# CELL CYCLE LENGTH AND LONG-TIME BEHAVIOUR OF AN AGE-SIZE MODEL

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ABSTRACT. We consider an age-size structured cell population model based on the cell cycle length. The model is described by a first order partial differential equation with initial-boundary conditions. Using the theory of semigroups of positive operators we establish new criteria for an asynchronous exponential growth of solutions to such equations. We discuss the question of exponential size growth of cells. We show how to incorporate into our description models with constant increase of size and with target size division. We also present versions of the model when the population is heterogeneous.

## 1. INTRODUCTION

The cell cycle is a series of events that take place in a cell leading to its replication. It is regulated by a complex network of protein interactions [28]. Modern experimental techniques concerning the cell cycle [7, 15, 26, 29, 39, 40, 41, 44] allow us not only to understand processes inside single cells, but also to build more precise cellular populations models.

Most of populations are usually heterogeneous. Thus it is important to consider the distribution of the population according to some significant parameters such as age, size, maturity, or proliferative state of cells. Models of this type are called structured. This type of models are usually represented by partial differential equations with some nonlocal perturbations and specific boundary conditions. Knowing the length of cell cycle allows us to predict the development of unicellular populations and tissues growth and maintenance.

The aim of the paper is twofold. Firstly, to construct an age-size structured model assuming that we know the growth of individual cells and the distribution of the cell cycle length. Secondly, to study the long-time behaviour of the solution of this model.

We consider a model which based on the following assumptions. The population grows in steady-state conditions. Cells can be described by their age $a$ and size $x$ alone and reproduction occurs by fission into two equal parts.

The distribution of the cell cycle length depends only on the initial size $x_b$ of a cell. The velocity of growth of an individual cell depends only on its size $x$, i.e. $x'(t) = g(x(t))$. We also assume that sizes of cells and cell cycle durations are bounded above and bounded away from zero. Moreover, we assume that the initial daughter cell sizes are distributed in some interval which contains the mother initial size. We formulate a mathematical model which describes the time evolution of distribution of cellular age and size. The model consists of a partial differential equation with an integral boundary condition and an initial condition. The novelty of our model is that we use the distribution of the length of the cell cycle, instead of a size dependent probability of division usually used in size-structured models [6, 8, 9, 12, 13, 14]. Such probability is difficult to measure experimentally in contrast to the length of the cell cycle.

We check that the solutions of our model generate a continuous semigroup of operators $\{U(t)\}_{t \geq 0}$ on some $L^1$ space. Under additional assumption that $g(2x) \neq 2g(x)$ for some $x$, we prove that the semigroup $\{U(t)\}_{t \geq 0}$ has asynchronous exponential growth (AEG), i.e.

$$U(t)u_0(x_b, a) \to Ce^{\lambda t}v(x_b, a) \quad \text{for } t \to \infty,$$

where $\lambda$ is the Malthusian parameter and $v$ is a stable initial size and age distribution, which does not depend on the initial distribution $u_0$. The property AEG plays important role in the study of structured population models [4, 8, 12, 45], because we can expect that the real process should be close to a stationary state and then it is easy to estimate biological parameters [21].

The proof of AEG of $\{U(t)\}_{t \geq 0}$ is based on the reduction of the problem to a stochastic (Markov) semigroup [19] by using the Perron eigenvectors and on the theorem that a partially integral stochastic semigroup having a unique invariant density is asymptotically stable [31]. A similar technique was applied to study other population models [5, 30, 37] and to some piecewise deterministic Markov processes [23, 32, 38]. We note that AEG property can be proved by using known results on compact semigroups but it seems to be difficult to check compactness and analyze the spectrum of the generator of our semigroup. It is interesting that even nonlinear models of cell population (cf. [22, 34]) can be reduced to stochastic semigroups.

The last two sections contain corollaries from our results (Section 6) and some remarks concerning other models and experimental data (Section 7). One of the main points of these sections is what can happen when $g(2x) = 2g(x)$ for all $x$? This is an important question because it is usually assumed that the size (volume) of a cell grows exponentially, which means that $g(x) = \kappa x$ and in this case $g(2x) = 2g(x)$. If we include in a model the assumption that $g(x) = \kappa x$, then we can obtain some paradoxical results. For example, if the size discrepancy between newborn cells is small, then the descendants of one cell can have the same size at the same time and the size of the population does not grow exponentially even in steady-state conditions. Of

course the law of exponential size growth is statistical in nature and we can modify it by considering some random fluctuations in the growth rate. Another problem considered in Section 7 is how to incorporate into our description some models of the cell cycle: a *constant* $\Delta$ *model* and a *model with target size division*. Finally, we present versions of the model when the population is heterogeneous, e.g. with an asymmetric division or with fast and slow proliferation.

## 2. MODEL

We consider the following model of the cell cycle. Denote, respectively, by $a$, $x_b$, and $x$ — the age, the initial size, and the size of a cell. We assume that $\underline{x}_b$ and $\overline{x}_b$ are the minimum and maximum sizes of newborn cells. We also assume that cells age with unitary velocity and grow with a velocity $g(x)$, i.e. if a cell has the initial size $x_b$, then the size at age $a$ satisfies the equation

$$(1) \qquad\qquad x'(a) = g(x(a)), \quad x(0) = x_b.$$

We denote by $\pi_a x_b$ the solution of (1). The length $\tau$ of the cell cycle is a random variable which depends on the initial cell size $x_b$; has values in some interval $[\underline{a}(x_b), \overline{a}(x_b)]$; and has the probability density distribution $q(x_b, a)$, i.e. the integral $\int_0^A q(x_b, a)\, da$ is the probability that $\tau \leq A$. According to the definition of $q$, if a cell has the initial size $x_b$, then $\Phi(x_b, a) = \int_a^\infty q(x_b, r)\, dr$ is its *survival function*, i.e. $\Phi(x_b, a)$ is the probability that a cell will not split before age $a$. We assume that if the mother cell has size $x$ at the moment of division, then the daughter cells have size $x/2$, i.e. if the initial size of the mother cell is $x_b$ and $\tau = a$ is the length of its cell cycle, then the initial size of the daughter cell is $S_a(x_b) = \frac{1}{2}\pi_a x_b$.

Now we collect the assumptions concerning the functions $g$ and $q$ used in the paper:

(A1) $g\colon [\underline{x}_b, 2\overline{x}_b] \to (0, \infty)$ is a $C^1$-function,

(A2) $q\colon [\underline{x}_b, \overline{x}_b] \times [0, \infty) \to [0, \infty)$ is a continuous function and for each $x_b$ the function $a \mapsto q(x_b, a)$ is a probability density,

(A3) $0 < \underline{a}(x_b) < \overline{a}(x_b) < \infty$, $q(x_b, a) > 0$ if $a \in (\underline{a}(x_b), \overline{a}(x_b))$, and $q(x_b, a) = 0$ if $a \notin (\underline{a}(x_b), \overline{a}(x_b))$ for each $x_b \in [\underline{x}_b, \overline{x}_b]$,

(A4) $x_b \mapsto \underline{a}(x_b)$ and $x_b \mapsto \overline{a}(x_b)$ are continuous functions,

(A5) $S_{\underline{a}(x_b)}(x_b) \geq \underline{x}_b$ and $S_{\overline{a}(x_b)}(x_b) \leq \overline{x}_b$ for each $x_b \in [\underline{x}_b, \overline{x}_b]$,

(A6) $S_{\underline{a}(x_b)}(x_b) < x_b < S_{\overline{a}(x_b)}(x_b)$ for each $x_b \in (\underline{x}_b, \overline{x}_b)$.

Fig. 1 and Fig. 2 illustrate our assumptions. Only assumption (A6) needs some explanation. We assume that a daughter cell can have the same initial size as the initial size of a mother cell. In Section 5 we will add an extra assumption (A7) which will be used only to show the long-time behaviour of the distribution of $(x_b, a)$.

Assume that a cell with initial size $x_b$ and age $a$ splits in the time interval of the length $\Delta t$ with probability $p(x_b, a)\Delta t + o(\Delta t)$. Since $\Phi(x_b, a) =$
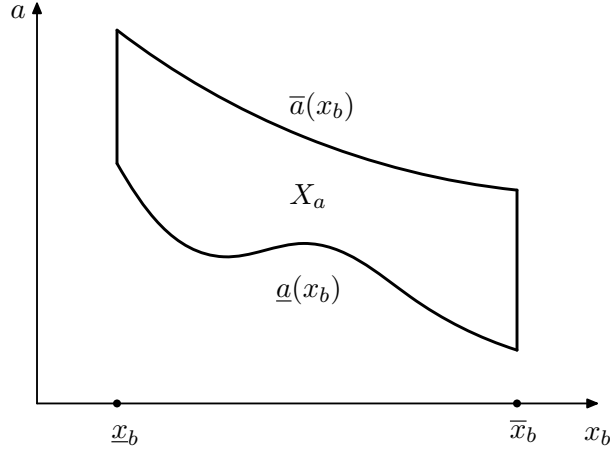
FIGURE 1. An example of functions $x_b \mapsto \underline{a}(x_b)$ and $x_b \mapsto \overline{a}(x_b)$. The function $q$ is positive in the interior of the set $X_a$.
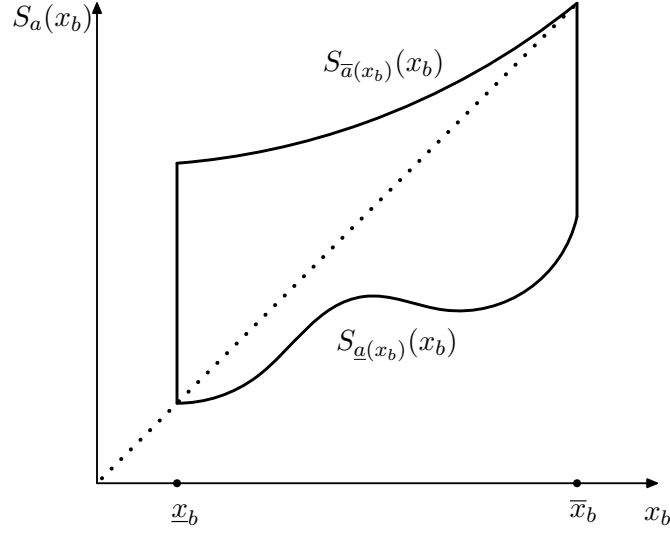


FIGURE 2. The relation between the initial sizes of mother and daughter cells (A5,A6).

$\exp\left(-\int_0^a p(x_b, r)\, dr\right)$, an easy computation shows that

$$q(x_b, a) = p(x_b, a)\exp\left(-\int_0^a p(x_b, r)\, dr\right),$$

(2)
$$p(x_b, a) = \frac{q(x_b, a)}{\int_a^\infty q(x_b, r)\, dr}$$

for $a < \overline{a}(x_b)$. As $\Phi(x_b, \overline{a}(x_b)) = 0$, we have $\int_0^{\overline{a}(x_b)} p(x_b, a)\, da = \infty$.

In order to derive a master equation for the distribution of the population with respect to $x_b$ and $a$ we need to introduce a family of Frobenius-Perron

operators which describe the relation between the initial sizes of mother and daugther cells. Assume that $f_0(x_b)$ is the density of initial sizes of mother cells, and that they have the fixed length of cell cycle $\tau = a$ for some $a \in (\underline{a}, \overline{a})$, where $\underline{a} = \min \underline{a}(x_b)$ and $\overline{a} = \max \overline{a}(x_b)$. Let $x_a$ be the minimum initial size of cells which can split at age $a$. Then $x_a = \underline{x}_b$ if $S_a(\underline{x}_b) \geq \underline{x}_b$ or $x_a = S_a^{-1}(\underline{x}_b)$ otherwise. It is clear that $q(x_b, a) = 0$ for $x_b < x_a$. If $f_1(x_b)$ is the density of initial sizes of daughter cells then

$$(3) \qquad \int_{S_a(x_a)}^{S_a(y)} f_1(x_b)\, dx_b = \int_{x_a}^{y} f_0(x_b)\, dx_b \quad \text{for } y \geq x_a$$

or, equivalently,

$$(4) \qquad \int_{S_a(x_a)}^{x} f_1(x_b)\, dx_b = \int_{x_a}^{S_a^{-1}(x)} f_0(x_b)\, dx_b \quad \text{for } x \geq S_a(x_a).$$

From (4) it follows that

$$(5) \qquad f_1(x_b) = \frac{d}{dx_b}\left(S_a^{-1}(x_b)\right) f_0\left(S_a^{-1}(x_b)\right) \mathbf{1}_{[S_a(x_a), \overline{x}_b]}(x_b).$$

Using the formula $S_a^{-1}(x_b) = \pi_{-a}(2x_b)$ we check that

$$(6) \qquad \frac{d}{dx_b}\left(S_a^{-1}(x_b)\right) = \frac{2g(\pi_{-a}(2x_b))}{g(2x_b)}.$$

In order to do it we introduce two functions:

$$\varphi(x_b, a) = \pi_{-a}(2x_b) \quad \text{and} \quad \psi(x_b, a) = \frac{\partial \varphi}{\partial x_b}(x_b, a).$$

From $\varphi(x_b, 0) = 2x_b$ we obtain $\psi(x_b, 0) = 2$. Since $\frac{\partial \varphi}{\partial a}(x_b, a) = -g(\varphi(x_b, a))$, we have

$$\frac{\partial \psi}{\partial a}(x_b, a) = \frac{\partial}{\partial a}\frac{\partial \varphi}{\partial x_b}(x_b, a) = \frac{\partial}{\partial x_b}\frac{\partial \varphi}{\partial a}(x_b, a)$$

$$= \frac{\partial}{\partial x_b}\left(-g(\varphi(x_b, a))\right) = -g'(\varphi(x_b, a))\psi(x_b, a).$$

We have received the linear equation $\partial \psi / \partial a = -g'(\varphi(x_b, a))\psi$ with the initial condition $\psi(x_b, 0) = 2$ which has the solution

$$(7) \qquad \psi(x_b, a) = 2\exp\left(-\int_0^a g'(\varphi(x_b, r))\, dr\right).$$

Substituting $y = \varphi(x_b, r)$ we receive $dy/dr = -g(y)$ and

$$(8) \qquad \psi(x_b, a) = 2\exp\left(\int_{2x_b}^{\pi_{-a}(2x_b)} \frac{g'(y)}{g(y)}\, dy\right) = \frac{2g(\pi_{-a}(2x_b))}{g(2x_b)}.$$

Finally we introduce a family of operators $\{P_a\}$ given by the formula

$$(9) \qquad P_a f(x_b) = \frac{2g(\pi_{-a}(2x_b))}{g(2x_b)} f(\pi_{-a}(2x_b)) \mathbf{1}_{[S_a(x_a), \overline{x}_b]}(x_b).$$

The operators $P_a$ are well defined for $a \in (\underline{a}, \overline{a})$ but we extend the definition of $P_a$ setting $P_a f \equiv 0$ for others $a$'s.

For each $a$ the operator $P_a \colon L^1[\underline{x}_b, \overline{x}_b] \to L^1[\underline{x}_b, \overline{x}_b]$ is linear and *positive*, i.e. if $f \geq 0$, then $P_a f \geq 0$. Moreover $\|P_a f\|_{L^1} \leq \|f\|_{L^1}$. The adjoint operator of $P_a$ acts on the space $L^\infty[\underline{x}_b, \overline{x}_b]$ and it is given by $P_a^* f(x_b) = f(S_a(x_b)) = f(\frac{1}{2}\pi_a x_b)$ for $x_b \geq x_a$ and $P_a^* f(x_b) = 0$ for $x_b < x_a$.

We denote by $u(t, x_b, a)$ the number of individuals in a population having initial size $x_b$ and age $a$ at time $t$. Then, according to our assumptions concerning the model, $p(x_b, a)u(t, x_b, a)\Delta t$ is the number of cells of initial size $x_b$ and age $a$ which split in a time interval of the length $\Delta t$. It means that $2\Delta t \int_0^\infty P_a(p(x_b, a)u(t, x_b, a))\, da$ is the number of new born cells in this time interval. It should be noted that the operator $P_a$ in the last integral acts on the function $\psi(x_b) = p(x_b, a)u(t, x_b, a)$ at fixed values $t$ and $a$. If there are no limitations concerning the growth of the population and all cells split then the function $u$ satisfies the following initial-boundary problem:

$$(10) \qquad \frac{\partial u}{\partial t}(t, x_b, a) + \frac{\partial u}{\partial a}(t, x_b, a) = -p(x_b, a)u(t, x_b, a), \quad a < \overline{a}(x_b),$$

$$(11) \qquad u(t, x_b, 0) = 2\int_0^\infty P_a(p(x_b, a)u(t, x_b, a))\, da,$$

$$(12) \qquad u(0, x_b, a) = u_0(x_b, a).$$

We assume that $u_0$ is a nonnegative measurable function such that

$$(13) \qquad \int_{\underline{x}_b}^{\overline{x}_b} \int_0^\infty u_0(x_b, a)\Psi(x_b, a)\, da\, dx_b < \infty,$$

where $\Psi(x_b, a) = \exp\left(\int_0^a p(x_b, \bar{a})\, d\bar{a}\right)$. In (13) we have assumed that the initial condition $u_0$ is integrable with weight $\Psi(x_b, a) = \Phi(x_b, a)^{-1}$ because $\Phi(x_b, a)$ is a fraction of cells which will survive beyond age $a$. Since $\overline{a}(x_b)$ is the maximum age of a cell with initial size $x_b$, it is reasonable to consider variables $x_b$ and $a$ only from the set

$$X = \{(x_b, a) \colon \underline{x}_b \leq x_b \leq \overline{x}_b,\ 0 \leq a \leq \overline{a}(x_b)\}.$$

Though we consider $a \leq \overline{a}(x_b)$, it will be convenient to keep the notation of integral $\int_0^\infty$ with respect to $a$ as in formula (11) assuming that $u(t, x_b, a) = 0$ for $a > \overline{a}(x_b)$.

Most of experiments concerning microorganisms are conducted in chemostats, where cells can be grown in a physiological steady state under constant environmental conditions. Then cells are removed from the system with the outflow with rate $D$. In this case we add to the right-hand side of equation (10) the term $-Du(t, x_b, a)$. Similarly, if cells die with rate $d(t, x_b, a)$, then we add to the right-hand side of (10) the term $-d(t, x_b, a)u(t, x_b, a)$. One can consider more advanced models with cellural competition, but in this case all functions $q$, $g$, and $d$ can depend also on the total number of cells and we do not investigate such models.

## 3. A SEMIGROUP APPROACH

It is convenient to substitute $z(t, x_b, a) = u(t, x_b, a)\Psi(x_b, a)$ and $z_0(x_b, a) = u_0(x_b, a)\Psi(x_b, a)$ in (10)–(12). Then the system (10)–(12) takes the form

$$(14) \qquad \frac{\partial z}{\partial t}(t, x_b, a) + \frac{\partial z}{\partial a}(t, x_b, a) = 0, \quad a < \bar{a}(x_b),$$

$$(15) \qquad z(t, x_b, 0) = 2 \int_0^\infty P_a(q(x_b, a)z(t, x_b, a)) \, da,$$

$$(16) \qquad z(0, x_b, a) = z_0(x_b, a).$$

Observe that $z_0$ is an integrable function.

The general solution of (14) and (16) is given by

$$(17) \qquad z(t, x_b, a) = \begin{cases} z_0(x_b, a - t), & a \geq t, \\ z(t - a, x_b, 0), & a < t. \end{cases}$$

Both above formulae for $z(t, x_b, a)$ coincide for $a = t$ if $z(0, x_b, 0) = z_0(x_b, 0)$.

Now we substitute (17) to (15) splitting the integral $\int_0^\infty$ into two integrals $\int_0^t$ and $\int_t^\infty$. We obtain

$$(18) \qquad z(t, x_b, 0) = 2 \int_0^t P_a(q(x_b, a)z(t - a, x_b, 0)) \, da + F(t, x_b),$$

where

$$(19) \qquad F(t, x_b) = 2 \int_t^\infty P_a\big(q(x_b, a)z_0(x_b, a - t)\big) \, da.$$

The function $F(t, x_b)$ is known because it depends only on $z_0$.

If we prove the existence and uniqueness of the solution of integral equation (18), then according to (17) the same holds for the problem (14)–(16). We will write $z(t)(x_b) = z(t, x_b, 0)$ and treat $z$ as a function with values in the space $L^1[\underline{x}_b, \overline{x}_b]$, i.e. $z$ describes the time evolution of density distribution of $x_b$. Let us fix $T > 0$. Let $\mathcal{F}$ be the space of continuous functions from the interval $[0, T]$ with values in the space $L^1[\underline{x}_b, \overline{x}_b]$. Then $\mathcal{F}$ is a Banach space with norm

$$\|z\|_0 = \max_{0 \leq t \leq T} \|z(t)\|_{L^1}, \quad L^1 = L^1[\underline{x}_b, \overline{x}_b].$$

We will prove the existence and uniqueness of solution of (18) using the Banach contraction principle, but we will use the Bielecki norm

$$\|z\|_\lambda = \max_{0 \leq t \leq T} e^{-\lambda t} \|z(t)\|_{L^1}$$

with properly chosen $\lambda > 0$. The norms $\|\cdot\|_0$ and $\|\cdot\|_\lambda$ are equivalent but the second one is more convenient.

**Proposition 1.** *For each $T > 0$ equation* (18) *has a unique solution $z \in \mathcal{F}$. Moreover if $z_0 \geq 0$, then $z \geq 0$.*

*Proof.* As $q$ is a bounded function, there is an $M$ such that $0 \leq q(x_b, a) \leq M$ for all $x_b$ and $a$. Let $F(t)(x_b) := F(t, x_b)$. We check that $F \in \mathcal{F}$. Indeed, from (19) we have

$$\int_{\underline{x}_b}^{\overline{x}_b} |F(t, x_b)| \, dx_b \leq 2M \int_{\underline{x}_b}^{\overline{x}_b} \int_t^\infty P_a\big(|z_0(x_b, a - t)|\big) \, da \, dx_b$$

$$= 2M \int_t^\infty \int_{\underline{x}_b}^{\overline{x}_b} P_a\big(|z_0(x_b, a - t)|\big) \, dx_b \, da$$

$$\leq 2M \int_t^\infty \int_{\underline{x}_b}^{\overline{x}_b} |z_0(x_b, a - t)| \, dx_b \, da < \infty,$$

and consequently $F(t) \in L^1[\underline{x}_b, \overline{x}_b]$. Continuity of $F$ as a function with values in $L^1$ easily follows from the fact that we can write $F$ in the following form

$$(20) \qquad F(t)(x_b) = \int_t^\infty j(x_b, a) z_0(\pi_{-a}(2x_b), a - t) \, da,$$

where $j$ is a continuous bounded function and $z_0$ is an integrable function. Now we define the operator $\mathcal{P}$ by the formula

$$\mathcal{P}z(t)(x_b) = 2 \int_0^t P_a(q(x_b, a) z(t - a)(x_b)) \, da + F(t)(x_b).$$

We prove that $\mathcal{P} \colon \mathcal{F} \to \mathcal{F}$ and that $\mathcal{P}$ is a contraction in the space $\mathcal{F}$ equipped with the norm $\| \cdot \|_\lambda$ for some $\lambda$. If $z \in \mathcal{F}$, then we check that $\mathcal{P}z \in \mathcal{F}$ by using similar arguments as for the function $F(t)$. As in the proof that $F(t) \in L^1[\underline{x}_b, \overline{x}_b]$, we show the inequality

$$(21) \qquad \|\mathcal{P}z(t) - \mathcal{P}v(t)\|_{L^1} \leq 2M \int_0^t \|z(s) - v(s)\|_{L^1} \, ds.$$

Set $\lambda = 4M$ and $w(t) = z(t) - v(t)$. Then $\|w(s)\|_{L^1} \leq e^{\lambda s} \|w\|_\lambda$ and from (21) we obtain

$$\|\mathcal{P}w\|_\lambda = \max_{0 \leq t \leq T} e^{-\lambda t} \|\mathcal{P}w(t)\|_{L^1} \leq 2M \max_{0 \leq t \leq T} e^{-\lambda t} \int_0^t \|w(s)\|_{L^1} \, ds$$

$$\leq 2M \max_{0 \leq t \leq T} e^{-\lambda t} \int_0^t e^{\lambda s} \|w\|_\lambda \, ds = 2M \max_{0 \leq t \leq T} e^{-\lambda t} \frac{e^{\lambda t} - 1}{\lambda} \|w\|_\lambda$$

$$\leq \frac{1}{2} \|w\|_\lambda.$$

Thus $\mathcal{P}$ is a contraction, which proves that equation (18) has a unique solution $z \in \mathcal{F}$. Let $\mathcal{F}_+ = \{z \in \mathcal{F} \colon z(t) \geq 0\}$. If $z_0 \geq 0$, then $F \in \mathcal{F}_+$ and we have $\mathcal{P}(\mathcal{F}_+) \subset \mathcal{F}_+$. Consequently, $z \in \mathcal{F}_+$. $\square$

It is worth to mention that the solution of (18) satisfies the initial condition

$$z(0)(x_b) = 2 \int_0^\infty P_a\big(q(x_b, a) z_0(x_b, a)\big) \, da.$$

Now we return to study properties of the solutions of (14)–(16). Let $\mathcal{B}(X)$ be the $\sigma$-algebra of Borel subsets of $X$, $\ell$ be the Lebesgue measure on $X$, and $E$ be the space $L^1(X, \mathcal{B}(X), \ell)$. By $\|\cdot\|_E$ we denote the norm in $E$. We will consider the solutions of (14)–(16) as continuous functions $z\colon [0, \infty) \to E$ defined by $z(t)(x_b, a) = z(t, x_b, a)$.

We first check that $z(t) \in E$ for each $t \geq 0$ and the existence of a continuous function $C\colon [0, \infty) \to \mathbb{R}$ independent on $z_0$ such that $\|z(t)\|_E \leq C(t)\|z_0\|_E$ for $t \geq 0$. Indeed from (17) it follows that

$$(22) \qquad \|z(t)\|_E \leq \int_0^t \int_{\underline{x}_b}^{\overline{x}_b} |z(s, x_b, 0)| \, dx_b \, ds + \|z_0\|_E.$$

Let $\varphi(s) = \int_{\underline{x}_b}^{\overline{x}_b} |z(s, x_b, 0)| \, dx_b$. According to (18) we have

$$\varphi(t) \leq 2M \int_0^t \varphi(s) \, ds + 2M\|z_0\|_E.$$

Using Gronwall's inequality we obtain

$$(23) \qquad \varphi(t) \leq 2Me^{\int_0^t 2Ms \, ds}\|z_0\|_E \leq 2Me^{Mt^2}\|z_0\|_E.$$

We conclude from (22) and (23) that

$$(24) \qquad \|z(t)\|_E \leq \int_0^t \varphi(s) \, ds + \|z_0\|_E \leq \int_0^t 2Me^{Ms^2}\|z_0\|_E \, ds + \|z_0\|_E,$$

which gives $\|z(t)\|_E \leq C(t)\|z_0\|_E$ with $C(t) = \int_0^t 2Me^{Ms^2} \, ds + 1$. Thus the maps $T(t)$ defined by $T(t)z_0 = z(t)$ are bounded linear operators on $E$.

Now we check that $\{T(t)\}_{t \geq 0}$ is a $C_0$-semigroup of positive operators on the space $E$. First we observe that if we set

$$(25) \qquad z(t, x_b, 0) = z_0(x_b, -t) \quad \text{for } t \leq 0,$$

then equation (17) can be written with a single expression

$$(26) \qquad z(t, x_b, a) = z(t - a, x_b, 0)$$

and the function $(t, x_b) \mapsto z(t, x_b, 0)$ satisfies the equation

$$(27) \qquad z(t, x_b, 0) = 2\int_0^\infty P_a\big(q(x_b, a)z(t - a, x_b, 0)\big) \, da.$$

We check that $T(s_2)T(s_1)z_0 = T(s_1 + s_2)z_0$ for $s_1, s_2 \geq 0$. Let $\bar{z}_0(x_b, a) = T(s_1)z_0(x_b, a)$ and let $\bar{z}$ be the solution of (14)–(15) with the initial condition $\bar{z}(0, x_b, a) = \bar{z}_0(x_b, a)$. Then

$$\bar{z}(t, x_b, 0) \overset{(25)}{=} \bar{z}_0(x_b, -t) = z(s_1, x_b, -t) \overset{(26)}{=} z(s_1 + t, x_b, 0) \quad \text{for } t \leq 0.$$

Since the function $q$ and the operator $P_a$ do not depend on $t$, we conclude that $\bar{z}(t, x_b, 0) = z(s_1 + t, x_b, 0)$ for all $t$ and $x_b$. Finally (26) implies that $\bar{z}(t, x_b, a) = z(s_1 + t, x_b, a)$ for all $t$, $x_b$, and $a$, which gives $T(s_2)T(s_1)z_0 = T(s_1 + s_2)z_0$.

It remains to prove that $\lim_{t \downarrow 0} T(t)z_0 \to z_0$. It is enough to check this condition for continuous functions with compact supports because the set of

these functions is dense in $E$ and there is some $C > 0$ such that $\|T(t)z_0\|_E \leq C\|z_0\|_E$ for $z_0 \in E$ and $t \leq 1$. Now, we write the function $T(t)z_0$ as a sum of two functions $z_1(t)(x_b, a) = \mathbf{1}_{[t,\infty)}(a)z(t, x_b, a)$ and $z_2(t)(x_b, a) = \mathbf{1}_{[0,t)}(a)z(t, x_b, a)$ and we use the formula (17). Since $z_0$ is a continuous function with a compact support and

$$z_1(t)(x_b, a) = \mathbf{1}_{[t,\infty)}(a)z_0(x_b, a - t),$$

the functions $z_1(t)$ converge uniformly to $z_0$ on each set $\{(x_b, a) \in X \colon a \geq \varepsilon\}$, $\varepsilon > 0$, as $t \downarrow 0$. As the functions $z_0$ and $z_1(t)$, $t \leq \varepsilon$, are uniformly bounded and vanish outside the same compact set, we have $z_1(t) \to z_0$ in $E$ as $t \downarrow 0$. Since

$$\|z_2(t)\|_E \leq \int_0^t \int_{\underline{x}_b}^{\overline{x}_b} |z(t - a, x_b, 0)| \, dx_b \, da,$$

from Proposition 1 we conclude that $\lim_{t\downarrow 0} \|z_2(t)\|_E = 0$. We have thus proved the following theorem.

**Theorem 1.** *The family $\{T(t)\}_{t\geq 0}$ is a $C_0$-semigroup of positive operators on the space $E$.*

The operator

$$\mathcal{A}f(x_b, a) = -\frac{\partial f}{\partial a}(x_b, a)$$

with the domain

$$\mathcal{D}(\mathcal{A}) = \left\{ f \in E, \quad \frac{\partial f}{\partial a} \in E, \quad f(x_b, 0) = 2\int_0^\infty P_a(q(x_b, a)f(x_b, a)) \, da \right\}$$

is the infinitesimal generator of the semigrup $\{T(t)\}_{t\geq 0}$. Let $z(t) = T(t)z_0$. We recall that if $z_0 \in \mathcal{D}(\mathcal{A})$, then $z(t) \in \mathcal{D}(\mathcal{A})$, $z'(t)$ exists and $z'(t) = \mathcal{A}z(t)$.

*Remark* 1. Till now we have considered the solution of (14)–(16) as a continuous function $z$ from $[0, \infty)$ to $E$. Let us assume that $z_0$ is a continuous bounded function and the derivative $\dfrac{\partial z_0}{\partial a}$ exists and it is also a continuous bounded function. Additionally we assume that

$$(28) \qquad\qquad z_0(x_b, 0) = 2\int_0^\infty P_a\big(q(x_b, a)z_0(x_b, a)\big) \, da.$$

Then the problem (14)–(16) has a unique classical solution. By the *classical solution* we understand a continuous function $z$, which has continuous derivatives $\dfrac{\partial z}{\partial a}$ and $\dfrac{\partial z}{\partial t}$ outside the plane $a = t$, $z$ satisfies (14) outside the plane $a = t$, and $z$ satisfies conditions (15), (16). In order to prove this statement it is sufficient to prove that the solution of equation (18) is a continuous function with values in the space $C[\underline{x}_b, \overline{x}_b]$ and has the derivative $z'(t)$ which has also values in this space. In the proof of this fact we use the same method as in the proof of Proposition 1. First we obtain that $z(t)$ is a continuous function with values in the space $C[\underline{x}_b, \overline{x}_b]$. Then we check that the function $v(t)(x_b) = z'(t)(x_b)$ satisfies some integral equation similar to

(18), which has also a continuous solution. In the rest of the paper we will only study *generalized solutions* given by $z(t) = T(t)z_0$, $z_0 \in E$.

## 4. Eigenvectors of $\mathcal{A}$ and $\mathcal{A}^*$

Our aim is to study the long-time behaviour of the semigroup $\{T(t)\}_{t\geq 0}$. The strategy is the following. First we will check that the adjoint opera-tor $\mathcal{A}^*$ of $\mathcal{A}$ has a positive eigenvector $v = v(x_b, a)$ corresponding to some positive eigenvalue $\lambda$. Then we introduce the semigroup $\{P(t)\}_{t\geq 0}$ given by $P(t)f = e^{-\lambda t}T(t)f$ defined on the space $E_1 = L^1(X, \mathcal{B}(X), \mu)$ with the measure $\mu$ given by $d\mu = v\,d\ell$. Then we prove that semigroup $\{P(t)\}_{t\geq 0}$ has an invariant density $f_i$ and $\lim_{t\to\infty} P(t)f = f_i$ for each density $f$. Finally, we translate this result in terms of the semigroup $\{T(t)\}_{t\geq 0}$.

We first find the adjoint operator of $\mathcal{A}$. Denote by $H$ the operator $H\colon E \to L^1[\underline{x}_b, \overline{x}_b]$ defined by $(Hf)(x_b) = 2\int_0^\infty P_a(q(x_b, a)f(x_b, a))\,da$. Then the op-erator $H^*\colon L^\infty[\underline{x}_b, \overline{x}_b] \to E^*$ is given by

$$(29) \qquad (H^*f)(x_b, a) = 2q(x_b, a)P_a^* f(x_b) = 2q(x_b, a)f(S_a(x_b)).$$

It should be noted that we omit in the last product the factor $\mathbf{1}_{[x_a, \overline{x}_b]}(x_b)$ because $q(x_b, a) = 0$ for $x_b \leq x_a$.

We check that

$$\mathcal{D}(\mathcal{A}^*) = \{f \in E^*, \ \frac{\partial f}{\partial a} \in E^*, \ f(x_b, \overline{a}(x_b)) = 0\},$$

and

$$(30) \qquad \mathcal{A}^* f = \frac{\partial f}{\partial a} + H^* \tilde{f}, \quad \tilde{f}(x_b) = f(x_b, 0).$$

Indeed, if $f \in \mathcal{D}(\mathcal{A}^*)$ and $\varphi \in \mathcal{D}(\mathcal{A})$ then

$$\langle \mathcal{A}^* f, \varphi \rangle = \langle f, \mathcal{A}\varphi \rangle = -\int_{\underline{x}_b}^{\overline{x}_b} \int_0^{\overline{a}(x_b)} f(x_b, a)\frac{\partial \varphi}{\partial a}(x_b, a)\,da\,dx_b$$

$$= \int_{\underline{x}_b}^{\overline{x}_b} f(x_b, 0)\varphi(x_b, 0)\,dx_b + \left\langle \frac{\partial f}{\partial a}, \varphi \right\rangle$$

$$= \int_{\underline{x}_b}^{\overline{x}_b} f(x_b, 0)(H\varphi)(x_b)\,dx_b + \left\langle \frac{\partial f}{\partial a}, \varphi \right\rangle$$

$$= \langle H^* \tilde{f}, \varphi \rangle + \left\langle \frac{\partial f}{\partial a}, \varphi \right\rangle.$$

Now we will check that the operator $\mathcal{A}^*$ has a positive eigenvector $v$ for some eigenvalue $\lambda > 0$. Let $\mathcal{A}^* v = \lambda v$. From (30) it follows that

$$(31) \qquad \lambda v - \frac{\partial v}{\partial a} = H^* \tilde{v}.$$

The problem is that the adjoint semigroup $\{T^*(t)\}_{t\geq 0}$ is not continuous. Instead of this semigroup we may use the sun dual semigroup, but it will be

more convenient to consider a little modification of the sun dual semigroup. Consider a semigroup $\{T^{\odot}(t)\}_{t\geq 0}$ defined on the space

$$\widetilde{C}(X) = \{f \in C(X): \ f(x_b, \overline{a}(x_b)) = 0\}$$

with the infinitesimal generator $\mathcal{A}^{\odot}$ with the domain

$$\mathcal{D}(\mathcal{A}^{\odot}) = \{f \in \widetilde{C}(X): \ \frac{\partial f}{\partial a} \in C(X)\}$$

and given by the same formula as $\mathcal{A}^*$. Let $\mathcal{A}_0^{\odot} f = \frac{\partial f}{\partial a}$, $\mathcal{D}(\mathcal{A}_0^{\odot}) = \mathcal{D}(\mathcal{A}^{\odot})$. Then $\mathcal{A}_0^{\odot}$ is the infinitesimal generator of a $C_0$-semigroup $\{T_0^{\odot}(t)\}_{t\geq 0}$ on the space $\widetilde{C}(X)$ given by the formula

$$T_0^{\odot}(t)f(x_b, a) = \begin{cases} f(x_b, a+t) & \text{for } a \leq \overline{a}(x_b) - t, \\ 0 & \text{for } a > \overline{a}(x_b) - t. \end{cases}$$

Let $H^{\odot}: C([\underline{x}_b, \overline{x}_b]) \to \widetilde{C}(X)$ be given by $(H^{\odot}f)(x_b, a) = 2q(x_b, a)f(S_a(x_b))$. Then $\mathcal{A}^{\odot}f = \mathcal{A}_0^{\odot}f + H^{\odot}\tilde{f}$ for $f \in \mathcal{D}(\mathcal{A}^{\odot})$.

Denote by $R(\lambda, \mathcal{A}_0^{\odot})$ the resolvent of the operator $\mathcal{A}_0^{\odot}$. If $v \in \widetilde{C}(X)$ satisfies the equation

(32) $$v = R(\lambda, \mathcal{A}_0^{\odot})H^{\odot}\tilde{v},$$

then $v$ also satisfies (31). Since $R(\lambda, \mathcal{A}_0^{\odot})f = \int_0^{\infty} e^{-\lambda s}T_0^{\odot}(s)f\,ds$ we find that

$$R(\lambda, \mathcal{A}_0^{\odot})f(x_b, a) = \int_a^{\infty} f(x_b, s)e^{-\lambda(s-a)}\,ds.$$

Now (32) can be written as the following integral equation

(33) $$v(x_b, a) = \int_a^{\infty} (H^{\odot}\tilde{v})(x_b, s)e^{-\lambda(s-a)}\,ds.$$

Observe that in order to find $v(x_b, a)$ it is enough to solve (33) for $a = 0$. Equation (33) for $a = 0$ takes the form

(34) $$v(x_b, 0) = \int_0^{\infty} (H^{\odot}\tilde{v})(x_b, s)e^{-\lambda s}\,ds.$$

In the above formula we replace $s$ by $a$ and apply (29). Then

$$v(x_b, 0) = \int_{\underline{a}(x_b)}^{\overline{a}(x_b)} 2e^{-\lambda a}q(x_b, a)v(S_a(x_b), 0)\,da.$$

Let

(35) $$K_{\lambda}\tilde{v}(x_b) = \int_{\underline{a}(x_b)}^{\overline{a}(x_b)} 2e^{-\lambda a}q(x_b, a)\tilde{v}(S_a(x_b))\,da.$$

We want to prove that there exists a constant $\lambda > 0$ and a positive function $\tilde{v} \in C[\underline{x}_b, \overline{x}_b]$ such that $K_{\lambda}\tilde{v} = \tilde{v}$. We split the proof of this fact into two lemmae.

**Lemma 1.** *For each $\lambda \geq 0$ the spectral radius $r(K_\lambda)$ of $K_\lambda$ is a positive, isolated and simple eigenvalue of $K_\lambda$ associated with a positive eigenfunction $\tilde{v}_\lambda \in C[\underline{x}_b, \overline{x}_b]$.*

*Proof.* In order to check this property we write the operator $K_\lambda$ in the standard integral form. We substitute $y(a) = S_a(x_b)$ in (35). Then $da = 2\,dy/g(2y)$ and we find that the operator $K_\lambda$ can be written in the form

$$K_\lambda \tilde{v}(x_b) = \int_{\underline{x}_b}^{\overline{x}_b} k_\lambda(x_b, y)\tilde{v}(y)\,dy, \quad k_\lambda(x_b, y) = \frac{4e^{-\lambda a(y;x_b)}q(x_b, a(y;x_b))}{g(2y)},$$

where

$$a(y; x_b) = \int_{x_b}^{2y} \frac{dr}{g(r)}.$$

The expression $a(y; x_b)$ has the following interpretation. If $x_b$ is the initial size of a mother cell and it splits at the age $a(y; x_b)$, then $y$ is the initial size of its daughter cells. Since the function $g$ is continuous and positive, the kernel $k_\lambda$ is continuous and nonnegative. Moreover, $k_\lambda(x_b, x_b) > 0$ for all $x_b \in (\underline{x}_b, \overline{x}_b)$. Indeed, $k_\lambda(x_b, x_b) > 0$ if and only if $q(x_b, a(x_b; x_b)) > 0$. The last inequality follows from (A6) (see Fig. 2). This implies that the spectral radius $r(K_\lambda)$ is a positive, isolated and simple eigenvalue of $K_\lambda$ associated with an eigenfunction $\tilde{v}_\lambda \in C[\underline{x}_b, \overline{x}_b]$ such that $\tilde{v}_\lambda(x_b) > 0$ for $x_b \in (\underline{x}_b, \overline{x}_b)$ (see comments after the proof of Theorem 7.4 of [2]). Observe that $\tilde{v}_\lambda$ is also positive at $\underline{x}_b$ and $\overline{x}_b$, because $\tilde{v}_\lambda(y) > 0$ for $y \in (\underline{x}_b, \overline{x}_b)$ and the functions $y \mapsto q(\underline{x}_b, a(y; \underline{x}_b))$ and $y \mapsto q(\overline{x}_b, a(y; \overline{x}_b))$ are positive on some nontrivial intervals. $\square$

**Lemma 2.** *There exists $\lambda > 0$ such that $r(K_\lambda) = 1$.*

*Proof.* Since $k_{\lambda_1} \geq k_{\lambda_2}$ for $\lambda_1 \leq \lambda_2$, the function $\lambda \mapsto r(K_\lambda)$ is nonincreasing. We check that this function is also continuous. Indeed, let $T_{\lambda_1, \lambda_2} = K_{\lambda_1} - K_{\lambda_2}$. Then

$$r(K_{\lambda_1}) = r(K_{\lambda_2} + T_{\lambda_1, \lambda_2}) \leq r(K_{\lambda_2}) + r(T_{\lambda_1, \lambda_2})$$
$$\leq r(K_{\lambda_2}) + \|T_{\lambda_1, \lambda_2}\|.$$

Since $\int q(x_b, a)\,da = 1$ and $e^{-\lambda_1 a} - e^{-\lambda_2 a} \leq \overline{a}(\lambda_2 - \lambda_1)$, we have

$$\|T_{\lambda_1, \lambda_2}\| \leq \max_{\underline{x}_b \leq x_b \leq \overline{x}_b} \int_{\underline{a}(x_b)}^{\overline{a}(x_b)} 2\left(e^{-\lambda_1 a} - e^{-\lambda_2 a}\right)q(x_b, a)\,da \leq 2\overline{a}(\lambda_2 - \lambda_1).$$

Thus $r(K_{\lambda_2}) \leq r(K_{\lambda_1}) \leq r(K_{\lambda_2}) + 2\overline{a}(\lambda_2 - \lambda_1)$, which proves the continuity of the function $\lambda \mapsto r(K_\lambda)$. Observe that, $r(K_0) = 2$, because $\|K_0\| = 2$ and $K_0 \mathbf{1}_{[\underline{x}_b, \overline{x}_b]} = 2 \cdot \mathbf{1}_{[\underline{x}_b, \overline{x}_b]}$. Now, let $\overline{\lambda} > 0$ be a constant such that $e^{-\overline{\lambda}\underline{a}} \leq 1/4$. Then

$$K_{\overline{\lambda}}\tilde{v}(x_b) \leq \frac{1}{2}\int_{\underline{a}(x_b)}^{\overline{a}(x_b)} q(x_b, a)\tilde{v}(S_a(x_b))\,da \leq \frac{1}{2}\|\tilde{v}\| \quad \text{for } \tilde{v} \geq 0,$$

and consequently $r(K_{\bar{\lambda}}) \leq \|K_{\bar{\lambda}}\| \leq \frac{1}{2}$. From the continuity of the function $\lambda \mapsto r(K_\lambda)$ it follows that there exists a $\lambda \in (0, \bar{\lambda})$ such that $r(K_\lambda) = 1$. $\quad\square$

Now we apply formula (33) to find a nonnegative eigenfunction $v(x_b, a)$ of the operator $\mathcal{A}^*$.

**Proposition 2.** *The operator $\mathcal{A}^*$ has an eigenvalue $\lambda > 0$ and a corresponding eigenfunction $v$ such that*

$$(36) \qquad\qquad c_1 \Phi(x_b, a) \leq v(x_b, a) \leq c_2 \Phi(x_b, a)$$

*for some positive constants $c_1$ and $c_2$ independent of $x_b$ and $a$.*

*Proof.* According to Lemma 2 there exists $\lambda > 0$ such that $r(K_\lambda) = 1$. Let $\tilde{v}_\lambda$ be a positive fixed point of $K_\lambda$. Then from formulae (29) and (33) it follows that

$$v(x_b, a) = \int_a^\infty 2q(x_b, s)\tilde{v}_\lambda(S_s(x_b))e^{-\lambda(s-a)}\, ds$$

is the eigenfunction of the operator $\mathcal{A}^*$ corresponding to $\lambda$. Since the functions $\tilde{v}_\lambda(S_s(x_b))$ and $e^{-\lambda(s-a)}$ are bounded above and bounded away from zero, there exist positive constants $c_1$ and $c_2$ such that

$$c_1 \int_a^\infty q(x_b, s)\, ds \leq v(x_b, a) \leq c_2 \int_a^\infty q(x_b, s)\, ds$$

and (36) follows from the definition of $\Phi$. $\quad\square$

From now on $\lambda$ denotes the eigenvalue from Proposition 2. If a function $f_i(x_b, a)$ is an eigenvector of $\mathcal{A}$ corresponding to $\lambda$, then the function $\tilde{z}(t, x_b, a) = e^{\lambda t} f_i(x_b, a)$ is a solution of (14)–(16). Substituting $\tilde{z} = e^{\lambda t} f_i$ into (14)–(15) we obtain

$$\lambda f_i(x_b, a) + \frac{\partial f_i}{\partial a}(x_b, a) = 0, \quad f_i(x_b, 0) = \int_0^\infty 2P_a(q(x_b, a)f_i(x_b, a))\, da.$$

Thus

$$(37) \qquad\qquad f_i(x_b, a) = e^{-\lambda a} f_i(x_b, 0) \quad \text{for} \quad a \leq \bar{a}(x_b)$$

and the function $x_b \mapsto f_i(x_b, 0)$ satisfies the following integral equation

$$(38) \qquad\qquad f_i(x_b, 0) = \int_0^\infty 2e^{-\lambda a} P_a\big(q(x_b, a)f_i(x_b, 0)\big)\, da.$$

Let $J$ be the integral operator on $L^1[\underline{x}_b, \overline{x}_b]$ given by

$$Jf(x_b) = \int_0^\infty 2e^{-\lambda a} P_a\big(q(x_b, a)f(x_b)\big)\, da.$$

The operators $J$ and $K_\lambda$ are adjoint, i.e.

$$(39) \qquad\qquad \int_{\underline{x}_b}^{\overline{x}_b} g(x_b)Jf(x_b)\, dx_b = \int_{\underline{x}_b}^{\overline{x}_b} K_\lambda g(x_b)f(x_b)\, dx_b$$

for $f \in L^1[\underline{x}_b, \overline{x}_b]$, $g \in L^\infty[\underline{x}_b, \overline{x}_b]$. Since

$$P_a\big(q(x_b, a) f(x_b)\big) = \frac{d}{dx_b}\big(S_a^{-1}(x_b)\big) q\big(S_a^{-1}(x_b), a\big) f\big(S_a^{-1}(x_b)\big),$$

the substitution $y = S_a^{-1}(x_b)$ gives

$$(40) \qquad J f(x_b) = \int_{\underline{x}_b}^{2x_b} 2 e^{-\lambda a(x_b; y)} q(y, a(x_b; y)) f(y)\, dy.$$

From the above formula it follows that $J$ is an integral operator with a continuous kernel. In particular $Jf \in C[\underline{x}_b, \overline{x}_b]$ for $f \in L^1[\underline{x}_b, \overline{x}_b]$ and the operator $J$ restricted to $C[\underline{x}_b, \overline{x}_b]$ is a continuous and positive.

**Lemma 3.** *There exists $\tilde{f}_i \in C[\underline{x}_b, \overline{x}_b]$ such that $J\tilde{f}_i = \tilde{f}_i$ and $\tilde{f}_i(x_b) > 0$ for $x_b \in (\underline{x}_b, \overline{x}_b)$. The function $\tilde{f}_i$ is the unique, up to a multiplicative constant, fixed point of $J$.*

*Proof.* Using the same arguments as in Lemma 1 we prove that there exists an eigenfunction $\tilde{f}_i \in C[\underline{x}_b, \overline{x}_b]$ of $J$ such that $\tilde{f}_i(x_b) > 0$ for $x_b \in (\underline{x}_b, \overline{x}_b)$. This eigenfunction is indeed a fixed point of $J$ because $\langle J\tilde{f}_i, \tilde{v}_\lambda \rangle = \langle \tilde{f}_i, K_\lambda \tilde{v}_\lambda \rangle = \langle \tilde{f}_i, \tilde{v}_\lambda \rangle$. Since $r = 1$ is an isolated and simple eigenvalue of $J$, the function $\tilde{f}_i$ is the unique, up to a multiplicative constant, fixed point of $J$. $\qquad\square$

*Remark* 2. It is generally not true that $\tilde{f}_i(\underline{x}_b) > 0$ and $\tilde{f}_i(\overline{x}_b) > 0$. If we assume additionally that $S_{\underline{a}(x_b)}(x_b) = \underline{x}_b$ for $x_b \in [\underline{x}_b, \underline{x}_b + \delta]$, $\delta > 0$, then $\tilde{f}_i(\underline{x}_b) > 0$ because a mother cell with the initial size $x_b \in [\underline{x}_b, \underline{x}_b + \delta]$ can have a daughter cell with the initial size $\underline{x}_b$. Analogously, if $S_{\overline{a}(x_b)}(x_b) = \overline{x}_b$ for $x_b \in [\overline{x}_b - \delta, \overline{x}_b]$, $\delta > 0$, then $\tilde{f}_i(\overline{x}_b) > 0$.

From Lemma 3 and from formulae (37) and (38) we have

**Proposition 3.** *Let $\tilde{f}_i$ be the function from Lemma 3. If $f_i(x_b, a) = e^{-\lambda a} \tilde{f}_i(x_b)$, then $\mathcal{A} f_i = \lambda f_i$. The function $f_i$ is the unique, up to a multiplicative constant, eigenfunction of $\mathcal{A}$ corresponding to the eigenvalue $\lambda$.*

## 5. Asymptotic behaviour

We precede the formulation of the main result of this section by some definitions and some general theorem concerning asymptotic stability of stochastic semigroups.

Let a triple $(X, \Sigma, m)$ be a $\sigma$-finite measure space. Denote by $D$ the subset of the space $L^1 = L^1(X, \Sigma, m)$ which contains all densities

$$D = \{f \in L^1 \colon f \geq 0, \ \|f\| = 1\}.$$

A $C_0$-semigroup $\{P(t)\}_{t \geq 0}$ of linear operators on $L^1$ is called *stochastic semigroup* or *Markov semigroup* if $P(t)(D) \subseteq D$ for each $t \geq 0$.

A stochastic semigroup $\{P(t)\}_{t\geq0}$ is *asymptotically stable* if there exists a density $f_i$ such that

$$(41) \qquad \lim_{t\to\infty} \|P(t)f - f_i\| = 0 \quad \text{for} \quad f \in D.$$

From (41) it follows immediately that $f_i$ is *invariant* with respect to $\{P(t)\}_{t\geq0}$, i.e. $P(t)f_i = f_i$ for each $t \geq 0$.

A stochastic semigroup $\{P(t)\}_{t\geq0}$ is called *partially integral* if there exists a measurable function $k\colon (0,\infty) \times X \times X \to [0,\infty)$, called a *kernel*, such that

$$(42) \qquad P(t)f(x) \geq \int_X k(t,x,y)f(y)\, m(dy)$$

for every density $f$ and

$$\int_X \int_X k(t,x,y)\, m(dx)\, m(dy) > 0$$

for some $t > 0$. The following result was proved in [31].

**Theorem 2.** *Let $\{P(t)\}_{t\geq0}$ be a partially integral stochastic semigroup. Assume that the semigroup $\{P(t)\}_{t\geq0}$ has a unique invariant density $f_i$. If $f_i > 0$ a.e., then the semigroup $\{P(t)\}_{t\geq0}$ is asymptotically stable.*

New results concerning positive operators on Banach lattices similar in spirit to Theorem 2 may be found in [11, 25].

Investigation of the long-time behaviour of the semigroup $\{T(t)\}_{t\geq0}$ can be reduced to study asymptotic stability of some stochastic semigroup. Let $\lambda$ and $v$ be the eigenvalue and the eigenfunction from Proposition 2. We define a semigroup $\{P(t)\}_{t\geq0}$ as the extension of semigroup $\{e^{-\lambda t}T(t)\}_{t\geq0}$ to the space $E_1 = L^1(X, \mathcal{B}(X), \mu)$ with measure $\mu$ given by $d\mu = v\, d\ell$. Observe that we can indeed extend the semigroup $\{e^{-\lambda t}T(t)\}_{t\geq0}$ to a stochastic semigroup on $E_1$. Since $\mathcal{A}^* v = \lambda v$, we have $T^*(t)v = e^{\lambda t}v$. If $f \in E$ then $P(t)f = e^{-\lambda t}T(t)f$ and

$$\iint_X P(t)f(x_b, a)\, \mu(dx_b, da) = \iint_X e^{-\lambda t}T(t)f(x_b, a)v(x_b, a)\, dx_b\, da$$

$$= \iint_X f(x_b, a)e^{-\lambda t}T^*(t)v(x_b, a)\, dx_b\, da = \iint_X f(x_b, a)v(x_b, a)\, dx_b\, da$$

$$= \iint_X f(x_b, a)\, \mu(dx_b, da).$$

Since the function $v$ is bounded and positive almost everywhere, $E$ is dense in $E_1$. If $f \in E_1$, we choose a sequence $(f_n)$ from $E$ such that $f_n \to f$ in $E_1$ and define $P(t)f = \lim_{n\to\infty} P(t)f_n$ in $E_1$. Since the operators $P(t)$ are positive and preserve the integral with respect to $\mu$, this extension is uniquely defined and $\{P(t)\}_{t\geq0}$ is a stochastic semigroup on $E_1$.

In order to prove asymptotic stability of the semigroup $\{P(t)\}_{t\geq 0}$ we need to add an additional assumption concerning function $g$:
(A7) there exists $x \in (\underline{x}_b, \overline{x}_b)$ such that $g(2x) \neq 2g(x)$.
We precede the formulation of a theorem on asymptotic stability of $\{P(t)\}_{t\geq 0}$ by the following lemma.

**Lemma 4.** *Assume (A1)–(A7). Then the semigroup $\{T(t)\}_{t\geq 0}$ is partially integral.*

*Proof.* Observe that the operator $T(t)$ has the kernel $k(t,x,y)$ if and only if the operator $T^*(t)$ has the kernel $k^*(t,x,y) = k(t,y,x)$. Thus, in order to prove that the semigroup $\{T(t)\}_{t\geq 0}$ is partially integral it is sufficient to check that the semigroup $\{T^{\odot}(t)\}_{t\geq 0}$ has the similar property. The semigroup $\{T^{\odot}(t)\}_{t\geq 0}$ is given by the *Dyson-Phillips expansion*

$$(43) \qquad T^{\odot}(t)f = \sum_{n=0}^{\infty} T_n^{\odot}(t)f,$$

where

$$(44) \qquad T_{n+1}^{\odot}f(t) = \int_0^t T_0^{\odot}(\tau)\mathcal{H}T_n^{\odot}(t-\tau)f\,d\tau, \quad n \geq 0,$$

where $(\mathcal{H}f)(x_b, a) = 2q(x_b, a)f(S_a(x_b), 0)$ and $T_0^{\odot}(t)f(x_b, a) = f(x_b, a+t)$. Since $\mathcal{H}T_0^{\odot}(t-\tau)f(x_b, a) = 2q(x_b, a)f(S_a(x_b), t-\tau)$, we have

$$T_1^{\odot}f(t)(x_b, a) = \int_0^t T_0^{\odot}(\tau)\mathcal{H}T_0^{\odot}(t-\tau)f(x_b, a)\,d\tau$$

$$= \int_0^t 2q(x_b, a+\tau)f(S_{a+\tau}(x_b), t-\tau)\,d\tau.$$

Analogously, since

$$T_1^{\odot}(t-\tau_1)f(x_b, a) = \int_0^{t-\tau_1} 2q(x_b, a+\tau)f(S_{a+\tau}(x_b), t-\tau_1-\tau)\,d\tau,$$

we have

$$\mathcal{H}T_1^{\odot}(t-\tau_1)f(x_b, a) = 2q(x_b, a)\int_0^{t-\tau_1} 2q(S_a(x_b), \tau)f(S_\tau(S_a(x_b)), t-\tau_1-\tau)\,d\tau,$$

and finally

$$T_2^{\odot}f(t)(x_b, a) = \int_0^t T_1^{\odot}(\tau_1)\mathcal{H}T_1^{\odot}(t-\tau_1)f(x_b, a)\,d\tau_1$$

$$= \int_0^t 2q(x_b, a+\tau_1)\int_0^{t-\tau_1} 2q(S_{a+\tau_1}(x_b), \tau)$$
$$\cdot f(S_\tau(S_{a+\tau_1}(x_b)), t-\tau_1-\tau)\,d\tau\,d\tau_1.$$

We substitute in the last integral $\tilde{x} = S_\tau(S_{a+\tau_1}(x_b))$ and $\tilde{a} = t - \tau_1 - \tau$. Then

$$
\begin{aligned}
\frac{\partial \tilde{x}}{\partial \tau} &= \frac{1}{2} g\big(S_\tau(S_{a+\tau_1}(x_b))\big), \\
\frac{\partial \tilde{x}}{\partial \tau_1} &= \frac{1}{2} \frac{g(\pi_\tau S_{a+\tau_1}(x_b))}{g(S_{a+\tau_1}(x_b))} \cdot \frac{1}{2} g\big(S_{a+\tau_1}(x_b)\big) = \frac{1}{4} g(\pi_\tau S_{a+\tau_1}(x_b)), \\
\frac{\partial \tilde{a}}{\partial \tau} &= \frac{\partial \tilde{a}}{\partial \tau_1} = -1.
\end{aligned}
$$

Let $\mathcal{J}_{\tau,\tau_1}$ be the Jacobian matrix of the transformation $(x_b, a) \mapsto (\tilde{x}, \tilde{a})$. Then

$$
\det \mathcal{J}_{\tau,\tau_1}(x_b, a) = \frac{1}{4} g(\pi_\tau S_{a+\tau_1}(x_b)) - \frac{1}{2} g\big(S_\tau(S_{a+\tau_1}(x_b))\big).
$$

Let $x \in (\underline{x}_b, \overline{x}_b)$ be such that $g(2x) \neq 2g(x)$. We find $x_b^1 \in (\underline{x}_b, \overline{x}_b)$ and $\tau^0 > 0$ such that $q(x_b^1, \tau^0) > 0$ and $S_{\tau^0}(x_b^1) = x$, i.e. $x$ and $x_b^1$ are the initial sizes of daughter and mother cells. Next we find $x_b^0 \in (\underline{x}_b, \overline{x}_b)$, $a^0 > 0$, and $\tau_1^0 > 0$ such that $q(x_b^0, a^0 + \tau_1^0) > 0$ and $S_{a^0 + \tau_1^0}(x_b^0) = x_b^1$. We also choose $t > 0$ such that the point $(x, t - \tau^0 - \tau_1^0)$ lies in the interior of the set $X$. Then we find a neighbourhood $\mathcal{U}$ of the point $(\tau^0, \tau_1^0, x_b^0, a^0)$ such that $\det \mathcal{J}_{\tau,\tau_1}(x_b, a) \neq 0$, $q(x_b, a + \tau_1) > 0$, $q(S_{a+\tau_1}(x_b), \tau) > 0$, $(S_\tau(S_{a+\tau_1}(x_b)), t - \tau - \tau_1) \in X$ for $(\tau, \tau_1, x_b, a) \in \mathcal{U}$. Thus there exist neighbourhoods $V_1$ and $V_2$ of the points $(x_b^0, a^0)$ and $(x, t - \tau_1^0 - \tau^0)$ and there exist $\varepsilon > 0$ and a nonnegative kernel $k(t, x_b, a, \tilde{x}, \tilde{a})$ such that $k(t, x_b, a, \tilde{x}, \tilde{a}) \geq \varepsilon$ for $(x_b, a, \tilde{x}, \tilde{a}) \in V_1 \times V_2$ and

$$
T_2^\odot f(t)(x_b, a) \geq \iint\limits_X k(t, x_b, a, \tilde{x}, \tilde{a}) f(\tilde{x}, \tilde{a}) \, d\tilde{x} \, d\tilde{a}.
$$

From (43) it follows that the semigroups $\{T^\odot(t)\}_{t \geq 0}$ and $\{T(t)\}_{t \geq 0}$ are partially integral. $\qquad\square$

**Theorem 3.** *Assume* (A1)–(A7). *Then the semigroup* $\{P(t)\}_{t \geq 0}$ *is asymptotically stable. The eigenfunction of* $\mathcal{A}$ *from Proposition 3 is the invariant density of* $\{P(t)\}_{t \geq 0}$.

*Proof.* We need to check that the semigroup $\{P(t)\}_{t \geq 0}$ satisfies assumptions of Theorem 2. Since the semigroup $\{T(t)\}_{t \geq 0}$ is partially integral and $P(t)f = e^{-\lambda t} T(t)f$ for $f \in E$, the same property has the semigroup $\{P(t)\}_{t \geq 0}$. According to Proposition 3 there exists a function $f_i$ such that $\mathcal{A}f_i = \lambda f_i$ and $f_i > 0$ a.e. As $\mu(X) < \infty$ and $f_i$ is bounded, $f_i$ is integrable with respect to $\mu$. Since the eigenfunction is determined up to a multiplicative constant, we may assume that $\int_X f_i \, d\mu = 1$. Also according to Proposition 3 the function $f_i$ is the unique invariant density of $\{P(t)\}_{t \geq 0}$. $\quad\square$

Condition of asymptotic stability of the semigroup $\{P(t)\}_{t\geq 0}$ can be written in the following equivalent form: for every $f \in E_1$ we have

$$(45) \qquad \lim_{t\to\infty} P(t)f = f_i \iint_X f(x_b, a)v(x_b, a)\, dx_b\, da \quad \text{in } E_1.$$

We can extend the semigroup $\{T(t)\}_{t\geq 0}$ to a $C_0$-semigroup on $E_1$ setting $T(t)f = e^{\lambda t}P(t)f$ for $f \in E_1$. From (45) it follows that

$$(46) \qquad \lim_{t\to\infty} e^{-\lambda t}T(t)f = f_i \iint_X f(x_b, a)v(x_b, a)\, dx_b\, da \quad \text{in } E_1.$$

Now we return to the problem (10)–(12). We recall that after substitution $z(t, x_b, a) = u(t, x_b, a)\Psi(x_b, a)$ and $z_0(x_b, a) = u_0(x_b, a)\Psi(x_b, a)$ we have replaced this problem by the system (14)–(16) and the semigroup $\{T(t)\}_{t\geq 0}$ describes the evolution of the solutions of this system. Since $z = u\Psi$ and $z_0 = u_0\Psi$, we have $u(t) = \Phi T(t)(u_0\Psi)$ because $\Phi = 1/\Psi$. Thus we can define a semigroup $\{U(t)\}_{t\geq 0}$ corresponding to (10)–(12) by

$$(47) \qquad U(t)u_0 = \Phi T(t)(u_0\Psi).$$

From inequalities (36) it follows that $u_0\Psi \in E_1$ if and only if $u_0 \in E$ and $\{U(t)\}_{t\geq 0}$ is a $C_0$-semigroup on the space $E$. It should be noted that we consider solutions of (10)–(12) for a wider class of initial conditions because we do not assume that $u_0$ satisfies inequality (13). From (46) it follows that

$$(48) \qquad \lim_{t\to\infty} e^{-\lambda t}\Psi U(t)u_0 = f_i \iint_X u_0(x_b, a)\Psi(x_b, a)v(x_b, a)\, dx_b\, da \quad \text{in } E_1.$$

Using again inequalities (36) we finally obtain

**Theorem 4.** *For every $u_0 \in E$ we have*

$$(49) \qquad \lim_{t\to\infty} e^{-\lambda t}U(t)u_0 = \Phi f_i \iint_X u_0(x_b, a)\Psi(x_b, a)v(x_b, a)\, dx_b\, da \quad \text{in } E.$$

*Moreover, $\Phi f_i$ and $\Psi v$ are eigenfunctions of the semigroups $\{U(t)\}_{t\geq 0}$ and $\{U^*(t)\}_{t\geq 0}$ corresponding to the eigenvalue $\lambda$.*

Property (49) is called the asynchronous exponential growth of the semigroup $\{U(t)\}_{t\geq 0}$. Precisely, we say that a semigroup $\{U(t)\}_{t\geq 0}$ on a Banach space $\mathbb{X}$ has *asynchronous* (or *balanced*) *exponential growth* if there exist $\lambda \in \mathbb{C}$, a nonzero $x_i \in \mathbb{X}$, and a nonzero linear functional $\alpha \colon \mathbb{X} \to \mathbb{C}$ such that

$$(50) \qquad \lim_{t\to\infty} e^{-\lambda t}U(t)x = x_i\alpha(x) \quad \text{for } x \in \mathbb{X}.$$

It should be mentioned that one can find in literature, e.g. [46], a more general definition of asynchronous exponential growth, where it is only assumed that $e^{-\lambda t}U(t)x$ converges to a nonzero finite rank operator.

## 6. REMARKS

**6.1. Chemostat.** In Section 2 we have mentioned that if we consider experiment in a chemostat, then we need to add to the right-hand side of equation (10) the term $-Du(t, x_b, a)$. In this case we substitute $u(t, x_b, a) = e^{-Dt}\bar{u}(t, x_b, a)$ and then we check that the function $\bar{u}$ satisfies the system (10)–(12). From Theorem 4 we deduce that

$$(51) \quad \lim_{t \to \infty} e^{(D-\lambda)t} U(t)u_0 = \Phi f_i \iint_X u_0(x_b, a)\Psi(x_b, a)v(x_b, a)\, dx_b\, da \quad \text{in } E.$$

From (51) it follows that in order to grow cells under constant environmental conditions cells should be removed from the system with rate $D = \lambda$.

**6.2. Age-size structured model.** Now we consider an age-size structured model consistent with our biological description. Let $\bar{p}(x, a)\Delta t$ be the probability that a cell with size $x$ and age $a$ splits in the time interval of the length $\Delta t$. Since such a cell had the initial size $x_b = \pi_{-a}x$, we see that

$$(52) \quad \bar{p}(x, a) = p(\pi_{-a}x, a) = q(\pi_{-a}x, a)\big/\int_a^\infty q(\pi_{-a}x, r)\, dr$$

for $a < \bar{a}(\pi_{-a}x)$. We set $\bar{p}(x, a) = 0$ for $a \geq \bar{a}(\pi_{-a}x)$. Let $w(t, x, a)$ be the number of cells having size $x$ and age $a$ at time $t$. Then the function $w$ satisfies the following initial-boundary problem:

$$(53) \quad \frac{\partial w}{\partial t}(t, x, a) + \frac{\partial w}{\partial a}(t, x, a) + \frac{\partial(gw)}{\partial x}(t, x, a) = -\bar{p}(x, a)w(t, x, a),$$

$$(54) \quad w(t, x, 0) = 4\int_0^\infty \bar{p}(2x, a)w(t, 2x, a)\, da,$$

$$(55) \quad w(0, x, a) = w_0(x, a).$$

We have the following relationship between solutions of the systems (10)–(12) and (53)–(55):

$$(56) \quad \int_0^a \int_0^x u(t, x_b, r)\, dx_b\, dr = \int_0^a \int_0^{\pi_r x} w(t, y, r)\, dy\, dr.$$

Differentiating both sides of (56) with respect to $a$ and $x$ we obtain

$$u(t, x, a) = \frac{\partial(\pi_a x)}{\partial x} w(t, \pi_a x, a) = \frac{g(\pi_a x)}{g(x)} w(t, \pi_a x, a).$$

Using the above formula and Theorem 4 we get

$$e^{-\lambda t} \frac{g(\pi_a x)}{g(x)} w(t, \pi_a x, a) \to (\Phi f_i)(x, a) \iint_X w_0(\pi_a x_b, a)h(x_b, a)\, dx_b\, da$$

in $E$ as $t \to \infty$, where $h(x_b, a) = \Psi(x_b, a)v(x_b, a)g(\pi_a x_b)/g(x_b)$. Finally we conclude that

$$e^{-\lambda t} w(t, x, a) \to h_i(x, a) \iint_X w_0(\pi_a x_b, a)h(x_b, a)\, dx_b\, da$$

in $L^1$, where $h_i(x,a) = (\Phi f_i)(\pi_{-a}x,a)g(\pi_{-a}x)/g(x)$.

6.3. **Solutions with values in the space of measures.** If we study the dynamics of population growth of microorganisms starting from a single cell, then initial distribution of the population is described by a singular measure, precisely with a delta Dirac measure. Thus it is natural to consider a model which describes the evolution of measures instead of $L^1$ functions. We can introduce such a model by considering weak solutions. Let $\{U(t)\}_{t\geq0}$ be the semigroup introduced in Section 5 and let $\{U^\odot(t)\}_{t\geq0}$ be the "dual semigroup" given by $U^\odot(t)u_0 = \Psi T^\odot(t)(\Phi u_0)$ (see formula (47)). Denote by $\mathcal{M}(X)$ the space of all finite Borel measures on $X$. For any measure $\nu_0 \in \mathcal{M}(X)$ we define the *weak solution* of the problem (10)–(12) as a function $u\colon [0,\infty) \to \mathcal{M}(X)$, $u(t) = \nu_t$, where the measures $\nu_t$ satisfy the condition

$$(57) \qquad \iint\limits_X f(x_b,a)\,\nu_t(dx_b,da) = \iint\limits_X U^\odot(t)f(x_b,a)\,\nu_0(dx_b,da).$$

Since the set $X$ is compact, the existence and uniqueness of the measures $\nu_t$ is a simple consequence of the Riesz representation theorem.

One can ask about the long-time behaviour of the measures $\nu_t$. We are interested in convergence of measures in the total variation norm. For $\nu, \bar\nu$ we denote by $d(\nu,\bar\nu)_{TV}$ the distance between $\nu$ and $\bar\nu$ in the *total variation norm* in $\mathcal{M}(X)$. We recall that

$$d(\nu,\bar\nu)_{TV} = (\nu - \bar\nu)^+(X) + (\nu - \bar\nu)^-(X),$$

where the symbols $\nu^+$ and $\nu^-$ denote the positive and negative part of a signed measure $\nu$. We can formulate Theorem 4 in a slightly stronger form:

**Proposition 4.** *Assume that conditions* (A1)–(A7) *hold. Let* $\nu_0 \in \mathcal{M}(X)$ *and let* $\nu_\infty$ *be the measure given by*

$$\nu_\infty(A) = \int\limits_A (\Phi f_i)\,dx_b\,da \cdot \iint\limits_X \Psi(x_b,a)v(x_b,a)\,\nu_0(dx_b,\,da)$$

*for* $A \in \mathcal{B}(X)$. *Then*

$$(58) \qquad\qquad \lim_{t\to\infty} d(e^{-\lambda t}\nu_t, \nu_\infty)_{TV} = 0.$$

We only give some idea of the proof of Proposition 4. We consider weak solutions connected with the semigroup $\{P^\odot(t)\}_{t\geq0}$, i.e. we replace in (57) the semigroup $\{U^\odot(t)\}_{t\geq0}$ by $\{P^\odot(t)\}_{t\geq0}$, where $P^\odot(t) = e^{-\lambda t}T^\odot(t)$. It is enough to check that if $\nu_0$ is a probability measure then $\lim_{t\to\infty} d(\nu_t, \mu_*)_{TV} = 0$, where $d\mu_* = f_i d\mu$. We write $\nu_t$ as a sum $\nu_t^a + \nu_t^s$, where $\nu_t^a$ is the absolutely continuous part of $\nu_t$ with respect to the Lebesgue measure and $\nu_t^s$ is the singular part of $\nu_t$. We deduce from conditions (A6) and (A7) that there exist $t_0 > 0$ and $\varepsilon > 0$ independent of $\nu_0$ such that $\nu_{t_0}^s(X) \leq 1 - \varepsilon$. The proof of this part is very technical but it uses similar arguments as the proof of Lemma 4. From the last inequality it follows that $\nu_t^s(X) \leq (1-\varepsilon)^n$

for $t \geq nt_0$. Fix $\eta > 0$ and let $t_1 > 0$ be such that $\nu_{t_1}^s(X) \leq \eta$. Let $f = d\nu_{t_1}^a/d\mu$. Then $\lim_{t\to\infty} \|P(t)f - f_i \int f \, d\mu\|_{E_1} = 0$. Since $\int f \, d\mu \geq 1 - \eta$ and $\nu_{t_1}^s(X) \leq \eta$, we have $d(\nu_t, \mu_*)_{TV} \leq 2\eta$. As $\eta > 0$ can be chosen arbitrary small we finally obtain $\lim_{t\to\infty} d(\nu_t, \mu_*)_{TV} = 0$.

It should be noted that a slightly weaker result than Proposition 4 can be obtained by using the theory of positive recurrent and aperiodic Harris processes [27], namely condition (58) holds for almost all delta Dirac measures $\delta_{(x_b,a)}$.

6.4. **Case $g(2x) = 2g(x)$.** A function $g$ satisfying condition $g(2x) = 2g(x)$ for all $x \in [\underline{x}_b, \overline{x}_b]$ can be constructed in the following way. Let $g \colon [\underline{x}_b, 2\underline{x}_b] \to (0, \infty)$ be a given $C^1$-function such that $g(2\underline{x}_b) = 2g(\underline{x}_b)$ and $g'(2\underline{x}_b) = g'(\underline{x}_b)$. Then we define $g(x) = 2^n g(2^{-n}x)$ for $x \in [2^n \underline{x}_b, 2^{n+1} \underline{x}_b]$.

Observe that if $g(2x) = 2g(x)$ for all $x \in [\underline{x}_b, \overline{x}_b]$, then the semigroup $\{U(t)\}_{t\geq 0}$ has no asynchronous exponential growth. Indeed, consider a cell with initial size $x_b$. Fix time $t > 0$ and assume that the cell splits at age $a \leq t$. Then the daughter cells at time $t$ have size

$$x(a) = \pi_{t-a}(\tfrac{1}{2}\pi_a x_b).$$

Since

$$x'(a) = -g(\pi_{t-a}(\tfrac{1}{2}\pi_a x_b)) + \frac{g(\pi_{t-a}(\tfrac{1}{2}\pi_a x_b))}{g(\tfrac{1}{2}\pi_a x_b)} \cdot \frac{1}{2}g(\pi_a x_b) = 0,$$

the function $x$ is constant and $x(a) = \tfrac{1}{2}\pi_t x_b$. Thus the size of all daughter cells is exactly twice smaller than the size of the mother cell. If $x_n(t)$ is the size of a cell from the $n$th generation then its mother, grandmother, etc. cells have sizes $2x_n(t)$, $4x_n(t)$, ... But since cells have minimum and maximum size $\underline{x}_b$ and $2\overline{x}_b$, the maximum number of existing generations at a given time $t$ is not greater than $2 + \log_2(\overline{x}_b/\underline{x}_b)$. Moreover, if $x_1 \in (\underline{x}_b, 2\underline{x}_b)$ and $f_1(x_b, a) = \mathbf{1}_{(\underline{x}_b, x_1)}(x_b)$, $f_2(x_b, a) = \mathbf{1}_{(x_1, 2\underline{x}_b)}(x_b)$, then $U(t)f_1 \cdot U(t)f_2 \equiv 0$ for all $t \geq 0$. Consequently, the semigroup $\{U(t)\}_{t\geq 0}$ has no asynchronous exponential growth.

Now we consider a special case when $g(x) = \kappa x$, $\kappa > 0$. We start at time $t = 0$ with a single cell with size $x$. Cells from the $n$th generation have size $2^{-n}e^{\kappa t}x$ at time $t$. Then $\bar{p}(2^{-n}e^{\kappa t}x, a)\Delta t$ is the probability that a cell from the $n$th generation with age $a$ splits in the time interval of the length $\Delta t$. This observation allows us to describe the evolution of the population using discrete parameters. Denote by $w_n(t, a)$ the number of cells from the $n$th generation with age $a$ at time $t$. Then the functions $w_n$ satisfy the following infinite system of partial differential equations with boundary conditions:

$$(59) \qquad \frac{\partial w_n}{\partial t}(t, a) + \frac{\partial w_n}{\partial a}(t, a) = -\bar{p}(2^{-n}e^{\kappa t}x, a)w_n(t, a),$$

$$(60) \qquad w_n(t, 0) = 2\int_0^\infty \bar{p}(2^{1-n}e^{\kappa t}x, a)w_{n-1}(t, a)\, da.$$

It should be noted that it is not easy to find a direct formula for the eigenvector $f_i(x_b, a)$ of the operator $\mathcal{A}$ even in the case $g(x) = \kappa x$. Indeed, we have $\pi_{-a}(2x_b) = 2e^{-\kappa a}x_b$ and

$$
(61) \qquad P_a f(x_b) = \frac{2g(\pi_{-a}(2x_b))}{g(2x_b)} f(\pi_{-a}(2x_b)) = \frac{2\pi_{-a}(2x_b)}{2x_b} f(\pi_{-a}(2x_b))
$$
$$
= 2e^{-\kappa a} f(2e^{-\kappa a}x_b).
$$

Then $f_i(x_b, a) = e^{-\lambda a} f_i(x_b, 0)$, where $\lambda$ and $f_i(x_b, 0)$ should be found by solving the following equation

$$
(62) \qquad f_i(x_b, 0) = \int_0^\infty 4e^{-(\lambda+\kappa)a} q(2e^{-\kappa a}x_b, a) f_i(2e^{-\kappa a}x_b, 0)\, da,
$$

which is not a simple task.

## 7. Comparison with experimental data and other models

Modern experimental techniques enable studies of individual cells growth in well-controlled environments. Especially interesting are experimental results concerning rod-shaped bacteria, for example *E. coli*, *C. crescentus* and *B. subtilis* [7, 15, 39, 44], because they change only their length. Although such bacteria have similar shape there are variety of distinct models of cell cycle and cell division. For example, we consider models with symmetric or asymmetric divisions, with different velocities of proliferation, deterministic or stochastic growth of individuals or models based on special assumptions as fixed cell length extension or models with target size division. We give a short review of such models and show how to incorporate them to our model.

### 7.1. Models with exponential growth. 
Since experimental data suggest that cells grow exponentially, one can find a number of models with the assumption $g(x) = \kappa x$ but with various descriptions of the cell cycle length.

In [7, 12, 39, 43] it is considered an *additive model* (or a *constant* $\Delta$ *model*), where it is assumed that the difference $\Delta(x_b) = x_d - x_b$ between the size at division $x_d$ and the initial size $x_b$ of a cell is a random variable independent of $x_b$. From this assumption it follows that

$$
\tau(x_b) = \kappa^{-1} \ln((x_b + \Delta)/x_b).
$$

If $h(x)$ is the density distribution of $\Delta$, then

$$
(63) \qquad q(x_b, a) = \kappa x_b e^{\kappa a} h\big(x_b e^{\kappa a} - x_b\big)
$$

is the density of $\tau(x_b)$. We obtain a special case of our model if the density distribution of $\Delta$ is positive on the interval $(\underline{x}_b, \overline{x}_b)$. According to experimental data from [39] the coefficient of variation $c_v$ of $\Delta$ for *E. coli* is in the range of 0.17 to 0.28 depending on the different growth conditions. We recall that $c_v = \sigma/\mu$, where $\sigma$ is the standard deviation, and $\mu$ is the mean.

In [1, 16] it is assumed that a cell with initial size $x_b$ attempts to divide at a target size $x_d = f(x_b)$. Then the expected length of the cell cycle is

$\tau_0(x_b) = \kappa^{-1}\ln(f(x_b)/x_b)$, but $\tau_0(x_b)$ is additively perturbed by a symmetric random variable $\xi$, and finally $\tau(x_b) = \tau_0(x_b) + \xi$. If $h(a)$ is the density distribution of $\xi$, then $q(x_b, a) = h(a - \tau_0(x_0))$ is the density of $\tau(x_b)$. The authors assume in these papers that $h$ has a normal distribution but in this case $\tau(x_b)$ can be negative therefore a truncated normal distribution located in some interval $[-\varepsilon, \varepsilon]$ seems to be more suitable. They also assume that $f(x_b) = 2x_b^{1-\alpha}x_0^{\alpha}$, $\alpha \in [0, 1]$ and $x_0 > 0$. If $\alpha > 0$, $\underline{x}_b = x_0 e^{-\kappa\varepsilon/\alpha}$ and $\overline{x}_b = x_0 e^{\kappa\varepsilon/\alpha}$ then we obtain a particular case of our model. If $\alpha = 0$, then $\tau_0 \equiv \kappa^{-1}\ln 2$ and the length of cell cycle does not depend on $x_b$. In this case a daughter cell size is distributed in some neighbourhood of the initial mother cell size, so there is no minimum $\underline{x}_b$ and maximum size $\overline{x}_b$.

7.2. **Paradoxes of exponential growth.** Models with exponential growth law can lead to some odd mathematical results. If the population starts with a single cell of size $x$, cells from $n$th generation have size $x_n(t) = 2^{-n}e^{\kappa t}x$ at time $t$. Since $\underline{x}_b \leq x_n(t) \leq \overline{x}_b$, population consists of a few generations at each time and all cells in each generation have the same size. Usually the quotient $\overline{x}_b/\underline{x}_b$ is not too large. The initial size for *E. coli* under steady-growth conditions is $x_b = 2.32 \pm 0.38\ \mu m$ (mean $\pm$ SD) [7]. Thus we can assume that in this case $\overline{x}_b/\underline{x}_b < 2$. Then it is easy to check that if

$$t \in \left(\frac{n + \log_2(\overline{x}_b/x)}{\kappa \log_2 e}, \frac{1 + n + \log_2(\overline{x}_b/x)}{\kappa \log_2 e}\right),$$

the population consists only cells from the $n$th generation, thus all cells have the same size and they cannot split in this time interval. Consequently the size of the population never reaches an exponential (balanced) growth. On this point we also observe that the large quotient $\overline{x}_b/\underline{x}_b$ helps the population to stabilize its growth, which explains why in the model with target size division [16] it takes the population a longer time to reach its balanced growth for greater $\alpha$, because $\overline{x}_b/\underline{x}_b = e^{2\kappa\varepsilon/\alpha}$.

The exponential growth law of cells should be a little bit modified in order to achieve AEG. For example it is enough to assume that $\kappa$ depends on the initial size $x_b$. But according to the experimental results, the average growth rate does not depend on the initial size of cells. On the other hand, even if a population grows under perfect conditions the individual cells have different growth rates: the standard deviation of the growth rate is 15% of their respective means [39]. Thus there is other factor called maturity, which decides about the growth rate of an individual cell. The mathematical models based on the concept of maturity were formulated in the late sixties [20, 36]. In such models the growth rate is identified with maturation velocity $v$ which is constant during the life of cell and is inherited in a random way from mother to daughter cells.

Rotenberg [35] considered a version of maturity models with random jumps of $v$ during the cell cycle. If we replace random jumps of $v$ by stochastic fluctuations of $\kappa$, we obtain a cell growth model described by a stochastic equation considered in the next subsection.

We consider here a simple generalization of our model assuming that $\kappa$ is a random variable with the distribution dependent on $x_b$. Let the function $r \mapsto k(r|x_b)$ be the density of $\kappa$. The question is how to describe the joint distribution of age and initial size in this case. Equations (10) and (12) remain the same and it is enough to derive a version of the boundary condition (11). Denote by $f(x; x_b, a)$ the density distribution of the random variable $\xi_a^{x_b} = x_b e^{\kappa a}$. Then (11) takes the form

$$(64) \qquad u(t, x, 0) = 4 \iint\limits_X f(2x; x_b, a) p(x_b, a) u(t, x_b, a) \, dx_b \, da.$$

It remains to find the function $f(x; x_b, a)$. We have

$$\mathrm{Prob}(x_b e^{\kappa a} \leq x) = \mathrm{Prob}\left(\kappa \leq a^{-1} \ln(x/x_b)\right) = \int_0^{a^{-1} \ln(x/x_b)} k(r|x_b) \, dr.$$

Hence

$$f(x; x_b, a) = \frac{1}{ax} k(a^{-1} \ln(x/x_b)|x_b).$$

At first glance formulae (11) and (64) differ significantly, but if we replace in (64) the term $f(2x; x_b, a)$ by the delta Dirac $\delta_{S_a(x_b)}(x)$ we will receive (11).

### 7.3. Stochastic growth of $x$.
The size of a cell having initial size $x_b$ grows according to Itô stochastic differential equation

$$(65) \qquad\qquad d\xi_t^{x_b} = \kappa \xi_t^{x_b} \, dt + \sigma(\xi_t^{x_b}) \, dB_t,$$

where $B_t$, $t \geq 0$, is a one dimensional Wiener process (Brownian motion), and $\kappa > 0$. In [15, 33] the authors assume that $\sigma(x) = \sqrt{D} x^\gamma$, where $D > 0$ and $\gamma \in (0, 1)$. The great strength of this formula is that equation (65) was intensively studied for such $\sigma$ and we can solve (65) and find various properties of solutions. But there is one weak point: the size can go to zero and even solutions can be absorbed at zero. To omit this problem we propose to assume that $\sigma \colon [\underline{x}_b, \infty) \to \mathbb{R}$ is a $C^1$-function and $\sigma(\underline{x}_b) = 0$. Then $\xi_t^{x_b} > \underline{x}_b$ for $t > 0$. It should be noted that solutions can decrease at some moments, i.e. a cell can shrink, but if the diffusion coefficient $\sigma$ is small, we observe exponential growth with small stochastic noise. If $f(x; x_b, a)$ is the density distribution of the random variable $\xi_a^{x_b}$, then the joint distribution of age and initial size $u(t, x_b, a)$ satisfies equations (10), (12), (64).

### 7.4. Models with asymmetric division and with slow-fast proliferation.
A lot of cellular populations are heterogeneous. For example, *C. crescentus* has an asymmetric cell division; *B. subtilis* occasionally produces minicells; melanoma cells have slowly and quickly proliferating cells [29]; and

precursors of blood cells replicate and maturate going through the levels of morphological development [24]. It is difficult to find one universal model of the evolution of heterogeneous populations. Now we present a model of the distribution of heterogeneous population based on similar assumptions as the model presented in Section 2. We divide the population into a number of subpopulations. We assume that cells in the $i$th subpopulation grow according to the equation $x' = g_i(x)$ and their length of the cell cycle has the probability density distribution $q_i(x_b, a)$. We also assume that $r_{ij}$ is the probability that a daughter of a cell from the $i$th subpopulation belongs to the $j$th subpopulation and the daughter has initial size $\beta_{ij}x$, where $x$ is the size of the mother cell at division. As in Section 2 we introduce the function

$$p_i(x_b, a) = \frac{q_i(x_b, a)}{\int_a^\infty q_i(x_b, r)\, dr}$$

and operators $P_a^{ij}$ which describe the relation between the density of the initial sizes of mother and daughter cells satisfying the equation:

$$(66) \qquad \int_{\underline{x_b}}^{\beta_{ij}\pi_a^i y} P_a^{ij} f(x_b)\, dx_b = r_{ij} \int_{\underline{x_b}}^{y} f(x_b)\, dx_b.$$

Then

$$(67) \qquad P_a^{ij} f(x_b) = \frac{r_{ij}}{\beta_{ij}} \frac{g(\pi_{-a}^i(x_b/\beta_{ij}))}{g(x_b/\beta_{ij})} f(\pi_{-a}^i(x_b/\beta_{ij})).$$

We denote by $u_i(t, x_b, a)$ the number of individuals in the $i$th population having initial size $x_b$ and age $a$ at time $t$. Then the system (10)–(12) will be replaced by the following one

$$(68) \qquad \frac{\partial u_i}{\partial t}(t, x_b, a) + \frac{\partial u_i}{\partial a}(t, x_b, a) = -p_i(x_b, a) u_i(t, x_b, a),$$

$$(69) \qquad u_j(t, x_b, 0) = 2 \sum_i \int_0^\infty P_a^{ij}(p_i(x_b, a) u_i(t, x_b, a))\, da,$$

$$(70) \qquad u_i(0, x_b, a) = u_{i0}(x_b, a).$$

In some cases of asymmetric division the size of daughter cells is not strictly determined and it is better to consider a model where the density $k(x_b|x_d)$ describes the distribution of the initial size of a daughter cell $x_b$ if the mother cell has the size $x_d$, see e.g. [3, 13, 14, 17, 37].

As an example of application of the model (68)–(70) we consider *C. crescentus* which has asymmetric cell division into a "stalked" cell which can replicate and a mobile "swarmer" cell which differentiates into a stalked cell after a short period of motility. Thus we have two subpopulations: the first – stalked cells and the second – swarmer cells. Then $r_{ij} = 1/2$ for $i = 1, 2$ and $j = 1, 2$. The stalked daughter has length of $0.56 \pm 0.04$ (mean $\pm$ SD) of the mother cell [7]. Hence we can assume that $\beta_{11} = \beta_{21} = 0.56$ and $\beta_{12} = \beta_{22} = 0.44$. If we assume that both stalked and swarmer cells have

the same growth rate $\kappa$, i.e. $g_i(x) = \kappa x$, then $q_2(x_b, a) = q_1(x_b, a - \rho)$, where $\rho$ satisfies the formula $e^{\kappa\rho} = 0.56/0.44$ and $q_1 = q$ is given by (63).

A model for the growth *B. subtilis* should be more advanced. *B. subtilis* can divide symmetrically to make two daughter cells (binary fission), but some mutants split asymmetrically, producing a single endospore, which can differentiate to a "typical" cell. Assume that the first population consists of typical cells and the second of minicells. If $\mathfrak{p}$ is the probability of asymmetric fission, then $r_{11} = r_{21} = 1 - \mathfrak{p} + \mathfrak{p}/2 = 1 - \mathfrak{p}/2$ and $r_{12} = r_{22} = \mathfrak{p}/2$. Some information on the size of minicells can be found in [18].

In a model which describes slowly and quickly proliferating cells we should assume that the length of the cell cycle of slowly proliferating cells is longer than in quickly proliferating cells and slowly proliferating cells also grow slower. Thus the sensible assumptions are: $g_1(x) < g_2(x)$ and

$$\int_0^a q_1(x_b, r)\, dr < \int_0^a q_2(x_b, r)\, da \quad \text{for } a < \bar{a}_1(x_b).$$

We should also assumed that there is some transition between both subpopulations. Other model of the growth of the population with slowly and quickly proliferating cells was recently studied in [42].

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