Reconciling transport models across scales: The role of volume exclusion

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Diffusive transport is a universal phenomenon, throughout both biological and physical sciences, and models of diffusion are routinely used to interrogate diffusion-driven processes. However, most models neglect to take into account the role of volume exclusion, which can significantly alter diffusive transport, particularly within biological systems where the diffusing particles might occupy a significant fraction of the available space. In this work we use a random walk approach to provide a means to reconcile models that incorporate crowding effects on different spatial scales. Our work demonstrates that coarse-grained models incorporating simplified descriptions of excluded volume can be used in many circumstances, but that care must be taken in pushing the coarse-graining process too far.

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I. INTRODUCTION

Throughout the physical and biological sciences, diffusive transport is ubiquitous, and it takes places on a wide range of spatial and temporal scales. For example, in biology, diffusion is a key transport process that regulates events and interactions on levels ranging from those describing the behaviors of ions and subcellular macromolecules, to those of cells, tissues, and organisms [1]. Less well understood, however, is how volume-exclusion-driven crowding impacts upon these diffusive transport processes, despite the inherent fact that all diffusing particles exclude other particles from occupying the same region in space [2,3].

The majority of models of diffusive processes neglect to take into account the excluded volume effects that arise as a result of the nonzero volume of the diffusing particles. The predominant models describing diffusive transport over a range of spatial scales, and with varying excluded volume fractions, are "diffusion" partial differential equation (PDE) models with a constant diffusion coefficient [4–6], and random-walk-based models of point particles [7,8], both of which entirely neglect the impact of volume exclusion. Other models include phenomenological descriptions of volume exclusion effects by imposing that, for example, the diffusion coefficients of PDE models or the "jump rates" associated with random walk models depend locally on the particle density [9–13]. However, these phenomenological descriptions are usually chosen on an *ad hoc* basis, and the ramifications of choosing one description over another rarely explored in detail.

In this Rapid Communication we employ the framework of a lattice-based random walk to explore how volume exclusion may be taken into account at different spatial scales, and describe how to define the jump rates of the random walkers so as to provide a consistent description of the effects of volume exclusion across spatial scales. An additional advantage of our approach is that it provides for significant time savings in

the computational simulation of volume excluding individual-particle-level models of diffusive transport.

II. MODELING DIFFUSIVE TRANSPORT ON DIFFERENT SCALES

For simplicity, we consider a one-dimensional, lattice-based random walk model of diffusive transport in which the motile particles have length h. We work with the domain $x \in [0,L]$, where $L = Nh$ for some $N \in \mathbb{N}$, so that the domain can hold at most N particles. We impose a uniform lattice consisting of K compartments on the domain, so that the length of each compartment is L/K, and we work only with choices of K for which $m = L/(Kh)$ is a positive integer. This means that $N = Km$ and at most m particles fit into each of the K compartments [9,14–16]. We model diffusion as a series of jumps between compartments, and impose zero-flux boundary conditions on the domain (so that the particle number is conserved).

We move between different levels of spatial resolution by varying the compartment capacity m: Smaller values of m resolve changes in particle density on a finer spatial scale than larger values. The two limiting cases are full exclusion, $m = 1$, so that compartments contain at most one particle (and the position of the particle is fixed), and no exclusion, $m \to \infty$, so there is no limit on the number of particles per compartment. In this work, we shall term the $m = 1$ case "accurate", in the sense that no assumptions are made on the positions of particles with each compartment.

The common, phenomenological approach taken in the literature is to define the jump rates between compartments as

$$T_j^{\pm} = \frac{D}{m^2 h^2}\big[1 - f^{(m)}\big(n_{j\pm1}^{(m)}\big)\big], \quad j = 1, \ldots, K, \quad (1)$$

where $n_j^{(m)}$ is the number of particles in compartment j when each compartment has capacity m [17]. The function $f^{(m)}$ describes the effects of volume exclusion, effectively specifying the proportion of jumps that "fail" due to crowding [18]. The scaling of the jump rate with the square of the compartment size (mh) can be justified from mean first
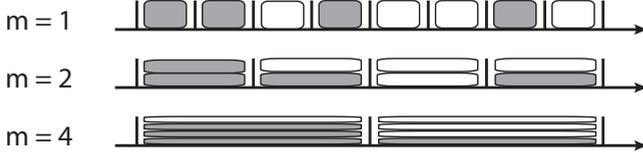
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FIG. 1. Representation of particle positions within compartments of different capacity. Shaded cells represent particles, and white cells represent unused capacity. As m increases, the spatial resolution coarsens, and this work reconciles the descriptions at these different scales.

passage time approaches [19]. Effects such as adhesion are often included by assuming the $T_j^{\pm}$ to also be a function of $n_j^{(m)}$ and $n_{j\pm1}^{(m)}$ [9,12]. In practice, the diffusion coefficient D may itself be a function of the length scale characterizing the transport process, especially at the smallest scales [20]. However, when modeling a range of biophysical phenomena, it is appropriate to approximate the diffusion coefficient as constant [21]. The implicit assumption in our framework is that the combined effects of other, nonmodeled, macromolecules and/or obstacles in the environment are encapsulated in the constant diffusion coefficient D.

Typically, these models on different scales are interrogated either by (i) using a repeated simulation of the random walk models to estimate summary statistics of interest, (ii) deriving and solving ordinary differential equations (ODEs) for the expected particle number per compartment, or (iii) deriving PDE models in the limit $h \to 0$ and using standard analytical and numerical techniques for PDEs to explore model behaviors. However, to the best of our knowledge, there has been little exploration of the effects of choosing different functional forms for $f^{(m)}$ on various summary statistics of the random walk models as the compartment capacity m varies. As such, one of the aims of this work is to understand how the mean and variance of particle numbers change as we move across spatial scales (by varying m, as illustrated in Fig. 1) and to provide a systematic derivation of coarse-grained ($m > 1$) models from the accurate ($m = 1$) model.

Sensible choices of $f^{(m)}$ require (i) the volume exclusion function to be zero when the compartment is empty, $f^{(m)}(0) = 0$, and (ii) the volume exclusion function to be unity when the compartment is at capacity, $f^{(m)}(m) = 1$. One of the goals of this work is to elucidate functional forms for $f^{(m)}$ that give rise to behaviors that are conserved across spatial scales. We do this by considering equations for mean and variance of particle numbers.

Mean particle numbers. The evolution of mean particle number in the jth compartment when the transition probabilities are as in Eq. (1) is given by the ordinary differential equation (see Ref. [22], Sec. I for a derivation of the master equation)

$$\frac{dM_j^{(m)}}{dt} = \frac{D}{m^2h^2}\big[-M_j^{(m)} + \langle n_j^{(m)} f^{(m)}(n_{j+1}^{(m)})\rangle$$
$$+ M_{j-1}^{(m)} - \langle n_{j-1}^{(m)} f^{(m)}(n_j^{(m)})\rangle\big]$$
$$+ \frac{D}{m^2h^2}\big[-M_j^{(m)} + \langle n_j^{(m)} f^{(m)}(n_{j-1}^{(m)})\rangle$$
$$+ M_{j+1}^{(m)} - \langle n_{j+1}^{(m)} f^{(m)}(n_j^{(m)})\rangle\big], \tag{2}$$

for $2 \leqslant j \leqslant K - 1$, where $\langle \cdot \rangle$ denotes the expectation and $M_j^{(m)} = \langle n_j^{(m)} \rangle$. Similar expressions apply for the boundary compartments, $j = 1, K$.

The case $m = 1$. Here at most one particle can occupy each compartment, the conditions stated above are enough to fully define $f^{(1)}$, and we have [23]

$$\frac{dM_j^{(1)}}{dt} = \frac{D}{h^2}\big(M_{j-1}^{(1)} - 2M_j^{(1)} + M_{j+1}^{(1)}\big), \tag{3}$$

for $2 \leqslant j \leqslant K - 1$. Similar expressions apply for the boundary compartments, $j = 1, K$. Equation (3) is a semidiscrete diffusion equation and, in the limit $h \to 0$, it gives rise to the diffusion equation with constant diffusion coefficient D.

The case $m = \infty$. Letting $m \to \infty$ entails the limit of zero volume exclusion. To analyze the evolution of mean particle number we represent the compartment size as $\tilde{h} = L/K$ so that, similar to the $m = 1$ case, we have

$$\frac{dM_j^{(\infty)}}{dt} = \frac{D}{\tilde{h}^2}\big(M_{j-1}^{(\infty)} - 2M_j^{(\infty)} + M_{j+1}^{(\infty)}\big), \tag{4}$$

for $2 \leqslant j \leqslant K - 1$. Similar expressions apply for the boundary compartments, $j = 1, K$. As for the $m = 1$ case, Eq. (4) is a semidiscrete diffusion equation and, in the limit $\tilde{h} \to 0$, it gives rise to the diffusion equation with constant diffusion coefficient D.

The case $1 < m < \infty$. To ensure the model is consistent across spatial scales, it is appropriate to confine choices for $f^{(m)}$ for $1 < m < \infty$ to those that also give rise to a semidiscrete diffusion equation with a constant diffusion coefficient for mean particle numbers. The only choice for $f^{(m)}$ is then

$$f^{(m)}(n_j^{(m)}) = \frac{n_j^{(m)}}{m}, \tag{5}$$

which gives, as anticipated,

$$\frac{dM_j^{(m)}}{dt} = \frac{D}{m^2h^2}\big(M_{j-1}^{(m)} - 2M_j^{(m)} + M_{j+1}^{(m)}\big), \tag{6}$$

for $2 \leqslant j \leqslant K - 1$. Similar expressions apply for the boundary compartments, $j = 1, K$.

Variance of particle numbers. For the choice of volume exclusion function given in Eq. (5) we can also obtain equations for the evolution of the variance of particle numbers,

$$\frac{dV_j^{(m)}}{dt} = \frac{D}{m^2h^2}\left[2\left(\frac{m-1}{m}\right)V_{j,j-1}^{(m)} - 4V_j^{(m)} + 2\left(\frac{m-1}{m}\right)V_{j,j+1}^{(m)}\right]$$
$$+ \frac{D}{m^2h^2}\left[M_{j-1}^{(m)}\left(1 - \frac{M_j^{(m)}}{m}\right) + M_j^{(m)}\left(1 - \frac{M_{j-1}^{(m)}}{m}\right) + M_j^{(m)}\left(1 - \frac{M_{j+1}^{(m)}}{m}\right) + M_{j+1}^{(m)}\left(1 - \frac{M_j^{(m)}}{m}\right)\right], \tag{7}$$

for $2 \leqslant j \leqslant K-1$, where $V_j^{(m)}$ is the variance of particle numbers in compartment j, and $V_{j,k}^{(m)}$ is the covariance of particle numbers in compartments j and k:

$$\frac{dV_{j-1,j}^{(m)}}{dt} = \frac{D}{m^2h^2}\left[\left(\frac{2}{m}-4\right)V_{j-1,j}^{(m)} + V_j^{(m)} + V_{j-1}^{(m)} + V_{j-2,j}^{(m)} + V_{j-1,j+1}^{(m)} - M_{j-1}^{(m)}\left(1-\frac{M_j^{(m)}}{m}\right) - M_j^{(m)}\left(1-\frac{M_{j-1}^{(m)}}{m}\right)\right];$$

$$\frac{dV_{j,k}^{(m)}}{dt} = \frac{D}{m^2h^2}\left[-4V_{j,k}^{(m)} + V_{j-1,k}^{(m)} + V_{j+1,k}^{(m)} + V_{j,k-1}^{(m)} + V_{j,k+1}^{(m)}\right] \quad \text{for} \quad 1 < j < k-1 < K, \quad 1 < k+1 < j < K. \quad (8)$$

Similar expressions can be found for the boundary compartments, $j = 1, K$.

III. CONSISTENCY OF THE CHOICE OF VOLUME EXCLUSION FUNCTION

We consider the $m = 1$ case to represent the most "accurate" model of volume exclusion effects for an on-lattice model of diffusion as it implies, simply, that one particle cannot overlap with another. When coarse graining this model, to consider random walk models with compartment capacities $m > 1$, our aim is that the mean and variance of particle numbers in each compartment are conserved. In what follows, we will sum the mean and variance of compartment occupancy of the accurate, $m = 1$, model over groups of m contiguous compartments to explore how accurate we can expect the coarse-grained model to be.

To this end, we will define

$$S_j^{(m)}(t) = \sum_{i=(j-1)m+1}^{jm} n_i^{(1)}(t), \quad (9)$$

with $\mu_j^{(m)}(t)$ the mean of $S_j^{(m)}(t)$, and $v_j^{(m)}(t)$ its variance. We wish to establish the relationship between (i) $\mu_j^{(m)}(t)$ and $M_j^{(m)}(t)$, and (ii) $v_j^{(m)}(t)$ and $V_j^{(m)}(t)$.

Steady state values. Equations (6)–(8), together with the additional constraint that the sum of all variance and covariance terms must be zero (since N is constant), gives the steady states

$$\hat{M}_i^{(m)} = \frac{N}{K}, \quad (10)$$

$$\hat{V}_i^{(m)} = \frac{N(K-1)}{K\left(K-\frac{1}{m}\right)}\left(1-\frac{N}{mK}\right), \quad (11)$$

$$\hat{V}_{i,j}^{(m)} = \frac{-N}{K\left(K-\frac{1}{m}\right)}\left(1-\frac{N}{mK}\right), \quad i \neq j, \quad (12)$$

where $1 \leqslant i, j \leqslant K$ and circumflexes are used to denote steady state values. It is then simple to check that

$$\hat{\mu}_j^{(m)} = \hat{M}_j^{(m)}, \quad (13)$$

$$\hat{v}_j^{(m)} = \hat{V}_j^{(m)}, \quad (14)$$

i.e., the steady state means and variances are conserved through the process of coarse graining.

Time evolution. To obtain an expression for the evolution of $\mu_j^{(m)}$, we note

$$\frac{d\mu_j^{(m)}}{dt} = \sum_{i=(j-1)m+1}^{jm} \frac{dM_i^{(1)}}{dt}$$

$$= \frac{D}{h^2}\sum_{i=(j-1)m+1}^{jm}\left(M_{i-1}^{(1)} - 2M_i^{(1)} + M_{i+1}^{(1)}\right)$$

$$= \frac{D}{h^2}\left(M_{(j-1)m}^{(1)} - M_{(j-1)m+1}^{(1)} - M_{jm}^{(1)} + M_{jm+1}^{(1)}\right). \quad (15)$$

We compare this to the coarse-grained model, Eq. (6), which we restate here for convenience:

$$\frac{dM_j^{(m)}}{dt} = \frac{D}{m^2h^2}\left(M_{j-1}^{(m)} - 2M_j^{(m)} + M_{j+1}^{(m)}\right).$$

To relate Eqs. (6) and (15), and understand when we expect the coarse-grained model to replicate the dynamics of the accurate, $m = 1$, model, we need to establish a relationship between the $M_j^{(1)}$ $(j = 1, \dots, N)$ and the $M_j^{(m)}$ $(j = 1, \dots, K)$.

A natural choice for the coarse graining would be to assume $M_i^{(1)} \approx M_j^{(m)}/m$ for $i = (j-1)m+1, \dots, jm$. However, Eq. (15) would then give rise to a diffusion equation with a constant diffusion coefficient m times larger than expected in the limit $h \to 0$. This means that our coarse-grained model does *not* require the stringent condition that particles in a compartment of size m are uniformly distributed throughout that compartment.

Instead, consistency between the accurate $(m = 1)$ and the coarse-grained $(m > 1)$ models arises from assuming particles in the $m > 1$ compartments are distributed, on average, according to a linear interpolation between $m > 1$ neighboring compartments rather than being uniformly distributed throughout the compartment,

$$M_{jm}^{(1)} = \frac{1}{m}\left(\frac{1}{2}\frac{m+1}{m}\mu_j^{(m)} + \frac{1}{2}\frac{m-1}{m}\mu_{j+1}^{(m)}\right), \quad (16)$$

$$M_{jm+1}^{(1)} = \frac{1}{m}\left(\frac{1}{2}\frac{m-1}{m}\mu_j^{(m)} + \frac{1}{2}\frac{m+1}{m}\mu_{j+1}^{(m)}\right), \quad (17)$$
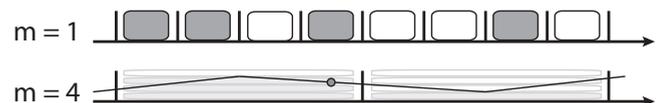

FIG. 2. Schematic of the interpolation process for $m = 4$.

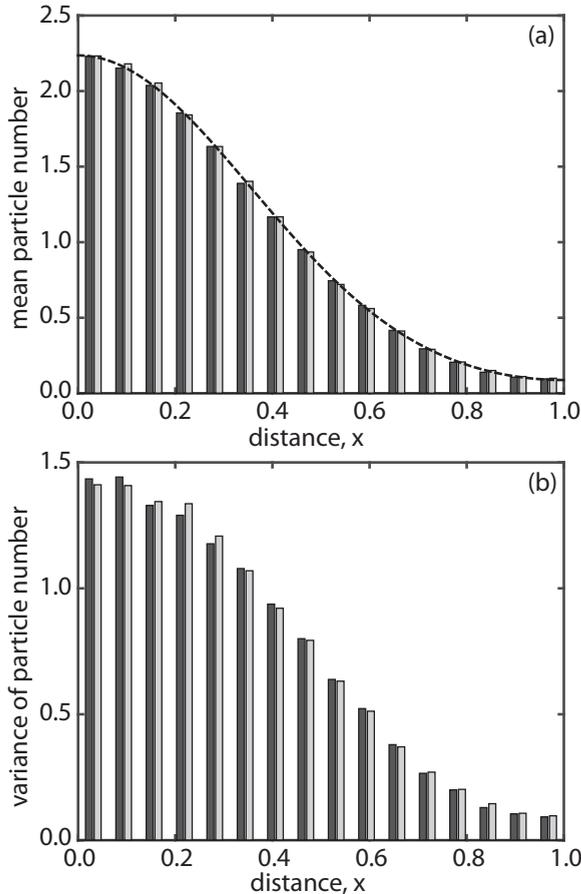FIG. 3. Comparing the (a) mean and (b) variance of particle numbers for the $m = 1$ and $m = 8$ cases at $t = 1$, with $K = 128/m$. Dark gray bars: Results from simulation of the random walk model with $m = 1$. Light gray bars: Results from the numerical solution of Eq. (6)/Eq. (7) with $m = 8$. Black dashed line in (a): Solution of the limiting diffusion equation.

as shown in Fig. 2, with similar values for $M^{(1)}_{(j-1)m}$ and $M^{(1)}_{(j-1)m+1}$. As a result, we have

$$\frac{d\mu^{(m)}_j}{dt} = \frac{D}{m^2 h^2}\left(\mu^{(m)}_{j-1} - 2\mu^{(m)}_j + \mu^{(m)}_{j+1}\right), \qquad (18)$$

and evolution of the mean particle numbers in the coarse-grained system matches that of the accurate model.

The entries of the covariances matrix $\{V^{(1)}_{i,j}\}$ cannot be interpolated in the same way, since its entries are positive on the diagonal and negative everywhere else. However, we can use similar reasoning to argue that the variances $v^{(m)}_j$ and $V^{(m)}_j$ will also match, as presented in the Supplemental Material [22].

IV. NUMERICAL INVESTIGATIONS

We now present numerical results to corroborate our findings. We consider the domain $x \in [0,1]$ with $h = 1/128$ and $D = 10^3/128^2$. The initial condition is $n^{(1)}_j(0) = 1$, for $j = 1, \ldots, 16$, and $n^{(1)}_j(0) = 0$ otherwise, and attempts by particles to jump left out of compartment 1 or right out of compartment 128 are aborted.

We compare results from 5000 realizations of the random walk model with $m = 1$ with 5000 realizations of the same model with $m = 8$ in Fig. 3. (See Ref. [22], Sec. III for details of the simulation algorithm.) The mean values predicted using both the $m = 8$ and PDE models are in excellent agreement with those predicted from the accurate $m = 1$ model. In addition, we see good agreement between the variances of the $m = 1$ and $m = 8$ models. Finally, we note that an additional advantage of the coarse-grained model is that generating realizations of the discrete random walk model with $m > 1$ can be achieved in $1/m^2$ of the time required by the $m = 1$ case, since the jump rates will be m^2 times smaller and so far fewer jumps will need to be simulated.

To compute the error in the coarse-graining process, we solved the ODEs for both the means and variances, Eqs. (6) and (7), over a range of values of m [24]. Results for $m > 1$ were compared against results with $m = 1$ using the histogram distance error (HDE) metric [25], HDE $= \frac{1}{2}\sum_{k=1}^{K}|e_k - p_k|$, where e_k is the normalized value of the kth aggregated compartment of the $m = 1$ model and p_k is the normalized value of the kth compartment of the $m > 1$ model. Figure 4 demonstrates the evolution of the error between the models with different values of m between $t = 0$ and $t = 1$. The HDE remains low in all cases observed, even though the initial condition does not satisfy the requirement that the densities in the $m = 1$ case can be accurately interpolated onto the coarse ($m > 1$) lattice.
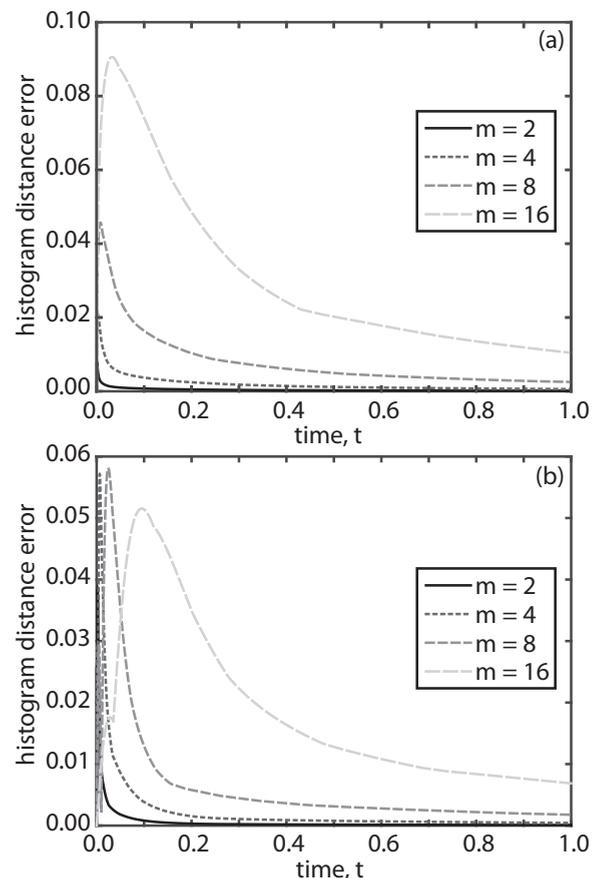

FIG. 4. HDEs for the (a) means and (b) variances in particle numbers as m is varied [22].

V. CONCLUSIONS

In this Rapid Communication we have used an on-lattice random walk approach to reconcile models of diffusive transport that incorporate the effects of excluded volume across spatial scales. Our work demonstrates that coarse-grained models incorporating simplified descriptions of excluded volume can be used in many circumstances, and these simplified models engender significantly lower computational costs than their accurate counterparts. These computational savings will be especially valuable for models in two or three spatial dimensions. However, care must be taken in pushing the coarse-graining process too far. For example, there is a delicate trade-off between the initial conditions of the model and the size of m.

Future work will be directed towards hybrid approaches, in which a detailed description of the spatial dynamics can be retained where necessary, and the computational savings associated with the coarse-grained model taken advantage of where possible. In addition, we will extend our approach to model reactions and take into account more general jump rules to incorporate effects such as bias [26], or interparticle adhesion. Zeroth and first order reactions, such as particles entering the system as a constant rate, or decaying with some rate, are relatively simple to implement, but higher order reactions provide a more significant challenge.

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