A kinetic theory for age-structured stochastic birth-death processes

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Classical age-structured mass-action models such as the McKendrick-von Foerster equation have been extensively studied but they are structurally unable to describe stochastic fluctuations or population-size-dependent birth and death rates. Stochastic theories that treat semi-Markov age-dependent processes using *e.g.*, the Bellman-Harris equation, do not resolve a population's age-structure and are unable to quantify population-size dependencies. Conversely, current theories that include size-dependent population dynamics (*e.g.*, mathematical models that include carrying capacity such as the Logistic equation) cannot be easily extended to take into account age-dependent birth and death rates. In this paper, we present a systematic derivation of a new fully stochastic kinetic theory for interacting age-structured populations. By defining multiparticle probability density functions, we derive a hierarchy of kinetic equations for the stochastic evolution of an ageing population undergoing birth and death. We show that the fully stochastic age-dependent birth-death process precludes factorization of the corresponding probability densities, which then must be solved by using a BBGKY-like hierarchy. However, explicit solutions are derived in two simple limits and steady-state conditions, and compared with corresponding mean-field results. Our results generalize both deterministic models and existing master equation approaches by providing an intuitive and efficient way to simultaneously model age- and population-dependent stochastic dynamics applicable to the study of demography, stem cell dynamics, and disease evolution.

INTRODUCTION

Age is an important controlling feature in populations of living organisms. Processes such as birth, death, and mutation are typically highly dependent upon an organism's chronological age. Age-dependent population dynamics, where birth and death probabilities depend on an organism's age, arise across diverse research areas such as demography [1], biofilm formation [2], and stem cell proliferation and differentiation [3, 4]. In this latter application, not only does a the cell cycle give rise to age-dependent processes [5, 6], but the often small number of cells requires a stochastic interpretation of the population. Despite the importance of age structure (such as that arising in the study of cell cycles [5–7]), there exists no theoretical method to fully quantify the stochastic dynamics of aging and population-dependent processes.

Past work on age-structured populations has focussed on *deterministic* models through the analysis of the so-called McKendrick-von Foerster equation, first studied by McKendrick [8, 9] and subsequently von Foerster [10], Gurtin and MacCamy [11, 12], and others [13, 14]. In these classic treatments, $\rho(a,t)\mathrm{d}a$ is used to define, at time t, the number of noninteracting agents with age between a and $a + \mathrm{d}a$. The total number of particles in the system at time t is thus $n(t) = \int_0^\infty \rho(a,t)\mathrm{d}a$. If $\mu(a;n(t))$ is the death rate for individuals of age a, the McKendrick-von Foerster equations are [11, 12]

$$\frac{\partial \rho(a,t)}{\partial t} + \frac{\partial \rho(a,t)}{\partial a} = -\mu(a;n(t))\rho(a,t), \tag{1}$$

with $\rho(a, t=0) = g(a)$ and

$$\rho(a = 0, t) = \int_0^\infty \beta(a;n(t))\rho(a,t)\mathrm{d}a \tag{2}$$

for initial and boundary conditions, respectively. The boundary condition (Eq. 2) reflects the fact that birth gives rise to age-zero individuals. Note in this formulation that the birth and death rates β and μ can depend upon both age a and sample size $n(t)$, a flexibility that facilitates a wide range of applications. For example, interacting populations that are limited can be modeled by birth and death rates $\beta(a;n(t))$ and $\mu(a;n(t))$ that are functions of $n(t)$ and specifically chosen to limit population growth. The McKendrick-von Foerster equations (Eqs. 1 and 2) needs to be self-consistently solved along with the definition of $n(t)$ [11, 12]. This was dealt with more recently [15] by perturbative expansion (see also [13, 16]). Important applications can also be found in evolutionary contexts [17, 18].

The population dependence of $\beta(a; n(t))$ and $\mu(a; n(t))$ in Eqs. 1 and 2 are assumed without explicit derivation and it is difficult generalize these self-consistent approaches to the stochastic domain. Therefore, a formal derivation will allow a deeper understanding of how population dependence and correlations arise in a fully stochastic age-structured framework.

Two approaches that have been used for describing stochastic populations include master equations [19, 20] and evolution equations for age-dependent branching process such as the Bellman-Harris process [21–25]. master-equation approaches can be used to describe population-dependent birth or death rates [11, 12, 26, 27] but implicitly assume exponentially distributed waiting times between events [20]. On the other hand, age-dependent models such as the Bellman-Harris branching process [21] allow for arbitrary distributions of times between birth/death events but they cannot resolve age-structure of the entire population nor describe population-dependent dynamics that arise from *e.g.,* regulation or environmental carrying capacities.

A number of approaches attempt to incorporate ideas of stochasticity and noise into age-dependent population models, [3, 22, 28–33]. For example, stochasticity can be implemented by assuming a random rate of advancing to the next age window (by *e.g.*, stochastic harvesting [30, 31] or a fluctuating environment [34, 35]). However, such models do not account for the intrinsic stochasticity of the underlying birth-death process that acts differently on individuals at each different age. One alternative approach might be to extend the mean-field, age-structured McKendrick-von Foerster theory into the stochastic domain by considering the evolution of $P(n(a); t)$, the probability density that there are n individuals within age window $[a, a + \mathrm{d}a]$ at time t [3, 36]. This approach is meaningful only if a large number of individuals exist in each age window, in which case a large system size van Kampen expansion within each age window can be applied [19]. However, such an assumption is inconsistent with the desired small-number stochastic description of the system.

A mathematical theory that addresses the age-dependent problem of constrained stochastic populations would provide an important tool for quantitatively investigating problems in demography, bacterial growth, population biology, and stem cell differentiation and proliferation. In this paper, we develop a new kinetic equation that intuitively integrates population stochasticity, age-dependent effects (such as cell cycle), and population regulation into a unified theory. Our equations form a hierarchy analogous to that derived for the BBGKY (Bogoliubov-Born-Green-Kirkwood-Yvon) hierarchy in kinetic theory [37, 38], allowing for a fully stochastic treatment of age-dependent process undergoing population-dependent birth and death.

KINETIC EQUATIONS FOR AGING POPULATIONS

To develop a fully stochastic theory for age-structured populations that can naturally describe both age- and population size-dependent birth and death rates, we invoke multiple-particle distribution functions such as those used in kinetic theories of gases [38]. Our analysis builds on the Boltzmann kinetic theory of D. Zanette and yields a BBGKY-like hierarchy of equations. Here, the positions of ballistic particles will represent the ages of individuals.

Changes in the total population require that we consider a family of multiparticle distribution functions, each with different dimensionality corresponding to the number of individuals. In this picture, birth and death are represented by transitions between the different distribution functions residing on different fixed particle-number "manifolds." Processes that generate newborns (particles of age zero) manifest themselves mathematically through boundary conditions on higher dimensional distribution functions.

The microscopic model we consider is represented in Fig. 1A. We let n represent the population size at some time t. Then each individual gives birth to a single progeny at rate $\beta_n(x)$, where x represents the age of the individual. This is a budding mode of birth where the parent does not instantaneously die or renew itself as a result of the birthing process. However, we do assume an age-dependent death rate $\mu_n(x)$ for each individual. One can also think of these age-dependent rates in terms of a waiting time distribution. For example, the probability that any one particle dies within time $(x, x + \mathrm{d}x]$ after its birth is $\mu_n(x) \exp\left[-\int_0^x \mu_n(x')\mathrm{d}x'\right] \mathrm{d}x$. However, in our formalism, we will only need to deal with the rates.

To begin, we define

$$f_n(x_1, x_2, x_3, \ldots, x_n; t)\mathrm{d}x_1\mathrm{d}x_2 \ldots \mathrm{d}x_n \tag{3}$$

as the probability that at time t, one observes n distinguishable (by virtue of their order of birth) individuals, such that the youngest one has age within $(x_1, x_1 + \mathrm{d}x_1)$, the second youngest has age within $(x_2, x_2 + \mathrm{d}x_2)$, and so on. If the individuals are identical (except for their ages) and one does not distinguish which are in each age window, one

can define $\rho_n(x_1, x_2, x_3, \ldots, x_n; t) dx_1 dx_2 \ldots dx_n$ as the probability that after randomly selecting individuals, the first one chosen has age in $(x_1, x_1 + dx_1)$, the second has age in $(x_2, x_2 + dx_2)$, and so on. For example, if there are three individuals with ordered ages $x_1 < x_2 < x_3$, the probability of making any specific random selection, such as choosing the individual with age x_2 first, the one with age x_1 second, and the one with age x_3 third, is $\frac{1}{3!}$. More generally, when the ages $\mathbf{x}_{1,n} \equiv \mathbf{x}_n = (x_1, x_2, \ldots, x_n)$ are unordered, the associated probability density is

$$\rho_n(\mathbf{x}_n; t) = \frac{1}{n!} f_n(\mathcal{T}(\{x_i\}); t), \tag{4}$$

in which $\mathcal{T}$ is the time-ordering permutation operator such that, for example, $\mathcal{T}(x_2, x_1, x_3) = (x_1, x_2, x_3)$. Note that in this formulation, $\rho_n(\mathbf{x}_n; t)$ is invariant under interchange of the elements of $\mathbf{x}_n$.

To derive kinetic equations for $\rho_n(\mathbf{x}_n; t)$, it is easiest to first define an ordered cumulative probability distribution

$$Q_n(\mathbf{a}_n; t) = \int_0^{a_1} dx_1 \int_{x_1}^{a_2} dx_2 \cdots \int_{x_{n-1}}^{a_n} dx_n f_n(\mathbf{x}_n; t), \tag{5}$$

where $\mathbf{a}_n = a_{1,n} = (a_1, \ldots, a_n)$. $Q_n(\mathbf{a}_n; t)$ describes the probability that there are n existing individuals at time t and that the youngest individual has age x_1 less than or equal to a_1, the second youngest individual has age $x_2 \in [x_1, a_2]$, and so on. The oldest individual has age $x_n \in [x_{n-1}, a_n]$.

We now compute the change in $Q_n(\mathbf{a}_n; t)$ over a small time increment ε: $Q_n(\mathbf{a}_n + \varepsilon; t + \varepsilon) = Q_n(\mathbf{a}_n; t) + \int_t^{t+\varepsilon} J(\mathbf{a}_n; t') dt'$, where $J(\mathbf{a}_n; t') = J^+(\mathbf{a}_n; t') - J^-(\mathbf{a}_n; t')$ is the net probability flux at time t'. The probability flux which increases the cumulative probability is denoted J^+ while that which decrease the cumulative probability is labelled J^-. Each of the $J^{\pm}$ include contributions from different processes that remove or add individuals. A schematic of our birth-death process, starting from a single parent, is depicted in Fig. 1A.

In the $\varepsilon \to 0$ limit, we find the conservation equation

$$\frac{\partial Q_n(\mathbf{a}_n; t)}{\partial t} + \sum_{i=1}^n \frac{\partial Q_n(\mathbf{a}_n; t)}{\partial a_i} = J^+(\mathbf{a}_n; t) - J^-(\mathbf{a}_n; t). \tag{6}$$

Eq. 6 is a "weak form" integral equation for the probability density which allows us to systematically derive an evolution equation and the associated boundary conditions for $f_n(\mathbf{x}_n; t)$. The probability fluxes can be decomposed into components representing age-dependent birth and death

$$J^{\pm}(\mathbf{a}_n; t) = J_{\beta}^{\pm}(\mathbf{a}_n; t) + J_{\mu}^{\pm}(\mathbf{a}_n; t), \tag{7}$$

where the birth and death that reduce probability can be expressed as

$$J_{\beta}^-(\mathbf{a}_n; t) = \int_0^{a_1} dx_1 \int_{x_1}^{a_2} dx_2 \cdots \int_{x_{n-1}}^{a_n} dx_n f_n(\mathbf{x}_n; t) \sum_{i=1}^n \beta_n(x_i), \tag{8}$$

$$J_{\mu}^-(\mathbf{a}_n; t) = \int_0^{a_1} dx_1 \int_{x_1}^{a_2} dx_2 \cdots \int_{x_{n-1}}^{a_n} dx_n f_n(\mathbf{x}_n; t) \sum_{i=1}^n \mu_n(x_i). \tag{9}$$

Similarly, the probability fluxes that increase probability are

$$J_{\beta}^+(\mathbf{a}_n; t) = \int_0^{a_2} dx_1 \cdots \int_{x_{j-1}}^{a_{j+1}} dx_j \cdots \int_{x_{n-2}}^{a_n} dx_{n-1} f_{n-1}(\mathbf{x}_{n-1}; t) \sum_{i=1}^{n-1} \beta_{n-1}(x_i), \tag{10}$$

$$J_{\mu}^+(\mathbf{a}_n; t) = \sum_{i=0}^n \int_0^{a_1} dx_1 \cdots \int_{x_{i-1}}^{a_i} dx_i \int_{x_i}^{a_{i+1}} dy \int_y^{a_{i+1}} dx_{i+1} \cdots \int_{x_{n-1}}^{a_n} dx_n \, \mu_{n+1}(y) f_{n+1}(\mathbf{x}_i, y, \mathbf{x}_{i+1,n}; t), \tag{11}$$
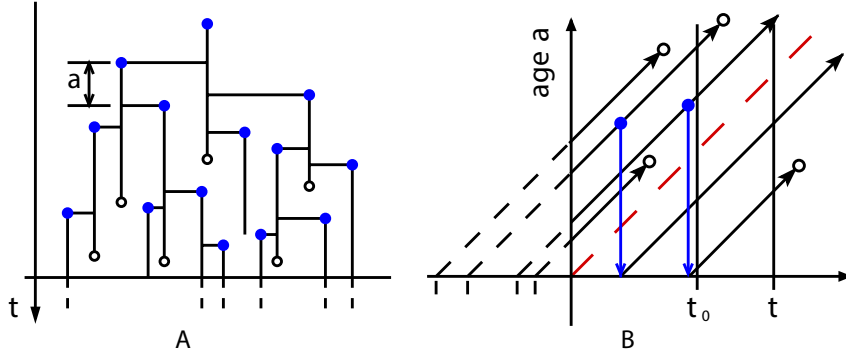
FIG. 1: (A) A simple age-dependent birth-death process. Each parent gives birth with an age-dependent rate $\beta_n(a)$, which may also depend on the total population size n. Individuals can also die (open circles) at an age- and population-dependent rate $\mu_n(a)$. (B) Age trajectories in the upper $(a > t)$ octant are connected to those in the lower one $(a < t)$ through the birth processes. Individuals that exist at time $t = 0$ can be traced back and defined by their time of birth b_i. Here, the labeling ordered according to increasing age. The pictured trajectories define characteristics $a_i(t)$ that can be used to solve Eq. 12.

in which $\mathbf{x}_{i,j} \equiv (x_i, x_{i+1}, \ldots, x_j)$, $x_0 \equiv 0$, $a_{n+1} \equiv \infty$, and the age- and population-dependent birth and death rates for individual i are denoted $\beta_n(x_i)$ and $\mu_n(x_i)$, respectively. The probability flux into $Q_n(\mathbf{a}_n; t)$ arises when birth from one of the $n-1$ individuals with ages $\mathbf{a}_{2,n} \equiv (a_2, a_3, \ldots, a_n)$ generates an individual of age zero. Hence, a key feature of $J_\beta^+(\mathbf{a}_n; t)$ is that it does not depend on a_1.

We can now describe the fully stochastic aging process in terms of the ordered distribution function $f_n(\mathbf{x}_n; t)$ by using Eqs. 7-11 in Eq. 6 and applying the operator $\frac{\partial}{\partial a_n} \cdots \frac{\partial}{\partial a_2} \frac{\partial}{\partial a_1}$ to find

$$\frac{\partial f_n(\mathbf{a}_n; t)}{\partial t} + \sum_{j=1}^n \frac{\partial f_n(\mathbf{a}_n; t)}{\partial a_j} = -f_n(\mathbf{a}_n; t) \sum_{i=1}^n \gamma_n(a_i) + \sum_{i=0}^n \int_{a_i}^{a_{i+1}} \mu_{n+1}(y) f_{n+1}(\mathbf{a}_i, y, \mathbf{a}_{i+1,n}; t) \mathrm{d}y, \tag{12}$$

where $a_0 \equiv 0$, $a_{n+1} \equiv \infty$, and the total age-dependent transition rate is

$$\gamma_n(a_i) = \beta_n(a_i) + \mu_n(a_i). \tag{13}$$

Note that the a_1-independent source term J_β^+ that had contributed to the ordered cumulative (Eq. 6) does not contribute to the bulk equation for $f_n(\mathbf{a}_n; t)$. Rather, it arises in the boundary condition for f_n, which can be found by setting $a_1 = 0$ in Eq. 6. Since $Q_n(0, a_2, \ldots, a_n; t) = 0$ and $J_\beta^+(\mathbf{a}_n; t)$ are independent of a_1, the remaining terms are

$$\int_0^{a_2} \mathrm{d}x_2 \cdots \int_{x_{n-1}}^{a_n} \mathrm{d}x_n f_n(x_1 = 0, \mathbf{x}_{2,n}; t) = J_\beta^+(\mathbf{a}_n; t). \tag{14}$$

Further taking the derivatives $\frac{\partial}{\partial a_n} \cdots \frac{\partial}{\partial a_2}$ of Eq. 14, we find the boundary condition

$$f_n(a_1 = 0, \mathbf{a}_{2,n}; t) = f_{n-1}(\mathbf{a}_{2,n}; t) \sum_{i=2}^n \beta_{n-1}(a_i). \tag{15}$$

We now consider *indistinguishable* individuals as described by the density defined in Eq. 4. Equation 12 can then be expressed in terms of $\rho_n(\mathbf{a}_n; t)$: the probability density that if we *randomly* label individuals, the first one has age between a_1 and $a_1 + \mathrm{d}a_1$, the second has age between a_2 and $a_2 + \mathrm{d}a_2$, and so on. The kinetic equation for ρ_n can then be expressed in the form

$$\frac{\partial \rho_n(\mathbf{a}_n; t)}{\partial t} + \sum_{j=1}^n \frac{\partial \rho_n(\mathbf{a}_n; t)}{\partial a_j} = -\rho_n(\mathbf{a}_n; t) \sum_{i=1}^n \gamma_n(a_i) + (n+1) \int_0^\infty \mu_{n+1}(y) \rho_{n+1}(\mathbf{a}_n, y; t) \mathrm{d}y, \tag{16}$$

and the boundary condition becomes

$$n\rho_n(a_1, \ldots, a_\ell = 0, \ldots, a_n; t) = \rho_{n-1}(a_1, \ldots, \hat{a}_\ell, \ldots, a_n; t) \sum_{i(\neq \ell)=1}^n \beta_{n-1}(a_i), \tag{17}$$

where the sum precludes the $i = \ell$ term and $\hat{a}_\ell$ indicates that the variable a_ℓ is omitted from the sequence of arguments [38]. Equation 16 and the boundary conditions of Eq. 17, along with an initial condition $\rho_n(\mathbf{a}_n; t = 0)$, fully define the stochastic age-structured birth-death process and is one of our main results. Eq. 16 is analogous to a generalized Boltzmann equation for n particles [38, 39]. The evolution operator corresponds to that of free ballistic motion in one dimension corresponding to age. However, instead of particle collisions typically studied in traditional applications of the Boltzmann equation, our problem couples density functions for n particles to those of $n + 1$ and $n - 1$ (through the boundary condition).

SOLUTIONS

Equation 16 defines a set of coupled linear integro-differential equations. We would like to find solutions for $\rho_n(\mathbf{a}_n; t)$ expressed in terms of an initial condition $g_n(\mathbf{a}_n - t; t = 0)$. However, we will see below that the presence of births during the time interval $(0, t]$ prevents a simple solution to Eq. 16 due to interference from the boundary condition in Eq. 17. Instead, we will obtain a solution for $\rho_n(\mathbf{a}_n; t)$ at time t in terms of the distribution $\rho_n(\mathbf{a}_n - (t - t_0); t_0)$ at an earlier time t_0 selected such that no births occur during the time interval $(t_0, t]$. That is, if $b_i = t - a_i$ represents the time of birth of the ith individual (see Fig. 1B), we have the condition $t_0 \geq b_i \forall i$. The dynamics described by Eq. 16 are then unaffected by the boundary condition (Eq. 17) and can be solved using the characteristics $a_i = t - b_i$ indexed by individual times of birth b_i. Note that any individual initially present (at time $t = 0$) has a projected negative time of birth. We can then solve $\rho_n(t - \mathbf{b}_n; t)$ explicitly along each characteristic and then re-express them in terms of $\mathbf{a}_n$, to obtain

$$\rho_n(\mathbf{a}_n; t) = U_n(\mathbf{a}_n; t_0; t)\rho_n(\mathbf{a}_n - (t - t_0); t_0) + (n + 1) \int_{t_0}^t U_n(\mathbf{a}_n; t'; t) \left[\int_0^\infty \mu_{n+1}(y)\rho_{n+1} \mathrm{d}y \right] \mathrm{d}t', \tag{18}$$

where $\rho_{n+1} \equiv \rho_{n+1}(\mathbf{a}_n - (t - t'), y; t')$ above, and

$$U_n(\mathbf{a}_m; t'; t) = \exp\left[-\sum_{i=1}^m \int_{t'}^t \gamma_n(a_i - (t - s)) \mathrm{d}s \right] \equiv U_n^{-1}(\mathbf{a}_m; t_0; t') U_n(\mathbf{a}_m; t_0; t) \tag{19}$$

is the propagator for any set of $m \leq n$ individuals from time t' to t. We now derive explicit solutions for processes with (1) pure death, (2) pure birth, and (3) conditions where the age-structure is in steady-state.

First, in the case of pure death process where no births occur ($\beta_n = 0$), we can set $t_0 = 0$. A complete solution can be found through successive iteration of Eq. 18. We further simplify matters by assuming an initial condition that factorizes into an initial total number distribution $\rho(n)$ and common initial age probability densities $g(a)$: $\rho_n(\mathbf{a}_n - t; 0) = \rho(n) \prod_{i=1}^n g(a_i - t)$. If we further assume a death rate $\mu_n(a) = \mu(a)$ that is independent of population size, Eq. 18 can be solved, after some algebra, to yield

$$\rho_n(\mathbf{a}_n; t) = U(\mathbf{a}_n; 0; t) \prod_{i=1}^n g(a_i - t) \sum_{k=0}^\infty \binom{n + k}{k} \rho(n + k) \left[\int_0^t g(y - s) \int_s^\infty U(y; 0; s)\mu(y) \mathrm{d}y \mathrm{d}s \right]^k. \tag{20}$$

Next, we consider a pure birth process where $\mu_n = 0$ and the second integral term in Eq. 18 disappears. In this case, we must use the boundary condition (Eq. 17) to successively bootstrap the solution by applying the propagator U between birth times. Assume a starting time $t = 0$ with an initial condition consisting of m individuals with corresponding ages $a > t$. The symmetry of $\rho_n(\mathbf{a}_n; t)$ and $U_n(\mathbf{a}_n; t'; t)$ implies that, without loss of generality, ages can be arranged in decreasing order: $a_1 > a_2 > \ldots > a_m > t > a_{m+1} > \ldots > a_n$, where the youngest was born most recently at time $t - a_n > 0$. If we select t_0 to be the moment of birth at time $b_n = t - a_n$ of the most recently born (n^{th}) individual, the density over all individuals is propagated forward according to

$$\rho_n(\mathbf{a}_n; t) = U_n(\mathbf{a}_n; b_n; t)\rho_n(\{\mathbf{a}_{n-1} - a_n, 0\}; t - a_n), \tag{21}$$

where $\rho_n(\{\mathbf{a}_{n-1} - a_n, 0\}; t - a_n)$ is the initial condition immediately after the birth of the nth individual and can be related to ρ_{n-1} through the boundary condition in Eq. 17. The density function thus obeys

$$\rho_n(\mathbf{a}_n; t) = \frac{1}{n} U_n(\mathbf{a}_n; b_n; t) \rho_{n-1}(\mathbf{a}_{n-1} - a_n; t - a_n) \sum_{i=1}^{n-1} \beta_{n-1}(a_i - a_n). \tag{22}$$

Eq. 22 can then be iterated back to $t = 0$ to find the solution for randomly selected individuals. For the case in which $\gamma_n = \gamma$ is independent of the population size, the propagator can be separated into a product across individuals. If $\beta_n = \beta$ is also independent of n, the solution takes the simple form

$$\rho_n(\mathbf{a}_n; t) = g_m(\mathbf{a}_m - t) U(\mathbf{a}_m; 0; t) \frac{m!}{n!} \prod_{k=m+1}^{n} U(a_k; b_k; t) \sum_{\ell=1}^{k-1} \beta(a_\ell - a_k), \tag{23}$$

where $b_k = t - a_k$ and g_m is the initial distribution of ages for the m individuals born before $t = 0$.

Finally, we also find a solution by assuming separation of time and age and seek solution of the form $\rho_n(\mathbf{a}; t) = \rho_n(t) \prod_{i=1}^{n} A(a_i)$, where $\int A(a)\mathrm{d}a = 1$ and $\rho_n(t)$ represents the probability of a population size n at time t. If this form is substituted into Eqs 16 and 17 and integrated over all $\mathbf{a}$ variables, one arrives at the following expression:

$$\frac{\partial \rho_n(t)}{\partial t} = (n-1)\rho_{n-1}(t) \int_0^\infty A(a)\beta_{n-1}(a)\mathrm{d}a - n\rho_n(t) \int_0^\infty A(a)(\beta_n(a) + \mu_n(a))\mathrm{d}a + (n+1)\rho_{n+1}(t) \int_0^\infty A(a)\mu_{n+1}(a)\mathrm{d}a. \tag{24}$$

Thus, if we define birth and death rates $b_n = \int_0^\infty A(a)\mu_n(a)\mathrm{d}a$ and $d_n = \int_0^\infty A(a)\mu_n(a)\mathrm{d}a$, we recover the standard age-independent Markovian master equation [26], and the population size evolves independently of the age structure $A(a)$. To find $A(a)$, we integrate Eqs. 16 and 17 over all but one age variable a. If we define the total expected population $X(t) = \sum_n n\rho_n(t)$, we find after straightforward algebra

$$\frac{\partial X}{\partial t} A(a) + X(t) \frac{\partial A}{\partial a} = -A(a) \sum_{n=0}^{\infty} n\mu_n(a)\rho_n(t),$$

$$X(t)A(0) = \sum_{n=1}^{\infty} (n-1)\rho_{n-1}(t) \int_0^\infty A(a)\beta_{n-1}(a)\mathrm{d}a. \tag{25}$$

In the case where birth and death rates $\beta_n(a) = \beta(a)$ and $\mu_n(a) = \mu(a)$ are independent of the population size n, Eqs. 25 represent precisely the separable version of the McKendrick-von Foerster equation that arises as a quasi-static solution [13, 14]. In this case, an explicit result for $A(a)$ can be obtained in the form $A(a) = A(0)e^{-ca}e^{-M(a)}$ where $M(a) = \int_0^a \mu(x)\mathrm{d}x$, $A(0) = \left[\int_0^\infty e^{-M(a)-ca}\mathrm{d}a\right]^{-1}$, and c satisfies $\int_0^\infty \beta(a)e^{-M(a)-ca}\mathrm{d}a = 1$.

Thus, we have demonstrated the existence of a solution of the form $\rho_n(\mathbf{a}; t) = \rho_n(t) \prod_{i=1}^{n} A(a_i)$, where the age-structure $A(a)$ is equivalent to the steady state age-structure of the McKendrick-von Foerster equation, and the population size evolves independently of the age-structure, with dynamics equivalent to a standard Markov process with effective *age-independent* birth and death rates.

FLUCTUATIONS

The above solutions for $\rho_n(\mathbf{a}_n; t)$ allow us to explicitly compare differences between the fully stochastic theory and the deterministic McKendrick-von Foerster model. As an example, consider the expected number of individuals at time t that have age between 0 and a,

$$P(a, t) = \int_0^a \rho(y, t)\mathrm{d}y, \tag{26}$$

where $\rho(y, t)$ is found from Eqs. 1 and 2. We wish to compare this quantity with the *probability* $P_m(a, t)$ that there are m individuals at time t with age between 0 and a. The probability $P_m(n, a, t)$ that there are n total individuals of which exactly m have age between 0 and a can be constructed from our fully stochastic theory via

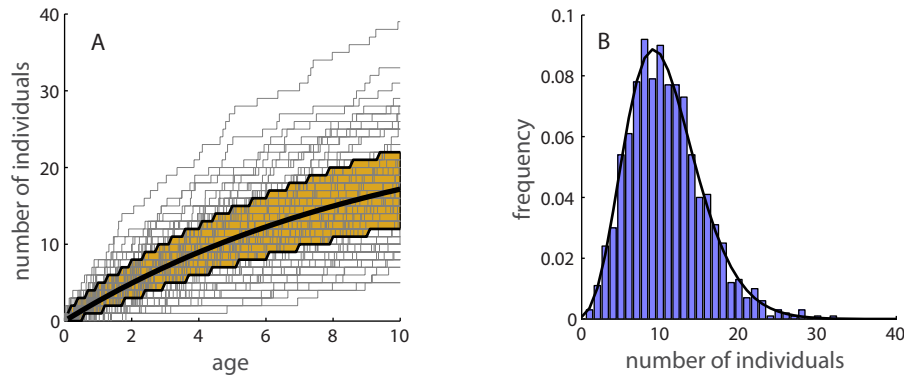FIG. 2: Comparison of $P(a,t)$ (Eq. 26) derived from the McKendrick-von Foerster equation with $P_m(a,t)$ of a fully stochastic pure birth process with constant $\beta = 0.1$. We start with $N = 10$ individuals and analyze our quantities at time $t = 10$ for ages $a < t$. (A) Each of the 100 grey lines count the number of individuals younger than age a in one simulation. The solid black curve indicates the deterministic (McKendrick-von Foerster) solution $P(a,t) = \int_0^a \rho(y,t)\mathrm{d}y$, which can also be obtained through $P(a,t) = \sum_{m=1}^{\infty} mP_m(a,t)$. The shaded region represents the inter-quartile range of $P_m(a,t)$, (the central count of individuals occupied by 50% of simulations). (B) Distribution constructed from 1000 simulations (bars) and theoretical distribution $P_m(a = 5, t = 10)$ (black curve).

$$P_m(n,a,t) = \binom{n}{m} \prod_{j=1}^{m} \int_0^a \mathrm{d}a_j \prod_{\ell=m+1}^{n} \int_a^{\infty} \mathrm{d}a_\ell \, \rho_n(\mathbf{a}_n; t). \tag{27}$$

The marginal probability $P_m(a,t)$ of having m individuals with age between 0 and a is then found by summing over the unwanted variable $n \geq m$:

$$P_m(a,t) = \sum_{n=m}^{\infty} P_m(n,a,t). \tag{28}$$

The comparison can be made more explicit by considering simple cases such as an age-independent birth-only process with fixed birth rate β. If the process starts with precisely N individuals, standard methods [13, 14] yields a simple solution of the McKendrick-von Foerster equation which when used in Eq. 26 gives $P(a < t; t) = Ne^{\beta t}\left(1 - e^{-\beta a}\right)$. Substituting the pure birth solution of Eq. 23 into Eqs. 27 and 28 yields

$$P_m(a,t) = \binom{m+N-1}{m} \frac{e^{-N\beta t}\left(1 - e^{-\beta a}\right)^m}{\left(1 - e^{-\beta a} + e^{-\beta t}\right)^{m+N}}. \tag{29}$$

In Fig. 2A we compare the expected value $P(a,t)$ derived from solutions to the McKendrick-von Foerster equation with stochastic simulations that sample the stochastic result $P_m(a,t)$. The fully stochastic nature of the process is clearly shown by the spread of the population about the expected value. Fig. 2B plots the corresponding number distribution $P_m(5, 10)$. This highlights one of the main advantages of our approach; the deterministic McKendrick-von Foerster theory captures only the expected population size, while the full probability distribution arise from our theory.

EQUATION HIERARCHIES

To connect our general kinetic theory with statistically-reduced (and deterministic) descriptions, we consider reduced $k-$dimensional distribution functions defined by integrating $\rho_n(\mathbf{a}_n; t)$ over $n - k$ age variables:

$$\rho_n^{(k)}(\mathbf{a}_k; t) \equiv \int_0^{\infty} \mathrm{d}a_{k+1} \ldots \int_0^{\infty} \mathrm{d}a_n \, \rho_n(\mathbf{a}_n; t). \tag{30}$$

The symmetry properties of $\rho_n(\mathbf{a}_n; t)$ indicate that it is immaterial which of the $n - k$ age variables are integrated out. If we integrate Eq. 16 over all ages ($k = 0$), and assume $\rho_n^{(1)}(a = \infty; t) = 0$, we find

$$\frac{\partial \rho_n^{(0)}(t)}{\partial t} = n\rho_n^{(1)}(a = 0; t) - n \int_0^\infty \gamma_n(y)\rho_n^{(1)}(y; t)\mathrm{d}y + (n + 1) \int_0^\infty \mu_{n+1}(y)\rho_{n+1}^{(1)}(y; t)\mathrm{d}y. \tag{31}$$

Furthermore, integrating Eq. 17 over $a_{i \neq \ell}$ yields $n\rho_n^{(1)}(a = 0; t) = (n - 1) \int_0^\infty \beta_{n-1}(y)\rho_{n-1}^{(1)}(y; t)\mathrm{d}y$. Thus, Eq. 31 can be written in the form

$$\frac{\partial \rho_n^{(0)}(t)}{\partial t} = (n - 1) \int_0^\infty \beta_{n-1}(y)\rho_{n-1}^{(1)}(y; t)\mathrm{d}y - n \int_0^\infty (\beta_n(y) + \mu_n(y))\rho_n^{(1)}(y; t)\mathrm{d}y + (n + 1) \int_0^\infty \mu_{n+1}(y)\rho_{n+1}^{(1)}(y; t)\mathrm{d}y. \tag{32}$$

Eq. 32 describes the evolution of the probability $\rho_n^{(0)}(t)$ that the system contains n individuals at time t, but it depends on the single-particle marginal density $\rho_n^{(1)}(y; t)$ and the equation is not closed. Upon deriving equations for $\rho_n^{(1)}(y; t)$, one would find that they depend on $\rho_n^{(2)}(y_1, y_2; t)$, and so on. Therefore, the marginal probability densities form a hierarchy of equations, as is typically seen in classic settings such as the kinetic theory of gases [37] and the statistical theory of turbulence [40]. Note that if the birth and death rates β_n and μ_n are age-independent, they are constants with respect to the integral and Eq. 32 reduces to the familiar constant birth and death rate master equation for the simple birth-death process:

$$\frac{\partial \rho_n^{(0)}(t)}{\partial t} = (n - 1)\beta_{n-1}\rho_{n-1}^{(0)}(t) - n(\beta_n + \mu_n)\rho_n^{(0)}(t) + (n + 1)\mu_{n+1}\rho_{n+1}^{(0)}(t), \tag{33}$$

where $\rho_n^{(0)}(t)$ is the probability the system contains n individuals at time t, regardless of their ages.

In general, integration of Eq. 16 over $n - k \geq 0$ age variables leaves k remaining independent age variables. The resulting kinetic equation for $\rho_n^{(k)}(\mathbf{a}_k; t)$ involves both $\rho_{n+1}^{(k+1)}(\mathbf{a}_k, y; t)$ and boundary terms $\rho_{n+1}^{(k+1)}(\mathbf{a}_k, a_{k+1} = 0; t)$. These boundary terms can be eliminated by using the result obtained from integration of the boundary condition (Eq. 17) over $n - k - 1$ age variables. By exploiting the symmetry properties of the marginals $\rho_n^{(k)}$, we find

$$\frac{\partial \rho_n^{(k)}(\mathbf{a}_k; t)}{\partial t} + \sum_{i=1}^k \frac{\partial \rho_n^{(k)}(\mathbf{a}_k; t)}{\partial a_i} = + \left(\frac{n - k}{n} \right) \rho_{n-1}^{(k)}(\mathbf{a}_k; t) \sum_{i=1}^k \beta_{n-1}(a_i) + \frac{(n - k)(n - k - 1)}{n} \int_0^\infty \beta_{n-1}(y)\rho_{n-1}^{(k+1)}(\mathbf{a}_k, y; t)\mathrm{d}y$$
$$- \rho_n^{(k)}(\mathbf{a}_k; t) \sum_{i=1}^k \gamma_n(a_i) - (n - k) \int_0^\infty \gamma_n(y)\rho_n^{(k+1)}(\mathbf{a}_k, y; t)\mathrm{d}y \tag{34}$$
$$+ (n + 1) \int_0^\infty \mu_{n+1}(y)\rho_{n+1}^{(k+1)}(\mathbf{a}_k, y; t)\mathrm{d}y.$$

Each function $\rho_n^{(k)}$ in the hierarchy not only depends on the functions in the $n \pm 1$ subspace, but is connected to functions with $k + 1$ variables. The latter coupling arises through the boundary condition for $\rho_n^{(k)}$ which involves densities $\rho_n^{(k-1)}$. As with similar equations in physics, the hierarchy of equations cannot be generally solved, and either factorization approximations or truncation (such as moment closure) must be used.

We now show that the $k = 1$ equation explicitly leads to the classic McKendrick-von Foerster equation and its associated boundary condition. For $k = 1$, $\rho_n^{(1)}(a; t)\mathrm{d}a$ is the probability that there are n individuals and that if one is randomly chosen, it will have age between a and $a + \mathrm{d}a$. Therefore, the probability that we have n individuals of which any one has age between a and $a + \mathrm{d}a$ is $n\rho_n^{(1)}(a; t)\mathrm{d}a$. Summing over all possible population sizes $n \geq 1$ gives us the probability $\rho(a, t)\mathrm{d}a$ that the system contains an individual with age between a and $a + \mathrm{d}a$:

$$\rho(a, t) \equiv \sum_{n=0}^\infty n\rho_n^{(1)}(a; t). \tag{35}$$

Multiplying Eq. 34 (with $k = 1$) by n and summing over all positive integers n, we find after carefully cancelling like terms

$$\frac{\partial \rho(a,t)}{\partial t} + \frac{\partial \rho(a,t)}{\partial a} = -\sum_{n=1}^{\infty} n\mu_n(a)\rho_n^{(1)}(a;t). \tag{36}$$

Equation 36 generalizes the McKendrick-von Foerster model to allow for population-dependent death rates, but does not reduce to the simple form shown in Eq. 1. Population-dependent effects in equation for $\rho(a,t)$ requires requires knowing the "single-particle" density function $\rho_n^{(1)}(a;t)$ and subsequently all higher order distribution functions.

A boundary condition is naturally recovered by integrating over all ages but a_ℓ in Eq. 17 and summing over all n:

$$\sum_{n=1}^{\infty} n\rho_n^{(1)}(a = 0;t) \equiv \rho(a = 0, t) = \sum_{n=1}^{\infty} n \int_0^{\infty} \beta_n(y)\rho_n^{(1)}(y;t)\mathrm{d}y. \tag{37}$$

Eqs. 36 and 37 represent the lowest order equations in the hierarchy. For the archetype models of Markovian and age-dependent birth death processes [14, 26], the population-wide birth and death rates are proportional to the population size and the mean field Eq. 37 reduces to the McKendrick-von Foerster theory only if both per individual birth and death rates $\beta_n(a) = \beta(a)$ and $\mu_n(a) = \mu(a)$ are independent of population size. In this case, $\mu(a)$ can be pulled out of the sum in Eq. 36 and $\sum_{n=1}^{\infty} n\mu_n(a)\rho_n^{(1)}(a;t) = \mu(a)\rho(a,t)$. Similarly, $\int_0^{\infty} \beta(y) \left[\sum_{n=1}^{\infty} n\rho_n^{(1)}(y;t)\right] \mathrm{d}y = \int_0^{\infty} \beta(y)\rho(y,t)\mathrm{d}y$, which is the simple boundary condition associated with the classic McKendrick-von Foerster model.

For more bespoke models (such as stochastic Verhulst-like models where birth rates have capacity dependent forms such as $\beta_n(a) = \beta(a)(1-n/K)$), we cannot derive a mean field equation without considering the hierarchy of population densities and closure approximations. For example, note that Eqs. 36 and 37 reduce to Eq. 25 if we assume the form $\rho_n^{(1)}(a;t) = \rho_n(t)A(a)$. This represents the simplest closure by neglecting all correlations between the ages of all particles. How much the solutions to Eq. 37 differ from those of the the standard McKendrick-von Foerster equation is an interesting mathematical issue that can be further pursued using asymptotic and numerical analyses.

DISCUSSION AND CONCLUSIONS

We have developed a general kinetic theory for age-structured birth-death processes important for the quantification small age-structured populations where fluctuations will play a significant role. To stochastically describe the age structure of a population requires a higher dimensional probability density. The evolution of this high-dimensional probability density mirrors that found in the Boltzmann equation for one-dimensional, ballistic, noninteracting gas dynamics. However, one crucial difference is that the number of individuals can increase or decrease according to the age-dependent birth and death rates. Thus, the dynamics are determined by a phase-space-conserving Liouville operator so long as the number of individuals does not change [37]. Once an individual is born or dies, the system jumps to another manifold in a higher or lower dimensional phase-space, immediately after which conserved dynamics resume until the next birth or death event. Such variable number dynamics share similarities with the kinetic theory of chemically reacting gases [41].

Our main mathematical results are Eqs. 16 and 17. These equations show that birth-death dynamics couple densities associated with different numbers n and describes the process in terms of ballistically moving particles all moving with unit velocity in the age "direction." The individual particles can die at rates that depend on their distance from their origin (birth). Particles can also give birth at rates dependent on their age. The injection of newborns at the origin (zero age) is described by the boundary condition (Eq. 17).

One important advantage of our approach is that it provides a natural framework for incorporating both age- and population-dependent birth and death rates into a stochastic description, which has thus far not been possible with other approaches. In general, our kinetic equations need to be solved numerically; however, we found analytic expressions for $\rho_n(\mathbf{a}_n;t)$ when either birth or death vanishes and the other is independent of population, along with a separable solution. Furthermore, we define marginal density functions and develop a hierarchy of equations analogous to the BBGKY hierarchy (Eq. 34). These equations for the marginal densities allow one to construct any desired statistical measure of the process and are also part of our main results. We explicitly showed how a zeroth order equation leads to the equation for the marginal probability of observing n individuals in the standard *age-independent* birth-death processes (Eq. 33) [27]. The first-order equation is also used to derive a hybrid equation

for the mean density $\rho(a,t)$ that involves the single-particle density function $\rho_n^{(1)}(a;t)$ (which ultimately depends on higher-dimensional densities $\rho_n^{(k>1)}(\mathbf{a}_k;t)$ through the hierarchy). Only when death is independent of population does the theory reduce to the deterministic McKendrick-von Foerster equation (Eq. 36) and the associated boundary condition (Eq. 37).

Extensions of our high-dimensional age-structured kinetic theory to more complex birth-death mechanisms such as sexual reproduction and renewal/branching processes can be straightforwardly investigated. The simple birth-death process we analyzed allows for the birth of only a single age-zero daughter from a parent at a time. We note that the Bellman-Harris process described via generating functions [23, 24] (which can describe age-dependent death and branching, but cannot be used to model population-dependent dynamics) assumes self-renewal at each branching event. That is, two (or more) daughters of zero age are simultaneously produced from a parent. Such differences in the underlying birth process can lead to qualitative differences in important statistical measures beyond mean-field, such as first passage times [25]. The branching/renewal process, as well as sexual reproduction, requires nontrivial extensions of our kinetic theory and will be explored in a future investigation.

ACKNOWLEDGEMENTS

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