Monte Carlo Methods for the Linearized Poisson-Boltzmann Equation

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Abstract

We review efficient grid-free random walk methods for solving boundary value problems for the linearized Poisson-Boltzmann equation (LPBE). First we introduce the "Walk On Spheres" (WOS) algorithm [1] for the LPBE. Based on this WOS algorithm, another, related, Monte Carlo algorithm is presented. This modified Monte Carlo method reinterprets the weights used in the original WOS algorithm as survival probabilities for the random walker used in the computation [2]. In addition, a Feynman-Kac path-integral implementation for solving the LPBE is given [3]. This Feynman-Kac approach uses the WOS method to provide a technique for estimating certain Gaussian path integrals without the need for simulating Brownian trajectories in detail. We then similarly interpret the exponential weight in the Feynman-Kac formula as a survival probability. It is then shown that this method is mathematically equivalent to the previous modified WOS method for the LPBE. The effectiveness of these methods is illustrated by computing four analytically solvable problems. In all four cases, excellent agreement is shown. In particular, for the problem of calculating the electrostatic potential in an electrolyte between two infinite parallel flat plates, our modified WOS method is compared with the old WOS method and with our Feynman-Kac WOS (FK WOS) method. Our modified WOS method is the most efficient one, but FK WOS method holds the promise of extension to more complicated equations such as the time-independent Schrödinger equation. Finally, we illustrate the use of a Monte Carlo approach for the LPBE in a more complicated setting related to the computation of the electrostatic free energy of a large molecule. Here, we couple the LPBE solution in the exterior of a compact domain (molecule) with the solution of the Poisson equation inside, and with continuity boundary conditions linking these two solutions. The Monte Carlo method performs quite well in this complicated situation.

Key words: Monte Carlo, linearized Poisson-Boltzmann, Walk on Spheres (WOS), Feynman-Kac

1 Introduction

The classical approach for treating a solution with ions dissolved in a solvent is to consider this electrolyte solution as a continuous medium with some constant permittivity, ϵ. From statistical mechanics considerations, ions should be distributed according to the Boltzmann law. This approach gives rise to the Poisson-Boltzmann equation (PBE) [4]:

$$\nabla\epsilon\nabla\psi = -\sum_i (n_i^0 z_i e)\exp(-\frac{z_i e}{k_B T}\ \psi)\ . \tag{1}$$

Here, e, k_B, and T are the electron charge, Boltzmann's constant, and the absolute temperature respectively. Above, z_i and n_i^0 represent the valence and the bulk concentration of the ith species of ion.

For small potential values, Eq.1 may be simplified, thus leading to the linearized Poisson-Boltzmann equation:

$$\Delta\psi(x) = \kappa^2\psi(x)\ . \tag{2}$$

Here, κ, the inverse Debye length, is defined as

$$\kappa = \sqrt{\Sigma_i \frac{n_i^0 z_i^2 e^2}{k_B T\epsilon}}\ . \tag{3}$$

Despite some significant recent progress [5–8] in computational methods for solving the original PBE, the LPBE is still far more amenable to numerical treatment.

One of the possible ways to solve the LPBE by a Monte Carlo method is to randomize a finite-difference algorithm. When applied to the LPBE and other elliptic equations, this approach leads to a discrete random walk on a grid algorithm [9,20]. At every step of this algorithm, the 'walker' either moves to one of the neighboring sites, or stays put , with some predetermined probabilities. Finally, with probability one (for a bounded domain) the random walker hits the boundary. There, if Dirichlet boundary conditions are considered, known point values of the solution can be used. In the case of the LPBE, the parameter κ's influence is taken into account through a multiplicative statistical weight. The other approach is to relate κ^2 to the survival

probability of the random walker [11]. This probabilistic interpretation of κ^2 can be also extended to continuous random walk methods once we know the survival probability distribution function of a random walker in continuous space. Note, that when κ^2 in (2) is zero, the problem becomes the Dirichlet problem for the Laplace equation.

It is well known that averages over Markov processes with continuous trajectories can be used to solve partial differential equations [12]. The most well-known implementation of these methods is the "Walks on Spheres" (WOS) Monte Carlo method. In WOS, the Markov process is not simulated in detail in the free-diffusion region; instead discrete jumps are made using the Brownian first-passage distribution function, which is uniform on a spherical surface with respect to its center. To terminate discrete WOS jumps, an ε-absorption layer of the boundary is introduced, that is, when a walker enters this ε-absorption layer, the walk is terminated by choosing a terminal boundary point closest to the point in the ε-absorption layer (usually the point in the ε-shell lies on the normal taken from the chosen boundary point). The WOS method for the Dirichlet problem for the Laplace and other elliptic equations has been widely used [13–19]. In this article, we show that the WOS algorithm also can be combined with the interpretation of weight factors as survival probabilities, thus incorporating the term involving κ^2 in the LPBE.

The rest of the paper is organized as follows. In §2, we introduce the "Walk On Spheres" algorithm for the LPBE [1]. Based on WOS, another, related, Monte Carlo algorithm is presented. This Monte Carlo method reinterprets the weights used in the original WOS algorithm as survival probabilities for the random walker used in the computation. The efficiency of this method is illustrated by computing four analytically solvable problems. In all four cases, excellent agreement is shown. In the case of one of the four problems, the electrical potential in an electrolyte between two infinite parallel flat plates, our modified WOS method is compared with the old WOS method and shows better performance. In §3, the Feynman-Kac path-integral implementation for solving the LPBE is given. This Feynman-Kac approach uses the WOS method to provide a technique for estimating certain Gaussian path integrals without the need for simulating Brownian trajectories in detail. We then similarly interpret the exponential weight in the Feynman-Kac formula as a survival probability, the same way as when we performed a modified WOS step. It is then shown that this method is mathematically equivalent to the previous modified WOS method for the LPBE [2]. This FK WOS method is somewhat slower than our modified WOS method, but shows the promise of extension to more complicated equations such as the time-independent Schrödinger equation. In §4, we investigate the relationship between the running time and the thickness of the ε-absorption layer, and the error associated with the ε-absorption layer in both the modified WOS and the FK WOS, and present some numerical illustrations. Next, in §5 we describe the use of this Monte Carlo LPBE solver

in a more complicated setting related to the computation of the electrostatic free energy of a large molecule. Here, we couple the LPBE solution in the exterior of a compact domain (molecule) with the solution to a Poisson equation inside, continuity boundary conditions link these two solutions. The Monte Carlo method performs quite well in this complicated situation. Conclusions are given in §6.

2 Modified "Walk On Spheres"

In this section [1], we introduce the "Walk On Spheres" (WOS) algorithm [1] for the LPBE and present a new modified WOS method to solve the LPBE by reinterpreting the weight function.

Consider the first boundary value problem (Dirichlet problem) for the LPBE in the domain $\Omega \subset \mathbb{R}^3$:

$$\Delta\psi(x) = \kappa^2\psi(x) \ , \quad x \in \Omega \ , \tag{4}$$

$$\psi(x) = \psi_0(x) \ , \quad x \in \partial\Omega \ . \tag{5}$$

The "Walk On Spheres" is defined as follows [1]. To find the solution of the LPBE at some point $x_0 \in \Omega$, a Markov chain $\{P^0, P^1, P^2, \ldots\}$ of points inside the domain Ω is constructed. The starting point, P^0, is set to x_0. Given the previous point $P^k, k \geq 0$, the next is simulated isotropically on the surface of the sphere $S(P^k, d^k)$, i.e. $P^{k+1} = P^k + d^k\omega^k$. Here, $\omega^k \in \mathbb{R}^3$ are independent isotropically distributed random vectors of unit length; d^k is the radius of kth sphere, which is equal to the distance from the point P^k to the boundary, $\partial\Omega$. Then (with probability one),

$$\psi(x_0) = \mathbb{E}\xi + \delta(\varepsilon) = \lim_{N\to\infty} \frac{1}{N} \sum_{i=1}^{N} \xi_i + \delta(\varepsilon) \ , \tag{6}$$

$$\xi_i = Q_i^{n_i}\psi_0(X_{n_i}) \ ,$$

where

$$Q_i^0 = 1, \quad Q_i^m = Q_i^{m-1} \frac{d_i^{m-1}\kappa}{\sinh(d_i^{m-1}\kappa)}, \quad m = 1, 2, \ldots, n_i \ . \tag{7}$$

[1] This section is based on: C.-O. Hwang and M. Mascagni, "Efficient Modified "Walk On Spheres" Algorithm for the Linearized Poisson-Boltzmann Equation," Appl. Phys. Lett. **78**, 787 (2001).

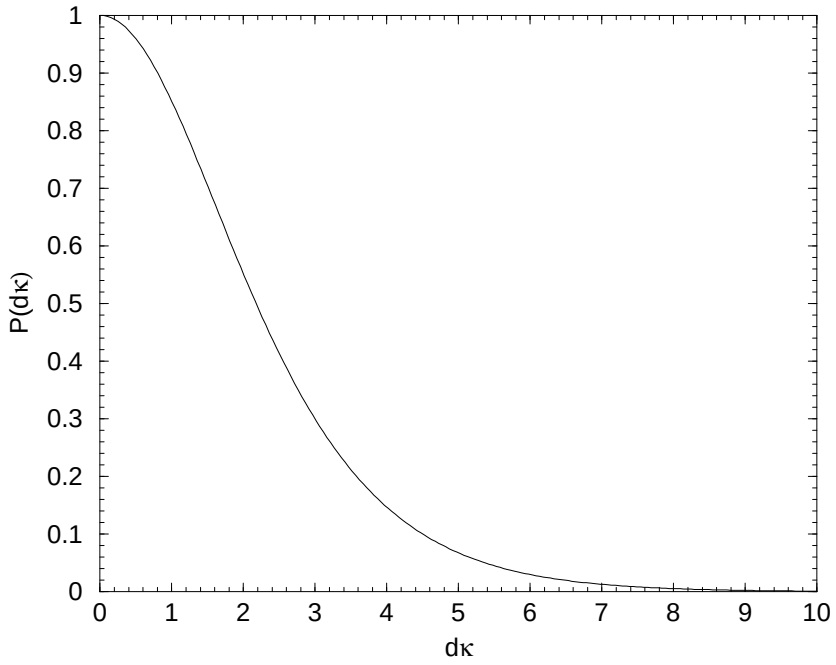

Fig. 1. The survival probability density function; d is the magnitude of the WOS step in the free diffusion region, and κ is the inverse Debye length.

Here, N is the total number of diffusing random walkers (simulated Markov chain trajectories); i refers to ith random walker; the point on the boundary X_{n_i} is the nearest to the position $P_i^{n_i}$ where the ith random walker is absorbed in the ε-layer after a random n_i WOS steps; $\delta(\varepsilon)$ is the bias in the estimate due to the finite thickness of the absorption layer.

If we interpret $Q_i^{n_i}$ as the survival probability of the ith random walker, $\sum_{i=1}^{N} Q_i^{n_i}$ is the mean total number of survived-and-absorbed random walkers (for a given ensemble of trajectories). Furthermore, only the survived-and-absorbed random walkers can be regarded as contributors to the solution. This reinterpretation of the weight function as a survival probability distribution function is a kind of the fractional sampling method, i. e. 'Russian Roullete' [20], which has been used extensively in neutron transport and similar problems. The survival probability of a random walker in a continuous and free diffusion region is given at every step of the Markov chain simulation by the weight factor [1]:

$$p(d) = d\kappa / \sinh(d\kappa), \tag{8}$$

where d is the radius of maximal sphere in the free diffusion region. Fig. 1 shows this probability density function. We modify the WOS method to incorporate the survival probability to solve the LPBE via a continuous random walk method. This probability combined with the WOS method is used to remove a random walker (to terminate the Markov chain trajectory) by the acceptance-

rejection method [20]. We generate a random number, η in $[0, 1)$ when we perform a WOS step, and compare η with $p(d)$, the survival probability at d, the radius of the current sphere in WOS. If $\eta > p(d)$, the random walker is removed at this WOS step.

The estimate for the solution of the LPBE at x_0, the starting point of the Markov chain, is given by S_N:

$$S_N = \frac{1}{N} \sum_{i=1}^{N_s} \psi_0(X_{n_i}). \tag{9}$$

Here, N is the total number of random walkers, N_s is the number of survived-and-absorbed random walkers, and X_{n_i} is the final position of the walker on the boundary when it is absorbed after n_i WOS steps. In this method, like the WOS method, errors are due to both statistical sampling and the ε-absorption layer which captures random walkers near the boundary to terminate the construction of the Markov chain. However, the error from the ε-absorption layer can always be made smaller than the statistical error [15,16]. On the same random walk, estimating the solution for different values of ε allows one to approximate $\delta(\varepsilon)$, the error as a function of ε [14]. On the one hand, by adjusting ε, we can make the error from the absorption layer less than the statistical error. This means that if we increase the number of random walkers in order to decrease the statistical error, consequently we must reduce ε, and thus increases the running time, as $O(\log \varepsilon)$ [14]. On the other hand, if one fixes the desired accuracy, then the bias and the statistical error can be adjusted to have the same order. This means that it is theoretically possible to choose the number of random walkers, N, beforehand.

In the following, we compare our simulation results with the known analytic results for four problems [2], which were used as test problems for the discrete random walk method [11]. The problems are to find the solution of the first boundary-value problem for the LPBE (4),(5) in four different domains: a) outside of a charged sphere with the radius of the unit Debye length; b) away from the infinitely long cylinder with the radius of the unit Debye length; c) away from the infinite flat surface; d) between two parallel flat plates 3 Debye lengths apart from each other. In all cases, the results are given as those normalized by the constant boundary condition, ψ_0, which is assumed to be sufficiently small for the LPBE to be valid. The number of random walks used for computing the solution at a point is 10^5, and the absorption layer thickness is $\varepsilon = 10^{-4}$. The analytic results [11] are shown with solid lines in Fig. 2 and our simulation results with circles. For all four cases, our simulation results show excellent agreement.

Our method has several features. First, it is easier to implement and is expected to be faster than the other discretized methods, such as the discrete

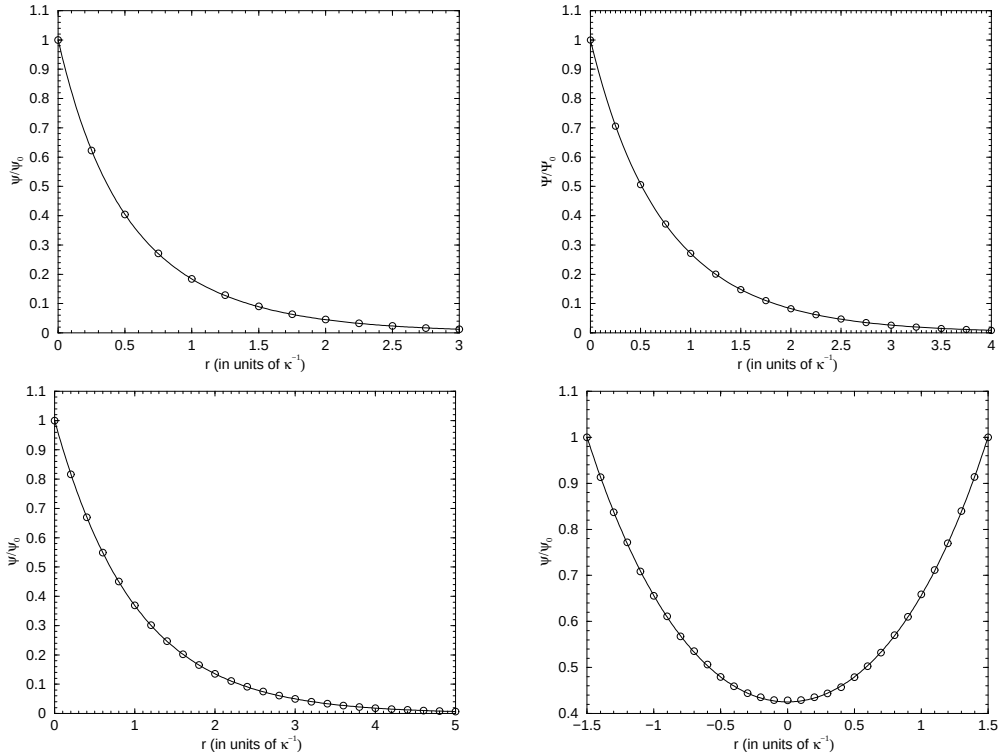

Fig. 2. The solid lines are the analytic solutions and the circles are the simulation results with 10^5 random walks and the width of absorption layer, $\varepsilon = 10^{-4}$. Here, κ is the inverse Debye length. (a) Electric potential away from the surface of a charged sphere in an electrolyte; Here, r is the distance from the surface of the sphere with unit radius. (b) Electric potential away from an infinitely long charged cylinder in an electrolyte; Here, r is the distance from the surface of the cylinder with unit radius. (c) Electric potential away from an charged infinite flat plate in an electrolyte; Here, r is the distance from the plate. (d) Electric potential in an electrolyte between two infinite charged parallel flat plates; Here, r is the distance from the mid-point between two plates.

random walk method [11], the finite difference method [21] and the boundary-element method [22], especially with complicated geometries. For the solution at a point, it takes only a few seconds to compute it with 10^5 random walkers and $\varepsilon = 10^{-4}$ on a 550 Mhz PC. However, it is hard to compare this method to other methods because they compute solutions at all grid points. We can safely say that continuous Monte Carlo methods are more efficient when the solution is required only at relatively small number of points. Secondly, the accuracy and the running time of our method depends primarily on the number of statistical samples. Naturally, these samples can be simulated in parallel. Thirdly, it is certain that our method is faster than the old WOS method [1], because while some of our random walkers are removed during the simulation, in the old method all trajectories must be completed and contribute to the solution according to the calculated weights. Also, in the unbounded domain cases, like the three examples, not the parallel plates, it is necessary to use

Table 1
The computational cost comparison of our algorithm with the old modified WOS in the case of parallel plates at the mid-point; the variances are obtained from 100 independent runs, the number of random walks per run is 10^5 and the width of absorption layer, $\varepsilon = 10^{-4}$.

method	CPU time per run (secs)	variance (10^{-7})	computational cost (10^{-6})
old method	13.47	4.63	6.24
our method	2.97	19.8	5.88

a certain cut-off in the old modified WOS [1] to kill random walkers, which will bias the results. As an example, in Table 1, for the case of the parallel plates, we compare our method with the old modified WOS method [1]. We use a conventional comparison criterion for the Monte Carlo methods, the computational cost (or time consumption) [23,20]: $t \times \sigma^2[\xi]$, where t is the CPU time needed to calculate a single sample of the estimate, and $\sigma^2[\xi]$ is the variance of the estimate. The less laborious the algorithm, the more efficient it is. The computational results in Table 1 show that the computational cost of our algorithm is less than that of the old modified WOS method. Finally, our method is easy to extend to solve the LPBE with source terms.

3 Feynman-Kac "Walks on Spheres"

In this section [2], we present a new modified WOS method for solving the Dirichlet problem for the LPBE based on the Feynman-Kac formula [3]. In addition, we show that this method is mathematically equivalent to our previous modified WOS method [3]. According to the Feynman-Kac formula, the solution to the first boundary value problem for the LPBE at the point x_0 is [12,24]

$$u(x_0) = \mathbb{E}[\psi_0(X(\tau_{\partial\Omega}))\exp\{-\int_0^{\tau_{\partial\Omega}} \kappa^2 d\tau\}] \ , \tag{10}$$

where $X(\tau)$ is a Brownian motion trajectory, $\tau_{\partial\Omega} = \inf\{\tau : X(\tau) \in \partial\Omega\}$ is the first-passage time of this trajectory, and $X(\tau_{\partial\Omega})$ is the first-passage point on the boundary. If we use a series of WOS steps to construct a Brownian path

[2] This section is based on: C.-O. Hwang, M. Mascagni and J.A. Given, "A Feynman-Kac Formula Implementation for the Linearized Poisson-Boltzmann Equation," Math. Comput. Simulation. **submitted**, (2002)

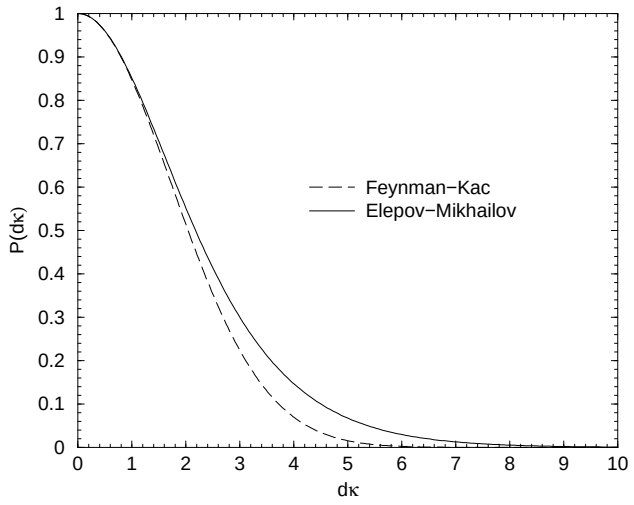

Fig. 3. The survival probability density function; the dashed line shows the survival probability from the Feynman-Kac solution representation [12,24] with only the first moment of the first passage time distribution function; the solid line is the survival probability from the Elepov-Mikhailov solution representation [1]; d is the distance of a random walker from the starting position, and κ is the inverse Debye length.

with only the first moment of the first passage time distribution function (see e.g. [17]), the corresponding survival probability (Feynman-Kac in Fig. 3) is

$$\exp(-\kappa^2 r^2/6) \ , \tag{11}$$

where r is the radius of each WOS (see Fig. 3 to compare with the previous Elepov-Mikhailov removal probability). The survival probability from the Feynman-Kac formula using the mean of the first passage time can be used only when r is small enough (less than 1 in units of κ^{-1}). If r is large, the entire first passage time distribution function (see Fig. 4)

$$P(t') = 1 + 2\sum_{n=1}^{\infty}(-1)^n \exp(-n^2\pi^2 t'), \tag{12}$$

should be used, not just the mean. Here, $t' = D\tau/r^2$ where D is the diffusion constant (in the LPBE, $D = 1$), τ is the first passage time, and r is the radius of the WOS step. To use this distribution function, we tabulate it.

At every WOS step, after sampling t', the corresponding survival probability is obtained. The survival probability is compared with a random number in $[0, 1)$ and if the random number is greater than the survival probability, the random walker is removed at this WOS step: the acceptance-rejection method. The estimated solution of the LPBE at x_0, where the random walkers start,

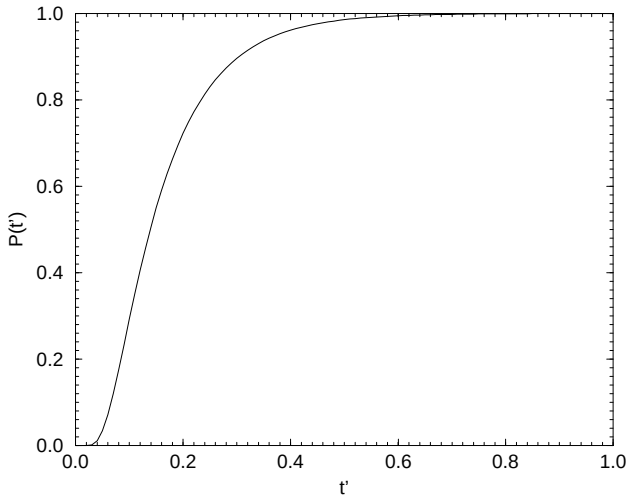

Fig. 4. The first passage time distribution function for spheres with respect to the normalized time t': here, $t' = D\tau/r^2$ and $D = 1$ is the diffusion constant, τ is the first passage time, and r is the radius of the sphere.

is

$$E(x_0) = \frac{1}{N}\sum_{i=1}^{N_s}\psi_0(X_{n_i}). \tag{13}$$

Here, N is the total number of random walkers, N_s is the number of survived-and-absorbed trajectories, and X_{n_i} is the nearest point on the boundary to where the walker hits the ε-absorption layer for the first time, n_i is the random number of WOS steps in the ith trajectory. Mathematically, this new survival probability density function derived with the entire first-passage time distribution function, is equivalent to the previous survival probability density for the following reason: the expected value of the exponential weight factor at every WOS step in our new Feynman-Kac formula implementation with respect to the entire first-passage time distribution function is equivalent to the previous Elepov-Mikhailov survival distribution function. To show it, we compute the average of the exponential weight factor, $\exp(-t'\kappa^2 r^2)$ (for $D = 1$), with respect to the probability density of t':

$$\begin{aligned}\int_0^\infty \exp(-t'\kappa^2 r^2)dP(t') &= 2\sum_{n=1}^{\infty}(-1)^n(-n^2\pi^2)\int_0^\infty \exp[-(n^2\pi^2+\kappa^2 r^2)t']dt' \\ &= -2\sum_{n=1}^{\infty}\frac{(-1)^n}{1+\kappa^2 r^2/(n^2\pi^2)} \\ &= \frac{\kappa r}{\sinh(\kappa r)}\ .\end{aligned} \tag{14}$$

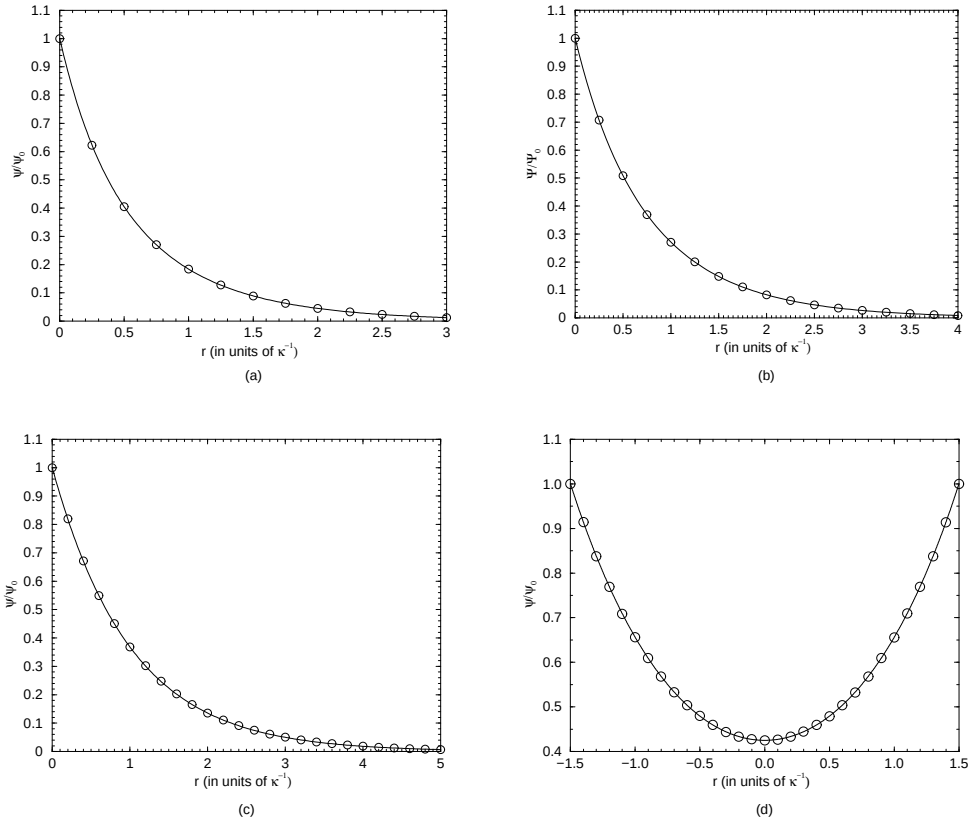

Fig. 5. The solid lines are the analytic solutions and the circles are the simulation results with 10^6 random walks and the absorption layer $\varepsilon = 10^{-4}$; here, κ is the inverse Debye length. (a) Electric potential away from the surface of a charged sphere in the electrolyte; here, r is the distance from the surface of the sphere with unit radius. (b) Electric potential away from the infinitely long charged cylinder in the electrolyte; here, r is the distance from the surface of the cylinder with unit radius. (c) Electric potential away from the charged infinite flat plate in the electrolyte; here, r is the distance from the plate. (d) Electric potential in the electrolyte between two infinite charged parallel flat plates; here, r is the distance from the mid-point of the plates.

This is the same as the survival probability in our previous modified WOS method [2].

The efficiency of this method is illustrated by computing the same four analytically solvable problems that were considered in the previous section. We compare our simulation results with known analytic expressions [11]. In all cases, the results are normalized by the boundary condition, ψ_0. The number of random walks used for finding the solution at a point is 10^6, and the absorption layer thickness is $\varepsilon = 10^{-4}$. In Fig. 5 the analytic results [11] are shown with the solid lines and our computed results are represented by circles. For all four cases, our simulation results show excellent agreement. Also, in the case of the electric potential in an electrolyte between two infinite charged parallel flat plates, we compare the FK WOS algorithm with our

previous one. The FK WOS method is slower because of the computational time spent on the interpolation routine when sampling t'. In Table 2, running times are given for the case when the piecewise linear interpolation is used to sample t'. While this method is somewhat slower than our previous one, it holds the promise of extension to more complicated equations such as the time-independent Schrödinger or Bloch equations.

4 Error and Running Time

In this section [3], we investigate the relationship between the running time and the thickness of the ε-absorption layer, and the error associated with the this layer in both the modified WOS and FK WOS algorithms, and give numerical illustrations. There are two error sources in these methods; the error associated with the number of trajectories (sampling error), and the error associated with the ε-absorption layer. We can reduce the statistical sampling error by increasing the number of trajectories. The error associated with the ε-absorption layer can be reduced by reducing ε, the layer thickness. However, increasing the number of trajectories will increase the running time linearly, while reducing ε will increase running time as $O(|\log \varepsilon|)$ [14]. In the case of FK WOS in Fig. 6 (a), we see the usual logarithmic relationship between running time and the thickness of the ε-absorption layer. The reason for this is that the running time increases proportionally to the number of WOS steps, n_i, which is itself $O(|\log \varepsilon|)$ [14]. This relation holds even though some of the trajectories are terminated during the WOS steps.

The error from the ε-absorption layer can be investigated empirically if we have enough trajectories so that the statistical sampling error is much smaller than

[3] This section is based on: C.-O. Hwang, M. Mascagni and J.A. Given, "A Feynman-Kac Formula Implementation for the Linearized Poisson-Boltzmann Equation", Math. Comput. Simulation **submitted**, (2002)

Table 2
Running time comparison of the Feynman-Kac WOS algorithm with our previous modified WOS in the case of computing the potential in the middle between parallel plates; the number of random walks per run is 10^6 and the width of absorption layer, $\varepsilon = 10^{-4}$. Both computations were performed on a 550 MHz Pentium workstation.

method	CPU time per run (secs)
previous method	48.9
new method	64.5

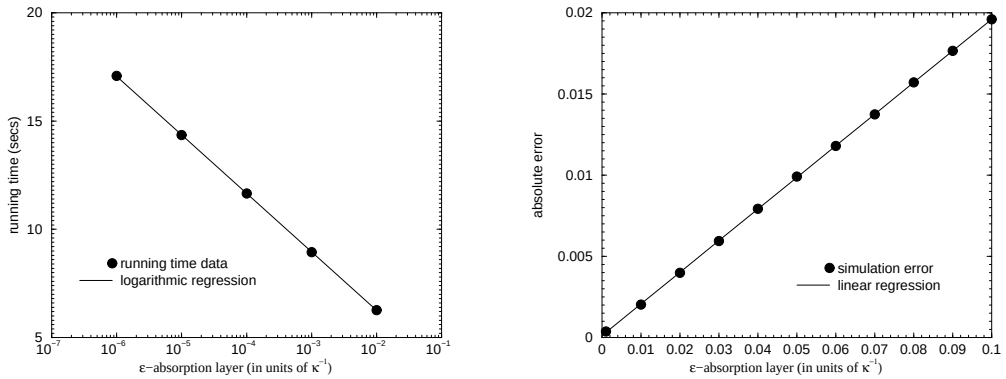

Fig. 6. Running time versus the thickness of the ε-absorption layer and error arising from the ε-absorption layer in Feynman-Kac WOS. (a) Running time versus the thickness of the ε-absorption layer with 10^6 Brownian trajectories in the case of computing the potential in the middle between the parallel plates. This shows the usual relation for WOS: running time (proportional to number of WOS steps for each Brownian trajectory) is $O(|\log \varepsilon|)$. (b) Error arising from the ε-absorption layer with 10^8 Brownian trajectories in the case of parallel plates in units of κ^{-1}. The error is linear in ε.

the bias from using the ε-absorption layer [26]. Fig. 6 (b) shows the empirical results with 10^8 Brownian trajectories: the ε-layer error grows linearly in ε for small ε just as in the case of the Dirichlet problem for the Laplace or Poisson equations [26]. The reason is that for small ε the probability of terminating a Brownian trajectory is linear in ε.

5 Biochemical Application

In this section [4], we consider the problem of calculating the internal energy of a molecule. To be more exact, we will calculate the electrostatic energy – the internal energy for non-bonded electrostatic interactions between atoms constituting a large molecule.

In biochemical applications, one of the possible and widely used electrostatic models is a continuum model. For a given charge distribution $\rho(x)$, the electrostatic potential is determined as a solution to Poisson's equation

$$-\nabla\epsilon\nabla\psi(x) = \rho(x) \ , \ x \in R^3 \ , \tag{15}$$

where ϵ is a position-dependent permittivity. In bio-molecular applications,

[4] This section is based on: M. Mascagni and N.A. Simonov, "Monte Carlo Method for Calculating the Electrostatic Energy of a Molecule", presented at ICCS-2003, St.Petersburg, Russia, June 2-4, 2003. To be published in LNCS by Springer-Verlag.

the geometry of a problem is taken into account by thinking of a molecule as a cavity with point charges and constant ϵ inside. The exterior is modelled as a dielectric medium with different permittivity and some charge distribution. We assume that the molecule in question can be described as a compact set $\Omega \in \mathbb{R}^3$ constructed of a large number of intersecting balls (atoms). Every spherical atom has its electrical charge, q_m, which is positioned at its center, x_m, and r_m is the radius of this atom. Hence, the electrostatic potential, $\psi(x)$, satisfies Poisson's equation (15) inside Ω for the particular charge density $\rho(x) = \sum_{m=1}^{M} q_m \delta(x - x_m)$. Here, the dielectric permittivity, $\epsilon = \epsilon_i$, is constant. The potential can be represented as the sum of two functions:

$$\psi(x) = \psi^{(0)}(x) + g(x) \ , \tag{16}$$

where $g(x) = \sum_{m=1}^{M} \frac{q_m}{4\pi\epsilon_i} \frac{1}{|x - x_m|}$. From (16) and (15) it follows that $\Delta\psi^{(0)}(x) = 0$ in Ω, and the boundary values of $\psi^{(0)}$ are equal to $\psi(x) - g(x)$. If the molecule is surrounded by some dielectric (e.g. water), the classical approach is to treat this surrounding medium as continuous with some constant permittivity, ϵ_e. The distribution of dissolved ions determines the charge density outside Ω, which leads to the non-linear Poisson-Boltzmann equation (1) in the exterior domain $G_1 \equiv \mathbb{R}^3 \setminus \overline{G}$. Linearizing it for small potential values, we come to the LPBE (2), where k is determined by (3) with the permittivity ϵ_e.

Equations (15) and (2) must be coupled by continuity conditions on the boundary of the molecule:

$$\psi_i(y) = \psi_e(y) \ , \ \epsilon_i \frac{\partial \psi_i}{\partial n(y)} = \epsilon_e \frac{\partial \psi_e}{\partial n(y)} \ , \ y \in \partial G \ . \tag{17}$$

Here, for convenience, we denote ψ_i as the solution to (15) in the interior of Ω, and ψ_e as the solution of (2) in the exterior of the molecule. We assume also that $\psi_e(x) \to 0$ as $|x|$ goes to infinity.

In the linear case the electrostatic free energy of the molecule is given by [27]:

$$E = \frac{1}{2} \sum_{m=1}^{M} \psi_m q_m \ , \tag{18}$$

where ψ_m is the non-singular part of the electrostatic potential at the center of the m-th atom. This means that in the calculation of E we exclude the infinite self-energy of the point charges, and take $\psi_m = \psi^{(0)}(x_m)$.

To find the energy, E, we construct a Monte Carlo algorithm based on the

properties of Brownian motion. Denote by $\xi[E]$ a Monte Carlo estimate for E. We represent it as a weighted sum of estimators for point values of the potential:

$$\xi[E] = \frac{1}{2} \sum_{m=1}^{M} \xi[\psi_m] \; q_m \; .$$

Construction of every $\xi[\psi_m] = \xi[\psi^{(0)}](x_m)$ is based on the simulation of a WOS Markov chain $\{x_m^{(j)}, j = 0, 1, \ldots, N_m\}$ with initial point $x_m^{(0)} = x_m, m = 1, \ldots, M$ and random length N_m. The geometry of the domain Ω makes it possible to simulate exit points $x_m^{(N_m)} \in \partial\Omega$ exactly. So we have

$$\psi_m = \mathbb{E}\left[\psi(x_m^{(N_m)}) - g(x_m^{(N_m)})\right] \; . \tag{19}$$

To estimate the unknown boundary values, we make use of the boundary conditions (17). We implement a finite-difference approximation (step h) to the normal derivative and randomize the resulting relation between the values of u at three points: on the boundary (y_0), inside Ω at the distance h along the normal vector (y_1), and outside the domain at the same distance from the boundary (y_2). This means that if the WOS Markov chain inside Ω terminates at the point y_0 on the boundary, we choose, with probability $p = \dfrac{\epsilon_i}{\epsilon_i + \epsilon_e}$, the next point to be y_1, and with the complementary probability we jump outside, to the point y_2. The solution at an interior point is estimated by the WOS algorithm for the Laplace equation, and exterior points use the modified WOS for the LPBE. The constructed Markov chain is terminated with probability $1 - p(d)$ at every WOS step in the exterior, where $p(d)$ is the WOS survival probability determined by (8). By (19), input in the estimate is made every time the WOS comes to the boundary from inside.

To test the proposed algorithm, we applied the constructed Monte Carlo estimate to solving several simple model problems. We consider first the simplest case, a spherical (one-atom) molecule. The analytical solution scaled by $\dfrac{q^2}{4\pi\epsilon_i R}$ is [28]

$$E = \frac{\epsilon_i}{\epsilon_e(1 + kR)} - 1 \; .$$

For the chosen parameters $\epsilon_i = 4.0$, $\epsilon_e = 78.5$, $k = 0.104$, one obtains the exact value, -0.9538. Our calculations provided the result -0.9536 in 418 seconds (on 1300 MHz PC workstation). For the calculation parameters $\varepsilon = h^2 = 10^{-6}$ and $N = 10000$, both the bias and the statistical error are equal to 9.6×10^{-4} (i.e. 0.1%). (We assume the statistical error is equal to two standard errors).

Note that the computation ensuring one per cent error ($\varepsilon = 10^{-4}$, $N = 120$) takes only 0.4 seconds.

Further, we consider a model molecule constructed of two equal unit spheres with unit charges of opposite signs. The distance between the centers is set to be 1.5. With the same parameters as were used for a spherical molecule, we obtained the result -0.3430 with 1% accuracy in 488 seconds.

6 Conclusions

In this article, we reviewed efficient grid-free random walk methods for solving the first boundary value problem for the linearized Poisson-Boltzmann equation. First, we introduced the "Walk On Spheres" (WOS) algorithm [1] for the LPBE. Based on this WOS algorithm, another, related, Monte Carlo algorithm was presented. This Monte Carlo method reinterprets the weights used in the original WOS algorithm as survival probabilities for the random walker used in the computation. In addition, the Feynman-Kac path-integral implementation for solving the LPBE was given. This Feynman-Kac approach uses the WOS method to provide a technique for estimating certain Gaussian path integrals without the need for simulating Brownian trajectories in detail. In this modified WOS method, a Brownian trajectory is constructed as a series of WOS steps, and the exponential weight factor at every WOS step is reinterpreted as a survival probability. Here, this factor is the averaged weight with respect to the entire first-passage time distribution function. It was shown then that this method is mathematically equivalent to the previous modified WOS method for the LPBE [2].

The efficiency of these methods was illustrated by computing solutions of four analytically solvable problems. In all four cases, excellent agreement was shown. The results for the problem of finding the electrical potential in the electrolyte between two parallel flat plates were compared with those obtained by our previous modified WOS method. Finally, we illustrated the use of this Monte Carlo LPBE solver in a more complicated setting related to the computation of the electrostatic free energy of a large molecule. There, we coupled the LPBE solution in the exterior of a compact domain (molecule) with the solution to a Poisson equation inside, and continuity boundary conditions linking these two functions. The performance of the method is quite good in this complicated situation.

In our computations for solving LPBE with constant boundary values, we observe the same relationship between the running time and the thickness of the ε-absorption layer as when the WOS algorithm was applied to solve the Laplace or Poisson equations [25]: the running time is $O(|\log \varepsilon|)$. In addition,

it is observed that for LPBE Dirichlet boundary value problems the bias error due to the ε-layer absorption grows linearly in ε for small ε: the same dependence that holds for the Dirichlet boundary-value problems for the Laplace or Poisson equations [26]. In the latter cases, this relation remains valid with non-constant boundary functions. Therefore, it is expected that in general non-constant Dirichlet boundary-value problems for the LPBE the error from the ε-absorption layer will also be linear in ε.

Our modified WOS method is faster than the Elepov-Mikhailov WOS method [1], because while some of our random walkers are removed during simulation, in the old method all trajectories must be followed until hitting the ε-absorption layer, and contribute to the solution according to their weights.

In the case of the electrostatic potential in an electrolyte between two infinite charged parallel flat plates, we compared our Feynman-Kac WOS method with our modified WOS method. While the Feynman-Kac WOS method is somewhat slower than our modified WOS method, it is promising in its potential for extension to other problems such as the time-independent Schrödinger equation.

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