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A CONTINUUM HARD-SPHERE MODEL OF PROTEIN ADSORPTION

Craig Finch^a, Thomas Clarke^b, and James J. Hickman^{a,*}

Craig Finch: cfinch@ieee.org

^aNanoScience Technology Center, University of Central Florida, 12424 Research Parkway, Orlando FL 32828, USA

^bInstitute for Simulation and Training, University of Central Florida, 3100 Technology Parkway, Orlando, FL 32826, USA

Abstract

Protein adsorption plays a significant role in biological phenomena such as cell-surface interactions and the coagulation of blood. Two-dimensional random sequential adsorption (RSA) models are widely used to model the adsorption of proteins on solid surfaces. Continuum equations have been developed so that the results of RSA simulations can be used to predict the kinetics of adsorption. Recently, Brownian dynamics simulations have become popular for modeling protein adsorption. In this work a continuum model was developed to allow the results from a Brownian dynamics simulation to be used as the boundary condition in a computational fluid dynamics (CFD) simulation. Brownian dynamics simulations were used to model the diffusive transport of hard-sphere particles in a liquid and the adsorption of the particles onto a solid surface. The configuration of the adsorbed particles was analyzed to quantify the chemical potential near the surface, which was found to be a function of the distance from the surface and the fractional surface coverage. The near-surface chemical potential was used to derive a continuum model of adsorption that incorporates the results from the Brownian dynamics simulations. The equations of the continuum model were discretized and coupled to a CFD simulation of diffusive transport to the surface. The kinetics of adsorption predicted by the continuum model closely matched the results from the Brownian dynamics simulation. This new model allows the results from mesoscale simulations to be incorporated into micro- or macro-scale CFD transport simulations of protein adsorption in practical devices.

Keywords

Protein adsorption; biomaterials; Brownian dynamics; computational fluid dynamics; continuum; random sequential adsorption

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*Corresponding author: 12424 Research Parkway, Suite 400, Orlando, FL 32826, Phone: 407-823-1925, Fax: 407-882-2819, jhickman@ucf.edu.

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1. Introduction

The simulation of protein adsorption in practical systems is a challenging multi-scale problem in which the nano-scale process of adsorption is coupled to the micro- or macro-scale process of protein transport. A continuum model was developed to predict the kinetics of adsorption of hard spheres onto a uniform surface. The continuum adsorption model was coupled with a conventional computational fluid dynamics (CFD) transport simulation that can be used to simulate transport-influenced adsorption on surfaces in complex geometries. The adsorption model incorporated empirical results from Brownian dynamics simulations of adsorption, which allowed the detailed results from mesoscopic simulations to be combined with the efficiency and practicality of continuum transport simulations.

Protein adsorption is the first step in many important biological processes, including the coagulation of blood, the vascularization of tissue in artificial scaffolds, and the adhesion of cells to surfaces [1]. Therefore, understanding how proteins interact with a particular surface is of critical importance in the design of implants, medical devices, or anything else that comes in contact with a biological system [2–4]. Although protein adsorption has been extensively studied it is still considered an open problem. Even the study of a single type of protein is challenging because its structure and function depend upon environmental factors such as the presence of nearby proteins, the pH and ionic strength of the solution and the presence and properties of a nearby interface [1]. The challenge is compounded by the enormous variety of proteins found in nature and the presence of multiple proteins in most realistic systems.

Computational methods have been applied to model and predict protein adsorption, but their success has been limited due to the complexity of the problem. While nanoscale simulation methods like molecular dynamics (MD) have the potential to predict protein adsorption from first principles, the small (femtosecond) time step required by atomistic techniques presents a significant obstacle. The adsorption of proteins and their subsequent rearrangement occurs on a time scale of seconds to hours [5]. MD has been used to simulate the adsorption of a fragment of fibrinogen with explicit solvent molecules for 5ns of simulated time [6]. A similar study was carried out to model the interaction between lysozyme and a graphite surface for 500ps [7]. It was recently reported that an advanced MD simulation utilizing a supercomputer specially designed for these systems has the ability to simulate several microseconds of protein behavior [8]. Because of the complexity of atomistic models, simplified models have been developed to model protein adsorption. A protein molecule can be represented as a colloidal particle with a simplified geometric shape such as a sphere or ellipsoid. Particle-particle and particle-surface interactions can be represented by potentials that may be derived from DLVO theory [9, 10]. Brownian dynamics simulations have been used to simulate the transport and adsorption of proteins with DLVO interactions [11–13].

A fundamental limitation of nanoscale and mesoscale simulation methods is that they are impractical for modeling transport in practical applications such as medical implants, engineered tissue constructs, blood flow simulations, and in microfluidic devices. CFD simulations are widely used to model transport in these systems. Simplified continuum models of adsorption based upon chemical kinetics have been used as adsorbing boundary conditions in CFD simulations [14]. Early kinetic models of adsorption were formulated based upon the assumptions of the Langmuir adsorption model [15]. More recently random sequential adsorption (RSA) models have been developed to characterize the blocking of the surface more rigorously for various particle shapes [16]. Similar principles have been used to create numerous models that account for observed phenomena such as denaturation of proteins after adsorption and multi-layer adsorption [1]. All of these models treat adsorption as a two-dimensional process in which simple shapes (typically discs) adsorb at random onto

a surface without overlapping. The fraction of the surface that is available for a new particle to adsorb is quantified through the available surface function $ASF(\theta)$, where θ is the (fraction of surface that is already covered by adsorbed particles).

Continuum models of discrete-particle adsorption can be formulated using the principles of chemical thermodynamics. The available surface function has been generalized to depend on the height above the adsorbing surface as well as the fractional surface coverage [17]. Adsorbed particles create an energy barrier which grows higher as the number of adsorbed particles increases, reducing the flux of particles to the surface. This barrier incorporates steric exclusion due to the blocking effect of hard particles and the longer-ranged repulsive effect of electrostatic interactions [18]. This model has been implemented by making simplifying assumptions about transport to the surface. For example, the surface boundary layer approximation (SFBLA) assumes that the interface is one-dimensional and the flux through the boundary layer is independent of the position above the surface [19]. Transport to the interface has been accounted for by coupling the adsorption model to a diffusive transport model, but the kinetic coefficients of the adsorption model were approximated with results from an RSA model [18].

The three-dimensional nature of the interface must be taken into account to develop more realistic models of protein adsorption. A schematic drawing of hard spheres adsorbing on a surface is shown in Figure 1. The variable h was defined as the distance between the edge of an adsorbing particle and the surface. The distance h and time t have been non-dimensionalized using the particle radius r_p and the diffusion coefficient D_{dim} :

$$\begin{aligned} h &= \frac{h_{\text{dim}}}{r_p} \\ t &= \frac{D_{\text{dim}}}{r_p^2} t_{\text{dim}} \end{aligned} \quad (1)$$

Using these dimensionless variables, adsorbing particles have a radius of 1. To accurately model the blocking effect of hard spheres, it cannot be assumed that the flux at the surface (J_s) is equal to the flux at the interface with the continuum (J_c). A particle may diffuse into the interface region ($0 < h < 2$), collide with adsorbed particles, and diffuse back out of the boundary region at a later time. At any instant, the flux at the surface will be less than or equal to the flux at the continuum interface. Brownian dynamics simulations of hard sphere adsorption were utilized to obtain configurations of adsorbed spheres, which were then analyzed to obtain the generalized blocking function $ASF(h, \theta)$. The principles of non-equilibrium thermodynamics were used to derive a generalized form of the diffusion equation with variable coefficients. The flux of particles was allowed to vary with the distance from the surface. The generalized blocking function from the Brownian dynamics simulations was used to determine the coefficients of the generalized diffusion equation, which was solved numerically in the region near the surface. This model was coupled to a conventional CFD simulation which was solved in the domain $h > 2$ to predict transport to the interface region. Good agreement was found between the kinetics obtained from the Brownian dynamics simulations and the kinetics predicted by the continuum model.

2. Derivation of the continuum model

The first steps of the derivation of the continuum model follow the method described in [17–19], starting with the continuity equation,

$$\frac{\partial n}{\partial t} = -\nabla \cdot \mathbf{J} \quad (2)$$

where n is the number density of particles in solution and $\mathbf{J}$ is the flux of particles. Adsorption is an equilibration process that can be described using non-equilibrium thermodynamics. In general, irreversible fluxes tend to be linear functions of thermodynamic gradients (such as Fick's first law) [20], so it was postulated that,

$$\mathbf{J} = -(\mathbf{M} \cdot \nabla E)n \quad (3)$$

where $\mathbf{M}$ is the mobility tensor and E is the total potential, which can be written as $E = \mu + \Phi$. The chemical potential μ represents particle-particle interactions, including interactions between particles in solution and adsorbed particles. The external potential Φ includes effects such as an electric field due to a charged surface or a gravitational potential. Using the relation $\mathbf{D} = kT\mathbf{M}$, the flux can be written in terms of the diffusion tensor $\mathbf{D}$:

$$\mathbf{J} = -\mathbf{D} \cdot (\nabla \mu/kT + \nabla \Phi/kT)n \quad (4)$$

The chemical potential can be written in terms of the activity coefficient γ :

$$\mu = \mu^\circ + kT \ln \gamma \frac{n}{n^\circ} \quad (5)$$

μ° is the potential in the standard state, which was defined as a pressure of 100kPa and a number density of one particle per unit volume ($n^\circ = 1$). The potential in the standard state is the potential of a particle in solution that is not interacting with other particles. The activity coefficient is a function of the number and configuration of particles and the particle-particle interaction potential. The activity coefficient can change as a function of position because the density and configuration of particles and the potential environment can vary with position. Expanding the potential and substituting into the flux equation results in,

$$\mathbf{J} = -\mathbf{D} \cdot \left[\frac{\nabla \mu^\circ}{kT} + \nabla \ln \frac{n}{n^\circ} + \nabla \ln \gamma + \frac{\nabla \Phi}{kT} \right] n \quad (6)$$

Since the potential in the standard state is constant, the gradient of the first term is zero. This expression for the flux was substituted into Equation 1 to obtain,

$$\frac{\partial n}{\partial t} = \nabla \cdot \left[\mathbf{D} \cdot \left(\nabla \ln \frac{n}{n^\circ} + \nabla \ln \gamma + \frac{\nabla \Phi}{kT} \right) n \right] \quad (7)$$

This equation can be applied to arbitrary potentials and geometries. To model adsorption at an interface, the general equation can be simplified by assuming that the interfacial region is thin with respect to the overall geometry. Transport parallel to the interface (including convection) was neglected to reduce the equation to a one-dimensional form:

$$\frac{\partial n}{\partial t} = \frac{\partial}{\partial h} \left[\mathbf{D} \cdot \left(\frac{\partial}{\partial h} \ln \frac{n}{n^\circ} + \frac{\partial}{\partial h} \ln \gamma + \frac{1}{kT} \frac{\partial}{\partial h} \Phi \right) n \right] \quad (8)$$

h is the distance between the edge of the particle and the surface, as shown in Figure 1.

For the case of hard spheres with no long-range potentials, $\Phi \equiv 0$. For simplicity the diffusion coefficient near the surface was assumed to be constant and hydrodynamic interactions were neglected. The notation n/n° was dropped with the understanding that n has been normalized by the standard-state number density n° . The equation was re-arranged to have the form of a generalized diffusion equation:

$$\frac{\partial n}{\partial t} = D \frac{\partial}{\partial h} \left[\left(\frac{1}{n} \frac{\partial n}{\partial h} + \frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \right) n \right] = D \left[\frac{\partial^2}{\partial h^2} n + \frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \frac{\partial n}{\partial h} + n \frac{\partial}{\partial h} \left(\frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \right) \right] \quad (9)$$

The result is a parabolic partial differential equation with variable coefficients. Let

$$\begin{aligned} k_1 &= \frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \\ k_2 &= \frac{\partial}{\partial h} \left(\frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \right) \end{aligned} \quad (10)$$

so that

$$\frac{\partial n}{\partial t} = D \left[\frac{\partial^2}{\partial h^2} n + k_1 \frac{\partial n}{\partial h} + k_2 n \right] \quad (11)$$

An equation is generated which predicts the evolution of number density over time at every point in a domain for which the activity coefficient is known. Equation 10 was used to formulate a boundary-value problem to predict the surface density of adsorbed particles over time. To conserve mass at the surface, the rate of adsorption must be equal to the net flux at the surface. This boundary condition can be stated as:

$$\frac{d\Gamma}{dt} = -J_s(t) \quad (12)$$

where Γ is the number of adsorbed particles per unit area and J_s is the flux at the surface. The total surface density of adsorbed particles can be found by integrating Equation 11:

$$\Gamma(t) = \int_0^t J_s(\tau) d\tau \quad (13)$$

The choice of boundary condition for the bulk solution depends upon the nature of the problem to be solved. If mass transport to the surface does not limit the rate of adsorption, the concentration at the continuum interface can be treated as constant. It is straightforward to couple the generalized diffusion equation to a conventional CFD simulation to predict transport-influenced adsorption in arbitrary geometries.

3. Computation of the activity coefficient

The coefficients of the generalized diffusion equation are functions of the activity coefficient γ , which is a function of the number and configuration of adsorbed particles. The activity coefficient changes with h because the density and configuration of particles change as functions of the distance from the surface. The activity coefficient was determined empirically from the results of Brownian dynamics simulations.

3.1. Brownian dynamics simulations

Brownian dynamics simulations of irreversible hard-sphere adsorption were used to obtain configurations of adsorbed particles. The Langevin position equation [21] was used to update the position of each particle at each time step:

$$\mathbf{r}_i(t+\Delta t) = \mathbf{r}_i(t) + \mathbf{g}_q \sqrt{2D\Delta t} \quad (14)$$

where $\mathbf{r}_i$ is the position of particle i , which is the simulation time step, D is the diffusion coefficient, and $\mathbf{g}_q \in \mathcal{R}^3$ is a vector of random numbers drawn from a Gaussian distribution with a mean of zero and a variance of one. At each time step, all particles in the domain were moved simultaneously, and overlaps were detected. Any particle which overlapped another was reset to its original position and moved again using a different random vector, until each particle found a valid position. Hydrodynamic interactions were not modeled.

The simulation domain was a rectangular box with height L and width and length S . Periodic boundary conditions were applied on the four sides of the simulation domain so that a particle that exited one side of the box re-entered on the opposite side. A particle that touched the bottom of the box without overlapping any previously adsorbed particles was considered to have adsorbed. Once adsorbed, a particle did not move or desorb. The configuration of adsorbed particles was recorded every time a new particle adsorbed. A non-blocking boundary condition was also implemented, in which adsorbed particles were moved out of the simulation domain so that they did not block the adsorption of additional particles.

Two different boundary conditions were used for the top of the box. To simulate constant near-surface concentration a reflecting boundary was used and at each time step, the particles in the box were counted. If there were too few particles in the box, particles were added at positions drawn from a uniform random distribution, ensuring that the newly added particles did not overlap with existing particles. If there were too many particles in the domain, a particle was chosen at random for deletion. To simulate diffusion to the surface from a semi-infinite domain, an open box top was used to allow the Brownian dynamics simulation to exchange particles with an infinite bulk solution. This boundary condition was implemented according to the multi-scale linking algorithm described in [22].

3.2. Implementation and validation of Brownian dynamics simulator

The Brownian dynamics simulator was implemented using Python programming language with the dimensionless variables defined as in [22]. Numerical data, such as the coordinates of the particles, were stored in NumPy arrays [23]. Routines from the SciPy library were used for standard operations such as interpolation and numerical integration [24]. Collision detection was implemented in the C programming language for speed, using the **weave** function from SciPy. Each time a particle adsorbed on the surface, the configuration of adsorbed particles was recorded, along with the profile of concentration vs. distance from the adsorbing surface and the fraction of the surface covered by particles (θ). The PyTables package was used to save the simulation results to binary files in HDF5 format [25, 26].

The Brownian dynamics simulator was validated using parameters from Magan and Sureshkumar [22]: particle radius $r_p = 5.8 \times 10^{-8}$ m, diffusion coefficient $D_{\text{dim}} = 3.77 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$ and volume fraction $\phi = \{0.001, 0.01, 0.05\}$. Although these values are more representative of colloidal particles than proteins, the simulator was based on dimensionless variables so its performance was independent of the absolute values of the parameters. The non-blocking boundary condition was also used to validate the simulator. When using this boundary condition, the rate of adsorption was controlled only by the rate at which particles diffused to the surface, so the results could be compared to the analytical solution of the diffusion equation on a semi-infinite domain with a perfect adsorbing boundary condition. It was verified that the kinetics of adsorption and the average concentration as a function of distance from the surface matched the predictions of the diffusion equation. Various box sizes $S = \{75r_p, 100r_p, 150r_p\}$ and time steps $\Delta t = \{10^{-5}, 10^{-6}, 10^{-7} \text{ s}\}$ were used to verify that the box size was sufficiently large and the time step was sufficiently small to achieve accurate results.

3.3. Calculation of the activity coefficient

The activity coefficient γ was determined empirically from the results of the Brownian dynamics simulations using the Widom particle insertion method [27]. A “test” particle was introduced into a fixed configuration of particles and the energy of interaction ψ between the test particle and the surrounding particles was calculated. The activity a can be computed by taking the canonical average of many such insertions, using equation 2 from reference [27],

$$\frac{n}{a} = \left\langle \exp \left(\frac{-\psi}{kT} \right) \right\rangle \quad (15)$$

For hard spheres, the energy of interaction was infinite if the test particle overlapped an existing particle or zero if it did not. Therefore, the activity coefficient $\gamma = a/n$ was infinite if the test particle overlapped another and one if it did not. To avoid dealing with infinite quantities, the available volume function (AVF) was defined as $AVF(h, \theta) = \gamma(h, \theta)^{-1}$, which is the three-dimensional equivalent of the available surface function $ASF(\theta)$. The value of the AVF was one if the test particle did not overlap with an adsorbed particle and zero if an overlap occurred, so the value of the AVF for h_i and θ_i was simply the fraction of test particles that did not overlap with adsorbed particles.

After the completion of an ensemble of Brownian dynamics simulations, the AVF was calculated for each run at multiple values of h and θ . For each θ_i a planar grid of non-overlapping test particles was constructed in the simulation domain at a given height $0 < h_i < 2$ above the adsorbing surface. Particles in solution with $h > 2$ cannot interact with adsorbed particles, as shown in Figure 1. The position of each test particle was offset by a small random vector in the x - y plane and each test particle was checked for overlaps with every simulation particle. The fraction of test particles without overlaps was recorded as the value of $AVF(h_i, \theta_i)$. Multiple replicates with different random displacements from the grid were performed for each h_i and θ_i and the results were averaged. The analysis was performed with 50 and 500 replicates, and 50 replicates were found to be sufficient to determine the AVF . The results from multiple runs of the Brownian dynamics simulation were averaged to obtain an estimate of the available volume function. The coefficients of the generalized diffusion equation were computed directly from the available volume function:

$$k_1 = \frac{1}{\gamma} \frac{\partial \gamma}{\partial h} = \frac{-1}{AVF} \frac{\partial AVF}{\partial h} \quad (16)$$

$$k_2 = \frac{\partial}{\partial h} \left(\frac{1}{\gamma} \frac{\partial \gamma}{\partial h} \right) = \frac{1}{AVF^2} \left(\frac{\partial AVF}{\partial h} \right)^2 - \frac{1}{AVF} \frac{\partial^2 AVF}{\partial h^2} \quad (17)$$

4. Implementation of the continuum model

The control volume formulation [28] was used to obtain a finite difference form of Equation (11) in the region $0 < h < 2$. Central differencing was used to approximate first derivatives in space, and a fully implicit scheme was used to approximate time derivatives. To ensure stability, the source term was linearized so that it was independent of the value of n . Since any particle that touched the surface adsorbed, the number density of particles at the surface was zero, which was represented by the Dirichlet (type 1) boundary condition $n = 0$ at $h = 0$. For simulations with constant near-surface concentration, the type 1 boundary condition $n =$

n_b was applied at $h = 2$. A time step of 10^{-6} seconds was used for continuum simulations of hard-sphere adsorption.

4.1. Coupling the continuum model of hard-sphere adsorption to a conventional CFD transport simulation

For simulations in which the concentration at $h = 2$ was influenced by diffusion, a second simulation domain was created for $h > 2$ to model diffusion in the bulk. The classical diffusion equation was discretized and solved in this domain in the same manner as the generalized diffusion equation. The generalized diffusion equation was solved in the interface region to obtain the net flux, using the value of number density at $h = 2$ from the previous time step. For small values of t the surface was mostly available for adsorption, so the net flux was limited by diffusive transport and the net flux was determined by J_c rather than J_s . Once the surface was mostly blocked, the net flux was determined by the rate at which particles could find available space on the surface, so the value of J_c was used for the net flux. To account for both cases, the correct value for the net flux was computed by

$$J(h=2, t) = \min(|J_s|, |J_c|) \quad (18)$$

The net flux from the generalized diffusion equation was used as a type 2 boundary condition to solve the classical diffusion equation in the bulk, which resulted in a new value for the number density at the interface. This number density was used to solve the generalized diffusion equation in the interfacial domain again, and the iterative process was repeated until the number density at the interface computed in each domain converged:

$$|n(h=2^-) - n(h=2^+)| < \delta \quad (19)$$

4.2. Validation of the continuum model

Equation 10 has the form of a diffusion equation. In the case that the activity coefficient is constant, this equation reduces to the classical one-dimensional diffusion equation. It was verified that the adsorption kinetics predicted by the continuum model with a constant activity coefficient ($AVF \equiv 1$) matched the kinetics predicted by the classical diffusion equation on a semi-infinite domain with a perfect adsorbing boundary condition.

5. Results and discussion

5.1. Brownian dynamics simulation results

The Brownian dynamics simulation was run with three different number densities of particles in solution. The number density had a significant impact on the kinetics of adsorption as shown in Figure 2. The configurations of adsorbed particles predicted by the Brownian dynamics simulations were characterized using the pair correlation function $g(r)$ and the results are shown in Figure 3. Both the kinetics of adsorption and the surface configurations agree well with published results [22]. The surface arrangement for a particular value of θ was not influenced by the bulk number density used in the simulation or the type of boundary condition used for the top of the simulation domain (exchanging particles with a semi-infinite domain or constant-concentration). Figure 3 also shows that configurations generated by the random sequential adsorption of disks were equivalent to those generated by Brownian dynamics simulations. These results indicate that the irreversible adsorption of non-interacting hard spheres is a random sequential adsorption process that is independent of transport to the surface. If kinetic information is not required,

surface configurations can be generated by RSA simulations, which are much less computationally intensive than Brownian dynamics simulations.

The available volume function was computed for the results of each Brownian dynamics simulation. A representative plot of the AVF for a volume fraction of 0.01 is shown in Figure 4, along with a plot of the available surface function for the RSA model [29]. The AVF was also independent of the bulk number density used in the simulation. Since Brownian dynamics and RSA simulations produce identical configurations of adsorbed particles, it was not surprising that the AVF for Brownian dynamics at $h = 0$ was identical to the ASF for the RSA model.

5.2. Continuum model results

The coefficients of the generalized diffusion equation were computed from the AVF from Brownian dynamics simulations. Representative plots of the coefficient values are shown in Figure 5. Figure 6 shows that the kinetics predicted by the continuum model and the Brownian dynamics simulation converged as the Brownian dynamics time step was reduced, confirming the validity of the continuum adsorption model derived here. Figure 7 shows the number density (normalized to the bulk number density) near the adsorbing surface predicted by Brownian dynamics and the continuum model. For small values of fractional surface coverage (Figure 7a), the number density in the continuum region ($h > 2$) decreased with time in a manner consistent with diffusion-limited adsorption. As the fractional surface coverage approached its maximum value and the surface became blocked, the flux of particles to the surface J_s decreased. Particles diffused in from the bulk and replenished the number density in the continuum region. Figure 7b shows that the number density of particles in the interaction zone increased as θ increased. In the limit $\theta \rightarrow \theta_{\max}$ and $t \rightarrow \infty$, the number density in the continuum region would be uniform and equal to its initial value.

In previous publications, the available surface function has been computed as the ratio of the flux of particles that actually adsorb to the flux of particles that arrive at the adsorbing surface [30]:

$$ASF(\theta) = \frac{J_s}{J_c} \quad (20)$$

This method was used to compute the overall ASF for the hard-sphere interface using the fluxes from the continuum adsorption model. Figure 8 demonstrates that this approach is of limited value when the interface region has a finite thickness because it predicts that the ASF will be greater than one for small values of fractional surface coverage. For $t \approx 0$ the magnitude of J_s is large because the surface is almost completely available for adsorption, while the magnitude of J_c is very small because the depletion of particles is confined to a very thin layer near the surface. This situation, which can be seen in Figure 7a, causes the ASF to be greater than one. Since the fraction of the surface that is available for adsorption cannot exceed one, this approach to computing the ASF is not valid for interfaces with non-negligible thickness at small values of θ . The available surface functions for RSA and hard-sphere adsorption converge as θ approaches 0.55. This method has also been used to estimate the overall ASF for hard-sphere adsorption using fluxes from Brownian dynamics simulations [22]. Figure 10 of [22] shows an ASF with a different shape from the one shown in Figure 8. Because fluxes obtained from Brownian dynamics have a high variance, only a rough estimate of the ASF can be obtained by this method. It should be possible to compute an accurate ASF for a Brownian dynamics simulation of hard-sphere adsorption by tracking each particle that crosses into the interaction region and measuring what fraction of these particles actually adsorb at each value of fractional surface coverage.

The continuum model required less than a minute to run on a desktop PC, while the Brownian dynamics simulation required up to several days of run time on a Linux cluster (depending on the number of time steps and number of particles) to obtain equivalent results. The continuum model can be scaled to larger domain sizes much more effectively than Brownian dynamic simulations, which require detecting collisions between N particles. Collision detection scales as $O(N^2)$ using a brute-force approach, however, algorithms have been developed that produce linear scaling with N [31]. Although the continuum adsorption model was coupled with a simple diffusion-only transport simulation in this work, it would be straightforward to couple the model to full-featured CFD simulation for predicting transport and adsorption in arbitrary geometries.

5.3. Future applications

This work focused on the adsorption of hard spheres so that the results of a continuum adsorption model could be validated by comparison to results from a RSA model and the classical diffusion equation. However, the theoretical foundation of the model was directly applicable to particles with arbitrary force fields. The Widom method of obtaining the generalized blocking function $ASF(h, \theta)$ can be applied to configurations of particles with long-range “soft” interaction potentials. Brownian dynamics simulations of particles that interact by means of DLVO forces have already been demonstrated [11–13]. An advantage of Brownian dynamics is that it is straightforward to add additional forces and second-order effects, such as hydrodynamic interactions, without changing the basic algorithm [11]. A practical challenge to using this method for particles with long-range interactions is that more computational resources are required for running the Brownian dynamics simulations and characterizing the chemical potential near the surface. Continuing advances in simulation algorithms, parallelization techniques, and computational hardware will make Brownian dynamics simulations even more useful in the near future.

6. Conclusions

The continuum model presented here reproduces the diffusion and adsorption of hard spheres predicted by Brownian dynamics simulations, while requiring significantly reduced computational resources. Configurations of adsorbed particles from Brownian dynamics were analyzed to obtain an available volume function, which extended the available surface function into three dimensions. The available volume function was used to calculate values for the coefficients of the generalized diffusion equation and the results were validated by comparison to results from the Brownian dynamics simulations. The continuum model can be coupled to a general-purpose CFD solver to predict transport and adsorption in practical applications such as biosensors and models of organs. The method presented here can be extended to make *a priori* predictions of protein adsorption if the particle-particle and particle-surface interaction potentials can be characterized.

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Figure 1.

Geometry used to model the adsorption of hard spheres. The distance from the edge of a particle to the surface h has been non-dimensionalized by the particle radius.

Figure 2. Kinetics of adsorption predicted by Brownian dynamics simulations for three different volume fractions (ϕ). θ represents the fraction of the surface covered by adsorbed particles. The dotted lines indicate plus or minus one standard deviation.

Figure 3. Radial distribution function for configurations of adsorbed particles generated by Brownian dynamics simulations for three different volume fractions. The radial distribution functions for configurations generated by an RSA simulation are also shown.

Figure 4. Available volume function for hard spheres adsorbed on a surface. The available surface function for RSA is shown as a dashed line at $h = 0$.

Figure 5. Coefficients of the generalized diffusion equation derived from the available volume function shown in Figure 3.

Figure 6. Kinetics of adsorption predicted by the Brownian dynamics simulation and the continuum model for a volume fraction of 0.01.

Figure 7.

Concentration (normalized to the bulk number density) near the adsorbing surface for low fractional surface coverage (a) and high surface coverage (b). Dashed lines represent results from the continuum model and symbols represent averaged Brownian dynamics results.

Figure 8. Available surface function (ASF) for the hard-sphere model, computed using equation 19, compared to the ASF for random sequential adsorption.