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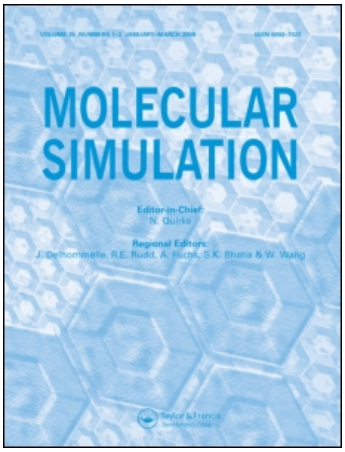

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Simulation of Bimolecular Reactions

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Preliminary Communication

SIMULATION OF BIMOLECULAR REACTIONS: SYNTHESIS OF THE ENCOUNTER AND REACTION STEPS

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Computer simulations are playing an increasingly important role in the study of chemical and biochemical reactions in condensed phases [1, 2, 3]. For bimolecular reactions, the events leading to reaction can be separated into two steps: the initial encounter, followed by the actual reaction of the properly juxtaposed reactants. Current simulation methods allow the analysis of reactions whose rates are controlled by one or the other of these steps [1]. Here, we describe an approach that can be used for the general case. An advantage of this approach is that it allows the rigorous integration of a hierarchy of models. E.g., the encounter step can be treated by models with continuum and Brownian elements, and the reaction step by fully atomistic models.

KEY WORDS: Bimolecular reactions, enzymatic reactions, Brownian dynamics

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INTRODUCTION

The current work was motivated by a desire to improve the theoretical analysis of enzymatic reactions. We therefore use an enzymatically-catalyzed reaction to introduce and illustrate the method. The enzyme superoxide dismutase (E) is known to catalyze the dismutation of superoxide anion (S) at rates that are close to diffusion controlled. The rates are in fact similar to those predicted by Brownian dynamics simulations in which the solvent is represented as a continuum and reactions are simply assumed to occur when a diffusing S comes within a certain distance of the active sites in E [4, 5]. But separate molecular dynamics simulations of ES complexes suggest that post-encounter events influence the overall rate and could play a more dominant role in mutagenized forms of E [6, 7]. These post-encounter events include passage of S through a narrow but hydrated channel of 10 Å length from the surface of E to the active site, and transfer of electrons and protons. For such events, a detailed description of the atomic structure, and Newtonian or even quantum dynamical treatment of the various particles, are essential for accurate treatment of the complicated rearrangements of the solvent molecules and the components of E and S.

For the usual conditions of steady-state kinetics, all of the above features can be synthesized by Markov chain methodology [8]. Markov chain models have a long

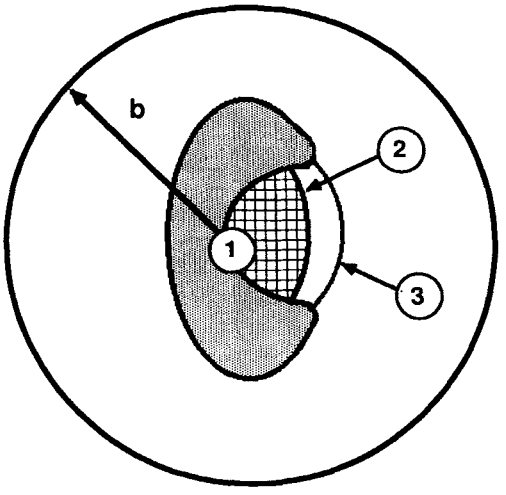

Figure 1 Schematic diagram of the example system. Beyond the surface of radius b, the interaction between the enzyme E (shaded) and substrate S is centrosymmetric; an analytic diffusion model can be used to describe S motion in this region. Between the b-surface and surface **2**, continuum electrostatic models and Brownian dynamics simulation provide a reasonably accurate description of S motion. Between surface **2** and the reactive surface **1**, fully atomistic models and molecular dynamics simulation may be required. In the example described in the text, E is actually a dimer with two active sites, and Brownian dynamics was used near the active sites for computational simplicity and to allow comparison with later molecular dynamics calculations.

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history in chemical kinetics [9, 10]; we use them here as a way to couple results from complementary simulations. To introduce the method, consider the following simple but specific example. Suppose that continuum descriptions of the solvent and the interior of E, and a Brownian description of the dynamics of S, form an adequate model when S is farther from the active site than surface **2**, located near the mouth of the channel (Figure 1). And suppose that a more detailed model is required when S is between surface **2** and the reactive surface **1** of the active site. As in previous studies of diffusion-controlled reactions catalyzed by enzymes, suppose that surface **1** is perfectly reactive, and that there is a surface at distance b from the center of E beyond which the forces between E and S are effectively centrosymmetric [11, 12, 13].

Previous studies have made use of fact that the rate constant k for substrate disappearance can be factored as

$$k = k(b)\beta \tag{1}$$

where $k(b)$ is the rate that S molecules beyond b first reach the distance b, and β is the probability that an S molecule initially at b will go on to react rather than escaping [11, 12, 13]. The quantity $k(b)$ can be calculated analytically, and β can be obtained from Brownian trajectory analysis. The Markov chain method again considers the fate of S molecules that start at distance b. But β is now calculated by analyzing trajectories computed in different regions of space using different models. For the simple example of Figure 1, trajectory analysis is used to compute

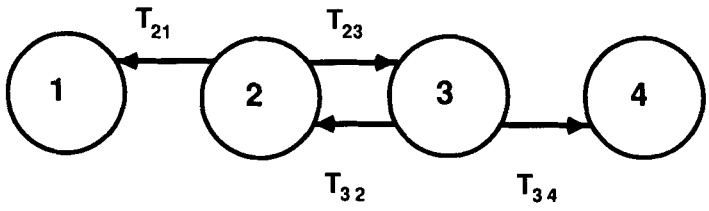

Figure 2 State diagram for the Markov chain used to integrate the results of calculations for the different spatial domains shown in Figure 1. States 1, 2, and 3 correspond to substrate S molecules at surfaces **1**, **2**, and **3** in Figure 1. State 4 corresponds to substrate escape to infinite distance from E. T_{ij} is the probability that an S molecule in state i will move to state j before reaching the state on the other side of i.

the probabilities T_{21} and $T_{23} = 1 - T_{21}$ that an S molecule starting at surface **2** will first encounter surface **1** or surface **3**, respectively. Accurate simulations in this region might require molecular dynamics with explicit solvent. Separate simulations, perhaps with Brownian dynamics, are used to compute the probabilities T_{32} and $T_{34} = 1 - T_{32}$ that an S molecule starting at surface **3** will encounter surface **2** or will escape and never return, respectively. These probabilities are components of a transition probability matrix **T**. All other components of **T** are equal to zero, except for $T_{11} = T_{44} = 1$, which are determined by the absorbing boundary conditions.

The transition matrix is used to determine the ultimate probability that an S molecule will react. The possible states of an S molecule are represented by a row vector $\mathbf{P} = (P_1, P_2, P_3, P_4)$. The components indicate the probabilities that an S molecule will have reached surfaces **1**, **2** or **3** (P_1, P_2, and P_3, respectively) or will have escaped (P_4) at any stage in the evolution of a Markovian sequence of events in the system. The initial value of the state vector is $\mathbf{P}^{(0)} = (0, P_2^0, 0, P_4^0)$. The nonzero elements are just the probabilities P_2^0 that an S molecule starting at b will reach surface **2** before escaping (with probability $P_4^0 = 1 - P_2^0$); these are readily calculated by standard methods [11, 12, 13]. The transition matrix is applied to $\mathbf{P}^{(0)}$ repeatedly from the right to obtain the state distributions of S after successive intervals of time. After an infinite number of operations, one obtains

$$\mathbf{P}^{(\infty)} = \lim_{N \to \infty} \mathbf{P}^{(0)} \mathbf{T}^N \tag{2}$$

in which the components are $\mathbf{P}^{(\infty)} = (\beta, 0, 0, 1 - \beta)$. The calculation of $\mathbf{P}^{(\infty)}$ is readily accomplished, and the resulting value of β yields the desired rate constant through equation 1.

RESULTS

To illustrate and test this method, calculations of the quantities described above have been made using Brownian dynamics and the UHBD software for all of the non-trivial components of **T**. The results will also be useful for comparison with future work in which T_{21} and T_{23} are calculated by full molecular dynamics simulation. As in previous Brownian dynamics studies of superoxide dismutase (E) and

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Table 1 State vectors and transition probability matrix

$\mathbf{P}^{(0)}$:	0.00	0.13	0.00	0.87
T:	1.00	0.00	0.00	0.00
	0.32	0.00	0.68	0.00
	0.00	0.91	0.00	0.09
	0.00	0.00	0.00	1.00
$\mathbf{P}^{(\infty)}$:	0.11	0.00	0.00	0.89

All vector and matrix elements that are not identically equal to 0 or 1 were calculated from sets of 2,000 to 3,000 Brownian dynamics trajectories, using the UHBD program [15]. Atomic charges and van der Waals radii were from the GROMOS parameter set [16] except for the charges on the metal ions and their ligands, which were estimated using ab initio calculations [17]. The dielectric coefficients were chosen to be 2 and 78 for the protein interior and the solvent, respectively. The ionic strength was zero. The diffusion constant of S relative to E was 0.13 $Å^2$/ps.

Error ranges estimated as 90% confidence limits were ± 0.02 or smaller.

its substrate superoxide (S), the X-ray structure is used for E [14], and S is treated as a charged sphere [4]. The b-surface is 41.5 Å from the center of the dimeric E. The surfaces **1**, **2**, and **3** are respectively located 6 Å from the active site *Cu*, where S has been suggested to react [7]; and 9 Å and 10 Å from the *Cu*, near the surface of E.

The results of the calculations are shown in Table 1. The final estimate of β calculated by the Markov method is 0.11 ± 0.02, where the error estimate is the 90% confidence limit. Direct calculation of β by allowing trajectories to evolve continuously from the b-surface to surface **1** also yields $\beta = 0.11 \pm 0.01$; this confirms the consistency of the direct and Markov chain calculations.

CONCLUSIONS

The above results demonstrate that the Markov chain method can be used reliably to integrate the results of separate simulations, carried out in different spatial domains of a system of reactants. This opens the way for hybrid calculations, in which two or more propagators and interaction models are used to balance the needs for accuracy and computational efficiency in a spatially-dependent fashion. Elaborations of the simple type of decomposition used here will sometimes be necessary. For example, only small patches of the **2** and **3** surfaces are accessible in the present case, because they intersect the channels to the active sites of E. Where large regions of such surfaces are accessible, it may be necessary to decompose the surfaces into sectors and to expand the state vector and transition matrix correspondingly. Fortunately, the Markov chain method readily admits of such generalization.

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