Piecewise deterministic Markov processes, applications in biology

Romain Yvinec

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R. Yvinec

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1 Introduction

We deal here with mathematical models used in biology that involved deterministic continuous dynamical systems (mostly: system of Ordinary Differential Equations) perturbed by random discrete events in time. Such perturbation may either take the form of a discontinuous jump, or a change in the rule of

the continuous motion (or both). This large class of non diffusion stochastic models has been introduced in the literature and rigorously defined (from the probabilistic perspective) by [Davis, 1984, Davis, 1993] (see also the more recent work by [Jacobsen, 2006]). Applications to biology date back at least to [Lasota et al., 1992]. We emphasize that in this latter work a rather deterministic approach is taken (semigroup theory and evolution equations on densities). Note also that in a more applied literature, such models are usually referred as stochastic hybrid models [Kouretas et al., 2006].

The aim of this note is to present some examples of Piecewise Deterministic Markov Processes (PDMP) applied to biological modeling, and to give an informal description of the probabilistic objects and techniques used for the study of such models for non-probabilist. We will try to convince the reader to the relative simplicity to define such model. In particular, we will detail the pathwise definition of PDMP, widely used for stochastic simulation of trajectories of the process. We will also give informal martingale properties and generator-definition of PDMP, as those are very useful both for concise definition of PDMP and for mathematical study (in particular long time behavior). We will finally highlight the link with semigroup techniques and evolution equations on densities, which should be more familiar for the reader used to partial differential equations.

The examples taken from the literature include cell-cycle model (or growth-fragmentation), bacteria movement (or random intermittent search), ion channels in neuron models (Gating model), integrate and fire models for excitable cells, gene expression models, microtubules growth and active transport inside cells. Most of the examples are taken from [Bressloff, 2014, Malrieu, 2014, Lasota et al., 1992]. An important class of models, that contains almost all examples, concern biochemical reaction network models. Although traditionally represented as system of ordinary differential equations, stochastic version have been recently widely used in systems biology, in order to take into account the observed experimental variability in cellular and molecular biology. We will explain how PDMP then naturally arise as (computational and theoretical) simplification of stochastic chemical reaction network.

2 Theoretical foundations: Poisson processes

The basic elements of a PDMP is a time-continuous deterministic system and a discrete random process. For the latter, we need a mathematical framework that allows to describe the time repartition of discrete events and to "count" them.

Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a probability space with the sample space a non-empty set, $\mathcal{F}$ a σ-algebra of subsets of Ω , and $\mathbb{P}$ a probability measure on $\mathcal{F}$. Definitions and properties in this section are taken from standard textbooks, see for instance [Bremaud, 1981, Jacobsen, 2006, Björk, 2005].

2.1 The Poisson process

We start by the definition of a simple Point process, and its associated counting process.

Definition 1 (Point process)**.** A point process is a sequence $\mathcal{T} = (T_n)_{n\geqslant 1}$ of $\mathbb{R}^+$-valued random variables defined on $(\Omega, \mathcal{F}, \mathbb{P})$ such that

- $\mathbb{P}\big\{0 < T_1 \leqslant T_2 \leqslant \dots\big\} = 1\,,$
- $\mathbb{P}\big\{T_n < T_{n+1}, T_n < \infty\big\} = \mathbb{P}\big\{T_n < \infty\big\}$, for all $n \geqslant 1\,,$
- $\mathbb{P}\big\{\lim_{n\to\infty} T_n = \infty\big\} = 1\,.$

Thus, a point process is an almost surely increasing sequence of strictly positive, possibly infinite random variables, strictly increasing as long as they are finite and with almost sure limit ∞. The interpretation of T_n is that, if finite, it is the timepoint at which the nth recording of an event takes place with less than n events occurring altogether (on the time axis $\mathbb{R}^+$) if $T_n = \infty$. By definition, no event can happen at time 0.

Definition 2 (Counting process)**.** A random process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a counting process if it satisfies the following conditions.

- The trajectories of $\mathcal{N}$ are, with probability one, right continuous and piecewise constant.
- The process starts at zero, $N_0 = 0$.
- For each t, $\Delta N_t = 0$ or $\Delta N_t = 1$ with probability one. Here ΔN_t denotes the jump size of N at time t, or more formally

$$\Delta N_t = N_t - N_{t^-}\,.$$

In more pedestrian terms, the process $\mathcal{N}$ starts at 0 and stays at the level 0 until some random time T_1 when it jumps to $N_{T_1} = 1$. It then stays at level 1 until another random time $T_2 > T_1$ when it jumps to the value $N_{T_2} = 2$ etc. We will refer to the random times $\mathcal{T} = (T_n)_{n\geqslant 1}$ as the jump (or event) times of $\mathcal{N}$. It should be clear at this point that $\mathcal{T}$ is a point process, and that both $\mathcal{N}$ and $\mathcal{T}$ carry the same information and are related by

$$N_t = \sum_{n\geqslant 1} \mathbf{1}_{T_n \leqslant t}\,.$$

For instance,

$$\Big(N_t \geqslant n\Big) \Leftrightarrow \Big(T_n \leqslant t\Big)\,.$$

Remark 1. A third view point (not considered here) is to define a discrete random measure. Although less intuitive, this is the right way to generalize it to counting process (measure) on arbitrary space (useful for individual based modeling for instance).

We now turn to the definition of a Poisson process. There are three equivalent definitions that we now give. The understanding of all three definitions is important to get a "feeling" of what is a Poisson process.

⟨def:inf⟩ **Definition 3** (The infinitesimal definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a Poisson process (of rate $\lambda > 0$) if:

- The process has independent increments, i.e., the number of events in disjoint intervals are independent random variables

$$\forall\, t_0 < t_1 < \ldots < t_n,\ \Big(N_{t_k} - N_{t_{k-1}}\Big)_{1\leqslant k\leqslant n} \text{ are independent.}$$

- The process has stationary increments, i.e.

$$\forall\, t, h > 0,\ \text{the law of } \Big(N_{t+h} - N_t\Big) \text{ is independent of } t\,.$$

- Only one event can occur at a time. More precisely, there is $\lambda > 0$ such that

$$\mathbb{P}\big\{N_h = 1\big\} = \lambda h + o(h),\ \mathbb{P}\big\{N_h > 1\big\} = o(h)\,.$$

⟨def:ax⟩ **Definition 4** (The axiomatic definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a Poisson process (of rate $\lambda > 0$) if:

- The process has independent increments, i.e., the number of events in disjoint intervals are independent random variables

$$\forall\, t_0 < t_1 < \ldots < t_n,\ \Big(N_{t_k} - N_{t_{k-1}}\Big)_{1\leqslant k\leqslant n} \text{ are independent.}$$

- The number of events in any time interval of length h is Poisson distributed with mean λh, i.e., for all $t, h > 0$:

$$\mathbb{P}\big\{N_{t+h} - N_t = k\big\} = e^{-\lambda h}\frac{(\lambda h)^k}{k!}$$

⟨def:cons⟩ **Definition 5** (The constructive definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a Poisson process (of rate $\lambda > 0$) if:

$$N_t = \sum_{n\geqslant 1} \mathbf{1}_{T_n\leqslant t}\,,$$

for a sequence (T_n) having independent identically distributed increments $\Delta T_n = T_n - T_{n-1}$, with an exponential distribution of parameter λ, i.e. for all $n \geqslant 1$

$$\mathbb{P}\big\{\Delta T_n > t\big\} = e^{-\lambda t}\,.$$

Equivalence of Definition. Def 3 ⇒ Def 4: One way to prove that $N_t \sim Po(\lambda t)$ is by the probability generating function:

$$G_{N_t}(z) = \sum_{k\geqslant 0} \mathbb{P}\big\{N_t = k\big\} z^k.$$

Since $N_{t+h} = N_t + (N_{t+h} - N_t)$, by independent increments, $G_{N_{t+h}} = G_{N_t} G_{N_{t+h}-N_t}$. Then

$$\frac{dG_{N_t}}{dt} = \lim_{h\to 0} \frac{G_{N_{t+h}} - G_{N_t}}{h} = \lim_{h\to 0} \frac{G_{N_t}\Big[G_{N_{t+h}-N_t} - 1\Big]}{h}$$

By the definition 3,

$$G_{N_{t+h}-N_t} = 1 - \lambda h + \lambda h z + o(h)\,,$$

so that

$$\frac{dG_{N_t}}{dt} = \lambda(z-1)G_{N_t}\,.$$

Hence $G_{N_t}(z) = e^{\lambda t(z-1)}$, which is the p.g.f of a Poisson random variable.

Remark 2. A different proof consider subdividing $[0,t]$ in n ($n \to \infty$) disjoints intervals and use the Poisson limit theorem, e.g.

$$\lim_{n\to\infty} Bin(n,\theta_n)(\{k\}) = Po(\lambda t)(\{k\})\,,$$

if $n\theta_n \to \lambda t$.

Def 4 $\Rightarrow$ Def 5: The distribution of the first jump time follows from

$$\mathbb{P}\big\{T_1 > t\big\} = \mathbb{P}\big\{N_t = 0\big\} = e^{-\lambda t}\,.$$

The rest follows by the independence and stationarity of the increments. Specifically, we show by induction that

$$\mathbb{P}\big\{\Delta T_n > x \mid \Delta T_1 = x_1\,, \Delta T_2 = x_2\,, \dots \Delta T_{n-1} = x_{n-1}\big\} = e^{-\lambda x}\,.$$

To prove that, we use that we can rewrite the event $\{\Delta T_1 = x_1\,, \Delta T_2 = x_2\,, \dots \Delta T_{n-1} = x_{n-1}\} = \{T_1 = t_1\,, T_2 = t_2\,, \dots T_{n-1} = t_{n-1}\}$ with $t_i = \sum_{k=1}^{i} x_k$, and the latter may be re-written as increments of $\mathcal{N}$.
Def 5 $\Rightarrow$ Def 3 : it only remains to show the independence of the increments. By the lack of memory property of the exponential, we can prove that $Z(t) = \Big(T_{N_t+1} - t, T_{N_t+2}, T_{N_t+3}, \dots\Big)$ is independent of $\Big(N_t, T_1, \dots, T_{N_t}\Big)$ and distributed as $Z(0) = \Big(T_n\Big)_{n\geqslant 1}$. Now, since $(N_{t+h} - N_t)_{t\geqslant 0} = H(Z(t))$ for some measurable function H, and all t, this implies the independence of N_t and $(N_{t+h} - N_t)_{t\geqslant 0}$. □

The main crucial property of the Poisson process may be summarized in this formula

$$\mathbb{P}\big\{N_{t+h} - N_t = 1 \mid (N_s)_{s\leqslant t}\big\} = \mathbb{P}\big\{N_{t+h} - N_t = 1\big\} = \lambda h e^{-\lambda h}\,.$$

As the jumps of $\mathcal{N}$ are 0 or 1, this may formally written as

$$\mathbb{E}\big[dN_t \mid (N_s)_{s\leqslant t}\big] = \lambda dt$$

Hence λ **is the expected number of jumps per unit of time**. Let $\mathcal{F}_t$ the σ-algebra generated by $(N_s)_{s\leqslant t}$, and define

$$M_t = N_t - \lambda t\,.$$

We have the Martingale property

Proposition 1. *For all s,t,*

$$\mathbb{E}\big[M_{t+s} \mid \mathcal{F}_t\big] = M_t\,.$$

Proof. The proof is trivial using the independence of the increments and the law of the increments, we have

$$\mathbb{E}\big[N_{t+s} - N_t \mid \mathcal{F}_t\big] = \mathbb{E}\big[N_{t+s} - N_t\big] = \lambda s\,.$$

□

We finish by stating some standard properties of Poisson Processes

Proposition 2.

- *If $\mathcal{N}_1$,$\mathcal{N}_2$ are independent Poisson processes of rate resp. λ_1 and λ_2, then $\mathcal{N}$ defined by*

$$N(t) = N_1(t) + N_2(t)$$

is a Poisson process of intensity $\lambda = \lambda_1 + \lambda_2$.

- *Let $\mathcal{N}$ a Poisson process of intensity λ. Suppose that $\mathcal{N}_1$ and $\mathcal{N}_2$ are counting process constructed as follows. For each arrival of $\mathcal{N}$, the first process $\mathcal{N}_1$ is augmented of 1 with probability p, and the second $\mathcal{N}_2$ is augmented of 1 with probability $(1-p)$, and so independently of the previous arrival. Then $\mathcal{N}_1$ and $\mathcal{N}_2$ are independent Poisson processes of rate resp. $p\lambda$ and $(1-p)\lambda$.*

- *if $\mathcal{N}$ a Poisson process of intensity 1, then $\mathcal{N}_\lambda$ defined by*

$$N_\lambda(t) = N(\lambda t)\,,$$

is a Poisson process of intensity λ.

- *Given that $N_t = n$, the n jump times $T_1, \ldots, T_n$ are distributed as the order statistics corresponding to n independent random variables uniformly distributed on $(0, t)$.*

2.2 Non homogeneous Poisson process

Again, we state three equivalent definitions

?⟨def:inf_inh⟩? **Definition 6** (The infinitesimal definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a non-homogeneous Poisson process of rate function $\lambda(t)$ if:

- The process has independent increments.
- For all t, h,

$$\mathbb{P}\big\{N_{t+h} - N_t = 1\big\} = \lambda(t)h + o(h),\ \mathbb{P}\big\{N_{t+h} - N_t > 1\big\} = o(h)\,.$$

?⟨def:ax_inh⟩? **Definition 7** (The axiomatic definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a non-homogeneous Poisson process of rate function $\lambda(t)$ if:

- The process has independent increments.
- The number of events in any time interval $(t, t+h]$ is Poisson distributed with mean $\int_t^{t+h} \lambda(s)ds$, e.g., for all $t, h > 0$:

$$\mathbb{P}\big\{N_{t+h} - N_t = k\big\} = e^{-(m(t+h)-m(t))}\frac{(m(t+h)-m(t))^k}{k!}\,,$$

where $m(t) = \int_0^t \lambda(s)ds$.

?⟨def:cons_inh⟩? **Definition 8** (The constructive definition)**.** A counting process $\mathcal{N} = \{N_t; t \in \mathbb{R}^+\}$ is a non-homogeneous Poisson process of rate function $\lambda(t)$ if there exists a standard Poisson process $\mathcal{Y}$ (rate = 1) such that:

$$N_t = Y\Big(\int_0^t \lambda(s)ds\Big)\,.$$

The latter definition deserves a particular comment, as it will be important in the next. A direct calculus shows that $Y\Big(\int_0^{t+h}\lambda(s)ds\Big) - Y\Big(\int_0^{t}\lambda(s)ds\Big)$ is indeed distributed as a Poisson distribution of mean $\int_t^{t+h}\lambda(s)ds$. Conversely, define

$$m^{-1}(t) = \inf\{s \geqslant 0 : m(s) \geqslant t\}\,,\ t \geqslant 0\,.$$

Then we define $\mathcal{Y}$ by $Y(t) := N(m^{-1}(t))$. Then

$$Y_t - Y_s = N(m^{-1}(t)) - N(m^{-1}(s)) \overset{(d)}{=} Po\Big(m(m^{-1}(t)) - m(m^{-1}(s))\Big) = Po(t-s)\,.$$

Note that the non-homogeneous Poisson process satisfy the survival relation (used in many deterministic models, such as renewal population dynamics)

$$\mathbb{P}\big\{N_t = 0\big\} = exp\Big(-\int_0^t \lambda(s)ds\Big)\,.$$

Furthermore, with

$$M_t = N_t - \int_0^t \lambda(s)ds\,,$$

we still have the Martingale property

Proposition 3. *For all s, t,*

$$\mathbb{E}\big[M_{t+s} \mid \mathcal{F}_t\big] = M_t\,.$$

2.3 Stochastic equation driven by a Poisson process

⟨ssec:stocheq⟩ We are already able at this point to define stochastic equations driven by Poisson processes, which are widely used to simulate stochastic chemical reactions networks. Let $\mathcal{Y}$ be a standard Poisson process, and let us consider the equation

$$N_t = N_0 + Y\Big(\int_0^t \lambda(N_s)ds\Big)\,, \tag{1}$$ eq:stocheq

where λ is such that $\int_0^t \lambda(N(s))ds < \infty$. It should be clear that such solution is still a counting process (modulo the initial condition). Hence to prove existence, we only need to know the jump times of $\mathcal{N}$. We will give an explicit construction with the help of the jump times of $\mathcal{Y}$.

Proposition 4. *Let $(\tau_n)_n$ be the jump times of $\mathcal{Y}$, then the unique solution of (1) is*

$$N_t = \sum_{n\geqslant 1} \mathbf{1}_{T_n \leqslant t}\,,$$

where, for all $n \geqslant 1$ ($\tau_0 = T_0 = 0$)

$$T_n = T_{n-1} + \frac{\tau_n - \tau_{n-1}}{\lambda(N_0 + n - 1)}\,.$$

Note that we still have the survival relation, for the law of next jump. At time t, the next jump time T follows

$$\mathbb{P}\{T > t+s \mid \mathcal{F}_t\} = exp\Big(-\int_t^{t+s} \lambda(N(u))du\Big) = exp\Big(-\lambda(N(t))s\Big)\,.$$

And the Martingale property now reads as follows. With

$$M_t = N_t - \int_0^t \lambda(N_s)ds\,,$$

we still have the Martingale property

Proposition 5. *For all s, t,*

$$\mathbb{E}\big[M_{t+s} \mid \mathcal{F}_t\big] = M_t\,.$$

We are already able to modify such construction to include a continuous dynamical system between jumps, hence to have a constructive definition of a PDMP. We postpone such construction as the generator characterization will also prove to be useful in the next.

2.4 Generator

For the homogeneous Poisson process, we have seen that $N_t - \lambda t$ is a Martingale. This is actually a characterization among the counting process (Watanabe theorem). A further even more general characterization among the Markov processes is provided by the generator.

Definition 9 (Generator)**.** For any compactly supported function $f : \mathbb{N} -> \mathbb{R}^+$, we define

$$Af(n) = \lambda\Big(f(n+1) - f(n)\Big)\,.$$

We now have

⟨prop:gene⟩ **Proposition 6.** *Let N be a homogeneous Poisson process of rate λ. Then, for any compactly supported function f,*

$$f(N(t)) - f(N(0)) - \int_0^t Af(N(s))ds \tag{2}$$ eq:gene

is a $\mathcal{F}_t$-Martingale. This holds as well for any function f such that $\mathbb{E}\big[f(N(t))\big] < \infty$, $\mathbb{E}\big[Af(N(t))\big] < \infty$, for all $t \geqslant 0$.

The sample path of $\mathcal{N}$ $(t \mapsto N_t(w))$ are piecewise continuous and have finite variation. As such, we may define a Lebesgue-Stieljes integral of bounded function on finite time integral against the measure $(dN_t(w))_t$. Note that such measure may formally be represented as

$$\sum_{k\geqslant 1} \delta_{T_k(w)}(ds)\,,$$

where (T_k) is the sequence of jump times associated to the Poisson process. As an important first step, we state the

Proposition 7 (Itô Lemma)**.** *Let N be a homogeneous Poisson process of rate λ. Then, for any measurable function f,*

$$f(N(t)) = f(N(0)) + \int_0^t \Big(f(N(s^-)+1) - f(N(s^-))\Big) dN(s)\,.$$

Proof. A simple calculus yields

$$\begin{aligned} f(N(t)) &= f(N(0)) + \sum_{k=1}^{N(t)} (f(k) - f(k-1)) \\ &= f(N(0)) + \sum_{k=1}^{N(t)} (f(N(T_k)) - f(N(T_{k-1}))) \\ &= f(N(0)) + \sum_{k=1}^{N(t)} (f(N(T_k^-)+1)) - f(N(T_k^-))) \\ &= f(N(0)) + \int_0^t \Big(f(N(s^-)+1) - f(N(s^-))\Big) dN(s)\,. \end{aligned}$$

□

Exercise 1. Let N a counting process and $t \mapsto \lambda_t$ a deterministic process such that

$$M_t = N_t - \int_0^t \lambda_s ds\,,$$

is a $\mathcal{F}_t$-Martingale. Shows that for all $t \geqslant s$,

$$\mathbb{E}\big[e^{iu(N_t - N_s)} \mid \mathcal{F}_s\big] = exp\Big\{(m(t) - m(s))(e^{iu} - 1)\Big\}\,.$$

[Hint: for $s = 0$, use Itô with $f(N_t) = e^{iu(N_t)}$.]
Deduce the Watanabe characterization: N is a Poisson process of intensity λ_t.

Proof of proposition 6. We conclude using the fact that $M(t) = N(t) - \lambda t$ is a Martingale, so that

$$\begin{aligned} f(N(t)) &= f(N(0)) + \int_0^t \Big(f(N(s^-)+1) - f(N(s^-))\Big) dN(s) \\ &= f(N(0)) + \int_0^t Af(N(s))ds + \int_0^t \Big(f(N(s^-)+1) - f(N(s^-))\Big) dM(s)\,, \end{aligned}$$

and we admit (long argument) that $\int_0^t \Big(f(N(s^-)+1) - f(N(s^-))\Big) dM(s)$ is a Martingale. □

As for the Watanabe characterization, knowing that $N(t)$ satisfies the so-called martingale problem, e.g. equation (2) for a sufficiently large class of test functions, will characterize the stochastic process $N(t)$, among the Markov processes.

Note that a differential version of equation (2) reads

$$\mathbb{E}\big[df(N_t) \mid (N_s)_{s \leqslant t}\big] = \mathbb{E}\big[Af(N(t))\big]dt\,.$$

And noting $\mathbb{E}_{s,n}\big[f(t,N_t)\big] = \mathbb{E}\big[f(t,N_t) \mid N_s = n\big]$, we can show that

$$Af(t,n) = \lim_{h\downarrow 0} \mathbb{E}_{t,n}\big[f(t+h, N_{t+h}) - f(t,N_t)\big]\,.$$

We conclude this section by giving the generator of the solution of the first stochastic equation we encountered in subsection 2.3.

Proposition 8. *The generator of the solution of equation (1) is, for any compactly supported function f,*

$$Af(n) = \lambda(n)\Big(f(n+1) - f(n)\Big)\,.$$

2.5 Chapman-Kolmogorov equation

A first consequence of the generator is to give any moment equation. Indeed, if A is the generator of $\mathcal{N}$, then, for any test functions

$$\mathbb{E}\big[f(N(t))\big] = \mathbb{E}\big[f(N(0))\big] + \int_0^t \mathbb{E}\big[Af(N(s))\big]ds\,.$$

In particular, using $f(k) = \mathbf{1}_{k=n}(k)$, we obtain an equation for $\mathbb{E}\big[f(N(t))\big] = \mathbb{P}\big\{N(t) = n\big\} =: p(n,t)$. Then, for the solution of equation (1),

$$\frac{dp(n,t)}{dt} = \lambda(n-1)p(n-1,t) - \lambda(n,t)p(n,t)\,,$$

for all $n \geqslant 0$ (with $p(-1,t) \equiv 0$).

Exercise 2. Let $\mathcal{N}$ the solution of equation (1). Calculate $\frac{d\mathbb{E}\left[N(t)\right]}{dt}$ and $\frac{d\mathbb{E}\left[N(t)^2\right]}{dt}$ by three different manners. In which case do you obtain closed equations?

3 PDMP

We now use our knowledge on stochastic equation driven by Poisson processes to define Piecewise Deterministic Markov processes.

3.1 One ode and one Poisson process

We will prove

Proposition 9. *Assume the ODE*

$$\left\{\begin{array}{rcl} \dfrac{dX_t}{dt} &=& \mu(X_t)\,, \\ X_0 &=& x_0\,, \end{array}\right.$$

has a unique global solution for every choice of x_0, and let $\beta : \mathbb{R} \to \mathbb{R}$ be an arbitrary chosen function, and $\mathcal{N}$ a Poisson process of intensity λ. Then the SDE

$$\left\{\begin{array}{rcl} dX_t &=& \mu(X_t)dt + \beta(X_{t^-})dN_t\,, \\ X_0 &=& x_0\,, \end{array}\right. \tag{3}$$ eq:sde1

has a unique global solution.

Proof. We have the following concrete algorithm.

- Denote the jump times of $\mathcal{N}$ by T_1 , T_2, ...
- For every fixed ω, solve the ODE

$$\begin{cases} \dfrac{dX_t}{dt} &= \mu(X_t)\,, \\ X_0 &= x_0\,, \end{cases}$$

  on $[0, T_1)$. In particular we have determined the value of $X_{T_1^-}$.
- Calculate X_{T_1} by the formula

$$X_{T_1} = X_{T_1^-} + \beta(X_{T_1^-})\,.$$

- Given $X_{T_1} = x_1$ solve the ODE

$$\begin{cases} \dfrac{dX_t}{dt} &= \mu(X_t)\,, \\ X_{T_1} &= x_1\,, \end{cases}$$

  on $[T_1, T_2)$, and so on ...

□

We give without proof (similar as proposition 6) the generator of the solution $X(t)$ of equation (3):

$$Af(x) = \mu(x)f'(x) + \lambda\Big(f(x + \beta(x)) - f(x)\Big)\,.$$

We can give a similar construction of solution of SDE when the counting process has now a state-dependent intensity. Using the time change representation, we prove

⟨prop:sde_statedep⟩ **Proposition 10.** *Assume the ODE*

$$\begin{cases} \dfrac{dX_t}{dt} &= \mu(X_t)\,, \\ X_0 &= x_0\,, \end{cases}$$

has a unique global solution for every choice of x_0, and let $\beta : \mathbb{R} \to \mathbb{R}$ be an arbitrary chosen function, $\mathcal{Y}$ a standard Poisson process, and $\lambda : \mathbb{R} \to \mathbb{R}^+$ a measurable locally integrable function, with λ/μ locally integrable too. Then the SDE

$$X_t = x_0 + \int_0^t \mu(X_s)ds + Y\Big(\int_0^t \lambda(X_s)ds\Big)\,, \tag{4}$$ eq:sde2

has a unique maximum solution on $[0, \tau_\infty)$ for a given τ_∞.

Proof. The proof is similar, we simply need to adapt the times of the jumps according to the time change. We have the following concrete algorithm.

- Denote the jump times of $\mathcal{Y}$ by T_1 , T_2, ...

- For every fixed ω, solve the ODE

$$\left\{ \begin{array}{rcl} \dfrac{dX_t}{dt} & = & \mu(X_t)\,, \\ X_0 & = & x_0\,, \end{array} \right.$$

on $[0, \tau_1)$, where τ_1 is given by

$$\tau_1 = \inf\{t > 0 : \int_0^t \lambda(X_s)ds \geqslant T_1\}\,.$$

If $\tau_1 = \infty$, we are done. Else, we have determined the value of $X_{\tau_1^-}$.

- Calculate X_{τ_1} by the formula

$$X_{\tau_1} = X_{\tau_1^-} + 1\,.$$

- Given $X_{\tau_1} = x_1$ solve the ODE

$$\left\{ \begin{array}{rcl} \dfrac{dX_t}{dt} & = & \mu(X_t)\,, \\ X_{\tau_1} & = & x_1\,, \end{array} \right.$$

on $[\tau_1, \tau_2)$, where τ_2 is given by

$$\tau_2 = \inf\{t > \tau_1 : \int_{\tau_1}^{\tau_2} \lambda(X_s)ds \geqslant T_2 - T1\}\,.$$

and so on ... The solution is constructed up to $\tau_\infty = \lim_n \tau_n$ (which may or may not be infinite).

□

The generator of the solution $X(t)$ of equation (4) is given by:

$$Af(x) = \mu(x)f'(x) + \lambda(x)\Big(f(x+1) - f(x)\Big)\,.$$

Remark 3. Note that the first jump time τ_1 in the above proof follows

$$\mathbb{P}\{\tau_1 \geqslant t\} = exp\Big(-\int_0^t \lambda(X_s)ds\Big) = exp\Big(-\int_{x_0}^{x_t} \frac{\lambda(x)}{\mu(x)}dx\Big)\,.$$

3.2 General PDMP

To define a general PDMP, following [Davis, 1984], we only need to let arbitrary jumps occurring at the discrete event, and to authorize to change the dynamical system as well. This is simply done by adding a discrete variable to the state space, that will keep track of the particular dynamical system we follow, and by choosing a transition measure that will dictate the jump law. More precisely, let I be a countable set, $d : I \to \mathbb{N}$ and for each $i \in I$, M_i an open subset of $\mathbb{R}^{d(i)}$. The state-space E is

$$E = \bigcup_{i \in I} M_i = \{z = (x, i); i \in I, x \in M_i\}\,.$$

Let $(E, \mathcal{E})$ the natural Borel space associated to E. The PDMP is determined by the following objects

- Vector fields $(H_i, i \in I)$ such that for all $i \in I$, all $x_0 \in M_i$, there is a unique global solution in M_i of

$$\left\{ \begin{array}{rcl} \dfrac{dX_t}{dt} & = & H_i(X_t)\,, \\ X_0 & = & x_0\,, \end{array} \right. \tag{5}$$ eq:ode_pdmp

- A measurable function $\lambda : E \to \mathbb{R}^+$, such that for all $z = (i, x_0) \in E$, the function $t \mapsto \lambda(X_t)$ is locally integrable along the solution of equation (5)
- A transition measure $Q : \mathcal{E} \times E \to [0, 1]$, such that $Q(A; z)$ is a measurable function of $z \in E$ for each fixed $A \in \mathcal{E}$, and is a probability measure on $(E, \mathcal{E})$ for each fixed $z \in E$.

A unique global solution is constructed as in the proof of proposition 10. The only needed changes concern the calculus of Z_{τ_1} from $Z_{\tau_1^-}$. The post jump location Z_{τ_1} is selected independently of τ_1, with distribution $Q(\cdot\,; Z_{\tau_1^-})$.

The generator of the general PDMP is given by:

$$Af(i,x) = H_i(x)\nabla_x f(i,x) + \lambda(i,x)\int_E \Big(f(j,y) - f(i,x)\Big)Q(dj \times dy; (i,x))\,.$$

If Q has a density, the Chapman-Kolmogorov equation are given by

$$\frac{\partial p(i,x,t)}{\partial t} + \frac{\partial H_i(x)p(i,x,t)}{\partial x} = -\lambda(i,x)p(i,x,t) + \int_E \lambda(j,y)p(j,y,t)Q((i,x);(j,y))djdy\,.$$

4 Numerical algorithms

We give below different algorithms that can be useful in various situation, and that are directly related to properties on Poisson process we just saw.

4.1 How to simulate several Poisson processes

Suppose one wish to simulate the following system of SDE (any Markovian discrete chemical reaction network)

$$X_i(t) = X_i(0) + \sum_{l=1}^{L} \nu_{il} Y_l\Big(\int_0^t \lambda_l(X(s))ds\Big)\,, \tag{6}$$ eq:next

where $(Y_l)_{1 \leqslant l \leqslant L}$ are independent standard Poisson processes. By the splitting properties of Poisson processes, the law of the solution of equation (6) is the same as the solution of

$$\left\{ \begin{array}{rcl} N(t) & = & Y\Big(\displaystyle\int_0^t \lambda(X(s))ds\Big)\,, \\ X_i(t) & = & X_i(0) + \displaystyle\sum_{l=1}^{L} \nu_{il} \int_0^t \mathbf{1}_{q_{l-1}(X(s^-)),q_l(X(s^-))}(\xi_{N(s^-)})dN(s)\,. \end{array} \right. \tag{7}$$ eq:gillespi

where $\lambda(x) = \sum_{l=1}^{L} \lambda_l(x)$, $q_l(x) = \sum_{i=1}^{l} \lambda_i(x)/\lambda(x)$, Y is a standard Poisson process, and $\xi_0, \xi_1, \ldots$ are independent uniform $[0, 1]$ random variable, independent of Y.

Both equivalent formulations equation (6) and (7) actually suggest two different algorithms, known in the literature as the next reaction method [Gibson and Bruck, 2000] and the Gillespie [Gillespie, 1977] (or stochastic simulation algorithm, ssa) respectively.

The Gillespie algorithm, corresponding to equations (7) can be described as follows:

- At each step, draw two random uniform $[0,1]$ independent numbers u, q.
- The next time step is given by $\Delta T_i = -1/\lambda(X(T_{i-1}))\log(u)$.
- The reaction is chosen according to $l = \min\{i \geqslant 1 : \sum_{j=1}^{i-1} \lambda_i(x)/\lambda(x) \leqslant \sum_{j=1}^{i} \lambda_i(x)/\lambda(x)\}$.
- Update X accordingly, that is $X_i = X_i + \nu_{il}$.

The next reaction method, corresponding to equations (6) can be described as follows:

- At time 0, for all $l = 1..L$, draw a random uniform $[0,1]$ independent number u_l, and calculate $T_l = -1/\lambda_l(X(0))\log(u_l)$.
- At each step, let j the index of the smallest T_l. Set $t = T_j$.
- Update X accordingly, that is $X_i = X_i + \nu_{ij}$.
- For any reaction $k \neq j$ whose intensities is modified by reaction j, update the new intensity $\lambda'_k = \lambda_k(X(t))$ (and keep the old λ_k). Set $T_k = t + (\lambda_k/\lambda'_k)(T_k - t)$. Forget the old intensity, e.g. $\lambda_k = \lambda'_k$.
- For reaction j, draw a random uniform $[0,1]$ independent number u, and calculate $T_j = -1/\lambda_j(X(t))\log(u)$.

4.2 How to simulate an ODE and a Poisson process

Suppose one wish to simulate a hybrid process, given by

$$\begin{cases} N(t) &= Y\Big(\int_0^t \lambda(s, X(s))ds\Big)\,, \\ X(t) &= X(0) + \int_0^t \mu(X(s))ds + \int_0^t \xi_{N(s^-)}(X(s^-))dN(s)\,, \end{cases}$$

where $\xi_0(x_0), \xi_1(x_1), \ldots$ are are independent random variable, independent of Y, and distributed according to a transition measure $Q(\cdot\,; x)$.

There are basically two options to simulate the jump times of such process. The first one can be convenient if the integral $\int_0^t \lambda(s, X(s))ds$ is known exactly (for instance if it is independent of X):

- At each step, draw a random uniform $[0,1]$ independent number u.
- Solve the ODE $X(t) = X(0) + \int_0^t \mu(X(s))ds$ until the next time step, given by

$$T_{i+1} = T_i + \inf\{t > 0 : \int_{T_i}^{T_i+t} \lambda(s, X_s)ds \geqslant -log(u)\}$$

- Set $t = T_{i+1}$ and draw an independent random variable according to $Q(\cdot\,; X(t^-))$
- Update X accordingly.

Note that the drawback of this method is that it requires the evaluation of the integral $\int \lambda(s, X_s)ds$ at each step. A second option uses an acceptance/reject method, based on a property of 2d-Poisson process. Assume $\sup_{t,x} \lambda(s, X(s)) \leqslant \lambda_0$.

- At each step, draw a random uniform $[0, 1]$ independent number u.
- Set an hypothetical time $T'_{i+1} = T_i - 1/\lambda_0 log(u)$.
- Solve the ODE $X(t) = X(0) + \int_0^t \mu(X(s))ds$ on $[T_i, T'_{i+1})$.
- Draw a random uniform $[0, 1]$ independent number q.
- If $q \leqslant \lambda(T'_{i+1}, X_{T'_{i+1}})/\lambda_0$, set $T_{i+1} = T'_{i+1}$, and update X accordingly to the jump law. Else repeat previous step with a new hypothetical jump time $T'_{i+1} = T'_{i+1} - 1/\lambda_0 log(u)$ (with a new random uniform number u).

4.3 General algorithm for a PDMP

General algorithm for a PDMP may be derived from both previous section (exercise!)

4.4 Approximations

Approximate algorithm can be drawn from limit theorems (law of large number, central limit theorem), by changing some of the Poisson processes by deterministic terms and/or Brownian term. Other methods such the τ-leaping method choose to fire many reaction in a single step. We refer to [Anderson et al., 2011, Hepp et al., 2014] for more details.

4.5 Large time

General results of Markov chain and Markov processes, [Meyn and Tweedie, 1993a, Meyn and Tweedie, 1993b, Meyn, , Costa and Dufour, 2008] Examples on specific models with particular emphasize to the convergence rate [Malrieu et al., 2010, Malrieu, 2014, Malrieu, 2012] Examples on specific models using semigroup techniques [Tyran-Kamińska, 2009, Pichór et al., 2012, Mackey and Tyran-Kamińska, 2008]

5 Examples from biology

5.1 growth-fragmentation

We look at a cell that growth continuously at rate $\tau(x)$, and divides at random times, of intensity $\lambda(x)$. At division, the size is decreased according to the kernel $\beta(x, y)$. We keep track of a single cell. The generator is

$$Af(x) = \tau(x)f'(x) + \lambda(x) \int_0^x \Big(f(y) - f(x)\Big)\beta(x, dy)\,.$$

Particular case: TCP, equal mitosis, cell cycle, integrate and fire.
See [Bardet et al., 2011, Cloez, 2012] for probabilistic approach, and [Lasota et al., 1992, Tyran-Kamińska, 2009, Doumic and Gabriel, 2009] for semigroup and entropy approaches.

5.2 degrowth-production

⟨ssec:burstin⟩ We look at a quantity (protein concentration, chemical content in a body) that is degraded continuously at rate $\gamma(x)$, and produced at random times, of intensity $\lambda(x)$. At production event, a random amount is added according to the kernel $\kappa(x, y)$. The generator is

$$Af(x) = -\gamma(x)f'(x) + \lambda(x)\int_x^\infty \Big(f(y) - f(x)\Big)\kappa(x, dy)\,.$$

Particular case: storage model, bursting in gene expression.
For extensive study of the storage model, see [Bardet et al., 2011], while for more general models applied to gene expression, see [Mackey et al., 2013]. See also [Cloez, 2012]

5.3 Switched flows

The following generic model is widely used

$$Af(x, n) = v_n(x)f'(x, n) + \lambda_n(x)\Big(\sum_{k\neq n}\rho_{k,n}(x)f(x, k) - f(x, n)\Big)\,.$$

with for all (x, n), $\sum_{k\neq n}\rho_{k,n}(x) = 1$.
Particular case: gene expression, chemotaxis, active transport, random intermittent search, gating model, ion channels, microtubules growth.
We refer to [Bakhtin and Hurth, 2012, Malrieu et al., 2012b, Benaïm et al., 2012, Malrieu et al., 2012a, Malrieu, 2012] for generic study of switched flows, and examples of quite surprising results (explosion of a PDMP by switching two stable linear flows).

5.4 Biochemical Reaction Network

We consider a network of r_0 chemical reactions involving s_0 chemical species $S_1, \ldots, S_{s_0}$, represented as

$$\sum_{i=1}^{s_0}\nu_{ik}S_i \to \sum_{i=1}^{s_0}\nu'_{ik}S_i\,,\ \ k = 1, \ldots, r_0\,,$$

where the ν_{ik}, ν'_{ik} are nonnegative integers (stoichiometric coefficients). Let $X(t) \in \mathbb{N}^{s_0}$ give the numbers of molecules of each species present at time t. Let $\nu_k = (\nu_{ik})_{1\leqslant i\leqslant s_0}$ be the vector that give the number of molecules consumed in the kth reaction, and $\nu'_k = (\nu'_{ik})_{1\leqslant i\leqslant s_0}$ the number of molecules produced by the

kth reaction. We suppose that each reaction is executed according to a counting process of intensity $\lambda_k(x)$, that is

$$X(t) = X(0) + \sum_k (\nu'_k - \nu_k) Y_k\Big(\int_0^t \lambda_k(X(s))ds \Big), \tag{8}$$ eq:sde_crn

where Y_k are independent standard Poisson processes. Accordingly, we emphasize that the probability that a reaction k fires in a small time interval is given by

$$\mathbb{P}\big\{\text{Reaction } k \text{ occurs in } (t, t+\delta t] \mid \mathcal{F}_t\big\} \approx \lambda_k(X(t))\delta t\,.$$

The function $\lambda_k(x)$ are called reaction rate. A typical example of such function is given by the law of mass-action,

$$\lambda_k(x) = \kappa_k \prod_i \binom{\nu_{ik}}{x_i},$$

where $\kappa_k > 0$ is the reaction rate constant.

The law of large numbers give for the following property for Poisson processes

⟨prop:lgn⟩ **Proposition 11.** *let $\mathcal{Y}$ be a standard Poisson process, then for each $t_0 > 0$,*

$$\lim_{n\to\infty} \sup_{t\leqslant t_0} \mid \frac{1}{n} Y(nt) - t \mid = 0 \ a.s.$$

The proposition 11 implies the standard scaling of biochemical reaction network: for large number of species, an appropriate re-scaling of $X(t)$ and of the reaction rate makes the solution of equation (8) to converge to the solution of

$$\frac{dx}{dt} = \sum_k \kappa_k(\nu'_k - \nu_k) \prod_i x_i^{\nu_{ik}}\,.$$

Recent work [Kang et al., 2014, Kurtz and Kang, 2013, Anderson and Kurtz, 2011, Crudu et al., 2012] provides general theorems to reduce equation (8) to a PDMP, when some species are present in large quantity (and/or some reaction occur in a faster time scale). Rather than presenting the general theorems, we will focus on a particular model of gene expression, for which reduced forms have been extensively used.

5.5 Standard gene expression models

One of the most simple and widely used model of gene expression consider two variables. The first one is a boolean variable (0 or 1), that represent the state of the gene. The second one is an integer variable, that represents the amount of gene products, to be either mRNA or protein quantity. In the following equation, $(\mathcal{Y}_i)_{i=1,\dots,4}$ are independent standard Poisson processes.

$$\left\{ \begin{array}{rcl} X_0(t) &=& X_0(0) + Y_1\Big(\int_0^t \mathbf{1}_{\{X_0(s)=0\}} \lambda_a(X_1(s))ds \Big) - Y_2\Big(\int_0^t \mathbf{1}_{\{X_0(s)=1\}} \lambda_i(X_1(s))ds \Big), \\ X_1(t) &=& X_1(0) + Y_3\Big(\int_0^t \mathbf{1}_{\{X_0(s)=1\}} \lambda_1(X_1(s))ds \Big) - Y_4\Big(\int_0^t \gamma_1 X_1(s)ds \Big). \end{array} \right. \tag{9}$$ eq:SD1

In such model, the gene state switches between 0 and 1 at rate $\lambda_a(X_1)$ and $\lambda_i(X_1)$. The gene product is degraded at a linear rate $\gamma_1 X_1$. When the gene is "ON" (state 1), the gene product may increase at rate $\lambda_1(X_1)$. The three functions $\lambda_a, \lambda_i, \lambda_1$ represent the auto-regulation of the gene production on its own production. There are constant for constitutive gene (no regulation), and are bounded strictly positive monotonous function in the general case (typical examples are Hill functions).

We refer to [Peccoud and Ycart, 1995] for a mathematical study of such model in the case without regulation ($\lambda_1, \lambda_a, \lambda_i$ constant). For large amount of gene products ($X_1 \gg 1$), this model may be simplified to a switching ODE. The results is limiting model is given by

$$\left\{ \begin{array}{rcl} X_0(t) & = & X_0(0) + Y_1\Big(\int_0^t \mathbf{1}_{\{X_0(s)=0\}} \lambda_a(x_1(s))ds \Big) - Y_2\Big(\int_0^t \mathbf{1}_{\{X_0(s)=1\}} \lambda_i(x_1(s))ds \Big), \\ x_1(t) & = & x_1(0) + \displaystyle\int_0^t \Big(\mathbf{1}_{\{X_0(s)=1\}} \lambda_1(x_1(s)) - \gamma_1 x_1(s) \Big) ds. \end{array} \right. \tag{10}$$

eq:SC1

The precise result is given by:

Theorem 1. *Let X^N be the solution of equation (9) with the rescaled rate functions*

$$\begin{array}{ll} \lambda_1^N(x) := N\lambda_1(x/N)\,, & \gamma_1^N := \gamma_1\,, \\ \lambda_a^N(x) := \lambda_a(x/N)\,, & \lambda_i^N(x) := \lambda_i(x)\,. \end{array}$$

Assume that λ_1 is a C^1 function of $x \in \mathbb{R}^+$, and that $\lambda_a, \lambda_i, \lambda_1$ are such that equations (10) defines a unique global solution (measurable linearly bounded is sufficient). Then let the rescaled process $x^N = (X_0^N, x_1^N)$ defined by $x_1^N = X_1^N/N$. Assume $x^N(0)$ converges in distribution to $x(0)$, then x^N converges in distribution to the PDMP whose law is uniquely defined by equations (10).

A further result in [Crudu et al., 2012] allows to reduce the PDMP defined by equations (10), by "averaging" the discrete motion, assuming it evolves in a fast time scale. The reduced model is know a deterministic ODE, given by

$$\frac{dx}{dt} = \frac{\lambda_a(x_1)}{\lambda_a(x_1) + \lambda_i(x_1)} \lambda_1(x_1) - \gamma_1 x_1 \tag{11}$$

eq:C1

The precise result requires that $\lambda_a, \lambda_i, \lambda_1$ are such that the equation (11) defines a global flow, not necessarily restrict to evolve in a compact. Furthermore, it requires that the fast motion given by the switch defines an ergodic semigroup, exponentially mixing, and uniformly with respect to the slow variable x_1. Here, it is easy to see that this semigroup is ergodic, with unique invariant law given by a Bernoulli law of parameter $\frac{\lambda_a(x_1)}{\lambda_a(x_1)+\lambda_i(x_1)}$. Its convergent rate is exponential with rate $\lambda_a(x_1)+\lambda_i(x_1)$. Hence, it is needed to suppose additionally that these rates are bounded with respect to x_1. As before, we rewrite the limiting theorem given in [Crudu et al., 2012] with our notation:

Theorem 2. *[Crudu et al., 2012, Theorem 5.1 p. 13] Assume $\lambda_1 \in \mathcal{C}^1(\mathbb{R}^+)$ and such that the model defined by equation (11) defines a global flow. Assume λ_a and λ_i are C^1 on $\mathbb{R}^+$ and bounded, positive such that one of them is strictly positive. Let $\lambda_a^n = n\lambda_a$ and $\lambda_i^n = n\lambda_i$ with $n \to \infty$. Let $(X_O^n(t), x_1^n(t))_{t\geqslant 0}$ the stochastic process defined by equations (10), and $(x_1(t))_{t\geqslant 0}$ the solution of*

equation (11). *Assume* $x_1^n(0)$ *converges in distribution to* $x_1(0)$ *in* $\mathbb{R}^+$, *then* $(x_1^n(t))_{t\geqslant 0}$ *converges in distribution to* $(x_1(t))_{t\geqslant 0}$ *in* $\mathcal{D}(\mathbb{R}^+;\mathbb{R}^+)$.

The restriction of bounded rate λ_a and λ_i in [Crudu et al., 2012] is essentially to ensure that the fast dynamics stay in a compact in some sense. Here, because the fast dynamics is on a compact state space, this assumption can be released easily. Note that no convergence on the fast variable is stated here. Convergence do actually occurs, but for a specific topology (in $L^\infty(0,T)$). See [Kurtz and Kang, 2013] for general results on averaging methods.

A different limit from the PDMP defined by equations (10) may be taken, and was also treated explicitly in [Crudu et al., 2012]. Now we let $\lambda_i^n = n\lambda_i$ and $\lambda_1^n = n\lambda_1$. Intuitively, the switching variable X_0^n will then spend most of its time in state 0. However, transition from $X_0^n = 0$ to $X_0^n = 1$ will still be possible (and will not vanish as $n \to \infty$). Convergence of X_0^n to 0 will hold in $L^1(0,t)$ for any finite finite time t. When $X_0^n = 1$, production of x_1 is suddenly very high, but for a brief time. Although x_1 follows a deterministic trajectory, the timing of its trajectory is stochastic. At the limit, this drastic production episode becomes a discontinuous jump, of a random size. All happen as the two successive jumps of X_0 (from 0 to 1 and back to 0) coalesce into a single one, and create a discontinuity in x_1. In such case, convergence cannot hold in the cad-lag space $\mathcal{D}(\mathbb{R}^+;\mathbb{R}^+)$ with the Skorohod topology. The authors in [Crudu et al., 2012] were able to prove tightness in $L^p([0,T],\mathbb{R}^+)$, $1 \leqslant p < \infty$. Their result requires the additional assumption that all rates λ_1,λ_i and λ_a are linearly bounded, and either λ_a or λ_i is bounded with respect to x_1. This is needed to get a bound on x_1 in $L^\infty([0,T],\mathbb{R}^+)$. The limiting theorem reads

Theorem 3. *[Crudu et al., 2012, Theorem 6.1 p. 17] Assume* $\lambda_1 \in \mathcal{C}^1(\mathbb{R}^+)$ *and let* $\lambda_i^n = n\lambda_i$ *and* $\lambda_1^n = n\lambda_1$ *with* $n \to \infty$. *Let* $(X_O^n(t), x_1^n(t))_{t\geqslant 0}$ *the stochastic process defined by equations* (10). *Assume* $x_1^n(0)$ *converges in distribution to* $x_1(0)$ *in* $\mathbb{R}^+$, *and* $X_O^n(0)$ *converges in distribution to* 0. *The reaction rates* λ_1,λ_i *and* λ_a *are such that*

- *there exists* $\alpha > 0$ *such that* $\lambda_i(x_1) \geqslant \alpha$ *for all* x_1 ;
- *there exists* $M_1 > 0$ *such that*

$$\begin{aligned}\lambda_1(x_1) &\leqslant M_1(x_1+1),\\ \lambda_a(x_1) &\leqslant M_1(x_1+1),\\ \lambda_i(x_1) &\leqslant M_1(x_1+1);\end{aligned}$$

- *In addition either* λ_a *or* λ_1 *is bounded with respect to* x_1 .

Then $(X_0^n(t))_{t\geqslant 0}$ *converges in distribution to* 0 *in* $L^1([0,T],\{0,1\})$ *and* $(x_1^n(t))_{t\geqslant 0}$ *converges in distribution to the stochastic process whose generator is given by*

$$\begin{aligned}A\varphi(x_1) &= -\gamma_1 x_1 \frac{\partial \varphi}{\partial x_1}\\ &+ \lambda_a(x_1)\int_0^\infty \Big(\varphi(\phi_1(t,x_1)) - \varphi(x_1)\Big)\lambda_i(\phi_1(t,x_1))e^{-\int_0^t \lambda_i(\phi_1(s,x_1))ds}dt, \quad (12)\end{aligned}$$

eq:geneswitchCrudu

for every $\varphi \in \mathcal{C}_b^1(\mathbb{R}^+)$ *and where* $\phi_1(t, x_1)$ *is the flow associated to*

$$\begin{aligned} \dot{x} &= \lambda_1(x), \\ x(0) &= x_1. \end{aligned}$$

Remark 4. Note that equation (12) may be rewritten as

$$Af(x) = -\gamma(x)f'(x) + \lambda_a(x)\int_x^\infty \Big(f(y) - f(x)\Big)h(y,x)dy, \tag{13}$$ eq:geneswitchCrudu2

for every $f \in C_b^1(\mathbb{R}^+)$ and where $h(y, x)$ is given by

$$\begin{aligned} h(y,x) &= -\frac{\nu'(y)}{\nu(x)}, \quad y >\!\!\geqslant x > 0., \\ \nu(x) &= \exp\Big(-\int_0^x \frac{\lambda_i(z)}{\lambda_1(z)}dz\Big). \end{aligned}$$

Let us now present in detail three examples.

Example 1. Consider the special case where both regulation rates λ_1 and λ_i are constant. Then the flow ϕ_1 is easily calculated and we have

$$\begin{aligned} \phi_1(t, x_1) &= x_1 + \lambda_1 t, \quad t \geqslant 0, \\ \int_0^t \lambda_i k_i(\phi_1(s, x_1))ds &= \lambda_i t, \end{aligned}$$

and the generator eq. (12) becomes

$$A\varphi(x_1) = -\gamma_1 x_1 \frac{\partial \varphi}{\partial x_1} + \lambda_a(x_1)\int_0^\infty \Big(\varphi(x_1 + z) - \varphi(x_1)\Big)\frac{\lambda_i}{\lambda_1}e^{-\frac{\lambda_i}{\lambda_1}z}dz,$$

which is a "Bursting" model (see subsection 5.2), with an exponential jump size distribution of mean parameter $\frac{\lambda_1}{\lambda_i}$. Such rate has an easy interpretation, being the number of molecules created during an ON period of the gene.

Other choice of regulation rate leads to different model, as illustrated in the next two examples.

Example 2. Let λ_1 be a constant and $\lambda_i(x_1) = \lambda_i x_1 + k_0$ (linear negative regulation), so that

$$\begin{aligned} \phi_1(t, x_1) &= x_1 + \lambda_1 t, \quad t \geqslant 0, \\ \int_0^t \lambda_i k_i(\phi_1(s, x_1))ds &= (\lambda_i x_1 + k_0)t + \frac{\lambda_1\lambda_i}{2}t^2, \end{aligned}$$

and the generator eq. (12) becomes

$$A\varphi(x_1) = -\gamma_1 x_1 \frac{\partial \varphi}{\partial x_1} + \lambda_a k_a(x_1)\int_{x_1}^\infty \Big(\varphi(z) - \varphi(x_1)\Big)\frac{\lambda_i z + k_0}{\lambda_1}e^{-\frac{z-x_1}{\lambda_1}\left[\lambda_i\frac{z+x_1}{2} + k_0\right]}dz.$$

The limiting model is then a bursting model where the jump distribution is a function of the jump position, and has a Gaussian tail.

Example 3. Let $\lambda_1(x_1) = x_1$ and λ_i be a constant (positive linear regulation), so that

$$\phi_1(t, x_1) = x_1 e^{\lambda_1 t}, \quad t \geqslant 0,$$
$$\int_0^t \lambda_i k_i(\phi_1(s, x_1))ds = \lambda_i t,$$

and the generator eq. (12) becomes

$$A\varphi(x_1) = -\gamma_1 x_1 \frac{\partial \varphi}{\partial x_1} + \lambda_a k_a(x_1) \int_{x_1}^{\infty} \Big(\varphi(z) - \varphi(x_1)\Big) \frac{\lambda_i}{\lambda_1} x^{\frac{\lambda_i}{\lambda_1}} z^{-1-\frac{\lambda_i}{\lambda_1}} dz.$$

This time, the limiting model is a bursting model where the jump distribution is a function of the jump position with a power-law tail.

The model obtained in equation (10) is a switching ODE. The advantage of reducing the model compared to equation (9) is to be able to calculate explicitly the stationary density (if it exists), which leads to specific strategy to prove convergence in large time towards a stationary state. We state the result for a slightly generalized model:

Theorem 4. *Let us look at the equation*

$$\left\{ \begin{array}{rcl} X_0(t) & = & X_0(0) + Y_1\Big(\displaystyle\int_0^t \mathbf{1}_{\{X_0(s)=0\}} \lambda_a(x_1(s))ds \Big) - Y_2\Big(\displaystyle\int_0^t \mathbf{1}_{\{X_0(s)=1\}} \lambda_i(x_1(s))ds \Big), \\ x_1(t) & = & x_1(0) + \displaystyle\int_0^t \Big(\mathbf{1}_{\{X_0(s)=1\}} \lambda_1(x_1(s)) + \mathbf{1}_{\{X_0(s)=0\}} \lambda_0(x_1(s)) \Big) ds. \end{array} \right. \tag{14}$$

eq:SC1_generic

Suppose there exists $y_* < y^*$ such that

$$\left\{ \begin{array}{l} \lambda_0(y_*) = 0\,, \lambda_1(y_*) > 0\,, \\ \lambda_0(y^*) < 0\,, \lambda_1(y_*) = 0\,. \end{array} \right.$$

Then, if $x_1(0)$ takes values on (y_*, y^*), so is $x_1(t)$ for all $t \geqslant 0$. Moreover, the stationary density of the continuous variable x_1 of the solution of equation (14) is solution of the first order differential equation

$$\frac{\partial}{\partial x} u = -\Big[\frac{\lambda_a}{\lambda_0} + \frac{\lambda_i}{\lambda_1} + \frac{\lambda_0' \lambda_1 / \lambda_0 - \lambda_1' \lambda_0 / \lambda_1}{\lambda_1 - \lambda_0} \Big] u\,, \ x \in (y_*, y^*)\,.$$

We refer to [Mackey et al., 2013] for systematic study to the model obtained in equation (13)

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