Competition between Geminate Recombination and Reaction with a Macromolecule

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Received: September 8, 1997; In Final Form: November 12, 1997

This paper reports the formulation of theories of nonhomogeneous kinetics based on the independent pairs approximation for systems where geminate recombination competes with scavenging by a (cylindrical model) macromolecule. The theory describes the spatial distribution of hits on the cylinder and is tested by comparison with Monte Carlo random flights simulation. The kinetics, the hit distribution, and the distribution of the separation between successive hits modeled by the independent pairs theory are in good agreement with the simulations. Some discrepancies are found, which originate from a three-body correlation effect. The origin of this effect, which may be important in understanding radiation damage in biological systems, is discussed in detail.

1. Introduction

When a fast electron passes through a liquid, it leaves a track consisting of very reactive free radicals and ions in a highly clustered spatial distribution.[1] The subsequent transient chemistry reflects the relaxation of this distribution. Theories of radiation-chemical kinetics must take account of two features of the radiation track: first, the microscopic nonhomogeneity of the particle distribution within the clusters, commonly termed spurs, and second, the small number of particles contained in each spur. The combination of these two effects poses challenging theoretical problems. Recently, stochastic simulation techniques and theories have been developed, helping to elucidate the physical,[2,3] physicochemical,[4,5] and chemical[6−8] processes of radiolysis.

In a complex system, a spur may be formed in close proximity to a larger structure, such as a macromolecule or a surface. This introduces competition between recombination in the spur, reaction with any scavenger present, and scavenging by reaction with the heterogeneous moiety. Not only is the chemistry affected by the presence of the structure, but the spatial distribution of hits may also be important. For example, in radiation biology, two reactions of free radicals with a DNA molecule in close proximity may lead to a double-strand break.[9,10]

The kinetics of reaction with a macroscopic structure and the spatial distribution of the sites of reaction depend strongly on the geometry of the structure. Several different geometries are of interest, including a sphere, an ellipsoid, a cylinder, a plane surface and a string of spheres. Many of these have been used in the literature to model free radical attack on, or energy deposition in, a macromolecule such as DNA.[11,12] The studies performed to date can be classified into three broad categories: (1) physical modeling of energy deposition events on DNA;[11] (2) rate constants for reaction between a macromolecule and a homogeneous concentration of free radicals;[13,14] and (3) Monte Carlo simulations of chemical attack by free radicals in the track.[12] These theoretical studies provide complementary information to experimental data on the chemical nature of radiation damage.

Monte Carlo simulations generally represent an attempt to model as accurately as possible the processes taking place in the radiation track and show many interesting effects at a qualitative level. Appropriate and accurate simulations contain much more detailed information about the competing physical and chemical processes than can be obtained experimentally, and a great deal can be learned from a detailed analysis of these simulations. For example, it is possible to analyze the spatial distribution of hit positions and its relationship with the initial configuration of the reactants in the track relative to the macromolecule. Unfortunately, as there remain many uncertainties about the details of the processes involved and consequently about the input parameters, it is unlikely that any Monte Carlo simulation can be quantitatively correct at present. Of course, the same is true of all other theoretical approaches which make approximations.

Experimental studies of the kinetics of free radical attack on DNA have led to attempts to find a pragmatic parametrization that can describe these kinetics acceptably. These studies have generally involved the use of kinetic rate equations with modified rate constants for the radical + DNA reaction, and for this purpose it is necessary to approximate the DNA to some simple geometrical figure, such as a cylinder or a sphere.[13,14] In recent years, it has been realized that nonhomogeneous kinetics in a radiation track do not obey simple rate laws,[15] and microscopic stochastic theories have been developed. These theories provide a more accurate description of the diffusion and reaction in a track than conventional theories because they recognize the individual nature of the reactive particles. The aim of this paper to formulate stochastic theories for systems where there is competition between recombination and scavenging by a large cylindrical structure. A similar study of a plane surface showed interesting correlation effects, both for the recombination kinetics and the spatial distribution of reactions with the surface.[16] In view of the importance of radical attack on macromolecular structures, such as DNA, it is of interest to investigate whether similar correlations are likely to arise when a cylindrical target is considered.

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S1089-5639(97)02926-5 CCC: $15.00
Published on Web 01/03/1998

All analytical theories of many-body diffusion-reaction problems, such as the competition between recombination and reaction with a macromolecule, make approximations. For example the Smoluchowski−Noyes treatment of diffusion-limited kinetics relies upon the independent pairs approximation.[17,18] It is this approximation that breaks down in the competition between recombination and scavenging by a plane surface.[16] In this paper, a Monte Carlo simulation technique is used to test the accuracy of the independent pairs approximation, both for the simulated kinetics and for the spatial distribution of the hits on the macromolecule. Since the aim is to test the independent pairs approximation and alternative formulations in the literature,[13,14] which employ an idealized cylindrical model of the macromolecule, a similar model has been used. Although the model is crude, it is possible to use it to investigate spatial correlation effects that would be much harder to find and analyze for a more realistic representation of the molecular structure, where other features and complexities are present. For example, in a cylindrical geometry, it is easy to measure the distance between two hits in the axial direction whereas in a more complex model there may be no such unique measure. The problem of determining whether a double-strand break takes place in DNA is more complicated than simply considering the axial distance between two hits, even in a simple cylindrical model. The helical structure of DNA means that the occurrence of a double-strand break, or a more complex damage site, will depend simultaneously on both the axial and the angular coordinates of the hits. The simulations reported in this paper could easily be analyzed in a manner that enables this to be modeled. One possibility would be to simulate the joint density of the position and angle of the hits or the differences between the *z*-coordinates and the θ coordinates of pairs of hits. This means at a minimum simulating a two-dimensional probability distribution, and the statistics are much worse than those of simulating a single variable, requiring one order of magnitude more computational resources for comparable precision. The statistical problem could be alleviated by taking a more discrete view and simply asking which nucleoside is hit, rather than recording the coordinates of the hit. Such an analysis has the disadvantage that it loses much of the spatial information about the hit distribution. For these reasons a single variable has been used as a measure of the hit position. A more detailed analysis including angular distributions will be performed when computational resources permit.

In this paper, the competition between geminate pair recombination and scavenging by a cylindrical macromolecule is investigated. Three techniques are employed: Monte Carlo random flights simulation,[19] a modification of the independent reaction times (IRT) model,[19] and an analytical formulation using a stochastic master equation.[20] The IRT model is an efficient and accurate stochastic simulation technique, and the master equation takes the form of a set of coupled differential rate equations describing the evolution of the probability distribution for the system, which have to be solved numerically. These models have demonstrated that the independent pairs approximation is successful for describing spur kinetics.[19,21,22] Reformulations of both techniques to analyze the spatial distribution of hit positions on a cylinder are also reported.

The following section deals with the random flights simulation, section 3 details the necessary alterations to the IRT model, and section 4 describes the modified master equation. The three methods are tested by comparison with the analytic solution for the diffusion-controlled reaction of a single particle with an absorbing cylinder, which is well-known.[23] The results are discussed in section 5. One interesting feature of the results is that hit positions are slightly further apart in the random flights simulation than the predicted by the independent pairs approximation. The origin of this three-body correlation effect is considered in section 6, and modifications of the IRT model to correct for its effects are presented. The final section contains a summary of the conclusions.

2. Random Flights Simulation

The random flights technique used in this paper for the simulation of the trajectories of diffusing particles is essentially equivalent to the diffusion approximation and has been described in detail elsewhere.[19,20,24] Time is divided into discrete steps, during which each particle undergoes a normally distributed random flight with a mean determined by any interparticle forces present and a standard deviation determined by the diffusion coefficient of the particle. This method is similar to the Brownian dynamics technique described by other authors[25−27] except in the detailed treatment of the boundary behavior. Here, methods of conditional probability are used to calculate the probability of an encounter occurring during a time step, given the positions of the particles at the start and the end of a time step.[24]

2.1. Modifications to the Random Flights Simulation. The introduction of an absorbing cylinder brings no great complication to the procedure used to model spur kinetics. The cylinder is assumed to be static, and its presence does not affect the diffusion of the radicals. The only necessary alterations to the reported method involve modeling the reaction with the cylinder and the calculation of the variable time step. Reaction with the cylinder is taken to occur with probability one during a time step if the radical encounters it. Encounter *must* have taken place if a radical occupies a reactive configuration (i.e., is found inside the cylinder) at the end of a time step. However, as argued elsewhere,[24] the use of this criterion alone underestimates the reaction rate because there is a nonzero probability that a radical occupying unreactive configurations at the start and the end of the time step has encountered the cylinder and reseparated during the step. This probability can be calculated by the method of ref 24, but for the problem of reaction with a cylinder, evaluation of the solution requires an infinite integral of ratios of zero-order Bessel functions (see section 3), which is too computationally expensive to use at every time step. In consequence, an approximate method is used, which is accurate if the time step is short enough that the radial drift of the radical relative to the cylinder is approximately constant.[20,24] In the case of interest, the instantaneous radial drift takes the value D/r, where D is the radical diffusion coefficient and r is the distance from the radical to the axis of the cylinder. The time step is calculated such that there is 95% confidence that the radial drift changes by less than 10% during the time step. In this way, the conditional reaction probability calculated from the Brownian bridge can always be used[24]

$$W_a(r_0,r,\delta t) = 1 - \exp[-(r_0 - a)(r - a)/D\delta t] \qquad (1)$$

where r_0 and r are the distances from the cylinder axis at the start and end of the time step (δt), respectively, and a is the radical−cylinder encounter distance.

The radical−radical distances are also used to calculate time steps in order to avoid the possibility of radicals jumping through one another, according to the procedure described in detail elsewhere.[24] Finally, the time step chosen is the minimum of all the time steps calculated, i.e., after consideration of each radical−cylinder distance and each radical−radical distance.

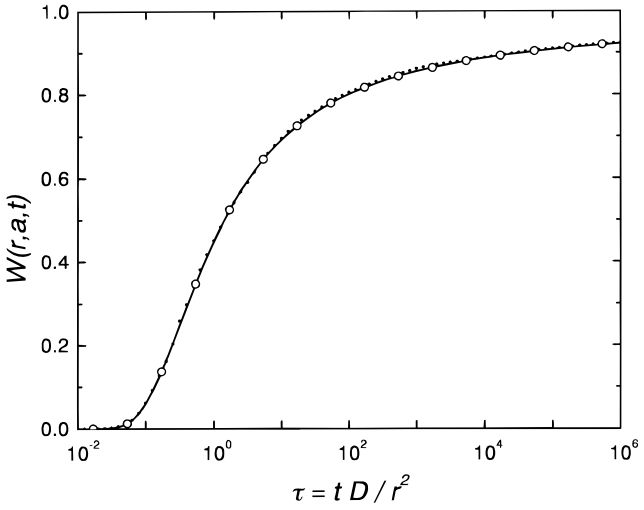

Figure 1. Diffusion-controlled reaction probability of a particle with an infinite cylinder. The solid line is the analytic solution, eq 2, the dotted line is the prediction of the IRT model, and the open points are the results of random flights simulation. $D = 2.8 \times 10^{-9}$ m^2 s^{-1}, $r =$ 2.28 nm, and $a_{\text{cylinder}} = 1.28$ nm.

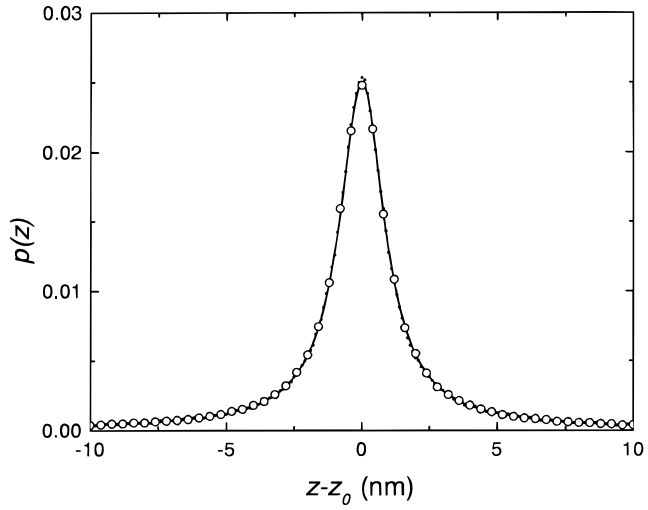

Figure 2. Probability density of the *z*-coordinate of the hits of a radical on a cylinder. Key as in Figure 1.

The simulation is followed, either until reaction is complete or until a preset cutoff time is reached. Each simulation provides very little information about the kinetics of interest, yielding simply a series of reactions, the times at which they occur, and the coordinates of the hits on the cylinder, which are modeled in the same way as for reaction with a plane surface.[16] The coordinates of the hits are recorded in cylindrical polar coordinates, with the *z*-axis along the axis of the cylindrical target. Thus the axial coordinate of the hit is the *z*-coordinate. Many independent realizations are necessary to obtain statistically significant results.

2.2. Tests of the Simulation Method. Since the modeling of reaction involves some approximation, it is necessary to test the simulation against a system whose exact solution is known within the diffusion approximation. Such tests have been reported for several other systems in the past.[20,22] In this case the appropriate system to test is that in which a single radical is generated at a fixed distance, *r*, from the axis of the cylinder. This problem reduces to two-dimensional diffusion with a circular absorbing boundary. The solution for the time-dependent survival probability has been known for many years in the theory of heat conduction[23]

$$W(r,a,t) = 1 - \frac{2}{\pi}\int_0^\infty \frac{Y_0(ur)J_0(ua) - J_0(ur)Y_0(ua)}{J_0^2(ua) + Y_0^2(ua)} \exp[-u^2\, Dt]\, \frac{\mathrm{d}u}{u} \quad (2)$$

where J_0 and Y_0 are Bessel functions.[28] Figure 1 shows comparisons of the time-dependent probability of reaction simulated by the random flights method together with the analytical solution calculated from eq 2. It can be seen that agreement is excellent.

It is also possible to calculate the density of the *z*-coordinate where the hit takes place. Diffusion in the *z*-direction is independent of diffusion in the *x*- and *y*- (or *r*- and θ-) directions. The time at which the hit takes place is determined entirely by the diffusion in the "sideways" *r*-coordinate. But during this time the *z*-coordinate is diffusing independently. Thus if the hit takes place at time *T*, the conditional density of the hit position is a normal distribution with mean equal to the initial *z*-coordinate, z_0, and variance *2DT*. To obtain the marginal density of the hit position, irrespective of the hitting time, it is necessary to convolute the normal distribution over the density of the hitting time, giving

$$p(z) = \frac{1}{\pi}\int_0^\infty \frac{Y_0(ur)J_0(ua) - J_0(ur)Y_0(ua)}{J_0^2(ua) + Y_0^2(ua)} \exp[-|z - z_0|u]\, \mathrm{d}u \quad (3)$$

A comparison is shown in Figure 2, from which it can be seen once again that the simulation is in excellent agreement with the analytical result. The mean hit position is zero, as expected, but all higher moments are infinite. This will now be demonstrated analytically.

Consider the variance of the hit position. If the probability density function of the first-passage time to the cylinder is denoted $w(r,a,t)$, the variance of the particle displacement in the *z*-direction at the hit time is

$$\sigma^2 = \int_\infty^{-\infty}\int_0^\infty w(r,a,t)\, z^2\, \frac{\exp[-z^2/4Dt]}{(4\pi Dt)^{1/2}}\, \mathrm{d}t\, \mathrm{d}z \quad (4)$$

After interchanging the order of the integration, this becomes

$$\sigma^2 = 2D\int_0^\infty t\, w(r,a,t)\, \mathrm{d}t \quad (5)$$

Since the expectation time to hit the cylinder is infinite, the variance of the hit position is also infinite.

The preceding result needs to be verified more carefully since the integrals are clearly not uniformly convergent. This may be done using the following artifice. A plane tangential to the cylinder and perpendicular to the initial particle position vector is constructed. The particle must pass through this plane before hitting the cylinder. The probability distribution of the *z*-coordinate of hits on the cylinder must therefore be wider than the distribution of hits on the plane. However, it is well-known that the *z*-coordinate of hits on the plane follows a Cauchy distribution[29]

$$p(z) = \frac{r}{\pi(r^2 + z^2)} \quad (6)$$

where *r* is the initial perpendicular distance of the particle from the plane. This distribution has a mean of zero and an infinite variance. Since the variance of hits on the cylinder may not

be smaller than this, it must also be infinite, verifying the conclusion above. Furthermore, the expectation of the absolute displacement in the *z*-direction must also be infinite for the same reason. It is therefore not sensible to use the simulated data to evaluate moments, either of the hit positions or of the distances between hit positions (apart from the mean). The values obtained will simply reflect the maximum cutoff time in the simulation.

3. The IRT Method

The IRT (independent reaction times) method is a fast simulation method based on the independent pairs approximation and has been described in detail elsewhere.[19] A random reaction time is generated for each reactive pair in the system, using the correct marginal probability density conditional on the initial separation of the pair. The first reaction takes place at the smallest time generated, the second reaction occurs at the smallest time generated for the pairs of particles surviving the first reaction, and the procedure continues until reaction is complete or until all remaining times are greater than the predetermined cutoff time.

The IRT method cannot be implemented unless random encounter times can be generated from the appropriate probability density. For reactions between spherical radicals the cumulative probability distribution is

$$W(r,a,t) = \frac{a}{r}\,\mathrm{erfc}\left(\frac{r-a}{\sqrt{4D't}}\right) \tag{7}$$

where r is the initial separation, a the encounter distance, and D' the relative diffusion coefficient. The random times are generated from this nonuniform distribution by the inversion method,[30] using the inverse error function algorithm given in Abramowitz and Stegun.[28]

For reaction between a radical and a cylinder the appropriate probability distribution is given in eq 2. Note that a separate probability distribution is needed for every different value of r. In the absence of a simple method of inverting this function, a numerical method was used similar to that described previously for modeling ionic reactions.[22] A grid of percentiles of W for various values of r/a was set up numerically. When a particular set of parameters is required, the table is interpolated to find percentiles of W for those parameters. A random number is then generated and the numerically generated, inverse function of W is interpolated to find the time at which W attains the value given by the random number generated.

The IRT method also has to be modified to enable the generation of hit positions on the cylinder. If the hit takes place at time T and the initial z-coordinate of the particle is z_0, then the probability density of the hit position is

$$p(z|T) = \frac{\exp[-(z-z_0)^2/4DT]}{(4\pi DT)^{1/2}} \tag{8}$$

It is not necessary to simulate using the more complex marginal density of the hit position, eq 3, because in the IRT method it is only necessary to generate hit positions when hits occur, so the hitting time is already known. The required density is that of the hit position conditional on the known hitting time.

3.1. Tests of the IRT Method. Since a numerical interpolation is used to generate the reaction times for the IRT simulation, it is necessary to test the numerical accuracy of the simulations against the exactly known solutions for the kinetics and the spatial distribution of hit positions. The same analytical solutions are used here as for the random flight simulations in section 2. Comparisons are included in Figures 1 and 2, from which it may be concluded that the method used for generating reaction times is accurate and can be applied to systems where there is competition between spur recombination and scavenging by the cylinder.

4. The Stochastic Master Equation

The IRT method described above simulates a stochastic process, which can be analyzed using a master equation. A general method for formulating a master equation model of nonhomogeneous radiation-chemical kinetics has already been presented.[20] This approach can be applied easily to the system under consideration, in which geminate recombination competes with scavenging by the cylinder.

The random variables of interest in the master equation are the numbers and types of particles surviving as a function of time: experiments essentially measure expectations of these numbers. A state space is therefore defined consisting of all possible sets of particles remaining. For the system of interest these states can be itemized as follows:

State 11: both particle A and B remain, no reaction has occurred yet.

State 10: only particle A remains, particle B has reacted with the cylinder.

State 01: only particle B remains, particle A has reacted with the cylinder.

State 00: neither particle remains as they have either recombined or reacted with the cylinder.

At any given time, the system is characterized by a probability distribution, which assigns a probability to each of these states. The master equation is an equation of motion for the probability distribution; it consists of a set of coupled linear rate equations that describe the rates of transition between the states listed above

$$\frac{\mathrm{d}P_{11}}{\mathrm{d}t} = -\lambda_{\mathrm{AB}}(t)P_{11}(t) - \lambda_{\mathrm{AC}}(t)P_{11}(t) - \lambda_{\mathrm{BC}}(t)P_{11}(t) \tag{9}$$

$$\frac{\mathrm{d}P_{10}}{\mathrm{d}t} = \lambda_{\mathrm{BC}}(t)P_{11}(t) - \lambda_{\mathrm{AC}}(t)P_{10}(t) \tag{10}$$

$$\frac{\mathrm{d}P_{01}}{\mathrm{d}t} = \lambda_{\mathrm{AC}}(t)P_{11}(t) - \lambda_{\mathrm{BC}}(t)P_{01}(t) \tag{11}$$

$$\frac{\mathrm{d}P_{00}}{\mathrm{d}t} = \lambda_{\mathrm{AB}}(t)P_{11}(t) + \lambda_{\mathrm{AC}}(t)P_{10}(t) + \lambda_{\mathrm{BC}}(t)P_{01}(t) \tag{12}$$

where $\lambda_{\mathrm{AB}}(t)$, $\lambda_{\mathrm{AC}}(t)$, and $\lambda_{\mathrm{BC}}(t)$ are time-dependent rate coefficients for the recombination reaction and the two reactions with the cylinder, respectively. It is only necessary to solve the first three of these equations since P_{00} is the complement of the sum of the other three probabilities.

The independent pairs approximation gives a prescription for the form of the time-dependent rate constant $\lambda(t)$[15]

$$\lambda(t) = -\mathrm{d}(\ln \Omega(t))/\mathrm{d}t \tag{13}$$

where $\Omega(t)$ is the survival probability that would pertain for the pair in isolation, i.e., in the absence of the third particle. For a given initial configuration, this prescription for λ is equivalent to the use of $\Omega(t)$ to generate a random reaction time for the pair in the IRT method. The kinetics predicted by the master equation should therefore be identical with those simulated by the IRT method. For the geminate recombination,

$\lambda_{AB}(t)$ is obtained by differentiating eq 7, and the rate constants for the cylinder reaction are obtained by differentiating eq 2.

4.1. Spatial Distribution. The master equation formulation described above can be modified to include the density of hit positions on the cylinder. As before, only the *z*-coordinates of the hits are considered. The state of the system is now specified, not only by the numbers and types of each particle remaining, but also by the *z*-coordinates of any hits that have taken place. For example, $P_{10}(z_B)$ denotes the probability density that the A particle remains and that the B particle hit the cylinder at position z_B. Similarly, $P_{00}(z_A,z_B)$ denotes the joint probability density that both particles have hit the cylinder at positions z_A and z_B.

In the independent pairs approximation, the *z*-coordinate of a hit of particle A on the cylinder at time *t* will have a Gaussian spatial density centered on the initial *z*-coordinate of particle A and with variance $2D_At$. This normalized Gaussian density will be denoted $g_A(z_A,t)$, and similarly for $g_B(z_B,t)$.

With these extensions the master equation becomes

$$\frac{dP_{11}}{dt} = -\lambda_{AB}(t)P_{11}(t) - \lambda_{AC}(t)P_{11}(t) - \lambda_{BC}(t)P_{11}(t) \quad (14)$$

$$\frac{dP_{10}(z_B,t)}{dt} = \lambda_{BC}(t)P_{11}(t)g_B(z_B,t) - \lambda_{AC}(t)P_{10}(z_B,t) \quad (15)$$

$$\frac{dP_{01}(z_A,t)}{dt} = \lambda_{AC}(t)P_{11}(t)g_A(z_A,t) - \lambda_{BC}(t)P_{01}(z_A,t) \quad (16)$$

$$\frac{dP_{00}(z_A,z_B,t)}{dt} = \lambda_{AC}(t)P_{10}(z_B,t)g_A(z_A,t) + \lambda_{BC}(t)P_{01}(z_A,t)g_B(z_B,t) \quad (17)$$

Although these functions contain all the necessary information about the spatial distribution of the hits, they are in an inconvenient form for numerical solution. $P_{00}(z_A,z_B,t)$ is a function of two spatial variables, and following spatial discretization, the numerical solution of the resulting set of differential equations is likely to be prohibitive because of the large number of differential equations to be solved. Three simpler functions are therefore considered: the marginal densities of A and B hits, $p_A(z_A,t)$ and $p_B(z_B,t)$, respectively, and the density of the distance between the two hits, $p(z,t)$, where z is defined as $z_B - z_A$. These functions can be defined in terms of those above by

$$p_A(z_A,t) = P_{01}(z_A,t) + \int_{-\infty}^{\infty} P_{00}(z_A,z_B,t)\, dz_B \quad (18)$$

$$p_B(z_B,t) = P_{10}(z_B,t) + \int_{-\infty}^{\infty} P_{00}(z_A,z_B,t)\, dz_A \quad (19)$$

$$p(z,t) = \int_{-\infty}^{\infty} P_{00}(z_A,z+z_A,t)\, dz_A \quad (20)$$

and they obey the following equations of motion:

$$\frac{\partial p_A(z_A,t)}{\partial t} = \lambda_{AC}(t)P_{11}(t) + \lambda_{AC}(t)P_{10}(t)g_A(z_A,t) \quad (21)$$

$$\frac{\partial p_B(z_B,t)}{\partial t} = \lambda_{BC}(t)P_{11}(t) + \lambda_{BC}(t)P_{01}(t)g_B(z_B,t) \quad (22)$$

$$\frac{\partial p(z,t)}{\partial t} = \lambda_{AC}(t)\int_{-\infty}^{\infty} P_{10}(z_B,t)g_A(z_B-z,t)\, dz_B + \lambda_{BC}(t)\int_{-\infty}^{\infty} P_{01}(z_A,t)g_B(z_A-z,t)\, dz_A \quad (23)$$

Discrete versions of eqs 14−16 and 21−23 are therefore integrated.

4.2. Test of Master Equation. The master equation was formulated and run with a simplified system, containing only one radical and the cylinder, to test the time-dependent rate coefficient for cylinder hits, which has to be obtained numerically from eq 13 following the differentiation of eq 2. As expected, results for both the kinetics and the spatial distribution of hits are indistinguishable from those obtained by IRT simulation, since the master equation is the formal description of the random process simulated by the IRT method.

5. Results

The calculations reported in this section apply the methods described above to the competition between recombination of a geminate pair of identical radicals and scavenging of those particles by reaction with a cylinder. The two radicals are labeled A and B for convenience. The geminate reaction distance for the pair, $a_{geminate}$, is 0.26 nm, the encounter surface for either particle with the cylinder, $a_{cylinder}$, is 1.28 nm (measured from the axis of the cylinder), and the diffusion coefficient for each particle is 2.8×10^{-9} m^2 s^{-1}. (These parameters are appropriate for the hydroxyl radical and the DNA molecule and are used because the OH radical is believed to be a significant cause of radiation-induced DNA damage.[9,10])

The kinetics of the competition between geminate recombination and scavenging by the cylinder are examined in Figure 3. The three configurations considered differ only in the distance between the surface of the cylinder and the center of the geminate pair (i.e., the midpoint between the radicals), $r' =$ 0.5, 1.0, and 3.0 nm. In each simulation, the initial coordinates of the two particles relative to the center of the pair were obtained by sampling from independent, identical, spherical Gaussian distributions, scaled to give a mean interparticle distance of 0.5 nm. The kinetics of the geminate reaction and of the encounters between the particles and the cylinder are qualitatively different, even when the geminate pair is close to the cylinder. The geminate reaction takes place on a significantly shorter time scale than the scavenging of the particles by the cylinder. This difference is obvious at the largest cylinder-pair separation considered, $r' = 3.0$ nm, where there are two distinct components to the decay kinetics. For all initial distances, the long-time asymptotics of the geminate reaction and the (cylinder) scavenging reaction are qualitatively different. The survival probability of a geminate pair diffusing in three dimensions has an asymptotic time dependence of $t^{-1/2}$, while the scavenging by the cylinder has an asymptotic time dependence of $1/\ln(t)$, as the relative diffusion is effectively in two dimensions. Furthermore, there is a nonzero probability that a geminate pair will escape recombination for all time, but the ultimate reaction of a radical with the cylinder is certain.

For each separation considered in Figure 3, the agreement between the results of the IRT and random flights simulations is good, although there are some minor discrepancies in the predictions for the yields of the two different reactions when the scavenging competes effectively with recombination. Under these conditions, where the interparticle distance and r' are comparable, the IRT model slightly underestimates the yield of geminate reaction and overestimates that of particle−cylinder reactions. There is no apparent difference in the decay kinetics predicted for the geminate pair by the two simulation methods as the errors in the yield of the geminate and the scavenging reactions approximately cancel one another. As the separation between the surface of the cylinder and the center of gravity of

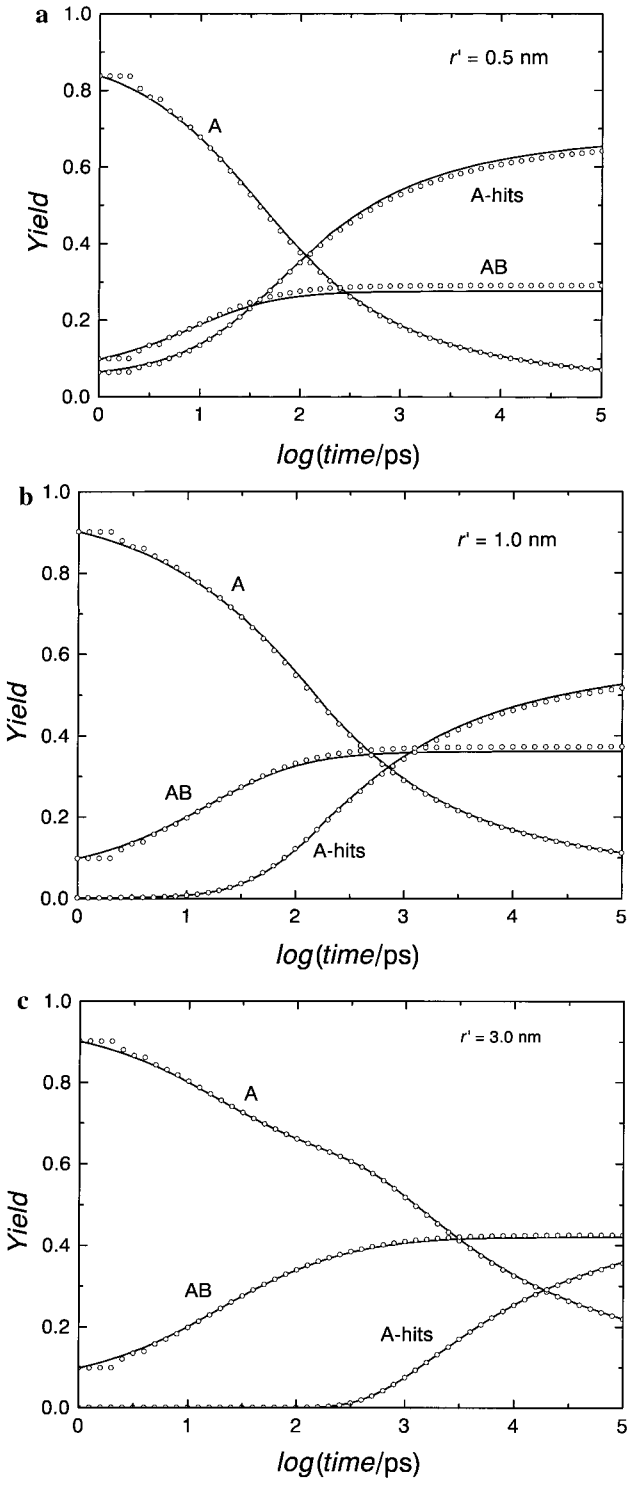

Figure 3. Competition kinetics between geminate recombination and reaction with a cylinder. The lines are the predictions of the IRT model, and the points are the results of random flights simulation. The particle coordinates were sampled from Gaussian distributions of $\sigma = 0.31$ nm, centered at a distance $r'$from the surface of the cylinder. $D_A = D_B = 2.8 \times 10^{-9}$ m^{2}s^{-1}, $r' = 1.0$ nm, $a_{\text{geminate}} = 0.26$ nm, and $a_{\text{cylinder}} = 1.28$ nm. (a) $r' = 0.5$ nm, (b) $r' = 1.0$ nm, (c) $r' = 3.0$ nm.

the geminate pair is increased, the differences decrease, so that when $r' = 3.0$ nm, the kinetics given by the random flights simulation and by the IRT model are indistinguishable.

The distributions of the positions of the A and B particle hits on the cylinder for a pair with center 1.0 nm from the surface of the cylinder (cf. Figure 3b) are presented in Figure 4, and appear to be identical. These distributions are centered on the

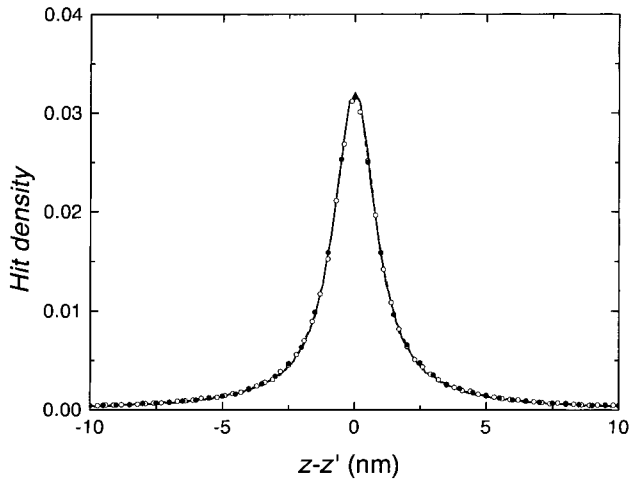

Figure 4. Density of A and of B hit positions on the cylinder in competition with geminate recombination. The lines are the predictions of the IRT model, and the points are the results of random flights simulation. The filled points and solid line refer to particle A, and the open points and the dashed line (masked by the solid line) refer to particle B. The particle coordinates were sampled from Gaussian distributions of $\sigma = 0.31$ nm centered at a distance $r' = 1.0$ nm from the surface of the cylinder. $D_A = D_B = 2.8 \times 10^{-9}$ m^{2}s^{-1}, $a_{\text{geminate}} = 0.26$ nm, and $a_{\text{cylinder}} = 1.28$ nm.

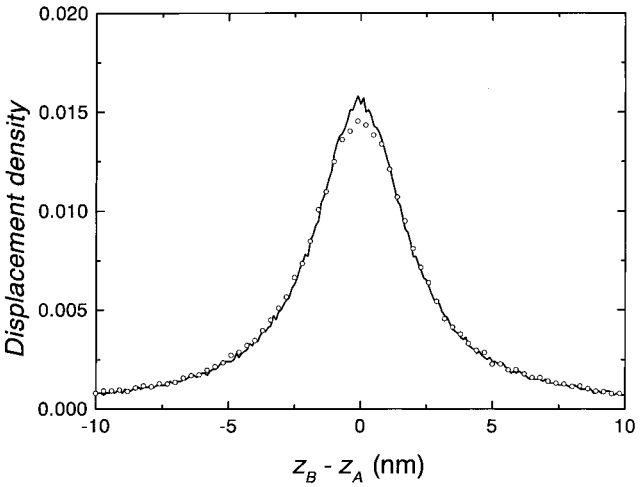

Figure 5. Density of the interhit distance in the competition between geminate recombination and reaction with a cylinder. The line is the prediction of the IRT model, and the points are the results of random flights simulation. The particle coordinates were sampled from Gaussian distributions of $\sigma = 0.31$ nm centered at a distance $r' = 1.0$ nm from the surface of the cylinder. $D_A = D_B = 2.8 \times 10^{-9}$ m^{2}s^{-1}, $a_{\text{geminate}} = 0.26$ nm, and $a_{\text{cylinder}} = 1.28$ nm.

z-coordinate of the pair center, $z' = 0$. Figure 5 shows the distribution of the relative displacement of the hits, $z_B - z_A$, for the same system. While the distributions of the hit positions of the A and B particles obtained using the two simulation methods appear to be equivalent, there is a discrepancy in the distribution of the interhit distance. The IRT model gives a narrower distribution than the random flights simulation, overestimating the number of small interhit displacements and underestimating the number of large interhit displacements. For these Gaussian pairs, the differences are not great, for example, the median absolute interhit distance predicted by random flights simulation is 2.1 nm, while the IRT model gives a median of 2.0 nm.

As clustered damage to biologically significant macromolecules such as DNA may arise from correlated hits of radicals originating from the same spur, any discrepancy between the

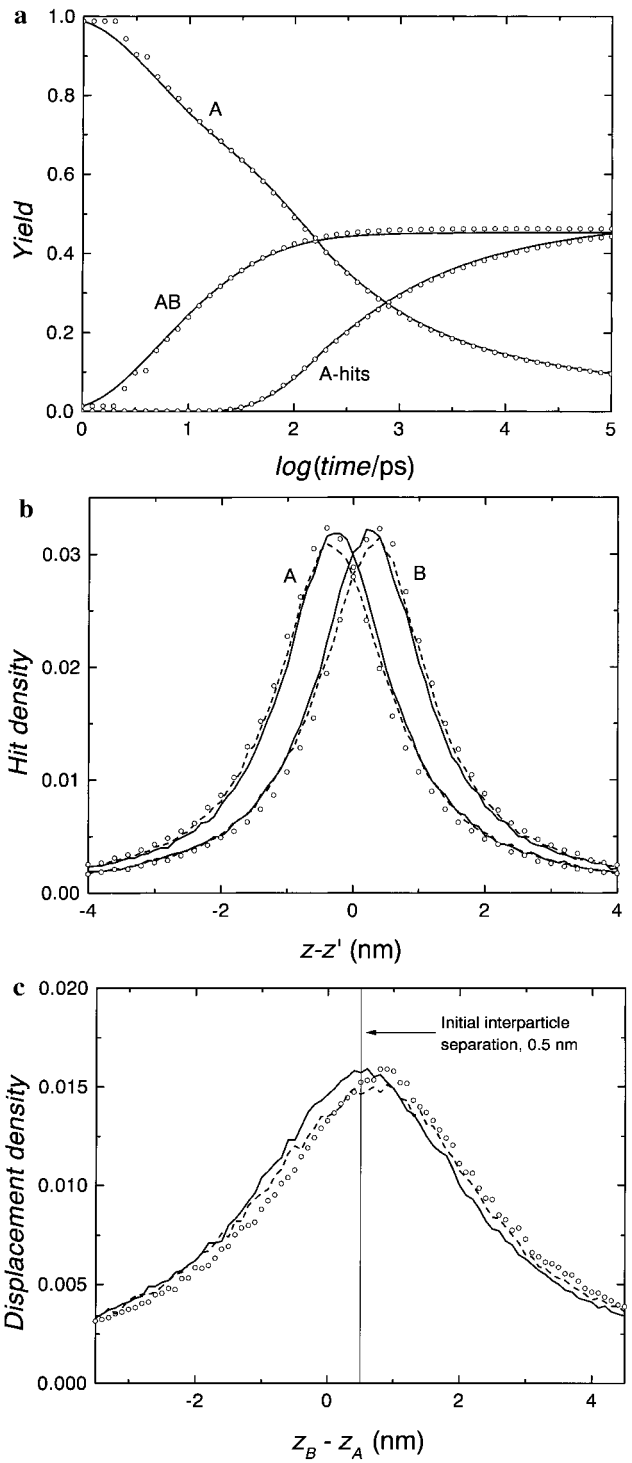

Figure 6. Effect of orientation angle θ on competition between geminate recombination and reaction with a cylinder, $\theta = 0$. The solid lines are the predictions of the IRT model, and the open points are the results of random flights simulation. The dashed line denotes the predictions of the modified IRT model. The center of the pair was a distance $r' = 1.0$ nm from the surface of the cylinder, and the interparticle distance was 0.5 nm. $D_A = D_B = 2.8 \times 10^{-9}$ m^{2}s^{-1}, $a_{\text{geminate}} = 0.26$ nm, and $a_{\text{cylinder}} = 1.28$ nm. (a) Kinetics, (b) density of A and B hit positions, (c) density of interhit displacement.

IRT and random flights methods warrants further examination. This has been achieved by using fixed configurations rather than random distributions for the initial state of the pair. The effect of the orientation of the initial interparticle vector with respect to the axis of the cylinder is considered in Figures 6 and 7. In both sets of calculations, the initial separation of the pair was

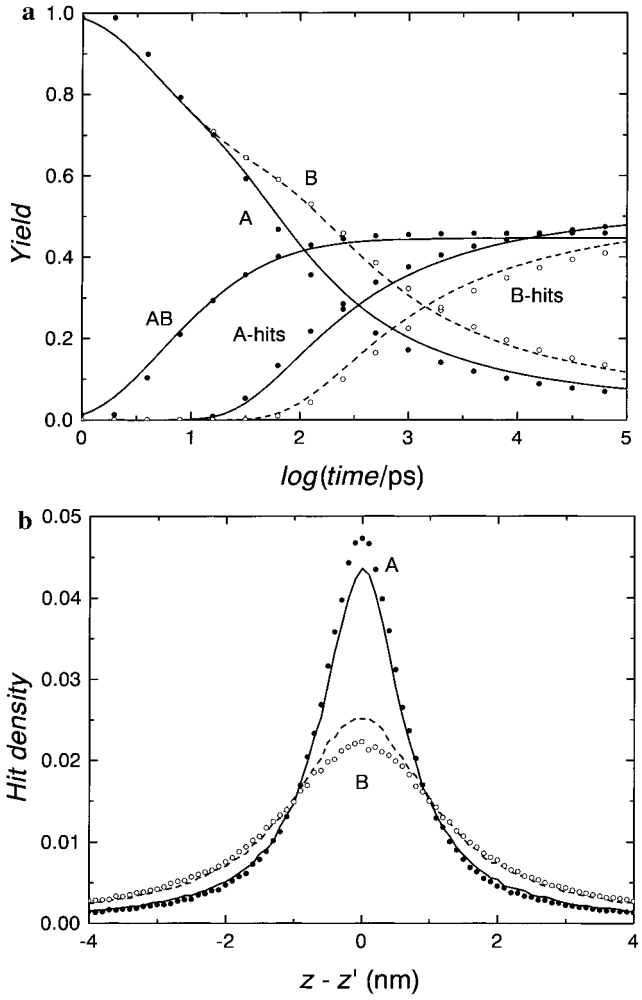

Figure 7. Effect of orientation angle θ on competition between geminate recombination and reaction with a cylinder, $\theta = \pi/2$. The lines are the predictions of the IRT model and the points are the results of random flights simulation. The filled points and solid line refer to particle A, and the open points and the dashed line refer to particle B. The center of the pair was a distance $r' = 1.0$ nm from the surface of the cylinder, and the interparticle distance was 0.5 nm. $D_A = D_B = 2.8 \times 10^{-9}$ m^{2}s^{-1}, $a_{\text{geminate}} = 0.26$ nm, and $a_{\text{cylinder}} = 1.28$ nm. (a) Kinetics, (b) density of A and B hit positions.

0.5 nm and the pair was centered 1.0 nm from the surface of the cylinder. In Figure 6, the initial interparticle vector was parallel to the cylinder axis. As the two particles are initially equidistant from the cylinder, their kinetics are indistinguishable and the distributions of the A hits and the B hits are mirror images about the z-coordinate of the pair center, z'. For this parallel configuration, the kinetics predicted by the IRT model and by random flights simulation are in good agreement. However, there is a significant discrepancy in the distributions of the hit positions. The difference is quite significant: in the IRT simulation the most probable interhit displacement is necessarily 0.5 nm, but in the random flights simulation it is 0.85 nm.

Figure 7 examines the reactions of a geminate pair whose interparticle vector is perpendicular to the cylinder axis in a radial direction, with the A particle closer to the cylinder than the B particle. As before, the initial separation of the pair is 0.5 nm and the pair is centered 1.0 nm from the cylinder. At short times the decay kinetics of the two radicals are similar, as they are dominated by geminate reaction. As time proceeds, the scavenging of A by the cylinder takes place more rapidly than that of B, with the result that the hit distributions for A

and B are very different. Both are centered about z', the initial z-coordinate of the pair, but the distribution for B is broader than that for A, reflecting its greater initial separation from the cylinder.

Comparison of the results of the IRT model with those from random flights simulations for the radially perpendicular configuration, presented in Figure 7, shows small discrepancies, both in the time-dependent kinetics and in the distributions for the positions of the particle−cylinder hits. (In Figure 6, when the pair was parallel to the cylinder, the discrepancy in the kinetics was much smaller.) The IRT kinetics are too slow for the A + cylinder reaction and too fast for B. The error seems to reside in the scavenging kinetics, since recombination is modeled accurately. The IRT hit distributions show corresponding discrepancies: the distribution of A + cylinder hits is too broad, and that for B is too narrow. The distribution of the interhit distance predicted by the IRT model is shifted to smaller separations, as was observed for the parallel configuration considered in Figure 6.

5.1. Discussion. The preceding results show that the IRT method tends to underestimate the distance between the two hits on the cylinder. This underestimate is most marked for the initial configuration in which the initial interparticle vector is parallel to the cylinder axis. There is also a discrepancy in the kinetics of radical attack on the cylinder, which is most marked when the pair is initially arranged in a radial direction relative to the cylinder. In this case, the particle that starts closer to the cylinder hits more rapidly than predicted by the IRT method and the other particle hits more slowly.

The observed phenomenon is believed to be a three-body correlation effect, similar to, but less pronounced than, that found for reaction with a plane surface.[16] The trajectories of the radical pair can be divided into two classes: (i) those which encounter one another and end in recombination, and (ii) those which do not recombine, but where the two radicals are intercepted by the cylinder. The former class consists of those trajectories where the radicals tend to diffuse toward one another, whereas in the latter class the particles tend to diffuse apart. When examining the distribution of hit positions only trajectories belonging to the latter class are considered. The limitation to one class of trajectories induces an apparent repulsion between the radicals and is the fundamental reason the hits are further apart than expected when the radical pair is initially parallel to the cylinder. This effect also accounts for the observed discrepancies in the kinetics for the perpendicular configuration.

6. A Modified IRT Method

The preceding interpretation can be justified by an approximate analysis of the "conditioning" effect, which has been incorporated into a modified IRT simulation method. The treatment is easiest for the parallel case and consists of finding the z-coordinates of the two particles at the time the first radical hits the cylinder. The strategy is for the simulation to proceed as normal until the first hit time T_1. At this time the interparticle distance, r, is generated at random from a probability distribution function conditional on the particles not encountering one another. The z-component of the interparticle vector is then found by generating, conditional on the value generated for r, a random orientation angle θ for the vector relative to the original orientation (parallel to the z-axis). The z-displacement is then $r \cos \theta$. This displacement is combined with the z-coordinate of the diffusive center of gravity to give the z-coordinates of the two particles at the instant of the first hit, T_1. The coordinate of the reacting particle is the hit position. The z-coordinate of the second hit (at T_2) is a normally distributed random variable of variance $2D(T_2 - T_1)$, centered on the z-coordinate generated for the particle at T_1.

6.1. Interparticle Separation. The pairs in which both particles hit the cylinder are those pairs that do not recombine. Consideration is therefore limited to those pairs that would never recombine in the absence of the cylinder. This class is more restrictive than the class of pairs that do not recombine *before* hitting the cylinder. However, Figure 3 shows that, unless the pair is initially close to the cylinder, the kinetics of recombination and scavenging take place on different time scales and so it is an acceptable approximation to restrict the trajectories in this way.

The probability density function of the interparticle separation, conditional on the pair never attaining the encounter radius a, can be calculated by standard techniques of probability theory.[31,32] According to Bayes' rule,[33] the probability density of the interparticle separation, conditional on the first-passage time to a being infinite and the initial particle separation being r_0, is

$$p(r,t|r_0;T_a = \infty) = p_a(r,t|r_0)\,\frac{P(T_a = \infty|r,t;r_0)}{P(T_a = \infty|r_0)} \qquad (24)$$

Here, $P(T_a = \infty|r,t;r_0)$ signifies the probability that an encounter at separation a will never occur if the pair separation is initially r_0, and the pair subsequently diffuses without reaction to r at time t. $p_a(r,t|r_0)$ is the probability density for transition from r_0 at time 0 to r at t without hitting a in between; i.e., p_a is the Green's function for the diffusion with a Smoluchowski (absorbing) boundary condition at a. Application of the Markov property[34] and the time homogeneity of the diffusion[35] gives

$$p(r,t|r_0;T_a = \infty) = p_a(r,t|r_0,0)\,\frac{P(T_a = \infty|r,0)}{P(T_a = \infty|r_0,0)} \qquad (25)$$

Substitution of well-known results[17] for the escape probability P and the density p_a yields the explicit form

$$p(r,t|r_0;T_a = \infty) = \frac{1}{\sqrt{4\pi D't}}\left(\frac{r-a}{r_0-a}\right)\left(\mathrm{e}^{-(r-r_0)^2/4D't} - \mathrm{e}^{-(r+r_0-2a)^2/4D't}\right) \qquad (26)$$

This is the transition density for a three-dimensional Bessel process (the radial part of three-dimensional Brownian motion) with the origin translated by a distance a. The origin shift keeps the process away from the encounter distance. The result above can also be derived by showing that the conditioned density obeys a normal three-dimensional radial diffusion equation with the origin shifted. The recipe for generating a random distance from this distribution is simple: generate three normally distributed random numbers with variance $2D't$, one (N_1) with mean $r_0 - a$ and the other two (N_2 and N_3) with mean zero. The resulting random variable

$$R = a + (N_1^2 + N_2^2 + N_3^2)^{1/2} \qquad (27)$$

has the correct probability distribution.

6.2. Orientation and Interparticle Vector. The preceding analysis gives the probability density function of the interparticle distance at any given time, including the time of the first hit on the cylinder. However, it does not give the z-coordinate of the first hit on the cylinder. To calculate this, the z-coordinates of the interparticle vector and of the diffusive center of gravity of the pair are required. The z-coordinate of the interparticle vector

can be obtained from the probability density of the orientation of the interparticle vector at the time of the hit conditional on the initial interparticle vector and the final interparticle distance, i.e.

$$p(\theta,\phi,t|r_0,0,0;r,t) = \frac{p(r,\theta,\phi,t|r_0,0,0)}{p(r,t|r_0)} \tag{28}$$

The numerator is the three-dimensional transition density in spherical polar coordinates for free diffusion from (r_0, 0, 0) to (r, θ, ϕ), and the denominator is the integral of this over the angular variables, representing the marginal transition density of the interparticle distance. Using the known Green's function for three-dimensional free diffusion gives the density

$$p(\theta,\phi,t|r_0,0,0;r,t) = \frac{rr_0 \sin\theta}{8\pi D't} \frac{\exp(rr_0 \cos\theta/2D't)}{\sinh(rr_0/2D't)} \tag{29}$$

where θ is the azimuth angle between the cylinder and the interparticle vector. This analysis is approximate since the densities should be constrained not to encounter before t. However, as the particles have already been repelled from each other by generating the separation distance from the conditioned distribution, eq 26, this approximation is not important. The angle ϕ is therefore uniformly distributed between 0 and 2π, and cos θ can be generated conveniently by the inversion method.[30] The z-coordinate of the interparticle vector is simply r cos θ.

6.3. Diffusive Center of Gravity. The interparticle vector is not sufficient to fix the absolute z-coordinates of the two particles at the time of the first hit. To do this, another linearly independent combination of the position vectors is needed. The most convenient combination is the diffusive center of gravity of the pair. This vector is statistically independent of the interparticle vector,[19,24] which means that it is unaffected by conditioning that the pair never encounter. If $\mathbf{R}_1$ and $\mathbf{R}_2$ are the two position vectors, the diffusive center of gravity is

$$\mathbf{S} = (D_2\mathbf{R_1} + D_1\mathbf{R_2})/D' \tag{30}$$

The displacement of the vector, $\mathbf{S}$, from its initial position at time T_1 follows a spherical normal distribution whose Cartesian components are independent normal random variables with mean zero and variance $2D_1D_2T_1/D'$. Once the z-component of the center of gravity is generated in this way, it can be combined with the z-component of the interparticle vector to regain the z-coordinates of the individual particle position vectors.

The effect of the modification to the IRT program described in this section is shown in the results that are included in Figure 6. The probability distribution function for the interhit distance is accurately modeled, but there are still small errors in the distributions for the positions of the hits predicted by the modified IRT model. The remaining differences between the distributions for the hit positions reflect an error in the positioning of the first particle−cylinder reaction in the IRT model and the modification reported correctly accounts for the effects of the three body correlation on the interhit distance.

7. Summary

The competition between geminate recombination and the reaction of the particles with a cylindrical macromolecule has been examined using random flights and IRT Monte Carlo simulations. The IRT model was reformulated to include reactions with a cylindrical macromolecule, and a methodology was developed for estimating the locations of the reactions on the molecule. The agreement between the kinetic predictions of the two simulation techniques is good. There is no discrepancy in the modeled decay kinetics; however, there is a small underestimate in the ratio of the geminate reaction to the macromolecule reaction when the separations between the geminate pair and the distance between the pair center and the surface of the cylinder are similar. This discrepancy is much smaller than that found for reaction with a plane surface.

A more significant, but still minor, discrepancy is found in the distribution of the interhit distance predicted by the IRT model. The distribution given by the IRT model is shifted to smaller distances than that obtained from random flights simulation. The differences between the results of the IRT and random flights techniques arise from a three-body correlation effect, and a modification to the IRT model is presented to correct for this effect. The recognition of a three-body effect is of considerable importance, as the correlated reaction of reactive particles from the same spur with a macromolecule is believed to be a major cause of radiation-induced damage to biological systems.

Acknowledgment. The work described herein was supported by the EPSRC (C.E.B.), British Nuclear Fuels Ltd. (R.H.), and the Office of Basic Energy Sciences of the U.S. Department of Energy (S.M.P.). This is Contribution NDRL-3649 from the Notre Dame Radiation Laboratory.

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