Generalization of Powell’s results to unbalanced population growth

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New experimental methods allow for studying the dynamics of cell populations with increasing precision and time resolution, providing us with a large amount of high-quality data. These data, in turn, stimulate the mathematical modeling of such systems. Here, using a generalization of the McKendrick-von Foerster model proposed by Lebowitz and Rubinow, we derive relationships between the instantaneous population growth rate and probability distributions of cell age and generation time. Such relationships (for example, the Euler-Lotka equation) are known for populations in a steady state of balanced growth, but we generalize them to include unbalanced growth. Some probability distributions of interest are unobservable, yet the present formalism allows us to express them using experimentally observable quantities. Our results remain valid for a class of more complex population-balance models, as these can be reduced to the McKendrick-von Foerster form (by integrating out the variables other than the cell age), and subsequently, they can be analyzed within the framework of the Lebowitz-Rubinow model. We also propose a generalization of the latter model in which cells are described not only by age and generation time but also by volume and a single-cell growth rate.

I. INTRODUCTION

Cell populations out of the steady-state of balanced growth have been investigated for decades, both from the point of view of experiment [1–3] and theory [4–13]. The problem of desynchronization (or lack thereof) of an initially almost synchronous population of bacteria or cancer cells and its evolution into the asynchronous steady state can serve as an example [6, 7, 12–14]. In recent years, there is a renewed interest in population dynamics out of the state of steady growth. For example, oscillatory behavior of cell number and population growth rate in an unsynchronized (asynchronous) bacterial culture has been studied [14–16] in the context of cell division timing strategies and noise in the intrinsic parameters of individual cells.

Importantly, not only the population size can be now measured, as during the previous period of an increased interest in the population dynamics models in the 1950s. The current single-cell tracking techniques allow for measurement of the parameters of individual cells, such as age, volume, individual growth rate or protein levels. Therefore extensions of the old models are needed, which would be able to describe the population statistics of these newly available parameters. Here, we present such an extension: A generalization of the model proposed fifty years ago by Lebowitz and Rubinow [11]. Within our approach, apart from cell age and generation time (variables used in the original Lebowitz-Rubinow model) each cell is described also by its volume and individual growth rate.

There is also a need to generalize results obtained previously for the steady-state to the case of unsteady population growth. For example, one may ask: How does the form of generation time distribution for newborn cells influence the population growth rate? Or how does that rate depend on generation-time correlations between mother and daughter cells? For the steady state of balanced growth, a single answer to these two questions is well known and given by Euler-Lotka equation [11, 17–19]. Here, we generalize the Euler-Lotka equation to the case of unbalanced growth.

The generation time \( \tau \) (termed also 'cell-cycle time' or 'interdivision time') is a 'hidden variable': Its value becomes known only at the cell division ending the cell cycle. For that reason, the generation time distribution for the mother cells (those just dividing) is experimentally observable whereas generation time distributions for both newborn cells (those just after cell division) and extant cells (all cells present in the population at a given moment) are unobservable [20]. Again, relationships between these distributions are known for the case of the population in the state of balanced growth. Our main goal here is to establish exact relationships between generation time distributions in the state of unbalanced growth, which will allow us to express the unobservable quantities through the observable ones.

What theoretical framework can be employed to find such relationships? Population dynamics is frequently modelled by population-balance equations (PBE) [8–10, 19–22]. Within this approach, each cell is characterized by its age and/or current volume (mass, size) and possibly by some additional variables like cell volume at birth, volume growth rate, number or concentration of protein molecules of a certain kind, etc. (The word 'balance', referring to the
bookkeeping’ of the number of cells of a given age, volume, etc., may be misleading here, as such population-balance models (PBM) can equally well describe the system which is not in the state of balanced growth. Other terms like ‘structured-population models’ or ‘continuous rate models’ are sometimes used, each pointing to a different aspect of such theoretical framework.) Population-balance models are based on first-order partial differential equations describing the deterministic time evolution of cell number density, supplemented with appropriate boundary and initial conditions. However, from the cell number density, one can construct various quantities which have a natural interpretation of probability distributions.

Perhaps the simplest PBM was proposed almost a century ago by McKendrick [23] and (in a different context) by von Foerster [24]. In this model, each cell is characterized only by its age \( a \). Any PBM where \( a \) is one of the state variables may be reduced to an effective McKendrick-von Foerster form by integrating out the remaining variables. Therefore the results that can be derived within the McKendrick-von Foerster model are valid for a much broader class of population-balance models (we discuss this point in Appendix C).

Yet, from our perspective, the McKendrick-von Foerster model has a serious limitation: It does not contain explicit information about the mother-daughter generation time inheritance and correlations. Therefore this model cannot be used to determine the dynamics of all generation time distributions of interest. We use plural here, because, as already mentioned, at least three distinct generation time distributions can be defined: \( f_0(t, \tau) \) for cells whose age \( a \) is equal zero (newborns), \( f_1(t, \tau) \) for just dividing cells for which \( a = \tau \) (mothers), and \( f_2(t, \tau) \) for all cells present in the population at a given moment (called extant cells).

The relationships between generation time distributions, cell age distribution, and population growth rate were found using different approaches by Powell [17, 22], by Lebowitz and Rubinow [11], and recently by other authors [18, 19], but only for the case of balanced growth in either batch or continuous bacterial cultures when all probability distributions are time-independent. To the best of our knowledge, the seminal results derived decades ago by Powell and others have not been generalized yet to the case of unbalanced population growth.

To make such an extension we use the generalization of the McKendrick-von Foerster model proposed by Lebowitz and Rubinow [11]. Within this approach, apart from the cell age \( a \), the generation time \( \tau \) becomes an additional parameter describing each cell. Roughly speaking, the Lebowitz-Rubinow model combines the McKendrick-von Foerster equation with the approach of Powell and describes the time evolution of the number density of cells with given \( a \) and \( \tau \): \( n(t, a, \tau) \). Using this formalism, we find the relationships between \( n(t, a, \tau) \), generation time distributions, cell age distribution and the instantaneous (time-dependent) population growth rate. All the generation-time probability distributions mentioned above, \( f_0(t, \tau) \), \( f_1(t, \tau) \), \( f_2(t, \tau) \), and the cell age distribution \( \phi(t, a) \) can be obtained as either conditional or marginal probabilities from a single quantity – the joint probability distribution of age and generation time, \( \chi(t, a, \tau) \). The latter is defined in a very simple way within the Lebowitz-Rubinow model: It is just the cell number density \( n(t, a, \tau) \) normalized by the current total number of cells \( N(t) \).

The explicit time-dependent solution to the Lebowitz-Rubinow equation has already been found by the authors of that equation [11]. It has a form of a series for \( n(t, a, \tau) \), where each term corresponds to the number of previous cell divisions. If only the initial condition is given, such a solution can be expressed using a single function that describes how the generation time is passed from mother to daughter. Here we derive similar series for various probability distributions.

Parts of the formalism presented here are a theoretical basis for numerical simulations of cell population dynamics, which we are going to publish in a separate paper [26]. Here, we provide a systematic derivation of the relationships used in the simulation algorithm. The present results can also provide a test for numerical results.

This paper is organized as follows: In Subsection II A we begin with a brief analysis of the McKendrick-von Foerster model. In Subsection II B we introduce the Lebowitz-Rubinow model and discuss some of its properties. Although we show some novel results (e.g., the relationship between generation time distribution of mother cells and cell age distribution) already in Section III, our main results are presented in Section III. These include the relationships between probability distributions of cell age and/or generation time (Subsection III C), as well as the generalization of the Euler-Lotka equation for the population out of the state of steady growth (Subsection III D). In Subsection III E we use the series solution of the Lebowitz-Rubinow model found in ref. [11] to obtain similar series for the cell age and generation time distributions. We also show that Lebowitz-Rubinow model reduces to the McKendrick-von Foerster model not only for the special, separable case of the initial conditions analysed in [11], but in a general situation (Subsection III A). The relationship between these two models is further elaborated and elucidated at the end of Subsection III C.

Another novel topic, where a grasp of population dynamics out of the steady-state is needed, is a quantification of the natural selection strength by a fitness landscape or by the growth rate of a subpopulation carrying a given phenotypic trait [22, 24, 28]. For that reason, in Subsection III F we show how the present results can be used to calculate a fitness landscapes for cell age and generation time.

In Subsection III G we present a generalization of the Lebowitz-Rubinow model, which allows us to extend our results to the cases of probability distributions of age \( a \), generation time \( \tau \), cell volume \( V \) and single-cell growth rate
λ. Finally, Subsection [LV] contains summary. In particular, we discuss there other possible generalizations of the present approach.

A number of results have been relegated to appendices. In particular, in Appendix A we provide an alternative formulation of the original Lebowitz-Rubinow model. In Appendix C we show that the McKendrick-von Foerster model may be derived from a more general population balance model. In Appendix E we present a generalization of the Lebowitz-Rubinow model which takes into account not only the generation time of a cell and its mother but also the generation times of the cell’s more distant ancestors. Finally, in Appendix F we show that if the ‘maturity’ $x$ is defined simply as cell age normalized by generation time $(x = a/\tau)$, then from the Lebowitz-Rubinow model [11] one can derive a model formally identical to that proposed by Rubinow in 1968 [29].

II. THEORY

A. McKendrick-von Foerster model

1. Time-evolution of the cell number density $n(t,a)$

The equations of the McKendrick-von Foerster model [23, 24, 30–32] read

\begin{align}
\frac{\partial n(t,a)}{\partial t} + \frac{\partial n(t,a)}{\partial a} + \gamma(t,a)n(t,a) + D(t)n(t,a) &= 0, \\
n(t,0) &= 2^\sigma \int_0^{\tau_1} \gamma(t,a)n(t,a)da, \\
n(0,a) &= n_0(a). 
\end{align}

Eq. (1) describes the time-evolution of the number density $n(t,a)$ of cells of age $a$; the boundary condition (2) describes the influx of newborn cells, whereas (3) is the initial condition. $\gamma(t,a)$ is the division rate and $\tau_1$ is the maximal possible cell age (maximal generation time), i.e. $n(t,a) = 0$ for $a > \tau_1$. We assume that the fermenter dilution rate $D(t)$ in (1) may vary with time but does not depend on the cell age $a$. We also neglect cell death. Combining (2) and (3) we obtain the consistency condition at $t = a = 0$:

\begin{equation}
n_0(0) = 2^\sigma \int_0^{\tau_1} \gamma(0,a)n_0(a)da.
\end{equation}

Eqs. (1)–(3) describe the batch culture ($D(t) = 0, \sigma = 1$), continuous culture ($D(t) \geq 0, \sigma = 1$) or mother machine experiments ($D(t) = 0, \sigma = 0$). (The mother machine may be viewed as an experimental realization of the ensemble of cell lineages.) For $\sigma = 1$, model defined by Eqs. (1)–(3) is a special case of the population balance model analyzed in ref. [20]. However, in contrast to [20], here we allow for an arbitrary dependence of the division rate $\gamma(t,a)$ and the dilution rate $D(t,a)$ on the observation time $t$.

If Eqs. (1)–(3) are derived from a more general population-balance model (by integrating out the variables like cell volume or individual cell’s growth rate), then the effective $\gamma(t,a)$ may explicitly depend on the observation time $t$ even if the environmental conditions are constant (time-independent), see Appendix C. The same situation may be encountered if the McKendrick-von Foerster model is derived from the Lebowitz-Rubinow model (see Section [I]) and if there are non-zero generation time correlations between mother and daughter.

The properties of the McKendrick-von Foerster equation and its time-dependent solution have been analyzed in detail in the mathematical literature, see for example [31, 32]. Here, we need the McKendrick-von Foerster model as both a point of departure and a point of reference for a more general formalism presented in the next Section. The McKendrick-von Foerster model can also be used to derive the relationship between the generation time distribution for mother cells (age distribution of mothers, $f_{f1}(t, \tau)$) and the age distribution for all cells present in the population, $\phi(t,a)$. The latter quantity is defined as [21, 32]

\begin{equation}
\phi(t,a) = \frac{n(t,a)}{\int_0^{\tau_1} n(t,a)da} = \frac{n(t,a)}{N(t)},
\end{equation}

where

\begin{equation}
N(t) = \int_0^{\tau_1} n(t,a)da.
\end{equation}
From (2) and (8) we get
\[ \phi(t,a) = \frac{\gamma(t,a)n(t,a)}{N(t)\Lambda(t)} = \frac{\gamma(t,a)\phi(t,a)}{\Lambda(t)}. \] (7)

(In the case of mother cells \( a = \tau \). In ref. [21], the age distribution of mothers \( f_1(t,a) \) is denoted by \( g(a) \), whereas the cell age distribution \( \phi(t,a) \) is denoted by \( f(t,a) \).) For both \( \sigma = 0 \) and \( \sigma = 1 \), \( \Lambda(t) \) appearing in (7) is given by
\[ \Lambda(t) = \int_0^t \gamma(t,a)\phi(t,a)da. \] (8)

From (2) and (8) we get
\[ n(t,0) = 2^\sigma \Lambda(t)N(t). \] (9)

Integrating (11) with respect to \( a \) and using (9) we get
\[ dN(t) dt = \sigma[\Lambda(t) - D(t)]N(t), \] (10)

hence
\[ N(t) = N(t_0) \exp \left\{ \sigma \int_{t_0}^t [\Lambda(t') - D(t')]dt' \right\}, \] (11)

for any \( t_0 \in [0,t) \). For the batch culture (\( \sigma = 1 \) and \( D(t) = 0 \)), \( \Lambda(t) \) defined by (8) is the instantaneous population growth rate. In a general case, the population growth rate is given by \( \sigma[\Lambda(t') - D(t')] \). It therefore vanishes both for the mother machine (\( \sigma = 0 \)) and for the continuous culture if dilution compensates the increase in cell number \( (\Lambda(t) = D(t)) \), in particular in the steady state limit \( (\Lambda(t) = \Lambda = D) \). Still, the solution to (11) with \( D(t) \neq 0 \) can be easily obtained from the solution to the case for which \( D(t) = 0 \). If \( n(t,a) \) is a solution to (11) with \( D(t) \neq 0 \) and \( \tilde{n}(t,a) \) is solution to (11) with \( D(t) = 0 \), then
\[ \tilde{n}(t,a) = n(t,a)e^{\int_0^t D(t')dt'}. \] (12)

Integrating (12) with respect to \( a \) we get
\[ \tilde{N}(t) = N(t)e^{\int_0^t D(t')dt'}, \] (13)

and therefore \( \tilde{\phi}(t,a) = \tilde{n}(t,a)/\tilde{N}(t) = n(t,a)/N(t) = \phi(t,a) \). Cell division does not depend on the dilution rate \( D(t) \):
\( \gamma(t,a) = \gamma(t,a) \). In consequence, from (7) and (8) we get \( \tilde{\Lambda}(t) = \Lambda(t) \) and \( f_1(t,a) = f_1(t,a) \). As neither \( \Lambda(t) \) nor probability distributions depend on \( D(t) \), we can put \( D(t) = 0 \) in (11) without loss of generality.

2. Time-evolution equation for the cell age distribution \( \phi(t,a) \). Relationship between \( \phi(t,a) \) and \( f_1(t,a) \)

From (11)–(5), (9) and (10) we obtain the time-evolution equation as well as the boundary and initial conditions for \( \phi(t,a) \) defined by (5):
\[ \frac{\partial}{\partial t} \phi(t,a) + \frac{\partial}{\partial a} \phi(t,a) + \gamma(t,a)\phi(t,a) + \sigma\Lambda(t)\phi(t,a) = 0, \] (14)
\[ \phi(t,0) = 2^\sigma \Lambda(t), \] (15)
\[ \phi(0,a) = \phi_0(a). \] (16)

Eqs. (14)–(15) are applicable to both batch and continuous cell culture (\( \sigma = 1 \)) as well as to the mother machine (\( \sigma = 0 \)).

There are two equations relating \( \phi(t,a) \) (5) and \( f_1(t,a) \) (7). The first of them is (7), i.e., the definition of \( f_1(t,a) \). In order to find the second one we rewrite (14) using (7) to get
\[ \frac{\partial}{\partial t} \phi(t,a) + \frac{\partial}{\partial a} \phi(t,a) + \sigma\Lambda(t)\phi(t,a) + \Lambda(t)f_1(t,a) = 0. \] (17)
Note that if the generation time distribution of mothers \( f_1(t, a) \) is known – either from some theoretical arguments or from the experiment – then, instead of (14), in order to find \( \phi(t, a) \) one can use (17) supplemented with the boundary (16) and initial (16) condition. In this way, one can bypass the problem of assuming a functional form of the division rate \( \gamma(t, a) \) or extracting it from the experimental data. One can treat the mother’s generation time distribution \( f_1(t, a) \) and not the cell division rate \( \gamma(t, a) \) as an “input” to the model. However, we only want to find the relationship between \( \phi(t, a) \) and \( f_1(t, a) \). To do this, one may use the method of characteristics, but here we prefer to apply the Laplace transform to Eq. (17) and get

\[
\frac{d\hat{\phi}(t, s)}{dt} + [s + \sigma \Lambda(t)]\hat{\phi}(t, s) = \Lambda(t)[2^\sigma - \hat{f}_1(t, s)],
\]

where

\[
\hat{\phi}(t, s) = \int_0^\infty e^{-sa} \phi(t, a) da,
\]

\[
\hat{f}_1(t, s) = \int_0^\infty e^{-sa} f_1(t, a) da.
\]

Using (17) or (18) we obtain the time-evolution equations for the moments of \( \phi(t, a) \),

\[
\frac{dA_r(t)}{dt} + \sigma \Lambda(t) A_r(t) - rA_{r-1}(t) = -\Lambda(t)T_r(t),
\]

where \( A_r(t) \) is the \( r \)-th moment of the age distribution \( \phi(t, a) \), and \( T_r(t) \) is the \( r \)-th moment of \( f_1(t, a) \):

\[
A_r(t) \equiv \int_0^\tau a^r \phi(t, a) da,
\]

\[
T_r(t) \equiv \int_0^\tau a^r f_1(t, a) da.
\]

In the steady-state limit, for \( \sigma = 1 \) from (20), we obtain Eqs. (18) and (20) of ref. [20],

\[
A_1 + T_1 = \Lambda^{-1},
\]

\[
A_2 = 2\Lambda^{-1}A_1 - T_2,
\]

whereas for \( \sigma = 0 \) we get Eq. (4) of ref. [15]:

\[
A_1 = \frac{1}{2} T_1 \left( 1 + \frac{T_2 - T_1^2}{T_1^2} \right) = \frac{T_2}{2T_1}.
\]

For \( r = 1, 2, \ldots, R \), Eq. (20) yields closed system of \( R \) equations which can be solved recursively for any \( R < \infty \). Still, it is much more convenient to solve (18) instead and find the moments using the generation function. We get

\[
\hat{\phi}(t, s) = e^{-st} e^{-\sigma \Omega(t)} \left\{ \hat{\phi}(0, s) + \int_0^t e^{\sigma \Omega(t') + st'} \Lambda(t') [2^\sigma - \hat{f}_1(t', s)] dt' \right\},
\]

where we define

\[
\Omega(t) \equiv \int_0^t \Lambda(\xi) d\xi.
\]

Inverting (20), we obtain

\[
\phi(t, a) = \begin{cases} e^{-\sigma \Omega(t)} \left[ \phi_0(a-t) - \int_0^t \Lambda(t') e^{\sigma \Omega(t')} f_1(t', a-t+t') dt' \right] , & a \geq t, \\
2^\sigma e^{\sigma \Omega(t-a)} \Lambda(t-a) - \int_{t-a}^t \Lambda(t') e^{\sigma \Omega(t')} f_1(t', a-t+t') dt' , & a \leq t. \end{cases}
\]

Eq. (28) is a generalization of Eq. (14) of ref. [20] to the case of unbalanced population growth. (In Eq. (14) of ref. [20], there is a constant \( D(t) = D \) instead of \( \Lambda \), because \( D = \Lambda \) in the steady state limit considered there.) Using (20) or (28) we obtain the equation relating moments of \( \phi(t, a) \) to those of \( \phi(0, a) = \phi_0(a) \) and \( f_1(t, a) \),

\[
A_r(t) = e^{-\sigma \Omega(t)} \left[ \sum_{k=0}^{r} \binom{r}{k} \int_0^t \Lambda(t') e^{\sigma \Omega(t')} (t-t')^r dt' \right] A_r(0) + 2^\sigma \int_0^t \Lambda(t') e^{\sigma \Omega(t')} \left[ (t-t')^r T_r(t') dt' \right] - \sum_{k=0}^{r} \binom{r}{k} \int_0^t \Lambda(t') e^{\sigma \Omega(t')} (t-t')^{r-k} T_r(t') dt'.
\]
Eq. (29) is a generalization of Eqs. (18) and (20) of ref. [20]. To the best of our knowledge, neither (28) nor (29) have been shown in the literature to date.

B. Lebowitz-Rubinow model

Starting from the McKendrick-von Foerster model as defined by (1)–(3) we have derived the relationship (28) between the two age distributions: \( \phi(t, a) \) for all cells in a population and \( f_1(t, a) \) for mother cells (the latter is also a generation time distribution as for just dividing cells \( a = \tau \)). But the generation time \( \tau \) and thus the generation time inheritance are not explicitly present in (1)–(3). Therefore the McKendrick-von Foerster model is not a preferred choice if one wants to obtain similar relationships involving the remaining generation time distributions: \( f_0(t, \tau) \) (newborns) and \( f_2(t, \tau) \) (extant cells) or the joint probability distribution of cell age and generation time, \( \chi(t, a, \tau) \).

For that reason, we employ the model proposed by Lebowitz and Rubinow [11]. Within this approach, apart from cell age \( a \), a generation time (duration of the cell cycle) \( \tau \) becomes an additional, non-dynamical variable (\( \dot{\tau} = 0 \)). We assume here that \( \tau \) is bounded: \( 0 < \tau_s < \tau < \tau_l < \infty \), hence \( \tau_l (\tau_s) \) is the longest (the shortest) possible generation time, respectively. For example, \( \tau_s < 20 \) minutes for bacterium \( E. coli \) growing in optimal conditions [33]. Assuming that all distributions of \( \tau \) vanish for the generation times that are too short (\( \tau < \tau_s \)) or too long (\( \tau > \tau_l \)), one can put \( \tau_s = 0 \) and \( \tau_l = \infty \), but in contrast to the original formulation of the Lebowitz-Rubinow model here we will not do so. (Only in the case of the generalized Lebowitz-Rubinow model consider in Subsection III G 2, for simplicity we extend the limits of integration with respect to \( \tau \), \( V \) and \( \lambda \) to 0 and \( \infty \).) Therefore we have

\[
0 \leq a \leq \tau, \quad \underline{a} \leq \tau \leq \tau_l
\]

where

\[
\underline{a} \equiv \max(a, \tau_s),
\]

as \( \tau \) must be larger then both \( a \) and \( \tau_s \). Cell number density \( n(t, a) \) appearing in (1)–(3) is now replaced by the number density of cells of age \( a \) and generation time \( \tau \): \( n(t, a, \tau) \). These two densities are related by

\[
n(t, a) = \int_{\underline{a}}^{\tau_l} n(t, a, \tau) d\tau.
\]

Consequently, the total number of cells in the population is given by

\[
N(t) = \int_0^{\tau_l} \int_{\underline{a}}^{\tau_l} n(t, a, \tau) d\tau da = \int_{\tau_s}^{\tau_l} \int_0^{\tau} n(t, a, \tau) da d\tau.
\]

1. Model equation, its boundary and initial conditions

Within the approach of ref. [11], equation (1) of the McKendrick-von Foerster model is replaced by

\[
\frac{\partial}{\partial t} n(t, a, \tau) + \frac{\partial}{\partial a} n(t, a, \tau) = 0,
\]

whereas boundary condition and initial condition read now

\[
n(t, 0, \tau) = 2\sigma \int_{\tau_s}^{\tau_l} h(\tau|\xi, t)n(t, \xi, \xi) d\xi \equiv \Psi(t, \tau),
\]

and

\[
n(0, a, \tau) = n_0(a, \tau) \equiv \Phi(a, \tau),
\]

respectively. At \( a = t = 0 \) we must impose a consistency condition:

\[
\Phi(0, \tau) = \Psi(0, \tau).
\]

In [35] we have \( \sigma = 0 \) for a single cell lineage or the mother machine experiment (which can be treated as a physical realization of the ensemble of such lineages) and \( \sigma = 1 \) for batch culture. Note that most quantities of interest are
different for \( \sigma = 0 \) and \( \sigma = 1 \). These include not only \( \Lambda(t) \) defined by (8) or by (11) below, and which can be termed ‘instantaneous population growth rate’ only for \( \sigma = 1 \), but also cell number densities \( n(t, a, \tau) \) and \( n(t, a) \) as well as probability distributions of age and/or generation time. Only the probability distribution of inherited generation times \( h(\tau|\tau', t) \) appearing in (33) and the initial condition \( \Phi(a, \tau) \) are the same for both cases. Therefore in principle we should use an index to distinguish between \( \sigma = 0 \) and \( \sigma = 1 \) cases: Instead of \( n(t, a) \), \( \Lambda(t) \), etc., we should write \( n_{\ell(\sigma)}(t, a) \), \( \Lambda_{\ell(\sigma)}(t) \), etc., where

\[
\ell(\sigma) = \begin{cases} 
F & \text{for } \sigma = 0, \\
B & \text{for } \sigma = 1.
\end{cases}
\]

(38)

\( F \) refers to ‘forward probabilities’ and \( B \) to ‘backward probabilities’, the terms ‘forward’ and ‘backward’ are related to the two ways the population lineage tree can be sampled, see [22, 28]. Still, we distinguish the \( \sigma = 0 \) and \( \sigma = 1 \) cases explicitly only when quantities with different values of \( \sigma \) appear in the same formula (as in Section III F) or in the steady state limit.

For the continuous culture, the term \( D(t)n(t, a, \tau) \) responsible for cell dilution should also be added to the l.h.s of (34). But we omit this term, as one can easily obtain the solution to (34) with \( D(t) \neq 0 \) from the solution to the \( D(t) = 0 \) case, exactly as in the case of the McKendrick-von Foerster model. The same remark applies to the term describing the possibility of cell death, included in the original formulation of the Lebowitz-Rubinow model [11].

2. Inheritance of generation time

Inheritance of generation time and the mother-daughter generation time correlations are modelled by parametrised probability distribution \( h(\tau|\tau', t) \) appearing in (33): \( h(\tau|\tau', t) \) is equal to the probability that the generation time of each of the two daughter cells born at a given cell division is equal to \( \tau \), provided that the generation time of their common mother was \( \tau' \).

We assume here that both the old- and the new-pole daughter cell (labelled by + and −, respectively) inherit the same value of generation time: \( \tau_+ = \tau_- = \tau \). This assumption can be relaxed and a more general model can be defined, which allows for an ‘asymmetric’ situation when \( \tau_+ \neq \tau_- \). Yet the model in which sister cells differ with respect to the value of inherited generation time can be reduced to the ‘symmetric’ one \( \tau_+ = \tau_- = \tau \) under certain (rather strong) conditions. In particular, we must treat the old- and new-pole cells as equivalent and thus neglect the effects of aging on the cell growth rate, see Appendix E 2.

The simplifying assumption \( \tau_+ = \tau_- = \tau \) can be also justified by the following argument. Consider first a general situation, when at cell division one of the daughter cells inherits generation time \( \tau_+ \) and the other \( \tau_- \) \( (\tau_+ \) does not have to be equal to \( \tau_- \)), provided that their common mother had generation time \( \tau' \). Such event may be denoted shortly as \( (\tau_+, \tau_-|\tau') \). Let the probability of \( (\tau_+, \tau_-|\tau') \) be \( P(\tau_+, \tau_-|\tau') \) and assume that it is equal to the probability of the situation when the values of \( \tau_+ \) and \( \tau_- \) are interchanged between daughter cells: \( P(\tau_+, \tau_-|\tau') = P(\tau_-, \tau_+|\tau') \). In such a case the number of \( (\tau_+, \tau_-|\tau') \) cell divisions between \( t \) and \( t + dt \) is equal (on the average) to the number of the \( (\tau_-, \tau_+|\tau') \) divisions. Now we can cut and rearrange the lineage tree in such a way that instead of two ‘asymmetric’ divisions \( (\tau_+, \tau_-|\tau') \) and \( (\tau_-, \tau_+|\tau') \) we have two ‘symmetric’ ones: \( (\tau_+, \tau_+|\tau') \) and \( (\tau_-, \tau_-|\tau') \). Clearly, such rearrangement alters generation time correlation between the sister cells but does not affect the number of cells born with a given value of generation time \( \tau \) at the observation time \( t \), hence both \( \Lambda(t) \) and \( n(t, 0, \tau) = \Psi(t, \tau) \) remain unchanged. Therefore as long as we are not interested in generation time correlation between the sisters, after this ‘reshuffling’ of a lineage tree all model predictions remain the same, but now at each division daughter cells inherit the same generation time.

For the vanishing mother-daughter generation time correlations we have \( h(\tau|\tau', t) = f(t, \tau) \): The inherited generation time no longer depends on \( \tau' \) but it may still depend on \( t \) for various reasons (for example, due to the changing environmental conditions).

In more general models of this kind, the inherited generation time \( \tau \) may depend not only on the mother’s generation time but also on the generation times of more distant ancestors. If Eqs. (33)–(36) are derived from such a more general model by integrating out generation times of more distant ancestors, \( h(\tau|\tau', t) \) may still depend on the observation time \( t \) even if the environmental conditions are constant, see Appendix E 2.

Note that by writing down (33) we assume that each cell ‘knows’ its generation time \( \tau \) already from the beginning of the cell cycle. It may seem that in consequence, we have to assume a constant (time-independent) environment, otherwise, the present approach would not be consistent. But this formalism is applicable as well for the environmental conditions that vary with the observation time \( t \). We can think of a fictitious situation when the mother cell predicts or anticipates future environmental conditions and the form of the probability distribution of inherited generation
times $h(\tau|\tau',t)$ appearing in (35) changes accordingly. (Strictly speaking, if environmental conditions are changing with the observation time $t$ then $\tau_l$ and $\tau_s$ may depend on $t$, too. However, here we assume that this is not the case and $\tau_s = \tau_l = 0$.)

3. Formal solution of the Lebowitz-Rubinow model

A general solution to (34) can be found by the method of characteristics or simply guessed: It is of the form $n(t,a,\tau) = F(t-a,\tau)$, where $F(x_1,x_2)$ is some function of two real variables. Taking into account initial and boundary conditions we obtain (11)

$$n(t,a,\tau) = \begin{cases} 
\Phi(a-t,\tau) = n(0,a-t,\tau) & \text{for } a \geq t, \\
\Psi(t-a,\tau) = n(t-a,0,\tau) & \text{for } a \leq t.
\end{cases} \quad (39)$$

In the above, the initial condition $\Phi(a,\tau)$ is defined by (36) and the boundary condition at $a = 0$: $n(t,0,\tau) = \Psi(t,\tau)$ is given by (37). The condition (37) ensures that $\Phi(a-t,\tau) = \Psi(t-a,\tau)$ for $a = t$.

For $a \geq t$ (39) reflects the simple fact: Cells which age was equal to $a - t_1$ at $t = 0$ are of age $a$ at $t = t_1$, provided there was no cell division, i.e. provided that $a < \tau$. For $a \leq t$, (39) expresses the fact that the number of cells whose age and generation time at the observation time $t$ are $a$ and $\tau > a$, respectively, is equal to the number of cells that were born at the earlier time $t-a$ and inherited generation time $\tau$, as there is no loss of such cells until cell division. But we must keep in mind that formula (39) is valid only for $\tau \geq a$ and $n(t,a,\tau)$ has no sensible interpretation for $\tau < a$. In contrast, $n(0,a-t,\tau)$ is meaningful for all $\tau \geq a - t$ and $n(t-a,0,\tau)$ for all $\tau \geq 0$. We may also impose the condition $a \leq \tau$ by hand, defining $n_0(t,a,\tau) = \Theta(\tau-a)n(t,a,\tau)$, where $\Theta(x)$ is Heaviside step function (33). However, if we decide to work with $n_0(t,a,\tau)$ instead of $n(t,a,\tau)$, we must modify equations (34) and (35), see Appendix A for details.

From (35) and (39) we obtain the following renewal equation:

$$\Psi(t,\tau) = 2^\tau \Theta(t - \tau_s) \int_{\tau_s}^\tau h(\tau|\xi,t)\Psi(t-\xi,\xi)d\xi$$
$$+ 2^\tau \Theta(\tau_l - t) \int_0^{\tau_l} h(\tau|\xi,t)\Phi(\xi-t,\xi)d\xi, \quad (40)$$

where

$$\tau_l \equiv \min(t,\tau_l), \quad \tau_s \equiv \max(t,\tau_s). \quad (41)$$

Condition (37) can be now rewritten as $\Phi(0,\tau) = \Psi(0,\tau) = \zeta(0,\tau) = 2^\tau \int_0^{\tau_l} h(\tau|\xi,0)\Phi(\xi,\xi)d\xi$; integrating this equation with respect to $\tau$ we obtain (40).

Even without solving (40) iteratively (which we do in Section III C) we can still use this equation to find relationships between various probability distributions appearing in the model of Lebowitz Rubinow (Subsection III C). Yet, before we can do it, we must first clarify the connection between the Lebowitz-Rubinow and the McKendrick-von Foerster models.

III. RESULTS

This Section contains our main results: Identities and relationships between probability distributions and other quantities which can be defined within the Lebowitz-Rubinow model. These relationships were not given (at least not in such a general form) in the original paper of Lebowitz and Rubinow (11).

A. Reduction of Lebowitz-Rubinow model to McKendrick-von Foerster model

If generation time $\tau$ is integrated out, Eqs. (34)-(35) should reduce to Eqs. (11) (39) of the McKendrick-von Foerster model, not only for the separable form of the initial condition considered in ref. (11), but in a general situation.
If \( a \geq \tau_s \) and therefore \( a = a \), then by integrating (8) with respect to \( \tau \) from \( a \) to \( \tau_l \) and using the Leibniz integral rule we obtain

\[
\frac{\partial}{\partial t} n(t, a) + \frac{\partial}{\partial a} n(t, a) + n(t, a, a) = 0,
\]

where \( n(t, a) \) is defined by (32). Likewise, integrating (35) with respect to \( \tau \) from \( 0 = \max(0, \tau_s) = \tau_s \) to \( \tau_l \) and keeping in mind that for any \( \tau' \) and \( t \geq 0 \) we have \( \int_{\tau_s}^{\tau_l} h(\tau|\tau', t)d\tau = 1 \), we get

\[
n(t, 0) = \int_{\tau_s}^{\tau_l} \Psi(t, \tau)d\tau = 2^a \int_{\tau_s}^{\tau_l} n(t, \xi, \xi)d\xi.
\]

Comparing (11) with (12) and (2) with (33) we see that the Lebowitz-Rubinow model is consistent with the McKendrick-von Foerster model if

\[
n(t, a, a) = \gamma(t, a)n(t, a) = f_1(t, a)N(t)\Lambda(t).
\]

(Note that (48) is valid for both \( t \leq a \) and \( t \geq a \). We also define

\[
\chi_0(a, \tau) = \frac{n(0, a, \tau)}{N_0} = \frac{\Phi(a, \tau)}{N_0}
\]

Using \( \chi(t, a, \tau) \) we can obtain the age distribution of all cells in the population,

\[
\phi(t, a) = \int_{a}^{\tau_l} \chi(t, a, \tau)d\tau,
\]
as well as the distribution of generation times of the extant cells

\[ f_2(t, \tau) = \int_0^\tau \chi(t, a, \tau) da. \] (51)

The age distribution of mothers ('carrier distribution') \( f_1(t, \tau) \) has been already defined by (44),

\[ f_1(t, a) \equiv \frac{\chi(t, a)}{\Lambda(t)} = \frac{n(t, a, a)}{N(t)\Lambda(t)}. \] (52)

As mentioned in the Introduction, \( f_1(t, \tau) \) is experimentally observable quantity. It is therefore reasonable and desired to express other probability distributions using \( f_1(t, \tau) \). Finally, generation time distribution for newborn cells is the following conditional distribution

\[ f_0(t, \tau) \equiv \chi(\tau|0, t) \equiv \frac{\chi(t, 0, \tau)}{\phi(t, 0)} = \frac{\chi(t, 0, \tau)}{2^\sigma \Lambda(t)} = \frac{n(t, 0, \tau)}{2^\sigma N(t)\Lambda(t)}. \] (53)

The identity

\[ \phi(t, 0) = 2^\sigma \Lambda(t) \] (54)

used in (52) follows from (49) and (44) or directly form (10).

C. Relationships between probability distributions of cell age and generation time

Now we are ready to derive relationships between probability distributions defined in the previous Subsection: \( \chi(t, a, \tau) \), \( \phi(t, a) \), \( f_0(t, \tau) \), \( f_1(t, \tau) \) and \( f_2(t, \tau) \). These relationships can be established without finding an explicit series solution to the equations (34)–(36) of the Lebowitz-Rubinow model.

1. Cell age distribution \( \phi(t, a) \) and generation time distribution for mother cells \( f_1(t, \tau) \)

In Subsection II A, using the formalism of McKendrick-von Foerster model we have derived equation (28) which links cell age distribution \( \phi(t, a) \) with the generation time distribution \( f_1(t, \tau) \) for mother cells. The Lebowitz-Rubinow model provides us with an alternative, more convenient way to obtain this equation. The derivation given below requires less effort then derivation of (28) as there is no need for solving partial differential equation (17) - we need only the solution of a very simple equation (34).

Consider first the case \( a \geq t \). Using (39), (45), (48), (49) and (50) we obtain

\[
\phi(t, a) = \int_a^\tau \chi(t, a, \tau) d\tau = \int_a^\tau \chi_0(a - t, \tau)e^{-\sigma \Omega(t)} d\tau
\]

\[
= \int_{a-t}^\tau \chi_0(a - t, \tau)e^{-\sigma \Omega(t)} d\tau - \int_{a-t}^a \chi_0(a - t, \tau)e^{-\sigma \Omega(t)} d\tau
\]

\[
= \phi_0(a - t)e^{-\sigma \Omega(t)} - \frac{1}{N(t)} \int_{a-t}^a n(0, a - t, \tau) d\tau,
\] (55)

where \( \phi_0(a) \equiv \phi(0, a) \) is defined by (15), \( \chi_0(a, \tau) \equiv \chi(0, a, \tau) \) by (49) and \( a \equiv \max(a, \tau_0) \) by (31).

Now consider the integral in the last line of (55). We have

\[
\int_{a-t}^a n(0, a - t, \tau) d\tau = \int_{a-t}^a n(t - a + \tau, \tau, \tau) d\tau
\]

\[
= \int_{t-a+\tau}^{t-a+\phi} n(t', t' - t + a, t' - t + a) d\tau
\]

\[
= \int_{t-a+\phi-t}^{t-a+\phi} \Lambda(t')N(t')f_1(t', t' - t + a) dt'.
\] (56)
In [50] we have used (39) and (44). Combining (55) and (60) we finally obtain

\[ \phi(t, a) = \phi_0(a-t)e^{-\sigma \Omega(t)} - \int_{t-a-t+\sigma}^{t-a+\sigma \Omega(t)} e^{-\sigma \Omega(t)} \Lambda(t') e^{\sigma \Omega(t')} f_1(t', t' - t + a) dt'. \tag{57} \]

\( \phi(t, a) \) (57) is identical to the first line of (28) if one puts \( \tau_s = 0 \), hence \( a - t = a - t, \ a = a \). (When deriving (28) we have assumed \( \tau_s = 0 \).)

For \( a \leq t \) we have

\[ N(t) \phi(t, a) = n(t, a) = \int_{\tau_s}^{\tau_{1}} n(t, a, \tau) d\tau = \int_{\tau_s}^{\tau_{1}} n(t - a, 0, \tau) d\tau - \int_{\tau_s}^{\tau_{0}} n(t - a, 0, \tau) d\tau \]

\[ = n(t - a, 0) - \left( \int_{\tau_s}^{\tau_{0}} n(t - a + \tau, \tau) d\tau \right) \]

\[ = 2^s \Lambda(t - a) N(t - a) - \int_{t - a + \tau_s}^{t - a + \sigma} n(t', t' - t + a) dt' \]

\[ = 2^s \Lambda(t - a) N(t - a) - \int_{t - a + \tau_s}^{t - a + \sigma} \Lambda(t') N(t') f_1(t', t' - t + a) dt'. \tag{58} \]

Dividing both sides of the above equation by \( N(t) \) (55) we arrive at the second line of (28).

Note that for \( a < \tau_s \) the second term on the r.h.s. of (57) as well as the second term on the r.h.s. of the last line of (58) vanish, and we are left with the age distribution of cells which are too young to divide,

\[ \tilde{\phi}(t, a) = \left\{ \begin{array}{ll}
\phi_0(a-t)e^{-\sigma \Omega(t)} & \text{for } a \geq t, \\
2^s e^{\Omega(t-a)} e^{-\sigma \Omega(t)} \Lambda(t-a) & \text{for } a \leq t. 
\end{array} \right. \tag{59} \]

Formulas expressing both \( \phi(t, a) \) and \( \tilde{\phi}(t, a) \) through \( f_0(t, \tau) \), valid for \( t \geq a \) will be derived in Paragraph III C 4.

2. Newborn and mother cells: \( f_0(t, \tau) \) and \( f_2(t, \tau) \)

Using (39), (44) and (63), we can rewrite (35) as

\[ n(t, 0, \tau) = \Omega(t, \tau) = 2^s N(t) \Lambda(t) \int_{\tau_s}^{\tau_{1}} h(\tau|\xi, t) f_1(t, \xi) d\xi = 2^s N(t) \Lambda(t) f_0(t, \tau), \tag{60} \]

where generation time distributions of newborn cells \( f_0(t, \tau) \) is defined by (63). In this way we obtain

\[ f_0(t, \tau) \equiv \int_{\tau_s}^{\tau_{1}} h(\tau|\tau', t) f_1(t, \tau') d\tau'. \tag{61} \]

One can regard (61) as a definition of \( f_0(t, \tau) \), alternative to (63). If there are no mother-daughter generation time correlations we have

\[ h(\tau|\tau', t) = h(\tau|t) = f_0(t, \tau) = f(t, \tau). \tag{62} \]

Assuming \( t \geq \tau \) from (35), (39), (52) and (60) we get

\[ N(t) \Lambda(t) f_1(t, \tau) = n(t, \tau, \tau) = n(t - \tau, 0, \tau) \tag{63} \]

\[ = 2^s \int_{\tau_s}^{\tau_{1}} h(\tau|\xi, t - \tau) n(t - \tau, \xi, \xi) d\xi \]

\[ = 2^s N(t - \tau) \Lambda(t - \tau) \int_{\tau_s}^{\tau_{1}} h(\tau|\xi, t - \tau) f_1(t - \tau, \xi) d\xi \]

\[ = 2^s N(t - \tau) \Lambda(t - \tau) f_0(t - \tau, \tau). \]

\( N(t) \Lambda(t) dt \) is the total number of cell divisions in a population at time \( t \) and the factor \( 2^s \) takes into account the number of daughter cells remaining in the population after each cell division. Interpretation of the identity (63) is
simple: Cells dividing at time $t$ are those which were born at earlier time $t - \tau$ and at birth inherited generation time $\tau$ from their mothers, i.e. were ‘programmed’ to divide after reaching age $a = \tau$. Using \ref{eq:45} we get

$$f_1(t, \tau) = \frac{2\sigma \Lambda(t - \tau)e^{-\int_0^{t - \tau} \sigma \Lambda(t')dt'}}{\Lambda(t)} f_0(t, \tau).$$

(64)

For $\sigma = 1$ in the steady-state limit from \ref{eq:45} we obtain the well-known relationship between generation time distributions of newborn and mother cells \cite{17, 19, 29}

$$f_{1B}(\tau) = 2e^{-\Lambda \tau} f_{0B}(\tau),$$

(65)

where we have used the index function \ref{eq:48}. For $\sigma = 0$ (the mother machine or single cell lineage) in the same limit we obtain

$$f_{1F}(\tau) = f_{0F}(\tau).$$

(66)

For $t \geq \tau$, by combining \ref{eq:61} and \ref{eq:64} we obtain generalization of Eq. \ref{eq:18} of ref. \cite{17}:

$$f_0(t, \tau) = 2\sigma \int_{\tau}^{\tau_1} h(\tau|\tau', t) \frac{\Lambda(t - \tau')e^{-\int_0^{t - \tau'} \sigma \Lambda(t')dt'}}{\Lambda(t)} f_0(t - \tau', \tau')d\tau'.$$

(67)

In a similar manner from \ref{eq:61} and \ref{eq:64} or directly from \ref{eq:63} we get the analogous equation for $f_1(t, \tau)$, valid for $t \geq \tau$

$$f_1(t, \tau) = 2\sigma \int_{\tau}^{\tau_1} h(\tau|\tau', t - \tau) f_1(t - \tau, \tau')d\tau'.$$

(68)

Both \ref{eq:67} and \ref{eq:68} provide us with a relationship between the distribution of inherited generation times $h(\tau|\tau', t)$, the instantaneous population growth rate $\Lambda(t)$ and the generation time distribution of newborn or mother cells ($f_0(t, \tau)$ and $f_1(t, \tau)$, respectively) out of the steady state. Additionally, for $\sigma = 1$ \ref{eq:48} can help select the functional forms of $h(\tau|\tau', t)$ that are consistent with the experimental data (measured values of $\Lambda(t)$ and $f_1(t, \tau)$).

3. Generation time distribution for extant cells expressed through distributions of mothers and newborns

In order to find the relationship between generation time distribution $f_2(t, \tau)$ for extant cells and the distribution of just dividing cells $f_1(t, \tau)$ we can proceed in a way similar to that of Paragraph \ref{3.1} where we related $\phi(t, a)$ and $f_1(t, \tau)$ using definition of $\phi(t, a)$ \ref{eq:50} and properties of the Lebowitz-Rubinow model. Assume first that $t \geq \tau \geq a$. Using \ref{eq:61} we get

$$f_2(t, \tau) = \int_0^\tau \chi(t, a, \tau)da = \frac{1}{N(t)} \int_0^\tau n(t - a, 0, \tau)da$$

$$= \frac{1}{N(t)} \int_0^\tau n(t - a + \tau, \tau, \tau)da = \frac{1}{N(t)} \int_t^{t+\tau} n(t', \tau, \tau)dt'$$

$$= \frac{1}{N(t)} \int_t^{t+\tau} \Lambda(t')N(t')f_1(t', \tau)dt' = e^{-\sigma \Omega(t)} \int_t^{t+\tau} \Lambda(t')e^{\sigma \Omega(t')} f_1(t', \tau)dt'. $$

(69)

For $t \leq \tau$ the derivation is analogous but slightly more complicated as we have to consider two cases: $t \leq a$ and $t \geq a$,

$$f_2(t, \tau) = \int_0^t \chi(t, a, \tau)da + \int_t^\tau \chi(t, a, \tau)da = \frac{1}{N(t)} \int_0^t n(t - a, 0, \tau)da + \frac{1}{N(t)} \int_t^\tau n(0, a - t, \tau)da$$

$$= \frac{1}{N(t)} \int_0^t n(t - a + \tau, \tau, \tau)da + \frac{1}{N(t)} \int_t^\tau n(t - a + \tau, \tau, \tau)da = \frac{1}{N(t)} \int_t^{t+\tau} n(t', \tau, \tau)dt'$$

$$= \frac{1}{N(t)} \int_t^{t+\tau} \Lambda(t')e^{\sigma \Omega(t')} f_1(t', \tau)dt'. $$

(70)

From \ref{eq:69} and \ref{eq:70} we see that we have in fact a single formula for both $t \leq \tau$ and for $t \geq \tau$:

$$f_2(t, \tau) = \int_t^{t+\tau} e^{-\sigma \Omega(t')} e^{\sigma \Omega(t')} \Lambda(t')f_1(t', \tau)dt' = \int_t^{t+\tau} e^{\sigma \int_{t'}^{t} \Lambda(t')dt} \Lambda(t')f_1(t', \tau)dt'.$$

(71)
For \( t \geq \tau \) another relationship between \( f_2(t, \tau) \), \( f_1(t, \tau) \) and \( f_0(t, \tau) \) can be derived. We first define
\[
\nu(t, \tau) \equiv \int_0^\tau n(t, a, \tau) \, da = N(t) f_2(t, \tau).
\] (72)

To get the time-evolution equation for \( \nu(t, \tau) \) we integrate (33) with respect to \( a \) as in (72) and use the boundary condition (36). Making use of (41) we obtain
\[
\dot{\nu}(t, \tau) = n(t, 0, \tau) - n(t, \tau, \tau) = 2^\sigma \int_{\tau_a}^{\tau} h(\tau|\xi) f_1(t, \xi) N(t) \Lambda(t) \, d\xi - \int_{\tau_a}^{\tau} h(\xi|\tau) f_1(t, \tau) N(t) \Lambda(t) \, d\xi = [2^\sigma f_0(t, \tau) - f_1(t, \tau)] N(t) \Lambda(t).
\] (73)

In (73) one can easily identify gain and loss terms: the influx of newborn cells with generation time \( \tau \) and therefore \( f \tau \sigma \). Alternative way to obtain (77) has been given in ref. [19].

In the steady-state limit, for \( \sigma = 1 \) from (74) we obtain
\[ f_{1B}(\tau) + f_{2B}(\tau) = 2 f_{0B}(\tau). \] (76)

4. Cell number density \( n(t, a, \tau) \) expressed through generation time distributions \( f_0(t, \tau) \) and \( f_1(t, \tau) \)

Here we express the cell number density \( n(t, a, \tau) \) and the joint distribution of cell age and generation time \( \chi(t, a, \tau) \) using generation time distributions for newborn cells, \( f_0(t, \tau) \) or mother cells \( f_1(t, \tau) \). In what follows we must assume that \( t \geq a \). From (39), (60), (63) and (64) we obtain
\[ n(t, a, \tau) = 2^\sigma \Lambda(t-a) N_0 e^{\sigma \Omega(t-a)} f_0(t-a, \tau) = \Lambda(t-a+\tau) N_0 e^{\sigma \Omega(t-a+\tau)} f_1(t-a+\tau, \tau) \] (78)

and therefore
\[ \chi(t, a, \tau) = 2^\sigma \Lambda(t-a) e^{\sigma \Omega(t-a)} e^{-\sigma \Omega(t)} f_0(t-a, \tau) = \Lambda(t-a+\tau) e^{\sigma \Omega(t-a+\tau)} e^{-\sigma \Omega(t)} f_1(t-a+\tau, \tau), \]
(79)

with \( \Omega(t) \) given by (27). Note that although r.h.s of both (78) and (79) is defined for all \( \tau \in [\tau_s, \tau_l] \), the l.h.s of each of these two formulas makes sense only for \( \tau > a \).
For \( \sigma = 1 \) in the \( t \to \infty \) limit we have \( \Lambda(t) = \Lambda_B \), \( f_0(t-a, \tau) = f_{0B}(\tau) \) and \( \ref{78} \) reduces to
\[
n_B(t, a, \tau) = 2\Lambda_B N_0 f_{0B}(\tau) e^{(t-a)\Lambda_B} = \Lambda_B N_0 f_{1B}(\tau) e^{(t-a+\tau)\Lambda_B},
\]
which depends on the observation time only through the exponential factor \( \exp(\Lambda_B t) \). From \( \ref{19} \) and \( \ref{78} \) in the same limit we get
\[
\chi_B(a, \tau) = 2\Lambda_B f_{0B}(\tau) e^{-\Lambda_B a} = \Lambda_B f_{1B}(\tau) e^{\sigma(\tau-a)\Lambda_B}.
\]
For the mother machine case \( (\sigma = 0) \) we obtain \( \ref{19} \)
\[
\chi_F(a, \tau) = \chi_F(0, \tau) = \frac{f_{0F}(\tau)}{\int_{\tau_0}^{\tau} \xi f_{0F}(\xi) d\xi} = \Lambda_f f_{0F}(\tau).
\]
\( \chi(t, a, \tau) \) \( \ref{79} \) can be used to derive other distributions of interest: \( \phi(t, a) \) and \( f_i(t, \tau) \) for \( i = 0, 1, \) and 2. One can convince herself or himself that the resulting expression is in agreement with those derived in previous Subsections. First, from \( \ref{79} \) we find that
\[
\phi(t, 0) = \int_{\tau_0}^{\tau_1} \chi(t, 0, \tau) d\tau = 2^\sigma \Lambda(t),
\]
in accordance with \( \ref{54} \). We can also check that we indeed obtain correct expression \( \ref{53} \) for the generation time distribution of newborns,
\[
f_0(t, \tau) = \frac{\chi(t, 0, \tau)}{\phi(t, 0)} = \chi(t, 0, \tau).
\]
Next, consider the following probability distribution
\[
\check{\chi}(t, a, \theta) \equiv \chi(t, a, a + \theta) = \Lambda(t + \theta) e^{\sigma \Omega(t + \theta)} e^{-\sigma \Omega(t)} f_1(t + \theta, a + \theta),
\]
where \( \theta = \tau - a \), and the corresponding conditional distribution
\[
\check{\chi}(a|t, \theta) = \frac{\check{\chi}(t, a, \theta)}{\int_{\tau_0}^{\tau} \check{\chi}(t, a, \theta) d\theta}.
\]
For mother cells, \( \theta = 0 \) and we should have \( \check{\chi}(a|t, 0) = f_1(t, a) \). Indeed, using \( \ref{79} \) and \( \ref{22} \) we obtain
\[
\check{\chi}(a|t, 0) = \frac{\check{\chi}(t, a, 0)}{\int_{\tau_0}^{\tau} \check{\chi}(t, a, 0) da} = \frac{\chi(t, a, a)}{\int_{\tau_0}^{\tau} \chi(t, a, a) da} = f_1(t, a).
\]

5. \( f_2(t, \tau) \) and \( \phi(t, a) \) expressed through \( f_0(t, \tau) \)

Using \( \chi(t, a, \tau) \) \( \ref{79} \) we can obtain yet another expression linking \( f_0(t, \tau) \) and \( f_2(t, \tau) \), as well as an expression linking \( \phi(t, a) \) and \( f_0(t, \tau) \). Consider first \( f_2(t, \tau) \). From \( \ref{21} \) and \( \ref{79} \) we get
\[
f_2(t, \tau) = \int_{\tau_0}^{\tau} \check{\chi}(t, a, \tau) da = 2^\sigma e^{-\sigma \Omega(t)} \int_{t-\tau}^{t} \Lambda(t') e^{\sigma \Omega(t')} f_0(t', \tau) dt'.
\]
Now we have three apparently different equations relating \( f_2(t, \tau) \) to the remaining two generation time distributions \( (f_1(t, \tau) \) or \( f_0(t, \tau) ) : \) \( \ref{71} \), \( \ref{72} \) and \( \ref{77} \). However, using \( \ref{78} \) or \( \ref{79} \), one can show that for \( t \geq \tau \) all these three expressions are equivalent. (Only \( \ref{71} \) is defined both for \( t \geq \tau \) and for \( t \leq \tau \).)
All three expressions for \( f_2(t, \tau) \) mentioned above have simple and intuitive interpretation, which is best seen when they are rewritten in terms of cell number density \( \nu(t, \tau) = \int_{\tau_0}^{\tau} n(t, a, \tau) da = N(t) f_2(t, \tau) \) \( \ref{72} \). For \( \ref{79} \) this interpretation has been already discussed in Subsection \( \ref{11} \). \( \ref{72} \) expresses nothing but a bookkeeping of cells with generation time \( \tau \) entering and leaving the population from \( t_{\text{obs}} = t_0 \) to \( t_{\text{obs}} = t \). Now multiplying both sides of \( \ref{71} \) by \( N(t) \) we obtain
\[
\nu(t, \tau) = \int_{t}^{t+\tau} N(t') \Lambda(t') f_1(t', \tau) dt' = \int_{t}^{t+\tau} n(t', \tau, \tau) dt'.
\]
Equation (88) expresses the fact that all cells with a given value of generation time \( \tau \) which were present in the population at the observation time \( t \) (and only such cells) will divide during the time interval \([t, t + \tau]\). In contrast, cells born within this time interval and inheriting generation time \( \tau \) will divide after \( t_{\text{obs}} = t + \tau \).

In a similar manner, by multiplying both sides of (87) by \( N(t) \) we get
\[
\nu(t, \tau) = \int_0^\tau n(t, a, \tau) da = 2\sigma \int_{t-\tau}^t \Lambda(t') N(t') f_0(t', \tau) dt'.
\]  
(89)

Interpretation of (87) is the following: All cells with generation time \( t \) which is the steady state limit of (92). For cells born within this time interval and inheriting generation time already divided.

where \ref{17}, we have introduced quantity

The first line of (94) is Eq. (16) of ref. \[20\], the second is Eq. (9) of \[17\], whereas in the last line, following Powell

Equation (88) expresses the fact that all cells with a given value of generation time \( a \) and \( \theta(a) \) expressed through \( f_0(a, \tau) \). 

For \( \sigma = 1 \), the steady-state state limit of \ref{91} reads
\[
\phi(a) = \Lambda e^{-\Lambda a} \left( 2 - \int_0^a f_1(\tilde{a}) e^{\Lambda \tilde{a}} d\tilde{a} \right)
\]
\[
= 2\Lambda e^{-\Lambda a} \left( 1 - \int_0^a f_0(\tilde{a}) d\tilde{a} \right) = 2\Lambda e^{-\Lambda a} \bar{F}_0(a).
\]
(94)

The first line of \ref{92} is Eq. (16) of ref. \[20\], the second is Eq. (9) of \[17\], whereas in the last line, following Powell

where

\[
\bar{F}_0(a) \equiv 1 - \int_0^a f_0(\tilde{a}) d\tilde{a} = \int_\bar{a}^\tau f_0(\tilde{a}) d\tilde{a}
\]
(95)

which is the steady state limit of \ref{92}. For \( \sigma = 0 \) in the same limit from \ref{91} we obtain Eq. (D6) of ref. \[19\]
\[
\phi_F(a) = \frac{\bar{F}_0(a)}{\int_\bar{a}^\tau \xi f_0F(\xi) d\xi} = \Lambda_F \bar{F}_0F(a).
\]
(96)

6. Back to McKendrick-von Foerster model: \( \phi(t, a) \) and \( \gamma(t, a) \) expressed through \( f_0(t, \tau) \)

For all \( a \) and \( t \) the division rate \( \gamma(t, a) \) of the McKendrick-von Foerster model \[11\]—\[31\] corresponding to the given Lebowitz-Rubinow model is given by \[43\]
\[
\gamma(t, a) = \frac{n(t, a, a)}{n(t, a)} = \frac{\chi(t, a, a)}{\phi(t, a)}.
\]
(97)
But if \( t \geq a \) then using (13) and (78) we can express \( \gamma(t, a) \) in terms of the generation times distribution for newborn cells, \( f_0(t, \tau) \). Assuming first that \( a \geq \tau_s \), we obtain

\[
\gamma(t, a) = \frac{f_0(t-a, a)}{\int_a^\infty f_0(t-a, \tau) d\tau} = \frac{f_0(t-a, a)}{\bar{F}_0(t-a, a)}
\]  

(98)

where \( \bar{F}_0(t, a) \) is defined by (92). For \( a < \tau_s \) we have \( n(t, a, a) = 0 \), hence \( \gamma(t, a) = 0 \) and (98) is again correct. In the steady state from (98) we get (c.f. [19])

\[
\gamma(a) = \frac{f_0(a)}{\int_a^\infty f_0(\tau) d\tau} = \frac{f_0(a)}{\bar{F}_0(a)}
\]  

(99)

Once again we see that although the distribution of inherited generation times \( h(\tau|\tau', t) \) is not explicitly present in the equations of the McKendrick-von Foerster model, it does not mean that this model excludes the mother-daughter generation time correlations. From (98) we also see that in the presence of such correlations \( \gamma(t, a) \) may explicitly depend on the observation time \( t \), because in this case \( f_0(t, \tau) \) as given by (63) usually depends on \( t \).

Now assume that there are no mother-daughter generation time correlations and that the distribution of inherited generation times no longer depends on the observation time \( t \):

\[
h(\tau|\tau', t) = f(\tau).
\]  

(100)

In consequence, from (51) we obtain \( f_0(t, \tau) = f(\tau) \) and from (98) we see that the division rate of the McKendrick-von Foerster model no longer depends on \( t \): \( \gamma(t, a) = \gamma(a) \). In such a case we have

\[
f(a) = \gamma(a)e^{-\int_0^a \gamma(a') da'}.
\]  

(101)

Now following [13] we define

\[
\tilde{n}(t, a) = n(t, a)e^{\bar{F}_0 \gamma(a') da'}.
\]  

(102)

From (14), (59), (61) and (102) it follows that

\[
f(a)\tilde{n}(t, a) = \gamma(a)n(t, a) = n(t, a, a) = f_1(t, a)N(t)\Lambda(t) = 2^n N(t-a)\Lambda(t-a)f(a),
\]  

(103)

hence

\[
\tilde{n}(t, a) = 2^n N(t-a)\Lambda(t-a).
\]  

(104)

Using (1) and (2) we immediately get the following time-evolution equation and the boundary condition for \( \tilde{n}(t, a) \) given in ref. [13],

\[
0 = \frac{\partial \tilde{n}(t, a)}{\partial t} + \frac{\partial \tilde{n}(t, a)}{\partial a},
\]  

(105)

\[
\tilde{n}(t, 0) = 2^n \int_0^t f(a)\tilde{n}(t, a) da = n(t, 0) = 2^n \int_0^t \gamma(a)n(t, a) da.
\]  

(106)

From (105) we see that \( \tilde{n}(t, a) \) is a function of \( t - a \) only, in accordance with (104), i.e., \( \tilde{n}(t, a) = \tilde{n}(t-a, 0) \).

Eq. (103) can serve as a definition of \( \tilde{n}(t, a) \) in the general case, when division rate \( \gamma(t, a) \) depends on the observation time \( t \) and we can no longer use (102). From (91) and (104) we obtain the following formula for \( \tilde{\phi}(t, a) \) [59], i.e. the age distribution of cells which are too young to divide \( (a < \tau_s) \),

\[
\tilde{\phi}(t, a) = \frac{\tilde{n}(t, a)}{N(t)} = 2^n e^{\Omega(t-a)} e^{-\sigma(t)} \Lambda(t-a) = \frac{\phi(t, a)}{F_0(t-a, a)} = \bar{F}_0(t-a, a)
\]  

(107)

Combining (95) and (107) we finally obtain Eq. (35) expressed in terms of \( \tilde{n}(t, a) \) and \( f_0(t, a) \) or \( \gamma(t, \xi) \) and \( n(t, a) \)

\[
n(t, 0, \tau) = 2^n \int_{\tau}^{\tau_a} h(\tau|\tau', t)N(t)\Lambda(t)h(t, \xi) d\xi
\]  

\[
= 2^n \int_{\tau}^{\tau_a} h(\tau|\tau', t)2^n N(t-\xi)\Lambda(t-\xi)f_0(t-\xi, \xi) d\xi
\]  

\[
= 2^n \int_{\tau}^{\tau_a} h(\tau|\tau', t)\tilde{n}(t, \xi)f_0(t-\xi, \xi) d\xi
\]  

\[
= 2^n \int_{\tau}^{\tau_a} h(\tau|\tau', t)\gamma(t, \xi)n(t, \xi) d\xi.
\]  

(108)
When $\tau$ in (108) is integrated out, $h(\tau|\xi,t)$ is replaced with unity and we obtain the corresponding formulas for $\tilde{n}(t,0) = n(t,0)$, i.e., for the cell number density of the McKendrick-von Foerster model.

### D. Euler-Lotka equation for the population out of the steady state

Euler-Lotka equation provides a relationship between generation time distributions and population growth rate. For the population in the state of balanced exponential growth ($\sigma = 1$), corresponding to backward sampling (B) in the terminology of Refs. [22, 28], Euler-Lotka equation reads [17, 18, 25]

$$1 = 2 \int_{\tau_s}^{\tau_i} e^{-\Lambda t \tau} f_{0B}(\tau)d\tau = \int_{\tau_s}^{\tau_i} f_{1B}(\tau)d\tau.$$  \hspace{1cm} (109)

In this Subsection, we generalize (109) to the case of a population which is not in a state of balanced growth. As can be seen from (109), the Euler-Lotka equation is nothing but the normalization condition for certain probability distributions - hence it can be formulated in more than one way (by using different distributions). Below we provide the Reader with three different expressions, each of which may be called (and regarded as) the Euler-Lotka equation.

#### 1. Euler-Lotka equation as a normalization conditions for $f_1(t,\tau)$ and $f_0(t,\tau)$

Consider first the normalization condition for $f_1(t,\tau)$. Integrating both sides of (64) and keeping in mind that $\tau \leq t$ we obtain

$$\int_{\tau_s}^{\tilde{\tau}} f_1(t,\tau)d\tau = 2\sigma \int_{\tau_s}^{\tilde{\tau}} \Lambda(t-\tau)e^{-\int_{t-\tau}^{t-\tau_1} \sigma \Lambda(t')dt'} \frac{\Lambda(t)}{\Lambda(t)} f_0(t-\tau,\tau)d\tau,$$  \hspace{1cm} (110)

where $\tilde{\tau} \equiv \min(t,\tau_1)$ [11]. For $t \geq \tau_1$ we have $\tilde{\tau} = \tau_1$, the r.h.s. of (110) becomes equal to unity and we obtain

$$1 = 2\sigma \int_{\tau_s}^{\tau_i} \Lambda(t-\tau)e^{-\int_{t-\tau}^{t-\tau_1} \sigma \Lambda(t')dt'} \frac{\Lambda(t)}{\Lambda(t)} f_0(t-\tau,\tau)d\tau$$

$$= 2\sigma \int_{\tau_s}^{\tau_i} \int_{t-\tau}^{t-\tau_1} \Lambda(t-\tau)e^{-\int_{t-\tau}^{t-\tau_1} \sigma \Lambda(t')dt'} \frac{\Lambda(t)}{\Lambda(t)} h(\tau|\tau',t-\tau)f_1(t-\tau,\tau')d\tau'd\tau.$$  \hspace{1cm} (111)

Strictly speaking, if $\tau_1 = \infty$ then (111) is fulfilled only in the $t \to \infty$ limit, when we obtain Eq. (109) for $\sigma = 1$ and the normalization condition for $f_{0B}(\tau)$ (if $\sigma = 0$). But one may hope that there exists an intermediate time scale for which replacing $t$ by $\infty$ in (111) leading to (111) provides a very satisfactory approximation, yet the system is still far enough from the steady state. Therefore (111) can be regarded as the Euler-Lotka equation for the population out of the steady state, albeit not entirely satisfactory.

In the absence of mother-daughter generation-time correlations, equation (111) has an identical form but $f_0(t,\tau)$ is replaced by its uncorrelated counterpart, $f(t,\tau)$, see Eq. (62). (To stress the lack of correlations, following Refs. [17, 18, 25] in the present paper we use different symbol for the uncorrelated generation time distribution for newborns [17, 18, 25].)

Assume now that there are non-vanishing generation-time correlations only between the cell and its mother (this situation is termed ‘Markovian’ scenario in ref. [32]). Clearly, in such case the distribution of inherited generation times $h(\tau|\tau',t)$ depends only on generation time of the cell’s mother, $\tau'$, but not on generation times of cells from earlier generations. Yet, the converse does not have to be true: Distribution of inherited generation times of the form $h(\tau|\tau',t)$ does not imply lack of correlations between the cell and its grandmother, grand-grandmother, etc., see Appendix [E2].

Moreover, explicit time-dependence of $h(\tau|\tau',t)$ may be interpreted as a hallmark of such higher-order correlations. This is because one can define generalization of the Lebowitz-Rubinow model in which the generation times $\tau_i$, $i = 1, 2, \ldots, G$ of cells from $G > 1$ previous generations in the cell lineage are explicitly included: $\tau_1$ is generation time of the mother of a given cell, $\tau_2$ generation time of its grandmother, etc. (see Appendix [E2]). By integrating out $\tau_i$ variables for $i = 2, \ldots, G$, such model can be reduced to the effective one which assumes the form of the original
Lebowitz-Rubinow model of Section 11. In this way one may obtain distribution of inherited generation times which may explicitly depend on the observation time even for constant environmental conditions.

Using normalization of \( f_0(t, \tau) \) given by (67), for \( t \geq \tau_1 \) we obtain an identity similar to (113), which is also a candidate for the Euler-Lotka equation:

\[
1 = 2^\sigma \int_{\tau_a}^{\tau_1} \int_{\tau_s}^{\tau_1} h(\tau|\tau', t) \frac{\Lambda(t - \tau') e^{-\int_{\tau'}^{t} \sigma A(t') dt'}}{\Lambda(t)} f_0(t - \tau', \tau') d\tau' d\tau.
\]

(112)

Essentially all the above remarks concerning the properties and limitations of equation (111) apply to (112) as well.

2. Euler-Lotka equation as a normalization condition for \( f_2(t, \tau) \)

Euler-Lotka equation for the population in the state of unbalanced growth can be also formulated by employing the normalization of generation time distribution for newborn cells, \( f_2(t, \tau) \). Integrating both sides of (11) with respect to \( \tau \) we get

\[
1 = \int_{\tau_s}^{\tau_1} \int_{t}^{t+\tau} \Lambda(t') e^{\sigma \int_{t}^{t'} \Lambda(t) dt} f_1(t', \tau) dt' d\tau.
\]

(113)

In contrast to (111) now there are no restrictions for \( t \), as (71) is valid for both \( \tau \leq t \) and \( \tau \geq t \). For that reason we regard (113) as a better candidate for the generalized Euler-Lotka equation then (111).

Consider now the steady-state limit of (113). For \( \sigma = 1 \) we obtain the following condition

\[
1 = \int_{\tau_s}^{\tau_1} (e^{\Lambda_0 \tau} - 1) f_1(\tau) d\tau.
\]

(114)

which due to (65) is equivalent to (109). For \( \sigma = 0 \) we have in turn

\[
1 = \Lambda_F \int_{\tau_s}^{\tau_1} \tau f_1(\tau) d\tau = \Lambda_F \int_{\tau_s}^{\tau_1} \tau f_0(\tau) d\tau,
\]

(115)

which is normalization of the steady-state distribution \( f_{2F}(\tau) \) (90).

E. Solution to the equations of the Lebowitz-Rubinow (54)–(36) model by 'summing over the division histories'

The solution to the equations (54)–(36) of the Lebowitz-Rubinow model can be expressed as a series for the number density of cells \( n(t, a, \tau) \), summing over previous cell division. In [1] this solution (Eqs. (5)–(9) of that Reference) was obtained in a heuristic way before the formal solution (Eq. (25) of [1]) was derived. Here, our point of departure is the renewal equation (40), corresponding to Eq. (21) of ref. [1]. Instead of deriving only the series for \( n(t, a, \tau) \) (which would be just a repetition of the derivation due to Lebowitz and Rubinow in a slightly different notation), we present here similar series for various probability distributions. To do this, it is most convenient to first obtain such series for \( \Psi(t, \tau) \) (35).

1. Determination of \( \Psi(t, \tau) \)

Making use of (10) one can construct an explicit solution for \( n(t, 0, \tau) = \Psi(t, \tau) \), i.e. express \( \Psi(t, \tau) \) solely in terms of \( h(\tau|\tau', t) \) and the initial condition \( \Phi(a, \tau) \) (35). To do this, consider a cell division taking place at \( t = t_1 \) and assume that both daughters inherit the generation time \( \tau_0 \). Using (10) we obtain

\[
\Psi(t_1, \tau_0) = 2^\sigma \Theta(t_1 - \tau_0) \int_{\tau_s}^{\tau_1} h(\tau_0|\tau_1, t_1) \Psi(t_1 - \tau_1, \tau_1) d\tau_1
\]

\[
+ 2^\sigma \Theta(\tau_1 - t_1) \int_{\tau_s}^{\tau_1} h(\tau_0|\tau_1, t_1) \Phi(\tau_1 - t_1, \tau_1) d\tau_1,
\]

(116)
where both $\tau_1 \equiv \min(t_1, \tau_1)$ and $l \equiv \max(t, \tau_n)$ were defined by (11). The first term on the r.h.s. of (110) vanishes for $t_1 < \tau_n$ and the second one for $t_1 > \tau_1$, both conditions are ensured by an appropriate Heaviside step functions $\Theta(x)$. Now if $t_1 > \tau_n$ we can again use (110) in order to rewrite $\Psi(t_1 - \tau_1, \tau_1) = \Psi(t_2, \tau_1)$ where $t_2 = t_1 - \tau_1$ is the observation time of the cell division preceding that at $t_1$. We get

$$
\Psi(t_2, \tau_1) = 2^\sigma \Theta(t_2 - \tau_n) \int_{\tau_n}^{t_2} h(\tau_1 | \tau_2, t_2) \Psi(t_2 - \tau_2, \tau_2) d\tau_2 + 2^\sigma \Theta(t_1 - t_2) \int_{\tau_n}^{t_1} h(\tau_1 | \tau_2, t_2) \Phi(\tau_2 - \tau_2, \tau_2) d\tau_2.
$$

(117)

Combining (116) and (117) we obtain

$$
\Psi(t_1, \tau_0) = 2^\sigma \int_{\tau_0}^{\tau_1} h(\tau_0 | \tau_1, t_1) \Phi(\tau_1 - t_1, \tau_1) \Theta(\tau_1 - t_1) d\tau_1 + (2^\sigma)^2 \int_{\tau_0}^{\tau_1} \int_{\tau_0}^{\tau_1} h(\tau_0 | \tau_1, t_1) h(\tau_1 | \tau_2, t_2) \Phi(\tau_2 - t_2, \tau_2) \Theta(\tau_1 - t_2) \Theta(\tau_2 - t_2) d\tau_2 d\tau_1
$$

$$
+ (2^\sigma)^2 \int_{\tau_0}^{\tau_1} \int_{\tau_0}^{\tau_1} \int_{\tau_0}^{\tau_2} h(\tau_0 | \tau_1, t_1) h(\tau_1 | \tau_2, t_2) h(\tau_2 | \tau_3, t_3) \Phi(\tau_3 - t_3, \tau_3) \Theta(\tau_2 - t_3) \Theta(\tau_3 - t_3) d\tau_3 d\tau_2 d\tau_1.
$$

(118)

$t_2 < t_1$, hence $\Theta(t_2 - t_2) \Theta(t_1 - t_2) = \Theta(t_2 - t_2)$. We can continue in this manner, applying Eq. (110) to expand $\Psi(t_2 - \tau_2, \tau_2) = \Psi(t_3, \tau_1)$, where $t_3 = t_2 - \tau_2 = t_1 - \tau_1 - \tau_2$ and so on. Eventually, we obtain

$$
\Psi(t_1, \tau_0) = \sum_m \Psi_m(t_1, \tau_0),
$$

(119)

where

$$
\Psi_m(t_1, \tau_0) = (2^\sigma)^m \int_{\tau_0}^{\tau_1} \int_{\tau_0}^{\tau_2} \cdots \int_{\tau_0}^{\tau_{m-1}} \int_{\tau_0}^{\tau_1} \prod_{j=1}^{m} h(\tau_{j-1} | \tau_j, t_j) \Theta(\tau_1 - t_m) \Theta(t_{m-1} - t_2) \Phi(\tau_m - t_m, \tau_m) d\tau_m \cdots d\tau_1.
$$

(120)

$\tau_i$ is the duration of the $i$-th cell cycle: $\tau_i = t_i - t_{i+1}$ and $t_i = t_1 - \sum_{j=1}^{i-1} \tau_j$. What are the values of $m$ for which we may have a non-vanishing $m$-th term in the sum (119)? Define

$$
M_s = \lfloor t_1 / \tau_1 \rfloor, \quad M_i = \lfloor t_1 / \tau_i \rfloor
$$

(121)

where $\lfloor x \rfloor$ denotes the floor function or the integer part of $x$. Between $t = 0$ and $t = t_1$ there is no less than $M_i$ and no more than $M_s$ complete cell cycles. Therefore the lower bound of summation in (119) is $M_i + 1 \geq 1$, the upper bound is $M_s + 1$ and (119) can be rewritten as

$$
\Psi(t_1, \tau_0) = \sum_{m=M_i+1}^{M_s+1} \Psi_m(t_1, \tau_0).
$$

(122)

Still, in this restricted sum some terms may vanish due to the presence of $\Theta(t_{m-1} - \tau_s)$ and $\Theta(\tau_1 - t_m)$ factors. The procedure described above has the following intuitive interpretation: Knowing the initial condition at $t = 0$: $\Phi(a, \tau)$ we calculate 'sum over division histories'. Consider newborn cells being born at some $t_1 > 0$ and inheriting generation time $\tau_0$. The number of such cells is proportional to $\Psi(t_1, \tau_0)$. Cell division taking place at $t = t_1$ we may be either the first, or the second, or the third, . . . , etc. cell division in the cell lineage of the dividing cells since $t = 0$. $\Psi_m(t_1, \tau_0)$ is a contribution to $\Psi(t_1, \tau_0)$ coming from all 'trajectories' with $m$ cell divisions.

2. Determination of the population growth rate $\Lambda(t)$ and total cell number $N(t)$

Having $\Psi(t, \tau)$ given by (119) and (120) at our disposal we can express both $\Lambda(t)$ and $N(t)$ in terms of $h(\tau | \tau', t)$ and $\Phi(a, \tau)$ (36). First, integrating (61) with respect to $\tau$ or combining (63) and (10) we obtain

$$
\int_{\tau_s}^{\tau_1} \Psi(t, \tau) d\tau = 2^\sigma N(t) \Lambda(t).
$$

(123)
For $\sigma = 0$, (128) can be solved for the $\Lambda(t)$, as in this case $N(t) = N(0) = N_0$ and the value of $N_0$ is assumed to be known from the initial condition. For $\sigma = 1$ we can rewrite Eq. (46) in the following way

$$N(t) = N_0 + \int_{t_0}^{t} \Lambda(t') \Lambda(t')dt' = N_0 + \frac{1}{2} \int_{t_0}^{t} \int_{t_0}^{t} \Phi(t', \tau)d\tau dt', \quad (124)$$

and then (119), (120), (123) and (124) can be used to determine $\Lambda(t)$. In the above equation, integration with respect to $\tau$ replaces $h(\tau|\tau', t')$ with unity. Analogously, the only effect of the integration of $\Psi_m(t_1, \tau_0)$ (120) with respect to $\tau_0$ is that $h(\tau_0|\tau_1, t_1)$ factor is replaced by unity.

3. Determination of probability distributions of age and generation time

Now we can use (119) and (120) to obtain series for both $n(t, a, \tau)$ and for all probability distributions of interest. First, consider series expansion for $f_0(t, \tau)$,

$$f_0(t, \tau) = \sum_{m=M_1+1}^{M_{s+1}} f_{0|m}(t, \tau). \quad (125)$$

$f_{0|m}(t, \tau)$ can be immediately obtained from (60) and (120):

$$f_{0|m}(t_1, \tau_0) = \frac{2^{\sigma(m-1)}}{\Lambda(t_1)e^{\sigma t_1}} \int_{\tau_1}^{T_1} \cdots \int_{\tau_{M-1}}^{T_{M-1}} \prod_{j=1}^{m} h(\tau_{j-1}|\tau_j, t_j) \Theta(\tau_{j-}\tau_{m}) \Theta(\tau_{M-1}-\tau_s) \chi_0(\tau_m-\tau_{m}, \tau_{m})d\tau_m \cdots d\tau_1. \quad (126)$$

$f_{0|m}(t_1, \tau_0)d\tau_0$ is the probability that a cell born at $t = t_1$ inherited generation time $\tau = \tau_0$ and in its cell lineage there have been $m$ cell divisions since $t = 0$ including the division at $t = t_1$. Consequently, we should have $\sum_{m} \int_{\tau_0}^{T_1} f_{0|m}(t_1, \tau_0)d\tau_0 = 1$ for all $t_1$.

Now consider the central quantity of the Lebowitz-Rubinow model, i.e., cell number density $n(t, a, \tau)$. Using (39) and series solution for $\Psi(t, \tau)$ given by (122) and (120) we immediately obtained desired series expansion for $n(t, a, \tau) = \Psi(t-a, \tau)$ but only for $a \leq t$. For $a \geq t$ the solution is given by an initial condition: $n(t, a, \tau) = \Phi(a-t, \tau)$.

We can obtain similar series expansions for other quantities, most importantly for $\chi(t, a, \tau)$. This follows immediately from the solution for $n(t, a, \tau)$ and the definition (48). For $a \geq t$ we get

$$\chi_0(t, a, \tau) = \chi_0(a-t, \tau)e^{-\sigma \Omega(t)}, \quad t \leq a, \quad (127)$$

where $\chi_0(a, \tau)$ is given by (49). Note that we use here two different functions denoted by $\chi_0$, but they are differing by number of independent variables.

In turn, for $t \geq a$ using (79), (119) and (120) we get

$$\chi(t, a, \tau) = \sum_{m=M_1+1}^{M_{s+1}} \chi_m(t, a, \tau), \quad t \geq a, \quad (128)$$

where $\chi_m(t, a, \tau) = \Psi_m(t-a, \tau)/N(t)$ is given by

$$\chi_m(t, a, \tau) = \frac{2^{\sigma m}}{e^{\sigma t(t)}} \int_{\tau_s}^{T_1} \cdots \int_{\tau_s}^{T_{m-1}} \prod_{j=2}^{m} h(\tau_{j-1}|\tau_j, t_j) \Theta(\tau_{j-}\tau_{m}) \Theta(\tau_{M-1}-\tau_s) \chi_0(\tau_{m-}\tau_{m}, \tau_{m})d\tau_m \cdots d\tau_1. \quad (129)$$

Using (50) and (51), from (127) and (129) we immediately obtain the analogous series for $\phi(t, a)$ and $f_2(t, \tau)$. Explicitly, for $m = 0, 1, \ldots, M_1 + 1$ we have

$$\phi_m(t, a) = \int_{\tau_0}^{\tau_1} \chi_m(t, a, \tau)d\tau, \quad (130)$$

and

$$f_2|m(t, \tau) = \int_{0}^{\tau} \chi_m(t, a, \tau)da. \quad (131)$$
Now \( \phi_m(t, a) da \) is the probability that a cell's age at the observation time \( t \) is equal to \( a \) provided that in its cell lineage there have already been \( m \) cell divisions since \( t = 0 \). Clearly, we have also an analogous interpretation for \( f_{2|m}(t, \tau) \) and \( \chi_m(t, a, \tau) \). The probability of drawing a cell that belongs to the lineage with \( m \) divisions since \( t = 0 \) is therefore given by

\[
\begin{aligned}
p_m(t) &= \int_0^{\tau} \int_0^{\tau} \chi_m(t, a, \tau) d\tau da = \int_0^{\tau} \phi_m(t, a) da \\
&= \int_0^{\tau} \int_0^{\tau} \chi_m(t, a, \tau) d\tau da = \int_0^{\tau} f_{2|m}(t, \tau) d\tau,
\end{aligned}
\]

where \( m = 0, 1, \ldots, M_s + 1 \) and we assumed that \( \tau_1 \) is large enough that we may have \( p_0(t) \geq 0 \) (the probability that there hasn't been yet any cell division may be non-zero). Clearly, \( p_m(t) \) for different values of \( m = 0 \) are probabilities of mutually exclusive and exhaustive events, hence \( \sum_{m=0}^{M_s+1} p_m(t) = 1 \).

Finally, let us consider the generation time distribution for mothers, \( f_1(t, \tau) \). The explicit formula for \( f_1(t, \tau) \) in the form of a series can be obtained using (60), (63) and (126). Alternatively, one can also use for that purpose the renewal equation (10) rewritten as:

\[
\begin{aligned}
f_1^c(t, \tau) &= 2^\sigma \frac{\Lambda(t-\tau)e^{\Theta(t-\tau)}}{\Lambda(t)e^{\Theta(t)}} \int_{\tau_1}^{\tau} \Theta(t-\tau-\tau_s)h(\tau|\xi, t-\tau)f_1^c(t-\tau, \xi) d\xi \\
&+ 2^\sigma \frac{\Lambda(t-\tau)e^{\Theta(t-\tau)}}{\Lambda(t)e^{\Theta(t)}} \int_{\tau}^{\tau_1} \Theta(\tau_1-\tau + \tau)h(\tau|\xi, t-\tau)f_1^c(t-\tau, \xi) d\xi,
\end{aligned}
\]

where by \( f_1^c(t, \tau) \) we denote \( f_1(t, \tau) \) for \( t \leq \tau \) and \( f_1^c(t, \tau) \) is \( f_1(t, \tau) \) for \( t \geq \tau \). Consider mother cell which is just dividing at \( t = t_1 \) and its age is equal to \( \tau = \tau_1 \). We obtain

\[
f_1(t_1, \tau_1) = \sum_{m=M_s+1}^{M_s+1} f_{1|m}(t_1, \tau_1),
\]

where

\[
f_{1|m}(t_1, \tau_1) = \frac{2^\sigma (m-1)}{\Lambda(t_1)e^{\Theta(t_1)}} \int_{\tau_1}^{\tau_2} \cdots \int_{\tau_s}^{\tau_1} \int_{\tau_1}^{\tau_m} \prod_{j=2}^{m} h(\tau_{j-1}, t_j) \Theta(\tau_1 - t_m) \Theta(t_m - \tau_s) \chi_0(\tau_m - \tau_m, \tau_m) d\tau_m \ldots d\tau_2.
\]

\( f_{1|m}(t_1, \tau_1) \) corresponds to the situation when before the cell division which is just about to take place at \( t = t_1 \) there have been \( m - 1 \) cell divisions since \( t = 0 \). For \( m = 1 \) and \( m = 2 \) the above formula is valid, too. Explicitly, we have

\[
f_{1|1}(t_1, \tau_1) = \frac{\Theta(\tau_1 - t_1) \chi_0(\tau_1 - t_1, \tau_1)}{\Lambda(t_1)e^{\Theta(t_1)}}
\]

and

\[
f_{1|2}(t_1, \tau_1) = \frac{2^\sigma}{\Lambda(t_1)e^{\Theta(t_1)}} \int_{\tau_1}^{\tau_2} h(\tau_1, t_2) \Theta(\tau_1 - t_2) \Theta(t_1 - \tau_s) \chi_0(\tau_2 - t_2, \tau_2) d\tau_2.
\]

4. Series solutions: Final remarks

Observation time \( t_1 \) of the last cell division may be chosen at will. Therefore in all formulas of the present Subsection we can eventually make the following change in notation: \( t_1 \to t \) (or \( t_1 \to t - a \) in case of \( n(t, a, \tau) \) and \( \chi(t, a, \tau) \)) and \( \tau_0 \to \tau \).

The fact that the series expansions of the present Subsection have a finite number of terms is due to the condition \( \tau \geq \tau_s > 0 \), indispensable from the point of view of physics and biology. In contrast, the condition \( \tau_1 < \infty \) can be safely relaxed and we can put \( \tau_1 = \infty \). In such a case the series expansion always begins with the \( m = 1 \) or \( m = 0 \) term, depending on the probability distribution in question.

There is little hope for an exact analytical computation of the multiple integrals appearing in expressions like (120), (126), (128) or (135). Still, they can be evaluated numerically (using exact numerical integration), at least in principle.
The problem is that both the initial condition \( \Phi(a, \tau) \) and \( h(\tau | \tau', t) \) - the two quantities which from the point of view of the theoretical description are assumed to be given as an input to the model - are experimentally unobservable.

Still, (129) and other equations of this Subsection can be used to study the influence of the particular form of the initial condition \( \Phi(a, \tau) \) and \( h(\tau | \tau', t) \) distribution on the properties of the population dynamics. In particular, on the loss of synchronization of initially synchronous (or almost synchronous) population, on the rate of convergence to the stationary solution, or the details of oscillatory behavior (if present).

### F. Application of the present formalism: evaluation of the fitness landscapes

Fitness landscape for a phenotypic trait \( S \) is defined as

\[
H(t, s) = \Lambda_B(t) + \frac{1}{t} \ln \left[ P_B(t, s) \right] = \frac{1}{t} \ln \left[ \frac{P_B(t, s)}{P_F(t, s)} \right].
\]

In the above equation, \( P_B(t, s) \) is a backward probability \((\sigma = 1)\) for the phenotypic trait \( S \) \((s\) is a particular value of \( S \)), \( P_F(t, s) \) is the corresponding forward probability \((\sigma = 0)\) whereas

\[
\Lambda_B(t) = \frac{1}{t} \int_0^t \Lambda_B(t') dt' = \frac{1}{t} \Omega_B(t),
\]

is a time-averaged instantaneous population growth rate \( \Lambda_B(t) \), i.e. \( \Lambda(t) \) for the \( \sigma = 1 \) case. So far, we have used indices \( F = \ell(0) \) and \( B = \ell(1) \) only in expressions describing the steady-state limit, like \((55), (66) \) and \((77)\); the index function \( \ell(\sigma) \) was defined by \((38)\). But now we have to carefully distinguish between the quantities referring to a single cell line (or mother machine device; \( \sigma = 0 \), \( \ell(\sigma) = F \)) and those referring to the population growing in a batch culture \((\sigma = 1, \ell(\sigma) = B)\) also in the case of time-dependent quantities, as we did in \((138) \) and \((139)\).

In the long-time limit, the fitness landscape is flat: \( H(t, s) \) \((138)\) approaches a constant, equal to the steady-state value of the population growth rate

\[
\lim_{t \to \infty} H(t, \tau) = \Lambda_B = \lim_{t \to \infty} \Lambda_B(t).
\]

To obtain from \( H(t, s) \) any additional information (besides the value of \( \Lambda_B \)) we have to use time-dependent probability distributions of different phenotypic traits and the instantaneous population growth rate \( \Lambda_B(t) \). This is also the case if one wants to compute values of the quantities related to fitness landscape: Averaged fitness landscape and growth rate of the sub-population, proposed and analyzed in Refs. \(22, 27, 28\).

#### Cell age as a phenotypic trait

Perhaps the simplest choice for \( S \) is cell age: \( s = a \) in \((138)\). In ref. \(22\) the following formula has been given for \( H(t, a) \) in the case of vanishing mother-daughter correlations of generation time (Eq. (45) of that Reference, rewritten here in our notation):

\[
H(t, a) = \Lambda_B + \frac{1}{t} \ln \left[ \frac{\phi_B(a)}{\phi_F(a)} \right] = \frac{1}{t} \ln \left[ (t - a)\Lambda_B + \ln \left( 2\Lambda_B \Lambda_F^{-1} \right) \right].
\]

Yet the above expression can only be treated as an approximation to the true fitness landscape as it contains the time-independent probability distributions and steady-state values of \( \Lambda_B(t) \) and \( \Lambda_F(t) \): \( \Lambda_B \) and \( \Lambda_F = \lim_{t \to \infty} \Lambda_F(t) \). In other words, in \(22\) it has been assumed that for some finite \( t \) a system is (to a good approximation) already in the steady-state.

But if one computes the fitness landscape using time-dependent quantities, one obtains

\[
H(t, a) = \Lambda_{tB}(t) + \frac{1}{t} \ln \left[ \frac{\phi_B(t, a)}{\phi_F(t, a)} \right] = \Lambda_{tB}(t) + \frac{1}{t} \ln \left[ \frac{\phi_B(t, a)}{\phi_F(t, a)} \right] + \frac{1}{t} \ln \left[ \frac{\bar{F}_B(t - a, a)}{\bar{F}_F(t - a, a)} \right]
\]

\[
= \frac{1}{t} \int_0^{t - a} \Lambda_B(t') dt' + \frac{1}{t} \ln \left[ \frac{2\Lambda_B(t - a)}{\Lambda_B(t - a)} \right] + \frac{1}{t} \ln \left[ \frac{\bar{F}_B(t - a, a)}{\bar{F}_F(t - a, a)} \right],
\]

where \( \bar{F}_0(t, a) \) and \( \bar{\phi}(t, a) \) are defined by \((32)\) and \((107)\), respectively.
If there are no mother-daughter generation time correlations (this is the case that should be compared with (134)) then \( h(\tau'|\tau, t) = h(\tau|\tau') = f(t, \tau) = f_0(t, \tau) \). In consequence \( f_{AB}(t, \tau) = f_{FB}(t, \tau) = f_{0B}(t, a) = f_{0F}(t, a) \) and the last term in (142) vanishes. Still, the resulting expression essentially differs from (143). But in (142) we too did not compute \( H(t, a) \) explicitly, i.e. we did not express by \( h(\tau|\tau', t) \) and the initial condition (36). To do this, one must invoke the results of Section III E.

*Generation time as a phenotypic trait*

We can also treat the second variable of the Lebowitz-Rubinow model: Generation time \( \tau \) as a phenotypic trait. That seems to be a more natural and better choice than cell age \( a \) because \( \tau \) does not change with time and is more directly related to both the growth rate of a single cell and the population growth rate than \( a \) is. The distribution of \( \tau \) that should be used in (138) is \( f_2(t, \tau) \) because only this distribution of generation time is defined for all cells present in the population. Using equation (71), valid both for \( t \leq \tau \) and for \( t \geq \tau \) we get

\[
H(t, \tau) = \Lambda_B(t) + \frac{1}{t} \ln \left[ \frac{f_{2B}(t, \tau)}{f_{2F}(t, \tau)} \right] = \frac{\Omega_B(t)}{t} + \frac{1}{t} \ln \left[ \frac{e^{-\Omega_B(t)} \int_0^{t+\tau} e^{\Omega_B(t')} \Lambda_B(t') f_{1B}(t', \tau) \, dt'}{\int_0^{t+\tau} \Lambda_F(t') f_{1F}(t', \tau) \, dt'} \right] 
\]

\[
= \frac{1}{t} \ln \left[ \frac{\int_0^{t+\tau} e^{\Omega_B(t')} \Lambda_B(t') f_{1B}(t', \tau) \, dt'}{\int_0^{t+\tau} \Lambda_F(t') f_{1F}(t', \tau) \, dt'} \right] = \frac{1}{t} \ln \left[ \frac{\int_0^{t+\tau} e^{\Omega_B(t')} \gamma(t', \tau) \phi_B(t', \tau) \, dt'}{\int_0^{t+\tau} \gamma(t', \tau) \phi_F(t', \tau) \, dt'} \right],
\]

where the last equality follows from (7). As in the case of \( s = a \) and \( H(t, a) \) (142), in order to compute \( \Omega_B(t) \) exactly for arbitrary \( t \) (i.e. express \( H(t, \tau) \) using only \( h(\tau|\tau', t) \) and the initial condition \( \Phi(a, \tau) \) (69) one must use results of Section III E.

To proceed further, we apply the same approximation as in (141). Following ref. 22 we assume that all quantities may be replaced by their steady-state values but the system is sufficiently far from the true long-time limit \( (t \to \infty) \), where according to (140) we have \( H(t, \tau) = \Lambda_B \). Using (65) and (66) we then obtain

\[
H(t, \tau) = \Lambda_B + \frac{1}{t} \ln \left[ \frac{(e^{\Lambda_B \tau} - 1) f_{1B}(\tau)}{\Lambda_F \tau f_{1F}(\tau)} \right] = \Lambda_B + \frac{1}{t} \ln \left[ \frac{2 (1 - e^{-\Lambda_B \tau}) f_{0B}(\tau)}{\Lambda_F \tau f_{0F}(\tau)} \right].
\]

If generation times of mother and daughter are not correlated, we have \( f_{0B}(\tau) = f_{0F}(\tau) = f(\tau) \) and (144) can be simplified further: \( f(\tau) \) cancels and we get

\[
H(t, \tau) = \Lambda_B + \frac{1}{t} \ln \left[ \frac{2 (1 - e^{-\Lambda_B \tau})}{\Lambda_F \tau} \right].
\]

*G. Generalization of the Lebowitz-Rubinow model*

In this Subsection, we generalize the model of Lebowitz and Rubinow 11 given by Eqs. 54–56. Now we describe each cell not only by its age \( a \) and generation time \( \tau \) but also by its current volume \( V \) and a single cell growth rate \( \lambda \). The latter quantity is defined by the following equation

\[
\frac{dV}{da} = \lambda V,
\]

and we assume that \( \lambda \) depends neither on \( a \) nor on \( t \). In consequence, cell volume grows exponentially:

\[
V(a) = V_b e^{\lambda a},
\]

where \( V_b = V(0) \) is cell volume at birth. We also assume that just after cell division both daughter cells have the same volume, equal to half of the volume their common mother had at cell division.

\[
V_d = V(\tau) = 2V_b = 2V(0).
\]

Clearly, state variables are bounded from either below or above, the more general (least restrictive) such bounds being

\[
0 < \tau_s \leq \tau \leq \tau_l,
\]

\[
0 \leq \lambda_s \leq \lambda \leq \lambda_l < \infty
\]

\[
0 < s \leq V \leq V_l < \infty.
\]
In this subsection, we assume that all probability distribution and cell number densities automatically vanish for too small or too large values of the state variables. Therefore instead of finite lower and upper limits of integration with respect to \(a, \tau, V, \) or \(\lambda\) we put zero and infinity, respectively.

1. **Generalized McKendrick-von Foerster model**

Before we move to the promised generalization of the Lebowitz-Rubinow model, we need first an analogous generalization of the McKendrick-von Foerster model which will serve as our point of reference. Such generalized McKendrick-von Foerster model describes the time evolution of the number density of cells of age \(a\), volume \(V\) and single-cell growth rate \(\lambda\): \(n(t, a, V, \lambda)\) and is defined by the following set of equations [22]

\[
\frac{\partial n(t, a, V, \lambda)}{\partial t} + \frac{\partial n(t, a, V, \lambda)}{\partial a} + \frac{\partial [\lambda V n(t, a, V, \lambda)]}{\partial V} + \gamma(t, a, V, \lambda)n(t, a, V, \lambda) = 0,
\]

\[
n(t, 0, V, \lambda) = 2^{\sigma+1} \int_0^\infty \int_0^\infty h(\lambda|a, 2V, \lambda', t) \gamma(t, a, 2V, \lambda') n(t, a, 2V, \lambda') d\lambda d\lambda',
\]

\[
n(0, a, V, \lambda) = n_0(a, V, \lambda).
\]

Note that generation time \(\tau\) does not appear in the above equations. As previously, we have here \(\sigma = 1\) for batch culture and \(\sigma = 0\) for the single cell lineage or the "mother machine". Parametrized probability distribution \(h(\lambda|a, 2V, \lambda, t)\) appearing in [151] models inheritance of the single cell growth rate by a daughter cells at cell division. If one wants to describe continuous culture one needs to introduce the term \(D(t)n(t, a, V, \lambda)\) in [150], where \(D(t)\) is the fermenter dilution rate. The model defined by [150] - [152] is a special case of yet more general population balance model, see ref. [20] and Appendix C.

The total number of cells in a population is now given by

\[
N(t) = \int_0^\infty \int_0^\infty \int_0^\infty n(t, a, V, \lambda) d\lambda dV da.
\]

We also have

\[
\int_0^\infty \int_0^\infty \int_0^\infty \gamma(t, a, V, \lambda)n(t, a, V, \lambda) d\lambda dV da = \Lambda(t)N(t),
\]

where \(\Lambda(t)\) is an instantaneous population growth rate, appearing in the time-evolution for \(N(t)\): \(\dot{N}(t) = \sigma \Lambda(t)N(t)\). Now in analogy to the case of the original McKendrick-von Foerster model we define

\[
\phi(t, a, V, \lambda) \equiv \frac{n(t, a, V, \lambda)}{N(t)},
\]

and

\[
f_1(t, a, V, \lambda) = \frac{\gamma(t, a, V, \lambda)n(t, a, V, \lambda)}{\Lambda(t)N(t)}.
\]

\(\phi(t, a, V, \lambda)\) defined by [155] is the joint probability density function of \(a, V\) and \(\lambda\) for all cells in the population and \(f_1(t, a, V, \lambda)\) is analogous distribution for just dividing cells (mothers). If \(V\) and \(\lambda\) are marginalized out, \(\phi(t, a, V, \lambda)\) reduces to the cell age distribution \(\phi(t, a)\) [4] and \(f_1(t, a, V, \lambda)\) to \(f_1(t, a)\) [4]. From [150], [155] and [156] it follows that \(\phi(t, a, V, \lambda)\) obeys the following time-evolution equation

\[
\frac{\partial \phi(t, a, V, \lambda)}{\partial t} + \frac{\partial \phi(t, a, V, \lambda)}{\partial a} + \frac{\partial [\lambda V \phi(t, a, V, \lambda)]}{\partial V} + \sigma \Lambda(t)\phi(t, a, V, \lambda) + \Lambda(t)f_1(t, a, V, \lambda) = 0,
\]

whereas boundary and initial condition for \(\phi(t, a, V, \lambda)\) follow immediately from [151], [162] and [166].

2. **Generalized Lebowitz-Rubinow model**

Now we are ready to write down equations of the generalized Lebowitz-Rubinow model, describing the time-evolution of the number density \(n(t, a, \tau, V, \lambda)\) of cells of age \(a\), generation time \(\tau\), volume \(V\) and single-cell growth rate \(\lambda\):

\[
\frac{\partial n(t, a, \tau, V, \lambda)}{\partial t} + \frac{\partial n(t, a, \tau, V, \lambda)}{\partial a} + \frac{\partial [\lambda V n(t, a, \tau, V, \lambda)]}{\partial V} = 0,
\]
\[ n(t, 0, \tau, V, \lambda) = 2^{\sigma+1} \int_0^\infty \int_0^\infty h(\tau, \lambda|\tau', 2V, \lambda', t) n(t, \tau', \tau', 2V, \lambda') d\tau' d\lambda' \equiv \Psi(t, \tau, V, \lambda), \tag{159} \]

\[ n(0, a, \tau, V, \lambda) \equiv \Phi(a, \tau, V, \lambda). \tag{160} \]

As before, we have \( \sigma = 0 \) (corresponding to the forward sampling, \( F \)) for a single cell line or mother machine device and \( \sigma = 1 \) for the batch culture (corresponding to the backward sampling, \( B \)). \( h(\lambda, \tau|\tau', 2V, \lambda', t) \) in (159) is the probability distribution of inherited single-cell growth rate and generation time.

We see that in contrast to (150) and (151) the division rate \( \gamma(t, a, V, \lambda) \) does not appear in Eqs. (158) and (159). It is no longer needed, though, due to the introduction of generation time \( \tau \). Cell division strategy, described by \( \gamma(t, a, V, \lambda) \) in a generalized McKendrick-von Foerster model (150)–(152) is now encoded in the dependence of \( h(\lambda, \tau|\tau', 2V, \lambda', t) \) on \( \tau, V \) and \( \lambda \).

Time-evolution equation (158) of the generalized Lebowitz-Rubinow model may be solved by the method of characteristics or its solution may be guessed by considering the time evolution of the cell’s volume given by (147). We obtain

\[ n(t, a, \tau, V, \lambda) = \begin{cases} 
\Phi(a - t, \tau, V e^{-\lambda t}, \lambda)e^{-\lambda t} = n(0, a - t, \tau, V e^{-\lambda t}, \lambda)e^{-\lambda t} & \text{for } a \geq t, \\
\Psi(t - a, \tau, V e^{-\lambda a}, \lambda)e^{-\lambda a} = n(t - a, 0, \tau, V e^{-\lambda a}, \lambda)e^{-\lambda a} & \text{for } a \leq t. 
\end{cases} \tag{161} \]

Using (158) and (161) we get

\[ \Psi(t, \tau, V, \lambda) = 2^{\sigma+1} \int_0^\infty \int_0^\infty \int_t^\infty h(\tau, \lambda|\tau', 2V, \lambda', t) \Psi(t - \tau', \tau', 2V e^{-\lambda \tau'}, \lambda') e^{-\lambda' \tau'} d\tau' d\lambda' \]

\[ + \quad 2^{\sigma+1} \int_0^\infty \int_0^\infty \int_t^\infty h(\tau, \lambda|\tau', 2V, \lambda', t) \Psi(t' - t, \tau', 2V e^{-\lambda \tau'}, \lambda') e^{-\lambda \tau'} d\tau' d\lambda'. \tag{162} \]

Finally, from (161) and (162) we obtain generalization of Eq. (25) of ref. [11]: For \( t \leq a \), the solution is completely determined by the initial condition, and all we have to do is to rewrite the first line of (161),

\[ n(t, a, \tau, V, \lambda) = \Phi(a - t, \tau, V e^{-\lambda t}, \lambda)e^{-\lambda t}. \tag{163} \]

In turn, for \( t \geq a \) we get the following renewal equation

\[ n(t, a, \tau, V, \lambda) = 2^{\sigma+1} \int_0^\infty \int_0^\infty \int_{t-a}^t h(\tau, \lambda|\tilde{\tau}, 2V e^{-\lambda a}, \tilde{\lambda}, t - a) n(t - a - \tilde{\tau}, 0, \tilde{\tau}, 2V e^{-\lambda a - \tilde{\lambda} \tilde{\tau}}, \tilde{\lambda}) e^{-\lambda a - \tilde{\lambda} \tilde{\tau}} d\tilde{\tau} d\tilde{\lambda} \]

\[ + \quad 2^{\sigma+1} \int_0^\infty \int_0^\infty \int_{t-a}^\infty h(\tau, \lambda|\tilde{\tau}, 2V e^{-\lambda a}, \tilde{\lambda}, t - a) n(0, \tilde{\tau} - t + a, \tilde{\tau}, 2V e^{-\lambda a - \tilde{\lambda} (t - a)}, \tilde{\lambda}) e^{-\lambda a - \tilde{\lambda} (t - a)} d\tilde{\tau} d\tilde{\lambda}. \tag{164} \]

Using (163) and (164) one can construct series solution for \( n(t, a, \tau, V, \lambda) \), which corresponds to that given by Eqs. (5)–(9) of ref. [11] and which can be used to construct analogous series for other cell number densities and probability distributions, in a manner similar to what we did in Subsection III E.

Before we move further we must ensure that generalization of the Lebowitz-Rubinow model defined (158)–(160) can be consistently reduced to the generalized the McKendrick-von Foerster model (150)–(152). First, the cell number densities of these two models are related by

\[ n(t, a, \tau, V, \lambda) = \int_a^\infty n(t, a, \tau, V, \lambda) d\tau. \tag{165} \]

Exactly as we did before in the case of the original Lebowitz-Rubinow and McKendrick-von Foerster models, to obtain (160)–(162) we must integrate out \( \tau \) in Eqs. (158)–(160). It is not difficult to check that if this procedure is to be consistent, we must assume that

\[ n(t, a, a, V, \lambda) = \gamma(t, a, V, \lambda) n(t, a, V, \lambda) = \Lambda(t) N(t) f_1(t, a, V, \lambda). \tag{166} \]

Condition (166) is a generalization of (44). Moreover, the probability distribution of inherited single cell growth rate \( h(\lambda|a, V, \lambda', t) \) appearing in (151) must be given by

\[ h(\lambda|a, V, \lambda', t) = \int_0^\infty h(\tau, \lambda|a, V, \lambda', t) d\tau. \tag{167} \]
If the conditions (166) and (167) are satisfied then \( n(t, a, V, \lambda) \) defined by (165) is the solution to the equations (150)–(152) of the generalized McKendrick-von Foerster model with \( \gamma(t, a, V, \lambda) \) and \( h(\lambda|a, V, \lambda', t) \) defined by (166) and (167), respectively.

By making use of quantities appearing in the generalized McKendrick-von Foerster model (150)–(152) we have already defined two probability distributions: \( \phi(t, a, V, \lambda) \) (155) and \( f_1(t, a, V, \lambda) \) (156). Now closely following our analysis of the original Lebowitz-Rubinow model we define

\[
\chi(t, a, \tau, V, \lambda) \equiv \frac{n(t, a, \tau, V, \lambda)}{N(t)}.
\]

In analogy to (50) and (52), using (168) we can again define \( \phi(t, a, V, \lambda) \) and \( f_1(t, a, V, \lambda) \), but now as

\[
\phi(t, a, V, \lambda) = \int_a^\infty \chi(t, a, \tau, V, \lambda) d\tau,
\]

and

\[
f_1(t, \tau, V, \lambda) = \frac{\chi(t, \tau, V, \lambda)}{\Lambda(t)}.
\]

(For mother cells \( \tau \) is equal to \( a \).) We can also define the remaining two joint probability distributions of \( \tau, V \) and \( \lambda \) which are direct generalizations of generation time distributions of extant and newborn cells, respectively:

\[
f_2(t, \tau, V, \lambda) \equiv \int_0^\tau \chi(t, a, \tau, V, \lambda) da,
\]

and

\[
f_0(t, \tau, V, \lambda) \equiv \chi(t, \tau, V, \lambda|0) = \frac{\chi(t, 0, \tau, V, \lambda)}{2^\sigma \Lambda(t)} = \frac{n(t, 0, \tau, V, \lambda)}{2^\sigma N(t) \Lambda(t)}
\]

where

\[
\chi(t, \tau, V, \lambda|a) \equiv \frac{\chi(t, a, \tau, V, \lambda)}{\phi(t, a)}
\]

and

\[
\phi(t, a) = \int_0^\infty \int_0^\infty \phi(t, a, V, \lambda) d\lambda dV.
\]

Marginalization of \( V \) and \( \lambda \) in \( f_0(t, \tau, V, \lambda) \), \( f_1(t, \tau, V, \lambda) \) and \( f_2(t, \tau, V, \lambda) \) yields the corresponding generation time distributions: \( f_0(t, \tau) \), \( f_1(t, \tau) \) and \( f_2(t, \tau) \). Using (150), (159) and (172) we obtain

\[
f_0(t, \tau, V, \lambda) = 2^\sigma \int_0^\infty \int_0^\infty h(\tau, \lambda|\tau', 2V, \lambda', t)f_1(t, \tau', 2V, \lambda') d\tau' d\lambda'.
\]

Time-evolution equation for \( \phi(t, a, V, \lambda) \) is given by (157). For completeness we give here the time-evolution equation for \( f_2(t, \tau, V, \lambda) \), which generalizes Eq. (74)

\[
\frac{\partial}{\partial t} f_2(t, \tau, V, \lambda) + \lambda V \frac{\partial}{\partial V} f_2(t, \tau, V, \lambda) + [\sigma \Lambda(t) + \lambda] f_2(t, \tau, V, \lambda) = \Lambda(t) [2^\sigma f_0(t, \tau, V, \lambda) - f_1(t, \tau, V, \lambda)].
\]

Using (161) and (172) we can also immediately generalize (78) and (79). We get

\[
n(t, a, \tau, V, \lambda) = 2^\sigma \Lambda(t - a) N_0 e^{\sigma \Omega(t - a)} e^{-\lambda a} f_0(t - a, \tau, V e^{-\lambda a}, \lambda)
\]

and

\[
\chi(t, a, \tau, V, \lambda) = 2^\sigma \Lambda(t - a) e^{\sigma \Omega(t - a) - \sigma \Omega(t) - \lambda a} f_0(t - a, \tau, V e^{-\lambda a}, \lambda).
\]

In the steady-state limit from (158) we obtain

\[
\chi_{\ell(\sigma)}(a, \tau, V, \lambda) = 2^\sigma \Lambda_{\ell(\sigma)} \exp \left[ -(\sigma \Lambda_{\ell(\sigma)} + \lambda a) \right] f_0(\tau, V e^{-\lambda a}, \lambda),
\]
where the index function $\ell(\sigma)$ is defined by (38): $\ell(0) = F$ and $\ell(\sigma) = B$. After integrating out $V$ and $\lambda$, cell number densities and probability distributions of the present generalized model reduce to the corresponding quantities of the original Lebowitz-Rubinow model defined in Section II.B. More generally, the same is also the case for the model equations (108)–(110). This is straightforward for both the time evolution equation (108) and the initial condition (109). However, in order to reduce the boundary condition (109) to (35) we must use the formal trick and introduce an effective $h_{\text{eff}}(\tau|\tau', t)$ defined by
\[ h_{\text{eff}}(\tau|\tau', t) \equiv \frac{2 \int_0^\infty \int_0^\infty h(\tau, \lambda|\tau', 2V, \lambda, t)n(t, \tau', \tau', 2V, \lambda)d\lambda d\lambda' dv}{\int_0^\infty \int_0^\infty n(t, \tau, \tau', V, \lambda)d\lambda d\lambda' dv}. \tag{180} \]
(This is necessary if probability distribution of inherited single cell growth rate and generation time, $h(\lambda, \tau, |\tau', 2V, \lambda, t)$ depends on $V$ and $\lambda$ in a nontrivial way, which is assumed to be the case here).

Therefore if $h(\tau|\tau', t)$ in (35) is given by (180) then all results valid for the Lebowitz-Rubinow model remain valid for its generalized counterpart. In particular, (123) and (124) can be again used to determine both $\Lambda(t)$ and $N(t)$.

The model presented in this Section can be generalized in several ways - in particular to the case of cell division during which mother cell divides into two unequal daughters (i.e., sister cells may differ with respect to their volume at birth), hence for which the condition (137) is not obeyed. One can also consider cell volume growth which is not exponential, i.e. not given by (137). Instead of (136) we have then a more general evolution equation for $V$
\[ \dot{V} = G(t, a, \tau, V), \tag{181} \]
where $G(t, a, \tau, V)$ depends on parameters ($\lambda_1, \lambda_2, \ldots, \lambda_P) \equiv \vec{\lambda}$ which may be stochastic variables. In such a situation instead of cell number density $n(t, a, \tau, V, \lambda)$ appearing in (108)–(110) we have $n(t, a, \tau, V, \vec{\lambda})$.

IV. CONCLUDING REMARKS

We studied here an extension of the McKendrick-von Foerster model, proposed by Lebowitz and Rubinow [11]. The analytical framework of the latter model allowed us to generalize the seminal results of Powell [17] to the case of cell populations out of the steady state of balanced growth. We derived exact relationships between cell age and generation time probability distributions, cell number densities, and the instantaneous population growth rate. Such relationships were found decades ago for the case of steady-state (balanced growth), but to the best of our knowledge were not yet derived for the time-dependent situation of unbalanced population growth. We found several exact relationships which could be - at least in principle - compared with the experimental data. In particular, we derived three generalizations of the Euler-Lotka equation.

But not all probability distributions appearing in the approach of Powell and the Lebowitz-Rubinow model are experimentally observable [20]. Therefore the role of the mathematical modeling of cell population dynamics is also to express unobservable quantities through observable ones. For that reason, we established identities linking unobservable distributions of generation time for newborn and extant cells with observable distribution for just dividing cells (mothers).

The solution to the equations of the Lebowitz-Rubinow model derived in [11] has a form of a series, summing over previous cell generations. We constructed here analogous series solutions for generation-time and cell age distributions. In principle, such series, involving multiple integrals, cannot be evaluated analytically, but it should be possible to compute them by means of exact numerical integration. These would allow one to investigate the influence of the initial condition and the probability distribution of inherited generation times on the properties of the solution of the Lebowitz-Rubinow model.

Analytical results derived here can be tested not only experimentally but also using stochastic simulations. Conversely, our results may be used to test the results of numerical simulations.

In contrast to Lebowitz and Rubinow, who obtained the McKendrick-von Foerster equation from their model only for a special, separable form of the initial condition [11], we showed here that the Lebowitz-Rubinow model can always be reduced to the corresponding McKendrick-von Foerster model. We also discussed a connection between the Lebowitz-Rubinow model and the model based on the ‘maturity representation’, proposed by Rubinow in 1968 [29], see Appendix C.

The present results can be generalized in several ways. First, we proposed an extension of the Lebowitz-Rubinow model in which each cell is described not only by its age and generation time but also by its growth rate (volume growth rate) and current volume. (Detailed investigation of this model will be given elsewhere.) Second, within the original model of Lebowitz and Rubinow, only the mother-daughter generation time correlations were explicitly included. For
that reason, we considered here yet another generalization of the latter model, which explicitly takes into account non-vanishing correlations between more distant generations (see Appendix E). Such extended Lebowitz-Rubinow model reduces to the original one after integrating out generation times of grandmother, grand-grandmother, etc., of a given cell.

V. AUTHOR CONTRIBUTIONS

JJ designed the study, performed analytical calculations, and wrote the paper. MR and A O-M wrote and reviewed the manuscript.

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Appendix A: Alternative formulation of the Lebowitz-Rubinow model

Cell number density \( n(t, a, \tau) \) of the Lebowitz-Rubinow model has no interpretation for \( \tau < a \). We may exclude such points of the first quadrant of the \( a-\tau \) plane 'by hand' by defining

\[
\Theta(\tau - a) \quad n(t, a, \tau),
\]

(\text{A1})

\(\Theta(x)\) is Heaviside step function. But \( n(t, a, \tau) \) \text{[A1]} does not obey Eq. \( \text{[34]} \), so if we want to use \( n(t, a, \tau) \) instead of \( n(t, a, \tau) \) we must also modify time-evolution equation of the Lebowitz-Rubinow model. It turns out that a change from \( n(t, a, \tau) \) to \( n(t, a, \tau) \) forces us to introduce the following singular 'division rate',

\[
\gamma_c(t, a, \tau) = 2 \delta(\tau - a),
\]

(\text{A2})

were \( \delta(\tau - a) \) is Dirac delta distribution. The rationale for the factor 2 in \( \text{[A2]} \) will be given in a moment. Eq. \( \text{[A2]} \) reflects the fact that regardless the observation time \( t \) each cell divides exactly when \( a = \tau \). In consequence, instead of \( \text{[34]} \) we have now

\[
\frac{\partial}{\partial t} n(t, a, \tau) + \frac{\partial}{\partial a} n(t, a, \tau) + \gamma_c(t, a, \tau) n(t, a, \tau) = 0.
\]

(\text{A3})

Introduction of \( \gamma_c(t, a, \tau) \) affects not only the form of the time-evolution equation but also the boundary condition,

\[
n(t, 0, \tau) = 2^\sigma \int_{\tau_s}^{\tau_l} \int_{\tau_s}^{\tau_l} h(\tau'|\tau, t) \gamma_c(t, a', \tau') n(t, a', \tau') d\tau' da' = \Psi(t, \tau) = \Psi(t, \tau) = n(0, 0, \tau).
\]

(\text{A4})

Note however, that \text{[A4]} is fully equivalent to \text{[55)}. Finally, the initial condition reads

\[
n(t, 0, \tau) = \Phi_0(a, \tau).
\]

(\text{A5})

Note that now the limits of integrations with respect to \( a \) and \( \tau \) are different than in Eqs. \( \text{[34]} \) and \( \text{[55]} \) because \( \Theta(\tau - a) \) appearing in the definition \text{[A1]} of \( n(t, a, \tau) \) automatically excludes points for which \( a > \tau \).

Written in the form \text{[A3]}–\text{[A5]}, the Lebowitz-Rubinow model more closely resembles the McKendrick-von Foerster model \text{[1]}–\text{[3]} (as compared with the formulation based on Eqs. \text{[34]}–\text{[50]}). It should be also more clear that the former model reduces to the latter when \( \tau \) is integrated out. For example, the division rate \( \gamma(t, a) \) of the McKendrick-von Foerster model (which is an ordinary function of \( a \)) is given by

\[
\gamma(t, a) = \frac{\int_{\tau_s}^{\tau_l} \gamma_c(t, a, \tau) n(t, a, \tau) d\tau}{\int_{\tau_s}^{\tau_l} n(t, a, \tau) d\tau}.
\]

(\text{A6})
We also exclude here state variables like generation time \( \tau \) where \( \lambda \) grow exponentially according to (146): cell age \( a \) models. In such models each cell is characterized not only by its age but also by other state variables:

in Subsection III E in a form of the series summing over cell divisions.

Some of the \( \omega_i \) may remain constant during the cell cycle, e.g. cell volume growth rate \( \omega \). Some of the \( \omega_i \) may be modeled as deterministic, as in the case of the original McKendrick-von Foerster equation. But due to (48), the dependence of \( \gamma \) and the initial condition follows from (36) and (48). The solution to (B1) may be found by the method of characteristics, as in the case of the original formulation of the Lebowitz-Rubinow model. For non-dynamical variables like \( \omega \) (which is assumed deterministic) may be modeled as deterministic, although details of the calculations are different (e.g. different limits of integration).

One can check that using Eqs. (A3)–(A5) we obtain identical results as in the case of the original formulation of the Lebowitz-Rubinow model, although details of the calculations are different (e.g. different limits of integration).

For completeness here we provide the Reader with the time-evolution equation for \( \chi(t, a, \tau) \) as in the case of the standard form of the Lebowitz-Rubinow model.

### Appendix B: Time-evolution equation for the joint probability density of cell age and generation time \( \chi(t, a, \tau) \)

For completeness here we provide the Reader with the time-evolution equation for \( \chi(t, a, \tau) \). From (34), (45) and (48) we obtain

\[
\frac{\partial \chi(t, a, \tau)}{\partial t} + \frac{\partial \chi(t, a, \tau)}{\partial a} + \sigma \Lambda(t) \chi(t, a, \tau) = 0.
\]  

(B1)

One may derive time-evolution equations for \( f_2(t, \tau) \) and \( \phi(t, a) \) by integrating (B1) with respect to \( a \) and \( \tau \), respectively.

The boundary condition for \( \chi(t, a, \tau) \) is obtained from (35) and (48),

\[
\chi(t, 0, \tau) = 2^\sigma \int_{\tau_0}^{\tau_1} h(\tau, \xi, t) \chi(t, \xi, \xi) d\xi = 2^\sigma \Lambda(t) f_0(t, \tau),
\]

(B2)

and the initial condition follows from (36) and (48). The solution to (B1) may be found by the method of characteristics, as in the case of the original McKendrick-von Foerster equation. But due to (48), the dependence of \( \chi(t, a, \tau) \) on \( t, a \) and \( \tau \) is known once we know the explicit form of the corresponding dependence for \( n(t, a, \tau) \). The later is given in Subsection III E in a form of the series summing over cell divisions.

### Appendix C: Derivation of the McKendrick-von Foerster model from a general population balance model

Equations (1)–(3) of the McKendrick-von Foerster model can be derived from a more complex population balance models. In such models each cell is characterized not only by its age but also by other state variables:

\[
(\omega_1, \omega_2, \ldots, \omega_d) \equiv \vec{\omega} \in \Omega \subset \mathbb{R}^d.
\]

(C1)

Some of the \( \omega_i \)'s may have non-trivial dynamics, the most obvious example being cell volume \( V \) or length. But some variables may remain constant during the cell cycle, e.g. cell volume growth rate \( \lambda \). Still, the time-evolution of \( \vec{\omega} \) (which is assumed deterministic) may be modeled as

\[
\dot{\vec{\omega}} = \vec{g}(t, a, \vec{\omega}),
\]

(C2)

or \( \dot{\omega_i} = g_i(t, a, \omega_1, \omega_2, \ldots, \omega_d), \ i = 1, 2, \ldots, d. \) The dot denotes derivative with respect to the observation time \( t \) or cell age \( a \) (either derivative can be used during each cell cycle). For example, cell volume \( V \) is frequently assumed to grow exponentially according to (146):

\[
\dot{V} = \lambda V,
\]

(C3)

where \( \lambda \) is constant, \( \lambda = 0 \). For non-dynamical variables like \( \lambda \) the corresponding \( g_i(t, a, \vec{\omega}) \) functions are equal to zero. We also exclude here state variables like generation time \( \tau \), which are values of dynamical variables at cell division.
Models in which such variables are present belong to the same class as the Lebowitz-Rubinow model - there is no division rate in the time-evolution equation of such model, or at least no division rate which is an ordinary function, as there can be singular one proportional to Dirac delta, see Appendix A.

The basic quantity here is the number density of cells, \( n(t,a,\vec{\omega}) \). We assume that \( n(t,a,\vec{\omega}) \) obeys the following population-balance equation [20]

\[
\left[ \partial_t + \partial_a + \gamma(t,a,\vec{\omega}) + D(t) \right] n(t,a,\vec{\omega}) = -\nabla\vec{\omega} \left[ \tilde{g}(t,a,\vec{\omega}) n(t,a,\vec{\omega}) \right],
\]

where \( \nabla\vec{\omega} = (\partial_{\omega_1}, \partial_{\omega_2}, \ldots, \partial_{\omega_d}) \) and \( \partial_a = \partial / \partial a \). \( \text{(C4)} \) must be supplemented with the boundary condition

\[
n(t,0,\vec{\omega}) = 2^a \int_0^1 \int_{\Omega} K(\vec{\omega}|t,a,\vec{\omega}') \gamma(t,a,\vec{\omega}') n(t,a,\vec{\omega}') d\vec{\omega}' da,
\]

(C5)

and

\[
\bar{g} = \tilde{g}(t,a,\vec{\omega}) n(t,a,\vec{\omega}) \bigg|_{\vec{\omega} \in \partial \Omega}
\]

(\( \partial \Omega \) denotes the boundary of \( \Omega \subset \mathbb{R}^d \))[20] as well as with the initial condition

\[
n_0(a,\vec{\omega}) = n(0,a,\vec{\omega}).
\]

(C7)

The kernel \( K(\vec{\omega}|t,a,\vec{\omega}') \) describing inheritance of \( \vec{\omega} \) is a probability distribution of \( \vec{\omega} \) parametrized by \( t, a, \vec{\omega}' \), therefore for arbitrary \( t, a \) and \( \vec{\omega}' \) we have

\[
1 = \int_{\Omega} K(\vec{\omega}|t,a,\vec{\omega}') d\vec{\omega}.
\]

(C8)

Let

\[
n(t,a) = \int_{\Omega} n(t,a,\vec{\omega}) d\vec{\omega},
\]

(C9)

where \( n(t,a,\vec{\omega}) \) is the solution to \( \text{(C4)} \) obeying \( \text{(C5)}, \text{(C6)}, \text{and (C7)} \). The r.h.s of \( \text{(C4)} \) integrated with respect to \( \vec{\omega} \) vanishes due to Ostrogradsky-Gauss theorem and \( \text{(C6)} \). We obtain

\[
\left[ \partial_t + \partial_a + \gamma_e(t,a) + D(t) \right] n(t,a) = 0,
\]

(C10)

where an effective division rate is defined as

\[
\gamma_e(t,a) = \frac{\int_{\Omega} \gamma(t,a,\vec{\omega}) n(t,a,\vec{\omega}) d\vec{\omega}}{\int_{\Omega} n(t,a,\vec{\omega}) d\vec{\omega}}.
\]

(C11)

Next, integrating \( \text{(C5)} \) with respect to \( \vec{\omega} \) and using \( \text{(C8)}, \text{(C13)}, \text{and (C11)} \) we get

\[
n(t,0) = 2^a \int_0^1 \gamma_e(t,a) n(t,a) da.
\]

(C12)

Clearly, \( \text{(C10)} \) is identical to \( \text{(1)} \) whereas \( \text{(C12)} \) is identical to \( \text{(2)} \) provided we identify \( \gamma_e(t,a) \) with \( \gamma(t,a) \). Reduction of the initial condition \( \text{(C7)} \) to \( \text{(3)} \) is obvious. In this way we obtain the von Foerster - McKendrick model \( \text{(1) - (3)} \) from the general population balance model given by \( \text{(C4) - (C7)} \). Obviously, many different models may yield the same effective von Foerster - McKendrick model.

Cell number density of the general population-balance model \( \text{(C4) - (C7)} \) normalized by a total number of cells in a population, \( N(t) \), has a natural interpretation of the probability density:

\[
p(t,a,\vec{\omega}) = \frac{n(t,a,\vec{\omega})}{\int_0^1 \int_{\Omega} n(t,a,\vec{\omega}) d\vec{\omega} da} = \frac{n(t,a,\vec{\omega})}{N(t)}.
\]

(C13)

But we may also define the following probability distribution function

\[
f_1(t,a,\vec{\omega}) = \frac{\gamma(t,a,\vec{\omega}) n(t,a,\vec{\omega})}{\int_0^1 \int_{\Omega} \gamma(t,a,\vec{\omega}) n(t,a,\vec{\omega}) d\vec{\omega} da}.
\]

(C14)

The denominator of the above expression is equal to \( \Lambda(t) N(t) \). One can replace \( \gamma(t,a,\vec{\omega}) n(t,a,\vec{\omega}) \) with \( \Lambda(t) f_1(t,a,\vec{\omega}) \) in \( \text{(C4)} \) and \( \text{(C5)} \), in analogy to the step made when going from \( \text{(14)} \) to \( \text{(17)} \). Then instead of introducing \( \gamma_e(t,a) \) \( \text{(C11)} \), following [20] we may marginalize \( f_1(t,a,\vec{\omega}) \) \( \text{(C14)} \) with respect to \( \vec{\omega} \) to obtain age distribution of the dividing cells (mothers),

\[
f_1(t,a) = \int_{\Omega} f_1(t,a,\vec{\omega}) d\vec{\omega}.
\]

(C15)
Appendix D: Existence and uniqueness of the solution to the renewal equation (40)

There exists a vast body of purely mathematical literature devoted to population models, in particular to the Lebowitz-Rubinow model. Such works are usually focused on the existence of the solution and its properties (e.g. is the solution unique, or does it exhibit chaotic behavior)?

Here, we give a simple proof that the solution of the Lebowitz-Rubinow model is unique provided we exclude 'pathological' forms of the distribution of inherited generation times $h(\tau|\tau', t)$. The proof breaks down for $h(\tau|\tau', t)$ containing part proportional to Dirac delta, $h(\tau|\tau', t) \sim \delta(\tau - \tau')$, for example for $h(\tau|\tau', t) = \beta \delta(\tau - \tau') + (1 - \beta) f(\tau)$ studied in [11], if $\beta \neq 0$. In such cases, the uniqueness of the solution and even the existence of the steady-state solution is not guaranteed.

Following [32, 37], in the space of continuous real functions of two variables $\Psi : [0, T] \times [\tau_s, \tau_l] \rightarrow \mathbb{R}$ we define the following norm:

$$
\|\Psi(t, \tau)\|_\omega = \max \left\{ e^{-\omega t} |\Psi(t, \tau)| : t \in [0, T], \tau \in [\tau_s, \tau_l] \right\},
$$

where

$$
\omega = 2 \max \left\{ 2^\sigma h(\tau|\tau', t) : t \in [0, T]; \tau, \tau' \in [\tau_s, \tau_l] \right\}.
$$

Using renewal equation (40) for a given initial condition $\Phi(t, \tau)$ we define

$$
S[\Psi(t, \tau)] = 2^\sigma \Theta(t - \tau_s) \int_{\tau_s}^{T} h(\tau|\tau', t) \Psi(t - \xi, \xi) d\xi
+ 2^\sigma \Theta(\tau_l - t) \int_{\xi}^{\tau_l} h(\tau|\tau', t) \Phi(\xi - t, \xi) d\xi.
$$

The uniqueness of the solution to (40) may be proved by invoking the Banach contraction principle applied to operation $S$ defined by (D3). Namely, we will show that for two solutions to (40): $\Psi(t, \tau)$ and $\Psi'(t, \tau)$ with the same initial condition ($\Phi(t, \tau) = \Phi'(t, \tau)$) we have

$$
\|S\Psi - S\Psi'\|_\omega = \max \left\{ e^{-\omega t} |S\Psi(t, \tau) - S\Psi'(t, \tau)| : t \in [0, T], \tau \in [\tau_s, \tau_l] \right\} \leq \frac{1}{2} \|\Psi - \Psi'\|_\omega.
$$

Indeed,

$$
|S\Psi(t, \tau) - S\Psi'(t, \tau)| = \left| \int_{\tau_s}^{T} 2^\sigma h(\tau|\tau', t) [\Psi(t - \xi, \xi) - \Psi'(t - \xi, \xi)] d\xi \right|
\leq \int_{\tau_s}^{T} 2^\sigma h(\tau|\tau', t) |\Psi(t - \xi, \xi) - \Psi'(t - \xi, \xi)| d\xi
\leq \frac{\omega}{2} \int_{\tau_s}^{T} |\Psi(t - \xi, \xi) - \Psi'(t - \xi, \xi)| d\xi.
$$

and consequently

$$
\|S\Psi - S\Psi'\|_\omega \leq \max \left\{ \frac{\omega e^{-\omega t}}{2} \int_{\tau_s}^{T} |\Psi(t - \xi, \xi) - \Psi'(t - \xi, \xi)| d\xi : t \in [0, T], \tau \in [\tau_s, \tau_l] \right\}
\leq \frac{\omega}{2} \max \left\{ e^{-\omega t} \int_{\tau_s}^{T} e^{\omega(t - \xi)} \|\Psi - \Psi'\|_\omega d\xi : t \in [0, T], \tau \in [\tau_s, \tau_l] \right\}
\leq \frac{\omega}{2} \|\Psi - \Psi'\|_\omega \int_{0}^{\infty} e^{-\omega \xi} d\xi = \frac{1}{2} \|\Psi - \Psi'\|_\omega.
$$

When passing from the second to the third line of (D5) we have made use of (D2), whereas in (D6) we have used the following inequality:

$$
\forall \in [0, T], \tau \in [\tau_s, \tau_l] : |\Psi(t, \tau)| \leq \exp(\omega t) \|\Psi\|_\omega,
$$

which is an immediate consequence of the definition (D1) of $\|\Psi\|_\omega$. 
Appendix E: More general description of the inheritance of generation time

Within the Lebowitz-Rubinow model \(34\)–\(36\) it is implicitly assumed that each of the two daughter cells (labelled as + and −) inherits the same value of the generation time at cell division: \(τ_+ = τ_− = τ\). Moreover, the common value of \(τ\) inherited by both daughter cells is assumed to depend only on the generation time \(τ'\) of their mother, but not on the generation times of more distant ancestors.

Both these assumptions can be relaxed. In this appendix, a more general model is proposed, which explicitly takes into account the generation time correlations between sisters as well as between the cell of interest and cells from \(G \geq 1\) previous generations in the cell lineage. We show that such a model can be reduced to the effective model of the form analyzed in the main text, provided certain simplifying assumptions are made.

1. Elimination of the generation time of the cell’s sister

Consider first the case of the population in the batch culture. At each cell division, we may (at least in principle) distinguish between the old- and the new-pole daughter cell. The former will be called ‘red’ and labeled by a plus (+); the latter will be called ‘blue’ and labelled by a minus (−). For \(E. coli\), it has been experimentally demonstrated that new-pole cells grow faster than old pole ones \(38\). However, here we disregard the effects of aging: We assume that the situation when one of the daughters inherits generation time \(τ_+\) and the other \(τ_−\) from their common mother is equally likely to the situation when values of \(τ_+\) and \(τ_−\) are being interchanged between daughter cells.

Additionally, we assume that each cell is characterized not only by its age \(a\) and inherited generation time \(τ\) but also by the generation time of its sister, \(\tilde{τ}\), and that of its mother (\(τ_1\), grandmother (\(τ_2\)), and by generation times of more distant ancestors: \(τ_3, ..., τ_G\)). Therefore instead of \(n(t, a, τ)\) appearing e.g. in \(34\) and \(35\) now we have to introduce the following cell number densities: \(n_+(t, a, τ, \tilde{τ}; τ, τ_1, ..., τ_G)\) for the ‘red’ cells and \(n_−(t, a, τ, \tilde{τ}; τ, τ_1, ..., τ_G)\) for the ‘blue’ ones. Clearly, we have

\[
n_+(t, 0, τ, \tilde{τ}; \tilde{τ}) = n_−(t, 0, \tilde{τ}, τ; \tilde{τ}) \tag{E1}
\]

where \(\tilde{τ} = (τ_1, τ_2, ..., τ_G)\). We also define

\[
n_+(t, a, τ, \tilde{τ}; \tilde{τ}) = n_+(t, a, τ, \tilde{τ}; \tilde{τ}) + n_−(t, a, τ, \tilde{τ}; \tilde{τ}) \tag{E2}
\]

and

\[
n(t, a, τ; \tilde{τ}) ≡ \int_{τ_+}^{τ_−} n_+(t, a, τ, \tilde{τ}; \tilde{τ})d\tilde{τ}. \tag{E3}
\]

Evolution equation for both \(n_+(t, a, τ, \tilde{τ}; \tilde{τ})\) and \(n_−(t, a, τ, \tilde{τ}; \tilde{τ})\) is identical to \(34\), i.e.

\[
\frac{∂n_+(t, a, τ, \tilde{τ}; \tilde{τ})}{∂t} + \frac{∂n_+(t, a, τ, \tilde{τ}; \tilde{τ})}{∂a} = 0, \tag{E4}
\]

\[
\frac{∂n_−(t, a, τ, \tilde{τ}; \tilde{τ})}{∂t} + \frac{∂n_−(t, a, τ, \tilde{τ}; \tilde{τ})}{∂a} = 0. \tag{E5}
\]

From \(32\) and \(33\) it also follows that both \(n_+(t, a, τ, \tilde{τ}; \tilde{τ})\) and \(n(t, a, τ, \tilde{τ})\) obey \(34\) too (the operator \(∂/∂t + ∂/∂a\) depends neither on \(\tilde{τ}\) nor on components of \(\tilde{τ}\)): \(τ_1, τ_2, τ_3, ..., τ_G\). In particular, we have

\[
\frac{∂n(t, a, τ, \tilde{τ})}{∂t} + \frac{∂n(t, a, τ, \tilde{τ})}{∂a} = 0. \tag{E6}
\]

Consider now the boundary condition: an influx of the newborn cells due to cell division and let us concentrate on ‘red’ newborns. Such cells can be daughters of both ‘red’ and ‘blue’ mothers, and likelihood of these two situations is proportional to \(h_+(τ, \tilde{τ} | \tilde{τ})\) and \(h_+(τ, \tilde{τ} | \tilde{τ})\), respectively. Here, \(h_+(τ, \tilde{τ} | \tilde{τ})\) describes the probability that a ‘red’ cell will inherit generation time equal to \(τ\) and its ‘blue’ sister - generation time equal to \(\tilde{τ}\) provided their mother is ‘red’ and generation times of \(G\) consecutive common ancestors of the two daughters in question are given by components of \(\tilde{τ}\). \(h_+(τ, \tilde{τ} | \tilde{τ})\) has an analogously interpretation. Therefore we have

\[
n_+(t, 0, τ, \tilde{τ}; \tilde{τ}) = \int_{τ_+}^{τ_−} \int_{τ_+}^{τ_−} h_+(τ, \tilde{τ} | \tilde{τ})n_+(t, τ, τ_1, τ_1, \tilde{τ}, \tilde{τ})dτ_1dτ_{G+1} + \int_{τ_+}^{τ_−} \int_{τ_+}^{τ_−} h_+(τ, \tilde{τ} | \tilde{τ})n_−(t, τ, τ_1, \tilde{τ})dτ_1dτ_{G+1}. \tag{E7}
\]
In the above, \( \bar{\tau}' = (\tau_2, \tau_3, \ldots \tau_{G+1}) \); primed quantities refer to mother cells. We have assumed here that generation time \( \tau \) inherited by the 'red' cells depends on generation times of its mother, grandmother, etc., up to \( G \)-th generation, but depends neither on \( \tau_{G+1} \), nor on generation times of ancestors' siblings. For simplicity, we also ignore the possible dependence of various distributions of inherited generation times on the observation time \( t \).

Now we make yet another simplifying assumption - the 'red' cell can be equally likely a daughter of a 'red' or 'blue' mother:

\[
h_+ + (\tau, \tilde{\tau} | \bar{\tau}) = h_+ - (\tau, \tilde{\tau} | \bar{\tau}) = h_+ (\tau, \tilde{\tau} | \bar{\tau})
\]

(E8)

Using (E9), (E10) and (E11) we can rewrite (E7) as

\[
n_+ (t_0, \tau, \tilde{\tau}; \bar{\tau}) = \int_{\tau_s}^{\tau_i} h_+ (\tau, \tilde{\tau} | \bar{\tau}) n(t, \tau, \tau_1, \tau_1', \bar{\tau}') d\tau G + 1.
\]

(E9)

We have analogous equations for the 'blue' cells:

\[
n_- (t_0, \tau, \tilde{\tau}; \bar{\tau}) = \int_{\tau_s}^{\tau_i} h_- (\tau, \tilde{\tau} | \bar{\tau}) n(t, \tau, \tau_1, \tau_1', \bar{\tau}') d\tau G + 1.
\]

(E10)

We have also

\[
h_+ (\tau, \tilde{\tau} | \bar{\tau}) = h_- (\tau, \tilde{\tau} | \bar{\tau}).
\]

(E11)

Now we make yet another strong assumption about the symmetry between 'blue' and 'red' cells,

\[
h_+ (\tau, \tilde{\tau} | \bar{\tau}) = h_- (\tau, \tilde{\tau} | \bar{\tau}) = h(\tau, \tilde{\tau} | \bar{\tau}).
\]

(E12)

Alternatively, adding (E9) and (E10) we get

\[
n_s (t_0, \tau, \tilde{\tau}; \bar{\tau}) = 2 \int_{\tau_s}^{\tau_i} h(\tau, \tilde{\tau} | \bar{\tau}) n(t, \tau, \tau_1, \tau_1', \bar{\tau}') d\tau G + 1,
\]

(E13)

where

\[
h(\tau, \tilde{\tau} | \bar{\tau}) = \frac{h_+ (\tau, \tilde{\tau} | \bar{\tau}) + h_- (\tau, \tilde{\tau} | \bar{\tau})}{2}.
\]

(E14)

Intuitive meaning and interpretation of (E14) are the following: One of the cells inherits generation time \( \tau \) at cell division, but we have no information if this is a red or blue cell. Now \( \tilde{\tau} \) may be integrated out, and we finally obtain

\[
n(t, 0, \tau, \tilde{\tau}) = 2 \int_{\tau_s}^{\tau_i} h(\tau | \tilde{\tau}) n(t, \tau, \tau_1, \tau_1', \bar{\tau}') d\tau G + 1,
\]

(E15)

where

\[
h(\tau | \tilde{\tau}) \equiv \int_{\tau_s}^{\tau_i} h(\tau, \tilde{\tau} | \bar{\tau}) d\tilde{\tau}.
\]

(E16)

So far we have considered batch culture. In order to obtain analogous results for the mother machine, we have to consider only 'red' cells and disregard the 'blue' ones. As the result, the factor of 2 in the boundary condition would be absent.

2. Elimination of generation times of grandmother and more distant ancestors

In the previous Subsection, we have shown how to eliminate the generation time of the cell’s sister from the model description, provided that certain simplifying conditions are satisfied. We derived the equations describing time evolution of cell density \( n(t, a, \tau, \tilde{\tau}) \), \( \tilde{\tau} = (\tau_1, \tau_2, \ldots \tau_G) \), where \( \tau_1 \) is the generation time of cell's mother, \( \tau_2 \) is a generation time of grandmother, etc.

Now our task is to keep the dependence of the distribution of inherited generation times \( h(\tau | \ldots) \) on the mother’s generation time \( \tau_1 \) but to get rid of generation times of more distant ancestors and to obtain equations (34)–(36) of the Lebowitz-Rubinow model: Time-evolution equation, initial and boundary condition for the cell number density

\[
n(t, a, \tau) = \int_{\tau_s}^{\tau_i} \ldots \int_{\tau_s}^{\tau_i} n(t, a, \tau, \tilde{\tau}) d\tau_1 \ldots d\tau_G.
\]

(E17)
Note that we do not require now that $a < \tau_i$ for $i = 1, 2, \ldots, G$.

Our point of departure for the subsequent analysis are now (E6) and (E15). Once again, we have

$$\frac{\partial n(t, a, \tau, \tau_1, \ldots, \tau_G)}{\partial t} + \frac{\partial n(t, a, \tau, \tau_1, \ldots, \tau_G)}{\partial a} = 0$$

(E18)

and

$$n(t, 0, \tau, \tilde{\tau}) = 2^\sigma \int_\tau^{t+1} h(\tau|\tilde{\tau}) n(t, \tau_1, \tau, \tilde{\tau}) d\tau_{G+1},$$

(E19)

where $h(\tau|\tilde{\tau})$ is given by (E16) and $\tilde{\tau} = (\tau_1, \tau_2, \ldots, \tau_G)$. We also define

$$n(0, a, \tau, \tilde{\tau}) = \Phi(a, \tau, \tilde{\tau}), \quad n(t, 0, \tau, \tilde{\tau}) = \Psi(t, \tau, \tilde{\tau}).$$

(E20)

Inherited value of generation time $\tau = \tau_0$ depends on $\tau_1, \tau_2, \ldots, \tau_G$ as described by $h(\tau|\tilde{\tau})$. We assume that correlations between more distant generations ($i > G$) are vanishing and that environment is constant.

Finally, invoking (E21) we integrate (E19) with respect to the components of $\tilde{\tau}$ and we arrive at (35): Reduction of the initial conditions (E20) to (36) is also obvious. But in order to obtain the boundary condition (35) from (E19) we have to define an effective distribution of inherited generation time:

$$h(\tau|\tau_1, t) = \frac{\int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} h(\tau|\tau_1, \tau_2, \ldots, \tau_G) n(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau_2 \ldots d\tau_G}{\int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} n(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau_2 \ldots d\tau_G}$$

$$= \frac{\int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} h(\tau|\tau_1, \tau_2, \ldots, \tau_G) f_1(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau_2 \ldots d\tau_G}{\int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} f_1(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau_2 \ldots d\tau_G}$$

$$= \frac{\mathcal{P}(t, \tau, \tau_1)}{\mathcal{P}(t, \tau_1)} = \mathcal{P}(\tau|\tau_1, t),$$

(E21)

where

$$f_1(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) = \frac{n(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1})}{N(t)\Lambda(t)},$$

is a generalization of the age distribution of mothers $f_1(t, \tau)$ considered in the main text. Clearly, we should have

$$\int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} f_1(t, \tau, \tilde{\tau}) d\tau_1 \ldots d\tau_G = f_1(t, \tau)$$

(E22)

with $f_1(t, \tau)$ given by (7). In (E24) we have also defined

$$\mathcal{P}(t, \tau, \tau_1) = \int_{\tau_1}^{\tau} \int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} \mathcal{P}(t, \tau, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau_2 \ldots d\tau_G d\tau_{G+1},$$

(E23)

$$\mathcal{P}(t, \tau_1) = \int_{\tau_1}^{\tau} \int_{\tau_1}^{\tau} \ldots \int_{\tau_1}^{\tau} \mathcal{P}(t, \tau, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) d\tau d\tau_2 \ldots d\tau_G d\tau_{G+1},$$

(E24)

where

$$\mathcal{P}(t, \tau, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}) = h(\tau|\tau_1, \tau_2, \ldots, \tau_G) f_1(t, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1}).$$

(E25)

Note that $\mathcal{P}(t, \tau, \tau_1, \tau_2, \ldots, \tau_G, \tau_{G+1})$ defined above is properly normalized. Importantly, the time dependence of $\mathcal{P}(t, \tau, \tau_1)$ and $\mathcal{P}(t, \tau_1)$ does not have to cancel out in (E21) and $h(\tau|\tau_1, t)$ may depend on the observation time $t$ even if $h(\tau|\tau_1, \tau_2, \ldots, \tau_G)$ did not.

Finally, invoking (E21) we integrate (E19) with respect to the components of $\tilde{\tau}$ and we arrive at (35):

$$n(t, 0, \tau) = \int_0^{\tau} \int_0^\tau \ldots \int_0^\tau n(t, 0, \tau, \tilde{\tau}) d\tau_1 d\tau_2 \ldots d\tau_G$$

$$= 2^\sigma \int_0^{\tau} \int_0^\tau \ldots \int_0^\tau h(\tau|\tau_1, \tilde{\tau}) n(t, \tau_1, \tau, \tilde{\tau}) d\tau_{G+1} \ldots d\tau_2 d\tau_1$$

$$= 2^\sigma \int_0^\infty h(\tau|\tau_1, t) n(t, \tau_1, \tau_1) d\tau_1.$$

(E26)

In this way we have reduced model defined by (E4), (E5) and (E7) to a simpler one given by (E1)–(30).
Appendix F: Derivation of Rubinow’s model from the Lebowitz-Rubinow model

Starting from the Lebowitz-Rubinow model (34)–(36) we derive here a model formally identical to the one proposed by Rubinow in 1968 [29]. In the latter model there is only a single state variable $x \in [0, 1]$ called maturity, which increases with cell age $a$ (or observation time $t$) from $x = 0$ at the beginning of the cell cycle to $x = 1$ at cell division. For each cell the time evolution of $x$ is assumed to be deterministic and given by the same ‘maturation velocity’ $g_r(t, x)$:

$$\frac{dx}{dt} = g_r(t, x).$$ (F1)

Now let $u(t, x)dx$ be the number of cells with maturity $x$ at time $t$. Equations of the Rubinow’s model read

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} [g_r(t, x)u(t, x)] = 0,$$ (F2)

$$g_r(t, 0)u(t, 0) = 2^{\sigma} g_r(t, 1)u(t, 1),$$ (F3)

$$u(0, x) = u_0(x).$$ (F4)

We consider here a slightly different set of the model equations than the one proposed originally by Rubinow [29] or the one analyzed in [32]. First, we allow $g_r(t, x)$ appearing in (F1), (F3) and (F2) to dependent on the observation time $t$. Second, in analogy to the case of Lebowitz-Rubinow model, we introduce parameter $\sigma$ in the boundary condition (F3): $\sigma = 1$ for both batch and continuous culture and $\sigma = 0$ for mother machine. However, in contrast to the original formulation of the model [29] we ignore the possibility of cell death. We also put dilution rate equal zero, $D(t) = 0$.

1. Lebowitz-Rubinow model (34)–(36) in maturity representation.

In [29] no unique, precise definition of $x$ was given [39]. Here, we define maturity simply as

$$x = \frac{a}{\tau}.$$ (F5)

If instead of cell age $a$, we use $x$ defined by (F5) as an independent variable of the Lebowitz-Rubinow model, then (34) reads

$$\frac{\partial n_r(t, x, \tau)}{\partial t} + \frac{1}{\tau} \frac{\partial n_r(t, x, \tau)}{\partial x} = 0,$$ (F6)

where

$$n_r(t, x, \tau) = n(t, xt, \tau)\tau$$ (F7)

and $n(t, a, \tau)$ is the solution to (34)–(36). Next, using (F7) we define

$$\chi_r(t, x, \tau) = \frac{n_r(t, x, \tau)}{N(t)} = \chi(t, xt, \tau)\tau,$$ (F8)

where $\chi(t, a, \tau)$ is given by (48). From (F6) and (F8) we obtain the time-evolution equation for $\chi_r(t, x, \tau)$

$$\frac{\partial \chi_r(t, x, \tau)}{\partial t} + \frac{1}{\tau} \frac{\partial \chi_r(t, x, \tau)}{\partial x} + \sigma \Lambda(t)\chi_r(t, x, \tau) = 0.$$ (F9)

We also define

$$u(t, x) = \int_{\tau_s}^{\tau_i} n_r(t, x, \tau)d\tau$$ (F10)

and

$$\varphi_r(t, x) = \frac{u(t, x)}{N(t)} = \int_{\tau_s}^{\tau_i} \chi_r(t, x, \tau)d\tau.$$ (F11)
One can easily show that the total number of cells in the population,

$$N(t) = \int_0^1 \int_{t_s}^{t} n_r(t, x, \tau) d\tau dx$$  \hspace{1cm} (F12)$$
is given by (45), as it should. Integrating both sides of (F6) with respect to \( \tau \) and making use of (F8), (F10) and (F11) we obtain (F2) provided that

$$g_r(t, x) u(t, x) = \int_{t_s}^{t} \frac{1}{\tau} \frac{\chi_r(t, x, \tau)}{\tau} d\tau = \int_{t_s}^{t} \frac{1}{\tau} \chi_r(\tau | x, t) d\tau \equiv \langle \frac{1}{\tau} \rangle.$$  \hspace{1cm} (F13)

Consequently

$$g_r(t, x) = \int_{t_s}^{t} \frac{1}{\tau} \frac{\chi_r(t, x, \tau)}{\tau} d\tau = \int_{t_s}^{t} \frac{1}{\tau} \chi_r(\tau | x, t) d\tau \equiv \langle \frac{1}{\tau} \rangle.$$  \hspace{1cm} (F14)

We can now derive (F3) from (35). After change of variables from \( a \) to \( x \) the latter equation reads

$$\frac{n_r(t, 0, \tau)}{\tau} = 2\sigma \int_{t_s}^{t} \chi_r(\tau | x, t) n_r(t, 1, \xi) \frac{d\xi}{\xi}.$$  \hspace{1cm} (F15)

Using (F13) we indeed obtain (F3) from (F10) and (F15). Finally, using (F7) and (F11) we obtain the initial condition (F3) from the initial condition \( n(0, a, \tau) = \Phi(a, \tau) \) of the Lebowitz-Rubinow model.

Note that although \( h(\tau | \xi, t) \) - the function describing the inheritance of generation time - does not appear explicitly in Rubinow’s model, it influences the form of the boundary condition (F3). We see that (F2), (F4) may be treated as an effective model with \( g_r(t, x) \) being equal to \( \tau^{-1} \) averaged over all cell cycle lengths for a given values of \( t \) and \( x \).

2. Stationary solution of the Rubinow model: Balanced exponential growth.

For \( \sigma = 1 \), in the steady-state limit we have \( \chi_r(t, x, \tau) = \chi_r(x, \tau), \Lambda(t) = \Lambda_B = const \) and \( N(t) = N_0 \exp(\Lambda_B t) \).

Invoking (81) with \( \sigma = 1 \) and changing variable \( a \rightarrow x \) we obtain

$$\chi_{rB}(x, \tau) = 2\Lambda_B f_{0B}(\tau) \tau \exp(-\Lambda_B x \tau).$$  \hspace{1cm} (F16)

The above equation may be also derived directly form (F9), which in the present case reads

$$\frac{d\chi_{rB}(x, \tau)}{dx} + \tau \Lambda_B \chi_{rB}(x, \tau) = 0.$$  \hspace{1cm} (F17)

Integrating (F16) with respect to \( x \) we obtain

$$\int_0^1 \chi_{rB}(x, \tau) dx = f_{2B}(\tau) = 2f_{0B}(\tau)(1 - e^{-\Lambda_B \tau}),$$  \hspace{1cm} (F18)
as expected. We also have

$$\varphi_{rB}(x) = \int_{t_s}^{t} \chi_{rB}(x, \tau) d\tau = \int_{t_s}^{t} \tau \Lambda_B f_{0B}(\tau) e^{-\Lambda_B \tau} d\tau = -2\Lambda_B \hat{f}_{0B}(z)_{z=\Lambda_B},$$  \hspace{1cm} (F19)

where \( f_{0B}(z) \) denotes Laplace transform of \( f_{0B}(\tau) \) and \( \hat{f}_{0B}(z) \) is the derivative of \( f_{0B}(z) \) with respect to \( z \). (We can extend the limits of integration in (F11), replacing \( t_s \) with 0 and \( t_l \) with \( \infty \), because \( f_{0B}(\tau) = 0 \) for \( \tau < t_s \) and \( \tau > t_l \). Alternatively, we can put \( t_s = 0 \), \( t_l = \infty \) If \( f_{0B}(\tau) \) is given by the gamma distribution with parameters \( \alpha \) and \( \beta \),

$$f_{0B}(\tau) = \frac{\tau^{\alpha-1} e^{-\tau/\beta}}{\beta^\alpha \Gamma(\alpha)}, \quad \hat{f}_{0B}(z) = \frac{1}{(1 + \beta z)^\alpha};$$ \hspace{1cm} (F20)

from (F19) we obtain

$$\varphi_{rB}(x) = \frac{2\alpha \beta \Lambda_B}{(1 + \beta \Lambda_B x)^{\alpha+1}}.$$  \hspace{1cm} (F21)
Normalization condition for ϕₐ(x) is the Euler-Lotka equation, which in the present case reads

\[ 1 = \frac{2}{(1 + \beta \Lambda_B)^\alpha}. \]  

(F22)

Using (F22) we can rewrite (F21) as

\[ \varphi_B(x) = \frac{2\alpha(2^\frac{1}{\alpha} - 1)}{[1 + (2^\frac{1}{\alpha} - 1)x]^{\alpha + 1}}. \]  

(F23)

From (F14) we can also find the explicit form of the 'maturation velocity' \( g_B(t, x) = g_B(x), \)

\[ g_B(x) = \frac{\hat{f}_B(z; \Lambda_B x)}{\hat{f}_B(z; \Lambda_B z)}. \]  

(F24)

In particular, for \( f_0B(\tau) \) given by (F20) we get

\[ g_B(x) = \frac{(1 + \beta \Lambda_B x)}{\alpha \beta} = \frac{[1 + (2^\frac{1}{\alpha} - 1)x]}{\alpha \beta}. \]  

(F25)

Eq. (F24) can be rewritten as

\[ \frac{\hat{f}_B(z)}{f_B(z)} = -\frac{1}{g_B \left( \Lambda_B^{-1} z \right)}, \]  

and therefore

\[ \hat{f}_B(\Lambda_B x) = \exp \left( -\int_0^x \frac{\Lambda_B}{g_B(x)} d\tilde{x} \right). \]  

(F27)

If \( g_B(x) \) is known, the above equation can be used to find \( \hat{f}_B(z) \).

3. **Stationary solution of the Rubinow model: 'Mother machine' experiments.**

For the mother machine experiments (\( \sigma = 1 \)) in the steady state, equation (F29) reduces to \( d\chi_F(x, \tau)/dx = 0 \), hence \( \chi_F(x, \tau) \) is a constant function of \( x \) and it depends in a nontrivial way only on \( \tau \). In order to find the explicit form of \( \chi_F(x, \tau) \) it is most convenient to use (F2)

\[ \chi_F(\tau, \tau) = \frac{f_{0F}(\tau)}{\int_0^\infty \xi f_{0F}(\xi) d\xi}, \]  

(F28)

and (F3), from which after change of variable we get

\[ \chi_F(x, \tau) = \frac{\tau f_{0F}(\tau)}{\int_0^\infty \xi f_{0F}(\xi) d\xi} = \int_0^1 \chi_F(x, \tau) dx = f_{2F}(\tau), \]  

(F29)

i.e. \( \chi_F(x, \tau) \) is identical to \( f_{2F}(\tau) \) given by (F2). In consequence, \( \varphi_F(x) = \int_{\tau_s}^{\tau_f} \chi_F(x, \tau) d\tau = 1. \)

(F30)

(More precisely, \( \varphi_F(x) = \Theta(x)\Theta(1 - x), \) where \( \Theta(x) \) is the Heaviside step function.) We also get the maturation velocity function for the present case:

\[ g_F(x) = \frac{1}{\int_{\tau_s}^{\tau_f} \tau f_{0F}(\tau) d\tau} = \frac{1}{\langle \tau \rangle_{0F}}. \]  

(F31)

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[39] 'By level of maturity is meant the various stages in the growth of the cell such as birth, onset of DNA synthesis, onset of mitosis, etc. These may or may not be readily observable. In fact it is difficult to say in what manner the maturity level of a cell should be determined. For bacterial cells such as E. coli in which DNA synthesis continues from the moment of birth, the amount of DNA in the cell could be utilized as a measure of cell maturity. Or x could simply be considered to represent the amount of DNA in the cell. However, for many cells in which DNA synthesis is only a portion of the life cycle, such a measure is not completely satisfactory. Thus, at the present time even the dimensions of x must be left unspecified. Another possibility is to let x represent cell volume.' [29]. (Here we have changed the original notation: We denote maturity by x and not by µ as in [29]).