Appendix A: Outline of transition rate derivations

Transition rates between compartments can be obtained from standard first passage process results [1]. Consider a particle undergoing Brownian motion, starting from x_j, the residence point of the j^{th} compartment. The probability distribution for its position, $p(x,t)$, evolves in time following the diffusion equation,

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2}. \tag{A1}$$

To calculate transition rates between compartments, we consider a first passage process on the interval $x \in [x_{j-1}, x_{j-1}]$ to determine the expected time until a particle starting from one residence point reaches one of its neighbouring residence points. For the diffusion equation, this means defining boundary conditions $p(x_{j-1},t) = p(x_{j-1},t) = 0$, and initial condition $p(x,0) = \delta(x - x_j)$. By applying a Laplace transform, it is possible to obtain the eventual hitting probabilities describing the likelihood of the particle leaving to either side of the interval [2]

$$\epsilon_-(x_j) = \frac{x_{j+1} - x_j}{x_{j+1} - x_{j-1}}, \tag{A2}$$

$$\epsilon_+(x_j) = \frac{x_j - x_{j-1}}{x_{j+1} - x_{j-1}}. \tag{A3}$$

Combining these values with the conditional mean exit times

$$\langle t(x_j)\rangle_- = \frac{(x_j - x_{j-1})(2x_{j+1} - x_j - x_{j-1})}{6D}, \tag{A4}$$

$$\langle t(x_j)\rangle_+ = \frac{(x_{j+1} - x_j)(x_{j+1} + x_j - 2x_{j-1})}{6D}, \tag{A5}$$

we can then obtain the unconditional exit time

$$\begin{aligned}
\langle t(x_j)\rangle &= \epsilon_-(x_j)\langle t(x_j)\rangle_- + \epsilon_+(x_j)\langle t(x_j)\rangle_+ \\
&= \frac{(x_j - x_{j-1})(x_{j+1} - x_j)\left([2x_{j+1} - x_j - x_{j-1}] + [x_{j+1} + x_j - 2x_{j-1}]\right)}{6D(x_{j+1} - x_{j-1})} \\
&= \frac{(x_j - x_{j-1})(x_{j+1} - x_j)\left(3x_{j+1} - 3x_{j-1}\right)}{6D(x_{j+1} - x_{j-1})} \\
&= \frac{(x_j - x_{j-1})(x_{j+1} - x_j)}{2D}.
\end{aligned} \tag{A6}$$

Inverting the unconditional exit times gives the unconditional exit rate, and by multiplying this value by the hitting probabilities we obtain the non-excluding transition rates

$$\mathcal{T}_j^- = \frac{\epsilon_-(x_j)}{\langle t(x_j)\rangle} = \frac{2D}{(x_j - x_{j-1})(x_{j+1} - x_{j-1})} = \frac{Dh}{\Delta x_j m_j},$$
$$\mathcal{T}_j^+ = \frac{Dh}{\Delta x_{j+1} m_j}. \tag{A7}$$

It is also possible to derive these values using a finite element approach [3]. Transition rates for the two boundary compartments, $j = 1, K$, can be derived similarly using the reflection principle of Brownian motion. For example, define a notional point $x_0 = -x_2$, then the unconditional expected exit time for the first box is

$$\langle t(x_1)\rangle = \frac{(x_1 - x_0)(x_2 - x_1)}{2D} = \frac{(x_1 + x_2)(x_2 - x_1)}{2D}. \tag{A8}$$

Clearly $\epsilon_+(x_1) = 1$, hence we write

$$\mathcal{T}_1^+ = \frac{Dh}{\Delta x_2 m_1}. \tag{A9}$$

We can similarly derive $\mathcal{T}_K^-$ by reflecting x_{K-1} about $x = L$.

Appendix B: Voronoi master equation derivations

The following derivations are based upon those found in the Supplemental Information of a previous paper, generalised here to a non-uniform Voronoi lattice [4]. Recall that a spatial lattice composed of K compartments has been defined. The distribution of particles over this domain is given by the vector $\mathbf{n}(t) = [n_1(t), n_2(t), ..., n_K(t)]$, where $n_i(t)$ denotes the number of particles in the i^{th} compartment at time t. Particles in compartment i may *attempt* to jump out to compartments $i-1$ or $i+1$ with rates $\mathcal{T}_i^-$ and $\mathcal{T}_i^+$, respectively.

We define two operators, $J_i^+ : \mathbb{R}^K \to \mathbb{R}^K$, for $i = 1, ..., K-1$, and $J_i^- : \mathbb{R}^K \to \mathbb{R}^K$, for $i = 2, ..., K$, as

$$J_i^+ : [n_1, ..., n_i, ..., n_K] \to [n_1, ..., n_{i-2}, n_{i-1}, n_i + 1, n_{i+1} - 1, n_{i+2}, ..., n_K], \tag{B1}$$

$$J_i^- : [n_1, ..., n_i, ..., n_K] \to [n_1, ..., n_{i-2}, n_{i-1} - 1, n_i + 1, n_{i+1}, n_{i+2}, ..., n_K]. \tag{B2}$$

Both operators move a particle into compartment i, taken from the compartment to the right or left, respectively. We assume that attempted jumps into some compartment j fail with probability n_j/m_j due to exclusion effects. We can then write the probability master equation as

$$\begin{aligned}
\frac{\mathrm{dPr}(\mathbf{n},t)}{\mathrm{d}t} &= \sum_{i=1}^{K-1} T_i^+ \left\{(n_i+1)\mathrm{Pr}(J_i^+\mathbf{n},t) - n_i\mathrm{Pr}(\mathbf{n},t)\right\} \\
&+ \sum_{i=2}^{K} T_i^- \left\{(n_i+1)\mathrm{Pr}(J_i^-\mathbf{n},t) - n_i\mathrm{Pr}(\mathbf{n},t)\right\}. \\
&= \sum_{i=1}^{K-1} \mathcal{T}_i^+ \left\{(n_i+1)\left[1-\frac{n_{i+1}-1}{m_{i+1}}\right]\mathrm{Pr}(J_i^+\mathbf{n},t) - n_i\left[1-\frac{n_{i+1}}{m_{i+1}}\right]\mathrm{Pr}(\mathbf{n},t)\right\} \\
&+ \sum_{i=2}^{K} \mathcal{T}_i^- \left\{(n_i+1)\left[1-\frac{n_{i-1}-1}{m_{i-1}}\right]\mathrm{Pr}(J_i^-\mathbf{n},t) - n_i\left[1-\frac{n_{i-1}}{m_{i+1}}\right]\mathrm{Pr}(\mathbf{n},t)\right\}.
\end{aligned} \tag{B3}$$

Define the mean vector, $\mathbf{M} = [M_1, ..., M_K]$, where

$$M_j = \sum_{n_1=1}^{N}\sum_{n_2=1}^{N}\cdots\sum_{n_K=1}^{N} n_j\mathrm{Pr}(\mathbf{n},t) := \sum_{n_1,n_2,...,n_K=0}^{\mathcal{N}} n_j\mathrm{Pr}(\mathbf{n},t). \tag{B4}$$

Multiplying Eq. (B3) by n_j and summing over all possible values that the vector $\mathbf{n}(t)$ can take we have

$$\begin{aligned}
\frac{\mathrm{d}M_j}{\mathrm{d}t} = \sum_{n_1,n_2,...,n_K=0}^{\mathcal{N}} n_j \Bigg(&\sum_{i=1}^{K-1} \mathcal{T}_i^+ \left\{(n_i+1)\left[1-\frac{n_{i+1}-1}{m_{i+1}}\right]\mathrm{Pr}(J_i^+\mathbf{n},t) - n_i\left[1-\frac{n_{i+1}}{m_{i+1}})\right]\mathrm{Pr}(\mathbf{n},t)\right\} \\
&+ \sum_{i=2}^{K} \mathcal{T}_i^- \left\{(n_i+1)\left[1-\frac{n_{i-1}-1}{m_{i+1}}\right]\mathrm{Pr}(J_i^-\mathbf{n},t) - n_i\left[1-\frac{n_{i-1}}{m_{i+1}}\right]\mathrm{Pr}(\mathbf{n},t)\right\}\Bigg).
\end{aligned} \tag{B5}$$

We begin by considering only the first term of this expression, with $\mathrm{Pr}(J_i^+\mathbf{n},t)$ expanded explicitly to give

$$\sum_{n_1,n_2,...,n_K=0}^{\mathcal{N}} n_j \sum_{i=1}^{K-1} d(n_i+1)\left[1-f(n_{i+1}-1)\right]\mathrm{Pr}(n_1,n_2,...,n_i+1,n_{i+1}-1,...n_K,t). \tag{B6}$$

When $i \neq j, j-1$ each term of this expression reduces to

$$\mathcal{T}_i^+\langle n_j n_i\rangle - \mathcal{T}_i^+\langle n_j n_i f(n_{i+1})\rangle, \tag{B7}$$

where $\langle n_j n_i\rangle$ indicates the mean of the product. When $i = j$,

$$\begin{aligned}
&\sum_{n_1,n_2,...,n_K=0}^{\mathcal{N}} n_j \mathcal{T}_j^+(n_j+1)\left[1-f(n_{j+1}-1)\right]\mathrm{Pr}(n_1,n_2,...,n_j+1,n_{j+1}-1,...n_K,t) \\
=& \sum_{n_1,n_2,...,n_K=0}^{\mathcal{N}} \mathcal{T}_j^+(n_j+1)^2\left[1-f(n_{j+1}-1)\right]\mathrm{Pr}(n_1,n_2,...,n_j+1,n_{j+1}-1,...n_K,t) \\
&- \mathcal{T}_j^+(n_j+1)\left[1-f(n_{j+1}-1)\right]\mathrm{Pr}(n_1,n_2,...,n_j+1,n_{j+1}-1,...n_K,t) \\
=& \quad \mathcal{T}_j^+[\langle n_j n_j\rangle - \langle n_j n_j f(n_{j+1})\rangle - M_j + \langle n_j f(n_{j+1})\rangle].
\end{aligned} \tag{B8}$$

Similarly for $i = j - 1$,

$$\begin{aligned} & \sum_{n_1, n_2, \ldots, n_K = 0}^{\mathcal{N}} \mathcal{T}_{j-1}^{+} n_j (n_{j-1} + 1) \left[1 - f(n_j - 1)\right] \Pr(n_1, n_2, \ldots, n_{j-1} + 1, n_j - 1, \ldots n_K, t) \\ = & \quad \mathcal{T}_{j-1}^{+} [\langle n_{j-1} n_j \rangle - \langle n_{j-1} n_j f(n_j) \rangle + M_{j-1} - \langle n_{j-1} f(n_j) \rangle]. \end{aligned} \tag{B9}$$

We then consider the second term,

$$- \sum_{n_1, n_2, \ldots, n_K = 0}^{\mathcal{N}} n_j \sum_{i=1}^{K-1} \mathcal{T}_i^{+} n_i \left[1 - f(n_{i+1})\right] \Pr(n_1, n_2, \ldots, n_i, \ldots, n_K, t), \tag{B10}$$

which evaluates to

$$- \sum_{i=1}^{K-1} \mathcal{T}_i^{+} \left[\langle n_i n_j \rangle - \langle n_i f(n_{i+1}) n_j \rangle\right]. \tag{B11}$$

When combined with the expressions derived from the first term these give us

$$- \mathcal{T}_j^{+} M_j + \mathcal{T}_j^{+} \langle n_j f(n_{j+1}) \rangle + \mathcal{T}_{j-1}^{+} M_{j-1} - \mathcal{T}_{j-1}^{+} \langle n_{j-1} f(n_j) \rangle. \tag{B12}$$

Applying the same approach to the third and fourth terms we obtain

$$- \mathcal{T}_j^{-} M_j + \mathcal{T}_j^{-} \langle n_j f(n_{j-1}) \rangle + \mathcal{T}_{j+1}^{-} M_{j+1} - \mathcal{T}_{j+1}^{-} \langle n_{j+1} f(n_j) \rangle. \tag{B13}$$

Adding this expression to Eq. (B12), we arrive at

$$\begin{aligned} \frac{\mathrm{d}M_j}{\mathrm{d}t} = & \quad \mathcal{T}_{j-1}^{+} \left(M_{j-1} - \frac{1}{m_j} \langle n_{j-1} n_j \rangle \right) - \mathcal{T}_j^{-} \left(M_j - \frac{1}{m_{j-1}} \langle n_{j-1} n_j \rangle \right) \\ & - \mathcal{T}_j^{+} \left(M_j - \frac{1}{m_{j+1}} \langle n_j n_{j+1} \rangle \right) + \mathcal{T}_{j+1}^{-} \left(M_{j+1} - \frac{1}{m_j} \langle n_j n_{j+1} \rangle \right), \end{aligned} \tag{B14}$$

as stated in Eq. (**??**) of the main text.

Variance equations can be derived using the same approach. We begin by using Eq. (B3) to obtain

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\sum^{\mathcal{N}} n_i^2 P(\mathbf{n}) = \; & \mathcal{T}_{i-1}^{+} \left(2\langle n_{i-1}n_i\rangle - \frac{2}{m_i}\langle n_{i-1}n_i n_i\rangle + M_{i-1} - \frac{1}{m_i}\langle n_{i-1}n_i\rangle\right) \\
& + \mathcal{T}_{i}^{+} \left(-2\langle n_i n_i\rangle + \frac{2}{m_{i+1}}\langle n_i n_i n_{i+1}\rangle + M_i - \frac{1}{m_{i+1}}\langle n_i n_{i+1}\rangle\right) \\
& + \mathcal{T}_{i}^{-} \left(-2\langle n_i n_i\rangle + \frac{2}{m_{i-1}}\langle n_{i-1} n_i n_i\rangle + M_i - \frac{1}{m_{i-1}}\langle n_{i-1} n_i\rangle\right) \\
& + \mathcal{T}_{i+1}^{-} \left(2\langle n_i n_{i+1}\rangle - \frac{2}{m_i}\langle n_i n_i n_{i+1}\rangle + M_{i+1} - \frac{1}{m_i}\langle n_i n_{i+1}\rangle\right), \\
\Rightarrow \frac{\mathrm{d}}{\mathrm{d}t}\langle n_i^2\rangle = \; & \mathcal{T}_{i-1}^{+} \left(2\langle n_{i-1}n_i\rangle + M_{i-1} - \frac{1}{m_i}\langle n_{i-1}n_i\rangle\right) \\
& + \mathcal{T}_{i}^{+} \left(-2\langle n_i n_i\rangle + M_i - \frac{1}{m_{i+1}}\langle n_i n_{i+1}\rangle\right) \\
& + \mathcal{T}_{i}^{-} \left(-2\langle n_i n_i\rangle + M_i - \frac{1}{m_{i-1}}\langle n_{i-1} n_i\rangle\right) \\
& + \mathcal{T}_{i+1}^{-} \left(2\langle n_i n_{i+1}\rangle + M_{i+1} - \frac{1}{m_i}\langle n_i n_{i+1}\rangle\right),
\end{aligned}
\tag{B15}
$$

where we have used $\mathcal{T}_i^-/m_{i-1} = \mathcal{T}_{i-1}^+/m_i$ and $\mathcal{T}_{i+1}^-/m_i = \mathcal{T}_i^+/m_{i+1}$. We then use $\langle n_i n_j\rangle = V_{i,j} - M_i M_j$ to obtain

$$
\begin{aligned}
\frac{\mathrm{d}V_j}{\mathrm{d}t} = & -2\left(\mathcal{T}_j^- + \mathcal{T}_j^+\right)V_j + 2T_{j-1}^+\left(1 - \frac{1}{m_j}\right)V_{j-1,j} + 2T_{j+1}^-\left(1 - \frac{1}{m_j}\right)V_{j,j+1} \\
& + \mathcal{T}_{j-1}^+ M_{j-1}\left(1 - \frac{M_j}{m_j}\right) + \mathcal{T}_j^- M_i\left(1 - \frac{M_{j-1}}{m_{j-1}}\right) \\
& + \mathcal{T}_j^+ M_j\left(1 - \frac{M_{j+1}}{m_{j+1}}\right) + \mathcal{T}_{j+1}^- M_{j+1}\left(1 - \frac{M_j}{m_j}\right),
\end{aligned}
\tag{B16}
$$

with equations for the covariances obtainable in a similar manner.

Appendix C: Outline of simulation algorithm

In second part of this paper, we compare realisations of four different models of volume-excluding diffusion. The following algorithm was used to generate realisations between $t = 0$ and $t = 25$:

1. Set *timeElapsed* $= 0$ to track the duration of the simulation, and initialise an array to track particle locations.

2. Generate the exponentially distributed

$$
timeUntilNextEvent = -\ln(rand)/totalEventPropensity, \tag{C1}
$$

where $rand$ is a uniformly distributed random number in the range $[0, 1]$.

3. If $timeElapsed + timeUntilNextEvent > 25$, then go to Step 7, otherwise continue to Step 4.

4. Use a uniformly distributed random number to determine what event has occured. The probability of each event being chosen is given by the array of $eventPropensities$ divided by the $totalEventPropensity$.

5. Update the array of particle locations to reflect the outcome of the event, and update the individual $eventPropensities$ and the $totalEventPropensity$ accordingly.

6. Set $timeElapsed = timeElapsed + timeUntilNextEvent$, and return to Step 2.

7. Store the array describing the particle positions at time $t = 25$.

In the first two test cases, the array of $eventPropensities$ consists of left and right jump propensities for each compartment, some of which will be reduced or elimated completely due to filled volumes in neighbouring compartments, and the $totalEventPropensity$ is their sum. For the morphogen gradient case, the $eventPropensities$ will also include decay propensities for each occupied compartment in the system and a constant particle in-flux term. The second test case also records particle positions at $t = 1, 2, \ldots, 24$, in addition to the final distribution at $t = 25$. For each test case, we generated 50,000 realisations of each model, plus another 50,000 realisations of the fully-excluding model to provide comparison data for the HDE, and then calculated the mean and variance of particle numbers in each compartment. This algorithm follows a deliberately simple design, demonstrating that no advanced programming ability is required to implement any of the models.

Appendix D: Comparison to non-excluding model

To illustrate the effects of multi-species volume exclusion in Section **??**, we compare the simulation results to the solution of the diffusion equation,

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}, \tag{D1}$$

where $c(x, t)$ is the concentration of particles. This PDE was solved using the Matlab routine `pdepe`, with grid spacing 1.05×10^{-2} and time step $\Delta t = 2.5 \times 10^{-3}$.

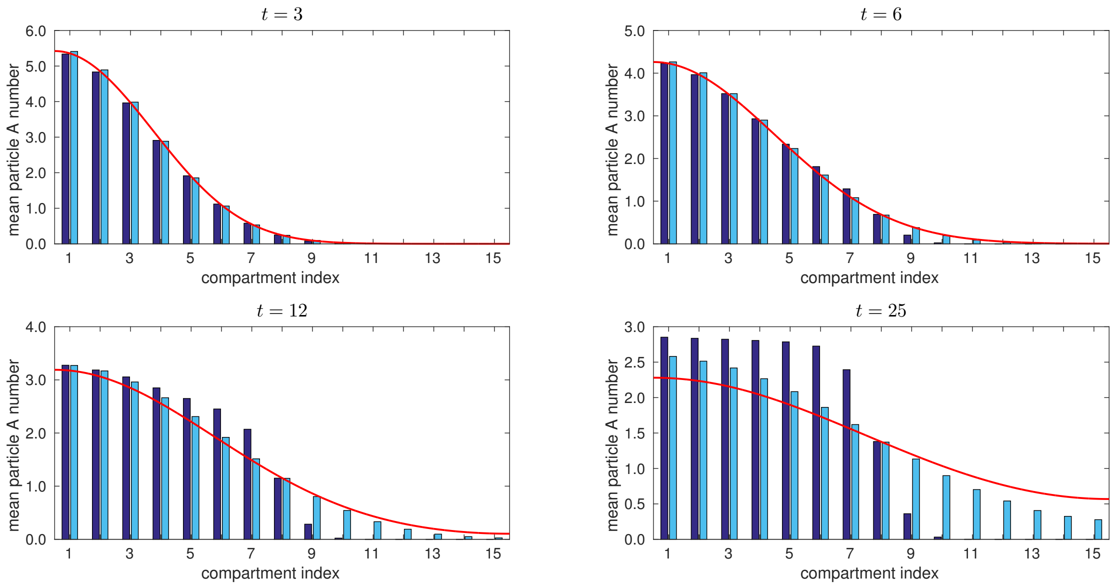

FIG. 1. A comparison of the results from Section **??** to a non-excluding PDE. The dark and light blue bars represent the mean number of species A particles, while the red line shows the solution of the non-excluding diffusion equation, starting from the same initial conditions. At time $t = 3$, when interaction with the species B particles is negligible, all three results agree well; by time $t = 6$ the effects of interaction with species B begin to be seen, and the models continue to diverge for the remainder of the simulation.

We plot comparisons between the PDE solution and the mean number of species A particles in Figure 1, using both the fully-excluding and partially-excluding models, (similar results can be obtained for species B particles). At time $t = 3$, all three sets of results are in agreement as we would expect. There has been little interaction with the species B particles for times $t < 3$, so the behaviour of species A particles can be approximated as a single species model. The fully-excluding results therefore match both the partially-excluding results and the diffusion equation. As t increases, however, the effects of volume exclusion become apparent and all three sets of results begin to diverge. As an aside, we note that if the mean total number of particles was plotted, counting both species A and B, then the resulting simulation results would be in agreement with the PDE [5].

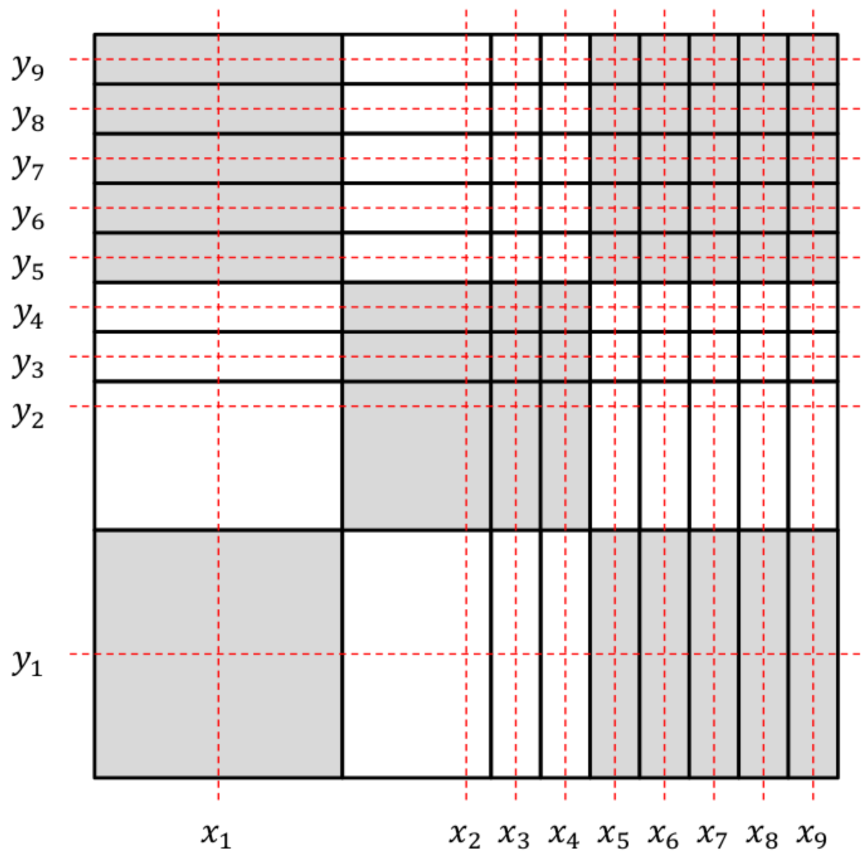

FIG. 2. An example rectilinear Voronoi partition in two spatial dimensions, illustrating one way in which a coarse-grained region in the bottom-left can be connected to the fine-grained region in the top-right. Residence points are located at the intersections of the red dashed lines and black lines mark compartment boundaries. Grey and white shading is used to indicate regions which would be aggregated to obtain $S_{i,j}^{(m)}$ terms.

Appendix E: Two-dimensional models

In this section, we sketch out how the hybrid methods could be extended to two spatial dimensions. For a rectilinear Voronoi partition, of the kind illustrated in Figure 2, we demonstrate that the mean master equation remains linear. We write $n_{i,j}^{(v)}$ and $m_{i,j}$ to denote the number of particles in, and the capacity of, the compartment with residence point at (x_i, y_j). As before, we write $M_{i,j}^{(v)} = \langle n_{i,j}^{(v)} \rangle$. To denote the distance between residence points, we use $\Delta x_i = x_i - x_{i-1}$ and $\Delta y_j = y_j - y_{j-1}$. By analogy to Eq. (**??**) in the main text, we assume that each particle is of size $h \times h$, and hence write

$$m_{i,j} = \frac{(\Delta x_i + \Delta x_{i+1})(\Delta y_j + \Delta y_{j+1})}{4h^2}, \quad 1 < i, j < K, \tag{E1}$$

with similar expressions obtainable for the capacities of compartments at the boundaries of the domain. Transition rates for diffusion on two-dimensional rectilinear Voronoi lattices, in the absence of volume exclusion, are given in [6] as

$$\mathcal{T}^r_{i,j} = \frac{2Dm_{i+1,j}}{m_{i,j}\Delta x_{i+1}(\Delta x_{i+1} + \Delta x_{i+2})}, \tag{E2}$$

$$\mathcal{T}^d_{i,j} = \frac{2Dm_{i,j-1}}{m_{i,j}\Delta y_j(\Delta y_{j-1} + \Delta y_j)}, \tag{E3}$$

$$\mathcal{T}^l_{i,j} = \frac{2Dm_{i-1,j}}{m_{i,j}\Delta x_i(\Delta x_{i-1} + \Delta x_i)}, \tag{E4}$$

$$\mathcal{T}^u_{i,j} = \frac{2Dm_{i,j+1}}{m_{i,j}\Delta y_{j+1}(\Delta y_{j+1} + \Delta y_{j+2})}, \tag{E5}$$

where $\mathcal{T}^r_{i,j}, \mathcal{T}^d_{i,j}, \mathcal{T}^l_{i,j}$ and $\mathcal{T}^u_{i,j}$ denote, respectively, the transition rates from the compartment indexed (i, j) to the compartments indexed $(i+1, j)$, $(i, j-1)$, $(i-1, j)$ and $(i, j+1)$ (i.e. movement up, right, down and left). After including standard blocking probabilities, we hence obtain the mean master equation

$$\begin{aligned}
\frac{\mathrm{d}M^{(v)}_{i,j}}{\mathrm{d}t} = \quad & \mathcal{T}^l_{i+1,j}\left(M^{(v)}_{i+1,j} - \frac{1}{m_{i,j}}\langle n^{(v)}_{i,j} n^{(v)}_{i+1,j}\rangle\right) - \mathcal{T}^r_{i,j}\left(M^{(v)}_{i,j} - \frac{1}{m_{i+1,j}}\langle n^{(v)}_{i,j} n^{(v)}_{i+1,j}\rangle\right) \\
& + \mathcal{T}^u_{i,j-1}\left(M^{(v)}_{i,j-1} - \frac{1}{m_{i,j}}\langle n^{(v)}_{i,j-1} n^{(v)}_{i,j}\rangle\right) - \mathcal{T}^d_{i,j}\left(M^{(v)}_{i,j} - \frac{1}{m_{i,j-1}}\langle n^{(v)}_{i,j-1} n^{(v)}_{i,j}\rangle\right) \\
& + \mathcal{T}^r_{i-1,j}\left(M^{(v)}_{i-1,j} - \frac{1}{m_{i,j}}\langle n^{(v)}_{i-1,j} n^{(v)}_{i,j}\rangle\right) - \mathcal{T}^l_{i,j}\left(M^{(v)}_{i,j} - \frac{1}{m_{i-1,j}}\langle n^{(v)}_{i-1,j} n^{(v)}_{i,j}\rangle\right) \\
& + \mathcal{T}^d_{i,j+1}\left(M^{(v)}_{i,j+1} - \frac{1}{m_{i,j}}\langle n^{(v)}_{i,j} n^{(v)}_{i,j+1}\rangle\right) - \mathcal{T}^u_{i,j}\left(M^{(v)}_{i,j} - \frac{1}{m_{i,j-1}}\langle n^{(v)}_{i,j-1} n^{(v)}_{i,j}\rangle\right),
\end{aligned} \tag{E6}$$

where the four rows describe, respectively, the exchange of particles between compartment (i, j) and the compartments right, below, left and above it. Examining the non-linear terms on the first row, we note that

$$\begin{aligned}
\left(\frac{-\mathcal{T}^l_{i+1,j}}{m_{i,j}} + \frac{\mathcal{T}^r_{i,j}}{m_{i+1,j}}\right)\langle n^{(v)}_{i,j} n^{(v)}_{i+1,j}\rangle = & \left(\frac{-2Dm_{i,j}}{m_{i,j}m_{i+1,j}\Delta x_{i+1}(\Delta x_i + \Delta x_{i+1})}\right. \\
& \left. + \frac{2Dm_{i+1,j}}{m_{i,j}m_{i+1,j}\Delta x_{i+1}(\Delta x_{i+1} + \Delta x_{i+2})}\right)\langle n^{(v)}_{i,j} n^{(v)}_{i+1,j}\rangle \\
= & \frac{2D}{m_{i,j}m_{i+1,j}\Delta x_{i+1}}\left(\frac{-m_{i,j}}{\Delta x_i + \Delta x_{i+1}} + \frac{m_{i+1,j}}{\Delta x_{i+1} + \Delta x_{i+2}}\right).
\end{aligned}$$

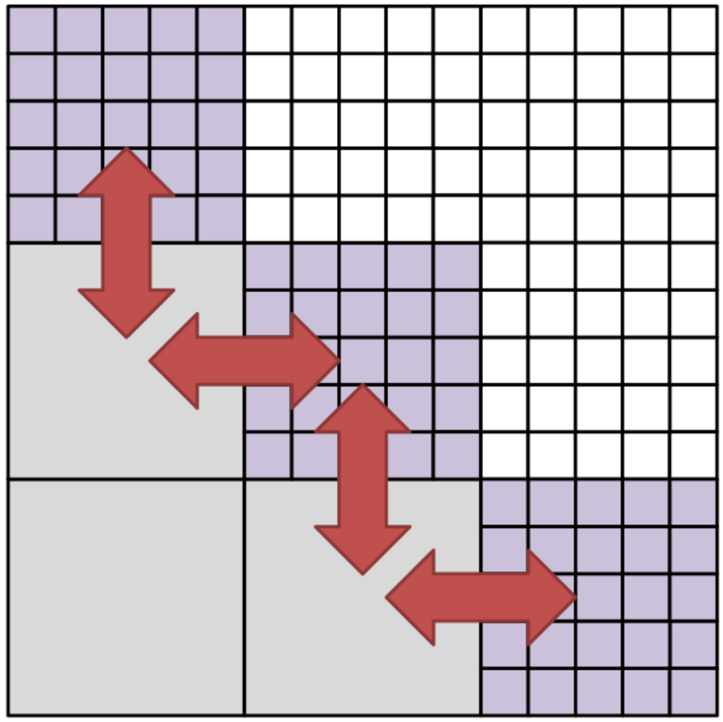

FIG. 3. An example pseudo-compartment method in two spatial dimensions. Partially-excluding compartments are shown in grey.

Using the definition of capacity from Eq. (E1), it can be seen that the terms inside the brackets of the final line cancel out, and hence the contribution from the non-linear terms is zero. Similar reasoning can be applied to the other lines of Eq. (E6) to obtain

$$\begin{aligned}\frac{\mathrm{d}M_{i,j}^{(v)}}{\mathrm{d}t} = &\quad \mathcal{T}_{i+1,j}^{l} M_{i+1,j}^{(v)} - \mathcal{T}_{i,j}^{r} M_{i,j}^{(v)} \\ &+ \mathcal{T}_{i,j-1}^{u} M_{i,j-1}^{(v)} - \mathcal{T}_{i,j}^{d} M_{i,j}^{(v)} \\ &+ \mathcal{T}_{i-1,j}^{r} M_{i-1,j}^{(v)} - \mathcal{T}_{i,j}^{l} M_{i,j}^{(v)} \\ &+ \mathcal{T}_{i,j+1}^{d} M_{i,j+1}^{(v)} - \mathcal{T}_{i,j}^{u} M_{i,j}^{(v)}, \end{aligned} \tag{E7}$$

which is linear, as expected from the corresponding mean master equation in one spatial dimension.

We do not present the details here, but the pseudo-compartment method could also be extended to two or three dimensions, with one illustrative example presented in Figure 3.

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