Facilitated diffusion of DNA-binding proteins: Efficient simulation with the method of excess collisions (MEC)

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In this paper, a new method to efficiently simulate diffusion controlled second order chemical reactions is derived and applied to site-specific DNA-binding proteins. The protein enters a spherical cell and propagates via two competing modes, a free diffusion and a DNA-sliding mode, to search for its specific binding site in the center of the cell. There is no need for a straightforward simulation of this process. Instead, an alternative and exact approach is shown to be essentially faster than explicit random-walk simulations. The speed-up of this novel simulation technique is rapidly growing with system size.

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1. INTRODUCTION

Diffusion controlled bio-chemical reactions play a central role in keeping any organism alive [1, 2]. The transport of molecules through cell membranes, the passage of ions across the synaptic gap, or the search carried out by drugs on the way to their protein receptors are predominantly diffusive processes. Further more, essentially all of the biological functions of DNA are performed by proteins that interact with specific DNA sequences [3, 4], and these reactions are diffusion-controlled.

However, it has been realized that some proteins are able to find their specific binding sites on DNA much more rapidly than is ‘allowed’ by the diffusion limit [1, 5]. It is therefore generally accepted that some kind of facilitated diffusion must take place in these cases. Several mechanisms, differing in details, have been proposed. All of them essentially involve two steps: the binding to a random non-specific DNA site and the diffusion (sliding) along the DNA chain. These two steps may be reiterated many times before proteins actually find their target, since the sliding is occasionally interrupted by dissociation. Berg [5] and Zhou [6] have provided thorough (but somewhat sophisticated) theories that allow estimates for the resulting reaction rates. Recently, Halfford has presented a comprehensive review on this subject and proposed a remarkably simple and semiquantitative approach that explicitly contains the mean sliding length as a parameter of the theory [7]. This approach has been refined and put onto a rigorous base in a recent work by the authors [8].

Although analytical models provide a good general understanding of the problem, they fail to give quantitative predictions for systems of realistic complexity. Therefore, numerical simulations are required to calibrate the set of parameters that form the backbone of these models. However, a straightforward simulation of a protein searching through mega-bases of non-target DNA to find its specific binding site would be prohibitive for all except for the most simple numerical models. Fortunately, there are better ways. Two of the authors (KK and JL) have recently introduced the method of excess collisions (MEC) for an efficient simulation of intramolecular reactions in polymers [9]. In the present work, this method is modified to apply to second order diffusion controlled chemical reactions (Section 2.1). We thereby construct a simple random walk approach to facilitated diffusion of DNA-binding proteins (Section 2.2) and apply the MEC and our analytical estimate for reaction times to this model (Section 2.3 and 2.4). Section 3 provides details about the generation of DNA-chains, followed by a set of simulations covering a large range of system dimensions (Section 5) to verify the performance of the MEC.

2. THEORY

2.1. Method of excess collisions (MEC)

We consider a (time-homogeneous) stochastic process. The problem is to find the average time $\tau_{BA}$ of the first arrival at a certain state A, provided that, at time $t = 0$, the system occupied another state B.

Suppose we observe the system for a long time interval $T$ and monitor the events of entering state A. These events will be referred to as collisions. Each collision that occurs for the first time after visiting state B will be called prime collision. We obtain the (asymptotically correct for $T \to \infty$) relation

$$T = n(T) \tau_R = n'(T) \tau_R' ,$$

where $n(T)$ and $n'(T)$ are the average numbers of all and of prime collisions during the time interval $T$, respectively, and $\tau_R$ and $\tau_R'$ are the corresponding mean
recurrence times. Hence,
\[ \tau'_R = \frac{n(T)}{n'(T)} \tau_R \equiv N \tau_R . \tag{2} \]

The ratio \( N \equiv n(T)/n'(T) \) defines the average number of collisions between two visits to state B and does actually not depend on \( T \), once \( T \) is chosen sufficiently large. The mean recurrence time \( \tau'_R \) of prime collisions is simply the average time the system requires to move from state A to B and back from state B to A:
\[ \tau'_R = \tau_{AB} + \tau_{BA} , \tag{3} \]
where \( \tau_{AB} \) is the mean time of first arrival at state B starting from A. With eq. \( \text{2} \) we then obtain
\[ \tau_{BA} = N \tau_R - \tau_{AB} . \tag{4} \]

This relation is useful for the numerical estimation of \( \tau_{BA} \) if \( \tau_{BA} \gg \tau_{AB} \). A simulation cycle then starts in state A and ends as soon as state B is reached, i.e. the reversed reaction \( A \to B \) is simulated in order to obtain the (much lower) reaction rate of the original reaction \( B \to A \). In this case we can write
\[ N = \langle N_{\text{coll}} \rangle + 1 , \tag{5} \]
where \( \langle N_{\text{coll}} \rangle \) is the average number of collisions in a simulation cycle and the second term accounts for the prime collision (which is not observed in the simulations, since the cycle starts at the time instant that immediately follows the prime collision). As will be shown later in Section \( \text{2.3} \) the recurrence time \( \tau_R \) can be renormalized and computed efficiently inside a small test system. Note that eq. \( \text{4} \) can be written as
\[ \tau_{BA} \equiv \langle N_E + 1 \rangle \tau_R , \tag{6} \]
where
\[ N_E \equiv \langle N_{\text{coll}} \rangle - \frac{\tau_{AB}}{\tau_R} \tag{7} \]
is the mean number of excess collisions per simulation cycle \( \text{2} \), since the ratio \( \tau_{AB}/\tau_R \) is just the mean number of collisions that would be observed in a simulation run of length \( \tau_{AB} \) with a starting point at an arbitrary state of the system (not necessary state A).

### 2.2. Simple model for facilitated diffusion of DNA-binding proteins

We consider a spherical volume (cell) of radius \( R \) and inside it a worm-like chain (DNA) of length \( L \) and radius \( r_c \). The protein is represented as a random walker moving inside the cell with a certain time step \( dt \). A collision takes place once the walker enters the active binding site, a spherical volume of radius \( r_a \) positioned in the middle of the chain that, in its turn, coincides with the center of the cell. We want to point out that the parameter \( r_a \) does not necessary correspond to any geometrical length in the real system. It defines a probability for the reaction to take place, and may cover additional variables which are not included explicitly in the model, like protein orientation and conformation. An attractive step potential is implemented as
\[ U(d) = \begin{cases} -E_o & d \leq r_c \\ 0 & d > r_c \end{cases} , \tag{8} \]
where \( d \) is the shortest distance between walker and chain. This defines a pipe with radius \( r_c \) around the chain contour that the walker is allowed to enter freely from outside, but to exit only with the probability
\[ p = \exp(-E_o/k_B T) , \tag{9} \]
where \( k_B T \) is the Boltzmann factor, otherwise it is reflected back inside the chain. We may therefore denote \( p \) as exit probability. It is important to note that \( p \) defines the equilibrium constant \( K \) of the two phases, the free and the non-specifically bound protein, according to
\[ K = \frac{c}{N} = \frac{\pi r_c^2}{p} , \tag{10} \]
where \( c \) is the concentration of free proteins and \( \sigma = c V_c/(p L) \) is the linear density of proteins that are non-specifically bound to the DNA, with \( V_c = \pi r_c^2 L \) being the geometric volume of the chain.

#### 2.3. Method of computation of the recurrence time

The two states of interest are the protein entering the cell, B, and the same protein reaching the active site in the center of the cell, A. More specifically, we are interested in finding the time \( \tau_{BA} \), the walker requires to reach a distance \( r = r_a \) when starting at distance \( r(t = 0) = R \).

We shall first define the excluded volume of the chain as
\[ V_{\text{ex}} \equiv \int_V \left[ 1 - \exp \left( \frac{-U(d(r))}{k_B T} \right) \right] dr = V_c \left( 1 - \frac{1}{p} \right) , \tag{11} \]
where \( U(d) \) is the energy of the walker as defined by eq. \( \text{3} \) and the integration is performed over the geometric volume of the cell, \( V = (4/3)\pi R^3 \). The effective volume \( V_{\text{eff}} \) of the cell is then
\[ V_{\text{eff}} \equiv V - V_{\text{ex}} = V_c \left( 1 - \frac{1}{p} \right) . \tag{12} \]
Next we assume that simulations were carried out within a small test system of radius \( R^* < R \) and that the recurrence time \( \tau_R^* \) of the walker was found. Its recurrence time in the larger system is then found as
\[ \tau_R(V) = \tau_{R^*} V_{\text{eff}} , \tag{13} \]
where we have defined
\[ \tilde{\tau}_R \equiv \frac{\tau_R^*}{V_{\text{eff}}^*}. \] (14)

This ratio does not depend on system size and may therefore be called specific recurrence time. It only depends on the potential-depth \( E_a \) and the step-size chosen for the random walk. The idea is to compute \( \tilde{\tau}_R \) (as described in Section 4) for a small test system with dimensions of the order of \( r_a \) (which is the radius of the specific binding site) to obtain \( \tau_R \) for the system of interest using eq. (13). Once \( \tau_R \) is known, \( \tau_{BA} \) is computed via random walk simulations in the large system, starting at \( r(t = 0) = r_a \) and terminating as soon as the periphery of the cell \( r(r_{BA}) = R \) is reached. Following the trajectory of the walker, the number of collisions \( \langle N_{\text{coll}} \rangle = N - 1 \) is monitored as well, so that eq. (4) can be used to determine the much longer reaction time \( \tau_{BA} \).

### 2.4. Analytical estimate for the collision time

As has been discussed in detail elsewhere \[8\], it is possible to estimate the reaction time for the protein using an analytical approach, once certain conditions are satisfied. The resulting expression is

\[ \tau_{BA}(\xi) = \left( \frac{V}{8D_{3d} \xi} + \frac{\pi L \xi}{4D_{1d}} \right) \left[ 1 - \frac{2}{\pi} \arctan \left( \frac{r_a}{\xi} \right) \right] \] (15)

with the ‘sliding’ variable

\[ \xi = \sqrt{\frac{D_{1d} K}{2\pi D_{3d}}} \] (16)

and \( D_{1d} \) and \( D_{3d} \) being the diffusion coefficients in sliding-mode and free diffusion, respectively. Generally, the equilibrium constant \( K \) has to be determined in simulations of a (small) test system, containing a piece of chain without specific binding site \[8\]. In the present model, \( K \) is known analytically via eq. (11). If the step-size \( dr \) of the random walker is equal both inside and outside the chain (the direction of the step being arbitrary), we further have \( D_{1d} = D_{3d} = dr^2/6 \), and hence obtain

\[ \xi = \sqrt{\frac{r_a^2}{2p}}. \] (17)

This variable has got the dimension of length; as we have pointed out in \[8\], it corresponds to the average sliding length of the protein along the DNA contour in Halford’s model \[7\]. In this light, a (non rigorous) interpretation of eq. (14) is as follows: The first term in the round brackets represents the time of free diffusion of the walker, whereas the second term stands for the time of one-dimensional sliding. With increasing affinity of the walker to the chain (expressed as a reduced value for the exit probability \( p \)), the sliding variable \( \xi \) increases and the contribution of free diffusion to the reaction time (first term in (15)) becomes less significant. At the same time, the second term of eq. (15) is growing. Depending on the choice of system parameters, there may be a turning point where the latter contribution over-compensates the former, so that the total reaction time increases once \( \xi \) is growing further.

For a random walk model as simple as used here, this analytical formula describes the reaction times well within 10% tolerance, as long as the following conditions are satisfied: (1) \( \xi \ll R \), i.e. the sliding parameter should be small compared to the system size. This restriction assures the correct normalization of the protein’s probability distributions and the diffusion efficiencies as discussed in \[8\]. (2) During the diffusion process, the system reaches its equilibrium, so that the constant \( K \) represents the average times the protein spends in free and in non-specifically bound mode. This requires either a crowded environment (the chain-density inside the cell is high enough) or a reasonably small value for \( \xi \), since the initial position of the walker is always at the periphery and outside the chain, i.e. not in equilibrium. (3) \( \xi < l_p \), where \( l_p \) is the persistence length of the chain. This restriction accounts for the assumption that the walker moves along an approximately straight line during one sliding period. However, numerical tests have shown that deviations from a straight geometry actually have little impact to the accuracy of the model. (4) The step-size of the random walk has to be small compared to the size of the binding site.

It should be pointed out that an analytical approach as simple as that is by no means supposed to simulate the actual situation in a living cell. Instead, it serves as a platform for a much wider class of semi-empirical models. The sliding-parameter \( \xi \) contains the affinity of non-specific protein-DNA binding and is flexible to vary with the potential chosen for the simulation. The diffusion coefficients \( D_{1d} \) and \( D_{3d} \) can be adapted to experimental measurements, and the target size \( r_a \) contains protein-specific reaction probabilities. These parameters can be fitted to either describe system-specific experimental results or the output of more sophisticated numerical codes which would otherwise not permit any analytical treatment.

### 3. NUMERICAL MODEL

In order to approximate the real biological situation, the DNA was modeled by a chain of straight segments of equal length \( l_0 \). Its mechanical stiffness was defined by the bending energy associated with each chain joint:

\[ E_b = k_B T \alpha \theta^2, \] (18)

where \( \alpha \) represents the dimensionless stiffness parameter, and \( \theta \) the bending angle. The numerical value of \( \alpha \) defines the persistence length \( (l_p) \), i.e. the “stiffness” of the chain. The excluded volume effect was taken into account...
account by introducing the effective chain radius \( r_e \). The conformations of the chain, with distances between non-
adjacent segments smaller than \( r_e \), were forbidden. The target of specific binding was assumed to lie exactly in
the middle of the DNA. The whole chain was packed in a spherical volume (cell) of radius \( R \) in such a way that
the target occupied the central position.

To achieve a close packing of the chain inside the cell, we used the following algorithm. First, a relaxed confor-
mation of the free chain was produced by the standard Metropolis Monte-Carlo (MC) method. For the further
compression, we defined the center-norm (c-norm) as the maximum distance from the target (the middle point) to
the other parts of the chain. Then, the MC procedure was continued with one modification. Namely, a MC step
was rejected if the c-norm was exceeding 105% of the lowest value registered so far. The procedure was stopped
when the desired degree of compaction was obtained.

The protein was modeled as a random walker within the cell with reflecting boundaries. During one time-step it
was displaced by the distance \( dr \) in a random direction. Once approaching the chain closer than its radius \( r_e \) de-
fining the “non-specific binding pipe”, it was al-
lowed to enter it freely and continue its random walk inside. Upon crossing the pipe boundary from inside, it
was either allowed to pass with the exit probability \( p \) or otherwise reflected back inside, as described in Section

Below in this paper, one step \( dt \) was chosen as the unit of
time and one persistence length \( l_p = 50 \text{ nm} \) of the
DNA chain as the unit of distance. The following values of
parameters were used. The length of one segment was
chosen as \( l_0 = 0.2 \), so that one persistence length was
partitioned into 5 segments. The corresponding value of
the stiffness parameter was \( \alpha = 2.403 \) [10]. The chain
radius was \( r_e = 0.06 \), and the active site was modeled as
a sphere of identical radius \( r_a = 0.06 \) embedded into the
chain. The step-size of the random walker both inside and
outside the chain was \( dr = 0.02 \), corresponding to a
diffusion coefficient \( D_{id} = D_{da} = dr^2/6 = 2 \cdot 10^{-4}/3 \)
. This choice was a compromise between accuracy and sim-
ulation time. Tests have confirmed that a smaller step-
size could somewhat reduce the gap between theoretical
(eq. [15]) and simulated reaction time at small values of \( \xi \).

4. COMPUTATION OF THE SPECIFIC RECURRENCE TIME

To compute the specific recurrence time \( \tau_R \) of eq. [14],
a very small test system is sufficient. Moreover, the com-
putations can be carried out for the collisions from within
the specific binding site of radius \( r_a \). The entire sys-

tem, i.e. the sphere and a short piece of chain, was embed-
ded into a cube of \( 4r_a \) side-length with reflective walls.

In principle, the size of the cube should be of no rele-



### 5. MODEL SYSTEMS OF VARIOUS SIZES

Next, simulations were carried out for cells of different volumes \( V_i = 4\pi R_i^3/3 \) (see table [11] for a summary of the system parameters). The chain lengths \( L_i \) were chosen so that the density \( L_i/V_i \) remained of the same order around 3/4. First, the chain conformation was generated using the procedure of Section 3. Then, each simulation cycle started at the periphery of the active binding site (state A) and ended as soon as the periphery of the cell (state

| \( R = r_a \) | \( R = 4.8 \) |
|---|---|
| \( \xi \) | \( \tau_R \) | \( \tau_B \) | \( \tau_A \) | \( \tau_B(MEC) \) | \( \tau_A \) |
| 0.042 | 1.039 | 4.464 | 4.928 | 58577 | 1.013 \cdot 10^7 | 1.029 \cdot 10^7 |
| 0.060 | 1.693 | 2594 | 7.019 | 58674 | 8.445 \cdot 10^6 | 8.131 \cdot 10^6 |
| 0.085 | 1.112 | 1413 | 10.88 | 59843 | 7.243 \cdot 10^6 | 6.818 \cdot 10^6 |
| 0.120 | 5.368 | 741.6 | 16.05 | 61225 | 5.776 \cdot 10^6 | 5.823 \cdot 10^6 |
| 0.170 | 5.496 | 379.7 | 25.66 | 65418 | 5.020 \cdot 10^6 | 4.876 \cdot 10^6 |
| 0.240 | 5.575 | 192.6 | 39.50 | 75501 | 4.370 \cdot 10^6 | 4.272 \cdot 10^6 |
| 0.330 | 5.606 | 96.81 \* | 58.56 | 90422 | 3.933 \cdot 10^6 | 3.982 \cdot 10^6 |
| 0.480 | 5.631 | 48.62 \* | 86.29 | 115401 | 3.911 \cdot 10^6 | 3.815 \cdot 10^6 |
| 0.670 | 5.629 | 24.30 \* | 122.8 | 172755 | 4.184 \cdot 10^6 | 4.119 \cdot 10^6 |
| 0.960 | 5.638 | 12.17 \* | 179.7 | 273757 | 5.110 \cdot 10^6 | 5.018 \cdot 10^6 |
| 1.358 | 5.642 | 6.899 | 253.1 | 422792 | 6.456 \cdot 10^6 | 6.243 \cdot 10^6 |
| 1.920 | 5.640 | 3.044 | 357.1 | 70443 | 8.502 \cdot 10^6 | 8.616 \cdot 10^6 |
FIG. 1: A ‘cell’ of radius $R = 4.8$ (persistence lengths) containing a chain of $L = 345.8$, corresponding to 240 nm and 17.3 µm, respectively. The chain was made of 1729 segments. The protein’s specific binding site is located at the center (dot, not to scale).

B) was reached. Whenever the walker returned back to the binding site ($r < r_a$), one collision was noted. As long as the walker remained inside the binding site, the clock was halted. For each value of the exit parameter $p$, which is related to the walker-chain affinity via eq. (9), 2000 cycles were carried out and the measurements were averaged, so that statistical fluctuations were reduced to about 2%. The simulations provided measurements of $\tau_{AB}$, the average time to reach B when starting from A, and $\langle N_{coll} \rangle$, the number of returns to A on the way towards B. Equations (13) and (14), which form the core of the MEC approach, were then applied to evaluate $\tau_{BA}$. Additionally, $\tau_{BA}$ was simulated explicitly, starting from B, as a verification of the speed-up and accuracy of the MEC approach. The results are summarized in table I.

In order to clarify the procedure, we shall first discuss the simulation of the largest cell $R = 4.8$ in more detail. Figure 1 displays the chain conformation inside the spherical cell in a 2-dimensional projection. The specific binding site is located at the center of the cell. Note that, wherever possible, the chain contour, constructed of 1729 cylindrical segments, tries to avoid large bond angles, a result of the bending potential as discussed in Section 3.

Table I contains details of the simulation results for 12 different values of the exit parameter $p$, varied as $p = 2^{-l}$, $l = 0, \ldots, 11$. The second column is the sliding parameter $\xi$. With increasing protein-chain affinity, the walker is spending more time inside the chain volume so that the sliding parameter is growing in size, reaching a value of almost two persistence lengths at $p = 2^{-11}$. The following two columns are the recurrence time $\tau^*_R$ and $\tau_R$ as discussed in Sec. 4. The next column is the number of collisions $N$ (eq. 5). The more time it spends inside the chain contour, i.e. with increasing influence of facilitated diffusion, the more often the walker returns back to state A to cause a collision, before being able to reach state B for the first time to finish the cycle. From $p = 1$ (free diffusion) to $p = 2^{-11}$, the value of $N$ gains almost two orders of magnitude. The next column is the average reaction time $\tau_{AB}$ of the direction $A \rightarrow B$. This quantity initially remains almost constant, but at higher values of protein-chain affinity it begins to grow rapidly. The reason is because the walker becomes more and more trapped inside the chain volume and is unable to access the cell periphery as effectively as it does during free diffusion. The next column is the reaction time $\tau_{BA}$ as delivered by the MEC approach using eq. (4). The recurrence time $\tau_R$ was determined using eq. (13), with the effective volume of eq. (12) and the specific recurrence time $\tilde{\tau}_R$ (column 4). The next column contains $\tau_{BA}$ as obtained by direct simulations. When averaged over all data points, both results for $\tau_{BA}$ differed by 2.4%. As shown in the last column, the ratio $\tau_{BA}/\tau_{AB}$ was of the order 10-100. This defines the speed-up of the MEC approach over the explicit simulation of $\tau_{BA}$. Integrated over all data points, the total speed-up was equal to 33.4.

FIG. 2: The first reaction time $\tau_{BA}$ for the cell of radius $R = 4.8$ persistence lengths as a function of the sliding parameter $\xi$. Dots: explicit simulation. Squares: MEC approach, which is exact within statistical errors. Speed-up: Factor 33.4 of simulation steps after integration over all data points. The solid curve is the analytical estimate eq. (15).
Figure 2 displays the first reaction times $\tau_{BA}$ as a function of the sliding parameter $\xi$. Both methods (explicit simulation and MEC approach) deliver identical results within the statistical errors. The solid curve is a plot of the analytical estimate eq. (15), which consistently under-estimates the first reaction time by 5-10% but otherwise describes the trends accurately, including the location of the minimum. The results prove that facilitated diffusion is able to accelerate the reaction considerably. It is also obvious that a very high affinity of the protein to the chain becomes counter-productive: The walker spends long periods of time trapped within a particular loop of the chain without being able to explore the remaining parts of the cell exhaustively. Ideally, the affinity has to be chosen so that the walker is occasionally able to dissociate from the chain and associate again after having passed some time in free diffusion. The actual value of the ideal affinity depends on the system parameters and is easily estimated using eq. (15) prior to any simulations.

Table 1 contains a summary of the simulation results for various system sizes. It appears that the speed-up delivered by the MEC approach increased proportional to the square of the cell radius, and gained a significant dimension in the largest of our test systems. Whereas a cell as small as $R = 1.2$ was treated within 30 minutes on a PC, including 2000 runs of explicit simulation $B \rightarrow A$ for 12 different values of the exit probability $p$, the large cell of $R = 4.8$ required more than 5 days for the same set of computations. The MEC method reduced that time to less than four hours.

### Table 1: Simulation parameters (cell radius $R$, chain length $L$) and total speed-up. Column 3 contains the total number of time-steps $n(BA)$ (integrated over all data points) for the explicit simulation of $\tau_{BA}$, column 4 is the integrated speed-up of MEC (the ratio $n(BA)/n(AB)$). The last column contains the deviation (averaged over all data points) between $\tau_{BA}$(explicit) and $\tau_{BA}$(MEC).

| Cell $R$ | Chain $L$ | Time-steps | Speed-up | Error (%) |
|---------|-----------|------------|----------|-----------|
| 1.2     | 1.68·10$^8$ | 2.3        | 3.9      |
| 2.0     | 9.31·10$^9$ | 6.9        | 3.9      |
| 3.2     | 4.17·10$^{10}$ | 16.6      | 2.3      |
| 4.8     | 1.44·10$^{11}$ | 33.4      | 2.4      |

### Table 2: Simulation parameters (cell radius $R$, chain length $L$) and total speed-up. Column 3 contains the total number of time-steps $n(BA)$ (integrated over all data points) for the explicit simulation of $\tau_{BA}$, column 4 is the integrated speed-up of MEC (the ratio $n(BA)/n(AB)$). The last column contains the deviation (averaged over all data points) between $\tau_{BA}$(explicit) and $\tau_{BA}$(MEC).

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| 4.8     | 1.44·10$^{11}$ | 33.4      | 2.4      |

A → $B$ (protein starts at the binding site and propagates to the cell-periphery) instead of $B \rightarrow A$. We have demonstrated how MEC led to a speed-up of up to two orders of magnitude, depending on protein-DNA affinity (Table 1), and gaining significance with increasing cell size (Table 2).

The cell model employed in this work was perhaps the most simple ansatz that was possible without being trivial, and intentionally so. The simulations had to cover a large range of system sizes in order to verify the efficiency of the MEC approach. The chain-lengths span a factor of 64 from the smallest to the largest system. Nevertheless, the validity of our results does not depend on the complexity of the model, such as protein-DNA potential, which modifies the equilibrium constant $K$ in eq. (16) and thereby the sliding parameter $\xi$ (eq. 18), hydrodynamic interactions, which would lead to effective diffusion coefficients, also modifying $\xi$, or the introduction of protein orientation and conformation, acting on the effective target size $r_a$. The speed-up is consistently evaluated in terms of simulation steps, not CPU-time, to ensure invariance on the complexity of the underlying protein/DNA model. Based on the results presented here, the MEC approach can be expected to reduce the numerical effort by orders of magnitude, once more sophisticated (and time consuming) simulation techniques are employed to study biochemical reaction times in systems of realistic dimensions.

6. SUMMARY

In this work, the method of excess-collisions (MEC), recently introduced as a technique to speed up the simulation of intramolecular reactions in polymers, is generalized to second order diffusion controlled reactions, and applied to the problem of facilitated diffusion of site-specific DNA-binding proteins. This method is based on eq. (1) and (18) to simulate the much faster back-reaction
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