Supplementary material for "Smoothing in linear multicompartment biological processes subject to stochastic input"

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1 Derivation of smoothing results

In the main text, the unscaled system of equations is given by

$$\begin{aligned}
\mathrm{d}I &= -\theta\Big(I-\mu\Big)\,\mathrm{d}t + \sigma\,\mathrm{d}W,\\
\mathrm{d}X_1 &= \Big(I - kX_1\Big)\,\mathrm{d}t,\\
\mathrm{d}X_\nu &= \Big(kX_{\nu-1} - kX_\nu\Big)\,\mathrm{d}t, \qquad \nu = 2,\dots,n,
\end{aligned} \tag{1}$$

where $\theta, \mu, \sigma, k > 0$ are positive parameters. We introduce the scaled variables

$$\hat{X}_\nu = kX_\nu, \qquad \hat{t} = kt, \tag{2}$$

such that

$$\begin{aligned}
\mathrm{d}I &= -\hat{\theta}\Big(I-\mu\Big)\,\mathrm{d}\hat{t} + \hat{\sigma}\,\mathrm{d}W,\\
\mathrm{d}\hat{X}_1 &= \Big(I - \hat{X}_1\Big)\,\mathrm{d}\hat{t},\\
\mathrm{d}\hat{X}_\nu &= \Big(\hat{X}_{\nu-1} - \hat{X}_\nu\Big)\,\mathrm{d}\hat{t}, \qquad \nu = 2,\dots,n,
\end{aligned} \tag{3}$$

and where $\hat{\theta} = \theta/k$, $\hat{\sigma} = \sigma/\sqrt{k}$. Thus, we have the equivalent matrix system

$$\mathrm{d}\hat{\mathbf{X}} = -\hat{\boldsymbol{\Theta}}\left(\mathbf{X}(t) - \boldsymbol{\mu}\right)\,\mathrm{d}\hat{t} + \hat{\mathbf{S}}\,\mathrm{d}\mathbf{W}, \tag{4}$$

with

$$\hat{\boldsymbol{\Theta}} = \begin{pmatrix} \hat{\theta} & 0 & 0 & 0 & \cdots & 0\\ -1 & 1 & 0 & 0 & \cdots & 0\\ 0 & -1 & 1 & 0 & \cdots & 0\\ & \vdots & & & \ddots & \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}, \qquad \boldsymbol{\mu} = \mu\begin{pmatrix} 1 \\ \boldsymbol{\Theta}_{22}^{-1}\mathbf{e}_1 \end{pmatrix}, \qquad \mathbf{S} = \begin{pmatrix} \hat{\sigma} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix}. \tag{5}$$

In this section of the supporting material, we detail how we formulate expressions for the covariance and autocorrelation of the scaled process and, by extension, the results for the unscaled process that are presented in the main document.

1.1 Covariance matrix

The stationary covariance matrix of the scaled process is given by

$$\mathrm{vec}(\hat{\boldsymbol{\Sigma}}_\infty) = \hat{\sigma}^2(\hat{\boldsymbol{\Theta}} \oplus \hat{\boldsymbol{\Theta}})^{-1}\mathbf{e}_1, \tag{6}$$

so we wish to find the first column of $(\hat{\boldsymbol{\Theta}} \oplus \hat{\boldsymbol{\Theta}})^{-1}$. Without loss of generality, we set $\hat{\sigma} = 1$ and rescale by the appropriate amount at the end.

The Kronecker sum is given by

$$\hat{\mathbf{\Theta}} \oplus \hat{\mathbf{\Theta}} = \begin{pmatrix} \mathbf{A} & \mathbf{0} & \mathbf{0} & \dots & \mathbf{0} \\ -\mathbf{I} & \mathbf{B} & \mathbf{0} & \dots & \mathbf{0} \\ \mathbf{0} & -\mathbf{I} & \mathbf{B} & \dots & \mathbf{0} \\ & \vdots & & \ddots & \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \dots & \mathbf{B} \end{pmatrix}, \tag{7}$$

with

$$\mathbf{A} = \begin{pmatrix} 2\hat{\theta} & 0 & 0 & \cdots & 0 \\ -1 & 1+\hat{\theta} & 0 & \cdots & 0 \\ 0 & -1 & 1+\hat{\theta} & \cdots & 0 \\ & \vdots & & \ddots & \\ 0 & 0 & 0 & \cdots & 1+\hat{\theta} \end{pmatrix}, \qquad \mathbf{B} = \begin{pmatrix} 1+\hat{\theta} & 0 & 0 & \cdots & 0 \\ -1 & 2 & 0 & \cdots & 0 \\ 0 & -1 & 2 & \cdots & 0 \\ & \vdots & & \ddots & \\ 0 & 0 & 0 & \cdots & 2 \end{pmatrix}. \tag{8}$$

The vec$(\cdot)$ forms a vector by stacking the columns of a matrix argument. Therefore, the entries in the block-lower-diagonal of eq. (7) refer simply to the entries in the preceeding row (or column, given the covariance matrix is symmetric) of the covariance matrix. It is trivial to solve for the first n elements of $(\hat{\mathbf{\Theta}} \oplus \hat{\mathbf{\Theta}})^{-1}$ using back substitution, corresponding to the first row and column of the covariance matrix, yielding the recurrence relation

$$\hat{\mathbf{\Sigma}}_{\infty}^{(1,1)} = \frac{1}{2\hat{\theta}}, \qquad \hat{\mathbf{\Sigma}}_{\infty}^{(1,j)} = \frac{\hat{\mathbf{\Sigma}}_{\infty}^{(1,j-1)}}{1+\hat{\theta}}, \quad j = 2, 3, \dots, \tag{9}$$

with solution

$$\hat{\mathbf{\Sigma}}_{\infty}^{(1,j)} = \frac{1}{2\hat{\theta}(1+\hat{\theta})^{j-1}}, \quad j = 2, 3, \dots. \tag{10}$$

Applying back substitution to the remaining rows and columns yields the recurrence relation for the remaining elements

$$\hat{\mathbf{\Sigma}}_{\infty}^{(i,j)} = \frac{\hat{\mathbf{\Sigma}}_{\infty}^{(i,j-1)} + \hat{\mathbf{\Sigma}}_{\infty}^{(i-1,j)}}{2}, \quad i, j = 2, 3, \dots. \tag{11}$$

While beyond the scope of the present work, a more general recurrence relation can be derived where the transfer rates vary throughout the system. In this case, the recurrence relation satisfied by elements of the covariance matrix is of the form

$$\begin{aligned} \hat{\mathbf{\Sigma}}_{\infty}^{(1,1)} &= \frac{1}{2\theta}, \\ \hat{\mathbf{\Sigma}}_{\infty}^{(1,i)} &= \frac{k_{i-1}}{\theta + k_i} \hat{\mathbf{\Sigma}}_{\infty}^{(1,i-1)} = \frac{\prod_{p=1}^{n-1} k_p}{2\theta \prod_{p=2}^{n} (\theta + k_p)}, \\ \hat{\mathbf{\Sigma}}_{\infty}^{(i,j)} &= \frac{k_{i-1} \hat{\mathbf{\Sigma}}_{\infty}^{(i-1,j)} + k_{j-1} \hat{\mathbf{\Sigma}}_{\infty}^{(i,j-1)}}{k_i + k_j}. \end{aligned}$$

For $\hat{\theta} = 1$ (i.e., $\theta = k$), this yields the solution

$$\hat{\mathbf{\Sigma}}_{\infty}^{(i,j)} = \frac{\Gamma(i+j-1)}{2^{i+j-1}\Gamma(i)\Gamma(j)}. \tag{12}$$

For the general case, the solution can be verified as

$$\begin{aligned}
\hat{\mathbf{\Sigma}}_{1,1} &= \frac{1}{2\theta}, \\
\hat{\mathbf{\Sigma}}_{i,j} &= \sum_{p=1}^{j-1} \binom{i+p-3}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} + \sum_{p=1}^{i-1} \binom{j+p-3}{p-1} \frac{1}{2^{j+p-1}\hat{\theta}(1+\hat{\theta})^{i-p}}.
\end{aligned}$$

To verify the solution to the recurrence relation, consider that

$$\begin{aligned}
\frac{\hat{\mathbf{\Sigma}}_{i-1,j} + \hat{\mathbf{\Sigma}}_{i,j-1}}{2} &= \underbrace{\sum_{p=1}^{j-1} \binom{i+p-4}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}}}_{S_1} + \underbrace{\sum_{p=1}^{i-2} \binom{j+p-3}{p-1} \frac{1}{2^{j+p}\hat{\theta}(1+\hat{\theta})^{i-p-1}}}_{S_2} \\
&\quad + \underbrace{\sum_{p=1}^{j-2} \binom{i+p-3}{p-1} \frac{1}{2^{i+p}\hat{\theta}(1+\hat{\theta})^{j-p-1}}}_{S_3} + \underbrace{\sum_{p=1}^{i-1} \binom{j+p-4}{p-1} \frac{1}{2^{j+p-1}\hat{\theta}(1+\hat{\theta})^{i-p}}}_{S_4},
\end{aligned}$$

and consider the first summation

$$\begin{aligned}
S_1 &= \sum_{p=1}^{j-1} \binom{i+p-4}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} \\
&= \frac{1}{2^i\hat{\theta}(1+\hat{\theta})^{j-1}} + \sum_{p=2}^{j-1} \binom{i+p-4}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} \\
&= \frac{1}{2^i\hat{\theta}(1+\hat{\theta})^{j-1}} + \sum_{p=2}^{j-1} \left\{ \binom{i+p-3}{p-1} - \binom{i+p-4}{p-2} \right\} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} \\
&= \frac{1}{2^i\hat{\theta}(1+\hat{\theta})^{j-1}} + \sum_{p=2}^{j-1} \binom{i+p-3}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} - \sum_{p=2}^{j-1} \binom{i+p-4}{p-2} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} \\
&= \frac{1}{2^i\hat{\theta}(1+\hat{\theta})^{j-1}} + \underbrace{\sum_{p=1}^{j-1} \binom{i+p-3}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}}}_{T_1} - \frac{1}{2^i\hat{\theta}(1+\hat{\theta})^{j-1}} - \sum_{p=2}^{j-1} \binom{i+p-4}{p-2} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}} \\
&= T_1 - \sum_{p=1}^{j-2} \binom{i+p-3}{p-1} \frac{1}{2^{i+p}\hat{\theta}(1+\hat{\theta})^{j-p-1}}.
\end{aligned}$$

Noting that the remainder term above is equal to S_3, we have that

$$S_1 + S_3 = T_1 = \sum_{p=1}^{j-1} \binom{i+p-3}{p-1} \frac{1}{2^{i+p-1}\hat{\theta}(1+\hat{\theta})^{j-p}}.$$

Similarly, it can be shown that

$$S_2 + S_4 = T_2 = \sum_{p=1}^{i-1} \binom{j+p-3}{p-1} \frac{1}{2^{j+p-1}\hat{\theta}(1+\hat{\theta})^{i-p}},$$

such that

$$\frac{\hat{\mathbf{\Sigma}}_{i-1,j} + \hat{\mathbf{\Sigma}}_{i,j-1}}{2} = \sum_{i=1}^{4} S_i = \hat{\mathbf{\Sigma}}_{i,j},$$

as required.

For $i = j = \nu - 1$, the scaled variance of the νth compartment is given by

$$\begin{aligned}
\hat{\sigma}_\nu^2 = \hat{\mathbf{\Sigma}}_{\nu+1,\nu+1} = 2\sum_{p=1}^{\nu} \binom{\nu+p-2}{p-1} \frac{1}{2^{\nu+p}\hat{\theta}(1+\hat{\theta})^{\nu-p+1}} \\
&= \frac{2^{1-\nu}}{\hat{\theta}(1+\hat{\theta})^{\nu+1}} \sum_{p=1}^{\nu} \binom{\nu+p-2}{p-1} \left(\frac{1+\hat{\theta}}{2}\right)^p \\
&= \frac{2^{1-\nu}}{\hat{\theta}(1+\hat{\theta})^{\nu+1}} \sum_{p=0}^{\nu-1} \binom{\nu+p-1}{p} \left(\frac{1+\hat{\theta}}{2}\right)^{p+1} \\
&= \frac{1}{\hat{\theta}(1-\hat{\theta}^2)^{\nu}} \sum_{p=0}^{\nu-1} \binom{\nu+p-1}{p} \left(\frac{1+\hat{\theta}}{2}\right)^p \left(\frac{1-\hat{\theta}}{2}\right)^{\nu} \\
&= \frac{1}{\hat{\theta}(1-\hat{\theta}^2)^{\nu}} \frac{\mathrm{B}\left(\frac{1-\hat{\theta}}{2}, \nu, \nu\right)}{\mathrm{B}(\nu,\nu)},
\end{aligned}$$

where we have exploited the simularity with the summand and the probability mass function of the negative binomial distribution [1].

1.1.1 Rescaled results

To obtain rescaled results we note that

$$\mathrm{cov}(I, X_\nu) = \mathrm{cov}\left(I, \frac{\hat{X}_\nu}{k}\right) = \frac{\mathrm{cov}(I, \hat{X}_\nu)}{k},$$

and that

$$\mathrm{cov}(X_{\nu_1}, X_{\nu_2}) = \mathrm{cov}\left(\frac{\hat{X}_{\nu_1}}{k}, \frac{\hat{X}_{\nu_2}}{k}\right) = \frac{\mathrm{cov}(\hat{X}_{\nu_1}, \hat{X}_{\nu_2})}{k^2}. \tag{13}$$

1.2 Autocorrelation function

We require $\mathrm{cov}(\hat{X}_\nu(\hat{s}), \hat{X}_\nu(\hat{t}))$ where $\hat{t} = \hat{s} + \hat{\ell}$ and $\hat{s}, \hat{t} \gg 1$. We therefore require the final element of the matrix product

$$\mathrm{e}^{-\hat{\mathbf{\Theta}}\hat{\ell}}\hat{\mathbf{\Sigma}}_\infty. \tag{14}$$

In the case that $\hat{\theta} = 1$ (i.e., $\theta = k$), we can write

$$-\hat{\mathbf{\Theta}} = \mathbf{L} - \mathbf{I}, \tag{15}$$

where $\mathbf{L}$ is a matrix comprising only 1 on the lower-diagonal (all other elements are zero), and $\mathbf{I}$ is an identity matrix. Since $\mathbf{I}_{\boldsymbol{\theta}}$ and $\mathbf{L}$ commute, we have that

$$\mathrm{e}^{-\hat{\mathbf{\Theta}}\hat{\ell}} = \mathrm{e}^{\mathbf{L}\hat{\ell}-\mathbf{I}\hat{\ell}} = \mathrm{e}^{\mathbf{L}\hat{\ell}}\mathrm{e}^{-\mathbf{I}\hat{\ell}} \in \mathbb{R}^{n\times n}, \tag{16}$$

where $n = \nu + 1$. The second factor, $\mathrm{e}^{-\mathbf{I}\hat{\ell}} = \mathrm{e}^{-\hat{\ell}}\mathbf{I}$ is trivial to compute. To compute $\mathrm{e}^{\mathbf{L}\hat{\ell}}$ (specifically, we are only interested in the last row), we note that

$$\mathbf{L}^n = \mathbf{0}. \tag{17}$$

Therefore,

$$\mathrm{e}^{\mathbf{L}\hat{\ell}} = \sum_{i=0}^{n-1} \frac{\hat{\ell}^i}{i!}\mathbf{L}^i. \tag{18}$$

Furthermore, we note that raising $\mathbf{L}$ to successive powers has the effect of shifting the diagonal downwards. Therefore, the only non-zero element of the last row of $\mathbf{L}^i$ is element $n - i$ for $0 \le i \le n$. This yields the elements of the last row of $\mathrm{e}^{\mathbf{L}\hat{\ell}}$ as

$$\left[\mathrm{e}^{-\mathbf{\Theta}\hat{\ell}}\right]_{n,i} = \frac{\hat{\ell}^{n-i}}{(n-i)!}. \tag{19}$$

Thus, the autocovariance is given by

$$\mathrm{cov}(\hat{X}_\nu(\hat{s}), \hat{X}_\nu(\hat{t})) = \mathrm{e}^{-\hat{\ell}} \sum_{i=1}^{n} \frac{\hat{\ell}^{n-i}\hat{\mathbf{\Sigma}}_\infty^{(i,n)}}{\Gamma(n-i+1)}. \tag{20}$$

The expression for the autocorrelation function of the νth compartment can be further simplified through the use of hypergeometric functions

$$\hat{\rho}_\nu(\hat{\ell}) = \frac{\mathrm{e}^{-\hat{\ell}}}{\hat{\sigma}_\nu^2} \sum_{i=1}^{\nu+1} \frac{\hat{\mathbf{\Sigma}}_\infty^{(\nu-i+2,\nu+1)}\hat{\ell}^{i-1}}{\Gamma(i)} \tag{21}$$

$$= \mathrm{e}^{-\hat{\ell}}{}_1F_1(-\nu, -2\nu, 2\hat{\ell}) \tag{22}$$

$$= \mathrm{e}^{-\hat{\ell}}\left(1 + \hat{\ell} + \mathcal{O}(\hat{\ell}^2)\right). \quad \nu \ge 2. \tag{23}$$

An exact expression for the second derivative at $\hat{\ell} = 0$ can be calculated as

$$\hat{\rho}_\nu''(0) = \frac{1}{1-2\nu}.$$

1.2.1 Rescaled results

To obtain the rescaled results we note that correlations are insensitive to scaling. Thus,

$$\rho_\nu(\ell) = \hat{\rho}_\nu(k\ell),$$

with the second derivative then given by

$$\rho_\nu''(0) = \frac{k^2}{1-2\nu}.$$

1.2.2 Expression in the general case

While not trivial and beyond the scope of the present work, an expression for the autocorrelation function can also be derived in the general case. We conjecture based on expressions for systems with $n \leq 6$ that that the scaled autocorrelation function is given in the general case by

$$\hat{\rho}_\nu(\hat{\ell}) = \frac{1}{\hat{\sigma}_\nu^2}\left\{\hat{\mathbf{\Sigma}}_\infty^{(1,\nu+1)}\left(\frac{(-1)^\nu \mathrm{e}^{-\hat{\theta}\hat{\ell}}}{(\hat{\theta}-1)^\nu} + \sum_{i=1}^{\nu}\frac{(-1)^{i+1}\mathrm{e}^{-\hat{\ell}}\hat{\ell}^{\nu-i}}{\Gamma(\nu-i+1)(\hat{\theta}-1)^i}\right) + \sum_{i=2}^{\nu+1}\frac{\hat{\mathbf{\Sigma}}_\infty^{(i,\nu+1)}\mathrm{e}^{-\hat{\ell}}\hat{\ell}^{\nu-i+1}}{\Gamma(\nu-i+2)}\right\}.$$

2 Vanishing covariance proof

Proposition 1. *Let $i, j \in \mathbb{Z}^+$ such that $i < j$ and let $\theta > 0$. If $j > i$, then $\hat{\boldsymbol{\Sigma}}_\infty^{(i,j)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,j-1)}$. Further, if $i > 1$, we additionally have that $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,j)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,j)}$.*

Proof. (By induction) Since $\hat{\boldsymbol{\Sigma}}_\infty^{(1,i)} = \hat{\boldsymbol{\Sigma}}_\infty^{(1,i-1)}/(1+\theta)$ and $\theta > 0$, we have that the statement is true for $i = 1$. For $i = 2$, consider first that $\hat{\boldsymbol{\Sigma}}_\infty^{(2,2)} = \hat{\boldsymbol{\Sigma}}_\infty^{(1,2)}$ where we have used the fact that $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,i)} = \hat{\boldsymbol{\Sigma}}_\infty^{(i,i-1)}$. Next, we have that $\hat{\boldsymbol{\Sigma}}_\infty^{(2,3)} = \frac{1}{2}\left(\hat{\boldsymbol{\Sigma}}_\infty^{(2,2)} + \hat{\boldsymbol{\Sigma}}_\infty^{(1,3)}\right)$. Since $\hat{\boldsymbol{\Sigma}}_\infty^{(1,3)} < \hat{\boldsymbol{\Sigma}}_\infty^{(1,2)} = \hat{\boldsymbol{\Sigma}}_\infty^{(2,2)}$, we have that $\hat{\boldsymbol{\Sigma}}_\infty^{(1,3)} < \hat{\boldsymbol{\Sigma}}_\infty^{(2,3)} < \hat{\boldsymbol{\Sigma}}_\infty^{(2,2)}$ and so the statement is true for $j = i + 1$. Assuming that the statement holds for $j = k \geq i$, then $\hat{\boldsymbol{\Sigma}}_\infty^{(i,k+1)} = \frac{1}{2}\left(\hat{\boldsymbol{\Sigma}}_\infty^{(i,k)} + \hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k+1)}\right)$. Now, $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,k)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,k-1)}$ and $\hat{\boldsymbol{\Sigma}}_\infty^{(i-2,k+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k)}$ and so $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,k)}$. Therefore, $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,k+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,k+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,k)}$ and so by the principle of mathematical induction, the statement holds for $j \geq i = 2$. The inductive step can be repeated following the assumption that the statement is true for all $j \geq i = \ell$ to complete the proof. □

Proposition 2. *For all $\nu \in \mathbb{N} \cup \{0\}$, $\sigma_{\nu+1}^2 < \sigma_\nu^2$.*

Proof. Given that as $\sigma_\nu^2 = \hat{\boldsymbol{\Sigma}}_\infty^{(\nu+1,\nu+1)}$, we need to show that $\hat{\boldsymbol{\Sigma}}_\infty^{(i+1,i+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,i)}$ for $i \geq 2$. First, we note that $\hat{\boldsymbol{\Sigma}}_\infty^{(i+1,i+1)} = \hat{\boldsymbol{\Sigma}}_\infty^{(i,i+1)}$. From the previous proposition, we have that $\hat{\boldsymbol{\Sigma}}_\infty^{(i-1,i+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,i+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,i)}$ and so $\hat{\boldsymbol{\Sigma}}_\infty^{(i+1,i+1)} < \hat{\boldsymbol{\Sigma}}_\infty^{(i,i)}$. □

Corollary 1. *For $\theta > 0$, $\lim_{\nu\to\infty} \sigma_\nu^2 = 0$*

Proof. It suffices to note that

$$\lim_{j\to\infty} \hat{\boldsymbol{\Sigma}}_\infty^{(1,j)} = \lim_{j\to\infty} \frac{1}{2\hat{\theta}(1+\hat{\theta})^{j-1}} = 0.$$

Similar logic to Proposition 1 can be applied to show that $\hat{\boldsymbol{\Sigma}}_\infty^{(1,j)} \geq \hat{\boldsymbol{\Sigma}}_\infty^{(j,j)}$, and so $\sigma_\nu^2 = \hat{\boldsymbol{\Sigma}}_\infty^{(\nu+1,\nu+1)} \leq \hat{\boldsymbol{\Sigma}}_\infty^{(1,\nu+1)}$, the latter of which vanishes as $\nu \to \infty$, thus σ_ν^2 also vanishes as $\nu \to \infty$. □

3 Stationary covariance in the presence of intrinsic noise

We now consider an extension of the model that considers intrinsic noise. Through the linear noise approximation, the extended model is given, for intermediate compartments, by

$$\mathrm{d}X_\nu = \Big(kX_{\nu-1}(t) - kX_\nu(t)\Big)\,\mathrm{d}t + \sqrt{k/V}\Big(\mathrm{d}W_{\nu-1} - \mathrm{d}W_\nu\Big), \qquad \nu = 2,\dots,n, \tag{24}$$

where V represents the so-called system size (the previous model is recovered in the limit $V \to \infty$). We now derive an analytical expression for the variance of X_ν in the case that V is finite. As before, we focus on the rescaled system $\hat{X}_\nu = kX_\nu$, $\hat{t} = kt$, such that

$$\mathrm{d}\hat{X}_\nu = \Big(\hat{X}_{\nu-1}(\hat{t}) - \hat{X}_\nu(\hat{t})\Big)\,\mathrm{d}\hat{t} + V^{-1/2}\Big(\mathrm{d}W_{\nu-1} - \mathrm{d}W_\nu\Big), \qquad \nu = 2,\dots,n, \tag{25}$$

and where the entire system can be expressed as a multivariate Ornstein-Uhlenbeck process

$$\mathrm{d}\hat{\mathbf{X}} = -\hat{\boldsymbol{\Theta}}\left(\mathbf{X}(t) - \boldsymbol{\mu}\right)\mathrm{d}\hat{t} + \hat{\mathbf{S}}_{\mathrm{intr}}\,\mathrm{d}\mathbf{W}, \tag{26}$$

with

$$\hat{\boldsymbol{\Theta}} = \begin{pmatrix} \hat{\theta} & 0 & 0 & 0 & \cdots & 0 \\ -1 & 1 & 0 & 0 & \cdots & 0 \\ 0 & -1 & 1 & 0 & \cdots & 0 \\ & \vdots & & & \ddots & \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}, \qquad \hat{\mathbf{S}}_{\mathrm{intr}} = \begin{pmatrix} \hat{\sigma} & 0 & 0 & \cdots & 0 \\ 0 & V^{-1/2} & 0 & \cdots & 0 \\ 0 & -V^{-1/2} & V^{-1/2} & \cdots & 0 \\ & \vdots & & \ddots & \\ 0 & 0 & 0 & \cdots & V^{-1/2} \end{pmatrix}. \tag{27}$$

We are interested in deriving analytical expressions for the diagonal elements of $\hat{\boldsymbol{\Sigma}}_{\infty,\mathrm{intr}}$ where

$$\mathrm{vec}(\hat{\boldsymbol{\Sigma}}_{\infty,\mathrm{intr}}) = (\hat{\boldsymbol{\Theta}} \oplus \hat{\boldsymbol{\Theta}})^{-1}\mathrm{vec}(\hat{\mathbf{S}}_{\mathrm{intr}}\hat{\mathbf{S}}_{\mathrm{intr}}^{\intercal}) = \underbrace{(\boldsymbol{\Theta} \oplus \boldsymbol{\Theta})^{-1}\mathrm{vec}(\hat{\mathbf{S}}\hat{\mathbf{S}}^{\intercal})}_{\mathrm{vec}(\hat{\boldsymbol{\Sigma}}_\infty)} + V^{-1}\underbrace{(\boldsymbol{\Theta} \oplus \boldsymbol{\Theta})^{-1}\mathrm{vec}(\tilde{\mathbf{S}}\tilde{\mathbf{S}}^{\intercal})}_{\mathrm{vec}(\hat{\boldsymbol{\Sigma}}_{\mathrm{adj}})}, \tag{28}$$

i.e., we only need to consider an adjustment to the variance of system that neglects intrinsic noise. The Kronecker sum $\hat{\boldsymbol{\Theta}} \oplus \hat{\boldsymbol{\Theta}}$ is given in eq. (7) and $\tilde{\mathbf{S}}\tilde{\mathbf{S}}^{\intercal}$ is given by

$$\tilde{\mathbf{S}}\tilde{\mathbf{S}}^{\intercal} = \begin{pmatrix} 0 & 0 & 0 & \cdots & 0 \\ 0 & 1 & -1 & \cdots & 0 \\ 0 & -1 & 2 & \cdots & 0 \\ & \vdots & & \ddots & \\ 0 & 0 & 0 & \cdots & 2 \end{pmatrix}. \tag{29}$$

We can determine the relevant columns of $(\boldsymbol{\Theta} \oplus \boldsymbol{\Theta})^{-1}$ by noting that

$$(\boldsymbol{\Theta} \oplus \boldsymbol{\Theta})\mathrm{vec}\big(\mathbf{x}_{i,j}\big) = \mathrm{vec}\big(\mathbf{e}_{i,j}\big), \tag{30}$$

where $\mathrm{vec}(\mathbf{x}_{i,j})$ is the $\big(i + (j-1)n\big)$th column of the inverse, and the basis vector $\mathrm{vec}\big(\mathbf{e}_{i,j}\big)$ is formulated using the single entry matrix $\mathbf{e}_{i,j}$ where element (i,j) is unity.

Similarly to our analysis in Section 1.1, we obtain the following governing equations for the elements of $\mathbf{x}_{i,j}$

$$\mathbf{x}_{i,j}^{(m,n)} = \begin{cases} 0, & m < i \text{ or } n < j, \\ \frac{1}{2}, & m = n = i, \\ \frac{1}{2}\left(\mathbf{x}_{m-1,n}^{(i)} + \mathbf{x}_{m,n-1}^{(i)}\right), & \text{otherwise.} \end{cases} \tag{31}$$

We see that the first $i-1$ rows and the first $j-1$ columns of $\mathbf{x}_{i,j}$ will always be zero. Furthermore, non-zero entries of the matrix $\mathbf{x}_{i+m,j+n}$ will be identical to those of $\mathbf{x}_{i,j}$, albeit shifted m rows down and n columns across, and truncated accordingly. Denoting the matrix of entirely non-zero elements that are shifted to create each $\mathbf{x}_{i,j}$ as $\tilde{\mathbf{x}}$ (i.e., such that $\mathbf{x}_{i,j}^{(m,n)} = \tilde{\mathbf{x}}^{(m-i+1,n-j+1)}$), we see that eq. (31) defines a recurrence relation analagous to that in Section 1.1 with $\hat{\theta} = 1$. Thus,

$$\tilde{\mathbf{x}}^{(m,n)} = \frac{\Gamma(m+n-1)}{2^{m+n-1}\Gamma(m)\Gamma(n)}. \tag{32}$$

Given that the system comprises no feedback, we can derive the diagonal element in row p of $\hat{\mathbf{\Sigma}}_{\text{adj}}$, denoted $\hat{\mathbf{\Sigma}}_{\text{adj}}^{(p,p)}$ by considering a system with $p-1$ compartments. Thus, we are only interested in the inner product of the last row of $(\hat{\mathbf{\Theta}} \oplus \hat{\mathbf{\Theta}})^{-1}$ and vec $\left(\tilde{\mathbf{S}}\tilde{\mathbf{S}}^{\intercal}\right)$. Denoting by vec$(\mathbf{y})$ the last (pth) row of $(\hat{\mathbf{\Theta}} \oplus \hat{\mathbf{\Theta}})^{-1}$, we see that

$$\mathbf{y}^{(i,j)} = \mathbf{x}_{i,j}^{(p,p)} = \frac{\Gamma(2k-i-j+1)}{2^{2k-i-j+1}\Gamma(k-i+1)\Gamma(k-j+1)}, \qquad \min(i,j) > 1. \tag{33}$$

Note that clearly $\mathbf{y}$ is symmetric. Furthermore, $\mathbf{y}_{i,i} = \mathbf{y}_{i+1,i} = \mathbf{y}_{i,i+1}$. Thus,

$$\hat{\mathbf{\Sigma}}_{\text{adj}}^{(p,p)} = \mathbf{y} \odot \hat{\mathbf{S}}\hat{\mathbf{S}}^{\intercal}, \tag{34}$$

$$= 2\mathbf{y}^{(p,p)} - \mathbf{y}^{(2,2)}, \tag{35}$$

$$= 1 - \frac{\Gamma(2p-3)}{2^{2p-3}\Gamma(p-1)^2}, \tag{36}$$

where $\odot$ represents the Frobenius inner product (element-wise product and sum). Therefore, the diagonal entries of vec$(\hat{\mathbf{\Sigma}}_{\infty,\text{intr}})$ are given by

$$\hat{\mathbf{\Sigma}}_{\infty,\text{intr}}^{(p,p)} = \hat{\mathbf{\Sigma}}_{\infty} + V^{-1}\hat{\mathbf{\Sigma}}_{\text{adj}}^{(p,p)}. \tag{37}$$

Re-dimensionalising, and noting that the relevant entries of $\hat{\mathbf{\Theta}}$ will be multiplied by k (as will the relevant entries of $\hat{\mathbf{S}}\hat{\mathbf{S}}^{\intercal}$), we see that

$$\sigma_{\text{intr},\nu}^2 := \mathbf{\Sigma}_{\infty,\text{intr}}^{(p,p)} = \sigma_{\nu}^2 + \frac{1}{V}\left(1 - \frac{\Gamma(2\nu-1)}{2^{2\nu-1}\Gamma(\nu)^2}\right). \tag{38}$$

4 Numerical solution to the Volterra equation

We solve the Volterra equation of the first kind

$$p(t) = \int_0^t K(s,t) f(s) \, \mathrm{d}s, \tag{39}$$

numerically, using the midpoint rule and regularisation to find an approximate solution for $f(t)$ [2]. First, consider that the Volterra equation of the second kind

$$p(t) = \alpha_1 f(t) + \int_0^t K(s,t) f(s) \, \mathrm{d}s, \tag{40}$$

is equivalent to eq. (39) for $\alpha_1 = 0$. We discretise the integral in eq. (40) using the midpoint rule, such that

$$p(t_n) = \alpha_1 f_n + \sum_{i=1}^{n-1} K(s_i, t_n) f_i \Delta_i, \tag{41}$$

where

$$s_i = \frac{t_i + t_{i+1}}{2} \quad \text{and} \quad \Delta_i = t_{i+1} - t_i,$$

and $f_i = f(t_i)$ is to be determined.

We create a grid $\{t_1, \dots, t_N\}$ with geometric spacing such that

$$t_N - t_{N-1} = \omega(t_2 - t_1),$$

where ω is a parameter to be chosen ($\omega = 1$ recovers linear spacing). Equation (41), therefore, gives a system of N linear equations in $\boldsymbol{f} = [f_1, \dots, f_N]^\intercal$ for $n = 1, 2, \dots, N$, such that

$$\boldsymbol{p} = \alpha_1 \mathbf{I} + \mathbf{A}\boldsymbol{f} = .\mathbf{M}\boldsymbol{f}, \tag{42}$$

for $\boldsymbol{p} = [p(t_1), \dots, p(t_N)]^\intercal$.

In general, the linear system eq. (42) may be poorly conditioned. Thus, we solve the minimisation problem

$$\min \|\mathbf{M}\boldsymbol{f} - \boldsymbol{p}\|^2 + \alpha_2 \|\boldsymbol{f}\|^2, \tag{43}$$

where α_2 is a second regularisation parameter. The solution to eq. (42) is given by the solution to the system

$$\left(\mathbf{M}^\intercal \mathbf{M} + \alpha_2 \mathbf{I}\right) \boldsymbol{f} = \mathbf{M}^\intercal \boldsymbol{p}. \tag{44}$$

Code implementing our numerical solution to the Volterra equation is given on Github at `https://github.com/ap-browning/multicompartment/blob/main/results/volterra.jl`.

5 Correlation between autocorrelation function curvature and expected first passage time

In the main document (fig. 4c,f), we demonstrate that the autocorrelation function (ACF) curvature provides a temporal scaling that allows us to approximate the expected first passage time (FPT). In fig. S1, we demonstrate that the strong correlationship between the ACF curvature and the expected FPT is consistent across multiple values of k and ν, with a Spearman correlation coefficient of -0.987.

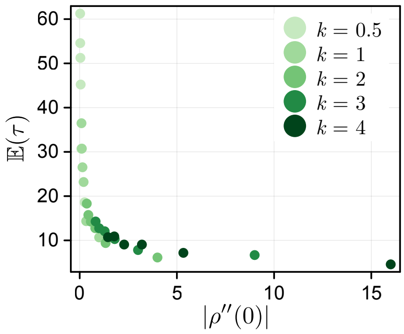

Figure S1. Mean FPT constructed from 1000 realisations of the SDE with the partially fixed initial condition, for various values of k, for compartments $\nu = 1, 2, ..., 6$. As given by Eq. (16) in the main document, the absolute value of the ACF curvature is a monotonically decreasing function of ν. The Spearman correlation coefficient between variables is -0.987.

6 Derivation of higher-order continuum limit approximation by multiple scales

In the limit $\Delta \to 0$, the discrete system yields to the advection equation with solution

$$x(\nu, t) = I(t - \nu/k),$$

where $x(0,t) = I(t)$ at the boundary. Thus, for $\Delta \to 0$, material is transported without smoothing along curves $\nu - kt = \beta$ for constant β in (ν, t) space. This formulation motivates the choice of slow variable, s, given by

$$\Delta^\alpha s = \nu - kt,$$

for $\alpha > 0$ such that $\Delta^\alpha s \ll 1$. Equivalently, for the discrete system $\nu = (i-1)\Delta$ so that

$$s = \Delta^{1-\alpha}(i-1) - \Delta^{-\alpha} kt, \tag{45}$$

To determine α, we write $X_i(t) = Z_i(s,t)$ such that

$$\begin{aligned} X_{i-1}(t) &= Z_{i-1}(s - \Delta^{1-\alpha}, t), \\ &= Z_{i-1}(s,t) - \Delta^{1-\alpha}\frac{\partial Z_{i-1}(s,t)}{\partial s} + \frac{\Delta^{2(1-\alpha)}}{2}\frac{\partial^2 Z_{i-1}(s,t)}{\partial s^2} + \mathcal{O}\left(\Delta^{3(1-\alpha)}\right). \end{aligned}$$

Here, we are motivated to consider the perturbation of $\Delta^{1-\alpha}$ to s as the adjustment to s moving from compartment i to compartment $i-1$.

Thus, the discrete system

$$\frac{\mathrm{d}}{\mathrm{d}t}X_i(t) = \frac{k}{\Delta}\big(X_{i-1}(t) - X_i(t)\big),$$

becomes

$$\left(\frac{\partial}{\partial t} - \Delta^{-\alpha}k\frac{\partial}{\partial s}\right) Z_i = \frac{k}{\Delta}\left(-Z_i + Z_{i-1} - \Delta^{1-\alpha}\frac{\partial Z_{i-1}}{\partial s} + \frac{\Delta^{2(1-\alpha)}}{2}\frac{\partial^2 Z_{i-1}}{\partial s^2} + \mathcal{O}\left(\Delta^{3(1-\alpha)}\right)\right),$$

or equivalently

$$\Delta\frac{\partial Z_i}{\partial t} - \Delta^{1-\alpha}k\frac{\partial Z_i}{\partial s} = k\left(Z_{i-1} - Z_i\right) - \Delta^{1-\alpha}k\frac{\partial Z_{i-1}}{\partial s} + \frac{\Delta^{2(1-\alpha)}k}{2}\frac{\partial^2 Z_{i-1}}{\partial s^2} + \mathcal{O}\left(\Delta^{3(1-\alpha)}\right). \tag{46}$$

Clearly, α must be rational to balance $\Delta\partial Z_i/\partial t$. To proceed, we set $\alpha = 1/2$ to balance the $\partial Z_i/\partial t$ with the diffusion term, $\frac{\partial^2 Z_{i-1}}{\partial s^2}$. Thus, eq. (46) becomes

$$\Delta\frac{\partial Z_i}{\partial t} - \sqrt{\Delta}k\frac{\partial Z_i}{\partial s} = k\left(Z_{i-1} - Z_i\right) - \sqrt{\Delta}k\frac{\partial Z_{i-1}}{\partial s} + \frac{\Delta k}{2}\frac{\partial^2 Z_{i-1}}{\partial s^2} + \mathcal{O}\left(\Delta^{3/2}\right). \tag{47}$$

We now proceed by considering an asymptotic expansion

$$Z_i(t) \sim Z_i^{(0)} + \sqrt{\Delta}Z_i^{(1)} + \Delta Z_i^{(2)} + \mathcal{O}\left(\Delta^{3/2}\right). \tag{48}$$

At $\mathcal{O}(1)$, eq. (47) yields

$$Z_{i-1}^{(0)}(s,t) = Z_i^{(0)}(s,t). \tag{49}$$

At $\mathcal{O}(\sqrt{\Delta})$, eq. (47) yields

$$\frac{\partial Z_{i-1}^{(0)}}{\partial t} - \frac{\partial Z_i^{(0)}}{\partial t} = Z_{i-1}^{(1)} - Z_i^{(1)} \Rightarrow Z_{i-1}^{(1)}(s,t) = Z_i^{(1)}(s,t), \tag{50}$$

where we have used eq. (49) in the last step.

At $\mathcal{O}(\Delta)$ we obtain

$$\frac{\partial Z_i^{(0)}}{\partial t} - \frac{k}{2}\frac{\partial^2 Z_i^{(0)}}{\partial s^2} + k\left(\frac{\partial Z_{i-1}^{(1)}}{\partial s} - \frac{\partial Z_i^{(1)}}{\partial s}\right) = k\left(Z_{i-1}^{(2)} - Z_i^{(2)}\right). \tag{51}$$

To keep the solution bounded as $i \to \infty$, we must enforce that the left-hand-side vanish, which using eq. (50) yields

$$\frac{\partial Z_i^{(0)}}{\partial t} = \frac{k}{2}\frac{\partial^2 Z_i^{(0)}}{\partial s^2}, \tag{52}$$

at leading order.

As in the main document, we denote $x(\nu, s, t) = Z_i(s,t)$, for s given by eq. (45) and $\nu = (i-1)\Delta$, thus yielding

$$\frac{\partial x}{\partial t} = \frac{k}{2}\frac{\partial^2 x}{\partial s^2}, \tag{53}$$

or equivalently

$$\frac{\partial x}{\partial t} = -k\frac{\partial x}{\partial \nu} + \frac{k\Delta}{2}\frac{\partial^2 x}{\partial \nu^2}, \tag{54}$$

as required.

References

[1] Rider PR. 1962 The negative binomial distribution and the incomplete beta function. *The American Mathematical Monthly* **69**, 302.

[2] Lamm PK. 2000 A survey of regularization methods for first-kind Volterra equations. In *Surveys on Solution Methods for Inverse Problems* pp. 53–82. Vienna: Springer.