Piecewise deterministic Markov processes in biological models

Ryszard Rudnicki and Marta Tyran-Kamińska

Abstract We present a short introduction into the framework of piecewise deterministic Markov processes. We illustrate the abstract mathematical setting with a series of examples related to dispersal of biological systems, cell cycle models, gene expression, physiologically structured populations, as well as neural activity. General results concerning asymptotic properties of stochastic semigroups induced by such Markov processes are applied to specific examples.

Key words: Piecewise Markov deterministic processes, stochastic semigroups, partial differential equation, biological models

1 Introduction

The aim of this article is to give a short mathematical introduction to piecewise deterministic Markov processes (PDMPs) including some results concerning their asymptotic behavior and providing biological models where they appear. According to a non-rigorous definition by Davis [4], the class of *piecewise deterministic Markov processes* is a general family of stochastic models covering virtually all non-diffusion applications. A more formal definition is the following: a continu-

Ryszard Rudnicki
Institute of Mathematics, Polish Academy of Sciences, Bankowa 14, 40-007 Katowice, Poland, e-mail: rudnicki@us.edu.pl

Marta Tyran-Kamińska
Institute of Mathematics, University of Silesia, Bankowa 14, 40-007 Katowice, Poland, e-mail: mtyran@us.edu.pl

ous time Markov process $X(t)$, $t \geq 0$, is a PDMP if there is an increasing sequence of random times (t_n), called jump times, such that the sample paths of $X(t)$ are defined in a deterministic way in each interval (t_n, t_{n+1}). We consider two types of behavior of the process at jump times: the process can jump to a new point or can change the dynamics which defines its trajectories. PDMPs is a large family of different stochastic processes which includes discrete time Markov processes, continuous time Markov chains, deterministic processes with jumps, processes with switching dynamics and some point processes. Although the discrete time Markov processes play important role in applications we will not investigate them here because their theory differs from that of continuous time PDMPs and their applications are sufficiently known [1].

The outline of this paper is as follows. In Section 2 we present a number of simple biological models to illustrate possible applications of such processes. In Section 3 we collect relevant definitions and examples of stochastic semigroups. In Section 4 we recall two general results concerning the long-time behavior (asymptotic stability and sweeping) of stochastic semigroups and we show how they can be applied in the context of PDMPs with switching dynamics. Examples of applications of these results to concrete biological models are also provided. The paper concludes with a short summary and discussion.

2 Examples

2.1 Pure jump-type and velocity jump Markov processes

The simplest examples of PDMPs are continuous time Markov chains. Their theory is well known, so we only mention here that they have a lot of biological applications such as birth-death processes, epidemic models (see [1]) and, more recently, models of genome evolution (see e.g. [21, 22]). Continuous time Markov chains belong to a slightly larger class of the so-called pure jump-type Markov processes. A *pure jump-type Markov process* is a Markov process which remains constant between jumps. For example, the process used in a simple description of the grasshopper and kangaroo movement [16] is an example of a pure jump-type Markov process, which is not a Markov chain. A grasshopper jumps at random times t_n from a point x to the point $x + Y_n$. We assume that jump times are the same as for a Poisson process $N(t)$ with intensity $\lambda > 0$, i.e., $N(t_n) = n$, and that (Y_n) is a sequence of independent and identically distributed (i.i.d.) random vectors. Then the position $X(t)$ of the grasshopper at time t is given by

$$X(t) = X(0) + \sum_{n=1}^{N(t)} Y_n. \tag{1}$$

The process as in (1) is called a *compound Poisson process*.

A general *pure jump-type homogeneous Markov process* on a measurable space (E, Σ) can be defined in the following way. Let $\lambda : E \to [0, \infty)$ be a given measurable function and let $P(x, B)$ be a given *transition probability* function on E, i.e., $P(x, \cdot)$ is a probability measure for each $x \in E$ and the function $x \mapsto P(x, B)$ is measurable for each $B \in \Sigma$. Let $t_0 = 0$ and let $X(0) = X_0$ be an E-valued random variable. For each $n \geq 1$ we can chose the *nth jump time t_n* as a positive random variable satisfying

$$\text{Prob}(t_n - t_{n-1} \leq t | X_{n-1} = x) = 1 - e^{-\lambda(x)t}, \quad t \geq 0,$$

and we define

$$X(t) = \begin{cases} X_{n-1} & \text{for } t_{n-1} \leq t < t_n, \\ X_n & \text{for } t = t_n, \end{cases}$$

where the *nth post-jump position X_n* is an E-valued random variable such that

$$\text{Prob}(X_n \in B | X_{n-1} = x) = P(x, B).$$

Another type of simple PDMPs is a *velocity jump process*. An individual is moving in the space $\mathbb{R}^d$ with a constant velocity and at jump times (t_n) it chooses a new velocity. We assume that jump times are the same as for a Poisson process $N(t)$ with intensity λ. It means that $F(t) = 1 - e^{-\lambda t}$ is the probability distribution function of $t_n - t_{n-1}$. Let $x(t)$ be the position and $v(t)$ be the velocity of an individual at time t. We assume that for every $x, v \in \mathbb{R}^d$, there is a probability Borel measure $P(x, v, B)$ on $\mathbb{R}^d$ which describes the change of the velocity after a jump, i.e.,

$$\text{Prob}(v(t_n) \in B | x(t_n^-) = x, v(t_n^-) = v) = P(x, v, B)$$

for every Borel subset B of $\mathbb{R}^d$, where $x(t_n^-)$ and $v(t_n^-)$ are the left-hand side limits of $x(t)$ and $v(t)$ at the point t_n. Between jumps the pair $(x(t), v(t))$ satisfies the following system of ordinary differential equations

$$\begin{cases} x'(t) = v(t), \\ v'(t) = 0. \end{cases} \tag{2}$$

Then $X(t) = (x(t), v(t))$, $t \geq 0$, is a PDMP corresponding to this movement.

There are a number of interesting examples of velocity jump processes with applications to aggregation and chemotaxis phenomena (see e.g. [8]). The simplest one is the symmetric movement on the real line $\mathbb{R}$. In this case we assume that an individual is moving with constant speed, say one, and at a jump time it changes the direction of movement to the opposite one. A PDMP corresponding to the symmetric movement has values in the space $\mathbb{R} \times \{-1, 1\}$ and $P(x, v, \{-v\}) = 1$ for $v = -1, 1$. This process was first studied by Goldstein [7] and Kac [10] in connection with the telegraph equation. It was called the Goldstein-Kac *telegraph process* afterwards and studied thoroughly in [11].

More advanced examples of velocity jump processes and their comparison with dispersal of cells, insects and mammals are given in [16, 26]. One can also consider velocity jump processes defined in a bounded domain G. Examples of such

processes are stochastic billiards [6] which do not change velocity in the interior of G but when an individual or a point hits the boundary, a new direction is chosen randomly from directions that point back into the interior of G, and the motion continues. PDMPs with jumps at the boundary appear as well in the theory of gene regulatory systems, for example in a model of the production of subtilin by the bacterium *Bachillus subtilis* [9].

2.2 Two phase cell cycle model

Now we consider another type of PDMPs which is a *flow with jumps* described in the following way. Let E be a topological space and let a continuous function $\pi \colon \mathbb{R}_+ \times E \to E$ be a semiflow on E, i.e.,

(a) $\pi_0 x = x$ for $x \in E$,
(b) $\pi_{s+t} x = \pi_t(\pi_s x)$ for $x \in E$, $s, t \in \mathbb{R}_+$.

The semiflow π_t describes the movement of points between jumps, i.e., if x is the position of the point at time t then $\pi_\tau x$ is its position at time $t + \tau$. The point located at x can jump with an intensity $\lambda(x)$ to a point y. The location of y is described by a transition function $P(x, B)$, i.e., $P(x, B)$ is the probability that $y \in B$. After the jump it continues movement according to the same principle.

A simple example of a flow with jumps is the following size-structure model of a cellular population (see e.g. [14]). The cell size (mass, volume) $x > 0$ grows with rate $g(x)$ and it splits with intensity $\varphi(x)$ into two daughter cells with size $x/2$, i.e., $P(x, B) = 1$ if $x/2 \in B$ and $P(x, B) = 0$ otherwise. After division we consider the size of a daughter cell, etc., and we obtain a process $X(t)$, $t > 0$, which describes the size of consecutive descendants of a single cell. The process $X(t)$, $t > 0$, is a PDMP.

Another example of a flow with jumps appears in the Rubinow model of a cellular population [18]. In this model we assume that a newborn cell has size $x = m$, then it grows with rate $g(x)$ and when it reaches size $x = 2m$ it splits into two daughter cells with sizes $x = m$. Similarly to the previous model we consider a process $X(t)$, $t > 0$, which describes the size of consecutive descendants of a single cell. Although the jump times in this process are not random, $X(t)$, $t > 0$, is also a PDMP.

A more advanced flow with jumps is a two phase cell cycle model which is a combination of the two size-structured models described above. The cell cycle is a series of events that take place in a cell leading to its replication [15]. There are several models of the cell cycle but from a mathematical point of view we can simplify these models and we assume that there are only two phases in the cell cycle: the resting phase A with a random duration t_A, when a cell is growing, and the proliferating phase B with a constant duration t_B. Here we describe a continuous time version of the Tyrcha model [29] and we show that it can be treated as a PDMP. The crucial role in the model is played by a parameter x which describes the state of a cell in the cell cycle. It is not clear what x exactly should be. We simply interpret x as a cell size. The cell size $x > 0$ grows with rate $g(x)$ and enters the phase B

with intensity $\varphi(x)$. It is clear that the process $X(t)$, $t > 0$, which describes the size of consecutive descendants of a single cell is piecewise deterministic but it is non-Markovian because its future $X(t)$, $t \geq t_0$, depends not only on the random variable $X(t_0)$ but also on the phase in which it is at the time t_0.

Now we extend the process $X(t)$, $t \geq 0$, to obtain a homogeneous PDMP. A new process $\widetilde{X}(t)$, $t \geq 0$, is defined on the state space $[0,\infty) \times [0,t_B] \times \{1,2\}$ in the following way. Let $\widetilde{X}(t) = (X(t), y, i)$, where $i = 1$ if at time t a cell is in the phase A and $i = 2$ if it is in the phase B. We let $y = 0$ if the cell is in the phase A and otherwise let y be the time which elapsed since the cell entered the phase B. Let s_n be a time when a cell from the nth generation enters the phase B. Since the duration of the phase B is constant and is equal to t_B, a cell from the nth generation splits at time $t_n = s_n + t_B$. Between these jump points the coordinates of the process $\widetilde{X}(t)$ satisfy the following system of ordinary differential equations

$$\begin{cases} \widetilde{X}_1'(t) = g(\widetilde{X}_1(t)), \\ \widetilde{X}_2'(t) = \begin{cases} 0, & \text{if } \widetilde{X}_3(t) = 1, \\ 1, & \text{if } \widetilde{X}_3(t) = 2, \end{cases} \\ \widetilde{X}_3'(t) = 0. \end{cases} \tag{3}$$

The transition rates at the jump points are given by

$$\widetilde{X}_1(s_n) = \widetilde{X}_1(s_n^-), \quad \widetilde{X}_2(s_n) = \widetilde{X}_2(s_n^-) = 0, \quad \widetilde{X}_3(s_n) = 2,$$

and

$$\widetilde{X}_1(t_n) = \tfrac{1}{2}\widetilde{X}_1(t_n^-), \quad \widetilde{X}_2(t_n) = 0, \quad \widetilde{X}_3(t_n) = 1.$$

Let $\pi_t x_0 = x(t)$ be the solution of the equation $x' = g(x)$ with initial condition $x(0) = x_0$. The distribution function of $s_n - t_{n-1}$ is given by

$$F(t) = 1 - \exp\left\{ -\int_0^t \varphi(\pi_s x_0)\, ds \right\}, \tag{4}$$

where $x_0 = \widetilde{X}_1(t_{n-1})$, while that of $t_n - s_n$ by $F(t) = 0$ for $t < t_B$ and $F(t) = 1$ for $t \geq t_B$.

The life-span $t_n - t_{n-1}$ of a cell with initial size x_0 has the distribution function

$$F(t) = \begin{cases} 0, & \text{if } t < t_B, \\ 1 - \exp\left\{ -\int_0^{t-t_B} \varphi(\pi_s x_0)\, ds \right\}, & \text{if } t \geq t_B, \end{cases} \tag{5}$$

and we have the following relation between the distributions of the random variables $\widetilde{X}(t_n)$ and $\widetilde{X}(t_{n-1})$:

$$\widetilde{X}(t_n) \stackrel{d}{=} \tfrac{1}{2}\pi_{t_B}\left(Q^{-1}\left(Q(\widetilde{X}(t_{n-1})) + \xi_n \right) \right), \tag{6}$$

where ξ_n is a random variable independent of $\widetilde{X}(t_{n-1})$ with exponential distribution of mean one and $Q(x) = \int\limits_0^x \dfrac{\varphi(r)}{g(r)}\,dr, x > 0$.

2.3 Gene expression

Another class of PDMPs is the family of processes with switching dynamics. Assume that we have a finite number of semiflows $\pi_t^i, i \in I = \{1, \ldots, k\}$ on a topological space E. The state of the system is a pair $(x, i) \in E \times I$. If the system is at state (x, i) then x can change according to the semiflow π_t^i and after time t reaches the state $(\pi_t^i(x), i)$ or it can switch to the state (x, j) with a bounded and continuous intensity $q_{ji}(x)$. The pair $(x(t), i(t))$ constitutes a Markov process $X(t)$ on $E \times I$.

Now we show how PDMPs can be applied to model gene expression. Gene expression is a complex process which involves three processes: gene activation/inactivation, mRNA transcription/decay, and protein translation/decay. We consider a simplified version of the model of gene expression introduced by Lipniacki et al. [13] and studied in [3]. We assume that the production of proteins is regulated by a single gene and we omit the intermediate process of mRNA transcription. A gene can be in an active or an inactive state and it can be transformed into an active state or into an inactive state with intensities q_0 and q_1, respectively. The rates q_0 and q_1 depend on the number of protein molecules $X(t)$. If the gene is active then proteins are produced with a constant speed P. Protein molecules undergo the process of degradation with rate μ in both states of the gene. It means that the process $X(t), t \geq 0$, satisfies the equation

$$X'(t) = PA(t) - \mu X(t), \tag{7}$$

where $A(t) = 1$ if the gene is active and $A(t) = 0$ in the opposite case. Then the process $\widetilde{X}(t) = (X(t), A(t)), t \geq 0$, is a PDMP. Since the right-hand side of equation (7) is negative for $X(t) > \dfrac{P}{\mu}$ we can restrict values of $X(t)$ to the interval $\left[0, \dfrac{P}{\mu}\right]$ and the process $\widetilde{X}(t)$ is defined on the state space $\left[0, \dfrac{P}{\mu}\right] \times \{0, 1\}$.

The process $\widetilde{X}(t)$ has jump points when the gene changes its activity. Formula (4) allows us to find the distribution of the time between consecutive jumps. Observe that if x_0 is the number of protein molecules at a jump time, then after time t we have

$$\pi_t^0 x_0 = x_0 e^{-\mu t}, \quad \pi_t^1 x_0 = \frac{P}{\mu} + \left(x_0 - \frac{P}{\mu}\right)e^{-\mu t},$$

protein molecules in an inactive and an active state, respectively. From (4) it follows that the probability distribution function of the length of an inactive state is given by

$$1 - \exp\left\{-\int_0^t q_0\left(x_0 e^{-\mu s}\right)ds\right\}$$

and of an active state by

$$1 - \exp\left\{ -\int_0^t q_0\left(\frac{P}{\mu} + \left(x_0 - \frac{P}{\mu}\right)e^{-\mu s}\right) ds \right\}.$$

2.4 Neural activity

A neuron is an electrically excitable cell that processes and transmits information through electrical signals. The neuron's membrane potential V_m is the difference between the inside potential and the outside potential. If a cell is in the resting state, then this potential, denoted by $V_{m,R}$, is about -70 mV. The *depolarization* is defined as

$$V = V_m - V_{m,R}.$$

A cell is said to be *excited* (or depolarized) if $V > 0$ and *inhibited* (or hyperpolarized) if $V < 0$. The Stein's model [24, 25] describes how the depolarization $V(t)$ is changing in time. The cell is initially at rest so that $V(0) = 0$. Nerve cells may be excited or inhibited through neuron's synapses — junctions between nerve cells (or between muscle and nerve cell) such that electrical activity in one cell may influence the electrical potential in the other. Synapses may be excitatory or inhibitory. We assume that there are two nonnegative constants a_E and a_I such that if at time t an excitation occurs then $V(t^+) = V(t^-) + a_E$ and if an inhibition occurs then $V(t^+) = V(t^-) - a_I$. The jumps (excitations and inhibitions) may occur at random times according to two independent Poisson processes $N^E(t)$, $N^I(t)$, $t \geq 0$, with positive intensities λ_E and λ_I, respectively. Between jumps the depolarization $V(t)$ decays according to the equation $V'(t) = -\alpha V(t)$. When a sufficient (threshold) level $\theta > 0$ of excitation is reached, the neuron emits an action potential (fires). This will be followed by an absolute refractory period of duration t_R, during which $V \equiv 0$ and then the process starts again.

We now describe the neural activity as a PDMP. Since the refractory period has a constant duration we can use a model similar to that of Section 2.2 with two phases A and B, where A is the subthreshold phase and B is the refractory phase of duration t_R. We consider two types of jump points: when the neuron is excited or inhibited and the ends of refractory periods. Thus, we can have one or more jumps inside the phase A.

Let $\widetilde{X}(t) = (V(t), 0, 1)$ if the neuron is in the phase A and $\widetilde{X}(t) = (V(t), y, 2)$ if the neuron is in the phase B, where y is the time since the moment of firing. The process $\widetilde{X}(t) = (\widetilde{X}_1(t), \widetilde{X}_2(t), \widetilde{X}_3(t))$, $t \geq 0$, is defined on the state space $(-\infty, \theta) \times [0, t_R] \times \{1, 2\}$ and between jumps it satisfies the following system of equations

$$
\begin{cases}
\widetilde{X}_1'(t) = -\alpha \widetilde{X}_1(t), \\
\widetilde{X}_2'(t) = \begin{cases} 0, & \text{if } \widetilde{X}_3(t) = 1, \\ 1, & \text{if } \widetilde{X}_3(t) = 2, \end{cases} \\
\widetilde{X}_3'(t) = 0.
\end{cases}
\tag{8}
$$

Let $t_0, t_1, t_2, \ldots$ be the subsequent jump times. We denote by $\mathscr{F}$ the subset of jump times consisting of firing points. If the neuron is in the phase A, i.e., $\widetilde{X}_3(t) = 1$, the depolarization can jump with intensity $\lambda = \lambda_E + \lambda_I$. It means that $F(t) = 1 - e^{-\lambda t}$ is the distribution function of $t_n - t_{n-1}$ if $t_{n-1} \notin \mathscr{F}$. If $t_{n-1} \in \mathscr{F}$ then the distribution of $t_n - t_{n-1}$ is $F(t) = 0$ for $t < t_R$ and $F(t) = 1$ for $t \geq t_R$. The transition at a jump point depends on the state of the neuron (its phase and the value of its depolarization). If $\widetilde{X}(t_n^-) = (0, t_R, 2)$ then $\widetilde{X}(t_n) = (0, 0, 1)$ with probability one; if $\widetilde{X}(t_n^-) = (x, 0, 1)$ and $x < \theta - a_E$ then $\widetilde{X}(t_n) = (x + a_E, 0, 1)$ with probability λ_E/λ and $\widetilde{X}(t_n) = (x - a_I, 0, 1)$ with probability λ_I/λ; while if $\widetilde{X}(t_n^-) = (x, 0, 1)$ and $x \geq \theta - a_E$ then $\widetilde{X}(t_n) = (0, 0, 2)$ with probability λ_E/λ and $\widetilde{X}(t_n) = (x - a_I, 0, 1)$ with probability λ_I/λ.

2.5 Size structured population model

In this section we return to size structured models but instead of a single cell line we consider the size distribution of all cells in the population. This model can serve as a prototype of individual based models like age and phenotype structured models as well as models of coagulation-fragmentation processes.

The size $x(t)$ of a cell grows according to the equation

$$
x'(t) = g(x(t)).
$$

A single cell with size x replicates with rate $b(x)$ and dies with rate $d(x)$. A daughter cell has a half size of the mother cell. Let us assume that at time t we have k cells and denote by $x_1(t), x_1(t), \ldots, x_k(t)$ their sizes. We can assume that a state of the population at time t is the set

$$
\{x_1(t), \ldots, x_k(t)\}
$$

and that the evolution of the population is a stochastic process

$$
X(t) = \{x_1(t), \ldots, x_k(t)\}.
$$

Since the values of this process are sets of points the process $X(t)$ is called a *point process*. Thought such approach is a natural one it has one important disadvantage. We are unable to describe properly a situation when two cells have the same size. One solution of this problem is to consider $X(t)$ as a process whose values are multisets. We recall that a *multiset* (or a *bag*) is a generalization of the notion of a set in which members are allowed to appear more than once. Another artful solution

of this problem is to consider $X(t)$ as a process with values in the space of measures given by

$$X(t) = \delta_{x_1(t)} + \cdots + \delta_{x_k(t)},$$

where δ_a denotes the *Dirac measure* at point a, i.e., δ_a is the probability measure concentrated at the point a. This approach has some disadvantages also, for example it is rather difficult to consider differential equations on measures. Yet another solution of this problem is to consider a state of the system as k-tuples $(x_1(t), \ldots, x_k(t))$. Since some cells can die or split into two cells, the length of the tuple changes in time. To omit this difficulty we introduce an extra "death state" $*$ and we describe the state of the population at time t as an infinite sequence of elements from the space $\mathbb{R}_*^+ = [0, \infty) \cup \{*\}$ which has numbers $x_1(t), \ldots, x_k(t)$ on some k positions and it has $*$ on the remaining positions. In order to have uniqueness of states we introduce an equivalence relation $\sim$ in the space E of all $\mathbb{R}_*^+$- valued sequences x such that $x_i = *$ for all but finitely many i. Two sequences $x \in E$ and $y \in E$ are equivalent with respect to $\sim$ if y can be obtained as a permutation of x, i.e., $x \sim y$ if and only if there is a bijective function $\sigma : \mathbb{N} \to \mathbb{N}$ such that $y = (x_{\sigma(1)}, x_{\sigma(2)}, \ldots)$. The state space $\widetilde{E}$ in our model is the space of all equivalence classes with respect to $\sim$, i.e., $\widetilde{E} = E/\sim$.

Now we can describe the evolution of the population as a stochastic process $X(t) = [(x_1(t), x_2(t), \ldots)]$ with values in the space $\widetilde{E}$ where $[]$ denotes an equivalence class. The process $X(t)$ has jump points when one of the cells dies or replicates. We define $g(*) = b(*) = b(*) = 0$ and admit a convention that $x(t) = *$ is the solution of the equation $x'(t) = 0$ with initial condition $x(0) = *$. Between jumps the process $X(t)$ satisfies the equation

$$X'(t) = [(g(x_1(t)), g(x_2(t)), \ldots)]. \tag{9}$$

For $t \geq 0$ and $x^0 \in \mathbb{R}_*^+$ we denote by $\pi(t, x^0)$ the solution $x(t)$ of the equation $x'(t) = g(x(t))$ with initial condition $x(0) = x_0$. Let $\mathbf{x}^0 = [(x_1^0, x_2^0, \ldots)] \in \widetilde{E}$ and define

$$\tilde{\pi}_t \mathbf{x}^0 = [(\pi_t x_1^0, \pi_t x_2^0, \ldots)].$$

The jump rate function $\varphi(\mathbf{x})$ at state $\mathbf{x} = [(x_1, x_2, \ldots)]$ is the sum of rates of deaths and divisions of all cells:

$$\varphi(\mathbf{x}) = \sum_{i=1}^{\infty} (b(x_i) + d(x_i)). \tag{10}$$

If $\mathbf{x}^0 \in \widetilde{E}$ is the initial state of the population at a jump time t_n, then the probability distribution function of $t_{n+1} - t_n$ is given by

$$1 - \exp\left\{ -\int_0^t \varphi(\tilde{\pi}_s \mathbf{x}^0) \, ds \right\}. \tag{11}$$

At time t_n one of the cells dies or replicates. If a cell dies we change the sequence by removing the cell's size from the sequence and we have

$$\text{Prob}\left(X(t_n) = [(x_1(t_n^-), \ldots, x_{i-1}(t_n^-), x_{i+1}(t_n^-), \ldots)]\right) = \frac{d_i(x_i(t_n^-))}{\varphi(X(t_n^-))}$$

for $i \in \mathbb{N}$. If a cell replicates we remove its size from the sequence and add two new elements in the sequence with sizes of the daughter cells and we have

$$\text{Prob}\left(X(t_n) = [(x_1(t_n^-), \ldots, x_{i-1}(t_n^-), \tfrac{1}{2}x_i(t_n^-), \tfrac{1}{2}x_i(t_n^-), x_{i+1}(t_n^-), \ldots)]\right)$$
$$= \frac{b_i(x_i(t_n^-))}{\varphi(X(t_n^-))}$$

for $i \in \mathbb{N}$. In this way we have checked that the point process $X(t)$, $t \geq 0$, is a homogeneous PDMP with values in $\widetilde{E}$.

We can identify the space $\widetilde{E}$ with the space $\mathcal{N}$ of finite counting measures on R_+ by a map $\eta \colon \widetilde{E} \to \mathcal{N}$ given by

$$\eta(\mathbf{x}) = \sum_{\{i:\, x_i \neq *\}} \delta_{x_i} \tag{12}$$

where $\mathbf{x} = [(x_1, x_2, \ldots)]$. It means that the process $\eta(X(t))$, $t \geq 0$, is a homogeneous PDMP with values in $\mathcal{N}$.

Remark 1. In order to describe the jump transformation at times t_n we need, formally, to introduce a σ-algebra Σ of subset of $\widetilde{E}$ to define a transition function $P \colon \tilde{E} \times \Sigma \to [0,1]$. Usually, Σ is a σ-algebra of Borel subsets of $\widetilde{E}$, thus we need to introduce a topology on the space $\widetilde{E}$. Since the space $\mathcal{N}$ is equipped with the topology of weak convergence of measures, we can define open sets in $\widetilde{E}$ as preimages through the function η of open sets in $\mathcal{N}$. Another way to introduce a topology is to construct directly a metric on the space $\widetilde{E}$. Generally, a point process describes the evolution of configurations of points in a state space which is a metric space (S, ρ). First, we extend the state space S by adding "the death element" $*$. We need to define a metric on $S \cup \{*\}$. The best situation is if S is a proper subset of a larger metric space S'. Then we simply choose $*$ as an element from S' which does not belong to S and we keep the same metric. In the other case, first we choose $x_0 \in S$ and define $\rho(*, x) = 1 + \rho(x_0, x)$ for $x \in S$. Next, we define a metric d on the space E by

$$d(x, y) = \max_{i \in \mathbb{N}} \rho(x_i, y_i)$$

and, finally, we define a metric $\widetilde{d}$ on the space $\widetilde{E}$ by

$$\widetilde{d}([x], [y]) = \min\{d(a, b) \colon\ a \in [x],\ b \in [y]\}.$$

We next show that the topology in $\widetilde{E}$ induced from $\mathcal{N}$ is equivalent to the topology defined by $\widetilde{d}$. Indeed, a sequence (μ_n) of finite counting measures converges weakly to a finite counting measure μ iff the measures μ and μ_n, $n \geq 1$ can be represented in the form

$$\mu = \sum_{i=1}^{k} \delta_{x_i}, \quad \mu_n = \sum_{i=1}^{k_n} \delta_{x_{i,n}},$$

where $k_n = k$ for sufficiently large n and $\lim_{n \to \infty} \rho(x_{i,n}, x_i) = 0$ for $i = 1, \ldots, k$. Thus the convergence of counting measures implies that the sequence $x^n = (x_{1,n}, \ldots, x_{k_n,n})$ converges to $x = (x_1, \ldots, x_k)$ in the metric d, and the sequence $[x^n]$ converges to $[x]$ in $\widetilde{d}$. The proof of the opposite implication goes in the same way.

3 Stochastic semigroups

Most of PDMPs define stochastic semigroups which describe the evolution of densities of the distribution of these processes. n this section we recall the definition of a stochastic semigroup and provide a couple of examples of such semigroups.

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

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

A linear operator $P \colon L^1 \to L^1$ is called a *stochastic (or Markov) operator* if $P(D) \subset D$. Let $\{P(t)\}_{t \geq 0}$ be a C_0-*semigroup*, i.e., it satisfies the following conditions:

(a) $P(0) = I$, i.e., $P(0)f = f$,
(b) $P(t+s) = P(t)P(s)$ for $s, t \geq 0$,
(c) for each $f \in L^1$ the function $t \mapsto P(t)f$ is continuous.

Then the C_0-semigroup $\{P(t)\}_{t \geq 0}$ is called *stochastic* iff each operator $P(t)$ is stochastic. The *infinitesimal generator* of $\{P(t)\}_{t \geq 0}$ is the operator A with domain $\mathscr{D}(A) \subseteq L^1$ defined as

$$Af = \lim_{t \downarrow 0} \frac{1}{t}(P(t)f - f), \quad \mathscr{D}(A) = \{f \in L^1 : \lim_{t \downarrow 0} \frac{1}{t}(P(t)f - f) \text{ exists}\}.$$

Our first example of a stochastic semigroup is the following. Let $g \colon \mathbb{R}^d \to \mathbb{R}^d$ be a C^1 function and consider the differential equation

$$x'(t) = g(x(t)). \tag{13}$$

Assume that E is a measurable subset of $\mathbb{R}^d$ with a positive Lebesgue measure such that for each point $x_0 \in E$ the solution $x(t)$ of (13) with $x(0) = x_0$ exists and $x(t) \in E$ for all $t \geq 0$. We denote this solution by $\pi_t x_0$. Let Σ be the σ-algebra of the Borel subsets of E and m be the Lebesgue on E. Let $f \colon E \to [0, \infty)$ be a density and let X_0 be a random vector with values in E with density f, i.e., $\mathrm{Prob}(X_0 \in B) = \int_B f(x)\, dx$ for each Borel subset B of E. Let $X(t) = \pi_t X_0$. Then the density of the distribution of the random vector $X(t)$ is given by

$$P(t)f(x) = \begin{cases} f(\pi_{-t}x) \det\left[\dfrac{d}{dx}\pi_{-t}x\right], & \text{if } x \in \pi_t(E), \\ 0, \text{ if } x \notin \pi_t(E), \end{cases}$$

where π_{-t} denotes the inverse of the one-to-one and onto mapping $\pi_t \colon E \to \pi_t(E)$. The operators $P(t)$, extended linearly from D to L^1, form a stochastic semigroup. If f is a C^1 function then the function $u(t,x) = P(t)f(x)$ satisfies the following partial differential equation

$$\frac{\partial u(t,x)}{\partial t} = -\mathrm{div}(g(x)u(t,x)). \tag{14}$$

If A is an infinitesimal generator of the semigroup $\{P(t)\}_{t\geq 0}$ then

$$Af(x) = -\mathrm{div}(g(x)f(x)) = -\sum_{i=1}^{d} \frac{\partial}{\partial x_i}(g_i(x)f(x)). \tag{15}$$

Now we consider the processes $X(t) = (x(t), i(t))$ with switching dynamics described in Section 2.3. We assume that each flow π_t^i, $i \in I = \{1,\dots,k\}$, is defined as the solution of a system of differential equations $x' = g_i(x)$ on a measurable subset E of R^d. Let $\{S^i(t)\}_{t\geq 0}$ be the stochastic semigroup related to π_t^i and let the operator A_i be its generator. If $f = (f_1,\dots,f_k)$ is a vertical vector consisting of functions f_i such that $f_i \in \mathscr{D}(A_i)$, we set $Af = (A_1f_1,\dots,A_kf_k)$ which is also a vertical vector. We define $q_{jj}(x) = -\sum_{i\neq j} q_{ij}(x)$ and denote by $Q(x)$ the matrix $[q_{ij}(x)]$. Then the process $X(t)$ induces a stochastic semigroup on the space $L^1(E \times I, \mathscr{B}(E \times I), m)$ with the infinitesimal generator $Q + A$. Here $\mathscr{B}(E \times I)$ is the σ-algebra of Borel subsets of $E \times I$ and m is the product measure on $\mathscr{B}(E \times I)$ given by $m(B \times \{i\}) = \mu(B)$.

Finally, we provide stochastic semigroups for the flows with jumps $X(t)$ from Section 2.2. Let $\pi_t x$ be a the semiflow describing solutions of equation (13) and let $\lambda(x)$ be the intensity of jumping from the point x to a point $y \in B$ chosen according to the transition probability $P(x,B)$. Suppose that there is a stochastic operator P on $L^1(E,\Sigma,m)$ induced by $P(x,\cdot)$, i.e.,

$$\int_E P(x,B)f(x)m(dx) = \int_B Pf(x)m(dx) \quad \text{for all } B \in \Sigma, f \in D. \tag{16}$$

If λ is bounded then the process $X(t)$ induces a stochastic semigroup on the space $L^1(E,\Sigma,m)$ with infinitesimal generator of the form $A_0f - \lambda f + P(\lambda f)$, where A_0 is as in (15). If λ is unbounded then one may need to impose additional constraints on A_0, λ, and/or P to obtain a stochastic semigroup for $X(t)$, see [27, 28] for necessary and sufficient conditions. For the particular example of the model of the cell cycle on $E = (0,\infty)$ with one phase we have $Pf(x) = 2f(2x)$ for $x > 0$. Suppose that $g \colon (0,\infty) \to (0,\infty)$ is continuous and φ/g is locally integrable with

$$\int_{\bar{x}}^{\infty} \frac{1}{g(r)} dr = \int_{\bar{x}}^{\infty} \frac{\varphi(r)}{g(r)} dr = \infty \tag{17}$$

for some $\bar{x} > 0$. Then the process $X(t)$ induces a stochastic semigroup $\{P(t)\}_{t\geq 0}$ on $L^1 = L^1((0,\infty), \Sigma, m)$, where Σ is the Borel σ-algebra of subsets of $(0,\infty)$ and m is the Lebesque measure, with infinitesimal generator of the form [14]

$$Af(x) = -\frac{d}{dx}(g(x)f(x)) - \varphi(x)f(x) + 2\varphi(2x)f(2x)$$

defined for $f \in \mathscr{D}(A) = \mathscr{D}_0 \cap L^1_\varphi$, where $L^1_\varphi = \{f \in L^1 : \varphi f \in L^1\}$ and

$$\mathscr{D}_0 = \{f \in L^1 : gf \text{ is absolutely continuous, } (gf)' \in L^1\},$$

together with the boundary condition $\lim_{x\to 0} g(x)f(x) = 0$ when $\int_0^{\bar{x}} 1/g(r)dr < \infty$.

For the two phase model we can restrict the state space to the set $(0,\infty) \times \{0\} \times \{1\} \cup (0,\infty) \times [0,t_B] \times \{2\}$. We consider the corresponding stochastic semigroup $\{P(t)\}_{t\geq 0}$ on the product space $L^1((0,\infty)) \times L^1((0,\infty) \times [0,t_B])$. Let $f = (f_1, f_2)$ be the density of the process at time t, where $f_1(t,x)$ and $f_2(t,x,y)$ denote the partial densities related to the phases A and B, respectively. If f_1, f_2 are smooth functions then they satisfy the following equations

$$\frac{\partial f_1(t,x)}{\partial t} = -\frac{\partial}{\partial x}(g(x)f_1(t,x)) - \varphi(x)f_1(t,x) + 2f_2(t,2x,t_B),$$

$$\frac{\partial f_2(t,x,y)}{\partial t} = -\frac{\partial}{\partial x}(g(x)f_2(t,x,y)) - \frac{\partial}{\partial y}(f_2(t,x,y)),$$

with the boundary conditions

$$f_2(t,x,0) = \varphi(x)f_1(t,x), \quad x > 0, t \geq 0,$$

$$\lim_{x\to 0} g(x)f_1(t,x) = \lim_{x\to 0} g(x)f_2(t,x,y) = 0, \quad y \in [0,t_B], t \geq 0.$$

4 Long time behavior

In this section we study asymptotic properties of stochastic semigroups induced by PDMPs. We will consider two properties: asymptotic stability and sweeping. A stochastic semigroup $\{P(t)\}_{t\geq 0}$ on $L^1(E,\Sigma,m)$ is called *asymptotically stable* if there is a density f_* such that

$$\lim_{t\to\infty} \|P(t)f - f_*\| = 0 \quad \text{for} \quad f \in D. \tag{18}$$

A density f_* which satisfies (18) is *invariant*, i.e., $P(t)f_* = f_*$ for each $t > 0$. A stochastic semigroup $\{P(t)\}_{t\geq 0}$ is called *sweeping* with respect to a set $B \in \Sigma$ if for every $f \in D$

$$\lim_{t\to\infty} \int_B P(t)f(x)m(dx) = 0.$$

Let us now recall two general results concerning asymptotic properties of partially integral semigroups. A stochastic semigroup $\{P(t)\}_{t\geq 0}$ on $L^1(E,\Sigma,m)$ is called *partially integral* if there exists a measurable function $k\colon (0,\infty) \times E \times E \to [0,\infty)$, called a *kernel*, such that

$$P(t)f(x) \geq \int_E k(t,x,y)f(y)\,m(dy)$$

for every density f and

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

for some $t > 0$.

Theorem 1 ([17]). *Let $\{P(t)\}_{t\geq 0}$ be a 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.*

To prove asymptotic stability, it is sometimes difficult to check directly that the semigroup $\{P(t)\}_{t\geq 0}$ has a unique invariant density f_*. Therefore, the following theorem can be useful in checking whether a semigroup is asymptotically stable or sweeping.

Theorem 2 ([19]). *Let E be a metric space and $\Sigma = \mathscr{B}(E)$ be the σ–algebra of Borel subsets of E. We assume that a partially integral stochastic semigroup $\{P(t)\}_{t\geq 0}$ with the kernel k has the following properties:*
(a) for every $f \in D$ we have $\int_0^\infty P(t)f\,dt > 0$ a.e.,
(b) for every $y_0 \in E$ there exist $\varepsilon > 0$, $t > 0$, and a measurable function $\eta \geq 0$ such that $\int \eta\,dm > 0$ and

$$k(t,x,y) \geq \eta(x)$$

for $x \in E$ and $y \in B(y_0,\varepsilon)$, where $B(y_0,\varepsilon)$ is the open ball with center y_0 and radius ε. Then the semigroup $\{P(t)\}_{t\geq 0}$ is asymptotically stable if it has an invariant density and it is sweeping with respect to compact sets if it has no invariant density. In particular, if E is a compact set then the semigroup $\{P(t)\}_{t\geq 0}$ is asymptotically stable.

We are now ready to apply Theorems 1 and 2 to stochastic semigroups induced by PDMPs with switching dynamics. In many applications a PDMP with switching dynamics is induced by flows π_t^i, $i \in I = \{1,\dots,k\}$, acting on an open subset G of $\mathbb{R}^d$, and we start with a stochastic semigroup $\{P(t)\}_{t\geq 0}$ defined on the space $L^1(G \times I, \mathscr{B}(G \times I), dx \times di)$, but this semigroup has a stochastic attractor having some additional properties. By a *stochastic attractor* we understand here a measurable subset S of G such that for every density $f \in L^1(G \times I)$ we have

$$\lim_{t\to\infty} \int\limits_{S\times I} P(t)f(x,i)\,dx\,di = 1. \tag{19}$$

For example, if there exists a measurable subset S of G such that $x(t)(\omega) \in S$ for $t > t(\omega)$ for almost every ω then S is a stochastic attractor. If a stochastic semigroup has a stochastic attractor S then it is enough to study the restriction of the semigroup $\{P(t)\}_{t \geq 0}$ to the space $L^1(E, \mathcal{B}(E), m)$, where $E = S \times I$ and $dm = dx \times di$.

Let us now explain how to check conditions (a) and (b) of Theorem 2. We can obtain condition (a) if we check that m-almost every two states $(x, i) \in E$, $(y, j) \in E$ can be joined by a path of the process $(x(t), i(t))$. To be precise there exist $n \in \mathbb{N}$, $\mathbf{i} = (i_1, \ldots, i_n) \in I^n$, and $\mathbf{t} = (t_1, \ldots, t_n) \in (0, \infty)^n$ such that $i_1 = i$, $i_n = j$, and

$$y = \pi_{\mathbf{t}}^{\mathbf{i}}(x) = \pi_{t_n}^{i_n} \circ \cdots \circ \pi_{t_2}^{i_2} \circ \pi_{t_1}^{i_1}(x).$$

Condition (b) can be checked by using Lie brackets. We now recall the definition of Lie brackets. Let $a(x)$ and $b(x)$ be two vector fields on $\mathbb{R}^d$. The *Lie bracket* $[a, b]$ is a vector field given by

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

Let a PDMP with switching dynamics be defined by the systems of differential equations $x' = g_i(x)$, $i \in I$, with intensities $q_{ji}(x)$. We say that the *Hörmander's condition* holds at a point x if $q_{ij}(x) > 0$ for all $1 \leq i, j \leq k$ and if vectors

$$g_2(x) - g_1(x), \ldots, g_k(x) - g_1(x), [g_i, g_j](x)_{1 \leq i, j \leq k}, [g_i, [g_j, g_l]](x)_{1 \leq i, j, l \leq k}, \ldots$$

span the space $\mathbb{R}^d$. Let $y_0 \in S$ and assume that there exist $n \in \mathbb{N}$, $\mathbf{i} \in I^n$ and $\mathbf{t} \in (0, \infty)^n$ such that the Hörmander's condition holds at the point y given by

$$y = \pi_{\mathbf{t}}^{\mathbf{i}}(y_0),$$

then y_0 satisfies condition (b). This fact is a simple consequence of [2, Theorem 4].

Finally, we give some examples of applications to biological models.

Example 1 (Gene expression). The model of gene expression from Section 2.3 is a special case of the following PDMP with switching dynamics. We have two flows induced by one-dimensional differential equations $x' = g_i(x)$, $i = 1, 2$, where g_i are C^∞-functions with the following property: there exist points $x_1 < x_2$ such that

$$g_i(x) > 0 \text{ for } x < x_i \text{ and } g_i(x) < 0 \text{ for } x > x_i.$$

It is obvious that almost all trajectories enter the set $S = [x_1, x_2]$. Observe that any two states (x, i) and (y, j) with $x, y \in (x_1, x_2)$ and $i, j \in \{0, 1\}$ can be joined by a path of the process $(x(t), i(t))$. Hence, condition (a) of Theorem 2 is fulfilled. Since $g_2(x) - g_1(x) > 0$ for $x \in S$, the Hörmander's condition holds at each point $x \in S$ and, therefore, condition (b) is fulfilled. Since the set $E = S \times \{1, 2\}$ is compact, the semigroup induced by our PDMP is asymptotically stable. More precisely, there exists a density $f_*: \mathbb{R} \times \{1, 2\} \to [0, \infty)$ such that $f_*(x, i) = 0$ for $x \notin [x_1, x_2]$ and $\lim_{t \to \infty} \|P(t)f - f_*\| = 0$ for every density $f \in L^1(\mathbb{R} \times \{1, 2\})$.

Example 2 (Population model with and without Allee effect). Consider a PDMP with switching dynamics induced by two differential equations

$$x'(t) = \lambda \left(1 - \frac{x(t)}{K} - \frac{Ai}{1 + Bx(t)} \right) x(t), \tag{20}$$

where $i = 0, 1$ and A, B, K are positive constants such that $KB > 1$ and

$$1 < A < \frac{(BK+1)^2}{4KB}. \tag{21}$$

The number $x(t) > 0$ describes the size of a population. If $i = 0$ then (20) reduces to a logistic equation and $\lim_{t\to\infty} x(t) = K$. If $i = 1$ then (20) has three stationary states x_0, x_1, x_2 such that $x_0 = 0 < x_1 < x_2 < K$ with the following properties. If $x(0) \in (0, x_1)$ then $\lim_{t\to\infty} x(t) = 0$ (called Allee effect) and if $x(0) \in (x_1, \infty)$ then $\lim_{t\to\infty} x(t) = x_2$. Now we consider a PDMP induced by these equations with positive and continuous intensities of switching. Almost all trajectories enter the interval $S = [x_2, K]$, thus S is a stochastic attractor. Since almost all states in $E = S \times \{0, 1\}$ can be joined by paths of the process $(x(t), i(t))$ and $g_0(x) > g_1(x)$, the assumptions of Theorem 2 are fulfilled and the semigroup induced by our process is asymptotically stable.

Example 3 (Population model with two different birth rates). Now we consider a population model with a constant death rate μ and birth rates $b_i(x) = b_i - cx$, $i = 0, 1$, which can change in time. Thus, the size $x \geq 0$ of the population is described by a PDMP with switching dynamics defined by two differential equations

$$x' = g_i(x)$$

with $g_i(x) = (b_i - cx)x - \mu x$ for $i = 0, 1$. Denote by $q_i(x)$ the intensities of changing the state i to $1 - i$. We assume that $b_0 < \mu$ and $b_1 > \mu$ and that the intensities $q_i(x)$ are continuous, positive, and bounded functions. Observe that $g_i(0) = 0$ for $i = 0, 1$, $g_0(x) < 0$ for $x > 0$ and that there exists a point $a > 0$ such that $g_1(x) > 0$ for $x \in (0, a)$ and $g_1(x) < 0$ for $x > a$. The interval $S = (0, a]$ is a stochastic attractor for this PDMP. Since almost all states in $E = S \times \{0, 1\}$ can be joined by paths of the process $(x(t), i(t))$ and $g_0(x) < g_1(x)$ for $x > 0$, conditions (a) and (b) of Theorem 2 are fulfilled. Consequently, the semigroup induced by our process is asymptotically stable or sweeping from compact subsets of E.

In order to get asymptotic stability of this semigroup, we need to check whether this semigroup has an invariant density. Observe that if $f(x, i)$ is an invariant density then the functions $f_i(x) = f(x, i)$ for $i = 0, 1$ should be stationary solutions of the Fokker-Planck equation, i.e., f_0, f_1 satisfy the following system of differential equations

$$\begin{cases} (g_0(x)f_0(x))' = q_1(x)f_1(x) - q_0(x)f_0(x), \\ (g_1(x)f_1(x))' = q_0(x)f_0(x) - q_1(x)f_1(x). \end{cases} \tag{22}$$

Fix a point $x_0 \in (0, a)$ and let

$$r(x) = \frac{q_0(x)}{g_0(x)} + \frac{q_1(x)}{g_1(x)} \text{ and } R(x) = \int_{x_0}^{x} r(s) \, ds.$$

Then the functions

$$\bar{f}_0(x) = -e^{-R(x)}/g_0(x) \text{ and } \bar{f}_1(x) = e^{-R(x)}/g_1(x)$$

are positive in the interval $(0, a)$ and they satisfy the system (22). If

$$\alpha = \int_0^a (\bar{f}_0(x) + \bar{f}_1(x)) \, dx < \infty, \tag{23}$$

then the semigroup $\{P(t)\}_{t\geq 0}$ has an invariant density $f_*(x, i)$ given by $f_*(x, i) = \alpha^{-1} \bar{f}_i(x)$, $i = 0, 1$, and, consequently, this semigroup is asymptotically stable.

If inequality (23) does not hold, then the semigroup $\{P(t)\}_{t\geq 0}$ has no invariant density. Indeed, if it has an invariant density, say $f_\diamond(x, i)$, then the semigroup $\{P(t)\}_{t\geq 0}$ should be asymptotically stable and, at the same time, if we extend the semigroup $\{P(t)\}_{t\geq 0}$ to nonnegative measurable functions then $\bar{f}(x, i)$ is a non-integrable stationary point of this semigroup. Let us define $f^n(x, i) = f_i^n(x) = \bar{f}_i(x) \wedge n$ and $c_n = \int_0^a (f_0^n(x) + f_1^n(x)) \, dx$. Then $\lim_{n \to \infty} c_n = \infty$ and

$$\liminf_{t \to \infty} P(t) \bar{f} \geq \lim_{t \to \infty} P(t) f^n = c_n f_\diamond,$$

for all $n \in \mathbb{N}$, which contradicts the fact that $P(t) \bar{f} = \bar{f}$. Thus, if inequality (23) does not hold, then the semigroup $\{P(t)\}_{t\geq 0}$ has no invariant density and according to Theorem 2 this semigroup is sweeping from compact subsets of E. Since $[\varepsilon, a] \times \{0, 1\}$ is a compact subset of E for each $\varepsilon \in (0, a)$, sweeping means here that

$$\lim_{t \to \infty} \int_{[0,\varepsilon] \times \{0,1\}} P(t) f(x, i) m(dx, di) = 1. \tag{24}$$

Let $p_i = q_{1-i}(0)/(q_0(0) + q_1(0))$. The numbers p_i can be interpreted as the mean time of staying in the state i if the population is small. One can check that condition (24) can be replaced by a stronger one: the measures μ_t given by $d\mu_t = P(t) f(x, i) m(dx, di)$ converge weakly to the measure $\mu^* = p_0 \delta_{(0,0)} + p_1 \delta_{(0,1)}$.

Now, we assume additionally, that $g_i'(0) \neq 0$ for $i = 0, 1$ and $g_1'(a) \neq 0$ and we check that stability and sweeping of the semigroup $\{P(t)\}_{t\geq 0}$ depends on the sign of the constant

$$r_0 = \frac{q_0(0)}{g_0'(0)} + \frac{q_1(0)}{g_1'(0)}.$$

It is easy to check that both functions $\bar{f}_i$ are integrable in each interval outside the neighborhood of 0. For any positive δ and sufficiently small x we have

$$(r_0 - \delta)x^{-1} \leq r(x) \leq (r_0 + \delta)x^{-1}.$$

It follows from these inequalities that there are some positive numbers c_1, c_2 such that

$$c_1 x^{-(r_0+\delta)} \leq e^{-R(x)} \leq c_2 x^{-(r_0-\delta)}$$

for x from a neighborhood of 0. Since $q_i(x) = q_i'(0)x + o(x)$, we obtain that inequality (23) holds when $r_0 < 0$ and that it does not hold when $r_0 > 0$. Observe that $r_0 > 0$ iff

$$q_0(0)q_1'(0) + q_1(0)q_0'(0) > 0.$$

This inequality can be rewritten in the following way

$$\lambda = p_0 q_0'(0) + p_1 q_0'(0) > 0. \tag{25}$$

In the initial model we have $\lambda = b - \mu$, where $b = p_0 b_0 + p_1 b_1$, and the number λ can be interpreted as the mean growth rate if the population is small. It explains why the population becomes extinct if $\lambda < 0$ and it survives if $\lambda > 0$.

5 Conclusions and summary

In this paper we have presented a number of biological models described by PDMPs. The models in Section 2 have been chosen in such a way as to show that biological processes can lead to various PDMPs, from a simple pure-jump Markov process with values in an Euclidean space to more advanced Markov processes connected with individual based models in Section 2.5. To study long-time behaviour of PDMPs we use the tool of stochastic semigroups on L^1-type spaces and their asymptotic properties. We provided several examples of such semigroups in Section 3. Theorems 1 and 2 give criteria about asymptotic stability and sweeping with respect to compact sets of such semigroups. Section 4 also contains examples of simple biological models which were used to illustrate advanced techniques required to check that the related stochastic semigroup is asymptotically stable or sweeping. Although these examples do not cover all models presented in Section 2, the authors believe that these results can be successfully applied to a wide range of models. In order to apply Theorem 2 one need to verify conditions (a) and (b), i.e., that the semigroup is irreducible and has some kernel minorant. As we have mentioned in Section 4 one can check (b) by using the Hörmander's condition. The final problem is to verify whether the semigroup is asymptotically stable if we already know that the alternative between asymptotic stability and sweeping holds. In more advanced models it might be very difficult to prove the existence of an invariant density in which case one can use the method of Hasminskiĭ function (see [20]) to exclude sweeping.

Our methods work quite well in the case of processes with switching dynamics or deterministic processes with jumps if the jumps are "non-degenerated". An example of a "degenerated" jump is when we jump from a large part of the phase space to one point. Such a "degenerated" jump appears in the neural activity model, when we jump from points $(x,0,1)$, $x > \theta - a_E$, to the point $(0,0,2)$. Also in this

model we have a "degenerated" jump from the point $(0, t_R, 2)$ to $(0, 0, 1)$ because $(0, 0, 1)$ is a stationary point of the related system of differential equations and the process visits point $(0, 0, 1)$ with positive probability. But even in this case one can induce a stochastic semigroup related to the PDMP if the measure m on the phase space is an atom measure at the point $(0, 0, 1)$ and the Lebesgue measure on the sets $\{(x, 0, 1) : x \in (-\infty, \theta)\}$ and $\{(0, y, 2) : y \in [0, t_R]\}$. We hope that it is possible to apply our technique to study the neural activity model and to prove that the stochastic semigroup related to this model is asymptotically stable if $a_E \lambda_E > a_I \lambda_I$. A priori our approach can not be applied to processes connected with individual based models from Section 2.5 where it would be more convenient to work with more general semigroups of probability measures. However, we are not aware of general results applicable in that example and further work is required here.

References

1. L. J. S. Allen, *An Introduction to Stochastic Processes with Applications to Biology*, Chapman Hall/CRC Press, Boca Raton, 2010.
2. Y. Bakhtin and T. Hurth, Invariant densities for dynamical system with random switching, *Nonlinearity* **25** (2012), 2937–2952.
3. A. Bobrowski, T. Lipniacki, K. Pichór, and 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.
4. M. H. A. Davis, Piecewise-deterministic Markov processes: a general class of nondiffusion stochastic models, *J. Roy. Statist. Soc. Ser.* B **46** (1984), 353–388.
5. M. H. A. Davis, *Markov models and optimization*, Monographs on Statistics and Applied Probability, vol. 49, Chapman & Hall, London, 1993.
6. S. N. Evans, Stochastic billiards on general tables, *Ann. Appl. Probab.* **11** (2001), 419–437.
7. S. Goldstein, On diffusion by discontinuous movements and on the telegraph equation, *Quart. J. Mech. Appl. Math.* **4** (1951), 129–156.
8. T. Hillen, K. P. Hadeler, Hyperbolic systems and transport equations in mathematical biology, in *Analysis and Numerics for Conservation Laws*, G. Warnecke (ed), pp. 257–279, Springer-Verlag, Berlin Heidelberg 2005.
9. J. Hu, W. C. Wu, S. S. Sastry, Modeling subtilin production in bacillus subtilis using stochastic hybrid systems, in *Hybrid Systems: Computation and Control*, R. Alur and G. J. Pappas (eds.), LNCS vol. 2993, pp. 417–431. Springer-Verlag, Berlin 2004.
10. M. Kac, A stochastic model related to the telegrapher's equation, *Rocky Mountain J. Math.* **4** (1974), 497–509.
11. J. Kisyński, On M. Kac's probabilistic formula for the solution of the telegraphist's equation, *Ann. Polon. Math.* **29** (1974), 259–272.
12. A. Lasota and M.C. Mackey, *Chaos, Fractals and Noise. Stochastic Aspects of Dynamics*, Springer Applied Mathematical Sciences **97**, New York, 1994.
13. T. Lipniacki, P. Paszek, A. Marciniak-Czochra, A.R. Brasier, and M. Kimmel, Transcriptional stochasticity in gene expression, *J. Theor. Biol.* **238** (2006), 348–367.
14. M.C. Mackey and M. Tyran-Kamińska, Dynamics and density evolution in piecewise deterministic growth processes, *Ann. Polon. Math.* **94** (2008), 111–129.
15. A. Murray and T. Hunt, *The Cell Cycle: An Introduction*, Oxford University Press, Oxford, 1993.
16. H. G. Othmer, S. R. Dunbar, and W. Alt, *Models of dispersal in biological systems*, J. Math. Biol. **26** (1988), 263–298.

17. K. Pichór and R. Rudnicki, Continuous Markov semigroups and stability of transport equations, *J. Math. Anal. Appl.* **249** (2000), 668–685.
18. S.I. Rubinow, A maturity time representation for cell populations, *Biophy. J.* **8** (1968), 1055–1073.
19. R. Rudnicki, On asymptotic stability and sweeping for Markov operators, *Bull. Pol. Ac.: Math.* **43** (1995), 245–262.
20. R. Rudnicki, K. Pichór, M. Tyran-Kamińska, Markov semigroups and their applications, in: *Dynamics of Dissipation*, P. Garbaczewski and R. Olkiewicz (eds.), Lecture Notes in Physics, 597, Springer, Berlin, 2002, 215-238.
21. R. Rudnicki, J. Tiuryn, and D. Wójtowicz, A model for the evolution of paralog families in genomes, *J. Math. Biology* **53**, 759–770, (2006).
22. R. Rudnicki and J. Tiuryn, Size distribution of gene families in a genome, *Math. Models Methods Appl. Sci.* **24** (2014), 697–717.
23. R. Rudnicki and R. Wieczorek, Fragmentation – coagulation models of phytoplankton, *Bull. Pol. Acad. Sci. Math.* **54** (2006), 175–191.
24. R. B. Stein, A theoretical analysis of neuronal variability, *Biophys. J.* **5** (1965), 173–194.
25. R. B. Stein, Some models of neuronal variability, *Biophys. J.* **7** (1967), 37–68.
26. D. W. Stroock, Some stochastic processes which arise from a model of the motion of a bacterium, *Z. Wahrscheinlichkeitstheorie verw. Gebiete* **28** (1974), 305–315.
27. M. Tyran-Kamińska, Substochastic semigroups and densities of piecewise deterministic Markov processes, *J. Math. Anal. Appl.* **357** (2009), 385–402.
28. M. Tyran-Kamińska, Ergodic theorems and perturbations of contraction semigroups, *Studia Math.* **195** (2009), 147–155.
29. J. Tyrcha, Asymptotic stability in a generalized probabilistic/deterministic model of the cell cycle, *J. Math. Biology* **26** (1988), 465–475.