Hybrid finite element and Brownian dynamics method for charged particles

Gary A. Huber,^{1,a)} Yinglong Miao,¹ Shenggao Zhou,² Bo Li,³
and J. Andrew McCammon^{4,5,6}

¹Howard Hughes Medical Institute, University of California San Diego, La Jolla, California 92093-0365, USA

²Department of Mathematics and Mathematical Center for Interdiscipline Research, Soochow University,
1 Shizi Street, Suzhou, 215006 Jiangsu, China

³Department of Mathematics and Quantitative Biology Graduate Program, University of California,
San Diego, 9500 Gilman Drive, La Jolla, California 92093-0112, USA

⁴Howard Hughes Medical Institute, University of California San Diego, La Jolla, California 92093, USA

⁵Department of Chemistry and Biochemistry, University of California San Diego, La Jolla,
California 92093-0365, USA

⁶Department of Pharmacology, University of California San Diego, La Jolla, California 92093-0636, USA

(Received 11 January 2016; accepted 2 April 2016; published online 25 April 2016)

Diffusion is often the rate-determining step in many biological processes. Currently, the two main computational methods for studying diffusion are stochastic methods, such as Brownian dynamics, and continuum methods, such as the finite element method. A previous study introduced a new hybrid diffusion method that couples the strengths of each of these two methods, but was limited by the lack of interactions among the particles; the force on each particle had to be from an external field. This study further develops the method to allow charged particles. The method is derived for a general multidimensional system and is presented using a basic test case for a one-dimensional linear system with one charged species and a radially symmetric system with three charged species. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4947086>]

I. INTRODUCTION

Two classes of methods are generally used in simulating diffusion in biological systems at the molecular level: methods that treat each diffusing molecule individually and those that use a continuum or probabilistic description of the diffusing species. In the first class, one would include Brownian dynamics^{1–6} and molecular dynamics methods. In the second class, one would include methods for solving the diffusion equations, such as finite difference and finite element methods^{7–19} and Markov chain models.²⁰ Over the past several years, hybrid methods have been developed to combine Brownian dynamics and diffusion equation solutions in the same simulation in order to adopt the advantages of both.^{21–30} Particularly, near complex boundaries and geometries that vary within small spatial scales, it is more efficient to track individual molecules using Brownian dynamics than trying to solve a diffusion equation, whereas solving the diffusion equation can be more efficient where the geometry is more simple and the number of diffusing molecules is large.

In this study, we extend the hybrid finite element and Brownian dynamics (FE-BD) method developed earlier³¹ to simulate charged particles. While the previous study was formulated for simple particles that move under the influence of an external field that depends only on particle position, the present study takes into account the dependency of the force on particle concentrations and charge density. This is important because many diffusing molecules of interest in biological systems carry charges. In addition to propagating Brownian dynamics trajectories and time-dependent finite-

element solutions to the diffusion equation, this study also solves the Poisson equation to resolve the electrostatic interactions of charged particles. We also introduce an improved approach for coupling the continuum and particle regions.

II. THEORETICAL BACKGROUND

The goal of the hybrid FE-BD method is to solve the system of diffusion equations

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot (\mathbf{D}_i \cdot \mathbf{F}_i c_i) + \nabla \cdot (\mathbf{D}_i \cdot \nabla c_i), \quad (1)$$

where c_i is the concentration of species i as number of molecules per unit volume, $\mathbf{D}_i$ is the diffusion matrix of species i , and $\mathbf{F}_i$ is the force on a particle of species i as function of position, divided by the Boltzmann factor $k_B T$. Equation (1) describes the evolution of an ensemble of particles in which a particle of species i moves according to the Brownian dynamics equation

$$d\mathbf{x}_i = \mathbf{D}_i \cdot \mathbf{F}_i dt + \sqrt{2\mathbf{D}_i} \cdot d\mathbf{w}, \quad (2)$$

where $\mathbf{w}$ is a vector of independent Gaussian random variables with a zero mean and variance of dt . We assume that the force $\mathbf{F}$ on a particle of species i can be described by a potential of mean force V ,

$$\mathbf{F}_i = -\nabla V_i. \quad (3)$$

To solve Eq. (1) by using the finite element method, the spatial domain is divided into simplices and hat functions are defined at the nodes between the simplices. A hat function has a value of 1 at its defining node and 0 at all other nodes,

^{a)}Electronic mail: ghuber@ucsd.edu

and varies linearly across each simplex bordering the defining node. We assume that each concentration and potential of mean force V (divided by the Boltzmann factor) can be represented using the hat functions u_k ,

$$c_i(\mathbf{x}, t) = \sum_k c_{ik}(t) u_k(\mathbf{x}), \quad (4)$$

$$V_i(\mathbf{x}) = \sum_k V_{ik} u_k(\mathbf{x}). \quad (5)$$

For this study, we will assume spatially constant and isotropic diffusivity, but varying and anisotropic diffusivity could also in the future be represented by using hat functions. Multiplying Eq. (1) by u_m , integrating over space, and using Green's first identity to simplify the integrals can be used to express the diffusion equation as a system of ordinary differential equations in the coefficients c_{ik} ,

$$\begin{aligned} \sum_n \langle u_m u_n \rangle \frac{dc_{in}}{dt} = & -D_i \sum_{nk} \langle \nabla u_m \cdot \nabla u_k u_n \rangle V_{ik} c_{in} \\ & - D_i \sum_n \langle \nabla u_m \cdot \nabla u_n \rangle c_n \\ & - \sum_n \mathcal{B}(n) \oint u_m \mathbf{J}_{in} \cdot \mathbf{n} dS, \end{aligned} \quad (6)$$

where the angle brackets express the integral over all space

$$\langle \cdot \rangle = \int \cdot d\mathbf{x}, \quad (7)$$

the normal vector $\mathbf{n}$ inside the surface integral points inward, the boundary flux of species i is

$$\mathbf{J}_{in} = -D_i(\nabla c_{in} + \nabla V_{in} c_{in}), \quad (8)$$

and the indicator function $\mathcal{B}(n)$ is 1 if element n borders the boundary and 0 otherwise. The volume integrals of the hat functions can be computed before the simulation; they can be computed analytically for the simple geometries described in this study. Dirichlet boundary conditions can be expressed directly,

$$c_i = C_{bi}, \quad (9)$$

while values of the flux on any part of the boundary can be specified by setting the relevant members of $\mathbf{J}_n$ in Eq. (6) to the desired values. As an alternative, one may express the force directly in terms of hat functions

$$\mathbf{F}_i(\mathbf{x}) = \sum_k \mathbf{F}_{ik} u_k(\mathbf{x}) \quad (10)$$

to obtain a similar system of equations

$$\begin{aligned} \sum_n \langle u_m u_n \rangle \frac{dc_{in}}{dt} = & +D_i \sum_{nk} \langle u_n u_k \nabla u_m \rangle \cdot \mathbf{F}_{ik} c_{in} \\ & - D_i \sum_n \langle \nabla u_m \cdot \nabla u_n \rangle c_{in} \\ & - \sum_n \mathcal{B}(n) \oint u_m \mathbf{J}_{in} \cdot \mathbf{n} dS \end{aligned} \quad (11)$$

with the flux of species i expressed as

$$\mathbf{J}_n = D_i(-\nabla c_{in} + \mathbf{F}_{in} c_{in}). \quad (12)$$

Eqs. (6), (8), and (9) (or Eqs. (11) and (12)) can be expressed in matrix form as

$$\mathbf{A} \cdot \frac{d\mathbf{c}}{dt} = \mathbf{B} \cdot \mathbf{c} + \mathbf{b}, \quad (13)$$

where $\mathbf{b}$ is a constant vector that depends on the boundary conditions. Because each hat function has local support and overlaps only a few neighbors, and the matrices $\mathbf{A}$ and $\mathbf{B}$ are sparse. In order to step this equation forward in time, the backward Euler method can be used,

$$\mathbf{A} \cdot (\mathbf{c}_{j+1} - \mathbf{c}_j) = \Delta t \mathbf{B} \cdot \mathbf{c}_{j+1} + \Delta t \mathbf{b}. \quad (14)$$

This equation can be re-written as

$$\mathbf{c}_{j+1} = (\mathbf{A} - \Delta t \mathbf{B})^{-1} \cdot (\mathbf{A} \cdot \mathbf{c}_j + \Delta t \mathbf{b}), \quad (15)$$

which can be used to calculate the diffusion over the finite element region at each time step in the simulation. The sparsity of the matrices allows rapid solution of Eq. (15).

III. COUPLING METHOD

As in the previous paper,³¹ the goal is to couple the stochastic model of Eq. (2) and the continuum model of Eq. (15). However, a different method, using a *dynamic boundary condition*, is presented here. The diffusion space is divided into three regions: the continuum region, the particle region, and the buffer region. (Fig. 1). The continuum region C consists of finite element simplices. The particle region P consists of a region occupied only by discrete particles governed by the Brownian dynamics equation. The buffer region lies between the continuum and particle regions and consists of a relatively small number of finite element simplices and also contains particles during part of forward time stepping. The boundary between the buffer region and the particle region is defined by $(N-1)$ -dimensional simplices in an N -dimensional system. At the beginning of a time step, the concentration in the buffer region is fully represented both by hat functions and by particles. All of the particles in the system, both in the particle and buffer regions, are stepped forward by Brownian dynamics Eq. (2), and the numbers of particles of each species crossing the boundary between the buffer region and the particle region, in either direction, are used to compute the net species fluxes across the boundary.

For a particular region of the boundary, the flux of species i is computed as

$$\mathbf{J}_i \cdot \mathbf{n} = \frac{\mathcal{N}_i}{A \Delta t}, \quad (16)$$

where $\mathcal{N}_i$ is the net number of particles of species i going into the buffer region through the boundary region with area A .

FIG. 1. Diagram of the continuum, buffer, and particle regions. The nodes are represented as dots on the line. Reproduced with permission from J. Chem. Phys. **136**, 164107 (2012). Copyright 2012 AIP Publishing LLC.

This flux is then used as the boundary value for the continuum system of Eq. (6). Now, in a 2-D or 3-D system, the flux term is defined on the nodes, so a method will be needed to distribute the flux across each line segment (for a 2-D system) or triangle (for a 3-D system) onto the bordering nodes. This will not concern us for now, since our systems in this paper are 1-D or spherically symmetric. For the 1-D system described below, the area is not defined but the area term in Eq. (16) would cancel with any “area” term in the surface integral, so the quantity $N_i/\Delta t$ is plugged directly into the 1-D J_{in} term in Eq. (6). For the spherically symmetric system described below, the area is that of the spherical boundary.

After the fluxes have been computed, all particles that are not in the particle region are deleted, without being absorbed into any of the hat functions as in the previous study. The system of diffusion equations is then stepped forward in time using the fluxes as the boundary conditions as described above. After the hat function coefficients are updated, the particles are regenerated in the buffer region. So, the particles generated in the buffer region serve as tracers to determine the flux boundary condition for the continuum representation.

The particles in the buffer region are generated using the same method as in the previous paper,³¹ but with one difference. The nodes that border both the buffer region and the particle region are included, but their hat functions do not extend into the particle region. So, for a 1-D system, these are “half-hat” functions. Let the integral of the hat function be

$$v_i = \langle u_i \rangle. \quad (17)$$

The number of particles generated is equal to

$$n_i = c_i v_i. \quad (18)$$

Because this number is generally not an integer, it is “stochastically rounded” to avoid fractional particles. The number n_i is rounded by computing the fractional part f and rounding up with probability f or rounding down otherwise. The resulting integer number of particles is placed by treating the normalized hat function u_i/v_i as a probability distribution function and using the rejection method to place the particles.

The procedure avoids two problems from the previous paper. First of all, there is no longer a zero boundary condition for the continuum equations to cause any unphysical loss of matter. Second, the absorption of particles into hat functions during a time step had the effect of smearing out the matter, resulting in an increased effective diffusivity. The resulting diffusivity gradient caused irregularities in concentrations in the buffer region and neighboring continuum elements. Representing the buffer region completely with both particles and hat functions and using the varying flux in the boundary condition avoid these problems. The buffer region still needs to be wide enough so that the chance of a hypothetical particle, starting at the edge of the continuum region, skipping over the buffer region to land in the particle region during one time step is very small. Roughly, this means that the time step should be bounded by

$$\Delta t < \frac{H^2}{18D}, \quad (19)$$

where H is the width of the boundary region.

Moreover, a hat function, with an amount of matter much less than a single particle, can sometimes produce a particle as a result of stochastic rounding. If the particle then diffused away, it could cause a very large flux relative to the actual amount of matter contained. The resulting continuum solution could lead to a significant negative concentration on the hat node, which would be unphysical. However, it is not efficient to use a finite element to represent less than one particle. In practice, each finite element would probably have enough matter corresponding to several particles. In non-steady state systems, finite elements could be added and removed adaptively during the simulation to keep the system efficiently partitioned between particle and continuum regions.

However, even when there are several particles in a buffer finite element, sometimes small time steps can amplify the instantaneous flux out of the element, since the time step size appears in the denominator in Eq. (16). This can cause negative concentrations. Rather than simply setting negative concentrations to zero, which can cause an apparent unphysical “generation” of matter, we have found that it helps to defer some of the flux to a later step. So, if a continuum time step results in a negative concentration in the buffer region, the continuum concentrations are reset to their previous values, the flux across the buffer-particle is cut in half, and half of it is added to what will be the flux at the next time step. The continuum time step is repeated, and half of the remaining flux is again deferred to the next time step, if needed. This is done as often as needed until there are no more zero concentrations. This has the effect of smoothing out the flux, but no more than needed.

IV. USE OF CHARGES

In order to simulate the motion of charged particles, we use a combination of Coulombic pairwise interactions and explicit solutions of the Poisson equation

$$\epsilon \nabla^2 \Phi = -\rho, \quad (20)$$

where ϵ is the electric permittivity of the solvent, ρ is the charge density as a function of position, and Φ is the electric potential. The Poisson equation is to be solved over the entire domain, including particle, buffer, and continuum regions. During the course of a time step, the Poisson equation is solved twice, and pairwise Coulombic particle interactions are explicitly computed once. Four types of electrostatic forces must be considered: the force of the continuum elements on each other, the force of the continuum elements on the particles, the force of the particles on the continuum elements, and the force of the particles on each other.

At the beginning of the time step, the charge density ρ is computed at the node points n from the hat functions by

$$\rho_n = \sum_i q_i c_{in}, \quad (21)$$

where q_i is the charge on a particle of species i . The potential that is used in Eq. (6) is

$$V_{ik} = q_i c_{ik} \Phi_k. \quad (22)$$

It is necessary for the charges of the particles to be included in the Poisson equation; this is done by projecting each particle onto the $N + 1$ hat functions that overlap the simplex containing the particle, with their coefficients increased accordingly. If we consider the particle to have a statistical weight of 1, then that weight must be divided among the hat functions in a manner that best preserves the location of the particle. Before the simulation starts, the “volume” and centroid of each hat function are computed and stored,

$$v_k = \int u_k(\mathbf{x}) d\mathbf{x}, \quad (23)$$

$$\mathbf{m}_k = v_k^{-1} \int \mathbf{x} u_k(\mathbf{x}) d\mathbf{x}. \quad (24)$$

If $N + 1$ weights w_k are added to the $N + 1$ surrounding hat functions, then the first moment induced by the weights is given by

$$\mathbf{m} = \sum_{k=1}^{N+1} w_k \mathbf{m}_k. \quad (25)$$

The rule that the moment in Eq. (25) be equal to the position of the particle

$$\mathbf{x} = \mathbf{m} \quad (26)$$

provides N equations. One more equation is needed to determine $N + 1$ weights; this is provided by the condition that the weights sum to 1,

$$\sum_{k=1}^{N+1} w_k = 1. \quad (27)$$

Equations (25) and (27) are solved to obtain the weights and the coefficient at each node is augmented according to its corresponding weight

$$\rho_k \leftarrow \rho_k + q_i \frac{w_k}{v_k}, \quad (28)$$

where the particle belongs to species i . Note that this is a correction to the original paper,³¹ in which Eq. (25) was formulated incorrectly (this did not significantly affect the results from the first paper).

Therefore, before any position or hat function coefficient is updated, the Poisson equation is solved, under appropriate boundary conditions, with the total charge density calculated from both continuum hat functions and the particles projected onto the particle-region hat functions. This solution, Φ_A , is stored. Next, the Poisson equation is solved for a second time, but without the particles projected onto the hat functions; this solution is Φ_B . Then, the particles are stepped forward by Brownian dynamics (Eq. (2)) and those that are absorbed at any reactive boundaries are removed. The force on particle j is computed from Φ_B ,

$$\mathbf{F}_j = -q_j \nabla \Phi_B, \quad (29)$$

and from the pairwise Coulombic interaction between particles j and l ,

$$\mathbf{F}_{jl} = \frac{q_j q_l}{4\pi\epsilon r_{jl}^3} \mathbf{r}_{jl}, \quad (30)$$

where $\mathbf{r}_{jl}$ is the position of particle l relative to j and $\mathbf{F}_{jl}$ is the force on particle l from j . The pairwise Coulombic sum accounts for the forces of the particles on particles, and the field Φ_B accounts for the force of the continuum elements on the particles. It is necessary for the particles to interact directly with each other, because significant accuracy would be lost if two particles near each other interacted only through projections onto hat functions.

Once the particles have moved, the fluxes across the boundary between the buffer and particle regions are computed. Then, the continuum finite elements are updated according to Eq. (15), using the field Φ_A and Eq. (22), which accounts for the force of the particles on the continuum elements and the force of the continuum elements on each other. Thus, all four combinations of forces are now accounted for. Finally, all particles that are not in the particle region are deleted, and new particles are regenerated in the buffer region from the buffer region continuum elements.

V. 1D EXAMPLE

The first example is similar to the 1D example from the previous paper, where the system is the line segment from 0 to 20. Units were chosen so that the diffusivity, Boltzmann factor $k_B T$, and electric permittivity were 1; this is equivalent to using dimensionless quantities. The concentration of the sole species was held fixed to a value of c_0 equal to 100 particles per unit length at $x = 0$, and there was a perfectly absorbing boundary at $x = 1$. The initial condition of the concentration was $c = c_0$ for all x . The electric potential boundary conditions were set as $\Phi(x = 0) = 100$ and $\Phi(x = 1) = 0$. The algorithm used was simplified from the above description; no direct particle-particle interactions were computed, so the Poisson equation was solved once per time step, using the finite element method, after projecting the particle's charges onto the hat functions. For advancing the continuum equations, the formulation of Eq. (6) was used. Forty line segments of equal length with 0.5 grid spacing were used for the finite element solutions, of which 20 were the continuum region, 4 were the buffer region, and 16 were the particle region. The time step was 0.01 time units. The fluxes were evaluated at $x = 20$; for the FE solution, they were evaluated from the concentration gradient, and for the hybrid method, they were computed from the number of absorbed particles. The hybrid results were compared to the solution computed solely by the FE method. Smaller finite elements (160 in the domain) were used for the FE solution because the very high initial flux at the right boundary needed to be resolved (something that gave the particles no difficulty in the hybrid method). These values were chosen in order to demonstrate a significant effect of charge and electric field on the fluxes and concentrations.

Fig. 2 shows the accumulated flux as a function of time and the averaged concentration profile at steady state obtained from hybrid FE-BD as compared with all finite element (FE) solutions. For systematic analysis, neutral ($q = 0$), negatively charged ($q = -e$) and positively charged ($q = +e$) particles were simulated, where $e = 0.01$, giving an initial charge density of ± 1 charge unit per unit length for the charged

FIG. 2. Comparison of equilibrium concentration profile and accumulated flux between the hybrid FE-BD and all FE models: ((a)-(b)) All FE solutions of the (a) equilibrium concentration profile and (b) accumulated flux. ((c)-(d)) Hybrid FE-BD solutions of the (c) equilibrium concentration profile and (d) accumulated flux. In (c), the two arrows mark the boundaries between the continuum, buffer, and particle regions.

cases. The equilibrium concentration profiles of the hybrid FE-BD method were obtained by averaging over the last 20% of simulation time (Fig. 2(c)). The neutral particles exhibit a linear concentration profile, reflecting the gradient of the two boundaries. In comparison, the negatively charged particles are attracted towards the left boundary, while the positively charged particles are pushed away from the left boundary, due to the potential gradient (Fig. 2(c)). Despite fluctuations, especially in the particulate and buffer regions, the equilibrium concentration profiles calculated using the hybrid FE-BD method agree quantitatively with the all FE solutions (Fig. 2(a)). The root mean squared differences in concentrations for the neutral, negative, and charged cases were 0.35, 0.52, and 0.45 concentration units, respectively, compared to the initial and boundary concentration of 100. The concentration fluctuations shown in Fig. 2(c) depend on the bin widths, since the concentration is measured by dividing the number of particles by the bin width. Therefore, smaller bins would show greater concentration fluctuations, although the average concentrations in each bin would still stay the same, given enough sampling time. The fluctuations shown here are consistent with the number of particles in each bin following a Poisson distribution. The fluctuations propagate into the continuum region, but are smoothed out as they move farther from the particle region.

For the accumulated flux, the cases of the positively and negatively charged particles exhibited significant increase and decrease, respectively, relative to the neutral particles (Fig. 2(d)), which resulted from electrical forces generated from the potential gradient and particle interactions. Again, the accumulated flux obtained from the hybrid FE-BD method are in excellent agreement with the FE solutions (see Figs. 2(b) and 2(d)). The relative differences between final accumulated fluxes for the FE-BD method and the purely FE method were -0.018 , 0.0014 , and -0.012 for the neutral, negatively charged, and positively charged particles. Most of these

relatively small differences in the concentrations and fluxes are likely accounted for by fluctuations in the FE-BD method due to discrete particles.

The results are not sensitive to the size of the buffer region, provided Eq. (19) is satisfied. For the finite element method, the size of the allowable time step appears to be bounded by the relation

$$\Delta t < \frac{h^2}{D}, \quad (31)$$

where h is the width of the finite element. In general, the finite elements need to be small enough to resolve any interesting variations in the concentration profile; if that holds true and Eq. (31) is satisfied, then the results are not significantly affected by the size and number of finite elements.

VI. SPHERICALLY SYMMETRIC EXAMPLE WITH THREE SPECIES

Our system consisted of a spherically symmetric system with an absorbing sphere at the center whose center had a fixed charge, a diffusing charged point-like reactant species, and two diffusing point-like non-reacting ionic species with opposite charges. The concentrations at the outer spherical boundary of the system were fixed and electroneutrality was enforced, so that

$$q_s c_{s,out} + q_{ion} c_{out}^+ - q_{ion} c_{out}^- = 0, \quad (32)$$

where $c_{s,out}$, c_{out}^+ , and c_{out}^- were the boundary concentrations of the substrate, positive and negative ions, and q_s and q_{ion} were the charges of the substrate and positive ion, respectively. We ignored dielectric boundary effects between the absorbing sphere and the mobile charged particles, so we assumed the same dielectric for sphere and solvent. We also assumed the same diffusivity for all three species. A dimensional analysis showed that we could set the dielectric, diffusivity, Boltzmann

factor, and radius of the absorbing sphere all to 1 without losing generality. As in the first paper, the finite elements were spherical shells of equal width, and the hat functions were spherically symmetric. As above, the parameters of the system were chosen so that charges and electric fields would have a significant effect on the system.

The Poisson equation in spherical coordinates is

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \Phi}{\partial r} \right) = -\rho(r). \quad (33)$$

The inner boundary condition at $r = 1$ was computed by Gauss's theorem

$$\left. \frac{\partial \Phi(r_0)}{\partial r} \right|_1 = -\frac{Q_c}{4\pi}, \quad (34)$$

where Q_c is the fixed center charge, and the outer boundary condition at $r = R_{out}$ was computed from the Debye-Hückel approximation

$$\Phi(R_{out}) = \frac{Q_c \exp(-\kappa R_{out})}{4\pi R_{out}}, \quad (35)$$

where κ is the inverse Debye length

$$\kappa^{-2} = c_{s,out} q_s^2 + c_{out}^+ q_{ion}^2 + c_{out}^- q_{ion}^2. \quad (36)$$

The Poisson equation can be solved by direct numerical integration; no finite element solution was necessary for this system. The electric field can be computed from Gauss's theorem: Rearranging and integrating once gives

$$\frac{d\Phi}{dr} = -E_0 - \frac{1}{r^2} \int_{r_0}^r s^2 \rho(s) ds, \quad (37)$$

where Node 0 is defined as the absorbing sphere surface. We can do one more integration,

$$\Phi = \Phi_{N+1} + \int_{r_{N+1}}^r \frac{d\Phi}{dr}(s) ds, \quad (38)$$

where Node $N + 1$ is defined as the outer sphere. The charge density ρ is defined on the nodes 0 to $N + 1$. The integrations were performed using the trapezoid rule.

The particles moved in three dimensions according to Eq. (2), with the pairwise potential between any two particles computed by Coulomb's law. Also, for oppositely charged particles, an additional repulsive potential was included in order to keep particles from collapsing into each other

$$V_{repul} = \alpha/r^4, \quad (39)$$

where factor α was set to 10^{-5} . This resulted in a potential that deviates from the Coulomb potential only at a separation less than 0.05 length units, thus minimizing deviations from the Nernst-Planck model for the concentrations used, and allowing comparisons with the pure finite-element solution.

The time step size was varied depending on the minimum of the distances between any two particles and the minimum of the distances from each particle to the absorbing inner sphere. At the beginning of each time step, an initial time step was computed as

$$\Delta t = \min \left(\frac{h^2}{4}, 0.4\pi \frac{d_{min}^3}{q_s^2}, 0.1 \frac{d_{min}^6}{\alpha}, \max(0.1 r_{min}, 10^{-4}) \right), \quad (40)$$

where d_{min} was the minimum of all pairwise distances, r_{min} was the minimum of particle distances to the absorbing sphere, and h was the width of each shell. This was necessary to ensure that the force on each particle does not change much between time steps and that the continuum solution be numerically stable. The forces were computed on each particle, and each particle was individually stepped forward using an inner time step of

$$\Delta t_{in} = \min(\Delta t, 0.25(r - 1)^2), \quad (41)$$

where r is the distance from the origin, until all of the values of Δt_{in} added up to Δt . This was necessary to ensure accurate resolution of the reaction boundary. The pairwise computations between particles was the most time-consuming part of the computation; thus, that part of the code was parallelized using OpenMP.³²

The system studied had an outer radius $R_{out} = 5$, outer concentrations $c_{s,out} = 1$, $c_{out}^+ = 1$, and $c_{out}^- = 2$ in units of number of particles per unit volume, particle charges $q_s = 1$ and $q_{ion} = 1$, and a central charge of $Q_c = -20$. The inner radius was 1 as noted above. The space between the inner and outer radii was divided into 100 equally spaced shells, with the outer 50 designated as the continuum solution and the next inner 4 designated as the buffer region.

The initial condition comprised equilibrium concentrations. This was computed by assuming an initial Debye-Hückel potential

$$\Phi(r) = \frac{Q_c \exp(\kappa(1 - r))}{(\kappa + 1)4\pi r} \quad (42)$$

and initial concentrations following the Boltzmann distribution

$$c_s(r) = c_{s,out} \exp(-q_s \Phi(r)), \quad (43)$$

(likewise for the ion concentrations), computing the next estimate of potential by computing the charge density from the concentrations and integrating as described above, and iterating back and forth between Eqs. (43) and (42) until convergence. This was done using finite elements over the whole domain, and then the finite elements in the particle region were converted to particles.

Twenty hybrid simulations were run for 16 time units. The amount of material that was absorbed at the center sphere is plotted as a function of time (Fig. 3). The smooth center curve is the purely finite element solution. The two curves on either side come from twenty hybrid simulations. At each point in time, the 2nd highest and 2nd lowest value from all of the twenty simulations are plotted. This forms a kind of 90% confidence level envelope of these hybrid simulations. The second plot, which focuses on the beginning, shows that the non-steady-state start-up is resolved by the hybrid method. The data are noisy because of the relatively small number of particles compared to the simulations in the first paper.³¹ As in the 1-D example, results did not depend significantly on the size and number of finite elements, provided the limits described above were honored.

FIG. 3. 3-species results. The middle curve is the purely finite-element solution, while the curves on either side represent a 90% confidence envelope.

VII. DISCUSSION

As in the first paper,³¹ the results from this method closely match those from the purely finite element methods. In addition to allowing charged particles, more accurate concentrations and avoidance of loss of matter at the interface are obtained by the improved dynamic boundary coupling between the particle and continuum regions. As seen in Fig. 2 in the 1-D simulation, it also avoids the spurious irregularity in concentration due to repeated conversions back and forth between particle and hat functions. Thus, this study represents a significant improvement over the formula presented in the previous paper.

However, further improvement of the hybrid FE-BD method might include the following. Perhaps the main weakness is the need to solve a continuum-based equation, the Poisson equation, over the entire domain. Avoiding the need to discretize the possibly complicated geometry of the particle region for a finite-element solution was one of the main motivations for this work in the first place. Work is in progress to confine the finite-element Poisson equation to the continuum region, treat the finite element simplices as charged bodies, and directly compute pairwise interactions between particles and the continuum elements. Multipole methods will be used to speed this up.³³ Finally, the response of the dielectric boundary, between the large molecular structures and the solvent, to electric fields will need to be included in both the particle and continuum regions.³⁴

Another area with room for improvement is the fact that the entire system must be stepped forward using the smallest time scale, namely, the motion of the individual particles. Ideally, it would be desirable to update large finite elements in relatively smooth regions of space much less frequently than the particle positions. Additional work using multistep time integrators³⁵ or use of Slotboom variables³⁶ in the continuum region might help overcome this limitation.

Because of the simplicity of the system studied, it is not yet possible to directly draw conclusions about performance with respect to computational resources required. However, consideration of the length and time scales involved in the physical system and the two different simulation regimes can help the user decide which regions should use finite elements and which should use discrete molecules. Three length scales can be considered in a region: that of the physical system's geometry (L_g), that of the average distance between neighboring diffusing particles (L_p), and that of the concentration gradient ($L_c \propto |\nabla^2 c|^{-\frac{1}{2}}$). The scales L_g and L_c

would limit the size of any finite elements used, and the scale L_p would determine how many particles would be required. In general, advancing N particles by a time step would require $O(N)$ time, since multipole methods can be used to compute the direct Coulombic interactions. Likewise, advancing N finite elements by a time step would require $O(N)$ time, and storage would likewise scale linearly with the number of particles and finite elements. So, it would make sense to use finite elements in places where $L_c > L_p$, and to use particles where $L_g \leq L_p$. Assuming that a future version of this method will not require the system to be updated everywhere at the same time, as mentioned above, the advantages of using the most suitable simulation regime for each region will be amplified, since the upper bound on the time step will scale as $L^2/\mathcal{D}$, where L is either the length scale of the finite element or distance between neighboring particles, and $\mathcal{D}$ is the diffusivity. As mentioned earlier in the paper, it might also be possible to adaptively change the different regions in a non-steady-state system. Further analysis and experience will elucidate the trade-offs between particles and finite elements.

Finally, there is a need to develop true three-dimensional models with this method in order to study systems of biological interest. The main goal is to embed atomically detailed models of receptors, with small particle regions, into much larger continuum domains at the cellular level, with structures from light and electron microscopy. Such systems of interest include the cardiomyocyte with calcium ions and their transporters and receptors,^{37–40} the neuromuscular junction with acetylcholine,^{8,11,41,42} and the node of Ranvier with sodium and potassium ions.¹⁵ All of these systems have multiple time and length scales, so multiscale methods such as that described above will be useful for predicting physiologically significant rates and fluxes.

ACKNOWLEDGMENTS

We are grateful to Dr. Michael White for suggesting the dynamic boundary condition method and for pointing out an error in the original formulas for converting a particle into the continuum description. The work was supported by the Howard Hughes Medical Institute, the National Institutes of Health, the National Science Foundation, the National Biomedical Computation Resource, and the San Diego Supercomputer Center. B.L. was partially supported by the NSF Grant No. DMS-1319731. S.Z. acknowledges start-up Grant No. Q410700415 at Soochow University.

- ¹D. Ermak and J. McCammon, *J. Chem. Phys.* **69**, 1352 (1978).
- ²S. Northrup, S. Allison, and J. McCammon, *J. Chem. Phys.* **80**, 1517 (1984).
- ³H. Zhou, *J. Chem. Phys.* **92**, 3092 (1990).
- ⁴B. Luty, J. McCammon, and H. Zhou, *J. Chem. Phys.* **97**, 5682 (1992).
- ⁵P. Bauler, G. Huber, T. Leyh, and J. A. McCammon, *J. Phys. Chem. Lett.* **1**, 1332 (2010).
- ⁶S. R. McGuffee and A. H. Elcock, *PLoS Comput. Biol.* **6**, e1000694 (2010).
- ⁷G. C. T. Oden and E. B. Becker, *Finite Elements: An Introduction. Volume I* (Prentice-Hall, Englewood Cliffs, NJ, USA, 1981).
- ⁸J. Smart and J. McCammon, *Biophys. J.* **75**, 1679 (1998).
- ⁹M. Holst, *Adv. Comput. Math.* **15**, 139 (2001).
- ¹⁰U. Hollerbach, D. P. Chen, and R. S. Eisenberg, *J. Sci. Comput.* **16**, 373 (2001).
- ¹¹K. Tai, S. Bond, H. MacMillan, N. Baker, M. Holst, and J. McCammon, *Biophys. J.* **84**, 2234 (2003).
- ¹²Y. Song, Y. Zhang, C. Bajaj, and N. Baker, *Biophys. J.* **87**, 1558 (2004).
- ¹³Y. Cheng, J. K. Suen, D. Zhang, S. D. Bond, Y. Zhang, Y. Song, N. A. Baker, C. L. Bajaj, M. J. Holst, and J. A. McCammon, *Biophys. J.* **92**, 3397 (2007).
- ¹⁴B. Lu, Y. C. Zhou, G. A. Huber, S. D. Bond, M. J. Holst, and J. A. McCammon, *J. Chem. Phys.* **127**, 135102 (2007).
- ¹⁵C. L. Lopreore, T. M. Bartol, J. S. Coggan, D. X. Keller, G. E. Sosinsky, M. H. Ellisman, and T. J. Sejnowski, *Biophys. J.* **95**, 2624 (2008).
- ¹⁶Y. C. Zhou, B. Lu, G. A. Huber, M. J. Holst, and J. A. McCammon, *J. Phys. Chem. B* **112**, 270 (2008).
- ¹⁷Q. Zheng, D. Chen, and G.-W. Wei, *J. Comput. Phys.* **230**, 5239 (2011).
- ¹⁸*Automated Solution of Differential Equations by the Finite Element Method*, edited by G. W. A. Logg and K.-A. Mardal (Springer, Berlin Heidelberg, 2012).
- ¹⁹B. Tu, Y. Xie, L. Zhang, and B. Lu, *Comput. Phys. Commun.* **188**, 131 (2015).
- ²⁰V. S. Pande, K. Beauchamp, and G. R. Bowman, *Methods* **52**, 99 (2010).
- ²¹T. Geyer, *BMC Biophys.* **4**, 7 (2011).
- ²²T. Geyer, C. Gorba, and V. Helms, *J. Chem. Phys.* **120**, 4573 (2004).
- ²³C. Gorba, T. Geyer, and V. Helms, *J. Chem. Phys.* **121**, 457 (2004).
- ²⁴W. Im, S. Seefeld, and B. Roux, *Biophys. J.* **79**, 788 (2000).
- ²⁵M. Robinson, M. Flegg, and R. Erban, *J. Chem. Phys.* **140**, 124109 (2014).
- ²⁶A. V. Berezkin and Y. V. Kudryavtsev, *J. Chem. Phys.* **139**, 154102 (2013).
- ²⁷M. B. Flegg, S. Hellander, and R. Erban, *J. Chem. Phys.* **289**, 1 (2015).
- ²⁸F. Spill, P. Guerrero, T. Alarcon, P. K. Maini, and H. Byrne, *J. Chem. Phys.* **299**, 429 (2015).
- ²⁹D. Boda and D. Gillespie, *J. Chem. Theory Comput.* **8**, 824 (2012).
- ³⁰I. Teo and K. Schulten, *J. Chem. Phys.* **139**, 121929 (2013).
- ³¹P. Bauler, G. A. Huber, and J. A. McCammon, *J. Chem. Phys.* **136**, 164107 (2012).
- ³²L. Dagum and R. Menon, *IEEE Comput. Sci. Eng.* **5**, 46 (1998).
- ³³H. Cheng, L. Greengard, and V. Rokhlin, *J. Comput. Phys.* **155**, 468 (1999).
- ³⁴B. Zhang, B. Peng, J. Huang, N. P. Pitsianis, X. Sun, and B. Lu, *Comput. Phys. Commun.* **190**, 173 (2015).
- ³⁵M. Tuckerman, B. Berne, and G. Martyna, *J. Chem. Phys.* **97**, 1990 (1992).
- ³⁶J. Slotboom, *IEEE Trans. Electron Devices* **20**, 669 (1973).
- ³⁷J. Hake and G. T. Lines, *Biophys. J.* **94**, 4184 (2008).
- ³⁸S. Lu, A. Michailova, J. Saucerman, Y. Cheng, Z. Yu, T. Kaiser, W. Li, R. Bank, M. Holst, J. McCammon, T. Hayashi, M. Hoshijima, P. Arzberger, and A. McCulloch, *IEEE Eng. Med. Biol. Mag.* **28**, 46 (2009).
- ³⁹Y. Cheng, Z. Yu, M. Hoshijima, M. J. Holst, A. D. McCulloch, J. A. McCammon, and A. P. Michailova, *PLoS Comput. Biol.* **6**, e1000972 (2010).
- ⁴⁰S. Lindert, P. M. Kekenus-Huskey, G. Huber, L. Pierce, and J. A. McCammon, *J. Phys. Chem. B* **116**, 8449 (2012).
- ⁴¹T. Bartol, B. Land, E. Salpeter, and M. Salpeter, *Biophys. J.* **59**, 1290 (1991).
- ⁴²J. Antosiewicz, M. K. Gilson, I. H. Lee, and J. A. McCammon, *Biophys. J.* **68**, 62 (1995).