# Finite Element Solution of the Steady-State Smoluchowski Equation for Rate Constant Calculations

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ABSTRACT This article describes the development and implementation of algorithms to study diffusion in biomolecular systems using continuum mechanics equations. Specifically, finite element methods have been developed to solve the steady-state Smoluchowski equation to calculate ligand binding rate constants for large biomolecules. The resulting software has been validated and applied to mouse acetylcholinesterase. Rates for inhibitor binding to mAChE were calculated at various ionic strengths with several different reaction criteria. The calculated rates were compared with experimental data and show very good agreement when the correct reaction criterion is used. Additionally, these finite element methods require significantly less computational resources than existing particle-based Brownian dynamics methods.

## INTRODUCTION

Diffusion plays a central role in numerous biological processes, governing the kinetic properties of events across a variety of length scales: from ligand binding (Antosiewicz et al., 1995, 1996b; Antosiewicz and McCammon, 1995; Lesyng and McCammon, 1993; McCammon and Karplus, 1977; Northrup et al., 1984; Tan et al., 1993; Tara et al., 1998; Wade et al., 1994) to protein-protein encounter (Elcock et al., 2001; Gabdoulline and Wade, 2001; Northrup and Erickson, 1992; Sheinerman et al., 2000; Zhou, 1997) to signal transmission at synaptic junctions (Franks et al., 2002; Kara and Friedlander, 1998; Roberts, 1994; Smart and McCammon, 1998; Tai et al., 2003; Zoli and Agnati, 1996). Biological simulations have been used to study such diffusion-controlled processes in a number of settings and have provided useful insight into the molecular determinants of the kinetic parameters. However, accurate modeling of diffusion within biomolecular systems while incorporating the effects of ionic strength, solvent, and protein charges, and applying to large biological systems with complex geometries, has proven to be the rate-limiting step for a variety of such simulations.

Currently, standard techniques for modeling diffusional processes can be loosely grouped into *particle-based* and *continuum* methods. Particle-based methods are typically stochastic in nature and include Monte Carlo (Berry, 2002; Genest, 1989; Saxton, 1992; Stiles and Bartol, 2000; Brownian dynamics (BD) (McCammon, 1987; Northrup et al., 1988a; Wade et al., 1993), and Langevin dynamics (Eastman and Doniach, 1998; Yeomans-Reyna and Medina-Noyola, 2001) simulations. The connection between BD simulations and of the calculation of association rate constants was established by Northrup, Allison, and McCammon (Northrup et al., 1984) and has been studied by numerous others (Antosiewicz et al., 1996a; Antosiewicz and McCammon, 1995; Chung et al., 2002; Northrup et al., 1988b; Tan et al., 1993; Tara et al., 1998; Wade et al., 1993; Zhou, 1993; Zhou et al., 1998a; Zhou and Szabo, 1996; Zou et al., 2000). In contrast to particle-based approaches, continuum methods describe diffusional processes in terms of probability or concentration profiles rather than simulating the stochastic motion of individual particles. Continuum methods are typically based on solutions of partial differential equations such as the diffusion or Smoluchowski equation (Chan and Halle, 1984; Gardiner, 1997; Lenzi et al., 2003; Smart and McCammon, 1998; Tai et al., 2003); these solutions can then be processed to determine ligand-protein binding (Agmon et al., 1991; Smart and McCammon, 1998; Tai et al., 2003; Zhou, 1990) or dissociation (Agmon, 1984). These methods have been particularly popular in the fields of ion channel (Coalson and Duncan, 1992; Gillespe et al., 2002; Im and Roux, 2002; Kurnikova et al., 1999a) and semiconductor (Selberherr, 1984) modeling.

Both particle-based and continuum diffusion methods have their relative strengths. Particle-based methods can deal with a wide range of diffusing molecular geometries, whereas continuum methods are restricted to spherical ligands. This spherical approximation is likely to be most appropriate for substrates with charge distributions with small multipole moments and reaction criteria that do not require

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a detailed fit between the substrate and macromolecule. Additionally, particle-based approaches permit the natural inclusion of stochastic reaction phenomena and other complicated boundary conditions. However, the stochastic nature of particle-based approaches can lead to convergence problems which are not present in the deterministic continuum method. Furthermore, continuum approaches facilitate the inclusion of other continuum phenomena such as elastic deformations and fluid flow. Finally, as illustrated in this article, the computational cost of the continuum simulations is significantly smaller than for particle-based methods.

Currently, there are a number of tools available for particle-based biomolecular diffusion simulations, including: SDA (Gabdoulline and Wade, 1997), UHBD (Briggs et al., 1995), MacroDox (Northrup et al., 1999), and MCell (Stiles and Bartol, 2000). However, there are no biomolecule-specific tools available for analyzing diffusion via continuum models and only a few general diffusion tools (Krissinel and Agmon, 1996). The objective of this study is to develop, validate, and apply algorithms to solve the steady-state Smoluchowski equation (SSSE) with finite element methods using realistic biomolecular geometries to determine the steady-state ligand binding rate constant. Specific aims in this study include: development of the adaptive meshing method to realistically describe biomolecular geometries; development of the finite element solver of the steady-state Smoluchowski equation to analyze the concentration of the diffusing particles and calculate the association rate constants; validation of the SSSE with a simple spherical biomolecular system through the comparison with the analytical results; and application of the validated SSSE solver to mouse acetylcholinesterase (mAChE) ligand binding.

## THEORY AND ALGORITHMS

### The steady-state Smoluchowski equation

The Smoluchowski equation describes the overdamped (i.e., instantaneous momentum relaxation) dynamics of multiple particles while neglecting interparticle interactions (Smoluchowski, 1917; Szabo et al., 1988; Zhou, 1990). For a stationary diffusion process, the Smoluchowski equation has the steady-state form of

$$Lp(x) = \nabla \cdot D(x)[\nabla p(x) + \beta p(x)\nabla W(x)] = 0, \qquad (1)$$

where $Lp(x)$ represents $(dp(x,t)/dt)$ ($t$ is the time), $p(x)$ is the distribution function of the reactants, $D(x)$ is the diffusion coefficient, $\beta = 1/kT$ is the inverse Boltzmann energy, $k$ is the Boltzmann constant, $T$ is the temperature, and $W(x)$ is the potential mean force (PMF) for the diffusing particle. The above steady-state Smoluchowski equation (SSSE) can also be written in terms of the flux operator $J$, which generates vector-valued functions and is defined as

$$Jp(x) = D(x)[\nabla p(x) + \beta p(x)\nabla W(x)], \qquad (2)$$

allowing Eq. 1 to be rewritten as

$$Lp(x) = \nabla \cdot Jp(x) = 0. \qquad (3)$$

The SSSE can be solved to determine bimolecular diffusional encounter rates. Following the work of Zhou (1990), the application of the SSSE to this problem involves the solution of Eq. 3 in a three-dimensional domain $\Omega$, with the following boundary conditions: a bulk Dirichlet condition on the outer boundary $\Gamma_b \subset \partial\Omega$,

$$p(x) = p_{bulk} \quad \text{for} \quad x \in \Gamma_b, \qquad (4)$$

specifying the bulk concentration $p_{bulk}$; a reactive Robin or Dirichlet condition on the active site boundary $\Gamma_a \subset \partial\Omega$,

$$n(x) \cdot Jp(x) = \alpha(x)p(x) \quad \text{for} \quad x \in \Gamma_a, \qquad (5)$$

or

$$p(x) = 0 \quad \text{for} \quad x \in \Gamma_a, \qquad (6)$$

providing either an intrinsic reaction rate $\alpha(x)$ or an absolute reactivity, respectively; and a reflective Neumann condition on the nonreactive boundary $\Gamma_r \subset \partial\Omega$,

$$n(x) \cdot Jp(x) = 0 \quad \text{for} \quad x \in \Gamma_r. \qquad (7)$$

The problem domain is depicted in Fig. 1; $\Delta$ is a simply connected domain with boundary $\boldsymbol{\Gamma_b}$, which represents the volume containing the reactive object and the solvent. The domain $\Xi \subset \Delta$ is a simply connected region representing the reactive object with boundary $\boldsymbol{\Gamma_{ar}} = \boldsymbol{\Gamma_a} \cup \boldsymbol{\Gamma_r}$ such that $\boldsymbol{\Gamma_a} \cup \boldsymbol{\Gamma_r} = \mathbf{0}$. The $\boldsymbol{\Gamma_r}$ portion of this boundary represents the

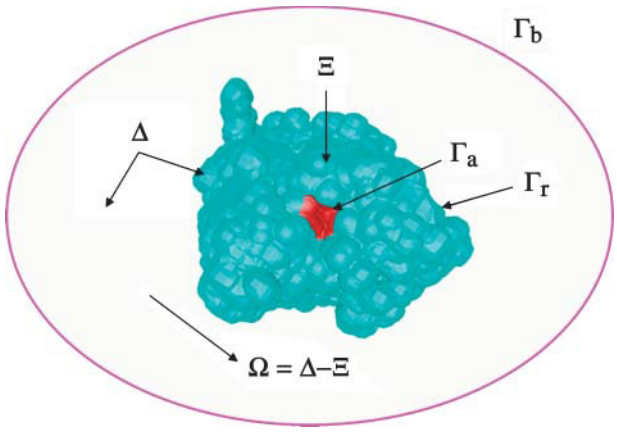


FIGURE 1 Schematic of problem domain denoting the various surfaces and volumes described in the text.