APPLICATIONS OF STOCHASTIC SEMIGROUPS TO CELL CYCLE MODELS

KATARZYNA PICHÓR
Institute of Mathematics, University of Silesia
Bankowa 14, 40-007 Katowice, Poland

RYSZARD RUDNICKI*
Institute of Mathematics, Polish Academy of Sciences
Bankowa 14, 40-007 Katowice, Poland

ABSTRACT. We consider a generational and continuous-time two-phase model of the cell cycle. The first model is given by a stochastic operator, and the second by a piecewise deterministic Markov process. In the second case we also introduce a stochastic semigroup which describes the evolution of densities of the process. We study long-time behaviour of these models. In particular we prove theorems on asymptotic stability and sweeping. We also show the relations between both models.

1. Introduction. The modeling of the cell cycle has a long history [27]. The core of the theory was formulated in the late sixties [16, 30, 38]. The important role in these models is played by maturity of cells. A lot of new models appear in the eighties and we can divide them into two groups. The first group contains discrete-time models (generational models) which describe the relation between the initial maturity of mother and daughter cells [13, 36, 37]. The second group is formed by continuous-time models characterizing the time evolution of distribution of cell maturity [6, 19, 29] or cell size [8, 11]. The long-time behaviour of continuous-time models was studied in [4, 20, 22, 28, 33]. Mathematical modelling of cell cycle is still important and topical and new interesting models appear [1, 2, 7, 9, 18].

In this paper we consider two-phase models of the cell cycle. The cell cycle is a series of events that take place in a cell leading to its replication. Usually the cell cycle is divided into four phases [3, 12, 21]. The first one is the growth phase $G_1$ with synthesis of various enzymes. The duration of the phase $G_1$ is highly variable even for cells from one species. The DNA synthesis takes place in the second phase $S$. In the third phase $G_2$ significant protein synthesis occurs, which is required during the process of mitosis. The last phase $M$ consists of nuclear division and cytoplasmic division. Some models of cell cycle contain also a $G_0$ phase, where the cell has left cycle and has stopped dividing. From a mathematical point of view we can simplify the model by considering only two phases [5, 35, 37]. The first phase is the growth phase $G_1$ and it is also called the resting phase. The second phase

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* Corresponding author: Ryszard Rudnicki.
called the proliferating phase consists of the phases $S$, $G_2$, and $M$. The duration of the first phase is a random variable and of the second phase is almost constant. A cell can move from the resting phase to the proliferating phase with some rate, which depends on the maturity of a cell. Each cell is characterized by its age and maturity. The maturity can be size, volume or contents of genetic material.

We investigate discrete and continuous-time models characterized by the same parameters. The discrete model is a slightly extended version of that of Tyrcha [37]. In our model the growth of maturity in both phases is described by different functions. We include the derivation of this model to have the paper self-contained. A cell can move from the resting phase to the proliferating phase with the rate which depends on its maturity. Then it spends a fixed time $\tau$ in the second phase and divides into two cells which have the same maturity. The maturity of a daughter cell is determined by the maturity of the mother cell at the moment of division. The mathematical model is given by a stochastic operator $P$ which describes the relation between densities of maturity of new born cells in consecutive generations.

The continuous-time model is given by a piecewise deterministic Markov process (PDMP), which describes consecutive descendants of a single cell. PDMPs are nowadays widely used in modeling of biological phenomena [26, 34]. Some PDMPs were applied to describe statistical dynamics of recurrent biological events and could be used in cell cycle models [15, 20]. The main problem with application of PDMPs to a two-phase model is to construct a stochastic process which has the Markov property. In the first phase the state of a cell depends on its maturity, but the second phase has a constant length, so the state of the cell depends on time of visit this phase. The novelty of our model is that it consists a system of three differential equations which describes age, maturity, and phase of a cell. We consider two different jumps. The first jump is a stochastic one, when a cell enters the proliferating phase. The second one is deterministic at the moment of division. After the division of a cell, we consider time evolution of its daughter cell, etc. Since we include into the model age, maturity and phase of a cell, our process satisfies the Markov property. The evolution of densities of the PDMP corresponding to our model leads directly to a continuous-time stochastic semigroup $\{P(t)\}_{t \geq 0}$. The densities of the PDMP satisfy a system of partial differential equations with boundary conditions similar to that in [19]. It is interesting that the density of maturity satisfies a first order partial differential equation in which there is a temporal retardation as well as a nonlocal dependence in the maturation variable (35). This observation suggests that even rather complicated transport equations can be introduced by means of simple PDMPs and one can find numerical solutions of these equations by Monte Carlo methods.

We study long-time behaviour of the discrete-time semigroup $\{P^n\}_{n \in \mathbb{N}}$ and the semigroup $\{P(t)\}_{t \geq 0}$. We are specially interested in asymptotic stability and sweeping [14]. We recall that a stochastic semigroup is sweeping from a set $A$ if

$$\lim_{t \to \infty} \int_A P(t)f \, d\mu = 0$$

for each density $f$. We prove that both semigroups satisfy the Foguel alternative, i.e. they are asymptotically stable or sweeping from compact sets. This result is based on a decomposition theorem of a stochastic semigroup into asymptotically stable and sweeping components [24] (see also [25] for substochastic semigroups). We give some sufficient conditions for asymptotic stability and sweeping of the continuous-time stochastic semigroup. We also present an example such that the operator $P$
is asymptotically stable but the semigroup \( \{P(t)\}_{t \geq 0} \) is sweeping from compact sets and explain this unexpected phenomenon. It should be noted that stochastic semigroups are widely applied to study asymptotic properties of biological models (see [32, 34] and references cited therein).

The organization of the paper is as follows. Section 2 contains the definitions and results concerning asymptotic stability, sweeping and the Foguel alternative for stochastic semigroups. Biological and mathematical description of the cell cycle is presented in Section 3. In Section 4 we investigate the discrete-time model and we prove that the stochastic operator \( P \) related to this model satisfies the Foguel alternative (Theorem 4.1). We also recall some sufficient conditions for asymptotic properties of \( F \). In Section 5 we introduce a continuous-time model as a PDMP and we show that the stochastic semigroup \( \{P(t)\}_{t \geq 0} \) corresponding to this process satisfies the Foguel alternative. In Section 6 we show the relations between discrete-time and continuous-time models, which allow us to formulate some conditions for asymptotic stability and sweeping of \( \{P(t)\}_{t \geq 0} \). Finally, we compare asymptotic properties of both models.

2. Asymptotic properties of stochastic operators and semigroups. Let a triple \((X, \Sigma, \mu)\) be a \(\sigma\)-finite measure space. Denote by \( D \) the subset of the space \( L^1 = L^1(X, \Sigma, \mu) \) which contains all densities

\[
D = \{f \in L^1: f \geq 0, \|f\| = 1\}.
\]

A linear operator \( P: L^1 \rightarrow L^1 \) is called stochastic if \( P(D) \subseteq D \). A family \( \{P(t)\}_{t \geq 0} \) of linear operators on \( L^1 \) is called a stochastic semigroup if it is a strongly continuous semigroup and all operators \( P(t) \) are stochastic. Now, we introduce some notions which characterize the asymptotic behaviour of iterates of stochastic operators \( P^n \), \( n = 0, 1, 2, \ldots \), and stochastic semigroups \( \{P(t)\}_{t \geq 0} \). The iterates of stochastic operators form a discrete-time semigroup and we can use notation \( P(t) = P^t \) for their powers and we formulate most of definitions and results for both types of semigroups without distinguishing them. A stochastic semigroup \( \{P(t)\}_{t \geq 0} \) is asymptotically stable if there exists a density \( f^* \) such that

\[
\lim_{t \to \infty} \|P(t)f - f^*\| = 0 \quad \text{for } f \in D.
\]  
(1)

From (1) it follows immediately that \( f^* \) is invariant with respect to \( \{P(t)\}_{t \geq 0} \), i.e. \( P(t)f^* = f^* \) for each \( t \geq 0 \). A stochastic semigroup \( \{P(t)\}_{t \geq 0} \) is called sweeping with respect to a set \( B \in \Sigma \) if for every \( f \in D \)

\[
\lim_{t \to \infty} \int_B P(t)f(x) \mu(dx) = 0.
\]

Our aim is to find such conditions that a stochastic semigroup \( \{P(t)\}_{t \geq 0} \) is asymptotically stable or sweeping from all compact sets called the Foguel alternative [14]. We also want to find simple sufficient conditions for asymptotic stability and sweeping for operators and semigroups related to cell cycle models.

We assume additionally that \((X, \rho)\) is a separable metric space and \( \Sigma = B(X) \) is the \(\sigma\)-algebra of Borel subsets of \( X \). We will consider a stochastic semigroup \( \{P(t)\}_{t \geq 0} \) such that for each \( t \geq 0 \) we have

\[
P(t)f(x) \geq \int_X q(t, x, y)f(y) \mu(dy) \quad \text{for } f \in D,
\]  
(2)
where \( q(t, \cdot, \cdot) : X \times X \to [0, \infty) \) is a measurable function and the following condition holds:

(K) for every \( y_0 \in X \) there exist an \( \varepsilon > 0, a t > 0, \) and a measurable function \( \eta \geq 0 \) such that \( \int \eta(x) \mu(dx) > 0 \) and

\[
q(t, x, y) \geq \eta(x)1_{B(y_0, \varepsilon)}(y) \quad \text{for } x, y \in X,
\]

where \( B(y_0, \varepsilon) = \{ y \in X : \rho(y, y_0) < \varepsilon \} \).

We define condition (K) for a stochastic operator \( P \) in the same way remembering the notation \( P(t) = P^t \). Condition (K) is satisfied if, for example, for every point \( y \in X \) there exist a \( t > 0 \) and an \( x \in X \) such that the kernel \( q(t, \cdot, \cdot) \) is continuous in a neighbourhood of \((x, y)\) and \( q(t, x, y) > 0 \).

Now, we formulate the Foguel alternative for some class of stochastic semigroups. We need an auxiliary definition. We say that a stochastic semigroup \( \{P(t)\}_{t \geq 0} \) overlaps supports if for every \( f, g \in D \) there exists \( t > 0 \) such that

\[
\mu(\text{supp } P(t)f \cap \text{supp } P(t)g) > 0.
\]

The support of any measurable function \( f \) is defined up to a set of measure zero by the formula

\[
\text{supp } f = \{ x \in X : f(x) \neq 0 \}.
\]

**Proposition 1.** Assume that \( \{P(t)\}_{t \geq 0} \) satisfies (K) and overlaps supports. Then \( \{P(t)\}_{t \geq 0} \) is sweeping or \( \{P(t)\}_{t \geq 0} \) has an invariant density \( f^* \) with a support \( A \) and there exists a positive linear functional \( \alpha \) defined on \( L^1(X, \Sigma, \mu) \) such that

(i) for every \( f \in L^1(X, \Sigma, \mu) \) we have

\[
\lim_{t \to \infty} \|1_A P(t)f - \alpha(f)f^*\| = 0,
\]

(ii) if \( Y = X \setminus A \), then for every \( f \in L^1(X, \Sigma, \mu) \) and for every compact set \( F \) we have

\[
\lim_{t \to \infty} \int_{F \cap Y} P(t)f(x) \mu(dx) = 0.
\]

In particular, if \( \{P(t)\}_{t \geq 0} \) has an invariant density \( f^* \) with the support \( A \) and \( X \setminus A \) is a subset of a compact set, then \( \{P(t)\}_{t \geq 0} \) is asymptotically stable.

The proof of Proposition 1 is based on theorems on asymptotic decomposition of stochastic operators [24, Theorem 1] and stochastic semigroups [24, Theorem 2].

**Theorem 2.1.** Assume that \( P \) satisfies (K). Then there exist an at most countable set \( J \), a family of disjoint measurable sets \( \{A_j\}_{j \in J} \) such that \( P^t 1_{A_j} \geq 1_{A_j} \) for \( j \in J \), a family \( \{S_j\}_{j \in J} \) of periodic stochastic operators on \( L^1(A_j, \Sigma_{A_j}, \mu) \) with \( \Sigma_{A_j} = \{ A \in \Sigma : A \subseteq A_j \} \) for \( j \in J \), and a family \( \{R_j\}_{j \in J} \) of positive projections \( R_j : L^1(X, \Sigma, \mu) \to L^1(A_j, \Sigma_{A_j}, \mu) \) such that

(i) for every \( j \in J \) and for every \( f \in L^1(X, \Sigma, \mu) \) we have

\[
\lim_{n \to \infty} \|1_{A_j} P^nf - S_j^n R_j f\| = 0,
\]

(ii) if \( Y = X \setminus \bigcup_{j \in J} A_j \), then for every \( f \in L^1(X, \Sigma, \mu) \) and for every compact set \( F \) we have

\[
\lim_{n \to \infty} \int_{F \cap Y} P^nf(x) \mu(dx) = 0.
\]
We recall that a stochastic operator $S$ is called periodic if there exists a sequence of densities $h_1, \ldots, h_k$ such that
\[ h_i h_j = 0 \text{ for } i \neq j \text{ and } h_1 + \cdots + h_k > 0 \text{ a.e.,} \]
and for every integrable function $f$ we have $Sf = SQf$, where
\[ Qf = \sum_{i=1}^{k} \alpha_i(f) h_i, \quad \alpha_i(f) = \int_{B_i} f(x) \mu(dx), \quad B_i = \text{supp } h_i. \]

The operator $P$ can be restricted to the space $L^1(A_j, \Sigma_{A_j}, \mu)$, i.e., if $\text{supp } f \subseteq A_j$ then $\text{supp } Pf \subseteq A_j$. The operators $S_j$ have the property $S_j h_i = P h_i$ (see the proof of Lemma 9 [24]), which means that the functions $h_i$ are periodic densities of $P$ such that $\text{supp } P^n h_i \cap \text{supp } P^n h_j = \emptyset$ for each $n$ and $i \neq j$. The space $L^1(A_j, \Sigma_{A_j}, \mu)$ can be canonically embedded in the space $L^1(X, \Sigma, \mu)$ and, therefore, $R_j$ can be treated as the transformation from $L^1(X, \Sigma, \mu)$ to itself. In the statement of Theorem 2.1 we use the following definition of a projection. A linear transformation $T$ from a vector space to itself is a projection if $T^2 = T$.

**Theorem 2.2.** Let $\{P(t)\}_{t \geq 0}$ be a stochastic semigroup which satisfies (K). Then there exist an at most countable set $J$, a family of invariant densities $\{f_j\}_{j \in J}$ with disjoint supports $\{A_j\}_{j \in J}$, and a family $\{\alpha_j\}_{j \in J}$ of positive linear functionals defined on $L^1$ such that

(i) for every $j \in J$ and for every $f \in L^1$ we have
\[ \lim_{t \to \infty} \|1_{A_j} P(t) f - \alpha_j(f) f_j^*\| = 0, \]
(ii) if $Y = X \setminus \bigcup_{j \in J} A_j$, then for every $f \in L^1$ and for every compact set $F$ we have
\[ \lim_{t \to \infty} \int_{F \cap Y} P(t) f(x) \mu(dx) = 0. \]

In particular, we have

**Corollary 1.** Assume that a continuous-time stochastic semigroup $\{P(t)\}_{t \geq 0}$ satisfies condition (K) and has no invariant densities. Then $\{P(t)\}_{t \geq 0}$ is sweeping from compact sets.

**Proof of Proposition 1.** First, we consider the case of a stochastic operator. If $P$ satisfies condition (K) and overlaps supports, then $J$ is an empty set or a singleton. Indeed, if $\text{supp } f \subseteq A_j$ then $\text{supp } Pf \subseteq A_j$, because $P^* 1_{A_j} \geq 1_{A_j}$. If $J$ has at least two elements, then $\text{supp } P^n f \cap \text{supp } P^n g \subseteq A_1 \cap A_2 = \emptyset$ for $n \in \mathbb{N}$ and $f, g \in D$ such that $\text{supp } f \subseteq A_1$ and $\text{supp } g \subseteq A_2$, which contradicts the assumption that $P$ overlaps supports. If $J$ is a singleton, then the periodic operator $S$ is in fact a projection on a one dimensional space because the overlapping property of $P$ excludes the existence of two periodic densities $h_1$ and $h_2$ such that $\text{supp } P^n h_1 \cap \text{supp } P^n h_2 = \emptyset$ for each $n$. Thus condition (6) takes the form (4). If $P$ is an invariant density $f^*$ with the support $A$ and $Y = X \setminus A$ is a subset of a compact set, then from condition (5) it follows that $\lim_{n \to \infty} \int_{Y} P^n f(x) \mu(dx) = 0$. Since $P$ is a stochastic operator, we have $\alpha(f) = 1$ for any density $f$, and consequently, $P$ is asymptotically stable. The proof for continuous-time stochastic semigroups is straightforward because we have at most one invariant density and conditions (4), (11) coincide. \qed
Figure 1. Evolution of maturity of a mother cell: (1) – resting phase; (2) – proliferating phase and a daughter cell: (3) – resting phase; (4) – proliferating phase.

If a continuous-time stochastic semigroup \( \{P(t)\}_{t \geq 0} \) has a unique invariant density \( f^* \) and \( f^* > 0 \), then according to Theorem 2.1 condition (K) implies asymptotic stability of \( \{P(t)\}_{t \geq 0} \). We can strengthen considerably this conclusion replacing condition (K) by the following one. A stochastic semigroup \( \{P(t)\}_{t \geq 0} \) is called partially integral if (2) holds and

\[
\int_X \int_X q(t, x, y) \mu(dx) \mu(dy) > 0
\]

for some \( t > 0 \).

**Theorem 2.3 ([23]).** Let \( \{P(t)\}_{t \geq 0} \) be a continuous-time partially integral stochastic semigroup. Assume that the semigroup \( \{P(t)\}_{t \geq 0} \) has a unique invariant density \( f^* \). If \( f^* > 0 \) a.e., then the semigroup \( \{P(t)\}_{t \geq 0} \) is asymptotically stable.

3. From the biological background to a mathematical description. We start with a short biological description of the two phase-cell cycle models. The cell cycle is divided into the resting and proliferating phase. The duration of the resting phase is random variable \( t_R \) which depends on the maturity of a cell. The duration \( t_P \) of the proliferating phase is almost constant. Therefore, we assume that \( t_P = \tau \), where \( \tau \) is a positive constant.

The crucial role in the model is played by a parameter \( m \) called maturity which describes the state of a cell in the cell cycle. Without loss of generality we can assume that the minimum cell maturity \( m_{\text{min}} \) equals zero.

A cell can move from the resting phase to the proliferating phase with rate \( \varphi(m) \), i.e., a cell with age \( a \) and with maturity \( m \) enters the proliferation phase during a small time interval of length \( \Delta t \) with probability \( \varphi(m) \Delta t + o(\Delta t) \).

We assume that cells age with unitary velocity and mature with a velocity \( g_1(m) \) in the resting phase and with a velocity \( g_2(m) \) in the proliferating phase. The variable \( a \) in the proliferating phase is assumed to range from \( a = 0 \) at the point of commitment to \( a = \tau \) at the point of cytokinesis. The maturity of the daughter cell \( m \) is a function of the maturity of the mother cell \( m \), i.e. \( m = h(m) \) (see Fig. 1).

For example if \( m \) is the volume of a cell, then \( h(m) = m/2 \).

Now we collect the assumptions concerning the model:
We assume that a new born cell has maturity \( m \).

The model describes the relation between initial maturity of mother and daughter cells.

\( \lambda \) and \( \psi \).

A discrete-time model.

\( t \) the distribution of maturity of the daughter cell. In order to do it we first need to set down \( \psi \).

From (M2) and (M3) it follows that the mother cell when it enters the proliferating phase, then \( \psi \) is the initial maturity of a daughter cell. From (M2) and (M3) it follows that \( \psi' > 0 \). Moreover \( \psi(m_P) = h(\pi_2(\tau, m_P)) = 0 \). Let \( \lambda(m) = \psi^{-1}(m) = \pi_2(-\tau, h^{-1}(m)) \). Then \( \lambda' > 0 \) and \( \lambda(0) = m_P \).

\[ m'(t) = g_i(m(t)), \quad i = 1, 2, \] (13)

with the initial condition \( m(0) = m_0 \geq 0 \). From (M3) it follows that \( \pi_i \) is a nonnegative and increasing function of both variables. It is obvious that \( h(\pi_2(\tau, m_P)) = m_{\min} = 0 \).

Now, we introduce two auxiliary functions, which are used in both models. Let \( \psi: [m_P, \infty) \to [0, \infty) \) be given by \( \psi(m) = h(\pi_2(\tau, m)) \). If \( m \) is the maturity of the mother cell when it enters the proliferating phase, then \( \psi(m) \) is the initial maturity of a daughter cell. From (M2) and (M3) it follows that \( \psi' > 0 \). Moreover \( \psi(m_P) = h(\pi_2(\tau, m_P)) = 0 \). Let \( \lambda(m) = \psi^{-1}(m) = \pi_2(-\tau, h^{-1}(m)) \). Then \( \lambda' > 0 \) and \( \lambda(0) = m_P \).

4. A discrete-time model. Now we consider a discrete-time model [37]. This model describes the relation between initial maturity of mother and daughter cells. We assume that a new born cell has maturity \( m_0 \) and we want to find the distribution of maturity of the daughter cell. In order to do it we first need to set down the distribution of \( t_R \).

Let \( \Phi(t) \) be the cumulative distribution function of \( t_R \), i.e. \( \Phi(t) = \text{Prob}(t_R \leq t) \). Then

\[ \text{Prob}(t < t_R \leq t + \Delta t | t_R > t) = \frac{\Phi(t + \Delta t) - \Phi(t)}{1 - \Phi(t)} = \psi(\pi_1(t, m_0)) \Delta t + o(\Delta t). \]

From this equation we obtain

\[ \Phi'(t) = (1 - \Phi(t))\psi(\pi_1(t, m_0)) \]

and we get

\[ \Phi(t) = 1 - \exp \left\{ - \int_0^t \psi(\pi_1(s, m_0)) \, ds \right\}. \] (14)

Since \( d\pi_1/ds = g_1(\pi_1(s, m_0)) \) we obtain

\[ \int_0^t \psi(\pi_1(s, m_0)) \, ds = \int_{m_0}^{\pi_1(t, m_0)} \frac{\psi(m)}{g_1(m)} \, dm = Q(\pi_1(t, m_0)) - Q(m_0), \]

where \( Q(m) = \int_0^m \frac{\psi(r)}{g_1(r)} \, dr \). Hence

\[ \Phi(t) = 1 - e^{Q(m_0) - Q(\pi_1(t, m_0))}. \] (15)
According to (M4) \( \lim_{m \to \infty} Q(m) = \infty \), which guaranties that each cell enters the proliferating phase with probability one. From (15) it follows that
\[
\Phi'(t) = \frac{d}{dt}(Q(\pi_1(t, m_0))) e^{Q(m_0) - Q(\pi_1(t, m_0))} \\
= \varphi(\pi_1(t, m_0)) e^{Q(m_0) - Q(\pi_1(t, m_0))}.
\]

(16)

Since the random variable \( \pi_1(t_R, m_0) \) is the maturity of the cell when it enters the proliferating phase, its maturity at the moment of division is given by \( \pi_2(\tau, \pi_1(t_R, m_0)) \). Finally the maturity of the daughter cell is given by the random variable \( \xi = \psi(\pi_1(t_R, m_0)) \).

In order to find the density of the random variable \( \xi \) we determine the expectation of the random variable \( E(F(\xi)) \), where \( F \) is any bounded and continuous real function. We have
\[
E(F(\xi)) = E(F(\psi(\pi_1(t_R, m_0)))) = \int_0^\infty F(\psi(\pi_1(t, m_0)))\Phi'(t) \, dt \\
= \int_0^\infty F(\psi(\pi_1(t, m_0)))\varphi(\pi_1(t, m_0)) e^{Q(m_0) - Q(\pi_1(t, m_0))} \, dt \\
= \int_{m_0}^\infty F(\psi(y)) Q'(y) e^{Q(m_0) - Q(y)} \, dy \\
= \int_{m_0}^\infty F(m)\lambda'(m) Q'(\lambda(m)) e^{Q(m_0) - Q(\lambda(m))} \, dm.
\]

Thus the random variable \( \xi \) has the density
\[
1_{[\lambda^{-1}(m_0), \infty)}(m)\lambda'(m) Q'(\lambda(m)) e^{Q(m_0) - Q(\lambda(m))}.
\]

Moreover, if we assume that the distribution of the initial maturity of mother cells has a density \( f \), then the initial maturity of the daughter cells has the density
\[
Pf(m) = \int_0^{\lambda(m)} \lambda'(m) Q'(\lambda(m)) e^{Q(y) - Q(\lambda(m))} f(y) \, dy.
\]

(17)

Then \( P \) is a stochastic operator on the space \( L^1[0, \infty) \).

**Theorem 4.1.** The operator \( P \) satisfies the Foguel alternative, i.e. \( P \) is asymptotically stable or sweeping from compact sets.

**Proof.** The operator \( P \) is of the form
\[
Pf(m) = \int_0^\infty q(m, y) f(y) \, dy
\]

with \( q(m, y) = w(m)1_{[0, \lambda(m)]}(y) e^{Q(y)} \) and \( w(m) = \lambda'(m) Q'(\lambda(m)) e^{-Q(\lambda(m))} \). Since \( \lambda(0) = m_P \) and \( \lambda' > 0 \), \( \lambda(m) > m_P \) for \( m > 0 \), and according to (M1) we have \( \varphi(\lambda(m)) > 0 \) for \( m > 0 \). Thus \( Q'(\lambda(m)) = \varphi(\lambda(m))/g_1(\lambda(m)) > 0 \) for \( m > 0 \). We also have
\[
\lambda'(m) = \frac{g_2(\lambda(m))}{g_2(h^{-1}(m)) h'(h^{-1}(m))} > 0
\]

for \( m > 0 \), which gives \( w(m) > 0 \) for \( m > 0 \). If we fix \( y_0 > 0 \), then we find \( m_0 > 0 \) such that \( \lambda(m_0) > y_0 \). Then the function \( \eta(m) = w(m)1_{[m_0, \infty)}(m) \) satisfies (3) for sufficiently small \( \varepsilon > 0 \). Thus condition (K) is fulfilled. Now we fix a density \( f \) and let \( \bar{y} \geq 0 \) be a point such that \( \int_{\bar{y}}^{\bar{y} + \varepsilon} f(y) \, dy > 0 \) for each \( \varepsilon > 0 \). Since \( \lambda \) is an increasing function and \( \lim_{m \to \infty} \lambda(m) = \infty \), there is \( \tilde{m} > 0 \) such that \( \lambda(m) > \bar{y} \) for
\[ m \geq m_\ast. \] From the definition of \( P \) it follows that \( Pf(m) > 0 \) if \( \int_0^{\lambda(m)} f(y) \, dy > 0. \) Hence \( Pf(m) > 0 \) for \( m \geq m_\ast. \) Since for any two densities \( f \) and \( g \) there is an \( \alpha > 0 \) such that \( Pf(m) > 0 \) and \( Pg(m) > 0 \) for \( m \geq \alpha, \) the operator \( P \) overlaps supports. Moreover, if \( P \) has an invariant density \( f^* \) then \( [0, \infty) \setminus \supp f^* \subseteq [0, c] \) for some \( c > 0. \) According to Proposition 1 the operator \( P \) satisfies the Foguel alternative.

Theorem 4.1 does not establish when the operator \( P \) is asymptotically stable or sweeping. Here we give some sufficient conditions for these properties.

**Proposition 2.** Let \( \alpha(m) = Q(\lambda(m)) - Q(m). \) The following conditions hold:

(a) if \( \liminf_{m \to \infty} \alpha(m) > 1, \) then \( P \) is asymptotically stable,

(b) if \( \alpha(m) \leq 1 \) for sufficiently large \( m, \) then \( P \) is sweeping from each bounded interval,

(c) if \( \inf \alpha(m) > -\infty, \) then the operator \( P \) is completely mixing, i.e.

\[ \lim_{n \to \infty} \| P^n f - P^n g \| = 0 \quad \text{for} \ f, g \in D. \]

These results were proved, respectively, (a) in [10], (b) in [17], and (c) in [31].

If the operator \( P \) has an invariant density \( f^*, \) then we can find the stationary distribution of age and maturity in both phases. From (15) it follows that if a cell has the initial maturity \( m_0, \) then it will not have left the resting phase before age \( a \) with probability \( e^{Q(m_0) - Q(\pi_1(a, m_0))} \) and has maturity \( \pi_1(a, m_0) \) at age \( a. \) Thus the probability that cell remains in the resting phase at age \( a \) and has maturity \( \leq m \) at this age is given by the formula

\[ \int_0^{\pi_1(-a, m)} f^*(m_0)e^{Q(m_0) - Q(\pi_1(a, m_0))} \, dm_0. \tag{18} \]

Denote by \( \tilde{f}^*(a, m, i) \) the stationary density of the distribution of age and maturity in both phases. Then from (18) it follows that

\[ \tilde{f}^*(a, m, 1) = c \frac{d}{dm} \int_0^{\pi_1(-a, m)} f^*(m_0)e^{Q(m_0) - Q(\pi_1(a, m_0))} \, dm_0 \]

\[ = c \frac{g_1(\pi_1(-a, m))}{g_1(m)} f^*(\pi_1(-a, m))e^{Q(\pi_1(-a, m)) - Q(m)} \tag{19} \]

for \( m \geq \pi_1(a, 0) \) and \( \tilde{f}^*(a, m, 1) = 0 \) for \( m < \pi_1(a, 0), \) where \( c > 0 \) is a normalized constant. Integrating (19) over the age variable \( a \) gives

\[ \tilde{f}^*(m, 1) = \int_0^\infty \tilde{f}^*(a, m, 1) \, da = \frac{c}{g_1(m)}e^{-Q(m)} \int_0^m e^{Q(x)} f^*(x) \, dx. \tag{20} \]

In order to find \( \tilde{f}^*(a, m, 2) \) we need to find the distribution of maturity at the beginning of proliferating phase. We claim that the density of this distribution is given by \( f^*_p(m) = \psi'(m)f^*(\psi(m)). \) Indeed, if \( \zeta \) is a random variable having density \( f^*, \) then the density of random variable \( \lambda(\zeta) \) coincides with the density of maturity at the beginning of proliferating phase. Thus

\[ \Prob(\lambda(\zeta) \leq m) = \Prob(\zeta \leq \psi(m)) = \int_0^{\psi(m)} f^*(r) \, dr, \]
which proves our claim. Analogously to (19) we find that
\[
\tilde{f}^*(a, m, 2) = c \frac{g_2(\pi_2(-a, m))}{g_2(m)} f_\pi^*(\pi_2(-a, m))
\]
(21)
for \(m \geq \pi_2(a, m_P)\) and \(\tilde{f}^*(a, m, 2) = 0\) for \(m < \pi_2(a, m_P)\). We have the same constant \(c\) in the both formulas (19) and (21) because \(\tilde{f}^*(\tau, m, 2) = h'(m)\tilde{f}^*(0, h(m), 1)\). We can find the constant \(c\) using the formula
\[
\int_0^\infty \int_0^\infty \tilde{f}^*(a, m, 1) \, da \, dm + \int_{m_P}^\infty \int_0^\tau \tilde{f}^*(a, m, 2) \, da \, dm = 1.
\]
It is clear that the second integral equals \(\tau\) and the first integral is the mean length \(T_R\) of the resting phase and
\[
T_R = \int_0^\infty \int_0^\infty \tilde{f}^*(a, m, 1) \, da \, dm
\]
\[
= \int_0^\infty \int_{\pi(a, 0)}^\infty \frac{g_1(\pi_1(-a, m))}{g_1(m)} f^*(\pi_1(-a, m)) e^{Q(\pi_1(-a, m)) - Q(m)} \, dm \, da.
\]
Substituting \(y = \pi_1(-a, m)\) and then \(x = \pi_1(a, y)\) we obtain
\[
T_R = \int_0^\infty \int_y^\infty f^*(y) e^{Q(y) - Q(\pi_1(a, y))} \, dy \, da
\]
\[
= \int_y^\infty \int_0^1 \frac{1}{g_1(x)} e^{Q(y) - Q(x)} f^*(y) \, dx \, dy.
\]
Thus \(c = 1/(T_R + \tau)\) assuming that \(T_R < \infty\).

5. A continuous-time model. Now we consider a continuous version of the model. The cell cycle can be described as a piecewise deterministic Markov process. We consider a sequence of consecutive descendants of a single cell. Let \(s_n\) be a time when a cell from the \(n\)-generation enters a resting phase and \(t_n = s_n + \tau\) be a time of its division. If \(t_{n-1} \leq t < t_n\) then the state \(\xi(t) = (a(t), m(t), i(t))\) of the \(n\)-th cell is described by age \(a(t)\), maturity \(m(t)\) and the index \(i(t)\), where \(i = 1\) if a cell is in the resting phase and \(i = 2\) if it is in the proliferating phase. Random moments \(t_0, s_1, t_1, s_2, t_2, \ldots\) are called jump times. Between jump times the parameters change according to the following system of equations:
\[
\begin{align*}
\frac{da}{dt} &= 1, \\
\frac{dm}{dt} &= g_{i(t)}(m(t)), \\
\frac{di}{dt} &= 0.
\end{align*}
\]
(23)
The process \(\xi(t)\) changes at jump points according to the following rules:
\[
a(s_n) = 0, \quad m(s_n) = m(s_n^-), \quad i(s_n) = 2,
\]
and
\[
a(t_n) = 0, \quad m(t_n) = h(m(t_n^-)), \quad i(t_n) = 1.
\]
If \(m(t_{n-1}) = m_0\) then the cumulative distribution function \(\Phi\) of \(s_n - t_{n-1}\) is given by (15). Then \(\xi(t)\) is a time-homogeneous Markov process. If the distribution of \(\xi(0)\)
is given by a density function $f(0,a,m,i)$, i.e. a measurable function of $(a,m,i)$ such that

$$\text{Prob}(\xi(0) \in A \times i) = \int \int_A f(0,a,m,i) \, da \, dm$$

for any Borel set $A$ and $i = 1, 2$, then $\xi(t)$ has a density $f(t,a,m,i)$.

Having a time-homogeneous Markov process $\xi(t)$ with the property that if the random variable $\xi(0)$ has a density $f_0$, then $\xi(t)$ has a density $f_t$, we can define a stochastic semigroup $\{P(t)\}_{t \geq 0}$ corresponding to $\xi(t)$ by $P(t)f_0 = f_t$. The proper choice of the space $X$ of values of the process $\xi(t)$ plays an important role in investigations of the process and the semigroup $\{P(t)\}_{t \geq 0}$. We define $X = \{(a,m,1): m \geq \pi_1(a,0), a \geq 0\} \cup \{(a,m,2): m \geq \pi_2(a,m_P), a \in [0,\tau]\}$, $\Sigma = B(X)$, and $\mu$ is the product of the two-dimensional Lebesgue measure and the counting measure on the set $\{1,2\}$ (see Fig. 2). Our aim is to check that the stochastic semigroup $\{P(t)\}_{t \geq 0}$ defined on $L^1(X, \Sigma, \mu)$ corresponding to the process $\xi(t)$ satisfies the Foguel alternative and then to give some conditions for its asymptotic stability and sweeping.

We need two additional assumptions:

$$\psi(m) = h(\pi_2(\tau,m)) < m \text{ for } m \geq m_P \quad (24)$$

and

$$h'(\pi_2(\tau,\bar{m}))g_2(\pi_2(\tau,\bar{m})))g_1(\bar{m}) \neq g_1(h(\pi_2(\tau,\bar{m})))g_2(\bar{m}) \quad (25)$$

for some $\bar{m} > m_P$.

Condition (24) is not particularly restrictive because if $h(\pi_2(\tau,m_0)) \geq m_0$ for some $m_0 > m_P$, then independently on the maturity of a cell, the probability that descended cells will have maturity $m < m_0$ goes to zero as $t \to \infty$ and we can consider a model with the minimal maturity $m_0$. If a mother cell has maturity $m > m_P$, then any number from the interval $(\psi(m), \infty)$ can be initial maturity of a daughter cell, any number from the interval $(\psi^2(m), \infty)$ can be initial maturity of a granddaughter cell if $\psi(m) > m_P$, etc. From condition (24) it follows that for sufficiently large $n$ we have $\psi^n(m) \leq m_P$. Since $\psi(m_P) = 0$ we conclude that after a finite number of generations the initial maturity of a descended cell can be any positive number $m$, $m > \pi_1(a,0)$ can be the maturity of a descended cell at age $a$.
in the resting phase and \( m > \pi_2(a, m_P) \) can be the maturity of a descended cell at age \( a \) in the proliferating phase.

Condition (25) seems to be technical but if

\[
    h'(\pi_2(\tau, m))g_2(\pi_2(\tau, m))g_1(m) = g_1(h(\pi_2(\tau, m)))g_2(m)
\]

for all \( m \geq m_P \), then all descendants of a single cell in the same generation have the same maturity at a given time \( t \). It means that the cells have *synchronous growth* and we cannot expect the model is asymptotically stable. In particular if \( g_1 \equiv g_2 \) and \( h(m) = m/2 \), then (25) reduces to \( 2g_2(m) \neq g_2(2m) \) for some \( m > \pi_2(\tau, m_P)/2 \). A similar condition appears in many papers concerning size-structured models [4, 8, 11, 33, 34].

Now we can formulate the Foguel alternative for semigroup \( \{P(t)\}_{t \geq 0} \) corresponding to the process \( \xi(t) \).

**Theorem 5.1.** The semigroup \( \{P(t)\}_{t \geq 0} \) satisfies the Foguel alternative, i.e. \( \{P(t)\}_{t \geq 0} \) is asymptotically stable or sweeping from compact sets.

**Proof.** First we check condition (K). Let \( a_0 > 0 \) and \( m_0 \in (\pi_1(a_0, 0), \bar{m}) \) be the age and maturity of a cell at time 0. Define the functions \( \theta_1(t_1, t_2) = t_1 - t_2 - 2\tau \) and \( \theta_2(t_1, t_2) = m_7 \), where

\[
    
    \begin{align*}
        m_1 &= \pi_1(a_0+t_1, m_0), \quad m_2 = \pi_2(\tau, m_1), \quad m_3 = h(m_2), \\
        m_4 &= \pi_1(t_2, m_3), \quad m_5 = \pi_2(\tau, m_4), \quad m_6 = h(m_5), \\
        m_7 &= \pi_1(t_1-t_2-2\tau, m_6).
    \end{align*}
\]

Then \( \theta = (\theta_1, \theta_2) \) is age and maturity of a granddaughter cell at time \( t > t_1 + t_2 + 2\tau \). It is easy to check that

\[
    \theta'(t_1, t_2) = \begin{bmatrix}
        -1 & -1 \\
        -g_1(m_7) + L_1L_2 & -g_1(m_7) + L_1
    \end{bmatrix},
\]

where

\[
    L_1 = \frac{h'(m_5)g_1(m_7)g_2(m_5)g_1(m_4)}{g_1(m_6)g_2(m_4)},
\]

\[
    L_2 = \frac{h'(m_2)g_2(m_2)g_1(m_1)}{g_1(m_3)g_2(m_1)}.
\]

Hence

\[
    \det \theta'(t_1, t_2) = g_1(m_7) + L_1L_2 - g_1(m_7) - L_1 = L_1(L_2 - 1)
\]

and since \( L_1 \neq 0 \), the determinant of \( \theta'(t_1, t_2) \) is different from zero if and only if

\[
    h'(m_2)g_2(m_2)g_1(m_1) \neq g_1(m_3)g_2(m_1). \tag{26}
\]

Since \( m_2 = \pi_2(\tau, m_1) \) and \( m_3 = h(\pi_2(\tau, m_1)) \) from (25) it follows that condition (26) holds for \( m_1 \) sufficiently close to \( \bar{m} \). Fix \( t_1^0, t_2^0, \) such that \( \pi_1(a_0 + t_1^0, m_0) = \bar{m}, \) \( t_2^0 > 0 \), and \( t > t_1^0 + t_2^0 + 2\tau \). The times \( t_1 \) and \( t_2 \) are random variables and we can find densities of their distributions using formula (16). According to this formula there exist \( \delta > 0 \) and \( \varepsilon_1 > 0 \) such that their joint density \( p(t_1, t_2) \) is bounded below by \( \varepsilon_1 \) for \( (t_1, t_2) \in (t_1^0 - \delta, t_1^0 + \delta) \times (t_2^0 - \delta, t_2^0 + \delta) \). Since the age and maturity of a granddaughter cell at time \( t \) is given by \( (a, m) = \theta(t_1, t_2) \) the function

\[
    \tilde{p}(a, m) = |\det(\theta^{-1})'(a, m)|p(\theta^{-1}(a, m))
\]
is the density of the distribution of \((a, m)\). Since \(p(t_1, t_2)\) is bounded below by 
\(\varepsilon_1 > 0\) and \(\det \theta'(t_1^0, t_2^0) \neq 0\) we conclude that the density \(\hat{p}(a, m)\) is bounded below by some \(\varepsilon_2 > 0\) for \((a, m)\) from some neighbourhood \(V\) of \(\theta(t_1^0, t_2^0)\). It means that
\[
q(t, (a, m, 1), (a_0, m_0, 1)) \geq \varepsilon_2
\]
for \((a, m) \in V\). We can also find a neighbourhood \(U\) of \((a_0, m_0, 1)\) such that
\[
q(t, x, y) \geq \varepsilon_2/2
\]
for \(x \in V\) and \(y \in U\), i.e. (3) holds for \(y_0 = (a_0, m_0, 1)\). Starting from any point \((\hat{a}, \hat{m}, \hat{i}) \in X\) we can find a trajectory of the process \(\xi\) which joins it with \((a_0, m_0, 1)\). Thus we can choose some neighbourhood \(W\) of \((\hat{a}, \hat{m}, \hat{i})\) and time \(\bar{t}\) such that if \(z \in W\) then the process \(\xi\) starting from \(z\) enters at time \(\bar{t}\) the set \(U\) with probability \(\geq p_1\), where \(p_1\) is a positive constant. Hence
\[
q(\bar{t} + t, x, z) \geq p_1\varepsilon_2/2
\]
for \(z \in W\) and \(x \in V\), and consequently, condition (K) is fulfilled.

Now we check that if \(f^*\) is an invariant density for the semigroup \(\{P(t)\}_{t \geq 0}\) then \(f^* > 0\) a.e. Let us take a point \(y_0 \in X\) such that the integral of \(f^*\) over each neighbourhood of \(y_0\) is positive. Then from (27) it follows that
\[
f^*(x) = P(\bar{t} + t)f^*(x) \geq \int_X q(\bar{t} + t, x, z)f^*(z) \mu(dz)
\]
\[
\geq p_1\varepsilon_2/2 \int_W f^*(z) \mu(dz) > 0,
\]
for \(x \in V\). Let \(\tilde{x} = (\hat{a}, \hat{m}, 1)\), where
\[
\hat{a} = \theta_1(t_1^0, t_2^0) = t - t_1^0 - t_2^0 - 2\tau \quad \text{and} \quad \hat{m} = \theta_2(t_1^0, t_2^0).
\]
For \(t_1 = t_1^0\) we have \(\tilde{m}_1 = m_1(t_1^0) = \tilde{m}\), \(\tilde{m}_2 = \pi_2(\tau, \tilde{m})\), \(\tilde{m}_3 = \psi(\tilde{m})\). Let \(\tilde{m}_4 = m_4(t_1^0, t_2^0) = \pi_1(t_1^0, \tilde{m}_3)\). Since \(t_2^0\) we can choose any positive number, \(\tilde{m}_4\) can be any number from the interval \((\psi(\tilde{m}), \infty)\). Let \(\tilde{m}_6 = m_6(t_1^0, t_2^0)\). Then \(\tilde{m}_6\) is any number from the interval \((c_1, \infty)\), where \(c_1 = 0\) if \(\psi(\tilde{m}) \leq m_P\) and \(c_1 = \psi(\tilde{m})\) if \(\psi(\tilde{m}) > m_P\). Since \(\tilde{a} = t - t_1^0 - t_2^0 - 2\tau\), \(\tilde{m}_7 = \pi_1(t - t_1^0 - t_2^0 - 2\tau, \tilde{m}_6)\) and \(t\) can be any number from the interval \((t_1^0 + t_2^0 + 2\tau, \infty)\), \(\tilde{x}\) can be any point from the set \(A_{11} = \{(a, m, 1) : a > 0, m > \pi_1(a, c_1)\}\). From (28) we obtain \(f^*(a, m, 1) > 0\) for \((a, m) \in A_{11}\). Since
\[
f^*(0, m, 2) = \varphi(m) \int_0^\infty f^*(a, m, 1) da
\]
we have \(f^*(0, m, 2) > 0\) for \(m > c_2 = \max(m_P, c_1)\). Hence \(f^*(a, m, 2) > 0\) for \((a, m) \in A_{12}\), where \(A_{12} = \{(a, m, 2) : a \in [0, \tau], m > \pi_2(a, c_2)\}\). Thus \(f^*(0, m, 1) > 0\) for \(m > c_3 = \psi(\tilde{c}_2)\), and consequently \(f^*(a, m, 1) > 0\) for \((a, m) \in A_{21}\), where \(A_{21} = \{(a, m, 1) : a \geq 0, m > \pi_1(a, c_3)\}\) and \(f^*(a, m, 2) > 0\) for \((a, m) \in A_{22}\), where \(A_{22} = \{(a, m, 2) : a \in [0, \tau], m > \pi_2(a, c_4)\}\), where \(c_4 = \max(m_P, c_3)\), etc. Since \(c_{2k-1} = 0\) for sufficiently large \(k\), we have \(f^*(a, m, 1) > 0\) for \(A_1 = \{(a, m, 1) : a \geq 0, m > \pi_1(a, 0)\}\) and \(f^*(a, m, 2) > 0\) for \(A_2 = \{(a, m, 2) : a \geq 0, m > \pi_2(a, m_P)\}\). Hence \(f^* > 0\) a.e. on \(X\). Moreover, \(f^*\) is the unique invariant density. Indeed, if a stochastic semigroup has two different invariant densities \(f_1\) and \(f_2\), then the function \(||f_1 - f_2||/||f_1 - f_2||\) is also an invariant density and has the support smaller than \(X\).
Therefore, if the semigroup \( \{P(t)\}_{t \geq 0} \) has an invariant density \( f^* \), then this density is unique and \( f^* > 0 \) a.e. and according to Theorem 2.3 this semigroup is asymptotically stable.

If \( \{P(t)\}_{t \geq 0} \) has no invariant density, then according to Corollary 1 it is sweeping from compact sets.

6. Master equation. Theorem 5.1 guarantees that the semigroup \( \{P(t)\}_{t \geq 0} \) satisfies the Foguel alternative but if we want to check if this semigroup is asymptotically stable or sweeping we need to prove that it has or does not have an invariant density. 

Time evolution of densities can be described by some partial differential equations with boundary conditions and knowing time independent solutions of this problem we can find an invariant density or check that such invariant density does not exist.

Let \( r(t, a, m) := f(t, a, m, 1) \) and \( p(t, a, m) := f(t, a, m, 2) \). Then the functions \( r \) and \( p \) satisfy the following system of equations:

\[
\begin{align*}
\frac{\partial r}{\partial t} + \frac{\partial r}{\partial a} + \frac{\partial (g_1(m)r)}{\partial m} &= -\varphi(m)r, \quad (29) \\
\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial (g_2(m)p)}{\partial m} &= 0, \quad (30)
\end{align*}
\]

and the boundary conditions

\[
\begin{align*}
r(t, 0, m) &= k'(m)p(t, \tau, k(m)), \quad (31) \\
p(t, 0, m) &= \varphi(m) \int_0^\infty r(t, a, m) da, \quad (32)
\end{align*}
\]

where \( k = h^{-1} \).

A similar system of equations was introduced in [19], where it described dynamics of a population of cells that are capable of simultaneous proliferation and maturation. That model includes, among other things, mortality and does not lead directly to a stochastic semigroup. In our case we replace one mother cell by one daughter cell which has allowed us to use a piecewise deterministic Markov process in the model’s description.

Let \( r(a, m) = \tilde{f}^*(a, m, 1) \) and \( p(a, m) = \tilde{f}^*(a, m, 2) \), where \( \tilde{f}^* \) is given by (19) and (21). It is not difficult to check that \( r(a, m) \) and \( p(a, m) \) are solutions of (29)–(30) with boundary conditions (31)–(32). If

\[
\int_0^\infty \int_0^\infty \tilde{f}^*(a, m, 1) da dm + \int_0^\infty \int_0^\tau \tilde{f}^*(a, m, 2) da dm < \infty, \quad (33)
\]

then an invariant density exists and the semigroup \( \{P(t)\}_{t \geq 0} \) is asymptotically stable. Condition (33) is equivalent to \( T_R < \infty \), where \( T_R \) is given by (22). Moreover, one can check that \( \tilde{f}^* \) is a unique, up to a multiplicative constant, positive stationary solution of (29)–(32), which gives that if \( T_R = \infty \) then the semigroup has no stationary densities, and therefore it is sweeping from compact sets. We skip here the rigorous justification of this statement.

The second integral in (33) is finite, and therefore, in order to check if an invariant density exists it is enough to check that the first integral is finite. In order to do it we investigate the function \( R(t, m) \), which is the total number of cells in the resting stage with given maturity \( m \) at time \( t \), i.e.

\[
R(t, m) = \int_0^\infty r(t, a, m) da.
\]
Integrating equation (29) over the age variable $a$ and using boundary condition (31) we obtain
\[
\frac{\partial R}{\partial t} + \frac{\partial (g_1 R)}{\partial m} = -\varphi(m) R + k'(m)p(t, \tau, k(m)).
\] (34)
Applying the method of characteristics to (30) and boundary condition (32) we find
\[
p(t, \tau, m) = p(t - \tau, 0, \pi_2(-\tau, m)) \frac{g_2(\pi_2(-\tau, m))}{g_2(m)}
\]
\[
= \varphi(\pi_2(-\tau, m)) R(t - \tau, \pi_2(-\tau, m)) \frac{g_2(\pi_2(-\tau, m))}{g_2(m)}.
\]
Now equation (34) can be written in the following form
\[
\frac{\partial R}{\partial t} + \frac{\partial (g_1 R)}{\partial m} = -\varphi(m) R + k'(m)\varphi(\lambda(m)) \frac{g_2(\lambda(m))}{g_2(k(m))} R(t - \tau, \lambda(m)).
\]
We recall that $\lambda(m) = \pi_2(-\tau, k(m))$ and, in consequence, we finally obtain
\[
\frac{\partial R}{\partial t} + \frac{\partial (g_1 R)}{\partial m} = -\varphi(m) R + \varphi(\lambda(m)) \lambda'(m) R(t - \tau, \lambda(m)).
\] (35)
Now we are looking for a stationary solution of (35). If $R(m)$ satisfies (35) then $R$ is a solution of the equation
\[
(g_1 R)'(m) = -\varphi(m) R(m) + \varphi(\lambda(m)) \lambda'(m) R(\lambda(m)).
\] (36)
It is not surprising that if $f^*(m, 1)$ is given by (20), then $R(m) = \tilde{f}^*(m, 1)$ is a solution of (36). Moreover, if $R$ is a solution of (36) with $R(0) = 0$, then the following formula holds:
\[
\varphi(m) R(m) = Q'(m) e^{-Q(m)} \int_{m_P}^{\lambda(m)} \lambda(x) e^{\tilde{Q}(x) - \tilde{Q}(\lambda(m))} f(x) \, dx.
\]
If we substitute $\tilde{Q}(m) = Q(\lambda^{-1}(m))$, then $\tilde{P} R = \varphi R$, where
\[
\tilde{P} f(m) = \int_{m_P}^{\lambda(m)} \lambda(x) \tilde{Q}'(\lambda(m)) e^{\tilde{Q}(x) - \tilde{Q}(\lambda(m))} f(x) \, dx.
\]
Then
\[
PU = U \tilde{P}, \quad U f(m) := \lambda(m) f(\lambda(m))
\]
and $U$ is an isometric operator from $L^1[m_P, \infty)$ onto $L^1[0, \infty)$. Therefore, $\tilde{P}^n = U^{-1} P^n U$, and, in consequence, the operators $P$ and $\tilde{P}$ have the same asymptotic properties. Observe that $P$ has an invariant density $f^*$ if and only if $\tilde{f}^* = U^{-1} f^*$ is an invariant density for $\tilde{P}$.

Let us assume that $P$ has an invariant density $f^*$ and $\varphi(m) \geq \varepsilon > 0$ for sufficiently large $m$. Since $R \varphi$ is a fixed point of $\tilde{P}$, we have $R \varphi = c U^{-1} f^*$ for some $c > 0$. Hence, $\int_{m_P}^{\infty} R(m) \, dm < \infty$, which implies that the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable. According to Proposition 2, if $\liminf_{m \to \infty} Q(\lambda(m)) - Q(m) > 1$ and $\varphi(m) \geq \varepsilon > 0$ for sufficiently large $m$, then the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable.

Now, we assume that $P$ has no invariant density and $\varphi$ is a bounded function. Then $R$ cannot be an integrable function. Assume contrary to our claim, that $R$ is integrable. Then $R \varphi$ is an integrable function and the operator $\tilde{P}$ has a positive fixed point. Hence $\tilde{P}$ and $P$ have invariant densities, a contradiction. According to Proposition 2, if $Q(\lambda(m)) - Q(m) \leq 1$ for sufficiently large $m$ and $\varphi$ is bounded, then the semigroup $\{P(t)\}_{t \geq 0}$ is sweeping.
Remark 1. It can happen that the operator $P$ is asymptotically stable but the semigroup $\{P(t)\}_{t \geq 0}$ is sweeping. Indeed, if we choose $g_2$, $h$ and $r$ such that $\lambda(m) = m + 2$ for $m \geq 0$ and we choose $g_1$ and $\varphi$ such that $Q(m) = m$ for $m \geq 3$, then $\liminf_{m \to \infty}(Q(\lambda(m)) - Q(m)) = 2$ and the operator $P$ is asymptotically stable. Let $f_i$ be an invariant density for $P$. The density $f^*$ depends only on $Q$ and $\lambda$, so we can choose $g_1$ and $\varphi$ such that $\varphi(m) = g_1(m) = f^*(m - 2)$ for $m \geq 3$. Then $R(m) = cU^{-1}f^*(m)/\varphi(m) = c$. Consequently, $R$ is not integrable and the semigroup $\{P(t)\}_{t \geq 0}$ is sweeping. The explanation of this phenomenon is that in this example the rate of entering the proliferating phase is very small for large $m$. Then the mean length of the resting phase can be large and more and more cells have arbitrary large maturity as $t \to \infty$.

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E-mail address: katarzyna.pichor@us.edu.pl
E-mail address: rudnicki@us.edu.pl