Supplementary Materials for the article "Particle-Environment Interactions In Arbitrary Dimensions: A Unifying Analytic Framework To Model Diffusion With Inert Spatial Heterogeneities"

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(Dated: May 14, 2022)

CONTENTS

I. DERIVATION OF THE HETEROGENEOUS PROPAGATOR

We consider a collection of heterogeneous connections as described in Section III of the main text, given by a set of M paired defects, $S = \{\{\boldsymbol{u}_1, \boldsymbol{v}_1\}, \cdots, \{\boldsymbol{u}_M, \boldsymbol{v}_M\}\}$. When not on a defective site, that is when $\boldsymbol{n} \neq \boldsymbol{u}_k, \boldsymbol{v}_k$ for any k, the dynamics are given by

$$\Phi(\boldsymbol{n}, t+1) = \sum_{\boldsymbol{m}} \underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}} \Phi(\boldsymbol{m}, t), \quad \boldsymbol{n} \neq \boldsymbol{u}, \boldsymbol{v}, \ \forall \{\boldsymbol{u}, \boldsymbol{v}\} \in S, \tag{S1}$$

with $\underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}}$ representing the transition probability from site $\boldsymbol{m}$ to site $\boldsymbol{n}$. When, instead, on any of the paired defective sites the dynamics are given by

$$\Phi(\boldsymbol{u}, t+1) = \sum_{\boldsymbol{m}} \underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}} \Phi(\boldsymbol{m}, t) + \lambda_{\boldsymbol{v},\boldsymbol{u}} \Phi(\boldsymbol{u}, t) - \lambda_{\boldsymbol{u},\boldsymbol{v}} \Phi(\boldsymbol{v}, t), \tag{S2}$$

and

$$\Phi(\boldsymbol{v}, t+1) = \sum_{\boldsymbol{m}} \underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}} \Phi(\boldsymbol{m}, t) - \lambda_{\boldsymbol{v},\boldsymbol{u}} \Phi(\boldsymbol{u}, t) + \lambda_{\boldsymbol{u},\boldsymbol{v}} \Phi(\boldsymbol{v}, t), \tag{S3}$$

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where the bounds on $\lambda_{\boldsymbol{v},\boldsymbol{u}}$ and $\lambda_{\boldsymbol{u},\boldsymbol{v}}$ are given by Eqs. (2) and (3) in the main text. Combining Eqs. (S1) to (S3) into a single equation and summing over all pairs in S gives the Master equation with defects

$$\Phi(\boldsymbol{n},t+1)=\sum_{\boldsymbol{m}}\underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}}\,\Phi(\boldsymbol{n},t)+\sum_{k=1}^{M}\delta_{\langle\boldsymbol{u}_k-\boldsymbol{v}_k\rangle,\boldsymbol{n}}\left[\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\Phi\left(\boldsymbol{u}_k,t\right)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\Phi\left(\boldsymbol{v}_k,t\right)\right], \tag{S4}$$

where $\delta_{\langle\boldsymbol{u}-\boldsymbol{v}\rangle,\boldsymbol{n}}=\delta_{\boldsymbol{u},\boldsymbol{n}}-\delta_{\boldsymbol{v},\boldsymbol{n}}$. Taking the z transform of Eq. (S4) we find

$$\widetilde{\Phi}(\boldsymbol{n},z)-\Phi(\boldsymbol{n},0)=\sum_{\boldsymbol{m}}\underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}}\,\widetilde{\Phi}(\boldsymbol{n},z)+z\sum_{k=1}^{M}\delta_{\langle\boldsymbol{u}_k-\boldsymbol{v}_k\rangle,\boldsymbol{n}}\left[\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}(\boldsymbol{v}_k,z)\right]. \tag{S5}$$

Solving first the homogeneous difference equation i.e. Eq. (S1) to get (in the absence of defects)

$$\widetilde{\Phi}(\boldsymbol{n},z)=\sum_{\boldsymbol{m}}\widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{n},z)\Phi(\boldsymbol{m},0) \tag{S6}$$

where $\widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{n},z)$ is the propagator of the homogeneous problem (e.g. see Eq. (23) of Ref. [1] or Eq. (33) of Ref. [2]), followed by a convolution (in time and space) with the inhomogeneous term in Eq. (S5) yields the formal solution

$$\widetilde{\Phi}(\boldsymbol{n},z)=\sum_{\boldsymbol{m}}\widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{n},z)\Phi(\boldsymbol{m},0)+z\sum_{k=1}^{M}\widetilde{\varphi}_{\langle\boldsymbol{u}_k-\boldsymbol{v}_k\rangle}(\boldsymbol{n},z)\left[\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}(\boldsymbol{v}_k,z)\right]. \tag{S7}$$

When the initial condition is localised, i.e. $\Phi(\boldsymbol{n},0)=\delta_{\boldsymbol{n},\boldsymbol{n}_0}$, we have the formal propagator

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)=\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)+z\sum_{k=1}^{M}\widetilde{\varphi}_{\langle\boldsymbol{u}_k-\boldsymbol{v}_k\rangle}(\boldsymbol{n},z)\left[\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{v}_k,z)\right]. \tag{S8}$$

In order to find $\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)$ in terms of the known propagator $\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)$ we first create simultaneous equations for each pair of defects in terms of the differences $\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{v}_k,z)$ giving

$$\begin{aligned}&\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{v}_k,z)=\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{v}_k,z)\\&+z\sum_{\ell=1}^{M}\left[\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\varphi}_{\langle\boldsymbol{u}_\ell-\boldsymbol{v}_\ell\rangle}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\varphi}_{\langle\boldsymbol{u}_\ell-\boldsymbol{v}_\ell\rangle}(\boldsymbol{v}_k,z)\right]\left[\lambda_{\boldsymbol{v}_\ell,\boldsymbol{u}_\ell}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{u}_\ell,z)-\lambda_{\boldsymbol{u}_\ell,\boldsymbol{v}_\ell}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{v}_\ell,z)\right],\end{aligned} \tag{S9}$$

whose solution via Cramer's rule, is given by

$$\lambda_{\boldsymbol{v}_k,\boldsymbol{u}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{u}_k,z)-\lambda_{\boldsymbol{u}_k,\boldsymbol{v}_k}\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{v}_k z)=-\frac{1}{z}\frac{|\underline{\boldsymbol{Y}}|}{|\underline{\boldsymbol{H}}|}, \tag{S10}$$

with $\underline{\boldsymbol{H}}$ defined in Eq. (6) and where $\underline{\boldsymbol{Y}}$ is the same as $\underline{\boldsymbol{H}}$, but with the k^{th} column replaced by

$$\left[\lambda_{\boldsymbol{v}_1,\boldsymbol{u}_1}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{u}_1,z)-\lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{v}_1,z),\cdots,\lambda_{\boldsymbol{v}_M,\boldsymbol{u}_M}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{u}_M,z)-\lambda_{\boldsymbol{u}_M,\boldsymbol{v}_M}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{v}_M,z)\right]^{\mathsf{T}}. \tag{S11}$$

Using Eq. (S10), Eq. (S8) becomes

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)=\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-\sum_{k=1}^{M}\widetilde{\varphi}_{\langle\boldsymbol{u}_k-\boldsymbol{v}_k\rangle}(\boldsymbol{n},z)\frac{|\underline{\boldsymbol{Y}}|}{|\underline{\boldsymbol{H}}|}. \tag{S12}$$

The summation in Eq. (S12) can be carried out explicitly giving

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)=\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-1+\frac{|\underline{\boldsymbol{H}}-\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)|}{|\underline{\boldsymbol{H}}|}. \tag{S13}$$

where,

$$\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j}=\widetilde{\varphi}_{\langle\boldsymbol{u}_i-\boldsymbol{v}_i\rangle}(\boldsymbol{n},z)\left[\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{u}_i,z)-\lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{v}_i,z)\right] \tag{S14}$$

and calling $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0)=\underline{\boldsymbol{H}}-\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)$ gives the solution presented in Eq. (5).

A. Sticky and Slippery Heterogeneities

We start with set of defective sites $S' = \{\boldsymbol{w}_1, \cdots, \boldsymbol{w}_L\}$ and use the notation $\boldsymbol{w}_i^{(l_s)}$ and $\boldsymbol{w}_i^{(r_s)}$ representing, respectively, the left and right neighbours of $\boldsymbol{w}_i$ in the s^{th}-dimension, given $\boldsymbol{w} = (w_1, \cdots, w_d)$, $\boldsymbol{w}^{(r_s)} = (w_1, \cdots w_s{+}1, \cdots, w_d)$ and $\boldsymbol{w}^{(l_s)} = (w_1, \cdots w_s{-}1, \cdots, w_d)$, with d the lattice dimension. A schematic representation of the jump probabilities on a defective site, $\boldsymbol{w}$ is given in Fig. A1 , from which it is clear that to ensure positive probabilities one must have

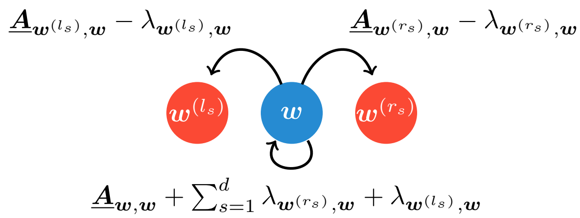

FIG. A1. A schematic representation showing the modified transition probabilities of a sticky (or slippery) heterogeneity. We highlight only the dynamics in the s^{th} dimension, but the same is present for the other dimensions.

$\lambda_{\boldsymbol{w}^{(r_s)},\boldsymbol{w}} \leq \underline{\boldsymbol{A}}_{\boldsymbol{w}^{(r_s)},\boldsymbol{w}}$ and $\lambda_{\boldsymbol{w}^{(l_s)},\boldsymbol{w}} \leq \underline{\boldsymbol{A}}_{\boldsymbol{w}^{(l_s)},\boldsymbol{w}}$ for all $s = 1, \cdots, d$, and $0 \leq \underline{\boldsymbol{A}}_{\boldsymbol{w},\boldsymbol{w}} + \sum_{s=1}^{d} \lambda_{\boldsymbol{w}^{(r_s)},\boldsymbol{w}} + \lambda_{\boldsymbol{w}^{(l_s)},\boldsymbol{w}}$ for all $\boldsymbol{w} \in S'$. These conditions are a recast of the one given by Eqs. (2) and (3) in the main text.

The full dynamics is described by the Master equation

$$\Phi(\boldsymbol{n}, t+1) = \sum_{\boldsymbol{m}} \underline{\boldsymbol{A}}_{\boldsymbol{n},\boldsymbol{m}} \Phi(\boldsymbol{m}, t) + \sum_{k=1}^{L} \Phi(\boldsymbol{w}_k, t) \left\{ \sum_{s=1}^{d} \lambda_{\boldsymbol{w}_k^{(r_s)},\boldsymbol{w}_k} \delta_{\left\langle \boldsymbol{w}_k - \boldsymbol{w}_k^{(r_s)} \right\rangle, \boldsymbol{n}} + \lambda_{\boldsymbol{w}_k^{(l_s)},\boldsymbol{w}_k} \delta_{\left\langle \boldsymbol{w}_k - \boldsymbol{w}_k^{(l_s)} \right\rangle, \boldsymbol{n}} \right\}. \tag{S15}$$

Using a localised initial condition $\Phi(\boldsymbol{n}, 0) = \delta_{\boldsymbol{n},\boldsymbol{n}_0}$ and proceeding as before by solving the homogeneous dynamics and convolution (in time and space) with the non-homogeneous part of Eq. (S15) gives the formal solution

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n}, z) = \widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n}, z) + z \sum_{k=1}^{M} \widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{w}_k, z) \widetilde{Q}_{\boldsymbol{w}_k}(\boldsymbol{n}, z), \tag{S16}$$

where

$$\widetilde{Q}_{\boldsymbol{w}}(\boldsymbol{n}, z) = \sum_{s=1}^{d} \lambda_{\boldsymbol{w}^{(r_s)},\boldsymbol{w}} \widetilde{\varphi}_{\left\langle \boldsymbol{w} - \boldsymbol{w}^{(r_s)} \right\rangle}(\boldsymbol{n}, z) + \lambda_{\boldsymbol{w}^{(l_s)},\boldsymbol{w}} \widetilde{\varphi}_{\left\langle \boldsymbol{w} - \boldsymbol{w}^{(l_s)} \right\rangle}(\boldsymbol{n}, z). \tag{S17}$$

This formal solution is as special case of Eq. (S8) where $M = 2Ld$ where each of the sites in S' bears two paired defects for each of d dimensions. However, by noticing that the incoming connections of the sticky sites are left unmodified, i.e. $\lambda_{\boldsymbol{w},\boldsymbol{w}^{(l_s)}} = \lambda_{\boldsymbol{w},\boldsymbol{w}^{(r_s)}} = 0$ one can to simplify Eq. (S8) to Eq. (S16) thereby reducing the number unknowns by a factor of $2d$.

To find the full solution we let $\boldsymbol{n} = \boldsymbol{w}_k$ and solve the simultaneous equations

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{w}_k, z) = \widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n}, z) + z \sum_{\ell=1}^{M} \widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{w}_\ell, z) \widetilde{Q}_{\boldsymbol{w}_\ell}(\boldsymbol{w}_k, z), \tag{S18}$$

with $k = 1, \cdots, M$ to get

$$\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{w}_k, z) = -\frac{1}{z} \frac{|\underline{\boldsymbol{Y}}|}{|\underline{\boldsymbol{H}}|} \tag{S19}$$

where, in this case, the matrix $\underline{\boldsymbol{H}}$ is simplified to

$$\underline{\boldsymbol{H}}_{i,j} = \widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{w}_i, z) - \frac{1}{z} \delta_{i,j} \tag{S20}$$

and $\underline{\boldsymbol{Y}}$ is the same as $\underline{\boldsymbol{H}}$ but with the k^{th} column replaced by $\left[\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{w}_1, z), \cdots, \widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{w}_M, z)\right]^{\mathsf{T}}$. Substituting Eq. (S19) into Eq. (S16) and summing over k gives the full solution in Eq. (5) where

$$\underline{\boldsymbol{H}}(\boldsymbol{n}, \boldsymbol{n}_0)_{i,j} = \underline{\boldsymbol{H}}_{i,j} - \widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}, z) \widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{w}_i, z). \tag{S21}$$

II. DERIVATIONS OF FIRST-PASSAGE STATISTICS IN THE PRESENCE OF HETEROGENEITIES

A. Mean first-passage time with arbitrary type and number of heterogeneities

From the renewal equation, the generating function of the first-passage probability from $\boldsymbol{n}_0$ to $\boldsymbol{n}$ ($\boldsymbol{n} \neq \boldsymbol{n}_0$) is given by

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)}{\widetilde{\Phi}_{\boldsymbol{n}}(\boldsymbol{n},z)} = \frac{\left(\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-1\right)|\underline{\boldsymbol{H}}| + |\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)|}{\left(\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)-1\right)|\underline{\boldsymbol{H}}| + |\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n})|}, \tag{S22}$$

where we have called $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0) = \underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)$ with $\underline{\boldsymbol{H}}$ and $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0)$ defined, respectively, in Eqs. (6) and (7) of the main text. Note that the matrix $\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{m})$ can be written in the form $\boldsymbol{a}\boldsymbol{b}^{\mathsf{T}}$, where $\boldsymbol{a}$ and $\boldsymbol{b}$ are column vectors with elements $\boldsymbol{a}_i = \lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{u}_i,z) - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{v}_i,z)$ and $\boldsymbol{b}_i = \widetilde{\varphi}_{\langle \boldsymbol{u}_i - \boldsymbol{v}_i\rangle}(\boldsymbol{n},z)$. We will exploit this property in the coming steps. Dividing both the numerator and denominator of Eq. (S22) by $\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)$ gives

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z) - 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\right)|\underline{\boldsymbol{H}}| + 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\,|\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)|}{\left(1 - 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\right)|\underline{\boldsymbol{H}}| + 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\,|\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n})|}. \tag{S23}$$

Using the property

$$\alpha\,|\underline{\boldsymbol{A}} - \underline{\boldsymbol{B}}| = |\underline{\boldsymbol{A}} - \alpha\underline{\boldsymbol{B}}| - (1-\alpha)\,|\underline{\boldsymbol{A}}| \tag{S24}$$

when α is a scalar and $\underline{\boldsymbol{B}} = \boldsymbol{a}\boldsymbol{b}^{\mathsf{T}}$ with $\boldsymbol{a}$ and $\boldsymbol{b}$ column vectors of appropriate size, we rewrite

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z) - 1\right)|\underline{\boldsymbol{H}}| + |\underline{\boldsymbol{H}} - 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)|}{|\underline{\boldsymbol{H}} - 1/\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n})|}. \tag{S25}$$

Dividing through by $\prod_{k=1}^{M}\widetilde{\varphi}_{\boldsymbol{u}_k}(\boldsymbol{u}_k,z)\widetilde{\varphi}_{\boldsymbol{v}_k}(\boldsymbol{v}_k,z)$, where M is the total number of paired defects one finds

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z) - 1\right)|\underline{\boldsymbol{J}}| + |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|}{|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|}. \tag{S26}$$

where the elements of the matrices $\underline{\boldsymbol{J}}$, $\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)$ and $\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})$ are given in terms of first-passage and return probabilities

$$\begin{aligned}\underline{\boldsymbol{J}}_{i,j} &= \lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\left[1-\widetilde{R}(\boldsymbol{v}_i,z)\right]\widetilde{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle}(\boldsymbol{u}_i,z) - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\left[1-\widetilde{R}(\boldsymbol{u}_i,z)\right]\widetilde{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle}(\boldsymbol{v}_i,z)\\ &\quad - \delta_{i,j}z^{-1}\left[1-\widetilde{R}(\boldsymbol{v}_i,z)\right]\left[1-\widetilde{R}(\boldsymbol{u}_i,z)\right],\end{aligned} \tag{S27}$$

$$\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j} = \underline{\boldsymbol{J}}_{i,j} - \widetilde{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle}(\boldsymbol{n},z)\left\{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\left[1-\widetilde{R}(\boldsymbol{v}_i,z)\right]\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{u}_i,z) - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\left[1-\widetilde{R}(\boldsymbol{u}_i,z)\right]\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{v}_i,z)\right\}, \tag{S28}$$

$$\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j} = \underline{\boldsymbol{J}}_{i,j} - \widetilde{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle}(\boldsymbol{n},z)\left\{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\left[1-\widetilde{R}(\boldsymbol{v}_i,z)\right]\widetilde{F}_{\boldsymbol{n}}(\boldsymbol{u}_i,z) - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\left[1-\widetilde{R}(\boldsymbol{u}_i,z)\right]\widetilde{F}_{\boldsymbol{n}}(\boldsymbol{v}_i,z)\right\}. \tag{S29}$$

The mean first-passage time is then given by

$$\mathcal{D}_z\cdot\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\Big|_{z=1} = \frac{(\mathcal{D}_z\cdot\mathbb{N})\,\mathbb{D} - (\mathcal{D}_z\cdot\mathbb{D})\,\mathbb{N}}{\mathbb{D}^2}\Bigg|_{z\to 1}, \tag{S30}$$

where $\mathcal{D}_z^k\cdot f$ is the k^{th} derivative of f with respect to z, $\mathbb{N} = \left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-1\right)|\underline{\boldsymbol{J}}| + |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|$ and $\mathbb{D} = |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|$. When $z\to 1$, $|\underline{\boldsymbol{J}}|$, $|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|$ and $|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|$ all reduce to zero and it becomes necessary to use de L'Hôpital's rule. In order to proceed, it helps to consider the k^{th} derivative of a determinant of a matrix with size $M\times M$ given by

$$\mathcal{D}_z^k\cdot|\underline{\boldsymbol{A}}| = \sum_{k_1+\cdots+k_M=k}\frac{k!}{k_1!\cdots k_M!}\begin{vmatrix}\mathcal{D}_z^{k_1}\cdot\underline{\boldsymbol{A}}_{1,1} & \mathcal{D}_z^{k_2}\cdot\underline{\boldsymbol{A}}_{1,2} & \cdots & \mathcal{D}_z^{k_M}\cdot\underline{\boldsymbol{A}}_{1,M}\\ \mathcal{D}_z^{k_1}\cdot\underline{\boldsymbol{A}}_{1,2} & \mathcal{D}_z^{k_2}\cdot\underline{\boldsymbol{A}}_{2,2} & \cdots & \mathcal{D}_z^{k_M}\cdot\underline{\boldsymbol{A}}_{2,M}\\ \vdots & \vdots & \ddots & \vdots\\ \mathcal{D}_z^{k_1}\cdot\underline{\boldsymbol{A}}_{M,1} & \mathcal{D}_z^{k_2}\cdot\underline{\boldsymbol{A}}_{i,j} & \cdots & \mathcal{D}_z^{k_M}\cdot\underline{\boldsymbol{A}}_{M,M}\end{vmatrix}. \tag{S31}$$

From Eq. (S31) and the expressions in Eqs. (S27) to (S29) it becomes clear that each of the columns in the matrices must be differentiated at-least twice to give a non zero determinant when $z \to 1$. The determinant must therefore be differentiated $2M$-times leading to de L'Hôpital's rule being used $4M$-times in Eq. (S30). Expanding the denominator using Leibniz general rule gives

$$\mathcal{D}_z^{4M} \cdot \mathbb{D}^2 = \sum_{k=0}^{4M} \binom{4M}{k} (\mathcal{D}_z^{k} \cdot \mathbb{D}) (\mathcal{D}_z^{4M-k} \cdot \mathbb{D}) = \binom{4M}{2M} (\mathcal{D}_z^{2M} \cdot \mathbb{D})^2 , \tag{S32}$$

where the only non-zero term is when $k = 2M$, expanding the first term in the numerator in Eq. (S30) yields

$$\begin{aligned} \mathcal{D}_z^{4M} \cdot [(\mathcal{D}_z \cdot \mathbb{N}) \mathbb{D}] &= \sum_{k=0}^{4M} \binom{4M}{k} (\mathcal{D}_z^{k+1} \cdot \mathbb{N}) (\mathcal{D}_z^{4M-k} \cdot \mathbb{D}) \\ &= \binom{4M}{2M-1} (\mathcal{D}_z^{2M} \cdot \mathbb{N}) (\mathcal{D}_z^{2M+1} \cdot \mathbb{D}) + \binom{4M}{2M} (\mathcal{D}_z^{2M+1} \cdot \mathbb{N}) (\mathcal{D}_z^{2M} \cdot \mathbb{D}) , \end{aligned} \tag{S33}$$

where the only surviving terms of the above summation are when $k = 2M - 1$, and $k = 2M$. Similarly for the second term in the numerator in Eq. (S30) the surviving terms are obtained when $k = 2M$ and $k = 2M + 1$, giving

$$\begin{aligned} \mathcal{D}_z^{4M} \cdot [(\mathcal{D}_z \cdot \mathbb{D}) \mathbb{N}] &= \sum_{k=0}^{4M} \binom{4M}{k} (\mathcal{D}_z^{k} \cdot \mathbb{N}) (\mathcal{D}_z^{4M-k+1} \cdot \mathbb{D}) \\ &= \binom{4M}{2M} (\mathcal{D}_z^{2M} \cdot \mathbb{N}) (\mathcal{D}_z^{2M+1} \cdot \mathbb{D}) + \binom{4M}{2M+1} (\mathcal{D}_z^{2M+1} \cdot \mathbb{N}) (\mathcal{D}_z^{2M} \cdot \mathbb{D}) . \end{aligned} \tag{S34}$$

Putting it all together gives

$$\mathcal{D}_z \cdot \widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n}, z)\Big|_{z=1} = \left. \frac{(\mathcal{D}_z^{2M+1} \cdot \mathbb{N}) (\mathcal{D}_z^{2M} \cdot \mathbb{D}) - (\mathcal{D}_z^{2M} \cdot \mathbb{N}) (\mathcal{D}_z^{2M+1} \cdot \mathbb{D})}{(2M+1) \left[\mathcal{D}_z^{2M} \cdot \mathbb{D}\right]^2} \right|_{z \to 1} . \tag{S35}$$

Considering the term $\mathcal{D}_z^{2M} \cdot \mathbb{N}$ we find that

$$\begin{aligned} \mathcal{D}_z^{2M} \cdot \mathbb{N}|_{z\to 1} &= \mathcal{D}_z^{2M} \cdot \left[\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n}, z) - 1 \right) |\underline{\boldsymbol{J}}| \right] \Big|_{z \to 1} + \mathcal{D}_z^{2M} \cdot |\underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n}_0)||_{z\to 1} && \text{(S36)} \\ &= \mathcal{D}_z^{2M} \cdot |\underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n}_0)||_{z\to 1} , && \text{(S37)} \end{aligned}$$

since $\left[\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n}, z) - 1\right]$ must be differentiated at least once and $|\underline{\boldsymbol{J}}|$ must be differentiated at least $2M$ times to give a non-zero contribution. From Eqs. (S28) and (S29) we observe that a non-zero contribution from $\underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n}_0)_{i,j}$, $\underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n})_{i,j}$ occurs when one differentiates the difference of first-passage probability, $\widetilde{F}_{\langle \boldsymbol{u}_j - \boldsymbol{v}_j \rangle}(\boldsymbol{n}, z)$, and the return probability terms, $\left[1 - \widetilde{R}(\boldsymbol{u}_i, z)\right]$ and $\left[1 - \widetilde{R}(\boldsymbol{v}_i, z)\right]$ at least once. As $\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{u}_i, z = 1) = \widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{v}_i, z = 1) = \widetilde{F}_{\boldsymbol{n}}(\boldsymbol{u}_i, z = 1) = \widetilde{F}_{\boldsymbol{n}}(\boldsymbol{v}_i, z = 1) = 1$, we have

$$\mathcal{D}_z^{2M} \cdot \mathbb{N}|_{z\to 1} = \mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n}_0)|_{z\to 1} = \mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}(\boldsymbol{n}, \boldsymbol{n})|_{z\to 1} = \mathcal{D}_z^{2M} \cdot \mathbb{D}|_{z\to 1} , \tag{S38}$$

and we can simplify Eq. (S35) to

$$\mathcal{D}_z \cdot \widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n}, z)\Big|_{z=1} = \left. \frac{\mathcal{D}_z^{2M+1} \cdot \mathbb{N} - \mathcal{D}_z^{2M+1} \cdot \mathbb{D}}{(2M+1)\mathcal{D}_z^{2M} \cdot \mathbb{D}} \right|_{z\to 1} . \tag{S39}$$

At this stage one can compute the derivatives explicitly, for the case $\mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}$ in Eq. (S31). With all $k_i = 2$, differentiating each column twice and taking the limit $z \to 1$, gives (after cancelling the 2^M term),

$$\mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}|_{z\to 1} = (-1)^M (2M)! \, |\underline{\boldsymbol{\mathcal{J}}}| , \tag{S40}$$

where

$$\underline{\boldsymbol{\mathcal{J}}}_{i,j} = \lambda_{\boldsymbol{v}_i, \boldsymbol{u}_i} \mathcal{R}_{\boldsymbol{v}_i} \mathcal{F}_{\langle \boldsymbol{u}_j - \boldsymbol{v}_j \rangle \to \boldsymbol{u}_i} - \lambda_{\boldsymbol{u}_i, \boldsymbol{v}_i} \mathcal{R}_{\boldsymbol{u}_i} \mathcal{F}_{\langle \boldsymbol{u}_j - \boldsymbol{v}_j \rangle \to \boldsymbol{v}_i} + \delta_{i,j} \mathcal{R}_{\boldsymbol{u}_i} \mathcal{R}_{\boldsymbol{v}_i} , \tag{S41}$$

and likewise for the other two matrices we find

$$\mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|_{z\to 1} = \mathcal{D}_z^{2M} \cdot \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|_{z\to 1} = (-1)^M (2M)! \left|\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right|, \tag{S42}$$

where

$$\underline{\boldsymbol{\mathcal{J}}}^{(2)}_{i,j} = \left(\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\mathcal{R}_{\boldsymbol{v}_i} - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\mathcal{R}_{\boldsymbol{u}_i}\right)\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{n}}. \tag{S43}$$

Let us now consider the term $\mathcal{D}_z^{2M+1}\cdot\mathbb{N}$. We apply Leibniz rule and obtain

$$\mathcal{D}_z^{2M+1}\cdot\mathbb{N} = \sum_{\ell=0}^{2M+1}\binom{2M+1}{\ell}\left[\mathcal{D}_z^{\ell}\cdot\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-1\right)\right]\left[\mathcal{D}_z^{2M+1-\ell}\cdot|\underline{\boldsymbol{J}}|\right] + \mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|, \tag{S44}$$

the only surviving term in the summation is when $\ell=1$ resulting in

$$\mathcal{D}_z^{2M+1}\cdot\mathbb{N} = (-1)^M\,(2M+1)!\mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}}\,|\underline{\boldsymbol{\mathcal{J}}}| + \mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|. \tag{S45}$$

Substituting the previous results into Eq. (S35) and simplifying yields

$$\mathcal{D}_z\cdot\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\Big|_{z=1} = \left.\frac{(-1)^M\,(2M+1)!\mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}}\,|\underline{\boldsymbol{\mathcal{J}}}| + \mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)| - \mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|}{(-1)^M(2M+1)!\left|\underline{\boldsymbol{\mathcal{J}}}-\underline{\boldsymbol{\mathcal{J}}}^{(2)}\right|}\right|_{z\to 1}. \tag{S46}$$

Consider the term $\mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)|$ and $\mathcal{D}_z^{2M+1}\cdot|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|$, using the multinomial expansion of the derivative of a determinant i.e. Eq. (S31), one can see that the only surviving terms appear when $M-1$ columns are differentiated twice, while one column is differentiated three times, hence,

$$\mathcal{D}_z^{2M+1}\cdot\{|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)| - |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|\} = \frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\boldsymbol{n}_0,\ell)}\right| - \left|\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\boldsymbol{n},\ell)}\right|, \tag{S47}$$

where

$$\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\boldsymbol{n}_0,\ell)}_{i,j} = 2\left(\delta_{j,\ell}-1\right)\left\{\underline{\boldsymbol{\mathcal{J}}}_{i,j} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}_{i,j}\right\} + \delta_{j,\ell}\left\{\mathcal{D}_z^{3}\cdot\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j}\Big|_{z=1}\right\}, \tag{S48}$$

$$\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\boldsymbol{n},\ell)}_{i,j} = 2\left(\delta_{j,\ell}-1\right)\left\{\underline{\boldsymbol{\mathcal{J}}}_{i,j} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}_{i,j}\right\} + \delta_{j,\ell}\left\{\mathcal{D}_z^{3}\cdot\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j}\Big|_{z=1}\right\}. \tag{S49}$$

The multilinear property of the determinant allows us to rewrite Eq. (S47) as

$$\mathcal{D}_z^{2M+1}\cdot\{|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)| - |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|\} = \frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\ell)}\right|, \tag{S50}$$

where

$$\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\ell)}_{i,j} = 2\left(\delta_{j,\ell}-1\right)\left\{\underline{\boldsymbol{\mathcal{J}}}_{i,j} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}_{i,j}\right\} + \delta_{j,\ell}\mathcal{D}_z^{3}\cdot\left\{\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j} - \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j}\right\}\Big|_{z=1}. \tag{S51}$$

Since

$$\begin{aligned}\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j} - \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j} = \widetilde{F}_{\langle\boldsymbol{u}_j-\boldsymbol{v}_j\rangle}(\boldsymbol{n},z)\Big\{&\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\left[1-\widetilde{R}(\boldsymbol{v}_i,z)\right]\widetilde{F}_{\langle\boldsymbol{n}_0-\boldsymbol{n}\rangle}(\boldsymbol{u}_i,z)\\ &-\lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\left[1-\widetilde{R}(\boldsymbol{u}_i,z)\right]\widetilde{F}_{\langle\boldsymbol{n}_0-\boldsymbol{n}\rangle}(\boldsymbol{v}_i,z)\Big\},\end{aligned} \tag{S52}$$

each of the first-passage and return probabilities in Eq. (S52) must be differentiated at-least once to give a non-zero contribution, hence,

$$\mathcal{D}_z^{3}\cdot\left\{\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j} - \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j}\right\}\Big|_{z=1} = 6\mathcal{F}_{\langle\boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{n}}\left\{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\mathcal{R}_{\boldsymbol{v}_i}\mathcal{F}_{\langle\boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_i} - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\mathcal{R}_{\boldsymbol{u}_i}\mathcal{F}_{\langle\boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{v}_i}\right\}, \tag{S53}$$

where the factor 6 comes from repeated application of the product rule. To carry out the summation in Eq. (S50) we employ the following property of determinants. Given two matrices, $\underline{\boldsymbol{A}}$ and $\underline{\boldsymbol{B}}$ of size $M \times M$, where $\underline{\boldsymbol{B}} = \boldsymbol{a}\boldsymbol{b}^{\mathsf{T}}$ and where $\boldsymbol{a}$ and $\boldsymbol{b}$ are two column vectors, the following relation

$$\sum_{\ell=1}^{M} \left|\underline{\boldsymbol{A}}^{(\ell)}\right| = |\underline{\boldsymbol{A}}| - |\underline{\boldsymbol{A}} - \underline{\boldsymbol{B}}| \tag{S54}$$

holds when $\underline{\boldsymbol{A}}^{(\ell)}$ is the same as $\underline{\boldsymbol{A}}$, but with the ℓ^{th} column replaced by the ℓ^{th} column of $\underline{\boldsymbol{B}}$. Comparing Eqs. (S50) and (S53) with Eq. (S54), we observe that $\underline{\boldsymbol{A}} \to \underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}$,

$$\begin{aligned} \boldsymbol{a} \to \big[&\lambda_{\boldsymbol{v}_1,\boldsymbol{u}_1}\mathcal{R}_{\boldsymbol{v}_1}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_1} - \lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\mathcal{R}_{\boldsymbol{u}_1}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_1}, \\ &\cdots, \lambda_{\boldsymbol{v}_M,\boldsymbol{u}_M}\mathcal{R}_{\boldsymbol{v}_M}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_M} - \lambda_{\boldsymbol{u}_M,\boldsymbol{v}_M}\mathcal{R}_{\boldsymbol{u}_M}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_M}\big]^{\mathsf{T}}, \end{aligned} \tag{S55}$$

and

$$\boldsymbol{b} \to 6\left[\mathcal{F}_{\langle \boldsymbol{u}_1-\boldsymbol{v}_1\rangle\to\boldsymbol{n}}, \cdots, \mathcal{F}_{\langle \boldsymbol{u}_M-\boldsymbol{v}_M\rangle\to\boldsymbol{n}}\right]^{\mathsf{T}}, \tag{S56}$$

and carrying out the summation we obtain

$$\frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\ell)}\right| = \frac{1}{3}\frac{(2M+1)!}{2^M}\left\{\left|-2\left(\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right)\right| - \left|-2\left(\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right) - 6\underline{\boldsymbol{\mathcal{J}}}^{(1)}\right|\right\}, \tag{S57}$$

with

$$\underline{\boldsymbol{\mathcal{J}}}^{(1)}_{i,j} = \left(\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}\mathcal{R}_{\boldsymbol{v}_i}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_i} - \lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}\mathcal{R}_{\boldsymbol{u}_i}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{v}_i}\right)\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{n}}. \tag{S58}$$

From Eq. (S57), we can factor out (-2) from the determinants using the property $|\alpha\underline{\boldsymbol{A}}| = \alpha^M\,|\underline{\boldsymbol{A}}|$ with $\underline{\boldsymbol{A}}$ an $M \times M$ determinant to yield

$$\frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\boldsymbol{\mathcal{J}}}}}^{(\ell)}\right| = \frac{(-1)^M(2M+1)!}{3}\left\{\left|\left(\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right)\right| - \left|\left(\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right) + 3\underline{\boldsymbol{\mathcal{J}}}^{(1)}\right|\right\}. \tag{S59}$$

The factor 1/3 can be taken into the determinants using the property given in Eq. (S24). For the first determinant on the right hand side (RHS) of Eq. (S59) we can equate $\underline{\boldsymbol{A}} \to \underline{\boldsymbol{\mathcal{J}}}$, from Eq. (S43) we can equate

$$\boldsymbol{a} \to \left[\lambda_{\boldsymbol{v}_1,\boldsymbol{u}_1}\mathcal{R}_{\boldsymbol{v}_1} - \lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\mathcal{R}_{\boldsymbol{u}_1}, \cdots, \lambda_{\boldsymbol{v}_M,\boldsymbol{u}_M}\mathcal{R}_{\boldsymbol{v}_M} - \lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\mathcal{R}_{\boldsymbol{u}_M}\right]^{\mathsf{T}}. \tag{S60}$$

and

$$\boldsymbol{b} \to \left[\mathcal{F}_{\langle \boldsymbol{u}_1-\boldsymbol{v}_1\rangle\to\boldsymbol{n}}, \cdots, \mathcal{F}_{\langle \boldsymbol{u}_M-\boldsymbol{v}_M\rangle\to\boldsymbol{n}}\right]^{\mathsf{T}}, \tag{S61}$$

to derive the relation

$$\frac{1}{3}\left|\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)}\right| = \left|\underline{\boldsymbol{\mathcal{J}}} - {}^{1}\!/\!{}_{3}\underline{\boldsymbol{\mathcal{J}}}^{(2)}\right| - \frac{2}{3}\left|\underline{\boldsymbol{\mathcal{J}}}\right|. \tag{S62}$$

Similarly, for the second determinant on the RHS of Eq. (S59), we can equate $\underline{\boldsymbol{A}} \to \underline{\boldsymbol{J}}$, and using Eq. (S58) we identify

$$\begin{aligned} \boldsymbol{a} \to \big[&\lambda_{\boldsymbol{v}_1,\boldsymbol{u}_1}\mathcal{R}_{\boldsymbol{v}_1}\left(1 - 3\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_1}\right) - \lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\mathcal{R}_{\boldsymbol{u}_1}\left(1 - 3\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{v}_1}\right), \\ &\cdots, \lambda_{\boldsymbol{v}_M,\boldsymbol{u}_M}\mathcal{R}_{\boldsymbol{v}_M}\left(1 - 3\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_M}\right) - \lambda_{\boldsymbol{u}_1,\boldsymbol{v}_1}\mathcal{R}_{\boldsymbol{u}_M}\left(1 - 3\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{v}_M}\right)\big]^{\mathsf{T}}, \end{aligned} \tag{S63}$$

and

$$\boldsymbol{b} \to \left[\mathcal{F}_{\langle \boldsymbol{u}_1-\boldsymbol{v}_1\rangle\to\boldsymbol{n}}, \cdots, \mathcal{F}_{\langle \boldsymbol{u}_M-\boldsymbol{v}_M\rangle\to\boldsymbol{n}}\right]^{\mathsf{T}}, \tag{S64}$$

to obtain the relation

$$\frac{1}{3}\left|\underline{\boldsymbol{\mathcal{J}}} - \underline{\boldsymbol{\mathcal{J}}}^{(2)} + 3\underline{\boldsymbol{\mathcal{J}}}^{(1)}\right| = \left|\underline{\boldsymbol{\mathcal{J}}} - {}^{1}\!/\!{}_{3}\underline{\boldsymbol{\mathcal{J}}}^{(2)} + \underline{\boldsymbol{\mathcal{J}}}^{(1)}\right| - \frac{2}{3}\left|\underline{\boldsymbol{\mathcal{J}}}\right|. \tag{S65}$$

Using the relations Eqs. (S62) and (S65) to simplify Eq. (S59) yields

$$\frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\mathcal{J}}}}^{(\ell)}\right| = (-1)^M(2M+1)!\left\{\left|\underline{\mathcal{J}} - {}^1\!/\!_3\underline{\mathcal{J}}^{(2)}\right| - \left|\underline{\mathcal{J}} - {}^1\!/\!_3\underline{\mathcal{J}}^{(2)} + \underline{\mathcal{J}}^{(1)}\right|\right\}. \tag{S66}$$

Lastly, employing the property

$$\left|\underline{\boldsymbol{A}} - \boldsymbol{a}\boldsymbol{b}^{\mathsf{T}}\right| - \left|\underline{\boldsymbol{A}} - \boldsymbol{c}\boldsymbol{b}^{\mathsf{T}}\right| = \left|\underline{\boldsymbol{A}} - (\boldsymbol{a}-\boldsymbol{c})\,\boldsymbol{b}^{\mathsf{T}}\right| - \left|\underline{\boldsymbol{A}}\right| \tag{S67}$$

with $\underline{\boldsymbol{A}} \to \underline{\mathcal{J}}$, $3\boldsymbol{a}$ with Eq. (S60), $3\boldsymbol{b}$ with Eq. (S61) and $3\boldsymbol{c}$ with Eq. (S63), we can simplify Eq. (S66) to

$$\frac{1}{3}\frac{(2M+1)!}{2^M}\sum_{\ell=1}^{M}\left|\underline{\underline{\widehat{\mathcal{J}}}}^{(\ell)}\right| = (-1)^M(2M+1)!\left\{\left|\underline{\mathcal{J}} - \underline{\mathcal{J}}^{(1)}\right| - \left|\underline{\mathcal{J}}\right|\right\}. \tag{S68}$$

Putting it all together gives the final mean first-passage time with M paired defects

$$\mathfrak{F}_{\boldsymbol{n}_0\to\boldsymbol{n}} = \frac{(\mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}} - 1)\left|\underline{\mathcal{J}}\right| + \left|\underline{\mathcal{J}} - \underline{\mathcal{J}}^{(1)}\right|}{\left|\underline{\mathcal{J}} - \underline{\mathcal{J}}^{(2)}\right|} \tag{S69}$$

If we divide through all the terms by $\prod_{(\boldsymbol{u},\boldsymbol{v})\in S}\mathcal{R}_{\boldsymbol{u}}\mathcal{R}_{\boldsymbol{v}}$, we obtain

$$\mathfrak{F}_{\boldsymbol{n}_0\to\boldsymbol{n}} = \frac{\mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}}\left|\underline{\boldsymbol{\mathcal{H}}} - 1/\mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}}\underline{\boldsymbol{\mathcal{H}}}^{(1)}\right|}{\left|\underline{\boldsymbol{\mathcal{H}}} - \underline{\boldsymbol{\mathcal{H}}}^{(2)}\right|}, \tag{S70}$$

where

$$\underline{\boldsymbol{\mathcal{H}}}_{i,j} = \frac{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}}{\mathcal{R}_{\boldsymbol{u}_i}}\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{u}_i} - \frac{\lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}}{\mathcal{R}_{\boldsymbol{v}_i}}\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{v}_i} + \delta_{i,j}, \tag{S71}$$

$$\underline{\boldsymbol{\mathcal{H}}}^{(1)}_{i,j} = \left(\frac{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}}{\mathcal{R}_{\boldsymbol{u}_i}}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{u}_i} - \frac{\lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}}{\mathcal{R}_{\boldsymbol{v}_i}}\mathcal{F}_{\langle \boldsymbol{n}_0-\boldsymbol{n}\rangle\to\boldsymbol{v}_i}\right)\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{n}}, \tag{S72}$$

$$\underline{\boldsymbol{\mathcal{H}}}^{(2)}_{i,j} = \left(\frac{\lambda_{\boldsymbol{v}_i,\boldsymbol{u}_i}}{\mathcal{R}_{\boldsymbol{u}_i}} - \frac{\lambda_{\boldsymbol{u}_i,\boldsymbol{v}_i}}{\mathcal{R}_{\boldsymbol{v}_i}}\right)\mathcal{F}_{\langle \boldsymbol{u}_j-\boldsymbol{v}_j\rangle\to\boldsymbol{n}}. \tag{S73}$$

These expressions, namely Eqs. (S71) to (S73), have been repeated, respectively, in Eqs. (A3) to (A5) of the main text. If the homogeneous propagator is diffusive with no bias and if the heterogeneity parameters are symmetric, i.e. $\lambda_{\boldsymbol{v},\boldsymbol{u}} = \lambda_{\boldsymbol{u},\boldsymbol{v}}$, $\underline{\boldsymbol{\mathcal{H}}}^{(2)} = 0$ and Eq. (S70) can be simplified further to

$$\mathfrak{F}_{\boldsymbol{n}_0\to\boldsymbol{n}} = \mathcal{F}_{\boldsymbol{n}_0\to\boldsymbol{n}} - 1 + \frac{\left|\underline{\boldsymbol{\mathcal{H}}} - \underline{\boldsymbol{\mathcal{H}}}^{(1)}\right|}{\left|\underline{\boldsymbol{\mathcal{H}}}\right|}. \tag{S74}$$

B. Mean first-passage in the presence of sticky or slippery sites

To build the first-passage probability with sticky and slippery heterogeneities (see Section I A and Fig. A1) we use the propagator given in Eq. (5), where the matrices $\underline{\boldsymbol{H}}$ and $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0)$ are given, respectively, by Eqs. (S20) and (S21). As the procedure is similar to the one used to derive the general MFPT given by Eq. (S70) (and also Eq. (8) in the main text), we outline only the key steps.

Starting from

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)}{\widetilde{\Phi}_{\boldsymbol{n}}(\boldsymbol{n},z)} = \frac{(\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)-1)\left|\underline{\boldsymbol{H}}\right| + \left|\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)\right|}{(\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n},z)-1)\left|\underline{\boldsymbol{H}}\right| + \left|\underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n})\right|}, \tag{S75}$$

where we have called $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0) = \underline{\boldsymbol{H}} - \underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)$, with $\underline{\boldsymbol{H}}$ and $\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0)$ given, respectively, by Eqs. (S20) and (S21). Since matrix $\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{m}) = \boldsymbol{a}\boldsymbol{b}^{\mathsf{T}}$, where $\boldsymbol{a}$ and $\boldsymbol{b}$ are column vectors with elements $\boldsymbol{a}_i = \widetilde{\varphi}_{\boldsymbol{m}}(\boldsymbol{w}_i,z)$ and $\boldsymbol{b}_i = \widetilde{Q}_{\boldsymbol{w}_i}(\boldsymbol{n},z)$ with $\widetilde{Q}_{\boldsymbol{w}}(\boldsymbol{n},z)$ given by Eq. (S17). Dividing both the numerator and denominator of Eq. (S75) by $\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\prod_{i=1}^{M}\widetilde{\varphi}_{\boldsymbol{w}_i}(\boldsymbol{w}_i,z)$ we find

$$\widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n},z) = \frac{\left(\widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{n},z) - 1\right)\left|\underline{\boldsymbol{J}}\right| + \left|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)\right|}{\left|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})\right|}. \tag{S76}$$

where we rewrite the elements of the matrices in terms of first-passage and first return probabilities giving the definitions

$$\underline{\boldsymbol{J}}_{i,j} = \widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{w}_i, z) - z^{-1}\delta_{i,j}\left[1 - \widetilde{R}(\boldsymbol{w}_i, z)\right], \tag{S77}$$

$$\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})_{i,j} = \underline{\boldsymbol{J}}_{i,j} - \widetilde{F}_{\boldsymbol{n}}(\boldsymbol{w}_i, z)\widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}, z), \tag{S78}$$

$$\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)_{i,j} = \underline{\boldsymbol{J}}_{i,j} - \widetilde{F}_{\boldsymbol{n}_0}(\boldsymbol{w}_i, z)\widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}, z), \tag{S79}$$

with

$$\widetilde{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}, z) = \sum_{s=1}^{d} \lambda_{\boldsymbol{w}_j^{(r_s)},\boldsymbol{w}_j} \widetilde{F}_{\left\langle \boldsymbol{w}_j - \boldsymbol{w}_j^{(r_s)}\right\rangle}(\boldsymbol{n}, z) + \lambda_{\boldsymbol{w}_j^{(l_s)},\boldsymbol{w}_j} \widetilde{F}_{\left\langle \boldsymbol{w}_j - \boldsymbol{w}_j^{(l_s)}\right\rangle}(\boldsymbol{n}, z). \tag{S80}$$

Note that Eqs. (S27) to (S29) are now different from Eqs. (S77) to (S79).

The derivative with respect to z yields Eq. (S30), however, to evaluate the limit $z \to 1$, one must employ de L'Hôpital's rule $2M$ times on Eq. (S30), where previously the rule was used $4M$ times. This is because the elements of the matrices given by Eqs. (S77) to (S79) need only be differentiated once to give non-zero contributions, i.e the determinants, $|\underline{\boldsymbol{H}}|, |\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n})|$ and $|\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n}_0)|$ must be differentiated M times. Following through one finds, instead Eq. (S81),

$$\mathcal{D}_z \cdot \widetilde{\mathbb{F}}_{\boldsymbol{n}_0}(\boldsymbol{n}, z)\Big|_{z=1} = \left.\frac{\mathcal{D}_z^{M+1}\cdot \mathbb{N} - \mathcal{D}_z^{M+1}\cdot \mathbb{D}}{(M+1)\mathcal{D}_z^{M}\cdot \mathbb{D}}\right|_{z\to 1}. \tag{S81}$$

After computing the derivatives explicitly one obtains Eq. (S70) but this time

$$\underline{\boldsymbol{\mathcal{H}}}_{i,j} = \frac{1}{\mathcal{R}_{\boldsymbol{w}_i}}\mathcal{Q}_{\boldsymbol{w}_j}(\boldsymbol{w}_i) + \delta_{i,j}, \tag{S82}$$

$$\underline{\boldsymbol{\mathcal{H}}}^{(1)}_{i,j} = \frac{1}{\mathcal{R}_{\boldsymbol{w}_i}}\mathcal{F}_{\langle \boldsymbol{n}_0 - \boldsymbol{n}\rangle \to \boldsymbol{w}_i}\mathcal{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}), \tag{S83}$$

$$\underline{\boldsymbol{\mathcal{H}}}^{(2)}_{i,j} = \frac{1}{\mathcal{R}_{\boldsymbol{w}_i}}\mathcal{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}), \tag{S84}$$

and with

$$\mathcal{Q}_{\boldsymbol{w}_j}(\boldsymbol{n}) = \sum_{s=1}^{d} \lambda_{\boldsymbol{w}_j^{(r_s)},\boldsymbol{w}_j} \mathcal{F}_{\left\langle \boldsymbol{w}_j - \boldsymbol{w}_j^{(r_s)}\right\rangle \to \boldsymbol{n}} + \lambda_{\boldsymbol{w}_j^{(l_s)},\boldsymbol{w}_j} \mathcal{F}_{\left\langle \boldsymbol{w}_j - \boldsymbol{w}_j^{(l_s)}\right\rangle \to \boldsymbol{n}}. \tag{S85}$$

C. Mean first-return time

Through the renewal equation we also have the return probability relation

$$\widetilde{\mathbb{R}}(\boldsymbol{n}, z) = 1 - \frac{1}{\widetilde{\Phi}_{\boldsymbol{n}}(\boldsymbol{n}, z)} = \frac{(\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n}, z) - 2)\,|\underline{\boldsymbol{H}}| + |\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n})|}{(\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n}, z) - 1)\,|\underline{\boldsymbol{H}}| + |\underline{\boldsymbol{H}}(\boldsymbol{n},\boldsymbol{n})|}. \tag{S86}$$

Dividing both the numerator and denominator of Eq. (S86) by $\widetilde{\varphi}_{\boldsymbol{n}}(\boldsymbol{n}, z)\prod_{i=1}^{M}\widetilde{\varphi}_{\boldsymbol{w}_i}(\boldsymbol{w}_i, z)$ and simplifying gives

$$\widetilde{\mathbb{R}}(\boldsymbol{n}, z) = \frac{\left(\widetilde{R}(\boldsymbol{n}, z) - 1\right)|\underline{\boldsymbol{J}}| + |\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|}{|\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})|}, \tag{S87}$$

where $\underline{\boldsymbol{J}}, \underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n}_0)$ and $\underline{\boldsymbol{J}}(\boldsymbol{n},\boldsymbol{n})$ are given by, Eq. (S27) , Eq. (S28) and Eq. (S29) in the case of the general paired defect. Whereas for the sticky-slippery defects one would use Eq. (S77), Eq. (S79) and Eq. (S78). In either case the Eq. (S87) is structurally identical to Eq. (S26) and one employs the same procedure as the one employed to derive the MFPT to obtain (also given in Eq. (9) in the main text)

$$\mathfrak{R}_{\boldsymbol{n}} = \frac{\mathcal{R}_{\boldsymbol{n}}\,|\underline{\boldsymbol{\mathcal{H}}}|}{\left|\underline{\boldsymbol{\mathcal{H}}} - \underline{\boldsymbol{\mathcal{H}}}^{(2)}\right|} \tag{S88}$$

where $\underline{\boldsymbol{\mathcal{H}}}$, $\underline{\boldsymbol{\mathcal{H}}}^{(2)}$ are given, respectively, by Eq. (A3) and Eq. (A5) in the case of paired defects, while for sticky-slippery defects one would use the definitions in Eq. (S82) and Eq. (S84).

III. STEADY STATE PROBABILITY

Using the final value theorem, the steady state probability is given by

$$\begin{aligned}(1-z)\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\Big|_{z\to1} =& (1-z)\widetilde{\varphi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\big|_{z\to1}\\ -& \frac{(1-z)\left|\underline{\boldsymbol{H}}\right|-(1-z)\left|\underline{\boldsymbol{H}}-\underline{\boldsymbol{G}}(\boldsymbol{n},\boldsymbol{n}_0)\right|}{\left|\underline{\boldsymbol{H}}\right|}\Bigg|_{z\to1},\end{aligned} \tag{S89}$$

taking the limit requires a similar procedure as the one given for the derivation of the MFPT see Section II, and after some algebra one finds

$$(1-z)\widetilde{\Phi}_{\boldsymbol{n}_0}(\boldsymbol{n},z)\Big|_{z\to1} = \frac{1}{\mathcal{R}_{\boldsymbol{n}}}\frac{\left|\underline{\boldsymbol{\mathcal{H}}}-\underline{\boldsymbol{\mathcal{H}}}^{(2)}\right|}{\left|\underline{\boldsymbol{\mathcal{H}}}\right|} \tag{S90}$$

which (as expected) is the reciprocal of the MRT and where the elements of $\underline{\boldsymbol{\mathcal{H}}}$, $\underline{\boldsymbol{\mathcal{H}}}^{(1)}$ and $\underline{\boldsymbol{\mathcal{H}}}^{(2)}$ are defined, respectively, in Eq. (S71), Eq. (S72) and Eq. (S73) for the general case, and Eq. (S82), Eq. (S83) and Eq. (S84) when the heterogeneities are only sticky and slippery.

IV. FIRST-PASSAGE STATISTICS IN ONE DIMENSIONAL DOMAINS

Here we display some explicit miscellaneous expressions for 1D systems that we have omitted from the main text.

A. Mean first-passage time in periodic domains

In a periodic domain when $n \le u < n_0$ or $n > u \ge n_0$ the MFPT can be shown to be equal to

$$\mathfrak{F}_{n_0\to n} = \mathcal{F}_{n_0\to n} + \frac{\lambda\left(n-n_0-\text{sign}(n-n_0)\right)\left[N\,\text{sign}(n-n_0)+1-2(n-u)\right]}{p\left[N\frac{p}{2}+\lambda(1-N)\right]}, \tag{S91}$$

while when both n and n_0 are to the right or left of the barrier ones finds

$$\mathfrak{F}_{n_0\to n} = \mathcal{F}_{n_0\to n} + \frac{\lambda\left(n-n_0\right)\left[N\,\text{sign}(u-n)+1-2(n-u)\right]}{p\left[N\frac{p}{2}+\lambda(1-N)\right]}, \tag{S92}$$

where $\text{sign}(m)=1$ for $m\ge0$ and $\text{sign}(m)=-1$ for $m<0$ is the discrete signum function.

B. Mean return time in 1D

Using Eq. (9) from the main text one can show that the mean return time in 1D with a single barrier at u with periodic boundary conditions is given by

$$\mathfrak{R}_n = \begin{cases} \frac{\frac{q}{2}\left[N^2-\left(N^2-N\right)(\lambda_u+\lambda_v)\right]}{N(q/2-\lambda_v)+\lambda_u(n-u)-\lambda_v(n-u-1)}, & n\le u,\\[2ex] \frac{\frac{q}{2}\left[N^2-\left(N^2-N\right)(\lambda_u+\lambda_v)\right]}{N(q/2-\lambda_u)+\lambda_u(n-u)-\lambda_v(n-u-1)}, & n\ge u+1. \end{cases} \tag{S93}$$

When the barrier is impenetrable in both directions, i.e. $\lambda_{u+1,u}, \lambda_{u,u+1} \to \frac{q}{2}$, the mean return time with periodic boundary condition remains $\mathfrak{R}_n = N$ as we have transformed the periodic boundary condition to a reflecting one. However, To recover the analogue with reflecting boundary condition requires careful consideration of each of the terms in

$$\mathfrak{R}_n^{(r)} = \begin{cases} N\left[\frac{q/2-\lambda_{u+1,u}}{q/2-\lambda_{u,u+1}}\right]-u\left[\frac{\lambda_{u,u+1}-\lambda_{u+1,u}}{q/2-\lambda_{u,u+1}}\right] & n\le u\\[2ex] N-u\left[\frac{\lambda_{u,u+1}-\lambda_{u+1,u}}{q/2-\lambda_{u+1,u}}\right] & n\ge u+1 \end{cases}. \tag{S94}$$

When $n \leq u$, by expanding the first term in Eq. (S94) it is obvious to see that it gives no contribution to $\mathfrak{R}_n^{(r)}$

$$N \lim_{\substack{\lambda_{u+1,u}\to\frac{q}{2}\\ \lambda_{u,u+1}\to\frac{q}{2}}} \left(\frac{\frac{q}{2}-\lambda_{u+1,u}}{\frac{q}{2}-\lambda_{u,u+1}}\right) = \frac{Nq}{2}\lim_{\lambda_{u,u+1}\to\frac{q}{2}}\left(\frac{1}{\frac{q}{2}-\lambda_{u,u+1}}\right) - \frac{Nq}{2}\lim_{\lambda_{u,u+1}\to\frac{q}{2}}\left(\frac{1}{\frac{q}{2}-\lambda_{u,u+1}}\right) = 0, \tag{S95}$$

while the second term gives

$$u \lim_{\substack{\lambda_{u+1,u}\to\frac{q}{2}\\ \lambda_{u,u+1}\to\frac{q}{2}}} \left(\frac{\lambda_{u,u+1}-\lambda_{u+1,u}}{\frac{q}{2}-\lambda_{u,u+1}}\right) = \frac{uq}{2}\lim_{\lambda_{u,u+1}\to\frac{q}{2}}\left(\frac{1}{\frac{q}{2}-\lambda_{u,u+1}}\right) - u\lim_{\lambda_{u,u+1}\to\frac{q}{2}}\left(\frac{\lambda_{u,u+1}}{\frac{q}{2}-\lambda_{u,u+1}}\right) = u. \quad , \tag{S96}$$

similar argument can be made for the case when $n > u$ to give $\mathfrak{R}_n^{(r)} = N - u$.

C. Mean exit time

In 1D, one find simple expressions for the mean exit times, using known expressions for the defect free exit time $\mathcal{E}_{n_0} = (N - n_0)(n_0 - 1)/q$ [1], and the overall survival probability of the 1D diffusive propagator with absorbing boundaries, given by

$$\lim_{z\to 1}\widetilde{\varphi}_{n_0}(n,z) = \frac{1}{q}\frac{2(N-n_>)(n_<-1)}{N-1}, \tag{S97}$$

where $n_> = \frac{1}{2}\left[|n-n_0| + (n+n_0)\right]$ and $n_< = \frac{1}{2}\left[|n-n_0| - (n+n_0)\right]$. When $n_0 \geq u+1$, we find the simple relatively relation

$$\mathfrak{E}_{\boldsymbol{n}_0} = \mathcal{E}_{\boldsymbol{n}_0} + \frac{(2u-N)(N-n_0)\left[u(\lambda_u-\lambda_v)-\lambda_u\right]}{q\left[N(\frac{q}{2}-\lambda_v)+\lambda_u+\lambda_v-u(\lambda_u-\lambda_v)-\frac{q}{2}\right]}, \tag{S98}$$

whereas $n_0 \leq u$ yields

$$\mathfrak{E}_{\boldsymbol{n}_0} = \mathcal{E}_{\boldsymbol{n}_0} + \frac{(2u-N)(1-n_0)\left[(u-N)(\lambda_u-\lambda_v)-\lambda_v\right]}{q\left[N(\frac{q}{2}-\lambda_v)+\lambda_u+\lambda_v-u(\lambda_u-\lambda_v)-\frac{q}{2}\right]}. \tag{S99}$$

V. EFFICIENT EVALUATION OF THE PROPAGATOR IN FINITE DOMAINS: THE BLOCK MATRIX CONSTRUCTION

When the number of paired defects is sufficiently small, e.g. $M \lessapprox 10$ it is convenient to compute the elements of the matrices in Eqs. (5) and (8) (of the main text) directly using, respectively, the homogeneous propagators and mean first-passage times. Whereas, for larger values of M it is more efficient to evaluate the heterogeneous propagator using a block matrix construction containing eigenvectors and eigenvalues of the transition matrix. In what follows we describe the procedure for a 1D system while the extension to higher dimension will be addressed in the following subsection. We define the matrices containing the right eigenvectors as

$$\underline{\boldsymbol{R}}_{i,k} = g^{(\gamma,r)}(u_i,k) \quad \text{and} \quad \underline{\boldsymbol{R}}'_{i,k} = g^{(\gamma,r)}(v_i,k), \tag{S100}$$

where $g^{(\gamma,r)}(u_i,k)$ and $g^{(\gamma,r)}(v_i,k)$ are, respectively the u_i^{th} and v_i^{th} component of the k^{th} right eigenvector given by Eq. (S114), with the type of boundary condition described by γ. Similarly for the matrices containing the left eigenvectors we define

$$\underline{\boldsymbol{L}}_{k,i} = g^{(\gamma,\ell)}(u_i,k) \quad \text{and} \quad \underline{\boldsymbol{L}}'_{k,i} = g^{(\gamma,\ell)}(v_i,k), \tag{S101}$$

where $g^{(\gamma,\ell)}(u_i,k)$ and $g^{(\gamma,\ell)}(v_i,k)$ are, respectively, the u_i^{th} and v_i^{th} component of the k^{th} right eigenvector given by Eq. (S114), while for the matrices of eigenvalues we define a diagonal matrix $\underline{\boldsymbol{K}}$ with elements $\underline{\boldsymbol{K}}_{k,k} = s^{(\gamma)}(k)$ where $s^{(\gamma)}(k)$ is the k^{th} eigenvalue of the homogeneous system given by e.g. Eq.(4) of Ref. [1] or Eq. (22) of Ref. [2]. For the dependence on the the occupation site n and the initial site n_0 we define the row vector $\boldsymbol{r}_n$ and the column $\boldsymbol{\ell}_{n_0}$

containing, respectively, the n^{th} and ${n_0}^{\text{th}}$ components of the right and left eigenvectors. Finally we define the diagonal matrices

$$\underline{\boldsymbol{\Lambda}}_{i,i} = \lambda_{u_i,v_i} \quad \text{and} \quad \underline{\boldsymbol{\Lambda}}'_{i,i} = \lambda_{v_i,u_i}, \tag{S102}$$

which contain all the heterogeneous parameter values. The size of these matricies depend on the number of heterogeneties, M, the size of the domain N or both: the matricies $\underline{\boldsymbol{R}}$ and $\underline{\boldsymbol{R}}'$ are of size $M \times N$; the matricies $\underline{\boldsymbol{L}}$ and $\underline{\boldsymbol{L}}'$ are of size $N \times M$; the matricies $\underline{\boldsymbol{\Lambda}}$ and $\underline{\boldsymbol{\Lambda}}'$ are of size $M \times M$; and lastly $\underline{\boldsymbol{K}}$ is of size $N \times N$. From these definitions it follows that

$$\underline{\boldsymbol{H}} = \underline{\boldsymbol{Y}} - z^{-1}\underline{\boldsymbol{I}} \quad \text{and} \quad \underline{\boldsymbol{G}}(n, n_0) = \boldsymbol{os} \tag{S103}$$

where

$$\underline{\boldsymbol{Y}} = \left[\underline{\boldsymbol{\Lambda}}\underline{\boldsymbol{R}} - \underline{\boldsymbol{\Lambda}}'\underline{\boldsymbol{R}}'\right]\left[\underline{\boldsymbol{I}} - z\underline{\boldsymbol{K}}\right]^{-1}\left[\underline{\boldsymbol{L}} - \underline{\boldsymbol{L}}'\right] \tag{S104}$$

$$\boldsymbol{o} = \left[\underline{\boldsymbol{\Lambda}}\underline{\boldsymbol{R}} - \underline{\boldsymbol{\Lambda}}'\underline{\boldsymbol{R}}'\right]\left[\underline{\boldsymbol{I}} - z\underline{\boldsymbol{K}}\right]^{-1}\boldsymbol{\ell}_0 \tag{S105}$$

$$\boldsymbol{s} = \boldsymbol{r}_n\left[\underline{\boldsymbol{I}} - z\underline{\boldsymbol{K}}\right]^{-1}\left[\underline{\boldsymbol{L}} - \underline{\boldsymbol{L}}'\right], \tag{S106}$$

By defining the block matrices

$$\underline{\boldsymbol{X}}_L = \begin{pmatrix}\underline{\boldsymbol{L}} - \underline{\boldsymbol{L}}' & \boldsymbol{l}_0\end{pmatrix} \text{ and } \underline{\boldsymbol{X}}_R = \begin{pmatrix}\underline{\boldsymbol{uR}} - \underline{\boldsymbol{u}'\boldsymbol{R}'} \\ \boldsymbol{r}_n\end{pmatrix} \tag{S107}$$

we find

$$\underline{\boldsymbol{X}}_R\left[\underline{\boldsymbol{I}} - z\underline{\boldsymbol{K}}\right]^{-1}\underline{\boldsymbol{X}}_L = \begin{pmatrix}\underline{\boldsymbol{Y}} & \boldsymbol{o} \\ \boldsymbol{s}^\intercal & \widetilde{\varphi}_{n_0}(n, z)\end{pmatrix}. \tag{S108}$$

A similar approach can be used for the matrices involved MFPT given by Eq. (S70).

A. The block matrix construction in higher dimensions

In higher dimension the transition dynamics of a lattice random walk are described by a tensor and extending the block matrix construction hinges on 'flattening' the vector coordinates to a scalar. There are many methods one can employ to achieve this and we outline a suitable one below. Given the site $\boldsymbol{n} = (n_1, \cdots, n_d)$ in a d-dimensional lattice of size $\boldsymbol{N} = N_1, \cdots N_d$, we define

$$\hat{n} = 1 + \sum_{i=1}^{d}\left(\prod_{j=1}^{i-1} N_j\right)(n_i - 1) \quad \text{and} \quad \hat{k} = 1 + \sum_{i=1}^{d}\left(\prod_{j=1}^{i-1} N_j\right)(k_i - 1), \tag{S109}$$

where $\hat{n}$ represents the 'flattened' site while $\hat{k}$ is the 'flattened' eigen-index. Using these indices we define

$$\underline{\boldsymbol{R}}_{i,\hat{k}} = \prod_{j=1}^{d} g_r^{(\gamma_j)}(u_{i_j}, k_j) \quad \text{and} \quad \underline{\boldsymbol{R}}'_{i,\hat{k}} = \prod_{j=1}^{d} g_r^{(\gamma_j)}(v_{i_j}, k_j), \tag{S110}$$

where the products ares over j^{th} component of the sites, e.g. $\boldsymbol{u}_i = (u_{i_1}, \cdots, u_{i_d})$. Similarly, the matricies containing the left eigenvectors are defined as

$$\underline{\boldsymbol{L}}_{\hat{k},i} = \prod_{j=1}^{d} g_\ell^{(\gamma_j)}(u_{i_j}, k_j) \quad \text{and} \quad \underline{\boldsymbol{L}}'_{\hat{k},i} = \prod_{j=1}^{d} g_\ell^{(\gamma_j)}(v_{i_j}, k_j), \tag{S111}$$

leaving the matrix of eigenvalues defined as $\underline{\boldsymbol{K}}_{\hat{k},\hat{k}} = \frac{1}{d}\sum_{j=1}^{d} s^{(\gamma)}(k_j)$. The i^{th} element of the vectors containing the dependence on $\boldsymbol{n}$, and $\boldsymbol{n}_0$ is given, respectively, by $\boldsymbol{r}_{\boldsymbol{n}_i} = \prod_{j=1}^{d} g_r^{(\gamma_j)}(n_{i_j}, k_j)$ and $\boldsymbol{\ell}_{\boldsymbol{n}_{0i}} = \prod_{j=1}^{d} g_\ell^{(\gamma_j)}(n_{0_{i_j}}, k_j)$. The remainder of the procedure is identical to the 1D case outlined previously.

B. Eigenvectors and eigenvalues of transition matrix of the one dimensional Lattice random walk

Since the high dimensional eigenvectors and eigenvalues are composed of the 1D case, repeat here the quantities of interest diffusive case as an example. The Master equation governing a random walk on a finite lattice with N distinct sites ($1 \leq n \leq N$) is written as

$$\varphi(n, t+t) = \sum_{m=1}^{N} \underline{\boldsymbol{A}}_{n,m} \varphi(m, t), \tag{S112}$$

where $\underline{\boldsymbol{A}}$ is the transition matrix. The matricial form allows one to write easily the propagator as

$$\varphi_{n_0}(n, t) = \sum_{k=1}^{N} g_r^{(\gamma)}(n, k) g_\ell^{(\gamma)}(n_0, k) s^{(k)}(k)^t, \tag{S113}$$

where $g_r^{(\gamma)}(n, k)$ and $g_\ell^{(\gamma)}(n, k)$ are the n^{th} component of, respectively, the k^{th} right and left eigenvectors of the transition matrix and $s^{(\gamma)}(k)$ is the k^{th} eigenvalue. The right eigenvectors are given by

$$g_r^{(\gamma)}(n, k) = \begin{cases} \frac{a_k}{\sqrt{N}} \cos\left[\left(n - \frac{1}{2}\right) \frac{(k-1)\pi}{N}\right] & \gamma = r, \\ \frac{1}{\sqrt{N}} \exp\left[\frac{2\pi n i (k-1)}{N}\right] & \gamma = p, \\ \sqrt{\frac{2}{N}} \sin\left[\left(\frac{n-1}{N-1}\right) k\pi\right] & \gamma = a, \\ \frac{2}{\sqrt{2N-1}} \cos\left[\left(n - \frac{1}{2}\right) \frac{2k-1}{2N-1}\pi\right] & \gamma = m, \end{cases} \tag{S114}$$

with $a_k = 2$ for $k = 1$ and $a_k = 1$ for all other values of k, while the left eigenvectors, $g_\ell^{(\gamma)}(n, k)$ are identical to Eq. (S114) for all cases except the periodic boundary condition $\gamma = p$, where instead it is given by $g_\ell^{(p)}(n, k) = 1/g_r^{(p)}(n, k)$, finally the eigenvalues can be found in Eq. (4) of Ref. [1]. For periodic ($\gamma = p$) and reflecting domains ($\gamma = r$) with N distinct sites we have $k \in [1, N]$ eigenvalues and eigenvectors, for absorbing boundary conditions ($\gamma = a$) with absorbing sites at $n = 1$ and $n = N$ we have $k \in [1, N-2]$ eigenvalues, lastly for mixed boundary condition ($\gamma = m$) with a reflecting end at $n = 1$ and an absorbing one at $n = N$ we have $k \in [1, N-1]$ eigenvalues.

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