - \sigma_1(x_1)}{\sigma(x_1)}. \quad (\text{F5})$$

Here  $\sigma_1(x_1)$  is the exact absorption probability, as given by the Green's functions of Appendices B and C; see in particular Eq. (B11). Here the Green's function is used with field point  $\mathbf{x}_1$  on the target sphere, not the first-passage sphere. The only change that must be made to accommodate this difference is to replace Eq. (B8) with

$$\theta = \begin{cases} 0, & \text{if } r_2 = d \\ \alpha, & \text{if } r_1 = d \end{cases} \quad (\text{F6})$$

We also show how to determine the point of absorption for a diffusing particle that is absorbed at a planar section of the target surface. In the limit  $b \rightarrow \infty$ , the conducting sphere becomes a conducting plane. In this case, we have  $\alpha = 1$  and

$$p_1(\theta', \phi') = \sigma(\theta', \phi') = \frac{1}{2\pi} \frac{|z|}{[r^2 + z^2]^{3/2}}, \quad (\text{F7})$$

where  $(r, z, \theta)$  are cylindrical coordinates of a point on the conducting plane with respect to the origin determined by the old position of the diffusing particle.

To sample this distribution, we determine a point  $(r, \theta)$  on the planar target section. Here the center of this polar coordinate system is the point on the planar target section closest to the last position of the diffusing particle. We normalize and invert the distribution (F7) as above to yield

$$r^2 = \frac{d^2}{[1 - (s/s_0)]^2} - d^2, \quad (\text{F8})$$

where the quantity  $d2$  is defined in Eq. (C2), and the quantity  $s$  is again a uniform random numbers  $s \in [0,1]$ . The coordinate  $\theta$  is uniformly distributed on  $[0,2\pi]$ . Finally,

$$s_0 \equiv \left[ 1 + \frac{d2^2}{c^2} \right] \cdot \left[ 1 + \frac{d2^2}{(c^2 + d2^2)} \right]^{1/2}. \quad (\text{F9})$$

<sup>1</sup>For a good overview of liquid-state statistical mechanics, see J. P. Hansen and I. R. McDonald, *Theory of Simple Liquids* (Academic, London, 1976).

<sup>2</sup>For applications to the study of disordered media, see M. J. Beran, *Statistical Continuum Theories* (Wiley, New York, 1968; P. M. Chaikin and T. C. Lubensky, *Principles of Condensed-Matter Physics* (Cambridge University, Cambridge, 1995).

<sup>3</sup>Early efforts to perform these averages are described in H. L. Weissberg and S. Prager, *Phys. Fluids* **5**, 1390 (1962), and other work is described in the book by Beran. More recent efforts are described in Ref. 1, and in M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics* (Clarendon, Oxford, 1986).

<sup>4</sup>A good overview of this research is provided in M. Friedlin, *Functional Differentiation and Partial Differential Equations* (Princeton University, Princeton, 1985); J. L. Doob, *Classical Potential Theory and Its Probabilistic Counterpart* (Springer, New York, 1984). Modern application of diffusion theory to problems in statistical physics was greatly enriched by the efforts of E. W. Montroll and his school; E. W. Montroll, *Soc. Ind. Appl. Math.* **4**, 241 (1956); *Proc. Symp. Appl. Math.* **16**, 193 (1964); G. Weiss, *Aspects and Applications of the Random Walk* (North-Holland, New York, 1994).

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<sup>10</sup>There are a vast number of relationships, both exact and approximate, between the capacitance of a body and its other physical properties. The literature on capacitance seems not to have been systematically reviewed in a monograph as of this time. Much of the literature is, however, noted in Ref. 6. We refer the interested reader to that reference and its footnotes. See also, J. F. Douglas and Friedman, *IMA Series on Mathematics and its Applications* (Springer, New York, 1995), Vol. 67, p. 166.

<sup>11</sup>The angle-averaging method is developed in J. B. Hubbard and J. F. Douglas, *Phys. Rev. E* **47**, 2983 (1993).

<sup>12</sup>For the basic theory of creeping flow about an irregular object, see J. Happel and H. Brenner, *Low-Reynolds Number Hydrodynamics* (Kluwer, Boston, 1991).

<sup>13</sup>For development of the powerful simplifications that occur when the relative motion between atoms of the solid phase is frozen out, see J. A. Given and G. Stell, in *Proceedings of the XVIth International Workshop on Condensed-Matter Theories*, June 1992 (Plenum, New York, 1993).

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<sup>22</sup>A good general reference is G. D. Doolen, *Lattice-Gas Methods for Partial Differential Equations* (Addison-Wesley, New York, 1990). For simulations of the multicomponent fluids in complex three-dimensional geometries by the lattice Boltzmann method, see, N. S. Martys and H. D. Chen, *Phys. Rev. E* **53**, 743 (1996).

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<sup>24</sup>A general reference is C. A. Brebbia, *The Boundary-Element Method for Engineers* (Pentech, London, 1984). Applications to diffusion and reaction-diffusion equations are A. Greenbaum, L. Greengard, and G. B. McFadden, *J. Comp. Phys.* **105**, 267 (1993).

<sup>25</sup>See, e.g., I. Vattulainen, T. Ala-Nissila, and K. Kankaala, *Phys. Rev. Lett.* **19**, 2513 (1994). We use here the random number generator by G. Marsaglia and A. Zaman, *Stat. Prob. Lett.* **8**, 329 (1990). This algorithm was later modified in F. James, *Comput. Phys. Commun.* **60**, 329 (1990). This algorithm is a combination of a Fibonacci sequence (with lags of 97 and 33, an operation “subtraction plus one, modulo one”) and an “arithmetic sequence” (using subtraction).

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<sup>32</sup>If a shape tiles a periodic lattice, each copy of the shape can be paired off with a finite subset of the lattice points (“its upper corners”) so as to partition the latter exactly. The “simplex approximation” consists of identifying the capacitance of the original shape with the discrete capacitance, on this periodic lattice, of the point set constituted by the upper corners of the shape. The latter quantity is calculated by allowing a lattice random walk to rigidly translate this set of corners, and calculating the total number of lattice points, per random walk step, contained in the envelope.

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