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On continuous time version of two-phase cell cycle model of Tyrcha

Abstract We consider a model of two-phase cell cycle in a maturity-structured cellular population, which consists of a system of first order linear partial differential equations (transport equations). The model is based on similar biological assumptions as models of Lasota-Mackey, Tyson-Hannsgen and Tyrcha. We examine behavior of the solutions of the system along characteristics, give conditions for existence of invariant density, and compare results with outcomes of generational model.

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1. Introduction Two-phase cell cycle is a theoretical model of maturation and proliferation of eukaryotic cell, which consists of two phases: the phase of growth, which corresponds to biological phase G_1, and the phase of division, which is equivalent to biological S, G_2, M phases. That kind of model is a research area, which is often studied from the standpoint of modern mathematical applications. In the paper [16] Tyrcha presents one of such models, having derived a Markov operator, which describes how the cellular generations change. Moreover, the survey on asymptotic behavior of a sequence of iterates of this operator is considered. The above-mentioned model is a generalization of two other models: a single-phase cell cycle model of Lasota-Mackey [4] and a deterministic/probabilistic model of Tyson-Hannsgen [17]. In the present paper we adopt assumptions of Tyrcha model, to derive a new continuous time model, which belongs to the group of age-structured population models (e.g. see [5,10,11]) with a cellular maturity described by ordinary differential equation. We consider the population of cells in which the maturation and replication take place simultaneously. It turns out that the evolution of probabilistic densities in the growth phase is described by the same Markov operator as in discrete model. The asymptotic properties of that operator, which were originally studied by Gacki/Lasota [1], Łoskot/Rudnicki [6] and

Rudnicki [14], are proved in the present paper, using different methods and general facts concerning so-called integral Markov operators.

This paper constitutes a part of author's master thesis entitled *"Asymptotyka rozwiązań równań transportu opisujących dwufazowy model cyklu komórkowego"*, which was defended in June 2012 at University of Silesia in Katowice (Poland) under the supervision of Ryszard Rudnicki. The master thesis was awarded by Polish Mathematical Society in 2012 in The XLVI Competition for the best students' paper in probability and applied mathematics. Although the present paper is a kind of survey work, it contains also a new approach of proving already known results. This approach arises from solutions to many problems given in the book [12], and is inspired by lots of hints and remarks from that monograph.

The scheme of the paper is following. In Section 2 we introduce assumptions and formulate the model as a system of first order partial differential equations, which describe subpopulations of cells in growth and division phases. Later on, we derive a partial differential equation for a distribution of all cells in the growth phase. For the solutions of that equation we prove the existence and uniqueness theorem in Section 3. Afterwards, we give conditions for existence of the invariant distribution of the population, and show other asymptotic properties of a Markov operator, which is connected with the model. In Section 4 we give final remarks and show differences between discrete and continuous time models.

2. Formulation of the model To formulate the model we consider two phases of the cell cycle: the phase of growth A, whose biological equivalent is phase G_1, and the phase of division B, which corresponds to the biological phases S, G_2, M. According to the biological knowledge the length of the phase B is constant. Henceforth, we denote it by τ.

We assume that a number $x \geqslant 0$ is a maturity of a single cell, and its change is described by the following differential equation

$$x'(t) = V(x(t)), \tag{1}$$

where $V\colon [0,\infty) \to [0,\infty)$ is a function of the class C^1, such that

$$V(0) = 0 \text{ and } V(x) > 0 \text{ for all } x > 0. \tag{2}$$

For convenience sake, the solution of the equation (1), which satisfies the initial condition $x(0) = x$, will be denoted by $\pi_t x$.

Let $\beta(x)$ be the rate of the transition from the phase A to the phase B of a cell with the maturity x. It means that the cell with the maturity x, in short interval of time $[t_0, t_0+h]$, enters the division phase with the probability $\beta(x)h + o(h)$, where $o(h)$ is some continuous function, such that $o(h)/h \to 0$ as $h \to 0$. We assume that the function β is nonnegative.

Let us suppose that the division is equal in the following sense: if x is a maturity of a mother cell at the time of the division, then $x/2$ is initial maturity of each of two daughter cells. Let $\delta(x)$ (resp. $\gamma(x)$) be a rate of natural death of a cell with the maturity x in the phase A (resp. the phase B). We assume that δ and γ are nonnegative functions.

System of equations. We write $n(t,a,x)$ (resp. $p(t,a,x)$) for distributions of cells with respect to age a, maturity x at the time t in the phase A (resp. the phase B). The conservation equations for $n(t,a,x)$ and $p(t,a,x)$ are of the following form

$$\frac{\partial n}{\partial t}+\frac{\partial n}{\partial a}+\frac{\partial(V(x)n)}{\partial x}=-(\delta(x)+\beta(x))n, \tag{3}$$

$$\frac{\partial p}{\partial t}+\frac{\partial p}{\partial a}+\frac{\partial(V(x)p)}{\partial x}=-\gamma(x)p. \tag{4}$$

We assume that the above system of the equations satisfies following initial conditions

$$n(t,a,x)=\Gamma_1(t,a,x), \quad \text{for} \quad (t,a,x)\in[-\tau,0]\times[0,\infty)\times[0,\infty), \tag{5}$$

$$p(t,a,x)=\Gamma_2(t,a,x), \quad \text{for} \quad (t,a,x)\in[-\tau,0]\times[0,\tau]\times[0,\infty), \tag{6}$$

where the functions Γ_1,Γ_2 are supposed to be continuous and nonnegative.

Boundary conditions. To finish the formulation of the problem, we add to the equations (3), (4) two boundary conditions. As a cell with the maturity x can enter the phase of division with the rate $\beta(x)$, the first boundary condition, which express the flow of new cells to the phase B, is

$$p(t,0,x)=\beta(x)\int_0^\infty n(t,a,x)da. \tag{7}$$

On the other hand, if we consider daughter cells with the maturities from the interval $[0,y]$, then their mother cells have, at the moment of the division, maturities from the interval $[0,2y]$. It follows from the equal division assumption. Hence

$$\int_0^y n(t,0,x)dx=\int_0^{2y}2p(t,\tau,x)dx.$$

Differentiating the both sides of the above equation with respect to y, at the point x, we obtain the second boundary condition

$$n(t,0,x)=4p(t,\tau,2x). \tag{8}$$

Cells in the growth phase. Integrating the both sides of the equation (3), with respect to the age variable a, over the interval $[0,\infty)$, we obtain

$$\frac{\partial}{\partial t}\int_0^\infty n(t,a,x)da + \lim_{a\to\infty} n(t,a,x) - n(t,0,x) + \frac{\partial}{\partial x}\Big(V(x)\int_0^\infty n(t,a,x)da\Big) = -(\delta(x)+\beta(x))\int_0^\infty n(t,a,x)da. \tag{9}$$

If we denote $\int_0^\infty n(t,a,x)da$ by $N(t,x)$, then $N(t,x)$ is a distribution of cells with the maturity x, which are in the phase A, at the moment t. We additionally assume that $\lim_{a\to\infty} n(t,a,x)=0$, what simply means that any cell can not live forever. The condition (8) implies that the equation (9) becomes

$$\frac{\partial N}{\partial t} + \frac{\partial (VN)}{\partial x} = -(\delta(x)+\beta(x))N + 4p(t,\tau,2x). \tag{10}$$

Now we express the term $4p(t,\tau,2x)$, using the function N. To this end, we rewrite the equation (4) in the form

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + V(x)\frac{\partial p}{\partial x} = -(V'(x)+\gamma(x))p. \tag{11}$$

According to the method of characteristics, if we write $z(t)=p(t+t_0,t,\pi_t y)$, then z satisfies the following differential equation $z'(t)=-(V'(\pi_t y)+\gamma(\pi_t y))z(t)$ and so

$$z(t) = z(0)\exp\Big\{-\int_0^t V'(\pi_s y)ds\Big\}\exp\Big\{-\int_0^t \gamma(\pi_s y)ds\Big\}. \tag{12}$$

Notice that

$$-\int_0^t V'(\pi_s y)ds = \left[\begin{array}{c} x=\pi_s y \\ dx = V(x)ds \end{array}\right] = -\int_y^{\pi_t y}\frac{V'(x)}{V(x)}dx = \ln\frac{V(y)}{V(\pi_t y)}. \tag{13}$$

Then from (12) we obtain (for $t=\tau$)

$$z(\tau) = z(0)\frac{V(y)}{V(\pi_\tau y)}\exp\Big\{-\int_0^\tau \gamma(\pi_s y)ds\Big\}. \tag{14}$$

By the definition of $z(t)$ and by setting $t=\tau+t_0$, $\pi_\tau y = 2x$ we can write

$$4p(t,\tau,2x) = 4p(t-\tau,0,\pi_{-\tau}2x)\frac{V(\pi_{-\tau}2x)}{V(2x)}\exp\Big\{-\int_{-\tau}^0 \gamma(\pi_s 2x)ds\Big\}. \tag{15}$$

The boundary condition (7) implies

$$4p(t,\tau,2x) = 4\beta(\pi_{-\tau}2x)\frac{V(\pi_{-\tau}2x)}{V(2x)}\exp\Big\{-\int_{-\tau}^0 \gamma(\pi_s 2x)ds\Big\}N(t-\tau,\pi_{-\tau}2x). \tag{16}$$

Finally, substituting (16) into (10), we obtain

$$\frac{\partial}{\partial t}N(t,x)+\frac{\partial}{\partial x}(V(x)N(t,x)) = -(\delta(x)+\beta(x))N(t,x)+\Psi(x)N_\tau(t,x), \quad (17)$$

where

$$\Psi(x) := 4\beta(\pi_{-\tau}2x)\frac{V(\pi_{-\tau}2x)}{V(2x)}\exp\Big\{-\int_{-\tau}^{0}\gamma(\pi_s 2x)ds\Big\},$$

and $N_\tau(t,x) := N(t-\tau,\pi_{-\tau}2x)$. According to (5), we study the equation (17) with a following initial condition

$$N(t,x) = \int_0^\infty n(t,a,x)da = \int_0^\infty \Gamma_1(t,a,x)da, \quad \text{for} \quad (t,x)\in[-\tau,0]\times[0,\infty). \tag{18}$$

The equation (17) is the main object of our interest in the present paper.

3. Behavior of the solutions We start this section from the proof of the existence and uniqueness theorem.

Theorem 1 *There exists an unique solution of the equation* (17)*, which satisfies the initial condition* (18)*.* □

PROOF We use the method of steps to solve the equation (17). We rewrite it in the following form

$$\frac{\partial N}{\partial t}+V(x)\frac{\partial N}{\partial x} = F(x)N+G(t,x), \tag{19}$$

where $F(x) = -(\delta(x)+\beta(x)+V'(x))$ and $G(t,x) = \Psi(x)N_\tau(t,x)$. If $t\in[0,\tau]$, then the function G is known from the initial condition (18). Using the method of characteristics, we obtain that there exists the only one solution $N(t,x)$ of the equation (17) for $(t,x)\in[0,\tau]\times[0,\infty)$ and is given by the formula

$$N(0,\pi_{-t}x)\exp\Big\{\int_0^t F(\pi_{s-t}x)ds\Big\}+\int_0^t G(s,\pi_{s-t}x)\exp\Big\{\int_s^t F(\pi_{r-t}x)dr\Big\}ds. \tag{20}$$

Now let the equation (17) have the unique solution for $(t,x)\in[(n-1)\tau,n\tau]\times[0,\infty)$. If $(t,x)\in[n\tau,(n+1)\tau]\times[0,\infty)$, then once again we can rewrite (17) in the form (19). The function G is known from the previous step. Using the method of characteristics we obtain that the only one solution of the equation (17) is given by the formula (20) for $(t,x)\in[n\tau,(n+1)\tau]\times[0,\infty)$. By the induction we can uniquely solve (17) for all $(t,x)\in[0,\infty)\times[0,\infty)$.■

To study the asymptotic properties of the solutions of the equation (17) we assume that the functions δ,β i γ are independent of the maturity variable x. Then the equation (17) can be written in the following form

$$\frac{\partial N}{\partial t}+\frac{\partial(V(x)N)}{\partial x} = -(\delta+\beta)N(t,x)+2\beta e^{-\gamma\tau}\lambda'(x)N(t-\tau,\lambda(x)), \tag{21}$$

where $\lambda(x) = \pi_{-\tau}2x$ and $\lambda(x) = 0$, when $x \leqslant \frac{1}{2}\pi_\tau 0$. We have to add the following boundary condition $N(t,0) = 0$. Biologically it means, that there is no entrance of the negative-mature cells to the population.

3.1. Total number of cells We integrate the both sides of the equation (21) with respect to the maturity variable x over the interval $[0,\infty)$ and use a substitution of the form $y = \lambda(x)$ to the second term of the right side of the equation. We obtain

$$\bar{N}'(t) = -(\delta+\beta)\bar{N}(t) + 2\beta e^{-\gamma\tau}\bar{N}(t-\tau), \tag{22}$$

where $\bar{N}(t) = \int_0^\infty N(t,x)dx$. The similar equations describe the dynamics of populations in cell replication models without maturity (see [7–9]).

Asymptotic behavior of the solutions of equation (22) can be divided into three types:

1. if the equality $2\beta e^{-\gamma\tau} = \delta + \beta$ holds, then each solution converges to some positive constant,
2. if the inequality $2\beta e^{-\gamma\tau} < \delta + \beta$ holds, then trivial solution ($\bar{N} \equiv 0$) is asymptotically stable,
3. if the inequality $2\beta e^{-\gamma\tau} > \delta + \beta$ holds, then each solution, which starts from positive boundary condition, tends to $+\infty$ as $t \to \infty$.

Now we discuss briefly each of the above-mentioned types.

Type 1. Let us define $a := 2\beta e^{-\gamma\tau} = \delta + \beta$. Then the equation (22) can be rewritten in the form

$$\bar{N}'(t) = -a\bar{N}(t) + a\bar{N}(t-\tau).$$

We assume that $\bar{N}(t) > 0$ for $t \in [-\tau, 0]$ and denote by M_n (resp. m_n) the maximum (resp. the minimum) of $\bar{N}(t)$ in the interval $[(n-1)\tau, n\tau]$. Then the solution $\bar{N}$ satisfies the following differential inequality

$$\bar{N}'(t) \leqslant -a\bar{N}(t) + aM_n = -a(\bar{N}(t) - M_n)$$

for $t \in [n\tau, (n+1)\tau]$. Since $N(n\tau) \leqslant M_n$, the difference $\bar{N}(t) - M_n$ is negative for all $t \in [n\tau, (n+1)\tau]$. Hence

$$\frac{\bar{N}'(t)}{\bar{N}(t) - M_n} \geqslant -a$$

and by the theorem of differential inequalities we obtain

$$\ln|\bar{N}(t) - M_n| - \ln|\bar{N}(n\tau) - M_n| \geqslant -a(t - n\tau) = -a\tau,$$

what is equivalent to

$$\bar{N}(t) \leqslant \bar{N}(n\tau)e^{-a\tau} + (1 - e^{-a\tau})M_n \tag{23}$$

for all $t \in [n\tau, (n+1)\tau]$. Particularly, if we change $\bar{N}(t)$ by M_{n+1} we obtain

$$M_{n+1} \leqslant M_{n+1}e^{-a\tau} + (1 - e^{-a\tau})M_n.$$

It implies that the sequence $(M_n)_{\mathbb{N}}$ is non-increasing. Analogously we show the inequality

$$\bar{N}(n\tau)e^{-a\tau} + (1 - e^{-a\tau})m_n \leqslant \bar{N}(t) \tag{24}$$

for all $t \in [n\tau, (n+1)\tau]$. The same argument as before implies that $(m_n)_{\mathbb{N}}$ jest non-decreasing. From (23) and (24) we obtain $M_{n+1} \leqslant \bar{N}(n\tau)e^{-a\tau} + (1 - e^{-a\tau})M_n$ and $\bar{N}(n\tau)e^{-a\tau} + (1 - e^{-a\tau})m_n \leqslant m_{n+1}$. Therefore,

$$M_{n+1} - m_{n+1} \leqslant (1 - e^{-a\tau})(M_n - m_n).$$

The last inequality confirms that there exists a constant $c > 0$, such that

$$\lim_{n\to\infty} M_n = \lim_{n\to\infty} m_n = c.$$

It is equivalent to the fact that each solution $\bar{N}(t)$ converges to a constant when $t \to \infty$.

Biologically the equality $\delta + \beta = 2\beta e^{-\gamma\tau}$ means that the amount of cells which leave the growth phase equals to the amount of new cells which enter the that phase after the division. In that case the number of cells stabilizes after a long period of time.

Type 2. It is well-known that the inequality $2\beta e^{-\gamma\tau} < \delta + \beta$ implies global stability of trivial solution (see [2] Chap. 5). Moreover each solution $\bar{N}(t)$ is exponentially convergent to 0, i.e. there exist constants $L > 0$ and $\varepsilon > 0$ such that

$$\bar{N}(t) \leqslant Le^{-\varepsilon t}.$$

The condition of asymptotically stable trivial solution simply means that the population of cells dies out after some time.

Type 3. Define $g(r) := \delta + \beta + r$ and $h(r) := 2\beta e^{-\gamma\tau}$. The assumed inequality implies that $g(0) < h(0)$. It is obvious that $\lim_{r\to\infty} g(r) > \lim_{r\to\infty} h(r)$. Thus there must exist $r^* > 0$ such that

$$\delta + \beta + r^* = 2\beta e^{-\gamma\tau}e^{-r^*\tau}.$$

The substitution $\bar{N}(t) = M(t)e^{r^*t}$ leads back to the case of Type 1. Consequently,

$$\lim_{t\to\infty} \bar{N}(t)e^{-r^*t} = c$$

for some constant $c > 0$, and therefore $\lim_{t\to\infty} \bar{N}(t) = \infty$. This condition obviously means that the population is unbounded and the total number of cells grows exponentially to infinity.

3.2. Invariant density Now we consider only the case of Type 1 from Subsection 3.1, i.e. we assume that $\delta + \beta = 2\beta e^{-\gamma\tau}$. We recall the definition of a density. We say that $f \in L^1[0,\infty)$ is a *density* if $f \geqslant 0$, and $\|f\| = 1$, where $\|\cdot\|$ is a standard (integral) norm in the space $L^1[0,\infty)$. We denote by D the set of all densities in $L^1[0,\infty)$.

Lemma 1 *If the solution $N(t,\cdot)$ of the equation (21) is a density for $t \in [-\tau, 0]$, then $N(t,\cdot)$ is a density for all $t \geqslant 0$.* □

Proof Denote $a := \delta + \beta = 2\beta e^{-\gamma\tau}$. We start from showing the positivity of solutions by the method of steps. Fix positive integer n and suppose that $N(t,x) \geqslant 0$ for all $t \in ((n-1)\tau, n\tau]$. Then, from the equation (21) it follows

$$\frac{\partial N}{\partial t} + \frac{\partial (V(x)N)}{\partial x} \geqslant -aN(t,x)$$

for $t \in ((n-1)\tau, n\tau]$. Let us denote $p(t) := N(t, \pi_t x)$. Then $p(t) \geqslant -(a + V'(\pi_t x))p(t)$. From the theorem of differential inequalities

$$p(t) \geqslant p(n\tau) \exp\left\{ -\int_{n\tau}^{t} (a + V'(\pi_s x))ds \right\}$$

for $t \in (n\tau, (n+1)\tau]$. From the assumption $p(n\tau) \geqslant 0$, and so $p(t) \geqslant 0$. Consequently $N(t,x) \geqslant 0$ for $t \in (n\tau, (n+1)\tau]$.

To complete the proof we need to show that the norm of the solution is 1 for each time. Suppose that $t \in [(n-1)\tau, n\tau]$. Then for each $t \in (n\tau, (n+1)\tau]$ equation (22) can be written in the form $\bar{N}'(t) = a(1 - \bar{N}(t))$. Obviously $N_0 \equiv 1$ is a stationary solution of that equation. From the uniqueness of solutions theorem we claim that $\bar{N}(t) = N_0 = 1$ for $t \in (n\tau, (n+1)\tau]$. Since n was arbitrary, $\bar{N}(t) = 1$ for all $t \geqslant 0$. ■

Lemma 1 allows us to consider the equation (21) only in the set of densities D. A stationary solution $N(t,x) = f(x)$ of the equation (21) satisfies following

$$(Vf)'(x) = -f(x) + a\lambda'(x)f(\lambda(x)), \tag{25}$$

where $a := \delta + \beta = 2\beta e^{-\gamma\tau}$, and the boundary condition $f(0) = 0$. By multiplying both sides of (25) by $e^{aT(x)}$, where $T(x) := \int_0^x 1/V(r)dr$, we obtain

$$(V(x)f(x)e^{aT(x)})' = (Vf)'(x)e^{aT(x)} + af(x)e^{aT(x)} = a\lambda'(x)f(\lambda(x))e^{aT(x)}. \tag{26}$$

The integration over the interval $[0, x]$ and the boundary condition $f(0) = 0$ yield together

$$V(x)f(x)e^{aT(x)} = a\int_0^x \lambda'(y)f(\lambda(y))e^{aT(y)}dy = a\int_0^{\lambda(x)} e^{aT(\lambda^{-1}(y))}f(y)dy.$$

Finally, f satisfies the equation (25) if and only if f is a fixed point of the operator of the form

$$Pf(x) = \lambda'(x)Q'(\lambda(x))e^{-Q(\lambda(x))}\int_0^{\lambda(x)} e^{Q(y)}f(y)dy, \qquad (27)$$

where $Q(x) = aT(\lambda^{-1}(x))$. It is clear that the operator P is a *Markov operator*, what means that it preserves the densities: $P(D) \subset D$ (for general information concerning Markov operators and their properties see [3,12,15]). It is important to notice that the operator of the same form appeared in discrete model of Tyrcha [16].

Now we recall some definitions, which are connected with asymptotic properties of Markov operator. We say that the Markov operator P is *asymptotically stable*, if there exists a density f^* such that $Pf^* = f^*$ and

$$\lim_{n\to\infty} \|P^n f - f^*\| = 0$$

for all $f \in D$ ($P^n f := P \circ \ldots \circ Pf$). The Markov operator P is called *sweeping* from a set A, if

$$\lim_{n\to\infty} \int_A P^n f(x)\mu(dx) = 0,$$

for all $f \in D$. We say that the Markov operator P is *completely mixing*, if

$$\lim_{n\to\infty} \|P^n f - P^n g\| = 0,$$

for all $f, g \in D$.

To examine an above-mentioned asymptotic properties of Markov operator P of the form (27) we use the following theorem

Theorem 2 *Let $\alpha(x) = Q(\lambda(x)) - Q(x)$. The following statements hold*

1. *if*

$$\liminf_{x\to\infty} \alpha(x) > 1, \qquad (28)$$

then the operator P is asymptotically stable (in particular there exist a stationary density),

2. *if*

$$\alpha(x) \leqslant 1, \qquad (29)$$

for sufficiently large x, then the operator P is sweeping from the intervals of the form $[0, c]$, for all $c > 0$,

3. *if*
$$\inf \alpha(x) > -\infty, \tag{30}$$
then the operator P is completely mixing. □

Theorem 2 is a connection of results from various papers. The first statement was originally proved by Gacki and Lasota in [1]. The proof of the second part can be found in a paper of Łoskot and Rudnicki [6]. The last point was proved by Rudnicki in [14].

We present here different proofs of statements 1. and 2. which are based on ideas contained in the book [12]. Before we start the proof, we quote some auxiliary definitions and theorems. During the proof we strongly use the special kind of the operators, namely integral Markov operators. We say that the Markov operator P is *integral*, if and only if there exists a nonnegative and measurable function $q(x, y)$, such that
$$\int_X \int_X q(x, y)\mu(dx)\mu(dy) > 0 \tag{31}$$
and
$$Pf(x) = \int_X q(x, y)f(y)\mu(dy) \tag{32}$$
for every density $f \in D$. For integral Markov operators the following theorem is valid.

Theorem 3 (see [13]) *Let P be an integral Markov operator. If the operator P have invariant density f^*, i.e. $Pf^* = f^*$, positive a.e., and has no other periodic points in the set of densities, then P is asymptotically stable.* □

Some of the Markov operators have the following property: they are either asymptotically stable or sweeping from the family of compact subsets of space. This property is called *Foguel alternative.* For integral Markov operators the following theorem is of the great importance.

Theorem 4 (see [12, 13]) *Let X be a metric space and Σ σ-algebra of Borel subset on X. Suppose that integral Markov operator P satisfies*

1. *for every $f \in D$ the inequality $\sum_{n=0}^{\infty} P^n f > 0$ holds a.e.,*

2. *for every $y_0 \in X$ there exist $\varepsilon > 0$ and nonnegative and measurable function η, such that $\int_X \eta(x)\mu(dx) > 0$ and*
$$q(x, y) \geqslant \eta(x)1_{B(y_0,\varepsilon)}(y),$$
where $1_{B(y_0,\varepsilon)}$ is a characteristic function of a ball $B(y_0, \varepsilon)$ centered at y_0 with radius ε, and q is a function satisfying conditions (31), (32).

Then the operator P satisfies Foguel alternative, i.e. P is either asymptotically stable or sweeping from every compact subset of X. □

We proceed to proofs of the points 1. and 2. of Theorem 2.

Proof (point 1.) Let us define $S : L^1[0,\infty) \to L^1[0,\infty)$ by the formula $Sf(x) = f(Q(x))Q'(x)$. Clearly, S is an isometry, and consequently S and S^{-1} are Markov operators. If we denote $S^{-1}PS$ by $\hat{P}$, then

$$\hat{P}f(x) = \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y f(y)dy, \tag{33}$$

where $\hat{\lambda}(x) = Q(\lambda(Q^{-1}(x)))$.

Since S, P, S^{-1} are Markov operators, the operator $\hat{P}$ also is Markov. Moreover, the operators P and $\hat{P}$ has the same asymptotic properties: operators P and $\hat{P}$ are simultaneously asymptotically stable or sweeping. In the case of the operator $\hat{P}$, function α has the form $\hat{\alpha}(x) = \hat{\lambda}(x) - x = \alpha(Q^{-1}(x))$. Thus the assumption (28) transfers onto the function $\hat{\alpha}$. Now we check the validity of inequality

$$\int_0^x \hat{P}f(x)dx \leqslant 1 - e^{-\hat{\lambda}(x)} \tag{34}$$

for any $f \in D$ and $x \geqslant 0$. Let $f \in D$ and $x \geqslant 0$ be fixed. Then

$$\int_0^x \hat{P}f(x)dx = \int_0^{\hat{\lambda}(x)} \left[e^{-x} \int_0^x e^y f(y)dy \right] dx.$$

From the change of integration order and integration by parts it follows that

$$\begin{aligned} \int_0^x \hat{P}f(x)dx &= \int_0^{\hat{\lambda}(x)} f(y)dy - \int_0^{\hat{\lambda}(x)} f(y)dy + e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} \left[e^y \int_0^y f(z)dz \right] dy \\ &\leqslant -e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y dy = 1 - e^{-\hat{\lambda}(x)}. \end{aligned}$$

Let us consider the set

$$Z = \{x \geqslant 0 : \hat{\lambda}(y) > y \quad \text{dla} \quad y \geqslant x\}. \tag{35}$$

The assumption (28), in the case of $\hat{P}$, changes into $\hat{\lambda}(x) - x \geqslant \alpha > 1$, and consequently the set Z is nonempty. Let us put $\bar{x} = \inf Z$. If $f \in D$, then

$$\int_0^{\bar{x}} \hat{P}f(x)dx = \int_0^{\bar{x}} \hat{P}f_{|[0,\bar{x}]}(x)dx = \|f_{|[0,\bar{x}]}\| \cdot \int_0^{\bar{x}} \hat{P}\left(\frac{f_{|[0,\bar{x}]}}{\|f_{|[0,\bar{x}]}\|} \right)(x)dx$$

and according to the inequality (34)

$$\int_0^{\bar{x}} \hat{P}f(x)dx \leqslant \left(1 - e^{-\hat{\lambda}(\bar{x})}\right) \int_0^{\bar{x}} f(x)dx.$$

Inductively we obtain

$$\int_0^{\bar{x}} \hat{P}^n f(x)dx \leqslant \left(1 - e^{-\hat{\lambda}(\bar{x})}\right)^n \int_0^{\bar{x}} f(x)dx.$$

The above inequality implies that the operator $\hat{P}$ is sweeping from the interval $[0, \bar{x}]$.

Now we consider $x \notin [\bar{x}, \infty)$. Since the function $\hat{\lambda}$ is increasing, the inequality $\hat{\lambda}(x) \leqslant \hat{\lambda}(\bar{x}) \leqslant \bar{x}$ holds and therefore

$$\hat{P}f(x) \leqslant \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^{\bar{x}} e^y f(y)dy.$$

From this inequality it follows that if $\operatorname{supp} f \subset [\bar{x}, \infty)$, then also $\operatorname{supp} \hat{P}f \subset [\bar{x}, \infty)$. The conclusion is that the operator $\hat{P}$ restricted to the space $L^1[\bar{x}, \infty)$ is also Markov.

Let us define the operator R by the formula

$$RF(x) = e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} \Big(e^y F(y)\Big)dy,$$

where $F(x) = \int_0^x f(z)dz$ is a distribution function with a density f. We show that the operator R transforms distribution function with a density f into distribution function with a density $\hat{P}f$. Indeed, integrating by parts, we obtain

$$RF(x) = \int_0^{\hat{\lambda}(x)} f(y)dy - e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y f(y)dy. \tag{36}$$

On the other hand, once again integrating by parts, we conclude

$$\int_0^x \hat{P}f(z)dz = \int_0^{\hat{\lambda}(x)} f(y)dy - e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y f(y)dy. \tag{37}$$

Comparing (36) and (37), finally we obtain $RF(x) = \int_0^x \hat{P}f(y)dy$.

We consider the distribution function F_0 given by

$$F_0(x) = \begin{cases} 0, & \text{dla} \quad x < x_0, \\ 1 - e^{-\beta(x-x_0)}, & \text{dla} \quad x \geqslant x_0. \end{cases}$$

We show that there exist constants $x_0 > 0$ and $\beta > 0$, such that $RF_0(x) \geqslant F_0(x)$ for every $x \geqslant 0$. For $x < x_0$ the inequality is obvious. Now, if $x \geqslant x_0$, then we obtain

$$RF(x) = 1 - \frac{1}{1-\beta} e^{-\beta(\hat{\lambda}(x)-x_0)} - \left(1 - \frac{1}{1-\beta}\right) e^{x_0 - \hat{\lambda}(x)}. \tag{38}$$

From the assumption there exists x_0, such that $\hat{\lambda}(x) - x \geqslant \alpha > 1$ for $x \geqslant x_0$. Then

$$-e^{-\beta(\hat{\lambda}(x)-x_0)} \geqslant -e^{-\beta\alpha} e^{-\beta(x-x_0)}. \tag{39}$$

From the Taylor expansion we obtain $e^{-\beta\alpha} = 1 - \beta\alpha + o(\beta\alpha)$, when β is close to zero. From the assumption we get $\alpha > 1$, and consequently the inequality $e^{-\beta\alpha} < 1 - \beta$ holds for sufficiently small $\beta > 0$. Thus the condition (39) implies

$$-\frac{1}{1-\beta} e^{-\beta(\hat{\lambda}(x)-x_0)} > -e^{-\beta(x-x_0)}$$

for $x \geqslant x_0$. Decreasing β if needed, we also obtain

$$-\frac{1}{1-\beta} e^{-\beta(\hat{\lambda}(x)-x_0)} - \left(1 - \frac{1}{1-\beta}\right) e^{-\alpha} \geqslant -e^{-\beta(x-x_0)}.$$

Since $x_0 - \hat{\lambda}(x) \leqslant -\alpha$, the above inequality together with (38) implies that $RF_0(x) \geqslant F_0(x)$. Last inequality means that the sequence $(R^n F_0)_{n=1}^{\infty}$ is increasing. Now we show inductively that this sequence is upper-bounded by the function, which is identically equal to 1. Let us suppose that for $n \in \mathbb{N}$ the inequality $R^n F_0(x) \leqslant 1$ is true. Then

$$R^{n+1} F_0 = e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y R^n F_0(y) dy \leqslant e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y dy = 1 - e^{-\hat{\lambda}(x)} \leqslant 1.$$

We conclude that the sequence $(R^n F_0)_{n=1}^{\infty}$ is convergent to some function F^*, which also is upper-bounded by function constantly equal to 1.

We show the equality $RF^* = F^*$. By the Lebesgue dominated convergence theorem we obtain that for fixed x

$$F^*(x) = \lim_{n\to\infty} R^n F_0(x) = R(\lim_{n\to\infty} R^{n-1} F_0(x)) = RF^*(x).$$

Hence the equality

$$F^*(x) = e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y F^*(y) dy \tag{40}$$

is valid. Since the derivative of the right-hand side of last equality exists, there also exists a derivative f^* of the function F^*. Notice that f^* is probabilistic density. Differentiating both sides of (40), we obtain

$$f^*(x) = -\hat{\lambda}'(x) e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^y F^*(y) dy + \hat{\lambda}'(x) F^*(\hat{\lambda}(x)). \tag{41}$$

On the other side, integration by parts leads to

$$\hat{P} f^*(x) = \hat{\lambda}'(x) e^{-\hat{\lambda}(x)} \Big[e^{\hat{\lambda}(x)} F^*(\hat{\lambda}(x)) - \int_0^{\hat{\lambda}(x)} e^y F^*(y) dy \Big]. \tag{42}$$

Comparing (41) and (42), we obtain the existence of invariant density of the operator $\hat{P}$, i.e. $\hat{P} f^* = f^*$.

Let us fix any $y > \bar{x}$, such that $\int_0^y f^*(r)dr > 0$. Then for $x > \hat{\lambda}^{-1}(y)$

$$f^*(x) = \hat{P}f^*(x) > \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} f^*(r)dr \geqslant> 0.$$

Hence for any $n \in \mathbb{N}$ we conclude that $f^*(x) > 0$ for any $x > \hat{\lambda}^{-n}(y)$. Since the sequence $(\hat{\lambda}^{-n}(y))_{n=1}^{\infty}$ is bounded below by the number $\bar{x}$ and decreasing, it converges to some $\bar{y}$ as $n \to \infty$. From continuity of the function $\hat{\lambda}^{-1}$ we obtain that $\bar{y} = \bar{x}$. Finally $f^*(x) > 0$ for every $x > \bar{x}$.

We show now that the operator $\hat{P}$ has only one periodic points. If not, then there exists $r \in \mathbb{N}$, such that the operator $\hat{P}^r$ has at least two invariant densities with disjoint supports. It is impossible, since from the definition of the operator $\hat{P}$ it follows that for any density $h \in D$ the support of the function $\hat{P}h$ contains the interval of the form $[b, \infty)$, where b depends only on h.

We have shown that all assumptions of Theorem 3 are satisfied. We conclude that the operator $\hat{P}$ is asymptotically stable on the space $L^1[\bar{x}, \infty)$. The extension of the result to the space $L^1[0, \infty)$ is straightforward. Since the operators $\hat{P}$ and P have the same properties, finally the operator P is asymptotically stable. ■

Proof (point 2.) Proof of the point 2. is similar to the previous one. We replace P with the operator $\hat{P}$ and notice that the assumption (29) transfers onto the function $\hat{\alpha}$. We consider the set Z defined by (35). Using the same argument we see that, if Z is empty, then the operator $\hat{P}$ is sweeping from the family of all bounded subsets of $[0, \infty)$. If Z is nonempty, then similarly to the previous case, the operator $\hat{P}$ restricted to $L^1[\bar{x}, \infty)$, where $\bar{x} = \inf Z$, is also Markov. Now we use Theorem 4.

We start from checking that the first assumption of Theorem 4 is satisfied. Let $y > \bar{x}$, $f \in D$ and $\int_0^y f(r)dr > 0$. Then

$$\hat{P}f(x) = \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} e^r f(r)dr \geqslant \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^y f(r)dr > 0,$$

provided $x > \hat{\lambda}^{-1}(y)$. We suppose that $\hat{P}^n f(x) > 0$ for $x > \hat{\lambda}^{-n}(y)$. Then, analogously as before

$$\hat{P}^{n+1}f(x) > \hat{\lambda}'(x)e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}^{-n}(y)} \hat{P}^n f(r)dr.$$

By the induction hypothesis, we obtain $\hat{P}^{n+1}f(x) > 0$ for $x > \hat{\lambda}^{-(n+1)}(y)$. Once again we show that the sequence $(\hat{\lambda}^{-n}(y))_{n=1}^{\infty}$ tends to $\bar{x}$. Hence

$$\sum_{n=0}^{\infty} \hat{P}^n f(x) > 0$$

for every $x > \bar{x}$. It means that the first assumption of Theorem 4 is satisfied. Clearly, the second assumption is also satisfied. According to Theorem 4 we conclude that the operator $\hat{P}$ satisfies Foguel alternative.

To show that the operator $\hat{P}$ is sweeping, we consider increasing function λ_0 of the class C^1, such that $\lambda_0(x) \geqslant \hat{\lambda}(x)$ for every $x \geqslant 0$ and $\lambda_0(x) = x + 1$ for sufficiently large x. Existence of such function follows immediately from the assumption (29). We denote by P_0 the Markov operator

$$P_0 f(x) = \lambda_0'(x) e^{-\lambda_0(x)} \int_0^{\lambda_0(x)} e^y f(y) dy$$

and notice that by repeating the argument from the previous paragraph and using Theorem 4, we obtain that the operator P_0 satisfies Foguel alternative. We suppose now that there exists an invariant density $f \in D$, i.e. $P_0 f = f$. Integrating by parts, we obtain

$$f(x) = e^{-(x+1)} \int_0^{x+1} f(z) dz - e^{-(x+1)} \int_0^{x+1} e^y \int_0^y f(z) dz dy \tag{43}$$

for sufficiently large x. Change of the integration order leads to

$$\int_0^{x+1} e^y \int_0^y f(z) dz dy = e^{x+1} \int_0^{x+1} f(z) dz - \int_0^{x+1} e^z f(z) dz,$$

what substituted into (43) implies

$$f(x) = e^{-(x+1)} \int_0^{x+1} f(z) dz - \int_0^{x+1} f(z) dz + e^{-(x+1)} \int_0^{x+1} e^z f(z) dz.$$

Since $P_0 f = f$, we conclude

$$e^{-(x+1)} \int_0^{x+1} f(z) dz - \int_0^{x+1} f(z) dz = 0.$$

Therefore $F(x+1) := \int_0^{x+1} f(z) dz = 0$ for sufficiently large x. This is a contradiction, because F is distribution function and in particular $\lim_{x\to\infty} F(x) = 1$. It means that P_0 has no invariant density and thus can not be asymptotically stable. According to Foguel alternative, we obtain that the operator P_0 is sweeping from the family of all compact subsets of $[0, \infty)$.

To finish the proof, we show that the sweeping of the operator P_0 causes sweeping of the operator $\hat{P}$. To this end, analogously as in the proof of the point 1., let us define the operator R by the formula

$$RF(x) = e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} \Big(e^y F(y) \Big) dy,$$

where $F(x) = \int_0^x f(z) dz$ is distribution function with the density f and the operator R_0 is given by the same formula as before, but with λ replaced by λ_0. Differentiating leads to

$$\frac{d}{dx} RF(x) = -\hat{\lambda}'(x) e^{-\hat{\lambda}(x)} \int_0^{\hat{\lambda}(x)} \Big(e^y F(y) \Big) dy + \hat{\lambda}'(x) e^{-\hat{\lambda}(x)} e^{\hat{\lambda}(x)} F(\lambda(x))$$

and integration by parts implies

$$-\hat{\lambda}'(x)e^{-\hat{\lambda}(x)}\int_0^{\hat{\lambda}(x)}\Big(e^yF(y)\Big)dy = -\hat{\lambda}'(x)e^{-\hat{\lambda}(x)}e^{\hat{\lambda}(x)}F(\lambda(x)) + \hat{P}f(x),$$

what finally leads to the equality $\frac{d}{dx}RF(x) = \hat{P}f(x)$. We conclude that $RF(x)$ is a distribution function with the density $\hat{P}f(x)$. Analogously, $R_0F(x)$ is a distribution function with the density $P_0f(x)$

We show now that the inequality

$$RF(x) \leqslant R_0F(x) \tag{44}$$

holds for any distribution function F. Since $\hat{\lambda} \leqslant \lambda_0$, integrating by parts, we obtain

$$RF(x) \leqslant \int_0^{\lambda_0(x)} f(y)dy - e^{-\lambda_0(x)}\int_0^{\lambda_0(x)} e^y f(y)dy = R_0F(x).$$

We suppose now that the inequality $\int_0^x \hat{P}^n f(y)dy \leqslant \int_0^x P_0^n f(y)dy$ holds for some $n \in \mathbb{N}$. Then, since R is positive operator, using (44) and induction hypothesis, we conclude

$$\int_0^x \hat{P}^{n+1}f(x)dx = R\left(\int_0^x P_0^n f(x)dx\right) \leqslant R_0\left(\int_0^x P_0^n f(x)dx\right) = \int_0^x P_0^{n+1}f(x)dx.$$

Hence, if K is a compact subset of $[0,b]$, then

$$\int_K \hat{P}^n f(x)dx \leqslant \int_0^b P_0^n f(x)dx$$

for every $n \in \mathbb{N}$. Passing with n to ∞ implies sweeping of the operator $\hat{P}$ from any compact subset of $[0,\infty)$, what was to be demonstrated. ■

4. Conclusions In our case the condition (28) can be rewritten in the following form

$$\liminf_{x\to\infty}(T(\lambda(x)) - T(x)) > \frac{1}{a}.$$

Then the operator P has invariant destiny f^* and is asymptotically stable, what biologically means that the population of cells has invariant distribution.

The condition (29) can be expressed in the form

$$T(\lambda(x)) - T(x) \leqslant \frac{1}{a},$$

for sufficiently large x. If it holds, then the Markov operator P is sweeping from the intervals $[0,c]$, what means that after long time low-mature cells die out. Then more and more mature cells start to dominate the population.

Finally, in our case the condition (30) changes into

$$T(\lambda(x)) - T(x) > -\infty.$$

It the above inequality holds, then the operator P is completely mixing and the distribution of cells becomes independent of the initial conditions, but not necessarily stabilize after any time.

We recall that the discrete-time Tyrcha model (see [16]) consists of a Markov operator of the following form

$$Pf(x) = \lambda'(x)Q'(\lambda(x))e^{-Q(\lambda(x))}\int_0^{\lambda(x)} e^{Q(y)}f(y)dy,$$

where $Q(x) = \int_0^x \frac{\beta(y)}{V(y)}dy$, and shows how a density $f \in D$ of n-th generation of cells changes into a density $Pf \in D$ of $(n+1)$-th generation. Properties of this operator can be given with the aid of Theorem 2. We show now how the same assumptions can lead to different results in discrete-time Tyrcha model than in continuous-time model. It is possible that both inequalities

$$\liminf_{x\to\infty}(T(\lambda(x))-T(x)) > \frac{1}{2\beta e^{-\gamma\tau}} \quad \text{and} \quad T(\lambda(x))-T(x) \leqslant \frac{1}{\beta} \quad \text{for large} \quad x,$$

hold simultaneously. Then the Markov operator which describes generational model of Tyrcha is sweeping (in particular there is no invariant density). On the other hand the Markov operator which is connected with continuous-time model is asymptotically stable and there exists an invariant density of cellular population.

To explain that phenomena notice that in the continuous-time model population consists of cells from different generations (what is not true in Tyrcha model). Assumption of quicker division of low-matured cells causes stabilization of population and existence of invariant density.

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Ociągłej wersji dwufazowego cyklu komórkowego

Paweł Zwoleński

Streszczenie W artykule rozważamy matematyczny opis dwufazowego modelu cyklu komórkowego w populacjach ze strukturą dojrzałości komórkowej. Model, którym się zajmujemy, składa się z układu dwóch równań różniczkowych cząstkowych (równań transportu) i jest budowany na podobnych biologicznych założeniach co modele Lasoty-Mackeya, Tysona-Hannsgena oraz Tyrchy. Rozwiązania otrzymanego układu równań badamy wzdłuż charakterystyk, podajemy warunki wystarczające na istnienie gęstości niezmienniczej i porównujemy wyniki z wynikami badań nad modelem Tyrchy.

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