

Random sampling of the Green's Functions for reversible reactions with an intermediate state



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ABSTRACT

Exact random variate generators were developed to sample Green's functions used in Brownian Dynamics (BD) algorithms for the simulations of chemical systems. These algorithms, which use less than a kilobyte of memory, provide a useful alternative to the table look-up method that has been used in similar work. The cases that are studied with this approach are (1) diffusion-influenced reactions; (2) reversible diffusion-influenced reactions and (3) reactions with an intermediate state such as enzymatic catalysis. The results are validated by comparison with those obtained by the Independent Reaction Times (IRT) method. This work is part of our effort in developing models to understand the role of radiation chemistry in the radiation effects on human body and may eventually be included in event-based models of space radiation risk.

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1. Introduction

Simulations based on the Green's functions of the diffusion equation (DE) have been used for years to study chemical reactions in solutions [1–10]. More recently, this approach has been used in radiation chemistry codes to simulate the radiolysis of water and aqueous solutions [11,12], chemical dosimeters [13] and to study of interaction of ligand molecules with receptors [14]. The purpose of this work is to propose and validate a sampling algorithm of the Green's function of the diffusion equation (DE), which is used to simulate chemistry in non-homogeneous systems. The algorithm is exact for 2-particles systems and requires less than 0.15 kB of memory. The cases that are studied with this approach are (1) diffusion-influenced reactions; (2) reversible diffusion-influenced reactions and (3) reactions with an intermediate state such as enzymatic catalysis. The results are compared with those obtained with the independent reaction times (IRT) method. The performance of the algorithm was compared to table look-up methods which are commonly used for this kind of simulations. This algorithm will eventually be used in Brownian Dynamics codes to simulate the radiation chemistry of the radiolytic species (such as the free radical $\cdot\text{OH}$) created by the interaction of ionizing radiation with water and study DNA damage by the indirect effect.

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2. Use of the diffusion equation in chemistry

2.1. Modeling of chemical reactions

The approach presented in this paper has been used to study complex problems such as reversible reactions with an intermediate state, which may be represented as follows [7]:



where k_a is the association rate constant, k_d is the complex dissociation rate constant and k_e is the products formation rate constant. The units of k_a are $[\text{length}]^3[\text{time}]^{-1}$, and the units of k_d and k_e are $[\text{time}]^{-1}$. As it is well known [8–9,15], the probability distribution of the separation vector between two particles is a Green's function of the DE. Therefore, the DE for a three-dimensional system with spherical symmetry is widely used to study chemical reactions of particles in solution [10]. This equation is [16]:

$$\frac{\partial p(r, t|r_0)}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left[r^2 \frac{\partial}{\partial r} p(r, t|r_0) \right], \quad r > R, \quad r_0 > R \quad (2)$$

where R is the reaction radius, D is the sum of the diffusion coefficients of the particles, and r_0 and r are the inter-particles distances at times 0 and t . The initial condition is [9]:

$$4\pi r_0^2 p(r, t|r_0) = \delta(r - r_0), \quad (3)$$

where δ is the Dirac's delta function. The boundary condition of this system at $r = R$ is [7,9]:

$$4\pi R^2 D \frac{\partial p(r, t|r_0)}{\partial r} \Big|_{r=R} = k_a p(R, t|r_0) - k_d p(*, t|r_0), \quad (4)$$

where $p(*, t|r_0)$ is the probability of the pair to be found in the reversibly bound state (*). The time evolution of the pair in the reversibly bound state is given by

$$\frac{dp(*, t|r_0)}{dt} = k_a p(R, t|r_0) - (k_d + k_e) p(*, t|r_0). \quad (5)$$

The time evolution of the product state (**) is given by

$$\frac{dp(**, t|r_0)}{dt} = k_e p(*, t|r_0). \quad (6)$$

2.2. Green's functions

The solution of the DE for the system described in the previous section (Green's function) is $p(r, t|r_0)$. It is useful at this point to introduce the functions $\text{Erfc}(x)$, $W(x, y)$ and $\Omega(x)$ ¹:

$$\text{Erfc}(x) \equiv \frac{2}{\sqrt{\pi}} \int_x^\infty e^{-\xi^2} d\xi, \quad (7a)$$

$$W(x, y) \equiv \exp(2xy + y^2) \text{Erfc}(x + y), \quad (7b)$$

$$\Omega(x) \equiv \exp(x^2) \text{Erfc}(x). \quad (7c)$$

The expression of $p(r, t|r_0)$ and related functions are quite long. To simplify them, we define the variables $\rho_r = (r - R)/\sqrt{4Dt}$, $\rho_0 = (r_0 - R)/\sqrt{4Dt}$, $\alpha' = \alpha\sqrt{Dt}$, $\beta' = \beta\sqrt{Dt}$ and $\gamma' = \gamma\sqrt{Dt}$.

The Green's function (also called "Brownian propagator") is given by [7]:

$$4\pi r r_0 p(r, t|r_0) = \frac{1}{\sqrt{4\pi Dt}} \{ \exp[-(\rho_r - \rho_0)^2] + \exp[-(\rho_r + \rho_0)^2] \} + \frac{\alpha(\beta + \alpha)(\gamma + \alpha)}{(\beta - \alpha)(\gamma - \alpha)} W(\rho_r + \rho_0, -\alpha') \\ + \frac{\beta(\gamma + \beta)(\alpha + \beta)}{(\gamma - \beta)(\alpha - \beta)} W(\rho_r + \rho_0, -\beta') + \frac{\gamma(\alpha + \gamma)(\beta + \gamma)}{(\alpha - \gamma)(\beta - \gamma)} W(\rho_r + \rho_0, -\gamma') \quad (8)$$

where α , β and γ are the roots of a 3rd order polynomial. The coefficients of this polynomial are linked to the reaction rate constants as follows:

$$\alpha + \beta + \gamma = -(1 + k_a/k_D)/R, \quad (9a)$$

¹ The arguments of these functions may be complex numbers. For complex arguments, the implementation of the Faddeeva function given in Ref. [17] is used.

$$\alpha\beta + \beta\gamma + \gamma\alpha = (k_e + k_d)/D, \quad (9b)$$

$$\alpha\beta\gamma = -[(1 + k_a/k_D)k_e + k_d]/DR, \quad (9c)$$

and $k_D = 4\pi RD$. Since $R > 0$, $D > 0$ and the rate constant are all real and ≥ 0 , at least one of the root (which will be α through this text) is real and negative. The roots β and γ are either real or complex conjugates.

The survival probability of a pair of particles $Q(t|r_0)$ is calculated by integrating $p(r, t|r_0)$ over the space outside the reaction radius R . This calculation yields:

$$\begin{aligned} Q(t|r_0) &= \int_R^\infty 4\pi r^2 p(r, t|r_0) dr \\ &= 1 + \frac{(R\alpha + 1)(\beta + \alpha)(\gamma + \alpha)}{r_0\alpha(\beta - \alpha)(\gamma - \alpha)} W(\rho_0, -\alpha') + \frac{(R\beta + 1)(\gamma + \beta)(\alpha + \beta)}{r_0\beta(\gamma - \beta)(\alpha - \beta)} W(\rho_0, -\beta') \\ &\quad + \frac{(R\gamma + 1)(\alpha + \gamma)(\beta + \gamma)}{r_0\gamma(\alpha - \gamma)(\beta - \gamma)} W(\rho_0, -\gamma') - \left(\frac{1}{r_0}\right) \left(\frac{\alpha\beta + \beta\gamma + \gamma\alpha}{\alpha\beta\gamma} + R\right) \text{Erfc}(\rho_0) \end{aligned} \quad (10)$$

For the simulations, the Green's function for the dissociation of a reversibly bound particle $p(r, t|*)$ and the probabilities of transitions $p(*, t|r_0)$, $p(**, t|r_0)$, $Q(t|*)$, $p(*, t|*)$ and $p(**, t|*)$ are also needed. They are given in [Appendix A](#).

These functions comprise several divisions by the roots and/or differences of the roots, which may lead to computational issues. The cases to consider are (1) $\alpha \neq \beta \neq 0$, $\gamma = 0$; (2) $\alpha \neq 0$, $\beta = \gamma \neq 0$; (3) $\alpha \neq 0$, $\beta = \gamma = 0$ and (4) $\alpha = \beta = \gamma$. The functions take different forms, which are presented in the [supplementary material](#). However, they are rarely an issue since $R > 0$ implies that at least one of the roots is negative and different from 0. For diffusion-controlled reaction ($k_a > 0$, $k_d = k_e = 0$), $\beta = \gamma = 0$. The Green's function is much simpler in this case [6,18]:

$$4\pi r r_0 p(r, t|r_0) = \frac{1}{\sqrt{4\pi Dt}} \left\{ \exp\left[-\frac{(r - r_0)^2}{4Dt}\right] + \exp\left[-\frac{(r + r_0 - 2R)^2}{4Dt}\right] \right\} + \alpha W\left(\frac{r + r_0 - 2R}{\sqrt{4Dt}}, -\alpha\sqrt{Dt}\right), \quad r \geq R \quad (11)$$

where $\alpha = -(k_a + 4\pi RD)/(4\pi R^2 D)$. The survival probability of a pair of particles, $Q(t|r_0)$, is calculated by integrating $p(r, t|r_0)$ over space outside the reaction radius R :

$$Q(t|r_0) = \int_R^\infty 4\pi r^2 p(r, t|r_0) dr = 1 + \frac{R\alpha + 1}{r_0\alpha} \left[W\left(\frac{r_0 - R}{\sqrt{4Dt}}, -\alpha\sqrt{Dt}\right) - \text{Erfc}\left(\frac{r_0 - R}{\sqrt{4Dt}}\right) \right]. \quad (12)$$

2.3. Discretization of time

A simulation is usually done in several time steps. During the simulation, after each time step, the state of the pair of particle or the inter-particle distance changes. However, the number of pairs in the different states as well as the distribution of distances of the pair at the end of the simulation only depend on the sum of the time steps. In [Appendix B](#), we show that the Green's functions are in accordance with this. This property of the Green's function is quite useful for the following reason. The values of r are distributed as $p(r, \Delta t_1|r_0)$ after the first time step. These values of r become the values of r_0 for the next sampling. But we know that the values of r sampled after the next time step (Δt_2) will be distributed as $p(r, \Delta t_1 + \Delta t_2|r_0)$. Therefore, since the sampling algorithm in the second time step is used with different r_0 , the algorithm is verified simultaneously for a whole range of the parameter r_0 . The property further allows the verification of the algorithm for dissociation, since the distribution of r after two time steps comprises the contribution of the dissociated pairs of particles.

2.4. Simulations with the independent reaction times (IRT) method

A major problem encountered in radiation chemistry simulations is the calculation time. The main reason for this is that the number of possible interactions in a system comprising N particles is $N(N - 1)/2$. This large number of interactions often makes the problem intractable, even for systems comprising a relatively small number of particles. To overcome this problem, a method named independent reaction times (IRT) has been developed about 30 years ago [20–22], and has been widely used to calculate the radiolytic yields in aqueous solutions [23–26] and in chemical dosimeters [27,28]. This method is useful because it allows the calculation of radiolytic yields much faster than full step-by-step Brownian Dynamics simulations. However, the positions of the particles are not calculated as function of time; therefore, the extension of the IRT method to problems of interest to radiobiology such as DNA damage simulations may be difficult. In this work, the IRT method is used for comparison with the algorithm presented in this paper.

3. Methods

3.1. Sampling of the Green's function with a reflective boundary

To construct a Brownian Dynamics algorithm it is necessary to generate random variates² (corresponding to inter-particle distance) from the Brownian propagator. Before discussing the case of diffusion-influenced reactions, an algorithm is proposed to generate random variates from the Green's function for the distance between two non-reacting particles, i.e. $p(r, t|r_0)$ with $k_a = 0$, $k_d = 0$ and $k_e = 0$. The boundary condition for this system is $\partial p(r, t|r_0)/\partial r|_{r=R} = 0$ (the reflecting boundary condition); consequently, this particular Green's function will be noted $p_{ref}(r, t|r_0)$. As it will be seen, the algorithm which will be obtained can be modified easily to sample Brownian propagators used to simulate chemical reactions. The distribution to sample is

$$4\pi r^2 p_{ref}(r, t|r_0) = \frac{r}{r_0 \sqrt{4\pi Dt}} \left\{ \exp \left[-\frac{(r-r_0)^2}{4Dt} \right] + \exp \left[-\frac{(r+r_0-2R)^2}{4Dt} \right] - \frac{\sqrt{4\pi Dt}}{R} W \left(\frac{r+r_0-2R}{\sqrt{4Dt}}, \frac{\sqrt{Dt}}{R} \right) \right\}, \quad r \geq R. \quad (13)$$

This distribution is normalized, i.e.:

$$\int_R^\infty 4\pi r^2 p_{ref}(r, t|r_0) dr = 1. \quad (14)$$

The objective is to generate random variates X from $f(x) \equiv 4\pi x^2 p_{ref}(x, t|r_0)$. This probability distribution is univariate, with four parameters r_0 , R , D and t . As shown in the [supplementary material](#), $f(x)$ can be written as a two parameters distribution. However, to avoid introducing more variables, the algorithm is given here in its original form.

Since $W \geq 0$, it is clear that $f(x) \leq h(x)$, where

$$h(x) = \frac{x}{r_0 \sqrt{4\pi Dt}} \left\{ \exp \left[-\frac{(x-r_0)^2}{4Dt} \right] + \exp \left[-\frac{(x+r_0-2R)^2}{4Dt} \right] \right\}, \quad x \geq R. \quad (15)$$

Therefore, von Neumann's rejection method [29–31] can be used. The rejection method is a well-know general technique to generate random variates of a probability distribution $p(x)$, which does not require that the cumulative distribution function (the indefinite integral of $p(x)$) be computable. To use this technique, we assume that $p(x) \leq Cg(x)$, where C is a proportionality constant such as $C \geq 1$ and $g(x)$ is a probability distribution for which random variates X distributed as $g(x)$ can be easily generated. To obtain random variates distributed as $p(x)$, a uniformly distributed random number U between 0 and 1 and a random variate X distributed as $g(x)$ are generated. The value of X is accepted if the condition $UCg(X) \leq p(X)$ is verified; otherwise, a new set of U and X are generated until the condition is true. From a geometric perspective, points are generated in the 2D plane bounded by the curve $Cg(x)$ and the domain of $g(x)$; the points are accepted are those which fall under $p(x)$.

In the actual problem, since $f(x)$ is bounded from above by the first two terms (h), the third (negative) term is ignored at this moment. The function h can be written as the sum of four terms and truncated to the positive ranges by using:

$$h_1(r) = \frac{r-r_0}{r_0 \sqrt{4\pi Dt}} \exp \left[-\frac{(r-r_0)^2}{4Dt} \right] \times \mathbf{1}_{[r \geq r_0]}, \quad (16a)$$

$$h_2(r) = \frac{r+r_0-2R}{r_0 \sqrt{4\pi Dt}} \exp \left[-\frac{(r+r_0-2R)^2}{4Dt} \right] \times \mathbf{1}_{[r \geq R]}, \quad (16b)$$

$$h_3(r) = \frac{r_0}{r_0 \sqrt{4\pi Dt}} \exp \left[-\frac{(r-r_0)^2}{4Dt} \right] \times \mathbf{1}_{[r \geq R]}, \quad (16c)$$

$$h_4(r) = \frac{2R-r_0}{r_0 \sqrt{4\pi Dt}} \exp \left[-\frac{(r+r_0-2R)^2}{4Dt} \right] \times \mathbf{1}_{[r \geq R]} \times \mathbf{1}_{[r_0 \leq 2R]}, \quad (16d)$$

where $\mathbf{1}_{[\text{condition}]}$ takes the value 1 when the condition is true, and 0 when it is false. The conditions $r \geq r_0$ and $r_0 \leq 2R$ appended to $h_1(r)$ and $h_4(r)$ are used to truncate h to the positive ranges. This truncated function is defined as $h^*(r) \stackrel{\text{def}}{=} \sum_i h_i(r)$.

We will also need the function:

$$h'_3(r) = \frac{r_0}{r_0 \sqrt{4\pi Dt}} \exp \left[-\frac{(r-r_0)^2}{4Dt} \right] \times \mathbf{1}_{[r \leq R]}. \quad (17)$$

² The terminology given in the book of Devroye [29] regarding non-uniform random variate generation will be used here.

Thus, $f(r) \leq h^*(r)$. It is possible to generate a random variate with density proportional to h^* easily, since h^* is a mixture of known probability distribution functions. The weights of the contributions of h_1 , h_2 and $h_3 + h_4$ are obtained by integration:

$$p_1 = \int h_1(y) dy = \sqrt{\frac{Dt}{\pi r_0^2}}, \quad (18a)$$

$$p_2 = \int h_2(y) dy = \sqrt{\frac{Dt}{\pi r_0^2}} \exp \left[-\frac{(R - r_0)^2}{4Dt} \right], \quad (18b)$$

$$p' = \int (h_3(y) + h_4(y)) dy = \Phi \left(\frac{r_0 - R}{\sqrt{2Dt}} \right) + 1_{[r_0 \leq 2R]} \frac{2R - r_0}{r_0} \Phi \left(\frac{R - r_0}{\sqrt{2Dt}} \right). \quad (18c)$$

where $\Phi(x)$ is the normal distribution function:

$$\Phi(x\sqrt{2}) = 1 - \text{Erfc}(x)/2. \quad (19)$$

Generating a random variate X with density proportional to h^* is straightforward, since h_1 and h_2 are the Rayleigh and tail of Rayleigh distributions [29]. Therefore, the following algorithm (given in the form of a pseudo-code) can be used:

Algorithm 1a

Compute p_1 , p_2 and p' . Set $s = p_1 + p_2 + p'$.

Generate a uniform $[0, 1]$ random variate U

If $sU \in [0, p_1]$, then set $X \leftarrow r_0 + \sqrt{4DtE}$, where E is standard exponential.³

If $sU \in (p_1, p_1 + p_2]$, then set $X \leftarrow 2R - r_0 + \sqrt{(r_0 - R)^2 + 4DtE}$, where E is standard exponential.

If $sU \in (p_1 + p_2, s]$, then let X be a random variate with density proportional to $h_3 + h_4$.

Return X .

To generate a random variate with density proportional to $h_3 + h_4$, it is noted that $h_4(r) \leq h'_3(2R - r)$ for $r \geq R$. But $h_3 + h'_3$ is identical to the standard normal density with variance $2Dt$ centered at r_0 . Therefore, an algorithm based on the rejection method can be used to generate a random variate from $h_3 + h_4$:

Algorithm 1b

Repeat {

Generate N standard normal,⁴ U uniform on $[0, 1]$

Set $X \leftarrow r_0 + \sqrt{2Dt}N$.

} Until $X > R$, or jointly $X < R$, $r_0 < 2R$ and $U \leq (2R - r_0)/r_0$.

In the former case, return X .

In the latter case, return $2R - X$.

where Repeat { ... } Until is a conditional “Do” loop. Finally, to obtain a variate X distributed as $f(x)$, pairs (X, U) with X having density proportional to h^* and U uniform $[0, 1]$ are generated until $Uh^*(Y) \leq f(X)$. The expected number of iterations is $p_1 + p_2 + p'$. As it was implicitly shown, $p' \leq 1$ (Eq. (18c)), so the contribution from $h_3 + h_4$ is minor.

3.2. Sampling of the Green's function for diffusion-influenced reactions

The Green's function for diffusion-influenced reactions is similar to $p_{\text{ref}}(r, t|r_0)$. Because $k_a > 0$, $\alpha < 0$ and the Green's function is bounded from above by $p_{\text{ref}}(r, t|r_0)$. Therefore, **Algorithm 1** can be used, replacing $p_{\text{ref}}(r, t|r_0)$ by $p(r, t|r_0)$ given by Eq. 11 in $f(X)$ in the final rejection step.

3.3. Sampling of the Green's function for the general case

The Green's function for more complex systems such as those used for reactions with an intermediate state, considering the range of the parameters used, is also bounded from above by $p_{\text{ref}}(r, t|r_0)$. Therefore, **Algorithm 1** can also be used by replacing $p_{\text{ref}}(r, t|r_0)$ by $p(r, t|r_0)$ given by Eq. 8 in $f(X)$ in the final rejection step. However, in addition to sampling the propagator $p(r, t|r_0)$, the BD algorithm require sampling the Green's function for the dissociation of a bounded pair $p(r, t|*)$. This can be done by writing $p(r, t|*)$ in a form suitable for rejection sampling, i.e. with a Gaussian function in evidence:

³ A standard exponential random variate is distributed as $p(x) = \exp(-x)$, $x \geq 0$. It can be generated from a uniform random number U between 0 and 1 by using $E = -\log(U)$.

⁴ A standard normal random variate is distributed as $p(x) = (2\pi)^{-1/2} \exp(-x^2/2)$. A normal random variate N can be generated from two random numbers uniformly distributed between 0 and 1 (U_1 and U_2) by using the Box-Muller method, i.e. $N = \sqrt{-2\ln U_1} \cos(2\pi U_2)$ [31].

$$p(r, t|*) = \frac{k_d}{4\pi r R D} \exp \left[-\frac{(r-R)^2}{4Dt} \right] \left[\frac{\alpha}{(\beta-\alpha)(\gamma-\alpha)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \alpha\sqrt{Dt} \right) + \frac{\beta}{(\gamma-\beta)(\alpha-\beta)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \beta\sqrt{Dt} \right) + \frac{\gamma}{(\alpha-\gamma)(\beta-\gamma)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \gamma\sqrt{Dt} \right) \right] \quad (20)$$

where $r \geq R$. The distribution function to sample is $4\pi r^2 p(r, t|*)$, which can be written as the product of the functions $g(r)$ and $h(r)$:

$$g(r) = r \exp \left[-\frac{(r-R)^2}{4Dt} \right], \quad (21)$$

$$h(r) = \frac{\alpha}{(\beta-\alpha)(\gamma-\alpha)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \alpha\sqrt{Dt} \right) + \frac{\beta}{(\gamma-\beta)(\alpha-\beta)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \beta\sqrt{Dt} \right) + \frac{\gamma}{(\alpha-\gamma)(\beta-\gamma)} \Omega \left(\frac{r-R}{\sqrt{4Dt}} - \gamma\sqrt{Dt} \right). \quad (22)$$

The function $g(r)$ is a mixture of know probability distributions, for which it is possible to develop a sampling algorithm. The function $h(r)$ comprises three terms with $\Omega(x)$. But since the value of $\Omega(x)$ ranges from 0 to 1 for $x \geq 0$, $h(r)$ can be used as the rejection function. The function $g(r)$ can be written as the sum of two functions:

$$g_1(r) = (r-R) \exp \left[-\frac{(r-R)^2}{4Dt} \right] \times 1_{[r>R]}, \quad (23)$$

$$g_2(r) = (R) \exp \left[-\frac{(r-R)^2}{4Dt} \right] \times 1_{[r>R]}, \quad (24)$$

The function $g(r) = g_1(r) + g_2(r)$ is not normalized. However, it is not an issue for sampling since only the relative contributions of g_1 and g_2 are needed. They are calculated by integration:

$$p_1 = \int_R^\infty g_1(r) dr = 2Dt, \quad (25)$$

$$p_2 = \int_R^\infty g_2(r) dr = \sqrt{\pi R^2 Dt}. \quad (26)$$

Therefore variates X distributed as $g(X)$ can be generated by using the following algorithm:

Algorithm 2

Compute p_1 and p_2

Generate U uniform on $[0, 1]$

If $U < p_1/(p_1 + p_2)$ Set $X \leftarrow R + \sqrt{-4Dt \log(V)}$, where V is uniform on $[0, 1]$

Else set $X \leftarrow R + |N|\sqrt{2Dt}$, where N is standard normal.

Return X

The sampled values (X) are then used in the rejection function $h(X)$, in which the maximum value $h_{\max}$ is needed. But since $h(r)$ is the sum of three terms comprising $\Omega(x)$, for which the value ranges from 0 to 1, the maximum value of $h(r)$ is given by sum and/or differences of the coefficients. However, the sum of the coefficients is 0; thus, the sum of the absolute value of the coefficients, i.e. $h_{\max} = |\alpha/(\beta-\alpha)(\gamma-\alpha)| + |\beta/(\gamma-\beta)(\alpha-\beta)| + |\gamma/(\alpha-\gamma)(\beta-\gamma)|$ is used. Therefore, **Algorithm 2** can be used with a rejection method using $h(r)$ and $h_{\max}$, i.e. the sampled values X are accepted if $Vh_{\max} \leq h(X)$, where V is a random number uniformly distributed between 0 and 1.

3.4. Look-up table methods

To evaluate the performance of the algorithm, look-up tables were built and used to generate values of R . The function $4\pi p(r, t|r_0)$ is a univariate probability distribution with two parameters. By fixing the time step, the number of parameters is reduced to one but the tables are different for different values of r_0 . Therefore one dimensional tables were built as in Ref. [7], depending on which simulation is done. The table should be recalculated for each different value of r_0 . The dissociation Green's function $4\pi r^2 p(r, t|*)$ is a univariate probability distribution for a fixed time step; therefore, a one-dimensional table can be built using Equation C3b of Ref. [7].

3.5. The IRT method

The IRT method is widely used in radiation chemistry [23–28]. A detailed description of this method is beyond the scope of this paper; therefore, only the most important points will be given here. Briefly, knowing the initial positions of the particles in the system, a reaction time is sampled for each pair of particles by solving numerically the equation

$$\frac{R\alpha + 1}{r_0\alpha} \left[W\left(\frac{r_0 - R}{\sqrt{4Dt}}, \alpha\sqrt{Dt}\right) - \text{Erfc}\left(\frac{r_0 - R}{\sqrt{4Dt}}\right) \right] = U, \quad (27)$$

where U is a random number uniformly distributed between 0 and 1. This time is infinite (and therefore not considered) if a reaction is not possible. Similarly, a reaction time is obtained for first-order processes by sampling an exponential distribution with parameter given by the inverse of the dissociation rate constant. The reaction times are sorted and the reactions are processed according to the time in the list, by deleting reactants and adding reaction products. The reaction time list is updated after each reaction. The reactions are done until the final time is reached. With this method, the competition between reactions is described via sorting the reaction times, and no provision is made to account for spatial correlations that could exist between reactants [24].

4. Results and discussion

The simulation results are presented in this section.

4.1. Reflective boundary

Since $k_d = k_e = k_r = 0$, $\alpha = -1/R$ and $\beta = \gamma = 0$. As expected, $Q(t|r_0) = 1$ since there are no reactions of particles. In Fig. 1, the function $4\pi r^2 p_{\text{ref}}(r, t|r_0)$ with parameters $R = 1$ and $r_0 = 1.5$ is plotted. The region $r < R$ is forbidden.

The Brownian propagator was sampled 1,000,000 times using **Algorithm 1**, and the sampled r values were stored in 89 bins of size 0.1 for $1 < r < 10$. The counts in each histogram bin were normalized and plotted as a histogram for comparison with the corresponding analytical Green's functions. The number of histories was chosen to ensure convergence of results in a reasonable calculation time. A χ^2 test was performed using 10,000, 100,000 and 1,000,000 histories to evaluate whether the sampled distributions were different from the analytical predictions. In all cases, we found $\chi^2(88) < 110$, indicating that the distributions were not statistically different ($p > 0.05$) from theory. However, to minimize dispersion due to sampling, 1,000,000 histories were used for all simulations done in this paper.

The first calculation is done for $t = 1$ with the initial value of $r_0 = 1.5$. The calculation for $t = 2$ is done by sampling the Green's function using the r values generated by the previous calculations as initial r_0 . Therefore the points at $t = 2$ are the result of two consecutive sampling of the Green's function. Similar results may be obtained by sampling the Green's function using one time step of $t = 2$. The results for $t = 4, 8, 16$ and 32 can be obtained in the same way, either by sampling the Green's function directly or by using multiple consecutive sampling with any combination of Δt which gives a total time of t .

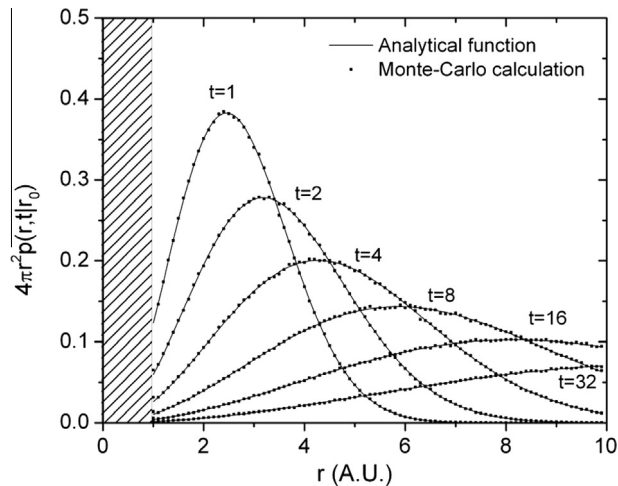


Fig. 1. Reflective Green function $4\pi r^2 p_{\text{ref}}(r, t|r_0)$ (Eq. (13)) for $D = 1$, $R = 1$, $r_0 = 1.5$ and $\alpha = -1$, at $t = 1, 2, 4, 8, 16$ and 32 . Analytical functions: (—); Result of sampling: (■).

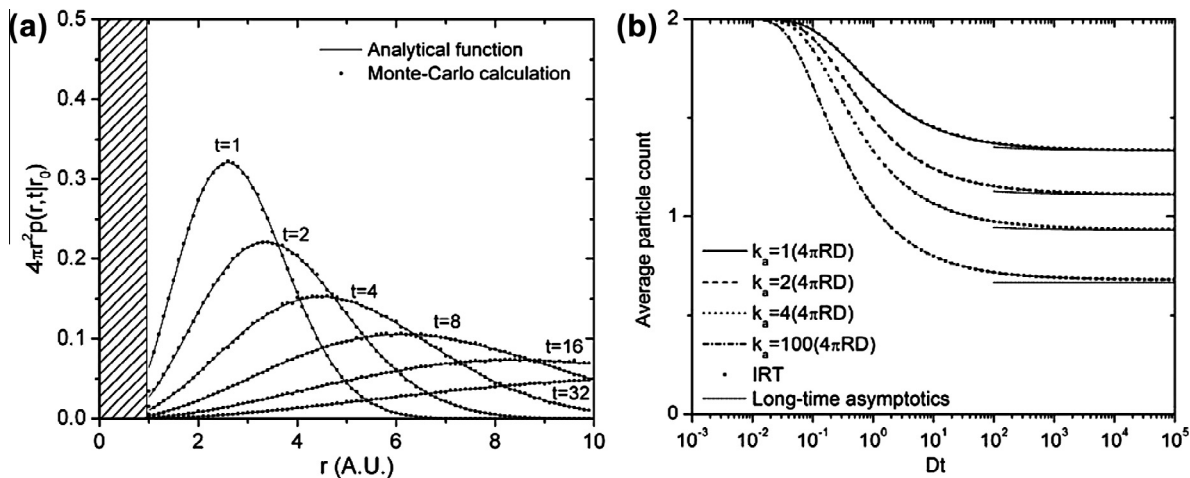


Fig. 2. (a) Green function of the diffusion-influenced reaction $4\pi r^2 p(r, t | r_0)$ (Eq. (11)) for $D = 1$, $R = 1$, $r_0 = 1.5$ and $\alpha = -2$ at $t = 1, 2, 4, 8, 16$ and 32 . Analytical functions: (—); Result of sampling: (■). (b) Average free particle count $2Q(t | r_0)$ as function of time for $D = 1$, $R = 1$, $r_0 = 1.5$ and $k_a = 4\pi RD$ (—), $2(4\pi RD)$ (---), $4(4\pi RD)$ (···) and $100(4\pi RD)$ (····). Results from IRT simulation: (■).

4.2. Diffusion-influenced chemical reactions

In this case, $k_a > 0$, $k_d = k_e = 0$. Since $\alpha < -1/R$, $Q(t | r_0) < 1$, indicating reaction of particles over time. In Fig. 2a, the function $4\pi r^2 p(r, t | r_0)$ (Eq. (12)) with $R = 1$, $D = 1$, $k_a = 4\pi RD$ ($\alpha = -2$) and $r_0 = 1.5$ is plotted. In Fig. 2b, the average free particle count (given by $2Q(t | r_0)$) are plotted for $k_a = 1 \times 4\pi RD$ ($\alpha = -2$), $k_a = 2 \times 4\pi RD$ ($\alpha = -3$), $k_a = 4 \times 4\pi RD$ ($\alpha = -5$) and $k_a = 100 \times 4\pi RD$ ($\alpha = -101$). Results obtained with the IRT method are also shown.

The Green's functions are very similar to those depicted in Fig. 1. The maximum of all corresponding curves are lower, due to reactions of particles. As in the previous section, 1,000,000 histories of pair of particles are simulated. In this case, the survival of a pair of particles is assessed at each time step by looking if $Q(t | r_0) < U$, where U is a uniformly distributed random number between 0 and 1. If a pair reacts, it is considered in a bound state and the Brownian propagator is not sampled anymore. Otherwise, a new value of r is obtained by sampling the Brownian propagator using **Algorithm 1**. The first calculation is done for $t = 1$ using the initial value of $r_0 = 1.5$. As in the previous section, the calculation for $t = 2$ is done by sampling the Green's function using the r values generated by the previous calculations as initial r_0 on surviving pairs of particles. Therefore the points at $t = 2$ are the result of two consecutive sampling of the Green's function. Similar results (not shown) may be obtained by sampling the Green's function using one time step of $t = 2$. The results for $t = 4, 8, 16$ and 32 can also be obtained by using multiple sampling of the Green's function, as previously described.

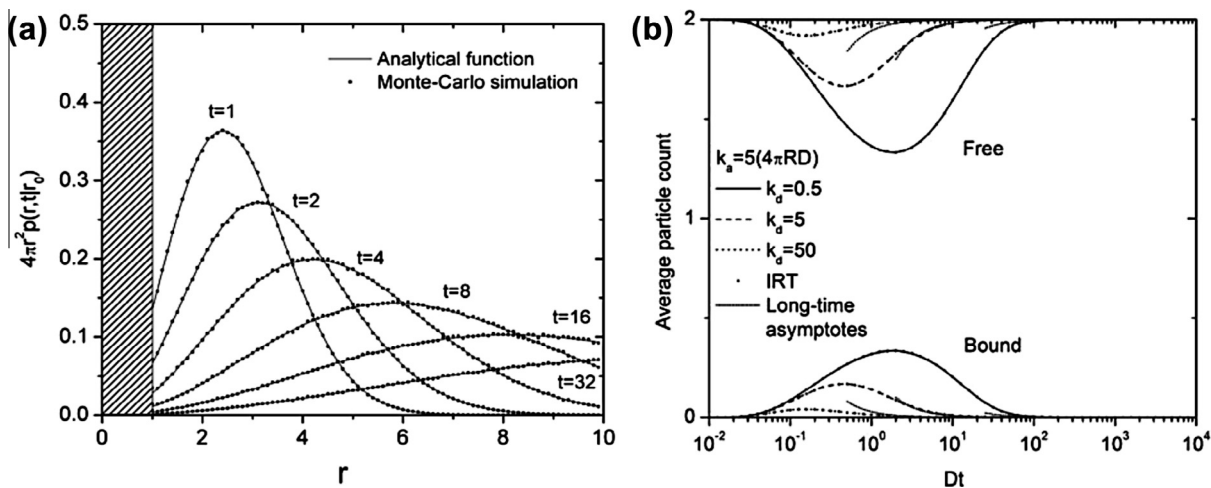


Fig. 3. (a) Green function for reversible reaction $4\pi r^2 p(r, t | r_0)$ (Eq. (8)) for $D = 1$, $R = 1$, $r_0 = 1.5$, $k_a = 10(4\pi RD)$, $k_d = 36$ and $k_e = 0$ ($\alpha = -2$, $\beta = -6$, $\gamma = -3$) at $t = 1, 2, 4, 8, 16$ and 32 . Analytical functions: (—); Result of sampling: (■). (b) Average count of free and reversibly bound particles (given by $2Q(t | r_0)$ and $p(r, t | r_0)$) as function of time for $R = 1$, $r_0 = 1.5$, $k_a = 5(4\pi RD)$, $k_d = 0.5$ (—), $k_d = 5$ (---) and $k_d = 50$ (···). Results from IRT simulation: (■).

In the long time limit, $Q(t \rightarrow \infty | r_0)$ takes the form

$$\lim_{t \rightarrow \infty} Q(t | r_0) \sim 1 - \frac{R\alpha + 1}{r_0\alpha} \left[1 + \frac{1}{\alpha\sqrt{\pi Dt}} \right]. \quad (28)$$

As shown in Fig. 2b, the average particle count plateaus at the predicted values for $t \rightarrow \infty$. In the limit of diffusion-controlled reactions ($k_a \rightarrow \infty$), $Q(t \rightarrow \infty | r_0) \rightarrow 1 - R/r_0$.

4.3. Reversible reaction

In this section, the case where $k_a > 0$, $k_d > 0$ and $k_e = 0$ is considered. Even if $k_e = 0$, it is possible for β and γ to be complex conjugates, so the general equations for the Green's functions should be used.

In Fig. 3a, the Green's functions $4\pi r^2 p(r, t | r_0)$ (Eq. (8)) are shown at $t = 1, 2, 4, 8, 16$ and 32 for $R = 1$, $D = 1$, $k_a = 10(4\pi RD)$, $k_d = 36$, and $r_0 = 1.5$ ($\alpha = -2$, $\beta = -6$, $\gamma = -3$). The Green's functions are similar to those obtained in the previous section. The time discretization property is also verified, i.e. the results at $t = 2$ are the simulation of two consecutive sampling of the Green's functions. As in diffusion-controlled reactions, the program verifies if the free pairs are in a bound state after a time step by using $Q(t | r_0)$. At the second (and subsequent) time steps, a bound pair may dissociate with probability $Q(t^* | r_0)$. If the pair dissociates, a new distance between particles is found by sampling $4\pi r^2 p(r, t^* | r_0)$ using **Algorithm 2**. Therefore, the simulation points depicted in Fig. 3 for $t \geq 2$ include contributions of the sampling of the Green's function from the pairs in the bound state. In Fig. 3b, the average free and reversibly bound particle count (given by $2Q(t | r_0)$ and $p^*(t | r_0)$) are plotted as a function of time for $R = 1$, $D = 1$, $k_a = 5(4\pi RD)$, $r_0 = 1.5$ and three different values of k_d . The results from the IRT simulations are also shown; they also match the results obtained with the Green's function with excellent agreement. It should be noted that the forward and backward (dissociation) reactions are treated separately by IRT, and that the Green's function given by Eq. (8) is not used by IRT.

As noted by Agmon [3], since the particles diffuse away from each other, the pair will always dissociate in the long-time limit. The long-time behavior of the survival probability is given by [6]:

$$\lim_{t \rightarrow \infty} Q(t | r_0) \sim \frac{k_a}{k_d} \frac{1}{(4\pi Dt)^{3/2}}. \quad (29)$$

4.4. Reversible reaction with an intermediate state

This is the general case with $k_a > 0$, $k_d > 0$ and $k_e > 0$, for which β and γ can be complex conjugates. The simulation of these reactions is similar to those of the previous section. In this case, the probabilities for the possible states of a pair of particles initially at distance r_0 are given by $Q(t | r_0)$ (free), $p^*(t | r_0)$ (reversibly bound) and $p^{**}(t | r_0)$ (reaction). For free pairs, the distance is sampled by using Algorithm 1. Similarly, the state of a reversible bound pair after a time step is determined by using $Q(t^* | r_0)$ (free), $p^*(t^* | r_0)$ (reversibly bound) and $p^{**}(t^* | r_0)$ (reaction).

In Fig. 4a, the Green's functions $4\pi r^2 p(r, t | r_0)$ (Eq. (8)) are shown at $t = 1, 2, 4, 8, 16$ and 32 for $R = 1$, $D = 1$, $k_a = 14(4\pi RD)$, $k_d = 65$ and $k_e = 1$ ($\alpha = -8$, $\beta = -2$ and $\gamma = -5$). As in previous sections, the data shown for $t = 2$ and subsequent times

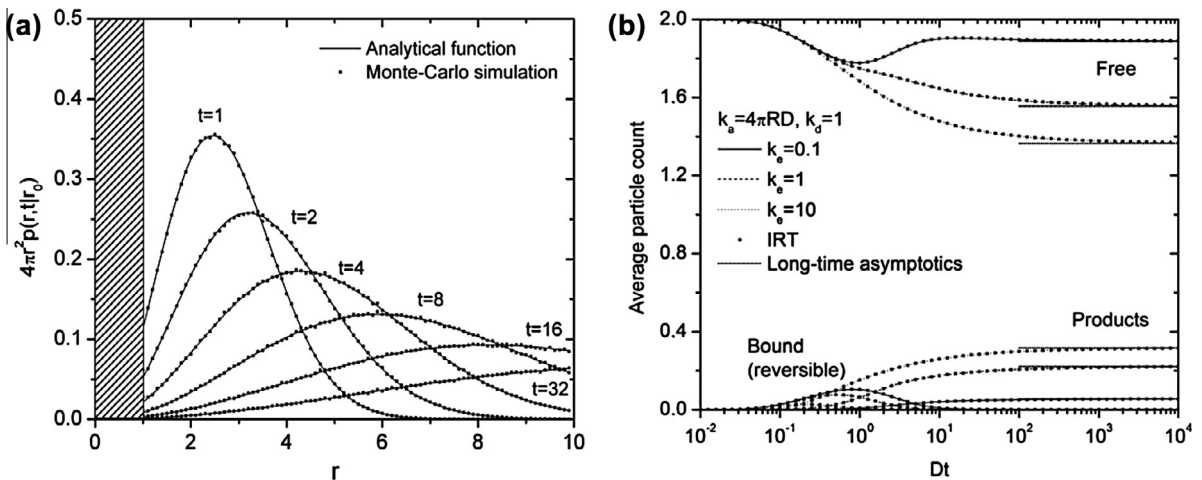


Fig. 4. (a) Green function for reversible reaction with intermediate state $4\pi r^2 p(r, t | r_0)$ (Eq. (8)) for $R = 1$, $r_0 = 1.5$, for $k_a = 14(4\pi RD)$, $k_d = 65$ and $k_e = 1$ ($\alpha = -8$, $\beta = -2$ and $\gamma = -5$) at $t = 1, 2, 4, 8, 16$ and 32 . Analytical functions: (—); Result of sampling: (■). (b) Average count of free, reversibly bound and irreversibly bound particles (given by $2Q(t | r_0)$, $p^*(t | r_0)$ and $p^{**}(t | r_0)$) as function of time for $D = 1$, $R = 1$, $r_0 = 1.5$, $k_a = 4\pi RD$, $k_d = 1$ and $k_e = 0.1$ (—), $k_e = 1$ (—) and $k_e = 10$ (···). Results from IRT simulation: (■).

Table 1Average calculation times (s) for 1,000,000 simulation histories ($R = 1$, $D = 1$).

	Reflection ($k_a = k_d = k_e = 0$)	Diffusion-influenced reactions ($k_a = 4\pi, k_d = k_e = 0$)	Reversible reactions ($k_a = 40\pi, k_d = 36, k_e = 0$)	General case ($k_a = 56\pi, k_d = 65, k_e = 1$)	General case ($k_a = 12\pi, k_d = 4, k_e = 5$) ^a
Our algorithm	199.2	30.1	24.0	45.6	41.1
Table look-up					
500 bins	24.6	19.6	34.7	32.4	55.9
1000 bins	34.7	31.1	57.1	51.2	82.0
2000 bins	69.4	66.0	130.1	126.4	182.7
4000 bins	218.7	202.2	419.7	424.5	577.3

^a The roots β and γ are complex.**Table 2**Maximum χ^2 values for the simulations ($R = 1$, $D = 1$).

	Reflection ($k_a = k_d = k_e = 0$)	Diffusion-influenced reactions ($k_a = 4\pi, k_d = k_e = 0$)	Reversible reactions ($k_a = 40\pi, k_d = 36, k_e = 0$)	General case ($k_a = 56\pi, k_d = 65, k_e = 1$)	General case ($k_a = 12\pi, k_d = 4, k_e = 5$) ^a
Our algorithm	97.2	106.2	78.5	97.6	100.9
Table look-up					
500 bins	113.5	122.7	339.7	145.1	157.0
1000 bins	107.9	96.4	145.2	90.0	112.0
2000 bins	108.0	103.5	87.7	100.1	89.8
4000 bins	107.9	96.0	104.3	98.7	108.9

^a The roots β and γ are complex.**Table 3**

Memory usage.

	Our algorithm	Table look-up (500 bins)	Table look-up (1000 bins)	Table look-up (2000 bins)	Table look-up (4000 bins)
Memory usage (kB)	<0.15	~30	~60	~120	~240

are obtained as the result of several consecutive sampling of the Green's functions. Once again, the agreement between results of sampling and analytical Green's functions is excellent at all times values. In Fig. 4b, the average count of free, reversibly bound and irreversibly bound particles (given by $2Q(t|r_0)$, $p^*(t|r_0)$ and $p^{**}(t|r_0)$) are plotted for $R = 1$, $D = 1$, $k_a = 4\pi RD$, $k_d = 1$, $r_0 = 1.5$ and different values of k_e . Results calculated by using the IRT method are also shown. The agreement of the results from IRT with the analytical functions is also excellent. In the long time limit, as shown in Fig. 4b, $Q(t \rightarrow \infty|r_0) \sim (R/r_0)k_e(k_a/k_D)/(k_d + k_e(1 + k_a/k_D))$.

4.5. Performance and limitations of the algorithms

Usually, table look-up methods are used to generate samples from the Green's functions of the DE in Brownian Dynamics simulations [7,32,33]. In Table 1, the simulation times of the algorithms presented in the paper are compared with the simulation obtained with table look-up method. In Table 2, the χ^2 values that were obtained by comparing the simulation results with the analytical Green's function are given.

The simulations were performed using an Intel Xeon CPU E5430 @ 2.66 GHz. The simulation times obtained with our algorithms are similar to the values obtained with those used algorithms for sampling the Green's functions in 1D [14]. The simulation time for both our algorithm and table methods increases with the complexity of the Green's functions. The rate constants for the simulations were chosen such as the roots α , β and γ are real. A simulation was also done with complex values of β and γ for comparison. The simulation time is significantly higher for this simulation, because the imaginary part of W needs to be calculated⁵. The simulation time for the table look-up method also increases with the resolution of the table. We found that resolutions of 500 and 1000 bins are not sufficient to keep the χ^2 values below the threshold of 110.8, but it is possible to do so by using 2000 bins. Increasing the resolution of the table to 4,000 bins doesn't improve results, but the calculation time significantly increases.

We evaluated the memory needed by our method and by the look-up tables. The results are shown in Table 3.

The memory usage of the algorithms was done by counting the number of bytes needed by each variables used, knowing that each double precision number requires 8 bytes of memory. The tables for W comprise complex numbers in double

⁵ Although the imaginary terms of the terms of the Green's functions cancels, they need to be calculated because the coefficients of W are complex.

precision. The table for the look-up method comprises real numbers in double precision. The memory requirement of the table methods is not very high, but it may increase quickly if the tables are pre-calculated to account for the different parameters. For example, in a system comprising several kind of particles interacting with different reaction rate constants, the tables should be calculated for each values of α , β and γ .

4.6. Applicability of the Green's functions

The Green's functions used here are exact only for systems comprising 2 particles. The problem becomes much more complex when there are more than 2 particles are involved, and the Green's functions used in this paper are no longer exact. If more than two particles are close to each other, the Green's function can be obtained numerically, and table look-up methods can be used [33]. If particles are too far from each other, the particles do not interact and therefore it is not necessary to sample the propagator of the inter-particle distance distribution.

The decision is usually based on the "reaction zone" of a particle, which is defined near each particle to determine if it is necessary to use the sampling algorithms [32]. The condition $r_0 < [R + 8(2Dt)^{1/2}]$ is used in Ref. [29] and many others to define the reaction zone.

If there is an electrostatic interaction between the particles e.g. a Coulomb potential, it is necessary to use the solution of the Debye–Smoluchowski equation [34]. However, in systems that are of interest to radiobiology, such as the DNA damage by the radical species created during the radiolysis of water, the majority of reactions is partially diffusion-controlled and can be simulated with the approach given in this paper. The only notable exception is the reaction $H^+ + e^-_{aq} \rightarrow H\cdot$ [11], for which a numerical calculation may be necessary considering the complexity of the analytical Green's function [34].

5. Conclusion

The Green's function are used in several codes to simulate chemical reactions in a system comprising particles. The sampling of the Brownian propagators are therefore of great interest for such codes. The Green's functions for reactions with an intermediate state are quite complex; however, it is possible to use the relatively simple algorithms presented in this paper to simulate the evolution in time and space of pair of particles. In general, the performance of our algorithm is similar or better than table methods. Table methods usually necessitate some memory to hold the pre-calculated data, which may become problematic when the table has more than one dimension [33].

In radiation chemistry, the IRT method was used to calculate the yields of the radiolytic species in solutions [22–26] and also in chemical dosimeters [27,28]. The IRT method is based on the survival probability of pair of particles, and the competition between reactions are taken into consideration by sorting the sampled reaction time. Although the purpose of this article is not the validation of the IRT method, it is interesting to note that in all cases studied, our simulation results cannot be distinguished from those calculated by IRT. In fact, to our knowledge, the comparison of the predictions of the analytical Green's functions with the IRT results for 2-particle systems with reversible diffusion-influenced reactions or reactions with an intermediate state such as enzyme catalysis has not been attempted before.

Because the algorithms are simple and use only a few kilobytes of memory, they can possibly be implemented on a general-purpose graphic processing unit (GPGPU). GPGPU is a computing device operating as a co-processor to the main central process unit (CPU). GPGPUs comprise up to several hundred cores and have their own memory. They are used to compute functions which are executed a large number of times, but independently on different data. Therefore, the algorithms could be implemented on a GPGPU to simulate a chemical system comprising different types of particles. This work should be useful for chemistry codes that are based on this approach to study DNA damage, which may eventually be included in event-based models of space radiation risk [35].

Acknowledgements

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Appendix A. Green's functions

The probability for a pair of particles initially at distance r_0 to be found in the reversible bound state (*) is given by

$$p(*, t|r_0) = \frac{k_a}{k_D r_0} \left[\frac{\alpha}{(\beta - \alpha)(\gamma - \alpha)} W(\rho_0, -\alpha') + \frac{\beta}{(\gamma - \beta)(\alpha - \beta)} W(\rho_0, -\beta') + \frac{\gamma}{(\alpha - \gamma)(\beta - \gamma)} W(\rho_0, -\gamma') \right]. \quad (A1)$$

The probability for the pair to have reacted and be in the product state (**) is:

$$p(**, t|r_0) = \frac{k_a k_e}{r_0 D k_D \alpha \beta \gamma} \left[\frac{\beta \gamma}{(\beta - \alpha)(\gamma - \alpha)} W(\rho_0, -\alpha') + \frac{\alpha \gamma}{(\gamma - \beta)(\alpha - \beta)} W(\rho_0, -\beta') + \frac{\alpha \beta}{(\alpha - \gamma)(\beta - \gamma)} W(\rho_0, -\gamma') - \text{Erfc}(\rho_0) \right]. \quad (A2)$$

The Green's function for particles in the reversible bound state is also needed. It can be obtained by using the material balance condition $k_d p(r, t|*) = k_d p(*, t|r)$. This yields:

$$p(r, t|*) = \frac{k_d}{4\pi r R D} \left[\frac{\alpha}{(\beta - \alpha)(\gamma - \alpha)} W(\rho_r, -\alpha') + \frac{\beta}{(\gamma - \beta)(\alpha - \beta)} W(\rho_r, -\beta') + \frac{\gamma}{(\alpha - \gamma)(\beta - \gamma)} W(\rho_r, -\gamma') \right]. \quad (A3)$$

The dissociation probability (to the reactant state) is given by integrating (A3) over $r > R$. This calculation gives:

$$Q(t|*) = \frac{k_d}{R D} \left[-\frac{1}{\alpha\beta\gamma} + \frac{(R\alpha + 1)}{\alpha(\beta - \alpha)(\gamma - \alpha)} \Omega(-\alpha') + \frac{(R\beta + 1)}{\beta(\gamma - \beta)(\alpha - \beta)} \Omega(-\beta') + \frac{(R\gamma + 1)}{\gamma(\alpha - \gamma)(\beta - \gamma)} \Omega(-\gamma') \right]. \quad (A4)$$

The probability of a pair in a reversibly bound state to remain in this state at time t is:

$$p(*, t|*) = -\frac{\alpha(\beta + \gamma)}{(\beta - \alpha)(\gamma - \alpha)} \Omega(-\alpha') - \frac{\beta(\alpha + \gamma)}{(\gamma - \beta)(\alpha - \beta)} \Omega(-\beta') - \frac{\gamma(\alpha + \beta)}{(\alpha - \gamma)(\beta - \gamma)} \Omega(-\gamma'). \quad (A5)$$

The probability of a pair in a reversibly bound state to react is given by:

$$p(**, t|*) = \frac{k_e}{D} \left[\frac{\alpha + \beta + \gamma}{\alpha\beta\gamma} - \frac{(\beta + \gamma)}{\alpha(\beta - \alpha)(\gamma - \alpha)} \Omega(-\alpha') - \frac{(\alpha + \gamma)}{\beta(\gamma - \beta)(\alpha - \beta)} \Omega(-\beta') - \frac{(\alpha + \beta)}{\gamma(\alpha - \gamma)(\beta - \gamma)} \Omega(-\gamma') \right]. \quad (A6)$$

The reaction rate constants can also be expressed as a function of α , β and γ :

$$k_d = -k_D[R(\alpha + \beta + \gamma) + 1], \quad (A7a)$$

$$k_d = \frac{R D (\alpha + \beta)(\beta + \gamma)(\gamma + \alpha)}{R(\alpha + \beta + \gamma) + 1}, \quad (A7b)$$

$$k_e = \frac{D(\alpha\beta + \beta\gamma + \gamma\alpha + R\alpha\beta\gamma)}{R(\alpha + \beta + \gamma) + 1}. \quad (A7c)$$

Appendix B. Time discretization equations

A simulation is usually done in a finite number of time steps Δt . If the time t is the sum of two time steps $t = \Delta t_1 + \Delta t_2$, the following possibilities may occur for a pair of particles initially separated by distance r_0 : (i) go at distance r_1 during Δt_1 and at final distance r during Δt_2 ; (ii) go at distance r_1 during Δt_1 and bind in a reversible state (*) during Δt_2 ; (iii) go at distance r_1 during Δt_1 and react to the product state (**) during Δt_2 ; (iv) reversibly bind during Δt_1 and dissociate to the final distance r during Δt_2 ; (v) reversibly bind during Δt_1 and remain in this state during Δt_2 ; (vi) reversibly bind during Δt_1 and react to the product state during Δt_2 ; or (vii) react to the product state during Δt_1 . This can be expressed mathematically as follows:

$$p(r, \Delta t_1 + \Delta t_2 | r_0) = \int_R^\infty 4\pi r_1^2 p(r, \Delta t_2 | r_1) p(r_1, \Delta t_1 | r_0) dr_1 + p(r, \Delta t_2 | *) p(*, \Delta t_1 | r_0), \quad (B1a)$$

$$p(*, \Delta t_1 + \Delta t_2 | r_0) = \int_R^\infty 4\pi r_1^2 p(*, \Delta t_2 | r_1) p(r_1, \Delta t_1 | r_0) dr_1 + p(*, \Delta t_2 | *) p(*, \Delta t_1 | r_0), \quad (B1b)$$

$$p(**, \Delta t_1 + \Delta t_2 | r_0) = \int_R^\infty 4\pi r_1^2 p(**, \Delta t_2 | r_1) p(r_1, \Delta t_1 | r_0) dr_1 + p(**, \Delta t_2 | *) p(*, \Delta t_1 | r_0) + p(**, \Delta t_1 | r_0). \quad (B1c)$$

Similarly, a pair initially in a reversibly bound state (*) can (i) dissociate to the distance r_1 during Δt_1 and go to the final distance r during Δt_2 ; (ii) dissociate to the distance r_1 during Δt_1 and re-bind reversibly during Δt_2 ; (iii) dissociate to the distance r_1 during Δt_1 and react to the product state during Δt_2 ; (iv) stay reversibly bound during Δt_1 and go to the final distance r during Δt_2 ; (v) stay reversibly bound during Δt_1 and Δt_2 ; (vi) stay reversibly bound during Δt_1 and react to the product state during Δt_2 ; or (vii) react to the product state during Δt_1 . From this the time discretization equations for the pair initially in the reversibly bound state are obtained:

$$p(r, \Delta t_1 + \Delta t_2 | *) = \int_R^\infty 4\pi r_1^2 p(r, \Delta t_2 | r_1) p(r_1, \Delta t_1 | *) dr_1 + p(r, \Delta t_2 | *) p(*, \Delta t_1 | *), \quad (B2a)$$

$$p(*, \Delta t_1 + \Delta t_2 | *) = \int_R^\infty 4\pi r_1^2 p(*, \Delta t_2 | r_1) p(r_1, \Delta t_1 | *) dr_1 + p(*, \Delta t_2 | *) p(*, \Delta t_1 | *), \quad (B2b)$$

$$p(**, \Delta t_1 + \Delta t_2 | *) = \int_R^\infty 4\pi r_1^2 p(**, \Delta t_2 | r_1) p(r_1, \Delta t_1 | *) dr_1 + p(**, \Delta t_2 | *) p(*, \Delta t_1 | *) + p(**, \Delta t_1 | *). \quad (B2c)$$

It was not possible to prove these equations directly by using the analytic expressions of the Green's functions, but they were verified numerically for different values of r , r_0 , D , Δt_1 , Δt_2 , α , β , and γ (see supporting Mathematica document). In fact, since the Green's functions describe Markov processes, Chapman-Kolmogorov type equations do hold [19]. As it was discussed in previous work [11,14], these equations offer a way to validate the algorithms presented in this paper, since the simulations are usually done in several time steps.

Appendix C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jcp.2013.02.001>.

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