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Letter to the editor

Comments concerning: Monte Carlo simulations for the study of drug release from matrices with high and low diffusivity areas

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In a recent paper published in this journal, Kosmidis and Macheras (2007) studied the effectiveness of using the Weibull function in providing an adequate description of a passive release process. As the above title suggests, the authors produce their diffusional drug release profiles by simulating the process using a lattice Monte Carlo algorithm designed to model polymeric matrices with spatially dependent diffusivities. The purpose of this letter is not to criticize the work of the authors but to present an alternative approach in describing some of their results.

It is current practice to fit drug release profiles with simple empirical formulae as an alternative to solving the diffusion equation analytically (which is impractical in most realistic cases). Following this approach, the release profiles obtained from experimental measurements (or computer simulations) are fitted with a stretched exponential that gives the number of particles remaining inside the drug delivery systems, $N(t)$, as a function of time t. In the context of drug delivery studies, the Weibull stretched exponential is traditionally given the following form:

$$N(t) = N_0 \exp(-at^b), \tag{1}$$

where $N_0 \equiv N(0)$ is equal to the total amount of drug initially present in the matrix at time $t = 0$ and the exponents a and b are simply fitting parameters. Written in this manner however, the parameter a in Eq. (1) has dimensionality which depends on b (Macheras and Iliadis, 2006, p. 94). This does not readily offer any physical insight. For instance, plotting the parameter a versus any other parameter then yields a graph with inconsistent units.

We would like to stress the fact that the natural way to write the Weibull function is actually

$$N(t) = N_0 \exp\left(-\left(\frac{t}{\tau}\right)^b\right), \tag{2}$$

where $\tau = a^{-1/b}$. This is advantageous since the resulting characteristic fitting parameter τ has a consistent unit of time (Macheras and Iliadis, 2006, p. 94) and can thus be compared to other natural time scales related to the system, as we discuss next. Therefore, one can study how τ changes when some experimental condition is modified. Of course, one recovers the standard exponential decay $e^{-t/\tau}$ when $b = 1$. Additionally, the same argument holds when using a power law to fit the release process (e.g., the Peppas model, Ritger and Peppas, 1987). We thus propose that writing the Peppas model as

$$\frac{M(t)}{M_0} = \left(\frac{t}{\tau_\alpha}\right)^\alpha \tag{3}$$

would offer a similar advantage. Here, $M(t)$ is the cumulative amount of drugs released at time t from a hydrogel that initially contains M_0 particles. The resulting time scale, τ_α, can be directly compared to the Weibull characteristic time τ for short times since a simple series expansion of the Weibull function gives the Peppas power law to first order.

We also note that for a given drug release problem, one can define a typical diffusion time scale using the size, R, of the system and the diffusion coefficient D of the drug molecules in the system:

$$\tau_c = \frac{R^2}{2dD}, \tag{4}$$

where d is the dimensionality of the system (Teraoka, 2002, p. 177). Since the fitting times τ and τ_α represent natural escape time scales, they can be compared to τ_c. A large discrepancy between the fitting times and the predicted diffusion time scale would normally indicate that one is in the presence of anomalous diffusion. In this case the time scale defined by Eq. (4) is not relevant. One must however exercise caution since τ and τ_α are difficult to define due to the dependence of their values on the portion of the release profile used to perform the fits (Casault and Slater, 2008).

In the first portion of the article (Kosmidis and Macheras, 2007), the authors present a two dimensional ($d = 2$) homogeneous system of linear size L (with $L = 100$ and $L = 200$) where each initially placed particle has the probability $1 - q$ to move at each time step. The typical displacement of particles before escape is $R \simeq L/2$. The simulation data was fitted using the Weibull function written as Eq. (1) and the fitting parameter a was studied as a function of the parameter q for the two system sizes. For the reasons given previously, this approach does not represent the optimal way to analyze the simulation data. We would like to offer an alternative analysis. As demonstrated by the authors, this system has a clearly defined coefficient of diffusion $D = 1 - q$ in Monte Carlo units. The

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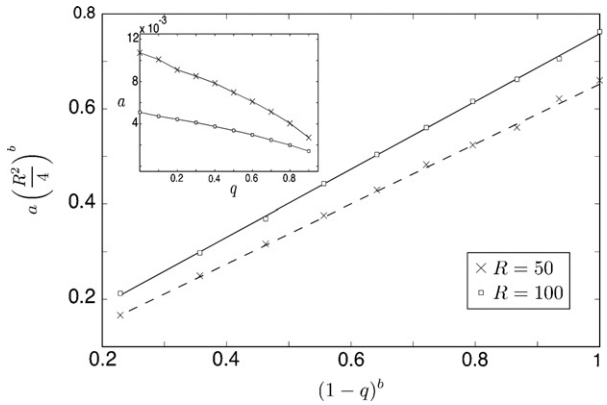

Fig. 1. Rescaled dependence of the parameter $a(R^2/4)^b$ as a function of $(1-q)^b$ for two (shown) system sizes (as in the article examined in this letter, $b = 0.64$). These data have been fitted with linear relationships with slopes of 0.64 and 0.71 for the systems of sizes $R \simeq L/2 = 50$ and $R = 100$, respectively. The inset shows the data from the original article (Kosmidis and Macheras, 2007).

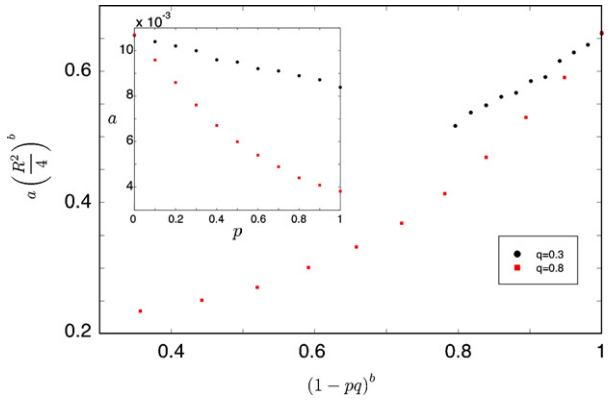

Fig. 2. Rescaled dependence of the parameter $a(R^2/4)^b$ as a function of $(1-pq)^b$ for two simulations with $R = 50$ (as in the original article, $b = 0.64$). The inset shows a view of the data from the original article.

characteristic diffusion time for this system is simply

$$\tau_c = \frac{R^2}{4(1-q)}. \tag{5}$$

This has been briefly explored in a previous article from the same authors (Kosmidis et al., 2003). Since we expect normal diffusion for this very simple system, the Weibull fitting time τ in Eq. (2) *must* be directly linked to the diffusion characterictic time τ_c defined in Eq. (5). Therefore, we predict that their fitting parameter a must scale like:

$$a = \frac{1}{\tau^b} \sim \left(\frac{4(1-q)}{R^2}\right)^b. \tag{6}$$

As we can see, the fitting parameter a used by these authors is actually expected to be a non-linear function of both the system size R and the diffusion parameter q. As we shall now demonstrate, it is possible to offer a clearer explanation of the results shown in Fig. 4 of their article (reproduced using a graph digitizer in the inset of Fig. 1) using our Eq. (6). The main part of our Fig. 1 shows that $a(R^2/4)^b$ varies linearly with $(1-q)^b$ for both system sizes, in agreement with Eq. (6). Moreover, the slopes are of order unity, which indicates that the Weibull fitting time τ and the system characteristic diffusion time τ_c are very close to each other. The fact that the two lines do not superpose is due to finite size effects (there is a depletion effect near the outer surface of such a drug delivery system (Kosmidis and Macheras, 2007); the ratio of the surface area to the volume decreases as $1/R$ in two dimensions, and this directly impacts the actual value of both b and τ for small systems).

In principle, it should be possible to perform a similar analysis of Fig. 6 from their article. In this figure, they create systems with varying probability p of having a site with sticking probability q. We can assume, as an approximation, that the diffusion coefficient is $D \approx (1-pq)$ and use it in Eq. (4) to perform a similar analysis as mentioned in the previous paragraphs. Such randomly distributed inhomogeneities will however have non-trivial effects on the diffusive motion of the particles. For example, if the site sticking probability q is high, the particles that are on these sites will act as obstacles for the other particles. Therefore, the real diffusion coefficient that one must use to compute the characteristic time τ_c is not proportional to $1/D$; instead, it must include the non-trivial many-particle effects mentioned above. Moreover, if both p and q are large, one may effectively be in the presence of a fractal system (i.e., a disordered system near its percolation threshold) for which one expects anomalous diffusion. Finally, it is important to note that these authors started with 50% of the sites occupied by drug particles; this means that the sticky sites were rapidly saturated for $p < 0.5$ but remained unsaturated for $p < 0.5$. The physics of saturated and unsaturated sticky sites is expected to be quite different, but the authors did not study this issue. Fig. 2 shows that there is an approximate linear relationship between our rescaled variables for the simulations performed at low sticking probability $q = 0.3$; but that this does not hold for $q = 0.8$. Consequently, fitting the dependency between a and p with a linear function (as presented by the authors) is not appropriate and obfuscates the physical subtleties in the diffusional mechanism. We note that the slope is of order unity for the $q = 0.3$ case in Fig. 2; therefore, we can conclude that we are still in the presence of normal diffusion in this limit.

In conclusion, we believe that the combination of Eqs. (2) and (4) provides a better way to analyze data. Using both a Weibull time scale and a diffusion time scale allows one to compare systems in a natural way and identify those cases where normal diffusion is probably not the main diffusion mechanism. The traditional Weibull parameter a does not directly provide such useful information.

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