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Monte Carlo simulations of drug release from matrices with periodic layers of high and low diffusivity

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Abstract

We have studied drug release from matrices with periodic layers of high and low diffusivity using Monte Carlo simulations. Despite the fact, that the differential equations relevant to this process have a form that is quite different from the classical diffusion equation with constant diffusion coefficient, we have found that the Weibull model continues to describe the release process as well as in the case of the "classical" diffusion controlled drug release. We examine the similarities and differences between release from matrices with periodic layers and matrices with random mixtures of high and low diffusivity area and show that the periodic geometrical arrangement of the low diffusivity areas has an influence in the release profile which is negligible for low diffusivity ratios, but becomes important in the case of high diffusivity ratios and for intermediate values of the periodic "length". Such an arrangement in periodic layers leads to Weibull exponent a which are lower than those of the corresponding random arrangement and exponents b which are higher than those of the random case.

Keywords: Controlled release; Diffusion; Periodic structures; Monte Carlo simulations; Weibull model

1. Introduction

The theoretical modelling of the processes involved in controlled drug release is rather an important task (Macheras and Iliadis, 2005), since the development of new pharmaceutical products is highly facilitated from the possibility to predict the desirable release kinetics in advance. Several models have been proposed for the description of drug release (Higuchi, 1961; Peppas, 1985; Ritger and Peppas, 1987a, b; Peppas et al., 1980; Gao et al., 1995; Siepmann et al., 1999; Siepmann and Peppas, 2000, 2001; Costa and Lobo, 2001; Weibull, 1951; Bonferoni et al., 1998; Sathe et al., 1996), such as the Higuchi law (Higuchi, 1961) and the power law (or Peppas model) (Peppas, 1985). Among these models, we feel that the Weibull model (Weibull, 1951; Bonferoni et al., 1998; Sathe et al., 1996; Kosmidis et al., 2003a):

$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b) \tag{1}$$

where a and b are constants, is of particular interest. This model is particularly successful in the description of experimental dissolution data (Gao et al., 1995). Moreover, there is a physical meaning of the constants a and b (Kosmidis et al., 2003a; Papadopoulou et al., 2006). For instance, the exponent b originates from the fact that a depletion zone is created gradually near the boundaries of the release device, and thus, the drug concentration in the device is not uniform.

Here, we will focus exclusively on diffusion controlled drug release. Monte Carlo simulations (Landau and Binder, 2000) have recently been used to study drug release from Euclidean and fractal geometries, yielding interesting results (Kosmidis et al., 2003a, b; Bunde et al., 1985; Villalobos et al., 2006, 2005; Haddish-Berhane et al., 2006; Barat et al., 2006a, b). In a recent paper, we have used this method to study drug release from matrices that consist of random mixtures of areas with different diffusivities (Kosmidis and Macheras, 2007).

In this paper, we are interested in the way the release rate is changed, when the release device is not uniform, but consists of a periodic arrangement of areas with high D_h and low D_l diffusion coefficients. We are interested in determining whether in this case the release rate is different from the case of release from random mixtures of high and low diffusivities and whether

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the Weibull model continues to provide an adequate description of the release process. Moreover, we are interested in quantifying the influence of the "length" l of the periodic arrangement on the release profile and particular the dependence of the Weibull parameters a and b on l.

2. Methods

We have studied the release process using Monte Carlo simulations. In order to get an idea of the complexity and possible difficulties involved in the release process, we present an analytical investigation of a simplified one-dimensional analog of a release device having a periodic structure, followed by a detailed description of our simulation method.

2.1. Analytical investigation

The problem in study is actually a diffusion process where the diffusion coefficient depends on the space coordinates. For simplicity, we are interested in the study of the release profile of a quasi-one-dimensional release device where thin layers of low diffusivity are followed by layers of high diffusivity with length l. i.e. the one-dimensional analog of Fig. 1. In this case the diffusion coefficient is a function of the x-coordinate, $D = D(x)$. The equation describing the problem is not simply the "classical" diffusion equation with the simple substitution of D by $D(x)$. One has to consider that the "classical" diffusion equation is derived from the first law of Fick and the continuity equation (Crank, 1980). Thus, in this case the correct one-dimensional equation is

$$\frac{\partial}{\partial x}\left[D(x)\frac{\partial u}{\partial x}\right] = \frac{\partial u}{\partial t} \tag{2}$$

where $u(x, t)$ is the density of the drug molecules inside the release device. In order to model the periodic structure, we may assume that

$$D(x) = (D_\mathrm{h} - D_\mathrm{l})\sin^2 lx + D_\mathrm{l} \tag{3}$$

where $D_\mathrm{h} > D_\mathrm{l}$ are constants and are equal to the maximum and minimum values of the diffusivity, respectively.

Substituting Eq. (3) into Eq. (2) leads to

$$((D_\mathrm{h} - D_\mathrm{l})\sin^2 lx + D_\mathrm{l})\frac{\partial^2 u}{\partial x^2} + (D_\mathrm{h} - D_\mathrm{l})l\,\sin(2lx)\frac{\partial u}{\partial x} = \frac{\partial u}{\partial t} \tag{4}$$

Eq. 4 is rather different from the classical diffusion equation, and has to be solved either analytically or numerically. We may use the separation of variables method to get an idea of the form of the solution. Indeed, we may look for solutions in the product form $u = X(x)T(t)$ and this will lead to the system of ordinary differential equations

$$f_1(x)\frac{\mathrm{d}^2 X}{\mathrm{d}x^2} + f_2(x)\frac{\mathrm{d}X}{\mathrm{d}x} + \lambda X = 0 \tag{5}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} + \lambda T = 0 \tag{6}$$

where $f_1(x) = ((D_\mathrm{h} - D_\mathrm{l})\sin^2 lx + D_\mathrm{l})$, $f_2(x) = (D_\mathrm{h} - D_\mathrm{l})l$ $\sin(2lx)$ and $-\lambda$ is the separation constant. Unfortunately, Eq. (5) has no analytic solution. Thus, we have to resort to numerical methods. Since the functional form of the last two equations is rather different from the corresponding equations for diffusion with constant diffusion coefficient, it is interesting to check if the Weibull model, which is proven to be a good approximation for the release from devices obeying the classical diffusion equation with constant D, is still a good approximation in this case.

2.2. Monte Carlo simulations

The Monte Carlo method (Landau and Binder, 2000) is a numerical method based on considering finite-size systems and using random numbers to mimic the system behavior. Thus, the system dynamics can be inferred by averaging the resulting configurations. Each decision corresponds to an arbitrary time unit (called Monte Carlo Step, MCS), which may eventually be shown to correspond to a real time unit. In this paper, we initially consider a two-dimensional square lattice of size $L \times L$. Then, we place a number of particles randomly on the sites of the lattice, according to the initial particle concentration c, avoiding double occupancy. Unless explicitly stated otherwise, we assume an initial particle concentration $c = 0.5$, meaning that 50% of the sites are initially occupied by particles, and the rest are empty. The "left" and "right" boundaries of the lattice are leak areas, while the top and bottom ones are reflecting sites. If a particle attempts to cross the leak boundaries, then it is immediately removed from the system. Sites of the lattice are periodically arranged in high and low diffusivity "stripes", with periodic length l. This simply means that a column of low diffusivity sites is followed by l columns of high diffusivity sites, see Fig. 1 for a schematic.

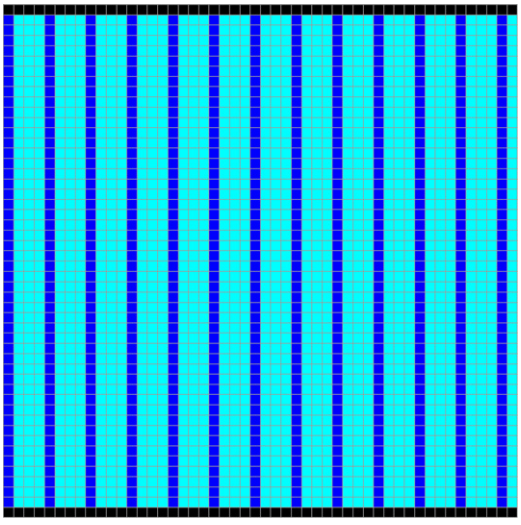

Fig. 1. Schematic: matrix $L = 50$ with $l = 4$, i.e. 3 stripes of high diffusivity followed by 1 stripe of low diffusivity.

Particles are moving inside the lattice performing random walks (Weiss, 1994). Particles are selected at random. They may stay immobile with a probability q, or move at a new randomly chosen neighboring site with probability $1 - q$. The case where $q = 0$, is identical to the classical random walk algorithm that is used to simulate diffusive motion (Kosmidis et al., 2003a, b; Landau and Binder, 2000; Bunde et al., 1985). The case $q \neq 0$ allows us to simulate diffusion processes with different diffusion coefficients (Kosmidis and Macheras, 2007; Landau and Binder, 2000; Bunde and Havlin, 1995). Let us consider a particle moving at a high diffusivity area. Then $q = 0$ and the diffusion coefficient is D_h. For a low diffusivity area there is a non-zero q and the diffusion coefficient is D_l. It can easily be shown (Kosmidis and Macheras, 2007) that these coefficients are related to the parameter q through the following equation:

$$\frac{D_l}{D_h} = 1 - q \tag{7}$$

Eq. (7) connects a quantity that is easily controlled in a Monte Carlo simulation with the ratio of the diffusion coefficients of the different areas.

If the site where the particle is located is marked as a high diffusivity area, then $q = 0$, otherwise q has a predefined non-zero value. If the new site is an empty site, then the move is allowed, and the particle is moved to this new site. If the new site is already occupied, the move is rejected (excluded volume interactions). The move is also rejected, if the new site is a reflecting boundary. A particle is removed from the lattice as soon as it migrates to a site lying within the leak area (the boundary). After each particle selection, time is increased by $1/N$, where N is the number of particles remaining in the system. Thus, in one MCS every one of the N particles has, on average, the possibility of moving one step. This is a typical approach in Monte Carlo simulations (Bunde et al., 1985). We monitor the number of particles that are present inside the lattice as a function of time until the lattice is completely empty of particles. A detailed description of the algorithm utilized is presented in Appendix A.

3. Results and discussion

Fig. 1 is a schematic of the geometry that we study. Each column of low diffusivity (dark colour) is followed by $l - 1$ columns of high diffusivity. The drug molecules are allowed to escape from the left and right boundaries only, and not from the top or bottom.

First, we are interested to check if the Weibull approximation, which is valid for release from Euclidean devices, devices comprised from random mixtures of areas with different diffusion coefficients and even fractal devices, is valid also in the present case. This is not trivial, taking into account the form of the differential equations that are relevant to this case, as discussed in Section 2. In Fig. 2, we present Monte Carlo simulation results of the fraction of drug released $M(t)/M_\infty$ as a function of time t, for a matrix with $L = 100$ and for different values of the parameter q, i.e. different diffusivity ratios and different periodic "length" l, namely $q = 0.5$, $l = 2$ (circles), $q = 0.90$, $l = 10$ (squares) and $q = 0.99 and l = 10$ (diamonds). Fitting of the Weibull model to the simulation data, shows that in all cases the Weibull model Eq. (1) is a rather good approximation of the release process in the case of periodic layers in the release device.

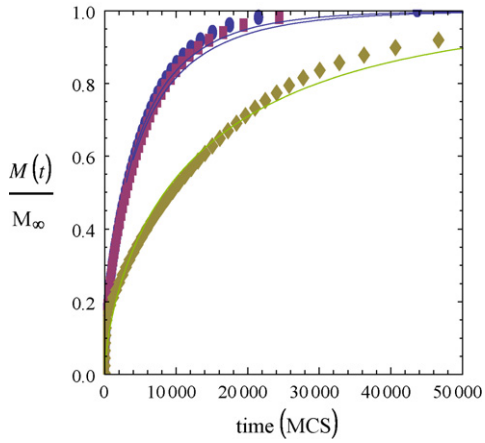

Fig. 2. Fraction of drug released from the matrix $M(t)/M_\infty$ as a function of time t. The points are Monte Carlo simulation data for a matrix with $L = 100$ and $q = 0.5, l = 2$ (circles), $q = 0.90, l = 10$ (squares) and $q = 0.99, l = 10$ (diamonds). The lines are fits of the Weibull model to the simulation data.

Next, we are interested in determining the influence of the periodic length l in the release profile. In Fig. 3 we plot the fraction of drug released from a matrix with $L = 100$, $M(t)/M_\infty$, as a function of time t, for two characteristic diffusivity ratios and several l values. The left plot presents the case where $q = 0.5$, i.e. the diffusion coefficient D_h is twice as large as the diffusion coefficient D_l. We examine different values of $l = 2, 6, 10$ (circles, squares, diamonds). We notice that in all cases the results are statistically the same and for this value of the diffusivity ratio the influence of l is practically negligible. The right plot presents the case of $q = 0.90$, i.e. the diffusion coefficient D_h is roughly ten times larger than the diffusion coefficient D_l, again for $l = 2, 6, 10$ (circles, squares, diamonds). We see that in this case for $l = 6, 10$ are statistically independent but there is an observable difference for $l = 2$ and the release process is considerably slower.

Next, we are interested in determining the reason of the slowing down of the release process. One simple explanation is that this is due to the introduction of a large number of slow diffusivity sites. For, $l = 2$ actually 50% of the device is comprised of low diffusivity areas, so it is natural to expect a slower process. However, we would like to examine if there is a part of the delay associated with the particular geometry as well. Thus, we have simulated the release process from release devices that have the same size with the periodic layered devices and the same amount of low and high diffusivity sites, but now the sites are randomly arranged inside the lattice. We use these "randomized" lattices as "control" devices. For example, the randomized lattice to be used as a comparison for the case of $l = 2$ is a lattice with 50% of its sites being low diffusivity sites, which are randomly placed inside the lattice. Any difference between the release profiles of the periodic and the corresponding randomized lattice is due to the specific periodic geometrical arrangement. In Fig. 4 we plot $M(t)/M_\infty$ as a function of time t for periodic lattices with $L = 100$ (circles) and the corresponding randomized lattices

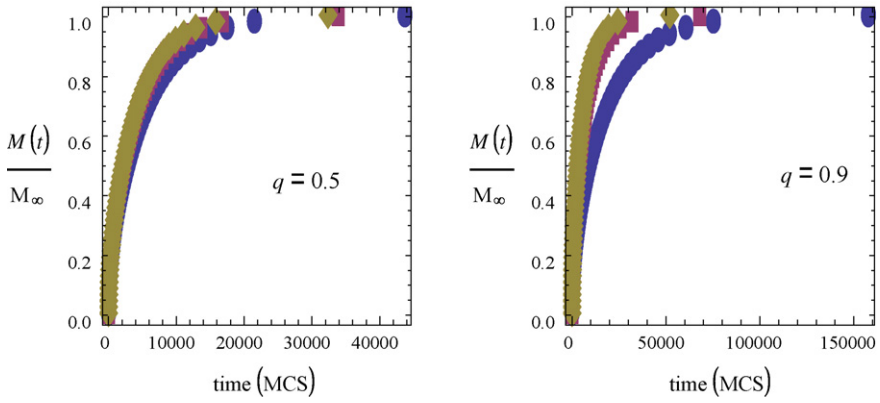

Fig. 3. Fraction of drug released from the matrix $M(t)/M_\infty$ as a function of time t. The points are Monte Carlo simulation data for a matrix with $L = 100$. Left: $q = 0.5$ and $l = 2, 6, 10$ (circles, squares, diamonds). Right: $q = 0.90$, and $l = 2, 6, 10$ (circles, squares, diamonds).

(squares). The top left plot shows the case of $q = 0.5$ and $l = 2$, the top right the case $q = 0.90$ and $l = 6$ (circles) the bottom left plot the case $q = 0.99$ and $l = 2$ and the bottom right the case of $q = 0.99$ $l = 10$. In the first three cases the release profile from the periodically arranged case are practically indistinguishable from the randomized case. However, the last plot shows considerable difference between the periodic and the randomized device indicating that the geometrical arrangement itself has an influence in the release profile and that the observed slowing down of the process cannot solely be attributed to the existence of an amount of low diffusivity sites.

Finally, we are interested in quantifying the above result and how it affects the parameters a and b of the Weibull model, Eq. (1). Thus, in Fig. 5 we plot the ratio of the Weibull exponent a (left plot) for release from periodic structures, to the exponent a_R for release from the corresponding randomized structure as a function of the "length" l. The same is done for the ratio of the Weibull exponent b (right plot) to the corresponding "randomized" exponent b_R. The different symbols correspond to different values of the parameter q, namely $q = 0.5$ (circles), $q = 0.90$ (squares) and $q = 0.99$ (diamonds). We observe that in all cases the exponent a is lower than the corresponding

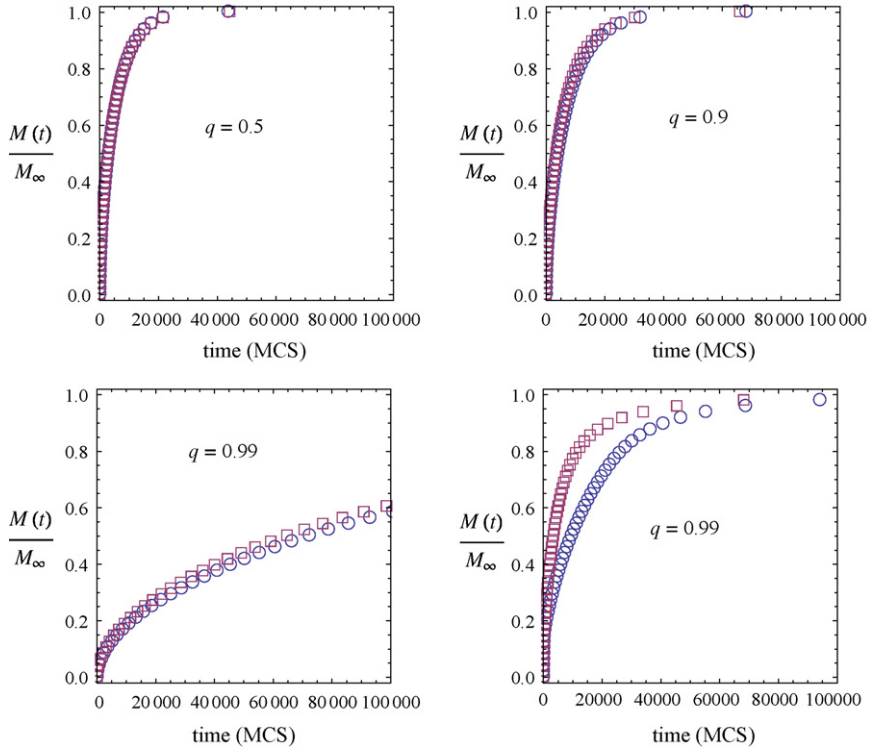

Fig. 4. Fraction of drug released from the matrix $M(t)/M_\infty$ as a function of time t. All points are Monte Carlo simulation data for matrices with $L = 100$. Top left: release fraction from a periodic structure, $q = 0.5$ and $l = 2$ (circles) and from a random structure with the same number of high and low diffusivity sites (squares). Top right: periodic structure $q = 0.90$, and $l = 6$ (circles), and the corresponding randomized structure (squares). Bottom left: periodic structure $q = 0.99$, and $l = 2$ (circles), and the corresponding randomized structure (squares). Bottom right: periodic structure $q = 0.99$, and $l = 10$ (circles), and the corresponding randomized structure (squares).

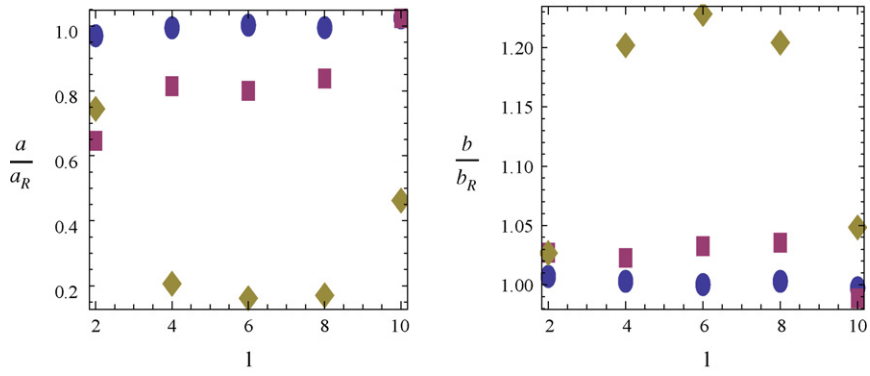

Fig. 5. Left: ratio of the Weibull exponent a for release from periodic structures to the corresponding exponent a_R for release from randomized structures as a function of the "length" l. Right: ratio of the Weibull exponent b for release from periodic structures to the corresponding exponent b_R for release from randomized structures as a function of the "length" l. Different symbols correspond to different values of the parameter q, namely $q = 0.5$ (circles), $q = 0.90$ (squares) and $q = 0.99$ (diamonds).

randomized exponent a_R, while the exponent b is in all cases larger than b_R. This last result has to be compared to the case of random mixing (Kosmidis and Macheras, 2007) where it was found that the exponent b was in most cases the same as the exponent for release from a uniform Euclidean device, or the case of release from fractal devices (Kosmidis et al., 2003b), where the exponent b is much lower than the case of a uniform Euclidean device. The differences between the randomized case and the periodic case are more profound when the ratio of diffusivities is high, i.e. in the case $q = 0.99$ (diamonds) where the diffusion coefficient D_h is roughly 100 times larger than the diffusion coefficient D_l. Moreover, the difference is more profound in intermediate values of l and not for $l = 2$ where the release device has a large part (50%) of low diffusivity sites. This can be qualitatively understood, since when there are a lot of sites that cause delay the drug molecules are "trapped" for a long time in these sites despite the fact that these sites are randomly placed in the lattice. When there are less low diffusivity sites the release is faster in the randomized case since there are not enough "delaying" sites, while in the periodic structure the same amount of sites causes considerable delay as there is no way for the drug molecules to bypass them. When on the other hand the l value is high (for example $l = 10$), there are only a few columns of low diffusivity in the lattice and the delay that they cause is again not very big. Again the difference between the periodic and randomized case is not big. Only for intermediate l values this difference becomes important leading to values of a/a_R and b/b_R which are significantly different from one.

4. Conclusions

We have studied drug release from matrices with periodic layers of high and low diffusivity. We have seen that the Weibull model describes the release process quite well. We have examined the similarities and differences between release from matrices with periodic layers and matrices with random mixtures of high and low diffusivity areas. We have found that the geometrical arrangement of the low diffusivity areas causes a difference in the release profile which is negligible for low diffusivity ratios but becomes important in the case of high diffusivity ratios and for intermediate values of the periodic "length". Such an arrangement in periodic layers will lead to Weibull exponent a which are lower than those of the corresponding random arrangement and exponents b which are higher than those of the random case.

Appendix A. Detailed description of the algorithm

1. Define an array $A(i, j)$, where $i = 0, \ldots, L + 1$ and $j = 0, \ldots, L + 1$. This array represents the release device and L is the system size.

2. $\forall i$ set $A(i, 0)$ and $A(i, L + 1)$ equal to -1. These are the absorbing boundaries. $\forall j$ set $A(0, j)$ and $A(L + 1, j)$ equal to -10. These represent the reflecting boundaries.

3. Set $A(i, j) = 0$ for all $i, j = 1, \ldots, L$. Next,

(a) Set $k = 1$ and $\forall i$ set $A(i, k) = 1$.

(b) Increase k by l (the length of the high diffusivity zones) (i.e. $k = k + l$) and repeat steps (a and b) until $k > L$. Sites where $A(i, j) = 1$ represent sites of low diffusivity.

4. For all $i, j = 1, \ldots, L$ draw a random number $x \in [0, 1]$. If $x < c = 0.5$ (the initial drug molecules concentration) insert a drug molecule in the system. Mark the coordinates of the molecule $x_n = i$, $y_n = j$ where n is an index for particle number n. At the end note the total number of drug molecules in the system N.

5. Select a particle n at random by drawing a random number. Check its coordinates i, j. If $A(i, j) = 0$ go to step number 6. Else go to step number 7.

6. (a) Select one of the four sites $(i + 1, j)$, $(i - 1, j)$, $(i, j + 1)$, $(i, j - 1)$ as destination site. Note the coordinates of the destination site as k, m. Check if the destination is free by ensuring that no particle has coordinates $x_d = k$, $y_d = m$ where d runs over all drug particle numbers. Check if $A(k, m) = -10$, i.e. if the destination is a reflecting boundary. If none of the above is true, then move the particle n setting $x_n = k$, $y_n = m$.

(b) Increase time t by an amount $1/N$, where N is the total number of drug molecules.

(c) If $A(k, m) = -1$, then remove the particle n from the system (do not allow further selection in step number 5). Set $N = N - 1$. Export N and time t in a file.

(d) Go to step number 8.

7. Draw a random number $x \in [0, 1]$. If $x < q$ (q is the ratio of diffusivities) then, return to step number 6. Else increase time t by an amount $1/N$.

8. Repeat steps numbers 3–7 until $N = 0$.

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