

Kinetic theory for structured populations: application to stochastic sizer-timer models of cell proliferation

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Abstract

We derive the complete set of kinetic equations describing the evolution of the probability density distribution for a structured population such as cells distributed according to their ages and sizes. The kinetic equations for such a ‘sizer-timer’ model incorporate both demographic and individual cell growth rate stochasticities. Averages taken over the densities obeying the kinetic equations can be used to generate a second order PDE that incorporates the growth rate stochasticity. On the other hand, marginalizing over the densities yields a modified birth–death process that shows how age and size influence demographic stochasticity. Our kinetic framework is thus a more complete model that subsumes both the deterministic PDE and birth–death master equation representations for structured populations.

Keywords: kinetic theory, cell proliferation, cell size control, birth–death process, age structured populations

(Some figures may appear in colour only in the online journal)

1. Introduction

Across many diverse applications, mathematical models have been formulated to describe the evolution of populations according to a number of individual attributes such as age, size, and/or added size since birth. For example, deterministic age-structured models that incorporate age-dependent birth and death were developed by McKendrick and have been applied to human

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populations [1]. More recently, there has been renewed interest in cell size control [2, 3], cellular division mechanisms [4], and structured cell population models [5, 6].

When considering proliferating cell populations, individual cell growth is interrupted by cell division events that generate smaller daughter cells. Cell division is a process that involves many biochemical steps and complex biophysical mechanisms that involves metabolism, gene expression, protein production, DNA replication, chromosome separation (for eukaryotic cells), and fission or cell wall formation [7–11]. To simplify the understanding of which factors trigger cell division, three basic models that subsume these complex processes have been proposed. Cells can divide based on their age since birth, volume (size), or added volume since birth y [2, 12]. PDE approaches for the timer, sizer, and adder models, as well as combinations of these models, have been well-studied [6, 13, 14]. These PDE approaches implicitly describe the mean density of cells in age, size, and/or added size, and are considered deterministic models.

However, there has been much less development of structured populations models that incorporate stochastic effects. In the presence of stochasticity, how would the PDEs be modified? In the sizer-timer type of structured population models, stochasticity can arise in growth dynamics of each cell as well as in random times of cell division and death (demographic stochasticity).

Stochasticity arising from random times of birth and death (demographic stochasticity) has been considered in timer-like models for age-structured populations [15, 16]. This approach generalized the classic deterministic McKendrick equation to a higher dimension (dynamically varying) associated with the number of individuals in the system. This higher-dimensional stochastic ‘kinetic theory’ allows one to systematically connect an age-independent birth–death master equation description to the deterministic age-structured McKendrick model. A comprehensive and general treatment of the age-structured stochastic process using a Doi-Peliti operator formalism has also been developed for calculation of correlation functions [17]. The full kinetic theory has only been developed for age-structured populations and only includes demographic stochasticity (since chronological age is a deterministic quantity proportional to time). Other approaches using stochastic hybrid systems [18] have been used to incorporate the influence of random birth times of population-level variations in cell size. Intrinsic stochasticity in the growth rate of an individual cell has been treated in terms of Langevin equations for cell size [19], effective potentials [3] and stochastic maps [12, 20]. Recently, Chapman–Kolmogorov equations have also been applied to study the effect of different sources of noise in cellular proliferation [21]. However, stochasticity in the intrinsic growth rate has not been considered within a demographically stochastic kinetic theory.

In this paper, we derive the kinetic equations for the sizer-timer model of cell proliferation that incorporates both demographic stochasticity and intrinsic stochasticity in the growth of individual cells. In the next section, we derive the Fokker–Planck equation for the size of an individual cell and define the probabilistic quantities needed to construct the full kinetic theory. This equation is then marginalized in section 3 to explicitly isolate and show the feature limits of intrinsic stochasticity and demographic stochasticity. Including both sources of stochasticity renders the calculations of marginalized densities rather technical, but by defining specific moments, we derive a hierarchy of models describing correlations that arise from growth rate stochasticity. These higher-order (and higher-dimensional) models cannot be derived from approaches that impose mean-field assumptions and are evident only when a kinetic approach such as ours is employed. The first-order model describing the single particle density is self-contained and simply reduces to the mean-field ‘sizer-timer’ model [4, 13]. Higher order models are connected to each other and the first-order mean-field model. Marginalization of higher moments of particle numbers can also be constructed from our kinetic theory. These hierarchical models describe demographic stochasticity and are not closed. Our results generalize

a large body of work on sizer-timer PDE models to include stochastic processes, both at the individual and population levels.

2. Derivation of kinetic theory

Here, we outline the derivation of the kinetic equation for a population of dividing cells of different ages a and sizes (volumes) x . We start from the SDE for the size³ of a single cell at time t :

$$dX_t = g(X_t, A_t, t)dt + \sigma(X_t, A_t, t)dW_t, \quad X_t, A_t \in \Lambda, \tag{1}$$

where $\Lambda := [0, \infty)$, A_t is the cell's age (time that has elapsed after its birth), $g(X_t, A_t, t) > 0$ is the size- and age-dependent growth rate, and W_t is a standard Wiener process with independent, normally distributed increments $W_t - W_s$, zero mean, and variance $t - s$. The parameter $\sigma(X_t, A_t, t)$ represents the strength of stochasticity in a cell's growth rate. Here, we assume both g and σ are Lipschitz continuous to ensure the existence and uniqueness of X_t given any initial conditions $X_0 > 0, A_0 \geq 0$. We also assume $\sigma \in C^1, \sigma(0, t, a) = \partial_x \sigma(0, t, a) = 0$ so that the noise vanishes at $x = 0$ and X_t remains positive.

Next, we investigate a system of $m + 2n$ cells, where m is the number of individual cells (singlets) and n is the number of twins (doublets). A twin means two daughter cells generated from the division of a common mother cell, and therefore they have the identical age. In this section, we use the notation

$$\begin{aligned} \mathbf{X}_t^{(m)} &= (X_t^1, X_t^2, \dots, X_t^m), & \mathbf{Y}_t^{(2n)} &= (Y_t^1, \dots, Y_t^{2n}), \\ \mathbf{A}_t^{(m)} &= (A_t^1, A_t^2, \dots, A_t^m), & \mathbf{B}_t^{(n)} &= (B_t^1, \dots, B_t^n), \end{aligned} \tag{2}$$

where $\mathbf{A}_t^{(m)}$ and $\mathbf{B}_t^{(n)}$ are ordered ages such that $A_i^j \geq A_i^{j+1} \geq 0, B_i^j \geq B_i^{j+1} \geq 0, \forall i > j$ and $\mathbf{X}_t^{(m)}$ and $\mathbf{Y}_t^{(2n)}$ are the vectors of the volumes of the m singlets and $2n$ doublets that are of ages $\mathbf{A}_t^{(m)}$ and $\mathbf{B}_t^{(n)}$, respectively, at time t . We first use ordered ages to facilitate our derivations and to better understand the boundary conditions representing newly born cells. Note that two cells in a doublet have the same age but can have different sizes; thus, the age vector $\mathbf{B}_t^{(n)}$ of the $2n$ twins stores n ages, while the size vector $\mathbf{Y}_t^{(2n)}$ stores $2n$ sizes.

Formally solving equation (1), each X_t^i and Y_t^j satisfies

$$\begin{aligned} X_t^i &= X_{t'}^i + \int_{t'}^t g(X_s^i, A_s^i, s)ds + \int_{t'}^t \sigma(X_s, A_s, s)dW_s^i, \\ Y_t^j &= Y_{t'}^j + \int_{t'}^t g(Y_s^j, B_s^{\lfloor \frac{j+1}{2} \rfloor}, s)ds + \int_{t'}^t \sigma(Y_s^j, B_s^{\lfloor \frac{j+1}{2} \rfloor}, s)dW_s^{m+j}, \end{aligned} \tag{3}$$

where dW_s^i, dW_s^{m+j} are intrinsic, independent fluctuations in growth rates. We assume that cell division rates are regulated by a 'timer' mechanism and do not depend on cell size, i.e. the probability that a cell in a population of m singlets and n doublets divides during $(t, t + \Delta t]$ is $\beta_{m,n}(A_t, t)dt + o(dt)$, a function of its age A_t , time t and population sizes m, n . The mathematical analysis that follow requires that the birth rate is independent of a cell's size X_t . Finally, we take the continuous time limit and assume that in a finite number of cells, the possibility of two cells dividing in $(t, t + dt]$ is $o(dt)$ as $dt \rightarrow 0$.

³ Alternatively, X_t might also represent the log of the cell size.

2.1. The forward equation

We evaluate the increment in time by Ito's formula applied to a function $f_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t; \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)})$ of m individual and n twin sizes given initial sizes and ages $\mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}$ at $t' < t$, where the ages are defined to be in the descending order $A^1 \geq A^2 \dots \geq A^m \geq 0, B^1 \geq B^2 \dots \geq B^n \geq 0$. Ordering the ages will eventually allow us to easily incorporate cell division as a boundary condition in which newborn cells are represented by $B^n = 0$. We start by constructing the difference

$$\begin{aligned}
 & f_{m,n}(\mathbf{X}_{t+dt}^{(m)}, \mathbf{Y}_{t+dt}^{(2n)}, t + dt | \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) - f_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) \\
 &= \int_t^{t+dt} \left[\frac{\partial f_{m,n}}{\partial s} + \sum_{i=1}^m g(X_s^i, A_s^i, s) \frac{\partial f_{m,n}}{\partial X_s^i} + \sum_{j=1}^{2n} g(Y_s^j, B_s^{\lfloor(j+1)/2\rfloor}, s) \frac{\partial f_{m,n}}{\partial Y_s^j} \right. \\
 &\quad \left. + \frac{1}{2} \sum_{i=1}^m \sigma^2(X_s^i, A_s^i, s) \frac{\partial^2 f_{m,n}}{(\partial X_s^i)^2} + \frac{1}{2} \sum_{j=1}^{2n} \sigma^2(Y_s^j, B_s^{\lfloor(j+1)/2\rfloor}, s) \frac{\partial^2 f_{m,n}}{(\partial Y_s^j)^2} \right] ds \\
 &\quad + \sum_{i=1}^m \int_t^{t+dt} \sigma(X_s^i, A_s^i, s) \frac{\partial f_{m,n}}{\partial X_s^i} dW_s^i + \sum_{j=1}^{2n} \int_t^{t+dt} \sigma(Y_s^j, B_s^{\lfloor(j+1)/2\rfloor}, s) \frac{\partial f_{m,n}}{\partial Y_s^j} d\tilde{W}_s^j.
 \end{aligned} \tag{4}$$

After taking the expectation of equation (4) we find

$$\begin{aligned}
 & \mathbb{E} \left[f_{m,n}(\mathbf{X}_{t+dt}^{(m)}, \mathbf{Y}_{t+dt}^{(2n)}, t + dt | \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) \right] - \mathbb{E} \left[f_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) \right] \\
 &= \mathbb{E} \left[\int_t^{t+dt} ds \left(\frac{\partial f_{m,n}}{\partial s} + \sum_{i=1}^m g(X_s^i, A_s^i, s) \frac{\partial f_{m,n}}{\partial X_s^i} + \sum_{j=1}^{2n} g(Y_s^j, B_s^{\lfloor(j+1)/2\rfloor}, s) \frac{\partial f_{m,n}}{\partial Y_s^j} \right. \right. \\
 &\quad \left. \left. + \frac{1}{2} \sum_{i=1}^m \frac{\partial^2 f_{m,n}}{(\partial X_s^i)^2} \sigma^2(X_s^i, A_s^i, s) + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2 f_{m,n}}{(\partial Y_s^j)^2} \sigma^2(Y_s^j, B_s^{\lfloor(j+1)/2\rfloor}, s) \right) \right].
 \end{aligned} \tag{5}$$

Specifically, we can take $f_{m,n}$ in equation (5) as a distribution of the form

$$\begin{aligned}
 f_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) &= \prod_{i=1}^m \delta(X^i - X_t^i) \prod_{j=1}^{2n} \delta(Y^j - Y_t^j) \\
 &\quad \times S_{1,m}(t|t', \mathbf{A}_{t'}^{(m)}) S_{2,n}(t|t', \mathbf{B}_{t'}^{(n)}),
 \end{aligned} \tag{6}$$

where $S_{1,m}$ and $S_{2,n}$ are joint survival possibilities

$$\begin{aligned}
 S_{1,m}(t|t', \mathbf{A}^{(m)}) &= \prod_{i=1}^m e^{-\int_{t'}^t \beta_{m,n}(A^i - t' + s, s) ds}, \\
 S_{2,n}(t|t', \mathbf{B}^{(n)}) &= \prod_{j=1}^n \left(e^{-\int_{t'}^t \beta_{m,n}(B^j - t' + s, s) ds} \right)^2,
 \end{aligned} \tag{7}$$

and the birth rate $\beta \equiv \beta_{m,n}$ can implicitly depend on the populations m, n .

Next, we define $\hat{p}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)})$ as the probability density of m singlets of volumes $\mathbf{X}_t^{(m)}$ and n doublets of volumes $\mathbf{Y}_t^{(2n)}$ at time t , conditioned on there being m singlets of volumes $\mathbf{X}_{t'}^{(m)}$ and ages $\mathbf{A}_{t'}^{(m)}$ and n doublets with volumes $\mathbf{Y}_{t'}^{(2n)}$ and ages $\mathbf{B}_{t'}^{(n)}$ at time t' , and that no cell division occurs during $[t', t]$. The quantity $\hat{p}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) S_{1,m}(t | t', \mathbf{A}_{t'}^{(m)}) S_{2,n}(t | t', \mathbf{B}_{t'}^{(n)})$ is thus the probability measure that the cell population at time t contains m singlets of size $\mathbf{X}_t^{(m)}$ and n doublets of size $\mathbf{Y}_t^{(n)}$ with no cell division occurring within $[t', t]$, conditioned on it containing m singlets with volumes $\mathbf{X}_{t'}^{(m)}$ and ages $\mathbf{A}_{t'}^{(m)}$ and n doublets with volumes $\mathbf{Y}_{t'}^{(2n)}$ and ages $\mathbf{B}_{t'}^{(n)}$ at t' .

After substitution of the $f_{m,n}$ defined in equation (6) into equation (5), dividing by dt , and taking the $dt \rightarrow 0$ limit, we obtain

$$\begin{aligned} & \frac{\partial}{\partial t} \left(\hat{p}(\mathbf{X}^{(m)}, \mathbf{Y}^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) S_{1,m}(t | t', \mathbf{A}_{t'}^{(m)}) S_{2,n}(t | t', \mathbf{B}_{t'}^{(n)}) \right) \\ &= \int_{\Lambda^m} d\mathbf{X}_t^{(m)} \int_{\Lambda^{2n}} d\mathbf{Y}_t^{(2n)} \hat{p}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) \left[\frac{\partial f}{\partial t} \right. \\ & \quad + \sum_{i=1}^m g(X_t^i, A_t^i, t) \frac{\partial f}{\partial X_t^i} + \sum_{j=1}^{2n} g(Y_t^j, B_t^{[(j+1)/2]}, t) \frac{\partial f}{\partial Y_t^j} \\ & \quad \left. + \frac{1}{2} \sum_{i=1}^m \frac{\partial^2 f}{\partial (X_t^i)^2} \sigma^2(X_t^i, A_t^i, t) + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2 f}{\partial (Y_t^j)^2} \sigma^2(Y_t^j, B_t^{[(j+1)/2]}, t) \right] \\ &= S_{1,m} S_{2,n} \left[- \left(\sum_{i=1}^m \beta_{m,n}(A_t^i, t) + 2 \sum_{j=1}^n \beta_{m,n}(B_t^j, t) \right) \hat{p}_{m,n} \right. \\ & \quad - \sum_{i=1}^m \frac{\partial (g(X_t^i, A_t^i, t) \hat{p})}{\partial X_t^i} - \sum_{j=1}^{2n} \frac{\partial (g(Y_t^j, B_t^{[(j+1)/2]}, t) \hat{p})}{\partial Y_t^j} \\ & \quad \left. + \frac{1}{2} \sum_{i=1}^m \frac{\partial^2 (\sigma^2(X_t^i, A_t^i, t) \hat{p})}{(\partial X_t^i)^2} + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2 (\sigma^2(Y_t^j, B_t^j, t) \hat{p})}{(\partial Y_t^j)^2} \right], \tag{8} \end{aligned}$$

where the last equality arises from integration by parts.

Finally, we derive the PDE satisfied by the unconditioned probability density $p_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, \mathbf{A}_t^{(m)}, \mathbf{B}_t^{(n)}, t)$ given $p_{m,n}(\mathbf{X}^{(m)}, \mathbf{Y}^{(2n)}, \mathbf{A}^{(m)}, \mathbf{B}^{(n)}, t')$. First, we note that if no division has occurred in $[t', t]$ and $t - t' < \min\{A_t^{(m)}, B_t^{(n)}\}$, a system at t with m singlets of volumes $\mathbf{X}_t^{(m)}$ and ages $\mathbf{A}_t^{(m)}$ and n doublets with volumes $\mathbf{Y}_t^{(2n)}$ and ages $\mathbf{B}_t^{(n)}$ can result only from a system at t' with m singlets with ages $\mathbf{A}_{t'}^{(m)} = \mathbf{A}_t^{(m)} - (t - t')$ and n doublets with ages $\mathbf{B}_{t'}^{(n)} = \mathbf{B}_t^{(n)} - (t - t')$. Thus, we use the Chapman–Kolmogorov relation between the two quantities $\hat{p}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) S_{1,m}(t | t', \mathbf{A}_{t'}^{(m)}) S_{2,n}(t | t', \mathbf{B}_{t'}^{(n)})$ and $p_{m,n}$ to construct

$$\begin{aligned} p_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, \mathbf{A}_t^{(m)} + t - t', \mathbf{B}_t^{(n)} + t - t', t) &= \int_{\Lambda^{(m+2n)}} \hat{p}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, t | \mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}) \\ & \quad \times S_{1,m}(t | t', \mathbf{A}_{t'}^{(m)}) S_{2,n}(t | t', \mathbf{B}_{t'}^{(n)}) p_{m,n}(\mathbf{X}_{t'}^{(m)}, \mathbf{Y}_{t'}^{(2n)}, \mathbf{A}_{t'}^{(m)}, \mathbf{B}_{t'}^{(n)}, t') d\mathbf{X}_{t'}^{(m)} d\mathbf{Y}_{t'}^{(2n)}. \tag{9} \end{aligned}$$

Assuming that $p_{m,n}$ is continuous and differentiable, and the integration is interchangeable with differentiation in equation (9), we take derivatives with respect to all variables t, X^i, Y^j, A^i, B^j

to obtain

$$\begin{aligned} & \frac{\partial p_{m,n}}{\partial t} + \sum_{i=1}^m \frac{\partial p_{m,n}}{\partial A_t^i} + \sum_{j=1}^n \frac{\partial p_{m,n}}{\partial B_t^j} + \sum_{i=1}^m \frac{\partial(g(X_t^i, A_t^i, t)p_{m,n})}{\partial X_t^i} + \sum_{j=1}^{2n} \frac{\partial(g(Y_t^j, B_t^j, t)p_{m,n})}{\partial Y_t^j} \\ &= - \left(\sum_{i=1}^m \beta_{m,n}(A_t^i, t) + 2 \sum_{j=1}^n \beta_{m,n}(B_t^j, t) \right) p_{m,n} \\ & \quad + \frac{1}{2} \sum_{i=1}^m \frac{\partial^2(\sigma^2(X_t^i, A_t^i, t)p_{m,n})}{(\partial X_t^i)^2} + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2(\sigma^2(Y_t^j, B_t^j, t)p_{m,n})}{(\partial Y_t^j)^2}, \end{aligned} \tag{10}$$

where $p_{m,n} \equiv p_{m,n}(\mathbf{X}_t^{(m)}, \mathbf{Y}_t^{(2n)}, \mathbf{A}_t^{(m)}, \mathbf{B}_t^{(n)}, t)$. Hereafter, we will omit the subscript t for notational simplicity. To facilitate further analysis, we define a symmetrized density $\rho_{m,n}$ that is symmetric to the interchange of variables:

$$\rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t) = \frac{1}{2^n m! n!} \sum_{\pi^{2n}} p_{m,n}(\mathbf{X}^{(m)}, \pi^{2n}(\mathbf{Y}^{(2n)}), \mathbf{A}^{(m)}, \mathbf{B}^{(n)}, t), \tag{11}$$

where $\mathbf{A}^{(m)} = (A^{\xi_a(1)}, \dots, A^{\xi_a(m)})$, $\mathbf{B}^{(n)} = (B^{\xi_b(1)}, \dots, B^{\xi_b(n)})$ are ordered ages, $\mathbf{X}^{(m)} = (X^{\xi_a(1)}, \dots, X^{\xi_a(m)})$, $\mathbf{Y}^{(2n)} = (Y^{2\xi_b(1)-1}, \dots, Y^{2\xi_b(n)})$ are the corresponding sizes, and π^{2n} is some permutation $\Lambda^{2n} \rightarrow \Lambda^{2n}$ such that $\pi^{2n}(Y^{2i}), \pi^{2n}(Y^{2i-1}) \in \{Y^{2i-1}, Y^{2i}\}$, $\pi^{2n}(Y^{2i}) \neq \pi^{2n}(Y^{2i-1}), i = 1, \dots, n$, i.e. π^{2n} can interchange the sizes of two cells in a doublet. Therefore, there are 2^n total permutations π^{2n} . $\xi_a(1), \dots, \xi_a(m)$ is a rearrangement such that $A^{\xi_a(1)} \geq A^{\xi_a(2)} \geq \dots \geq A^{\xi_a(m)}$ and $\xi_b(1), \dots, \xi_b(n)$ is a rearrangement such that $B^{\xi_b(1)} \geq B^{\xi_b(2)} \geq \dots \geq B^{\xi_b(n)}$. Defining such a $\rho_{m,n}$ allows us to remove the restriction that the ages must be presented in a descending order. Moreover, changing the order of two cells within in a doublet will not affect the value of $\rho_{m,n}$. Definite integrals over $\rho_{m,n}$ are then related to those over $p_{m,n}$ via

$$\begin{aligned} & \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t) = \int_{\Lambda^{(m+2n)}} d\mathbf{X}^{(m)} d\mathbf{Y}^{(2n)} \int_{\Lambda} dA^{\xi_a(1)} \dots \\ & \quad \dots \int_0^{A^{\xi_a(m-1)}} dA^{\xi_a(m)} \int_{\Lambda} dB^{\xi_b(1)} \dots \int_0^{B^{\xi_b(n-1)}} dB^{\xi_b(n)} p_{m,n}(\mathbf{X}^{(m)}, \mathbf{Y}^{(2n)}, \mathbf{A}^{(m)}, \mathbf{B}^{(n)}, t), \end{aligned} \tag{12}$$

so $\rho_{m,n}$ is also a probability density distribution if $p_{m,n}$ is. Furthermore, the differential equation satisfied by $\rho_{m,n}$ for $\mathbf{A}^m, \mathbf{B}^n > 0$ is the same as the differential equation satisfied by $p_{m,n}$

$$\begin{aligned} & \frac{\partial \rho_{m,n}}{\partial t} + \sum_{i=1}^m \frac{\partial \rho_{m,n}}{\partial A^i} + \sum_{j=1}^n \frac{\partial \rho_{m,n}}{\partial B^j} + \sum_{i=1}^m \frac{\partial(g(X^i, A^i, t)\rho_{m,n})}{\partial X^i} + \sum_{j=1}^{2n} \frac{\partial(g(Y^j, B^{\lfloor \frac{j+1}{2} \rfloor}, t)\rho_{m,n})}{\partial Y^j} \\ &= - \left(\sum_{i=1}^m \beta_{m,n}(A^i, t) + 2 \sum_{j=1}^n \beta_{m,n}(B^j, t) \right) \rho_{m,n} \\ & \quad + \frac{1}{2} \sum_{i=1}^m \frac{\partial^2(\sigma^2(X^i, A^i, t)\rho_{m,n})}{(\partial X^i)^2} + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2(\sigma^2(Y^j, B^{\lfloor \frac{j+1}{2} \rfloor}, t)\rho_{m,n})}{(\partial Y^j)^2}. \end{aligned} \tag{13}$$

2.2. Boundary conditions

We now specify appropriate boundary conditions for $\rho_{m,n}$ that represent the birth of new cells with age zero. By using ordered ages, it is easy to derive the corresponding boundary conditions for $p_{m,n}$ defined in equation (9), which we omitted here, but which are nonzero if $B^n = 0$ and zero if any entry in $\mathbf{X}^{(m)}, \mathbf{Y}^{(2n)}, \mathbf{A}^{(m)}, \mathbf{B}^{(k < n)}$ is zero. The boundary conditions for $\rho_{m,n}$ are then derived from the boundary conditions for $p_{m,n}$. Homogeneous boundary conditions also arise at any $X^i = 0, \infty$ or $Y^j = 0, \infty$ indicating that no cell can have 0 or infinite size. If one cell divides at time t in a system of m singlets and n doublets, the system could either convert to $m - 1$ singlets and $n + 1$ doublets when this dividing cell is a singlet, or $m + 1$ singlets and n doublets when the dividing cell is one cell in a doublet. A simpler but similar discussion of boundary conditions for the ‘timer’ model which has no size dependence has been discussed [15, 16]. Hereafter, we use the notation $\mathbf{X}_{-i}^m = (X^1, X^2, \dots, X^{i-1}, X^{i+1}, \dots, X^m)$, $\mathbf{A}_{-i}^m = (A^1, A^2, \dots, A^{i-1}, A^{i+1}, \dots, A^m)$ to describe vectors of one lower dimension in which element i is removed. The boundary conditions are given by

$$\rho_{m,n} = 0 \begin{cases} \text{if any element in } \{\mathbf{X}^m, \mathbf{Y}^{2n}\} = 0, \infty, \\ \text{or any element in } \mathbf{A}^m = 0, \\ \text{or more than one element in } \mathbf{B}^n = 0, \end{cases} \quad (14)$$

and

$$\begin{aligned} \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}[Y^{2j-1} = y_1, Y^{2j} = y_2], \mathbf{A}^m, \mathbf{B}^n[B^j = 0], t) = \\ \frac{m+1}{n} \int_0^\infty ds \tilde{\beta}_{m+1,n-1}(y_1 + y_2, y_1, s, t) \rho_{m+1,n-1}(\mathbf{X}^{m+1}[X^{m+1} = y_1 + y_2], \\ \mathbf{Y}^{n-1}, \mathbf{A}^{m+1}[A^{m+1} = s], \mathbf{B}^{n-1}, t) \\ + \frac{2}{m} \sum_{i=1}^m \tilde{\beta}_{m-1,n}(y_1 + y_2, y_1, A^i, t) \rho_{m-1,n}(\mathbf{X}_{-i}^m, \mathbf{A}_{-i}^m, \mathbf{B}^n[B^n = A^i], \\ \mathbf{Y}^{2n}[Y^{2n-1} = X^i, Y^{2n} = y_1 + y_2], t), \end{aligned} \quad (15)$$

Equation (14) enforces that no cell can have a zero or infinitely large size and no more than one cell can divide at the same instant (continuous time assumption). In equation (15), the notation $\mathbf{X}^{m+1}[X^i = x]$ indicates that the i^{th} component in \mathbf{X}^{m+1} is x , with similar definitions for $\mathbf{Y}^{2n}[Y^j = y], \mathbf{A}^m[A^i = a], \mathbf{B}^n[B^j = b]$. The first term on the rhs of equation (15) results from the division of a singlet while the second term results from the division of one cell in a doublet, leaving a singlet and giving rise to a new doublet. Division is described by $\tilde{\beta}_{m,n}(x, z, a, t) dz$, the rate that in a population of m singlets and n doublets, a cell of volume x and age a divides into one cell with volume $\in [z, z + dz]$. By allowing $\tilde{\beta}_{m,n}$ to explicitly depend on both the mother cell’s size x and daughter cell’s size z , we can readily allow for asymmetric division and daughter cells of different sizes. Moreover, from volume conservation, we impose $\tilde{\beta}_{m,n}(x, z, a, t) = \tilde{\beta}_{m,n}(x, x - z, a, t)$. Finally, if we assume the simple form $\tilde{\beta}_{m,n}(x, z, a, t) = h(z/x)\beta_{m,n}(a, t)/x$ [13], $\int_0^x \tilde{\beta}_{m,n}(x, z, a, t) dz = \beta_{m,n}(a, t)$ is independent of size x as we have assumed. In the appendix, we explicitly demonstrate that probability conservation is preserved under these boundary conditions.

3. Hierarchies and moment equations

In this section, we will assume that $\tilde{\beta}$ and β are independent of the population sizes m, n . Under this assumption, we are able to derive lower-dimensional (e.g. marginalized) projections of our kinetic theory (equation (13)) by integrating over a specific number of cell sizes:

$$\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = \int_{\Lambda} d\mathbf{X}^{h+1:m} d\mathbf{Y}_o^{2k+2\ell+1:2n} d\mathbf{A}^{h+1:m} d\mathbf{B}^{k+\ell+1:n} \rho_{m,n}, \quad (16)$$

where $\rho_{m,n} \equiv \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t)$, $\Lambda \equiv \Lambda^{(m-h)+(2n-k-2\ell)+(m-h)+(n-k)}$, and we define the notation $\mathbf{X}^{h+1:m} := (X^{h+1}, \dots, X^m)$, $\mathbf{Y}_o^{2k+2\ell+1:2n} := (Y^1, Y^3, \dots, Y^{2k-1}, Y^{2k+2\ell+1}, \dots, Y^{2n})$, $\mathbf{A}^{h+1:m} := (A^{h+1}, \dots, A^m)$, $\mathbf{B}^{k+\ell+1:n} := (B^{k+\ell+1}, \dots, B^n)$ and $\mathbf{Y}_e^{2k+2\ell} := (Y^2, Y^4, \dots, Y^{2k}, Y^{2k+1}, Y^{2k+2}, \dots, Y^{2k+2\ell})$. The marginalized densities require three indices to describe because although the size \mathbf{X}^m and age \mathbf{A}^m have a one-to-one correspondence for singlets, the twins, while carrying the same age, almost surely have different sizes due to asymmetric division and independent growth fluctuations immediately after birth. Thus, the number of ways to exit and enter each state depends on which types of cells are ‘integrated over’. By marginalizing over equation (13), we find the kinetic equation satisfied by $\rho_{m,n}^{(h,k,\ell)}$ (in the remaining space $\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^k > 0$) becomes

$$\begin{aligned} & \frac{\partial \rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t)}{\partial t} + \sum_{i=1}^h \frac{\partial \rho_{m,n}^{(h,k,\ell)}}{\partial A^i} + \sum_{j=1}^{k+\ell} \frac{\partial \rho_{m,n}^{(h,k,\ell)}}{\partial B^j} + \sum_{i=1}^h \frac{\partial (g(X^i, A^i, t) \rho_{m,n}^{(h,k,\ell)})}{\partial X^i} \\ & + \sum_{j=1}^k \frac{\partial (g(Y^{2j}, A^j, t) \rho_{m,n}^{(h,k,\ell)})}{\partial Y^{2j}} + \sum_{j=1}^{2\ell} \frac{\partial (g(Y^{2k+j}, A^j, t) \rho_{m,n}^{(h,k,\ell)})}{\partial Y^{2k+j}} \\ & - \frac{1}{2} \sum_{i=1}^h \frac{\partial^2 (\sigma^2(X^i, A^i, t) \rho_{m,n}^{(h,k,\ell)})}{(\partial X^i)^2} - \frac{1}{2} \sum_{j=1}^k \frac{\partial^2 (\sigma^2(Y^{2j}, B^{[\frac{j+1}{2}]}, t) \rho_{m,n}^{(h,k,\ell)})}{(\partial Y^{2j})^2} \\ & - \frac{1}{2} \sum_{j=1}^{2\ell} \frac{\partial^2 (\sigma^2(Y^{2k+j}, B^{k+[\frac{j+1}{2}]}, t) \rho_{m,n}^{(h,k,\ell)})}{(\partial Y^{2k+j})^2} \\ & = - \sum_{i=1}^h \beta(A^i, t) \rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) - \sum_{j=1}^{k+\ell} 2\beta(B^j, t) \rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) \\ & - (m-h) \int_{\Lambda^2} d\mathbf{X}^{h+1} d\mathbf{A}^{h+1} \beta(A^{h+1}, t) \rho_{m,n}^{(h+1,k,\ell)}(\mathbf{X}^{h+1}, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^{h+1}, \mathbf{B}^{k+\ell}, t) \\ & - 2(n-k-\ell) \int_{\Lambda^2} d\mathbf{Y}^{2k+2} d\mathbf{B}^{k+1} \beta(B^{k+1}, t) \rho_{m,n}^{(h,k+1,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell+2}, \mathbf{A}^h, \mathbf{B}^{k+\ell+1}, t) \\ & + \frac{(n-k-\ell)(m+1)}{n} \int_{\Lambda^2} d\mathbf{X}^{h+1} d\mathbf{A}^{h+1} \beta(A^{h+1}, t) \rho_{m+1,n-1}^{(h+1,k,\ell)}(\mathbf{X}^{h+1}, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^{h+1}, \mathbf{B}^{k+\ell}, t) \\ & + \frac{2(n-k-\ell)(m-h)}{m} \int_{\Lambda^2} d\mathbf{Y}^{2k+2} d\mathbf{B}^{k+1} \beta(B^{k+1}, t) \rho_{m-1,n}^{(h,k+1,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell+2}, \mathbf{A}^h, \mathbf{B}^{k+\ell+1}, t) \\ & + \frac{2(n-k-\ell)}{m} \sum_{i=1}^h \beta(A^i, t) \rho_{m-1,n}^{(h-1,k+1,\ell)}(\mathbf{X}_{-i}^h, \mathbf{Y}_e^{2k+2+2\ell} [Y^{2k+2} = X^i], \mathbf{A}_{-i}^h, \mathbf{B}^{k+\ell+1} [B^{k+1} = A^i], t), \end{aligned} \quad (17)$$

and the associated boundary conditions become

$$\begin{aligned}
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell} [Y^{2k} = y], \mathbf{A}^h, \mathbf{B}^{k+\ell} [B^k = 0], t) \\
 &= \frac{m+1}{n} \int_{\Lambda^2} dA^{h+1} ds \tilde{\beta}(y+s, y, A^{h+1}, t) \rho_{m+1,n-1}^{(h+1,k-1,\ell)}(\mathbf{X}^{h+1} [X^{h+1} = y+s], \\
 &\qquad\qquad\qquad \mathbf{Y}_e^{2k+2\ell-2}, \mathbf{A}^{h+1}, \mathbf{B}^{k+\ell-1}, t) \\
 &+ \frac{2(m-h)}{m} \int_{\Lambda^2} dB^k ds \tilde{\beta}(y+s, y, B^k, t) \rho_{m-1,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k} [Y^{2k} = y+s], \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) \\
 &+ \frac{2}{m} \sum_{i=1}^h \int_{\Lambda} ds \tilde{\beta}(y+s, y, A^i, t) \rho_{m-1,n}^{(h-1,k-1,\ell+1)}(\mathbf{X}_{-i}^h, \\
 &\qquad\qquad\qquad \mathbf{Y}_e^{2k+2\ell} [Y^{2k+2\ell-1} = y+s, Y^{2k+2\ell} = X^i], \mathbf{A}_{-i}^h, \mathbf{B}^{k+\ell} [B^{k+\ell} = A^i], t),
 \end{aligned} \tag{18}$$

$$\begin{aligned}
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell} [Y^{2k+2\ell-1} = y_1, Y^{2k+2\ell} = y_2], \mathbf{A}^h, \mathbf{B}^{k+\ell} [B^{k+\ell} = 0], t) \\
 &= \frac{m+1}{n} \int_{\Lambda} dA^{h+1} \tilde{\beta}(y_1+y_2, y_1, A^{h+1}, t) \rho_{m+1,n-1}^{(h+1,k,\ell-1)}(\mathbf{X}^{h+1} [X^{h+1} = y_1+y_2], \\
 &\qquad\qquad\qquad \mathbf{Y}_e^{2k+2\ell-2}, \mathbf{A}^{h+1}, \mathbf{B}^{k+\ell-1}, t) \\
 &+ \frac{2(m-h)}{m} \int_{\Lambda} dB^{k+1} \tilde{\beta}(y_1+y_2, y_1, B^{k+1}, t) \rho_{m-1,n}^{(h,k+1,\ell-1)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell} [Y^{2k+2} = y_1+y_2], \\
 &\qquad\qquad\qquad \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) \\
 &+ \frac{2}{m} \sum_{i=1}^h \tilde{\beta}(y_1+y_2, y_1, A^i, t) \rho_{m-1,n}^{(h-1,k,\ell)}(\mathbf{X}_{-i}^h, \mathbf{Y}_e^{2k+2\ell} [Y^{2k+2\ell-1} = y_1+y_2, Y^{2k+2\ell} = X^i], \\
 &\qquad\qquad\qquad \mathbf{A}_{-i}^h, \mathbf{B}^{k+\ell} [B^{k+\ell} = A^i], t),
 \end{aligned} \tag{19}$$

and

$$\begin{aligned}
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h [X^i = 0], \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = \rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h [X^i = \infty], \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = 0, \\
 &\qquad i = 1, 2, \dots, h, \\
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell} [Y^j = 0], \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = \rho_{m,n}^{(h,k)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell} [Y^j = \infty], \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = 0, \\
 &\qquad j = 2, 4, \dots, 2k, 2k+1, \dots, 2k+2\ell, \\
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h [A^i = 0], \mathbf{B}^k, t) = 0, \\
 &\qquad i = 1, 2, \dots, h, \\
 &\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^{k+\ell}, t) = 0,
 \end{aligned}$$

if two or more entries in $\mathbf{B}^{k+\ell}$ are 0. (20)

The first two terms on the rhs of equation (17) represent the division of a singlet/doublet in the current system whose age is specified; the third and fourth terms on the rhs describe the division of a singlet and one cell of a doublet, respectively, whose age is not specified; the fifth term results from the division of a singlet, whose age and volume are unspecified, that induces

the state transition $(m + 1, n - 1) \rightarrow (m, n)$. The sixth term arises from division of one cell of a doublet that converts the system from $(m - 1, n)$ to (m, n) . Finally, the last term represents the division of one cell in a doublet whose age is A^i , $1 \leq i \leq h$ and its undividing twin has size X^i . In equations (18) and (19), the first term on their rhss represents the division of a singlet, and the second term on their rhss describes the division of one cell in a doublet, giving rise to a newborn doublet and leaving a singlet whose volume and age are integrated over. The last term in the boundary conditions in equations (18) and (19) results from the division of a cell in a doublet, giving rise to a newborn doublet and leaving a singlet whose volume and age are $X^i \in \mathbf{X}^h$ and $A^i \in \mathbf{A}^h$, respectively.

The differential equations satisfied by the fully marginalized density $\rho_{m,n}^{(0,0,0)}$ are

$$\begin{aligned} \frac{\partial \rho_{m,n}^{(0,0,0)}(t)}{\partial t} = & \int_{\Lambda^2} dX^1 dA^1 \beta(A^1, t) \left[(m + 1)\rho_{m+1,n-1}^{(1,0,0)}(\mathbf{X}^1, \mathbf{A}^1, t) - m\rho_{m,n}^{(1,0,0)}(\mathbf{X}^1, \mathbf{A}^1, t) \right] \\ & + 2n \int_{\Lambda^2} dY^2 dB^1 \beta(B^1, t) \left[\rho_{m-1,n}^{(0,1,0)}(\mathbf{Y}_e^2, \mathbf{B}^1, t) - \rho_{m,n}^{(0,1,0)}(\mathbf{Y}_e^2, \mathbf{B}^1, t) \right], \end{aligned} \quad (21)$$

which, for an age-independent division rate, explicitly reduces to the simple birth–death master equation

$$\frac{1}{\beta(t)} \frac{\partial \rho_{m,n}^{(0,0,0)}(t)}{\partial t} = (m + 1)\rho_{m+1,n-1}^{(0,0,0)}(t) - m\rho_{m,n}^{(0,0,0)}(t) + 2n\rho_{m-1,n}^{(0,0,0)}(t) - 2n\rho_{m,n}^{(0,0,0)}(t). \quad (22)$$

In equations (21) and (22), the division rates $\beta(A^1, t)$ and $\beta(t)$ can be replaced by their full (m, n) -dependent forms.

3.1. Number-weighted density functions

We now define a class of number-weighted density functions from the marginalized densities $\rho_{m,n}^{(h,k,\ell)}$ that incorporates higher moments and that has useful closure properties:

$$\begin{aligned} u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t) := & \sum_{m,n=0}^{\infty} \sum_{r=0}^k \sum_{\xi^{(0,r)} \in S_k} 2^{k+\ell-r} (m)_r (n)_{k+\ell-r} \rho_{m,n}^{(r,k-r,\ell)} \left(\mathbf{X}^r [X^i = x^{\xi^{(0,r)}(i)}], \right. \\ & \mathbf{Y}_e^{2(k-r)+2\ell} [Y^{2j} = x^{\xi^{(r,k-r)}(j)}, Y^{2(k-r)+p} = y^p], \mathbf{A}^r [A^i = a^{\xi^{(0,r)}(i)}], \\ & \left. \mathbf{B}^{k-r+\ell} [B^j = a^{\xi^{(r,k-r)}(j)}, B^{k-r+\lfloor \frac{p+1}{2} \rfloor} = b^{\lfloor \frac{p+1}{2} \rfloor}], t \right), \\ & 1 \leq i \leq r, 1 \leq j \leq k - r, 1 \leq p \leq 2\ell, \end{aligned} \quad (23)$$

where $\mathbf{x}^k := (x^1, \dots, x^k)$, $\mathbf{y}^{2\ell} := (y^1, \dots, y^{2\ell})$, $\mathbf{a}^k := (a^1, \dots, a^k)$, $\mathbf{b}^\ell := (b^1, \dots, b^\ell)$, and $(m)_r = m!/(m - r)!$ is the falling factorial, $S_k = \{1, 2, \dots, k\}$. The sum $\sum_{\xi^{(0,r)} \in S_k}$ includes all elements in

the set $\xi^{(0,r)} \in \Omega_r$ containing all possible choices of r elements in S_k and $\xi^{(r,k-r)} := (\xi(r + 1), \xi(r + 2), \dots, \xi(k)) = S_k \setminus \xi^{(0,r)}$. We require $\xi^{(0,r)}(i) < \xi^{(0,r)}(j)$, $\xi^{(r,k-r)}(i) < \xi^{(r,k-r)}(j)$, $\forall i < j$, and $r \leq m$, and $k - r \leq n$ in equation (23). Note that $u^{(0,0)} \equiv 1$ from normalization. The lowest order number-weighted density functions $u^{(k,\ell)}$ are explicitly given in appendix B.

Since our kinetic equations (equations (13)–(15)) subsume all hierarchical equations for $\rho_{m,n}^{(h,k,\ell)}$ (equations (17)–(20)), equations for $u^{(k,\ell)}$ can be derived. For example, if β is

independent of m, n , the PDE satisfied by $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t)$ is

$$\begin{aligned} & \frac{\partial u^{(k,\ell)}}{\partial t} + \sum_{i=1}^k \frac{\partial u^{(k,\ell)}}{\partial a^i} + \sum_{j=1}^{\ell} \frac{\partial u^{(k,\ell)}}{\partial b^j} + \sum_{i=1}^k \frac{\partial(g(x^i, a^i, t)u^{(k,\ell)})}{\partial x^i} + \sum_{j=1}^{2\ell} \frac{\partial(g(y^j, b^{\lfloor \frac{j+1}{2} \rfloor}, t)u^{(k,\ell)})}{\partial y^j} \\ &= - \left(\sum_{i=1}^k \beta(a^i, t) + \sum_{j=1}^{\ell} 2\beta(b^j, t) \right) u^{(k,\ell)} \\ &+ \frac{1}{2} \sum_{i=1}^k \frac{\partial^2(\sigma^2(x^i, a^i, t)u^{(k,\ell)})}{(\partial x^i)^2} + \frac{1}{2} \sum_{j=1}^{2\ell} \frac{\partial^2(\sigma^2(y^j, b^{\lfloor \frac{j+1}{2} \rfloor}, t)u^{(k,\ell)})}{(\partial y^j)^2}, \end{aligned} \tag{24}$$

along with the boundary conditions

$$\begin{aligned} u^{(k,\ell)}(\mathbf{x}^k[x^v = x], \mathbf{y}^{2\ell}, \mathbf{a}^k[a^v = 0], \mathbf{b}^\ell, t) &= \sum_{m,n=0}^{\infty} \sum_{r=0}^{k-1} \sum_{\xi^{(0,r)} \in S_k^{-v}} 2^{\ell+k-r} (m)_r (n)_{k+\ell-r} \\ &\times \rho_{m,n}^{(r,k-r,\ell)} \left(\mathbf{X}^r[X^i = x^{\xi^{(0,r)}(i)}], \mathbf{Y}_e^{2k-2r+2\ell}[Y^{2j} = x^{\xi^{(r,k-r)}(j)}, Y^{2k+p} = y^p], \right. \\ &\quad \left. \mathbf{A}^r[A^i = a^{\xi^{(0,r)}(i)}], \mathbf{B}^{\ell+k-r}[B^j = a^{\xi^{(r,k-r)}(j)}, B^{k-r+\lfloor \frac{\ell+1}{2} \rfloor} = b^{\lfloor \frac{\ell+1}{2} \rfloor}], t \right) \\ &= 2 \int_{\Lambda^2} ds da \tilde{\beta}(x+s, x, a, t) u^{(k,\ell)}(\mathbf{x}^k[x^k = x+s], \mathbf{y}^{2\ell}, \mathbf{a}^k[a^k = a], \mathbf{b}^\ell, t) \\ &+ 2 \sum_{w=1, \neq v}^k \int_{\Lambda} ds \tilde{\beta}(x+s, x, a^w, t) u^{(k-2, \ell+1)}(\mathbf{x}_{-v, -w}^k, \mathbf{a}_{-v, -w}^k, \\ &\quad \mathbf{y}^{2\ell+2}[y^{2\ell+1} = x^w, y^{2\ell+2} = x+s], \mathbf{b}^{\ell+1}[b^{\ell+1} = a^w], t), \end{aligned} \tag{25}$$

$$\begin{aligned} u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}[y^{2v-1} = y_1, y^{2v} = y_2], \mathbf{a}^k, \mathbf{b}^\ell[b^v = 0], t) &= \sum_{m,n=0}^{\infty} \sum_{r=0}^k \sum_{\xi^{(0,r)} \in S_k} 2^{\ell+k-r} (m)_r (n)_{k+\ell-r} \rho_{m,n}^{(r,k-r,\ell)} \left(\mathbf{X}^r[X^i = x^{\xi^{(0,r)}(i)}], \right. \\ &\quad \mathbf{Y}_e^{2\ell+k-r}[Y^{2j} = x^{\xi^{(r,k-r)}(j)}, Y^{2k+q} = y^q], \mathbf{A}^r[A^i = a^{\xi^{(0,r)}(i)}], \\ &\quad \left. \mathbf{B}^{\ell+k-r}[B^j = a^{\xi^{(r,k-r)}(j)}, B^{k-r+\lfloor \frac{q+1}{2} \rfloor} = b^{\lfloor \frac{q+1}{2} \rfloor}], t \right) \\ &= 2 \int_{\Lambda} da \tilde{\beta}(y_1 + y_2, y_1, a, t) \\ &\quad \times u^{(k+1, \ell-1)}(\mathbf{x}^{k+1}[x^{k+1} = y_1 + y_2], \mathbf{y}_{-(2v-1), -2v}^{2\ell}, \mathbf{a}^{k+1}[a^{k+1} = a], \mathbf{b}_{-v}^\ell, t) \\ &+ 2 \sum_{w=1}^k \tilde{\beta}(y_1 + y_2, y_1, a^w, t) \\ &\quad \times u^{(k-1, \ell)}(\mathbf{x}_{-w}^k, \mathbf{a}_{-w}^k, \mathbf{y}^{2\ell}[y^{2v-1} = y_1 + y_2, y^{2v} = x^w], \mathbf{b}^\ell[b^v = a^w], t), \end{aligned} \tag{26}$$

where $\mathbf{x}_{-v}^k := (x^1, \dots, x^{v-1}, x^{v+1}, \dots, x^k)$, $\mathbf{a}_{-v}^k := (a^1, \dots, a^{v-1}, \dots, a^{v+1}, \dots, a^k)$, $\mathbf{x}_{-v,-w}^k := (x^1, \dots, x^{v-1}, x^{v+1}, \dots, x^{w-1}, x^{w+1}, \dots, x^k)$, $\mathbf{a}_{-v,-w}^k := (a^1, \dots, a^{v-1}, a^{v+1}, \dots, a^{w-1}, a^{w+1}, \dots, a^k)$, $\mathbf{y}_{-(2v-1),-2v}^{2\ell} := (y^1, \dots, y^{2v-2}, y^{2v+1}, \dots, y^{2\ell})$, $\mathbf{b}_{-v}^\ell := (b^1, \dots, b^{v-1}, b^{v+1}, \dots, b^\ell)$ and $S_k^{-v} := \{1, 2, \dots, v-1, v+1, \dots, k\}$. The additional conditions,

$$u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t) = 0 \begin{cases} \text{if any } x_i, y_j = 0, \infty \\ \text{if two or more } a_i \text{ or } b_j = 0, \end{cases} \quad (27)$$

are found by using equation (20) in equation (23). Note that the PDE (equation (24)) for each $u^{(k,\ell)}$ is ‘closed’ and does not involve other density functions $u^{(k',\ell')}$. However, the boundary conditions (equations (25) and (26)) couple $u^{(k,\ell)}, k + \ell > 1$ with $u^{(k+1,\ell-1)}, u^{(k-1,\ell)}$, or $u^{(k-2,\ell+1)}$, preventing direct closure at the level of each set of indices k, ℓ . Nonetheless, although the full models for $u^{(k,\ell)}, k + \ell > 1$ are not closed, the boundary conditions will only involve $u^{(k',\ell')}$ such that $k' + 2\ell' \leq k + 2\ell$, and therefore all $u^{(k,\ell)}, k + \ell > 1$ can be solved sequentially after we have found $u^{(1,0)}$, which can be completely determined by solving the PDE

$$\frac{\partial u^{(1,0)}}{\partial t} + \frac{\partial u^{(1,0)}}{\partial a} + \frac{\partial (gu^{(1,0)})}{\partial x} = -\beta(a, t)u^{(1,0)}(x, a, t) + \frac{1}{2} \frac{\partial^2 (\sigma^2 u^{(1,0)})}{(\partial x)^2}, \quad (28)$$

with associated boundary conditions specified at $a = 0, x = 0, x = \infty$

$$\begin{aligned} u^{(1,0)}(x, 0, t) &= 2n \sum_{m=0}^{\infty} \sum_{n=1}^{\infty} \rho_{m,n}^{(0,1,0)}(\mathbf{Y}_e^2[Y^2 = x], \mathbf{B}^1[B^1 = 0], t) \\ &= 2 \int_x^{\infty} dz \int_{\Lambda} d\mathbf{a} \tilde{\beta}(z, x, a, t) u^{(1,0)}(z, a, t), \\ u^{(1,0)}(0, a, t) &= u^{(1,0)}(\infty, a, t) = 0. \end{aligned} \quad (29)$$

The model for $u^{(1,0)}$ is essentially the standard mean-field sizer-timer model [4, 13] but with an additional diffusion term $\frac{\partial^2 (\sigma^2 u^{(1,0)})}{(\partial x)^2}$ representing the random growth rate of each independent cell. To explicitly illustrate how growth rate stochasticity affects the evolution of the structured population, we numerically solve equations (28) and (29). We set $g(x, a, t) = x/2$ and a constant rate $\beta(x, a, t) = (2 \ln 2)^{-1}$ describing an exponentially distributed division time with mean $2 \ln 2$. We also assume $\tilde{\beta} = \beta(x, a, t)\delta(z/x)/x$ where δ is a Dirac measure enforcing symmetric division. The initial condition is $u^{(1,0)}(x, a, 0) = x e^{-2a-x/5}$. We use the adaptive spectral method proposed in [22] to numerically compute $u^{(1,0)}(x, a, t)$ for different growth noise $\sigma = 0, \sqrt{x}, \sqrt{2x}$. We construct the mean cell size

$$\langle x(t) \rangle = \frac{\int_{\Lambda^2} x u^{(1,0)}(x, a, t) dx da}{\int_{\Lambda^2} u^{(1,0)}(x, a, t) dx da}, \quad (30)$$

and plot its evolution in figure 1.

Given the solution to $u^{(1,0)}(x, a, t)$, we can calculate $u^{(0,1)}$ and then $u^{(2,0)}, u^{(1,1)}$, and so on. How the different $u^{(k,\ell)}$ are connected through the boundary conditions is illustrated in figure 2, demonstrating the sequence to follow to fully solve the single-density problem. The differential equation satisfied by the lowest order moment $\mathbb{E}[N(t)]$ requires $u^{(1,0)}$, as indicated by the shaded blue arrow in figure 2(a). The two sequences traced by the boundary conditions (25) and (26) are shown in figures 2(a) and (b), respectively. In figure 2(c) we show the combined sequence of boundary condition calculations to find $u^{(1,2)}$: the equations satisfied by $u^{(1,0)}$ are fully closed so $u^{(1,0)}$ can be first calculated. In the second step, we use $u^{(1,0)}$ to construct the boundary condition

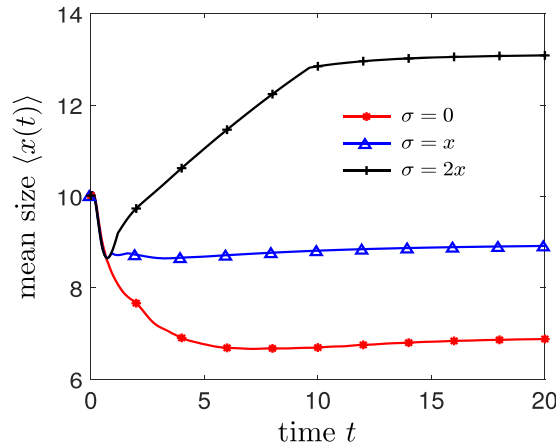


Figure 1. Mean cell sizes $\langle x(t) \rangle$ under symmetric division for different growth rate noise functions $\sigma = 0, \sqrt{x}, \sqrt{2x}$. After an initial transient, we see that a larger σ leads to larger average sizes. Even when the mean division times are kept fixed, larger noise in growth rates lead to broader distributions of cell sizes which increases the mean.

and solve for $u^{(0,1)}$. The third step is to use $u^{(0,1)}$ to construct the boundary condition and solve for $u^{(2,0)}$. The boundary condition dependences of $u^{(1,0)}, u^{(2,0)}$ are indicated by blue arrows. The fourth and fifth steps are to solve for $u^{(1,1)}$ and $u^{(3,0)}$, whose boundary condition dependences are indicated by the green arrows. Next, we calculate $u^{(2,1)}, u^{(0,2)}$, and finally $u^{(1,2)}$, whose boundary condition dependences are shown by the red arrows. These higher-dimensional results capture the stochasticity arising only from noisy growth of each cell (through the diffusive terms in equations (24) and (28)). When the coefficients satisfy certain conditions, it is also possible to further reduce the full kinetic models for $u^{(k,\ell)}$ in equations (24) and (27) to simpler models, which are derived in previous literatures like [5, 16] by integrating over the size variable x or age variable a . This is explicitly shown in appendix C.

3.2. Moments of the total population

In addition to the number-weighted densities defined in equation (23), one can also investigate moments of the total cell number $N = m + 2n$. The expected moments of the total cell population

$$\mathbb{E}[N^k(t)] = \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} (m + 2n)^k \rho_{m,n}^{(0,0,0)}, \tag{31}$$

can be used to find, for $k = 1$

$$\begin{aligned} \frac{d\mathbb{E}[N(t)]}{dt} &= \sum_{m,n=0}^{\infty} \left[m \int_{\Lambda^2} dX^1 dA^1 \beta(A^1, t) \rho_{m,n}^{(1,0,0)}(\mathbf{X}^1, \mathbf{A}^1, t) \right. \\ &\quad \left. + 2n \int_{\Lambda^2} dY^2 dB^1 \beta(B^1, t) \rho_{m,n}^{(0,1,0)}(\mathbf{Y}_e^2, \mathbf{B}^1, t) \right] \\ &= \int_{\Lambda^2} dx da \beta(a, t) u^{(1,0)}(x, a, t). \end{aligned} \tag{32}$$

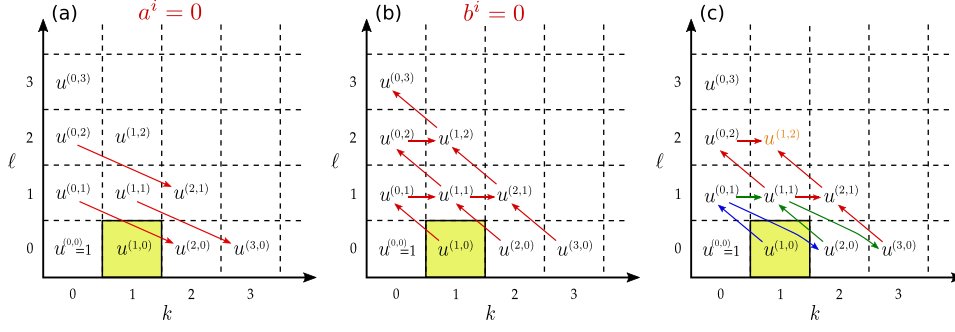


Figure 2. A map of boundary condition interdependences for single-density kinetic theory. In (a) we indicate the dependence of the boundary condition for $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{a}^k, \mathbf{y}^{2\ell}, \mathbf{b}^\ell, t)$ if any $a^i = 0$. The boundary condition for $u^{(k,\ell)}$ depends on itself and $u^{(k-2,\ell+1)}$; for example, $u^{(0,1)}$ is required for the boundary condition for $u^{(2,0)}$, so the red arrow points from $u^{(0,1)}$ to $u^{(2,0)}$. In (b) we indicate the dependence of the boundary condition for $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{a}^k, \mathbf{y}^{2\ell}, \mathbf{b}^\ell, t)$ if any $b^j = 0$. Here, the boundary condition for $u^{(k,\ell)}$ depends on $u^{(k+1,\ell-1)}$ and $u^{(k-1,\ell)}$. (c) An example of an explicit sequence of calculations to find $u^{(1,2)}$ starting from $u^{(1,0)}$.

The differential equation for $\mathbb{E}[N(t)]$ does not involve any boundary condition, but depends on $u^{(1,0)}$. Nonetheless, using the solutions to equations (28) and (29) one can explicitly solve equation (32) to find $\mathbb{E}[N(t)]$.

The demographic stochasticity arising from random birth (and possibly death) times affects the total population and is most directly summarized by higher total-population correlations. For example, the differential equation satisfied by $\mathbb{E}[N^2(t)]$ is found to be

$$\begin{aligned} \frac{d\mathbb{E}[N^2(t)]}{dt} = & \sum_{m,n=0}^{\infty} \left[(2m^2 + 4mn + m) \int dX^1 dA^1 \beta(A^1, t) \rho_{m,n}^{(1,0,0)}(\mathbf{X}^1, \mathbf{A}^1, t) \right. \\ & \left. + (8n^2 + 4mn + 2n) \int dY^2 dB^1 \beta(B^1, t) \rho_{m,n}^{(0,1,0)}(\mathbf{Y}_e^2, \mathbf{B}^1, t) \right], \end{aligned} \tag{33}$$

which cannot be solved even knowing all $u^{(k,\ell)}$. However, the expectations decouple if $\beta(t)$ is independent of age and take on the simple form

$$\frac{d\mathbb{E}[N^k(t)]}{dt} = \beta(t) \sum_{j=0}^{k-1} \binom{k}{j} \mathbb{E}[N^{j+1}(t)], \tag{34}$$

which can then be solved by starting with the solution of $\mathbb{E}[N(t)]$. For general age-dependent division rates $\beta(a, t)$, $\mathbb{E}[N^{k>1}(t)]$ cannot be directly computed/approximated without also closing equation (17). Such equations, as well as those for higher-number moments such as $\sum_{m,n} m^k \rho_{m,n}^{(h,k,\ell)}$ are *not* closed and form complex hierarchies that need additional assumptions to close.

4. Generalizations and extensions

4.1. Incorporation of death

Here, we show how our kinetic theory is modified when an age and size-dependent death, occurring with rate $\mu(a, t)$, is incorporated. By defining

$$\gamma(a, t) = \beta(a, t) + \mu(a, t), \tag{35}$$

the joint survival probabilities $S_{1,m}$ and $S_{2,n}$ in equation (6) are modified by

$$\tilde{S}_{1,m}(t|t', \mathbf{A}_t^m) = \prod_{i=1}^m e^{-\int_{t'}^t \gamma(A_i^i - t' + s, s) ds}, \quad \tilde{S}_{2,n}(t|t', \mathbf{B}_t^n) = \prod_{j=1}^n \left[e^{-\int_{t'}^t \gamma(B_j^j - t' + s, s) ds} \right]^2. \tag{36}$$

Following the previous derivations, we find

$$\begin{aligned} & \frac{\partial \rho_{m,n}}{\partial t} + \sum_{i=1}^m \frac{\partial \rho_{m,n}}{\partial A^i} + \sum_{j=1}^n \frac{\partial \rho_{m,n}}{\partial B^j} + \sum_{i=1}^m \frac{\partial (g(X^i, A^i, t) \rho_{m,n})}{\partial X^i} + \sum_{j=1}^{2n} \frac{\partial (g(Y^j, B^j, t) \rho_{m,n})}{\partial Y^j} \\ &= - \left(\sum_{i=1}^m \gamma(A^i, t) + 2 \sum_{j=1}^n \gamma(B^j, t) \right) \rho_{m,n} \\ &+ \frac{1}{2} \sum_{i=1}^m \frac{\partial^2 (\sigma^2(X^i, A^i, t) \rho_{m,n})}{(\partial X^i)^2} + \frac{1}{2} \sum_{j=1}^{2n} \frac{\partial^2 (\sigma^2(Y^j, B^j, t) \rho_{m,n})}{(\partial Y^j)^2} \\ &+ (m+1) \int_{\Lambda^2} dA^{m+1} dX^{m+1} \mu(A^{m+1}, t) \rho_{m+1,n}(\mathbf{X}^{m+1}, \mathbf{Y}^{2n}, \mathbf{A}^{m+1}, \mathbf{B}^n, t) \\ &+ \frac{2(n+1)}{m} \sum_{i=1}^m \int_{\Lambda} dx \mu(A^i, t) \rho_{m-1,n+1}(\mathbf{X}_{-i}^m, \mathbf{Y}^{2n+2} [Y^{2n+1} = x, Y^{2n+2} = X^i], \\ &\quad \mathbf{A}_{-i}^m, \mathbf{B}^{n+1} [B^{n+1} = A^i], t), \end{aligned} \tag{37}$$

where the argument of $\rho_{m,n}$ in the first two lines is $(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t)$.

The boundary conditions for $\rho_{m,n}$ are the same as equations (14) and (15) since only cell division contributes to the boundary term. Similarly, we can define the marginal distribution $\rho_{m,n}^{(h,k,\ell)}(\mathbf{X}^h, \mathbf{Y}_e^{2k+2\ell}, \mathbf{A}^h, \mathbf{B}^k, t)$ and the higher-dimensional number-weighted densities functions $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t)$ in the same way as in equations (17) and (23), respectively. The $k = 1, \ell = 0$ density obeys

$$\frac{\partial u^{(1,0)}}{\partial t} + \frac{\partial (gu^{(1,0)})}{\partial x} + \frac{\partial u^{(1,0)}}{\partial a} = -(\beta(a, t) + \mu(a, t))u^{(1,0)}(x, a, t) + \frac{1}{2} \frac{\partial^2 (\sigma^2 u^{(1,0)})}{(\partial x)^2}, \tag{38}$$

and boundary conditions specified in equation (29).

4.2. Correlated noise in growth rate

In this subsection we consider a model in which the noise in growth rates is correlated across cells. By defining $\mathbf{Z}^{m,2n} = (\mathbf{X}^m, \mathbf{Y}^{2n})$ and $\mathbf{C}^{m,2n} = (\mathbf{A}^m, B^1, B^1, \dots, B^n, B^n)$ to be the volumes

and ages of m singlets and n doublets at time t , we can describe the growth rate as

$$d\mathbf{Z}_t^{m,2n} = G^{m,2n}(\mathbf{Z}_t^{m,2n}, \mathbf{C}_t^{m,2n}, t)dt + \Sigma^{m,2n}(\mathbf{Z}_t^{m,2n}, \mathbf{C}_t^{m,2n}, t)d\mathbf{W}_t^p, \tag{39}$$

where $G^{m,2n} \in \mathbb{R}^{m+2n}$, $\Sigma^{m,2n}(\mathbf{Z}_t^{m,2n}, \mathbf{C}_t^{m,2n}, t) = (\sigma)_{ij} \in \mathbb{R}^{(m+2n) \times p}$ and \mathbf{W}_t^p is a p -dimensional i.i.d. standard Wiener process [23]. For simplicity, we assume that the i^{th} component of $G^{m,2n}$ is $g_i(\mathbf{Z}_t^i, \mathbf{C}_t^i, t) = g(\mathbf{Z}^i, \mathbf{C}^i, t)$, indicating that the deterministic part of the growth rate is identical for all cells. Following our derivation in section 2, we find that $\rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t)$ satisfies

$$\begin{aligned} & \frac{\partial \rho_{m,n}}{\partial t} + \sum_{i=1}^m \frac{\partial \rho_{m,n}}{\partial A^i} + \sum_{j=1}^n \frac{\partial \rho_{m,n}}{\partial B^j} + \sum_{i=1}^m \frac{\partial(g(t, X^i, A^i)\rho_{m,n})}{\partial X^i} + \sum_{j=1}^{2n} \frac{\partial(g(t, Y^j, B^{[(j+1)/2]})\rho_{m,n})}{\partial Y^j} \\ & = - \left(\sum_{i=1}^m \beta(A^i, t) + \sum_{j=1}^n 2\beta(B^j, t) \right) \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t) + \frac{1}{2} \sum_{s_1, s_2=1}^{m+2n} \frac{\partial^2 (D_{s_1, s_2} \rho_{m,n})}{\partial Z^{s_1} \partial Z^{s_2}}, \end{aligned} \tag{40}$$

where $D_{s_1, s_2} = \sum_{\ell=1}^p \sigma_{s_1, \ell} \sigma_{s_2, \ell}$. The boundary conditions for $\rho_{m,n}$ are the same as that described by equations (14) and (15). Similarly, we can define the marginal distribution density function $\rho_{m,n}^{(h,k,\ell)}$ in the same way as in section 3, and it can be verified that the differential equations as well as the boundary conditions satisfied by $\rho_{m,n}^{(1,0,0)}(\mathbf{X}^1[X^1 = x], \mathbf{A}^1[A^1 = a], t)$, $\rho_{m,n}^{(0,1,0)}(\mathbf{X}^1[X^1 = x], \mathbf{A}^1[A^1 = a], t)$ are the same as those satisfied by $\rho_{m,n}^{(1,0,0)}(\mathbf{X}^1[X^1 = x], \mathbf{A}^1[A^1 = a], t)$ and $\rho_{m,n}^{(0,1,0)}(\mathbf{Y}^1[Y^1 = x], \mathbf{B}^1[B^1 = a], t)$ in equations (17) and (19), although the differential equations satisfied by $\rho_{m,n}$ in equation (40) and in equation (11) are different. If we further assume that the variance in growth rates for all cells is identical: $\sum_{\ell=1}^p \sigma_{i,\ell}^2 = \sigma^2, \forall i$, then the equation and boundary conditions for the ‘1-point’ density function $u^{(1,0)}(x, a, t)$ are identical to those in equations (28) and (29) since correlations in growth rate noise are not captured by a mean-field description of only one coordinate (x, a) . The differences between correlated and uncorrelated growth noise among cells may arise in the differential equations for $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^\ell, \mathbf{a}^k, \mathbf{b}^\ell, t), k + \ell \geq 2$.

5. Summary and conclusions

In this paper, we rigorously constructed a kinetic theory for structured populations, in particular for age- and size-structured cell proliferation models. We considered stochasticity in both an individual cell’s growth rate (‘intrinsic’ stochasticity) and the cell number fluctuations from random birth and death event times (‘demographic’ stochasticity). Derivations of the kinetic theory requires separation of ‘singlet’ and ‘doublet’ populations, as was proposed in [16]. However, taking into account both size and age dependences, as well as randomness in growth rates leads to the much more complex computation which we performed here.

One of our main results is the kinetic equations and boundary conditions described by equations (13)–(15). Marginalized densities are also found to obey more complex equations that form a hierarchy (equations (17), (19), and (20)). By taking single-density averages over these equations, we find closed PDEs that govern multi-point density functions (equation (24)). However, the associated boundary conditions, equation (25), couple density functions of different dimensions. Nonetheless, density function of all dimensions can be successively solved starting from the ‘1-point’ density $u^{(1,0)}(x, a, t)$ which obeys equations (28) and (29), a 2 + 1-dimensional second order PDE and boundary condition that is analogous to the classic

McKendrick equation but that includes a diffusive size term arising from stochasticity in growth rates. The explicit equations for the first and second moments of the total population are given by equations (32) and (33), respectively.

Generalizations and extensions to our basic kinetic theory are also investigated. For example, we derived the kinetic equations when a Markovian age-dependent death process is included (equations (29), (37), and (38)). We also considered noise in growth rates that are correlated across cells and showed these effects arising in ‘cross-diffusion’ terms in the associated kinetic (and higher moment) equations.

Our unifying kinetic theory enables one to systematically analyze cell populations at both the individual and population levels. A full kinetic theory may be useful for studying other processes such as failure in multicomponent systems that age and evolve [24]. Further extensions of our kinetic equations that are feasible are to include spatial distribution [25] or correlations in growth rates across generations [13]. It is also possible to consider stochasticity for different cell division strategies [21]. Finally, efficient numerical methods for solving our kinetic equations can be developed, for instance in [22], equations similar to equations (28) and (29) which describe the dynamics of $u^{(1,0)}$ are solved accurately and efficiently.

Data availability statement

No new data were created or analysed in this study.

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Appendix A. Conservation of probability

We now define probability fluxes

$$\begin{aligned}
 J_{m,n;m+1,n-1}(t) &= (m+1) \int d\mathbf{X}^m d\mathbf{Y}^{2n-2} d\mathbf{A}^m d\mathbf{B}^{n-1} \int_{\Lambda^3} dy_1 dy_2 ds \tilde{\beta}_{m+1,n-1}(y_1+y_2, y_1, s, t) \\
 &\quad \times \rho_{m+1,n-1}(\mathbf{X}^{m+1}[\mathbf{X}^{m+1} = y_1+y_2], \mathbf{Y}^{2n-2}, \mathbf{A}^{m+1}[\mathbf{A}^{m+1} = s], \mathbf{B}^{n-1}, t), \\
 J_{m,n;m-1,n}(t) &= \frac{2n}{m} \int d\mathbf{X}^m d\mathbf{Y}^{2n-2} d\mathbf{A}^m d\mathbf{B}^{n-1} \int_{\Lambda^2} dy_1 dy_2 \sum_{i=1}^m \tilde{\beta}_{m-1,n}(y_1+y_2, y_1, A^i, t) \\
 &\quad \times \rho_{m-1,n}(\mathbf{X}_{-i}^m, \mathbf{Y}^{2n}[Y^{2n-1} = X^i, Y^{2n} = y_1+y_2], \mathbf{A}_{-i}^m, \mathbf{B}^n[B^n = A^i], t), \\
 J_{m,n;m',n'}(t) &= 0, \quad \text{if } m+2n-m'-2n' \neq 1.
 \end{aligned} \tag{41}$$

$J_{m,n;m',n'}(t)dt$ is the probability flux within time $[t, t+dt]$ from state (m', n') to state (m, n) arising from cell division. When dt is sufficiently small, the probability that more than one cell divides during $[t, t+dt]$ is $o(dt)$, which is negligible, allowing us to set $J_{m,n;m',n'}(t) = 0$ if $m+2n-m'-2n' \neq 1$. We now verify the conservation of probability flux

$$\begin{aligned}
 & J_{m-1,n+1;m,n}(t) + J_{m+1,n;m,n}(t) \\
 &= \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \left(\sum_{i=1}^m \beta_{m,n}(A^i, t) + \sum_{j=1}^n 2\beta_{m,n}(B^j, t) \right) \rho_{m,n} \\
 &= \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n (m\beta_{m,n}(A^m, t) + 2n\beta_{m,n}(B^n, t)) \rho_{m,n}, \tag{42}
 \end{aligned}$$

where $\rho_{m,n} = \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t)$. The first term is

$$\begin{aligned}
 J_{m-1,n+1;m,n}(t) &= m \int d\mathbf{X}^{m-1} d\mathbf{Y}^{2m} d\mathbf{A}^{m-1} d\mathbf{B}^n \int_{\Lambda^3} dy_1 dy_2 dA^m \\
 &\quad \tilde{\beta}_{m,n}(y_1 + y_2, y_1, A^m, t) \rho_{m,n}(\mathbf{X}^m[X^m = y_1 + y_2], \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t) \\
 &= m \int d\mathbf{X}^{m-1} d\mathbf{Y}^{2n} d\mathbf{A}^{m-1} d\mathbf{B}^n \int_{\Lambda^2} dA^m dy \int_0^y ds \\
 &\quad \tilde{\beta}_{m,n}(y, s, A^m, t) \rho_{m,n}(\mathbf{X}^m[X^m = y], \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t) \\
 &= m \int d\mathbf{X}^{m-1} d\mathbf{Y}^{2n} d\mathbf{A}^{m-1} d\mathbf{B}^n \int_{\Lambda^2} dA^m dX^m \beta_{m,n}(A^m, t) \rho_{m,n}, \tag{43}
 \end{aligned}$$

which is exactly the first term on the right-hand side of equation (42). The second term

$$\begin{aligned}
 J_{m+1,n;m,n}(t) &= \frac{2n}{m+1} \int d\mathbf{X}^{m+1} d\mathbf{Y}^{2n} d\mathbf{A}^{m+1} d\mathbf{B}^{n-1} \int_{\Lambda^2} dy_1 dy_2 \\
 &\quad \times \sum_{i=1}^{m+1} \tilde{\beta}_{m,n}(y_1 + y_2, y_1, A^i, t) \\
 &\quad \times \rho_{m,n}(\mathbf{X}_{-i}^{m+1}, \mathbf{Y}^{2n}[Y^{2n-1} = X^i, Y^{2n} = y_1 + y_2], \mathbf{A}_{-i}^{m+1}, \mathbf{B}^n[B^n = A^i], t) \\
 &= \frac{2n}{m+1} \sum_{i=1}^{m+1} \int d\mathbf{X}^{m+1} d\mathbf{Y}^{2n-2} d\mathbf{A}^{m+1} d\mathbf{B}^{n-1} \int_{\Lambda} dy \int_0^y ds \tilde{\beta}_{m,n}(y, s, A^i, t) \\
 &\quad \times \rho_{m,n}(\mathbf{X}_{-i}^{m+1}, \mathbf{Y}^{2n}[Y^{2n-1} = X^i, Y^{2n} = y], \mathbf{A}_{-i}^{m+1}, \mathbf{B}^n[B^n = A^i], t) \\
 &= 2n \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \beta_{m,n}(B^n, t) \rho_{m,n}, \tag{44}
 \end{aligned}$$

which is precisely the second term on the right-hand side of equation (42). We have thus verified that the probability flux out of state (m, n) due to cell division is the sum of probability currents into $(m - 1, n + 1)$ and into $(m + 1, n)$. Summing up over m and n , we obtain for $m + n > 0$

$$\begin{aligned}
 & \sum_{m,n=0}^{\infty} (J_{m-1,n+1;m,n}(t) + J_{m+1,n;m,n}(t)) \\
 &= \sum_{m,n=0}^{\infty} \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n (m\beta_{m,n}(A^m, t) + 2n\beta_{m,n}(B^n, t)) \rho_{m,n}. \tag{45}
 \end{aligned}$$

Finally, it is readily observed that

$$\begin{aligned}
 & \sum_{m,n=0}^{\infty} \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \frac{\partial \rho_{m,n}}{\partial t} \\
 &= \sum_{m,n=0}^{\infty} \sum_{j=1}^n \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n_{-j} \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n[B^j = 0], t) \\
 &\quad - \sum_{m,n=0}^{\infty} \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \left(\sum_{i=1}^m \beta_{m,n}(A^i, t) + 2 \sum_{j=1}^n \beta_{m,n}(B^j, t) \right) \rho_{m,n} \\
 &= \sum_{m=1}^{\infty} \sum_{n=0}^{\infty} (J_{m,n;m-1,n} - J_{m-1,n+1;m,n}) - \sum_{m,n=0}^{\infty} J_{m+1,n;m,n} + \sum_{m=0}^{\infty} \sum_{n=1}^{\infty} J_{m,n;m+1,n-1} = 0.
 \end{aligned} \tag{46}$$

Therefore, we have verified that

$$\sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \int d\mathbf{X}^m d\mathbf{Y}^{2n} d\mathbf{A}^m d\mathbf{B}^n \rho_{m,n}(\mathbf{X}^m, \mathbf{Y}^{2n}, \mathbf{A}^m, \mathbf{B}^n, t),$$

is time-independent.

Appendix B. Explicit expressions for $u^{(k,\ell)}$

Below, we display the explicit expressions of $u^{(k,\ell)}$ in terms of $\rho_{m,n}^{(h,k,\ell)}$ for $k + \ell \leq 2$:

$$u^{(1,0)}(x, a, t) = \sum_{m,n=0}^{\infty} m \rho_{m,n}^{(1,0,0)}(X^1 = x, A^1 = a, t) + \sum_{m,n=0}^{\infty} 2n \rho_{m,n}^{(0,1,0)}(\mathbf{Y}_e^2[Y^2 = x], B^1 = a, t), \tag{47}$$

$$u^{(0,1)}(y_1, y_2, b_1, t) = \sum_{m,n=0}^{\infty} 2n \rho_{m,n}^{(0,0,1)}(Y^1 = y_1, Y^2 = y_2, B^1 = b_1, t), \tag{48}$$

$$\begin{aligned}
 & u^{(1,1)}(x_1, y_1, y_2, a_1, b_1, t) \\
 &= \sum_{m,n=0}^{\infty} 4n(n-1) \rho_{m,n}^{(0,1,1)}(\mathbf{Y}_e^4[Y^2 = x_1, Y^3 = y_1, Y^4 = y_2], B^1 = a_1, B^2 = b_1, t) \\
 &\quad + \sum_{m,n=0}^{\infty} 2mn \rho_{m,n}^{(1,0,1)}(X^1 = x_1, Y^1 = y_1, Y^2 = y_2, A^1 = a_1, B^1 = b_1, t),
 \end{aligned} \tag{49}$$

$$\begin{aligned}
 & u^{(2,0)}(x_1, x_2, a_1, a_2, t) \\
 &= \sum_{m,n=0}^{\infty} m(m-1) \rho_{m,n}^{(2,0,0)}(X^1 = x_1, X^2 = x_2, A^1 = a_1, A^2 = a_2, t) \\
 &\quad + \sum_{m,n=0}^{\infty} 2mn \rho_{m,n}^{(1,1,0)}(X^1 = x_1, A^1 = a_1, \mathbf{Y}_e^2[Y^2 = x_2], B^1 = a_2, t)
 \end{aligned} \tag{50}$$

$$\begin{aligned}
 & + \sum_{m,n=0}^{\infty} 2mn\rho_{m,n}^{(1,1,0)}(X^1 = x_2, A^1 = a_2, \mathbf{Y}_e^2[Y^2 = x_1], B^1 = a_1, t) \\
 & + \sum_{m,n=0}^{\infty} 4n(n-1)\rho_{m,n}^{(0,2,0)}(\mathbf{Y}_e^4[Y^2 = x_1, Y^4 = x_2], B^1 = a_1, B^2 = a_2, t), \\
 u^{(0,2)}(y_1, y_2, y_3, y_4, b_1, b_2, t) & = \sum_{m,n=0}^{\infty} 4n(n-1)\rho_{m,n}^{(0,0,2)}(\mathbf{Y}^4 = [y_1, y_2, y_3, y_4], \mathbf{B}^2 = [b_1, b_2], t).
 \end{aligned} \tag{51}$$

Appendix C. Reduction to simpler models

Besides the general marginalizations we have considered (equations (17) and (23)), we can define other useful quantities by e.g. integrating over all volumes or all ages. Under some additional assumptions these additional integrations reduce the full kinetic theory to simpler, known models. For example, if the solution $u^{(k,\ell)}$ of equations (24) and (27) satisfies $\lim_{x_i \rightarrow \infty} \frac{\partial(\sigma^2 u^{(k,\ell)})}{\partial x_i} = \lim_{y_j \rightarrow \infty} \frac{\partial(\sigma^2 u^{(k,\ell)})}{\partial y_j} = 0$ for any i, j , integrating $u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t)$ over all sizes \mathbf{x}^k and $\mathbf{y}^{2\ell}$ yields

$$u_a^{(k,\ell)}(\mathbf{a}^k, \mathbf{b}^\ell, t) := \int_{\Lambda^{k+2\ell}} d\mathbf{x}^k d\mathbf{y}^{2\ell} u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t) \tag{52}$$

which satisfies

$$\frac{\partial u_a^{(k,\ell)}(\mathbf{a}^k, \mathbf{b}^\ell, t)}{\partial t} + \sum_{i=1}^k \frac{\partial u_a^{(k,\ell)}}{\partial a^i} + \sum_{j=1}^\ell \frac{\partial u_a^{(k,\ell)}}{\partial b^j} = - \left(\sum_{i=1}^k \beta(a^i, t) + \sum_{j=1}^\ell 2\beta(b^j, t) \right) u_a^{(k,\ell)}, \tag{53}$$

with corresponding boundary conditions

$$\begin{aligned}
 u_a^{(k,\ell)}(\mathbf{a}^k[a^v = 0], \mathbf{b}^\ell, t) & = 2 \int_{\Lambda} da \beta(a, t) u_a^{(k,\ell)}(\mathbf{a}^k[a^k = a], \mathbf{b}^\ell, t) \\
 & + 2 \sum_{w=1, \neq v}^k \beta(a^w, t) u_a^{(k-2, \ell+1)}(\mathbf{a}_{-v, -w}^k, \mathbf{b}^{\ell+1}[b^{\ell+1} = a^w], t),
 \end{aligned} \tag{54}$$

$$\begin{aligned}
 u_a^{(k,\ell)}(\mathbf{a}^k, \mathbf{b}^\ell[b^v = 0], t) & = 2 \int_{\Lambda} da \beta(a, t) u_a^{(k+1, \ell-1)}(\mathbf{a}^{k+1}[a^{k+1} = a], \mathbf{b}_{-v}^\ell, t) \\
 & + 2 \sum_{w=1}^k \beta(a^w, t) u_a^{(k-1, \ell)}(\mathbf{a}_{-w}^k, \mathbf{b}^\ell[b^v = a^w], t),
 \end{aligned} \tag{55}$$

and $u_a^{(k,\ell)}(\mathbf{a}^k, \mathbf{b}^\ell, t) = 0$ if two or more $a_i = 0$ or $b_j = 0$. This model describes age-structured cell populations similar to that discussed in [16].

On the other hand, integrating over age variables \mathbf{a}, \mathbf{b} defines size-dependent weighted densities

$$u_s^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, t) := \int_{\Lambda^{k+\ell}} d\mathbf{a}^k d\mathbf{b}^\ell u^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, \mathbf{a}^k, \mathbf{b}^\ell, t). \tag{56}$$

In this case, if $\tilde{\beta}, \beta, g, \sigma$ do not depend on $a, n_s^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}, t)$ is found to obey

$$\begin{aligned} & \frac{\partial u_s^{(k,\ell)}}{\partial t}(\mathbf{x}^k, \mathbf{y}^{2\ell}, t) + \sum_{i=1}^k \frac{\partial(g(x^i, t)u_s^{(k,\ell)})}{\partial x^i} + \sum_{j=1}^{2\ell} \frac{\partial(g(y^j, t)u_s^{(k,\ell)})}{\partial y^j} \\ &= - \sum_{i=1}^k (k + 2\ell)\beta(t)u_s^{(k,\ell)} + \frac{1}{2} \sum_{i=1}^k \frac{\partial^2(\sigma^2(x^i, t)u_s^{(k,\ell)})}{(\partial x^i)^2} + \frac{1}{2} \sum_{j=1}^{2\ell} \frac{\partial^2(\sigma^2(y^j, t)u_s^{(k,\ell)})}{(\partial y^j)^2} \\ &+ 2 \sum_{v=1}^k \int_{\Lambda} ds \tilde{\beta}(x^v + s, x^v, t)u_s^{(k,\ell)}(\tilde{\mathbf{x}}^k[x^v = x^v + s], \mathbf{y}^{2\ell}, t) \\ &+ 2 \sum_{v=1}^k \sum_{w=1, \neq v}^k \int_{\Lambda} ds \tilde{\beta}(x^w + s, x^w, t)u_s^{(k-2, \ell+1)}(\mathbf{x}_{-w, -v}^{k-2, \ell+1}, \mathbf{y}^{2\ell+1}[y^{2\ell+1} = x^w, y^{2\ell+2} = x^v + s], t) \\ &+ 2 \sum_{v=1}^{\ell} \tilde{\beta}(y^{2v-1} + y^{2v}, y^{2v}, t)u_s^{(k+1, \ell-1)}(\mathbf{x}^{k+1}[x^{k+1} = y^{2v-1} + y^{2v}], \mathbf{y}_{-(2v-1), -2v}^{2\ell}, t) \\ &+ 2 \sum_{v=1}^{\ell} \sum_{w=1}^k \tilde{\beta}(y^{2v-1} + y^{2w}, y^{2w}, t)u_s^{(k-1, \ell)}(\mathbf{x}_{-w}^{k-1, \ell}, \tilde{\mathbf{y}}^{2\ell}[\tilde{y}^{2v-1} = y^{2v-1} + y^{2w}, \tilde{y}^{2v} = x^w], t), \quad (57) \end{aligned}$$

where $\tilde{\mathbf{x}}^k$ shares the same components with \mathbf{x}^k except for the v th element and $\tilde{\mathbf{y}}^{2\ell}$ shares $2\ell - 2$ common components with $\mathbf{y}^{2\ell}$ except for the $(2v - 1)$ th and $(2v)$ th elements, as indicated by the replacements $[\dots]$ following each variable. By integrating over age, the boundary conditions in equations (25) and (26) for newborn cells have been assimilated into equation (57). The remaining conditions are

$$\begin{aligned} & u_s^{(k,\ell)}(\mathbf{x}^k[x^i = 0], \mathbf{y}^{2\ell}, t) = u_s^{(k,\ell)}(\mathbf{x}^k[x^i = \infty], \mathbf{y}^{2\ell}, t) = 0, \\ & u_s^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}[y^j = 0], t) = u_s^{(k,\ell)}(\mathbf{x}^k, \mathbf{y}^{2\ell}[y^j = \infty], t) = 0. \end{aligned} \quad (58)$$

Notice that if $k = 1, \ell = 0$, the last three terms on the rhs of equation (57) vanish and the equation reduces to the size-structured PDE model [5] except for the additional diffusion term describing growth noise.

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References

[1] von Foerster H 1959 Some remarks on changing populations *The Kinetics of Cellular Proliferation* ed F Stohlman (New York: Grune and Stratton) pp 382–407
 [2] Taheri-Araghi S, Bradde S, Sauls J T, Hill N S, Levin P A, Paulsson J, Vergassola M and Jun S 2015 *Curr. Biol.* **25** 385–91
 [3] Burov S and Kessler D 2017 arXiv:1701.01725
 [4] Robert L, Hoffmann M, Krell N, Aymerich S, Robert J and Doumic M 2014 *BMC Biol.* **12** 17
 [5] Perthame B 2008 Introduction to structured equations in biology *CNA Summer School Lecture Notes*

- [6] Metz J A J and Diekmann O 1986 *The Dynamics of Physiologically Structured Populations* (New York: Springer)
- [7] Sompayrac L and Maaløe O 1973 *Nat. New Biol.* **241** 133–5
- [8] Huisman O and D’Ari R 1981 *Nature* **290** 797–9
- [9] Chandler-Brown D, Schmoller K M, Winetraub Y and Skotheim J M 2017 *Curr. Biol.* **27** 2774–83
- [10] Delarue M, Weissman D and Hallatschek O 2017 *PLoS One* **12** e0182633
- [11] Wessels J G H 1994 *Annu. Rev. Phytopathol.* **32** 413–37
- [12] Modi S, Vargas-Garcia C A, Ghusinga K R and Singh A 2017 *Biophys. J.* **112** 2408–18
- [13] Xia M, Greenman C D and Chou T 2020 *SIAM J. Appl. Math.* **80** 1307–35
- [14] Bernard E, Doumic M and Gabriel P 2016 *Kinet. Relat. Models* **12** 551–71
- [15] Greenman C D and Chou T 2016 *Phys. Rev. E* **93** 012112
- [16] Chou T and Greenman C D 2016 *J. Stat. Phys.* **164** 49–76
- [17] Greenman C D 2017 *J. Stat. Mech.* **033101**
- [18] Vargas-Garcia C A, Soltani M and Singh A 2016 *IEEE Life Sci. Lett.* **2** 47–50
- [19] Ho P-Y, Lin J and Amir A 2018 *Annu. Rev. Biophys.* **47** 251–71
- [20] Kessler D A and Burov S 2017 *Phys. Rev. E* **96** 042139
- [21] Nieto C, Vargas-Garcia C and Pedraza J M 2020 (<https://doi.org/10.1101/2020.09.29.319251>)
- [22] Xia M, Shao S and Chou T 2020 arXiv:2009.13170
- [23] Durrett R 2019 *Probability: Theory and Examples* 5th edn (Cambridge: Cambridge University Press)
- [24] Popescu D M and Sun S X 2018 *J. R. Soc. Interface.* **15** 20180086
- [25] Auger P, Magal P and Ruan S 2008 *Structured Population Models in Biology and Epidemiology* vol 1936 (New York: Springer)