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A STOCHASTIC PERTURBATION OF THE FRACTION OF SELF-RENEWAL IN THE MODEL OF STEM CELLS DIFFERENTIATION

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ABSTRACT. This paper is devoted to a piece-wise deterministic Markov process (PDMP) constructed from the deterministic model of stem cell differentiation. The deterministic model was presented by Anna Marciniak-Czochra. A crucial parameter for the stationary solutions of the deterministic model is a fraction of self-renewal. We modify the model by converting the parameter of the fraction of self-renewal from a constant parameter into a discrete Markov process. In this way we obtain a piece-wise deterministic Markov process. The main goal of this paper is to investigate the long-time behaviour of the Markov semi-group related to the PDMP.

Keywords: Stochasticity in the stem cells dynamics · Piece-wise deterministic Markov process · Markov semi-groups · Foguel Alternative

1. INTRODUCTION

Differentiation of the stem cells is the crucial process in the most of the high specialised organisms. Every tissue is exposed for an exterior or interior influences. Such perturbations may intensively harm some part of tissue. Since, such disturbance may act continuously, each tissue need to be repaired all the time. Additively, almost all cells in tissue get old and become useless. Therefore, specialised cells which create the body of tissue are continuously replaced by new cells. However, mature cells do not posses an ability to divide and replenish themselves. Hence, this important role is played by stem cells which are known because of their ability to self-renew and ability of division into more specialised cells. In this way stem cells may regenerate old and harmed part of tissue. In most cases the process of stem cells differentiation include several stages of cells maturation. Well known example of such process is the differentiation of the white blood stem cells which consists of eight stages of maturation [6]. An illustration (1) presents a brief scheme of the process of stem cells differentiation which consist several stages of maturation. Where a_i for $i = 1, \dots, n$ are the fraction of self-renewal and $s(t)$ is a level of a cytokine which influence on the processes of self-renew and differentiation of stem cells and cells at different stages of maturation. According to the work of Anna Marciniak et. al. we may describe the dynamic of this process as the system of the following differential equations.

$$\begin{aligned}
 \frac{dc_1}{dt} &= (2a_1s_{k_1}(t) - 1)p_1c_1(t) - \mu_1c_1, \\
 \frac{dc_2}{dt} &= (2a_2s_{k_1}(t) - 1)p_2c_2(t) + 2(1 - a_1s_{k_1}(t))p_1c_1(t) - \mu_2c_2(t), \\
 &\vdots \\
 (1) \quad \frac{dc_n}{dt} &= 2(1 - a_{n-1}s_{k_1}(t))p_{n-1}c_{n-1}(t) - \mu_nc_n(t),
 \end{aligned}$$

where c_1, \dots, c_n denote numbers of cells at different stages of differentiation, p_1, \dots, p_n , μ_1, \dots, μ_n are proliferation rates and death rates for the population at each stage $i = 1, \dots, n$ and a_1, \dots, a_{n-1} are parameters of the fraction of self-renewal. We call the fraction of self-renewal as a fraction of cells progeny which posses the same physical and functional properties as its progenitors.

In previous work [8] it was shown that the two-dimensional version of the model (1) exposed on environmental stochastic perturbations is stochastically stable. Additionally, it was shown by numerical simulations that the increasing number of the maturation stages stabilise the production of mature cells. The aim of this paper is to continue the research on the behaviour of the model of tissue regeneration exposed on different type of stochastic perturbations. Anna Marciniak et. al. shows in [5] that the existence of the positive steady state for the model (1) is strictly related to the fraction of renewal. In further sections of this paper we examine a response of the two-dimensional version of the model (1) for a stochastic perturbation of the parameter of the fraction of self-renewal.

In the first paragraph we briefly present basic information about the deterministic system of differential equations presented by Anna Marciniak-Czochra et. al. in [6]. The second paragraph is devoted to the mathematical description of the piece-wise deterministic Markov process (PDMP) generated by the previous model. The third section stands for the mathematical background of the Markov semi-groups theory and is an introduction to the main part of this paper. Additionally we show a simplified condition for the general real PDMP to satisfy the Foguel alternative. This condition is related to the Hörmander-like condition [34] and the work [1]. The subsequent paragraph contain a proof of the asymptotic stability of the semi-group related to the piece-wise deterministic Markov process described in the second paragraph. Last paragraph is devoted to some numerical simulation of the trajectories of the model and its densities. We also try to interpret those simulation according to the biological foundations of the process of stem cells differentiation.

2. DETERMINISTIC SYSTEM

We consider the following system of differential equations

$$(2) \quad \begin{aligned} u_1'(t) &= \left(\frac{2a}{1+ku_2(t)} - 1 \right) pu_1(t) \\ u_2'(t) &= 2 \left(1 - \frac{a}{1+ku_2(t)} \right) pu_1(t) - du_2(t) \end{aligned}$$

where $1 > a > 0$, $k, p, d > 0$ and initial conditions $u_{1,0}$, $u_{2,0}$ are positive. It is shown in [5] that the model (2) has unique solution and for non-negative initial conditions the solution remains non-negative. We may notice that the system (2) has different solutions for different values of the parameter a . We distinguish two compartments of the parameter a . The first compartment is $[0, \frac{1}{2}]$ and we denote parameter $a_0 \in [0, \frac{1}{2}]$. The second one is $(\frac{1}{2}, 1]$ and let $a_1 \in (\frac{1}{2}, 1]$.

For a_0 , there is only one stationary solution of the model (2)

$$(3) \quad (u_1^*, u_2^*) = (0, 0)$$

and it is locally asymptotically stable which is depicted in the Fig. 2.

For a_1 we may compute that the model has two steady states

$$(4) \quad \begin{aligned} (u_1^*, u_2^*) &= (0, 0) \\ (u_1^{**}, u_2^{**}) &= \left(\frac{(2a-1)d}{kp}, \frac{2a-1}{k} \right) \end{aligned}$$

where (u_1^{**}, u_2^{**}) is locally asymptotically stable and (u_1^*, u_2^*) is a saddle point what is presented in the Fig. 3. Let us call U_0 , U_1 as the vector fields of the system (2) for a_0 and a_1 respectively.

For each $i = 0, 1$ and initial condition $\bar{u} = (u_{1,0}, u_{2,0})$ we define the solution of the system (2) as

$$(5) \quad \pi_i^i(\bar{u}) = (u_1(t), u_2(t)).$$

3. SYSTEM OF ODE'S WITH RANDOM SWITCHING

We assume that the parameter a in the system (2) is a discrete random variable which may take the following values $\{a_0, a_1\}$ where

$$(6) \quad 0 < a_0 < \frac{1}{2} < a_1 < 1.$$

Therefore, the system (2), according to the theory presented in [33], become a piece-wise deterministic Markov process (PDMP). In order to avoid some misunderstandings of assigning of deterministic and stochastic variables, let $\xi(t) = (x_1(t), x_2(t), a(t))$ be the solution of the following PDMP

$$(7) \quad \begin{aligned} x_1'(t) &= \left(\frac{2a_t}{1+kx_2(t)} - 1 \right) px_1(t) \\ x_2'(t) &= 2 \left(1 - \frac{a_t}{1+kx_2(t)} \right) px_1(t) - dx_2(t) \end{aligned}$$

Briefly saying, the piecewise deterministic Markov process is a stochastic process which at random but finite period of time is a deterministic process. It means that if we set an initial value $x_0 = (a_i, x_1^0, x_2^0)$ then the motion of x_t is given by the solution of (7) with $a_t = a_i$ until the first jump time T_1 occurs. Afterwards the motion of the process x_t for $t \geq T_1$ is given by the solution of (7) with $a_t = a_j$ where $j = 1 - i$. As it is described above we may define process $\xi(t)$ starting at $x = (x_1, x_2)$ up to time T_1 as

$$(8) \quad \xi(t) = \begin{cases} (\pi_t^i(x), i), & t < T_1, \\ (\pi_{T_1}^j(x), 1 - i), & t = T_1. \end{cases}$$

For each switching times $T_i, T_1 - i$ and for $t \in (T_i, T_1 - i)$

$$(9) \quad \xi(t) = \begin{cases} (\pi_t^i(y), i(T_i)), & T_i < t < T_1 - i, \\ (\pi_{T_1 - i}^j(y), i(T_1 - i)), & t = T_1 - i, \end{cases}$$

where $y = \pi_{T_i}^i(x)$. Jumps occurs spontaneously according to the Poisson distribution with rates $q_0(x_1, x_2)$ and $q_1(x_1, x_2)$. We assume that functions $q_0(x_1, x_2)$ and $q_1(x_1, x_2)$ are continuous and non-negative on \mathbb{R}_+^2 . We also assume that for $i = 0, 1$

$$(10) \quad \begin{aligned} q_i(u_1^*, u_2^*) &\neq 0 \quad \text{for } i = 0, 1 \\ q_i(u_1^{**}, u_2^{**}) &\neq 0 \quad \text{for } i = 1 \end{aligned}$$

which guarantee that the probability of a switch at the stationary points is positive. According to [1] we may define the cumulative distribution function of the first jump T_1 of the process that starts at time $t = 0$ and point $(x, i) = (x_0, i_0)$ as follows

$$(11) \quad Prob(T_1 \leq t) = F_{(x_0, i_0)}(t) = 1 - \exp\left\{-\int_0^t q_i(\pi_s^{i_0}) ds\right\}.$$

Additionally in [1], it is shown that there are infinitely many jumps, hence,

$$(12) \quad \lim_{k \rightarrow \infty} T_k = \infty.$$

Let $m \in \mathbb{N}$ and $t = (t_1, t_2, \dots, t_m)$ be a sequence of waiting times between subsequent switches i_1, i_2, \dots, i_m , where $i_j \in \{0, 1\}$ and $i_j \neq i_{j+1}$ for $j = 1, \dots, m$. For $t \in \mathbb{R}_+^m$ and $i = (i_1, i_2, \dots, i_m)$ we define

$$(13) \quad \psi_t^i(x) := \pi_{t_m}^{i_m} \circ \pi_{t_{m-1}}^{i_{m-1}} \circ \dots \circ \pi_{t_1}^{i_1}(x)$$

as the cumulative flow along trajectories of u_{i_1}, \dots, u_{i_m} starting at point x .

4. MATHEMATICAL BACKGROUND

4.1. "Hörmander-like condition". In this paragraph we present some results made by Y. Bakhtin and T. Hurth related to the Hörmander theory. In [34] authors show some results on an existence of an invariant measure of a Piece-wise deterministic Markov process providing that vector fields composing the PDMP satisfy a Hörmander-like condition. In order to prove further results of the model (7) we present a definition of the Hörmander-like condition and some result related to the regularity of the cumulative flow of the PDMP process.

Definition 1 (Lie brackets). *Let $V(M)$ be the set of real smooth vector field on the manifold $M \subset \mathbb{R}^d$, and let $C^\infty(M)$ denote the set of real-valued smooth functions on $V(M)$. Let $a(x), b(x)$ be two vector fields in $V(M)$. The Lie bracket $[a, b]$ is a vector field given by*

$$(14) \quad [a, b]_j(x) = \sum_{k=1}^d \left(a_k \frac{\partial b_j}{\partial x_k}(x) - b_k \frac{\partial a_j}{\partial x_k}(x) \right)$$

Let $V(M)$ be equipped with Lie brackets operator $[\cdot, \cdot]$. Then $V(M)$ become a Lie algebra over the reals. We call a subset of $V(M)$ involute if it is closed under taking the Lie bracket. An involute subspace of $V(M)$ is called sub-algebra of $V(M)$. Let $I(D)$ be the smallest sub-algebra of $V(M)$ that contains $D \in V(M)$ and let $I'(D)$ be the smallest algebra containing Lie brackets of vector field in $I(D)$. Further, we denote $I_0(D)$ as the set of the vector fields given by the following form

$$(15) \quad v + \sum_{i=1}^d \lambda_i u_i,$$

where $v \in I'(D)$ and $u_1, \dots, u_k \in D$ and $\sum_{i=1}^k \lambda_i = 0$. Then, we may define the following set

$$(16) \quad I_0(D)(\xi) := \{u(\xi) : u \in I_0(D)\}$$

for any $\xi \in M$.

Definition 2 (Hörmander-like condition). *We say the point $\xi \in M$ satisfies a condition (I) for the vector field $D \in V(M)$ if $\dim I_0(D)(\xi) = d$.*

According to the [34, T.4] for the point $x \in \mathbb{R}_+$ satisfying the condition (I) the cumulative flow defined in (13) as a function of the time vector $t = (t_1, \dots, t_m)$ has non-degenerated derivative

$$(17) \quad \det \left[\frac{d\psi_t^i(x)}{dt} \right] \neq 0.$$

4.2. Markov semi-groups. Let (S, Σ, m) be a σ -finite measure space and let $D \subset L^1 = L^1(S, \Sigma, m)$ be the set of densities i.e.

$$(18) \quad D = \{f \in L^1; f \geq 0, \|f\| = 1\}$$

We call a linear mapping $P : L^1 \rightarrow L^1$ a Markov operator if $P(D) \subset D$. A family $\{P(t)\}_{t \geq 0}$ of Markov operators is called a Markov semi-group if and only if

- (1) $P(0) = id$
- (2) $P(t+s) = P(t)P(s)$ for every $t, s \geq 0$
- (3) for each $f \in L^1$ the function $t \rightarrow P(t)f$ is continuous with the respect to the L^1 norm.

Definition 3. *A Markov semi-group $\{P(t)\}_{t \geq 0}$ is called partially integral or partially kernel if there exist $t_0 > 0$ and a measurable function $k : S \times S \rightarrow (0, \infty)$ called a kernel, such that*

$$(19) \quad \int_S \int_S k(p, q) m(dp) m(dq) > 0$$

and

$$(20) \quad P(t_0)f(p) \geq \int_S k(p, q)f(q)m(dq)$$

for every density f .

Definition 4. A density f^* is called invariant if $P(t)f^* = f^*$ for each $t > 0$.

Definition 5. The Markov semi-group $\{P(t)\}_{t \geq 0}$ is called asymptotically stable if there is an invariant density f^* such that

$$(21) \quad \lim_{t \rightarrow \infty} \|P(t)f - f^*\| = 0 \quad \text{for every } f \in D.$$

Definition 6. A Markov semi-group $\{P(t)\}_{t \geq 0}$ is called sweeping with respect to a set $A \in \Sigma$ if for every $f \in D$

$$(22) \quad \lim_{t \rightarrow \infty} \int_A P(t)f(x)m(dx) = 0.$$

Definition 7 (Foguel alternative). [2, p 10] We say that a Markov semi-group $\{P(t)\}_{t \geq 0}$ satisfies the Foguel alternative if it is asymptotically stable or sweeping from a sufficiently large family of sets. For example this family can consist of all compact sets.

Theorem 8. [2, p. 10] Let $\{P(t)\}_{t \geq 0}$ be a Markov semi-group. We assume that there exist $t > 0$ and a continuous function $q : S \times S \rightarrow (0, \infty)$ such that

$$(23) \quad P(t)f(x) \geq \int_S q(x, y)f(y)m(dy) \quad \text{for } f \in D$$

then the semi-group is asymptotically stable or sweeping with the respect to compact sets.

In [1, p.762] we may find an explicit formula for the Markov semi-group of the PDMP. Let us call $\{P(t)\}_{t \geq 0}$ as the Markov semi-group generated by the model (7). Assume additively that for some set $E \subset \mathbb{R}_+^2$ and for any point $x_0, y_0 \in E$ and number $i_0 \in \{0, 1\}$ there exists $m \in \mathbb{N}$ and a finite sequence $t = (t_1, \dots, t_m)$ such that

$$(24) \quad \psi_t^{i_0}(y_0) = x_0$$

where $i = (i_0, 1 - i_0, \dots, i_m)$. In other words we may call this condition as a "communication between states". In [1, p.767] it is formulated as the "Communication lemma". Let the condition (I) hold for any point $x \in E$. Hence, by the proposition 1 and 2 from [1] the semi-group $\{P(t)\}_{t \geq 0}$ is partially integral with the kernel $k(x, y)$ and $k(x, y) > 0$ for $x, y \in E$. Therefore we may formulate the following remark related to the Foguel alternative of the piece-wise deterministic Markov process.

Remark 9. Let $\{P(t)\}_{t \geq 0}$ be the semi-group generated by the PDMP defined on some manifold M . Assume that the PDMP satisfies

- (1) "Hörmander-like" condition
- (2) "Communication lemma"

for some $K \subset M$ then the semi-group $\{P(t)\}_{t \geq 0}$ is asymptotically stable or sweeping from the family of the compact subsets of K .

5. LONG-TIME BEHAVIOUR OF THE SEMI-GROUP RELATED TO THE MODEL (7)

In this section we present sufficient conditions for the parameters a_0, a_1, q_0, q_1 to guarantee an asymptotic stability of the semi-group $\{P(t)\}_{t \geq 0}$ generated by the model (7). Firstly we graphically illustrate an invariant set of the semi-group $\{P(t)\}_{t \geq 0}$ which then is used for a proof of the "communication lemma" for the model (7).

As we mentioned in the previous section, for $0 \leq a \leq \frac{1}{2}$ we have a saddle point in $(0, 0)$ hence according to theory of stable and unstable manifolds there exists a unique unstable manifold which goes from zero to the stationary point $(\frac{d(2a-1)}{kp}, \frac{2a-1}{k})$. Let $\Phi(x) = y$ be

such an unstable manifold of the model (2) for the parameter a_0 . Let $\Psi(\bar{x}) = y$ be a solution of the system (2) for the parameter a_1 . We assume that $\bar{\Psi}(x) = y$ is the one solution such that it is tangent to the manifold $\Phi(\bar{x}) = y$. Now, let (x^*, y^*) be the point of osculation for the curves $\Phi(\bar{x}), \Psi(\bar{x})$. Define the curve $\Phi(x)$ as the $\Phi(\bar{x}) = y$ stopped at the point (x^*, y^*) , and $\Psi(x)$ as a solution of the model (2) for the parameter a_2 starting at the point (x^*, y^*) . Hence, we obtain a compact set A bounded by the curves $\Psi(x)$ and $\Psi(x)$ illustrated in the figure (4).

Theorem 10. *Let $\{P(t)\}_{t \geq 0}$ be the semi-group related to the model (7) and let*

$$(25) \quad A = \{(x_1, x_2) \in \mathbb{R}_+^2 : \Phi \leq (x_1, x_2) \leq \Psi\}$$

Then for the a_0, a_1, q_0, q_1 satisfying the following condition

$$(26) \quad \frac{2a_0 - 1}{1 - 2a_1} > \frac{q_0}{q_1}$$

the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable. Moreover, the invariant density f_ is supported by $\mathbb{A} = A \times \{a_0, a_1\}$.*

The proof of this theorem is complicated and consist of several parts. In order to clear the sense of the proof, we divide it in a couple of the following lemmas. At first, we show that the set \mathbb{A} is an invariant set for the semi-group $\{P(t)\}_{t \geq 0}$. Next, we should show that the condition (I) from the definition (2) holds for every point $\xi \in A \setminus \{(0, 0)\}$ for the vector fields (U_0, U_1) . Checking of the condition (I) is rather simple task but because of the length of exact algebraic formulas of the points of the set $I_0(D)$, hence, we omit them. Calculation of the following

$$(27) \quad \begin{aligned} & [u_0, u_1], \quad [[u_0, u_1], u_1], \quad [[u_0, u_1], u_0], \\ & [[u_0, u_1], u_1] - u_0 + u_1, \quad [[u_0, u_1], u_0] - u_0 + u_1 \end{aligned}$$

shows that the condition (I) holds for every $(x, y) \in A \setminus \{(0, 0)\}$. Subsequently we present a graphical illustration of the proof of the "communication lemma" for the semi-group $\{P(t)\}_{t \geq 0}$. Consequently, by the remark (9) the Foguel alternative holds for $\{P(t)\}_{t \geq 0}$. Since we have an alternative for the long-time behaviour of the semi-group $\{P(t)\}_{t \geq 0}$ we exclude sweeping for the condition (26) and obtain the asymptotic stability.

Lemma 11. *Let $\{P(t)\}_{t \geq 0}$ be the Markov semi-group generated by the process (7) then for every density $f \in L^1(S)$*

$$(28) \quad \lim_{t \rightarrow \infty} \int_{\mathbb{R}} P(t)f(p)m(dp) = 1.$$

Proof. Let $\lambda(x) = y$ be the straight line connecting stationary points of the model (2) and cut to \mathbb{R}_+^2 . We define

$$(29) \quad \begin{aligned} A_+ &= \{(x, y); y \geq \lambda(x)\} \\ A_- &= \{(x, y); y < \lambda(x)\}. \end{aligned}$$

Then, there exist $t_1, t_2 > 0$ such that for every $(x, y) \in A_+$ $\pi_{t_1}^1(x, y) \in A_-$ and for every $(x, y) \in A_-$ $\pi_{t_1}^1(x, y) \in A_+$. Consider the stochastic process defined by the system (7). As we mentioned in the second paragraph the stochastic process $a(t)$ switches infinitely many times. Let $\tau_0 < \tau_1 \dots$ be the moments of jumps for the process (2). Define $\Delta_n = \tau_n - \tau_{n-1}$ for $n \geq 1$ and let $\mu = \max\{q_0(x), q_1(x)\}$. Hence, $\mathbb{P}(\Delta_n > T) \geq e^{-\mu T}$. Since $\xi(t)$, for $t > 0$ is a feller cadlac strong Markov process [1] and T_n for $n \geq 0$ are stopped times, we obtain that $\mathbb{P}(\Delta_i \leq T, i = 1, 2, \dots, n) \leq (1 - e^{-\mu T})^n$, $n \geq 1$. Therefore, for almost every $\omega \in \Omega$ there exists $t_0(\omega) > 0$ such that $x(t, \omega) \in A$ for $t > t_0$. Hence, the set A is an invariant and consequently

$$(30) \quad \lim_{t \rightarrow \infty} \mathbb{P}(\xi(t) \in A) = \lim_{t \rightarrow \infty} \int_A P(t)f(p)m(dp) = 1,$$

where f is a density of the process $\xi(0)$. \square

Lemma 12. *For every $(x, i), (y, j) \in \text{Int}A \times \{a_0, a_1\}$ there exist a finite sequence of time switches $t = (t_1, t_2, \dots, t_n)$ such that*

$$(31) \quad \psi_t^i(x) = y$$

A graphical proof of this lemma consists of eight different cases for different initial states i, j and position of the points x, y in the set A . Since, all of such cases are similar we restrict a presentation just to four of those cases and gather them in the figure (5).

Since, the semi-group $\{P(t)\}_{t \geq 0}$ satisfy the Foguel alternative, to proof asymptotic stability we need to exclude sweeping to zero. Let us consider the following Fokker-Planck-like equation related to the system (7)

$$(32) \quad \begin{aligned} \frac{\partial u_0}{\partial t} &= -\frac{\partial}{\partial x}(u_0 g_{0,1}) - \frac{\partial}{\partial y}(u_0 g_{0,2}) + q_1 u_1 - q_0 u_0 \\ \frac{\partial u_1}{\partial t} &= -\frac{\partial}{\partial x}(u_1 g_{1,1}) - \frac{\partial}{\partial y}(u_1 g_{1,2}) + q_0 u_0 - q_1 u_1 \end{aligned}$$

with the following boundary conditions

$$(33) \quad u(t, x, 0) = u(t, x, \infty) = u(t, 0, x) = u(t, \infty, x) = 0.$$

Where

$$(34) \quad \begin{aligned} g_{i,1} &= \left(\frac{2a_i}{1+ky} - 1 \right) px \quad \text{for } i = 1, 1 \\ g_{i,2} &= 2 \left(1 - \frac{a_i}{1+ky} \right) px - dy \quad \text{for } i = 0, 1. \end{aligned}$$

We check the behaviour of the following " $-\alpha$ " moments of the PDMP

$$(35) \quad \mathbb{I}_i(t) = \int_0^\infty \int_0^\infty x^{-\alpha} u_i(x, y, t) dx dy \quad \text{for } i = 0, 1.$$

Hence, we derive the functions \mathbb{I}_i for $i = 0, 1$

$$(36) \quad \begin{aligned} \frac{d}{dt} \mathbb{I}_i(t) &= \frac{d}{dt} \int_0^\infty \int_0^\infty x^{-\alpha} u_i(x, y, t) dx dy \\ &= \int_0^\infty \int_0^\infty x^{-\alpha} \left(\frac{\partial}{\partial x}(u_i g_{i,1}) + \frac{\partial}{\partial y}(u_i g_{i,2}) - q_{1-i} u_{1-i} + q_i u_i \right) dx dy \\ &= I_1 + I_2 + \int_0^\infty \int_0^\infty x^{-\alpha} (-q_j u_j + q_i u_i) dx dy \\ &= \left(\begin{array}{l} I_1 = \int_0^\infty (-x^{-\alpha} (g_{i,1} u_i|_0^\infty)) dy - \int_0^\infty \int_0^\infty \alpha x^{-\alpha-1} u_i g_{i,1} dx dy \\ I_2 = \int_0^\infty (-x^{-\alpha} (g_{i,1} u_i|_0^\infty)) dx - \int_0^\infty \int_0^\infty \frac{d}{dy}(x^{-\alpha}) u_i g_{i,1} dx dy \end{array} \right) \\ &= - \int_0^\infty \int_0^\infty \alpha x^{-\alpha-1} g_{i,1} u_i dx dy + \int_0^\infty \int_0^\infty x^{-\alpha} (q_{1-i} u_{1-i} - q_i u_i) dx dy. \end{aligned}$$

Since in the neighbourhood of zero K_ε , the trajectories of the model (2) behave like trajectories of the linearised model we may assume that

$$(37) \quad \begin{aligned} \int_0^\infty \alpha x^{-\alpha-1} g_{i,1} u_i dx dy &= \int_{K_\varepsilon} \alpha x^{-\alpha-1} \bar{g}_{i,1} u_i dx dy + \int_{\mathbb{R}_+^2 \setminus K_\varepsilon} \alpha x^{-\alpha-1} g_{i,1} u_i dx dy \\ &\geq \int_{K_\varepsilon} \alpha x^{-\alpha-1} \bar{g}_{i,1} u_i dx dy + \int_{\mathbb{R}_+^2 \setminus K_\varepsilon} \alpha x^{-\alpha-1} g_{i,1} u_i dx dy. \end{aligned}$$

Where $\bar{g}_{i,1}$ are the functions for a linearised version of the system (2). Hence, from the lemma (11) and since that $x^{-\alpha}$ is small outside K_ε we may assume that there exists a finite constant C such that

$$(38) \quad - \int_{\mathbb{R}_+^2 \setminus K_\varepsilon} \alpha x^{-\alpha-1} g_{i,1} u_i dx dy \leq - \int_{\mathbb{R}_+^2 \setminus K_\varepsilon} \alpha x^{-\alpha-1} \bar{g}_{i,1} u_i dx dy + C.$$

Hence, by (37), (38) we obtain the following system of differential inequalities

$$(39) \quad \begin{aligned} \mathbb{I}'_0(t) &\leq -\alpha(2a_0 - 1)p\mathbb{I}_i + q_0\mathbb{I}_0 - q_1\mathbb{I}_0 + C_0 \\ \mathbb{I}'_1(t) &\leq -\alpha(2a_1 - 1)p\mathbb{I}_i + q_1\mathbb{I}_1 - q_0\mathbb{I}_0 + C_1, \end{aligned}$$

where C_0, C_1 are finite constants.

Therefore, if the condition in the theorem (10) holds then,

$$(40) \quad \int_0^\infty \int_0^\infty x^{-\alpha} u_i(x, y, t) dx dy < M$$

for some constant $M > 0$. Since, if the semi-group $\{P(t)\}_{t \geq 0}$ is sweeping to zero then

$$(41) \quad \lim_{t \rightarrow \infty} \mathbb{P}(\xi_t \in K_\varepsilon) = \int_{K_\varepsilon} \int u(x, y, t) dx dy = 1.$$

Hence, for some $\varepsilon > 0$ we have

$$(42) \quad \begin{aligned} M &> \int_0^\infty \int_0^\infty x^{-\alpha} u_i(x, y, t) dx dy \geq \int_{K_\varepsilon} \int x^{-\alpha} u_i(x, y, t) dx dy \\ &\geq \int_{K_\varepsilon} \int \varepsilon^{-\alpha} u_i(x, y, t) dx dy = \varepsilon^{-\alpha} \int_{K_\varepsilon} \int u(x, y, t) dx dy = \varepsilon^{-\alpha} \end{aligned}$$

and we obtain a contradiction. Since, the semi-group $\{P(t)\}_{t \geq 0}$ satisfies the Foguel Alternative, it is asymptotically stable and the theorem (10) is proved.

6. NUMERICAL SIMULATION

The following section is devoted to numerical simulations of the trajectories and densities of the piece-wise deterministic Markov process described by the system (7). We may distinguish several different types of the dynamics of the PDMP trajectories. By the theorem (10) we differ two possible long-time behaviour, an asymptotic stability and sweeping to zero. In the figure (6) two different behaviour is presented. First one present a case for which the condition (26) holds and the second one for which the condition (26) is not satisfied. Hence, in the figure (7) one may notice to cases, when the distribution of the process converges to the stationary distribution or converges to the singular distribution.

Additionally, the long-time as well as short-time behaviour of the PDMP trajectories depends also on the frequencies q_0, q_1 . We may ask about the rate of changes of its dynamics. Does it change every hour, twice a day, in the morning and in the evening or maybe once a month or even rarer. To model those different cases we may manipulate the frequencies q_0, q_1 providing that the condition (26) holds. In the figure (8) we present two different simulations of the sample trajectories of the system (7) for two different sets of q_0, q_1 .

7. DISCUSSION

In this paper we presented an example of the piece-wise deterministic Markov process which describe the process of stem cells differentiation with random parameter of the fraction of self-renewal. It is shown that under the condition (26) a Markov semi-group related to the model (7) is asymptotically stable. The proof of the asymptotic stability is based on the theory of Markov semi-groups and Hörmander theory. Some parts of the proof might be applied for different PDMP models with constant frequencies of switches. Numerical simulations presented in this paper shows a different cases of long and short-time behaviour. We may assume that the frequencies of the switches correspond with natural daily changes in order to model short-time dynamics of stem cells differentiation.

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REFERENCES

- [1] A. Bobrowski, T. Lipniacki, K. Pichor, R. Rudnicki, *Asymptotic behavior of distributions of mRNA and protein levels in a model of stochastic gene expression*, J. Math. Anal. Appl. 333 (2007) 753–769
- [2] R. Rudnicki, K. Pichór, M. Tyran-Kaminska *Markov semigroups and their applications*, Dynamics of Dissipation, Lecture Notes in Physics 597, Springer, Berlin(2002), 215–238.
- [3] K. Pichór, R. Rudnicki, *Stability of Markov semigroups and applications to parabolic systems*, J. Math. Anal. Appl. 215 (1997), 56–74.
- [4] R. Rudnicki *Long-time behaviour of a stochastic prey-predator model*, Stochastic Processes and their Applications, 2003, vol. 108, issue 1, pages 93-107
- [5] T. Stiehl, A. Marciniak-Czochra, *Characterization of stem cells using mathematical models of multistage cell lineages*, Mathematical and Computer Modelling (2010), doi:10.1016/j.mcm.2010.03.057.
- [6] A. Marciniak-Czochra, T. Stiehl, W. Jaeger, A.D. Ho, W. Wagner, *Modeling of asymmetric cell division in hematopoietic stem cells-regulation of self-renewal is essential for efficient repopulation*, Stem Cells Dev. 18 (3) (2009) 377-385.
- [7] A. Marciniak-Czochra, T. Stiehl, *Mathematical models of hematopoietic reconstruction after stem cell transplantation*, In "Model Based Parameter Estimation: Theory and Applications" Bock, H.G. Carraro, T. Jäger, W. Körkel, S. Rannacher, R. Schlöder, J.P., (Eds.) Contributions in Mathematical and Computational Sciences, Vol. 3, Springer Verlag. To appear.
- [8] P.R. Paździorek *Mathematical model of stem cell differentiation and tissue regeneration with stochastic noise*, see preprint at <http://mmns.mimuw.edu.pl/preprints/2012-029.pdf>
- [9] S. Ehnert, M. Glanemann, A. Schmitt, S. Vogt, N. Shanny, N.C. Nussler, A. Stoeckle, A. Nussler, *The possible use of stem cells in regenerative medicine: dream or reality?*, Langenbecks Arch. Surg. (2009).
- [10] A. Gratwohl, H. Baldomero, *Trends of hematopoietic stem cell transplantation in the third millennium.*, Curr. Opin. Hematol. 16 (6) (2009) 420–426.
- [11] J. E. Till, E. A. McCulloch, L. Siminovitch, *A stochastic model of stem cell proliferation, based on the growth of spleen colony-forming cells.*, Proc Natl Acad Sci U S A. 1964 January; 51(1): 29–36.
- [12] Z. Wu, K. Luby-Phelps, A. Bugde, L. A. Molyneux, B. Denard, W. Li, G. M. Süel, and D. L. Garbers, *Capacity for stochastic self-renewal and differentiation in mammalian spermatogonial stem cells*, JCB vol. 187 no. 4 513-524.
- [13] Macarthur, B. D. Ma'ayan, A. Lemischka, I. R, *Systems biology of stem cell fate and cellular reprogramming*, Nature reviews. Molecular cell biology (2009) vol. 10 no. 10 672-681.
- [14] E. Clayton, D. P. Doupé, A. M. Klein, D. J. Winton, B. D. Simons, P. H. Jones, *A single type of progenitor cell maintains normal epidermis.*, Nature (2007) Volume: 446, Issue: 7132, Publisher: Nature Publishing Group, Pages: 185-189.
- [15] A. M. Klein, T. Nakagawa, R. Ichikawa, S. Yoshida, B. D. Simons, *Mouse germ line stem cells undergo rapid and stochastic turnover.*, Cell stem cell (2010) Volume: 7, Issue: 2, Publisher: Elsevier Inc., Pages: 214-224.
- [16] B. Hajek *Mean Stochastic Comparison of Diffusions*, Z. Wahrscheinlichkeitstheorie verw. Gebiete 68, 315-329 (1985).
- [17] L. Qi, M. Xuerong *Stochastic population dynamics under regime switching*, Journal of Mathematical Analysis and Applications (2009) Volume: 334, Issue: 1, Publisher: Elsevier, Pages: 69-84
- [18] L. Qi, M. Xuerong *Stochastic population dynamics under regime switching II*, Journal of Mathematical Analysis and Applications (2009) Volume: 335, Issue: 2, Publisher: Elsevier, Pages: 577-583
- [19] W. Fried, *Erythropoietin and erythropoiesis*, Exp. Hematol. 37 (9) (2009) 1007-1015
- [20] D. Metcalf, *Hematopoietic cytokines*, Blood 111 (2008) 485-491
- [21] C. L. Semerad, F. Liu, A. D. Gregory, K. Stumpf, D. C. Link, *G-CSF Is an Essential Regulator of Neutrophil Trafficking from the Bone Marrow to the Blood*, (2002) Immunity, 17 (4), pp. 413-423
- [22] A. Lasota, M. Mackey, M. Ważewska-Czyżewska, *Minimizing therapeutically induced anemia*, J. Math. Biol., 13 (1981), pp. 149–158
- [23] J. Lei, M. C. Mackey, *Stochastic Differential Delay Equation, Moment Stability, and Application to Hematopoietic Stem Cell Regulation System*, SIAM J. Appl. Math. 67, pp. 387-407
- [24] J. W. Adamson, *The relationship of erythropoietin and iron metabolism to red blood cell production in humans*, Sem. Oncol., 21 (1994), pp. 9–15
- [25] C. Colijin, M. C. Mackey, *A mathematical model of hematopoiesis: I. Periodic chronic myelogenous leukemia*, J. Theoret. Biol., 237 (2005), pp. 117–132.

- [26] C. Colijn, M. C. Mackey, *A mathematical model of hematopoiesis: II. Cyclical neutropenia*, J. Theoret. Biol., 237 (2005), pp. 133–146
- [27] T. H. Price, G. S. Chatta, and D. C. Dale, *Effect of recombinant granulocyte colony-stimulating factor on neutrophil kinetics in normal young and elderly humans*, Blood, 88 (1996), pp. 335–340
- [28] M. Z. Ratajczak, J. Ratajczak, W. Marlicz, C. H. Pletcher, Jr., B. Machalinshi, J. Moore, H. Hung, and A. M. Gewirtz, *Recombinant human thrombopoietin (TPO) stimulates erythropoiesis by inhibiting erythroid progenitor cell apoptosis*, Br. J. Haematol., 98 (1997), pp. 8–17
- [29] M. Silva, D. Grillot, A. Benito, C. Richard, G. Nunez, and J. Fernandez-Luna, *Erythropoietin can promote erythroid progenitor survival by repressing apoptosis through bcl-1 and bcl-2*, Blood, 88 (1996), pp. 1576–1582
- [30] S. Tanimukai, T. Kimura, H. Sakabe, Y. Ohmizono, T. Kato, H. Miyazaki, H. Yamagishi, and Y. Sonoda, *Recombinant human c-Mpl ligand (thrombopoietin) not only acts on megakaryocyte progenitors, but also on erythroid and multipotential progenitors in vitro*, Exp. Hematol., 25 (1997), pp. 1025–1033
- [31] M. Doumic, A. Marciniak-Czochra, B. Perthame, J. P. Zubelli, *A Structured Population Model of Cell Differentiation*, SIAM J. Appl. Math. 71, pp. 1918-1940
- [32] M. Iosifovich Freldin, A. D. Wentzell, *Random Perturbations of Dynamical Systems*, Springer, 1998
- [33] M.H.A. Davis, *Piecewise-deterministic Markov processes: A general class of non-diffusion stochastic processes*. J.R Stat. Soc. B, (1994), 46, No. 3, pp 353-388.
- [34] Y. Bakhtin, T. Hurth, *Invariant densities for dynamical system with random switching*. 2012 Nonlinearity 25 2937

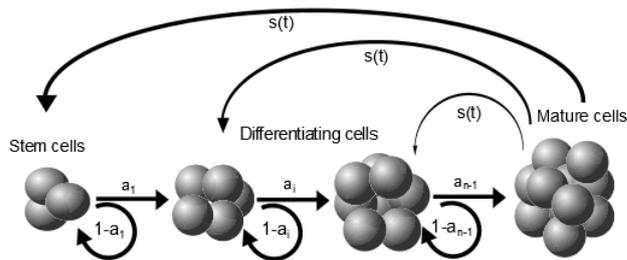


FIGURE 1. A scheme of a stem cells differentiation with a cytokine regulation

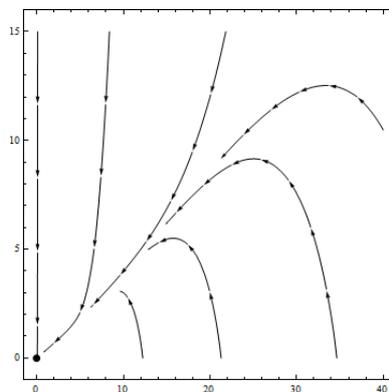


FIGURE 2. Phase portrait of the model (2) for $a \in [0, \frac{1}{2}]$

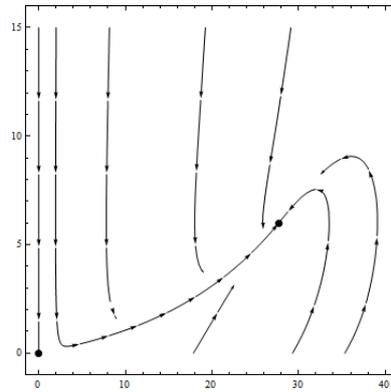


FIGURE 3. Phase portrait of the model (2) for $a \in (\frac{1}{2}, 1]$

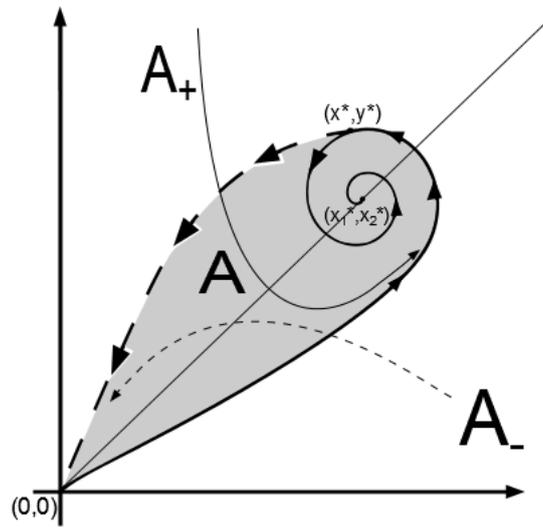


FIGURE 4. Illustration of a sets A , A_- , A_+ with an examples of trajectories of the model (2)

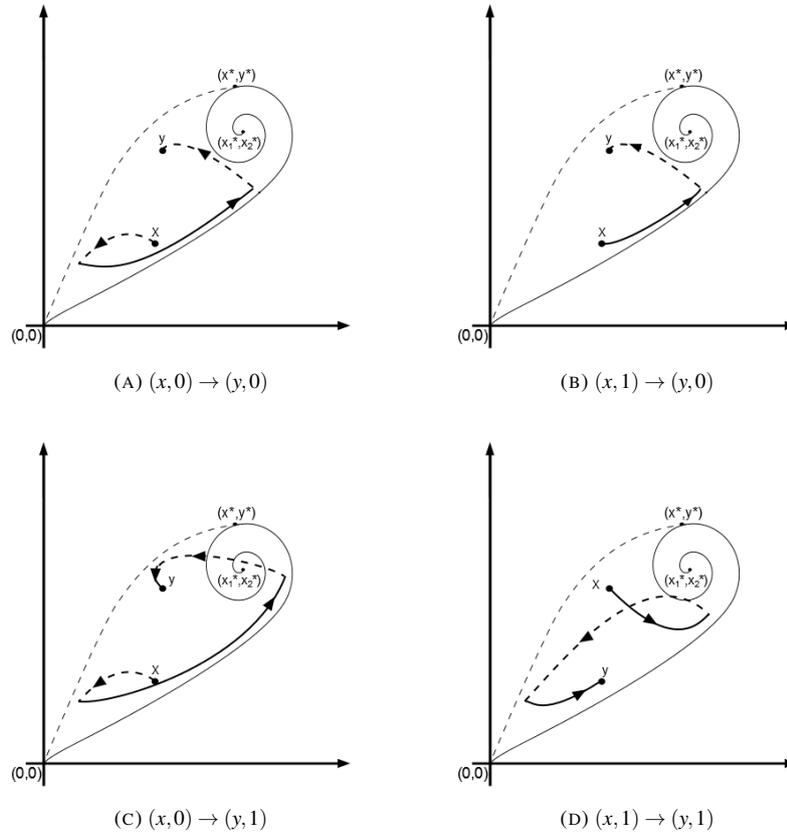


FIGURE 5. Communication between states (x, i) and (y, j) . For every $i, j \in \{0, 1\}$ and $x, y \in A \setminus \{(0, 0)\}$ it is possible to reach a point (y, j) starting from a point (x, i) with at maximum three switches for the model (7).

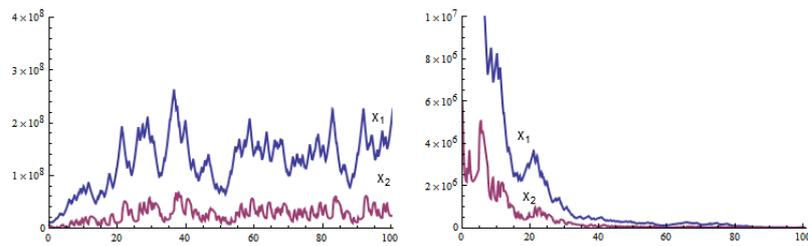


FIGURE 6. Trajectories of the processes of the model (7) for $T_{end} = 100$, $p = 0.6$, $\mu = 2.77$, $k = 1,28 \cdot 10^{-6}$, $q_2 = 3$, $q_1 = 1$ and $a_2 = 0.3$, $a_1 = 0.9$ (left one), $a_2 = 0.2$, $a_1 = 0.6$ (right one)

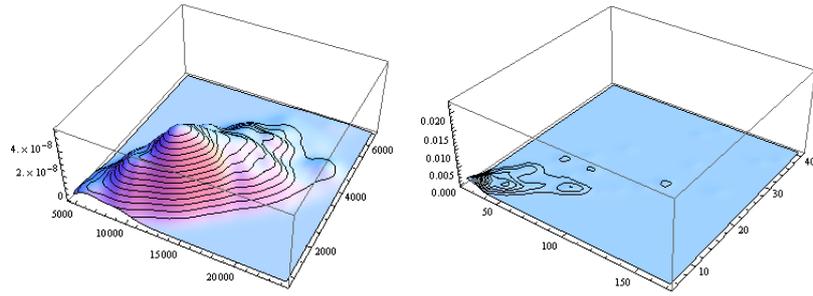


FIGURE 7. Density of the process (7) for $T_{end} = 150$ and two different sets of parameters: $a_1 = 0.8, a_2 = 0.3$ and $a_1 = 0.6, a_2 = 0.2, p = 0.6, \mu = 2.77, k = 1,28 \cdot 10^{-4}$.

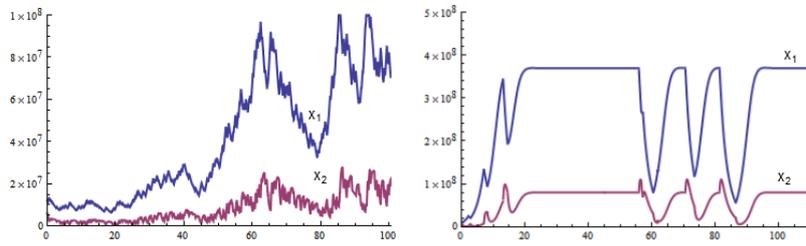


FIGURE 8. Trajectories of the processes of the model (7) for $T_{end} = 100, p = 0.6, \mu = 2.77, k = 1,28 \cdot 10^{-6}, a_2 = 0.3, a_1 = 0.9$ and $q_0 = 4, q_1 = 6$ (left one), $q_0 = 0.3, q_1 = 0.1$ (right one)