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Convergence of stochastic gene networks to hybrid piecewise deterministic processes

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Abstract

We study the asymptotic behavior of multiscale stochastic gene networks using weak limits of Markov jump processes. Depending on the time and concentration scales of the system we distinguish four types of limits: continuous piecewise deterministic processes (PDP) with switching, PDP with jumps in the continuous variables, averaged PDP, and PDP with singular switching. We justify rigorously the convergence for the four types of limits. The convergence results can be used to simplify the stochastic dynamics of gene network models arising in molecular biology.

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Keywords: Stochastic gene networks, piecewise deterministic processes, perturbed test functions.

1 Introduction

Modern molecular biology emphasizes the important role of the gene regulatory networks in the functioning of living organisms. Recent experimental advances in molecular biology show that many gene products do not follow deterministic dynamics and should be modeled as random variables (Kepler and Elston (2001); Kaufmann and van Oudenaarden (2007)).

Markov processes approaches to gene networks dynamics, originating from the pioneering ideas of Delbrück (M. Delbrück (1940)), capture diverse features of the experimentally observed expression variability, such as bursting (Cai et al. (2006)), various types of steady-state distributions of RNA and protein numbers (Kaern et al. (2005)), noise amplification or reduction by network propagation (Paulsson (2004); Warren et al. (2006)), clock de-synchronization (Barkai and Leibler (2000)), stochastic transitions in cellular memory storage circuits (Kaufmann et al. (2007)).

However, the study of the full Markov dynamics of biochemical networks is a difficult task. Even the simplest Markovian model, such as the production module of a single protein involves tens of variables and biochemical reactions and an equivalent number of parameters (Kierzek et al. (2001); Krishna et al. (2005)). The direct simulation of such models by the Stochastic Simulation Algorithm (SSA) (Gillespie (1976)) is extremely time consuming.

In order to increase computational efficiency, several accelerated simulation algorithms are hybrid and treat fast biochemical reactions as continuous variables (Haseltine and Rawlings (2002); Alfonsi et al. (2005); Alfonsi et al. (2004)). Similar approaches reducing fast reactions can be justified by diffusion approximations for Markov processes (Ball et al. (2006)).

A different hybrid approach is to distinguish between molecular species according to their abundances. Species in small amounts can be treated as discrete variables, whereas species in large amounts can be considered continuous. It has been proposed that, the dynamics of gene networks with well separated abundances, can be well approximated by piecewise deterministic Markov processes (Radulescu et al. (2007); Crudu et al. (2009)). Piecewise deterministic processes (PDP) are used in operational research in relation with optimal control and various technological applications (Boxma et al. (2005); Ghosh and Bagchi (2005); Pola et al. (2003); Bujorianu and Lygeros (2004)). Their popularity in physical, chemical and biological sciences is also steadily increasing as they provide a natural framework to deal with intermittent phenomena in many contexts (Radulescu et al. (2007); Zeiser et al. (2008)).

By looking for the best PDP approximation of a stochastic network of biochemical reactions, and depending on the time scales of the reaction mechanism, we can distinguish several cases (Crudu et al. (2009)):

- Continuous PDP with switching: continuous variables evolve according to ordinary differential equations. The trajectories of the continuous variables are continuous, but the differential equations depend on one or several discrete variables.
- PDP with jumps in the continuous variables: the same as the previous case, but the continuous variables can jump as well as the discrete variables.
- Averaged PDP: some discrete variables have rapid transitions and can be averaged. The resulting approximation is an averaged PDP.
- Discontinuous PDP with singular switching: the continuous variable has two time scaling. The switch between the two regimes is commanded by a discrete variable. The rapid parts of the trajectory of the continuous variable can be approximated by discontinuities.

In this paper, we justify rigorously these approximations that were illustrated by models of stochastic gene expression in Crudu et al. (2009). More precisely, we present several theorems on the weak convergence of biochemical reactions processes towards piecewise deterministic processes of the type specified above. The resulting piecewise deterministic processes can be used for more efficient simulation algorithms, also, in certain cases, can lead to analytic results for the stochastic behavior of gene networks. Higher order approximations of multiscale stochastic chemical kinetics, corresponding to stochastic differential equations with jumps, though not discussed in this paper, represent straightforward extensions of our results.

The structure of this article is as follows. In section 2, we present the PDP, a useful theorem on the uniqueness of the solution of a martingale problem and the Markov jump model for stochastic regulatory networks. The four remaining sections discuss the asymptotic behaviors of the models, corresponding to the four cases presented above.

2 Piecewise Deterministic Processes

We begin with a brief description of Piecewise Deterministic Processes (PDP) and collect useful results on these. We do not consider PDPs in their full generality. The reader is referred to Davis (1993) for further results.

Standard conditions:

In this article, a PDP taking values in $E = \mathbb{R}^n \times \mathbb{N}^d$ is a process $x_t = (y_t, \nu_t)$, determined by its three local characteristics :

1. For all $\nu \in \mathbb{N}^d$, a Lipschitz continuous vector field in \mathbb{R}^n , denoted by F_ν , which determines a unique global flow $\phi_\nu(t, y)$ in \mathbb{R}^n such that, for $t > 0$,

$$\frac{d}{dt}\phi_\nu(t, y) = F_\nu(\phi_\nu(t, y)), \quad \phi_\nu(0, y) = y, \quad \forall y \in \mathbb{R}^n.$$

We also use the notation: $F(y, \nu) = F_\nu(y)$.

2. A jump rate $\lambda : E \rightarrow \mathbb{R}^+$ such that, for each $x = (y, \nu) \in E$, there exists $\epsilon(x) > 0$ such that

$$\int_0^{\epsilon(x)} \lambda(\phi_\nu(t, y), \nu) dt < \infty.$$

3. A transition measure $Q : E \rightarrow \mathcal{P}(E)$, $x \mapsto Q(\cdot; x)$, where $\mathcal{P}(E)$ denotes the set of probability measures on E . We assume that $Q(\{x\}; x) = 0$ for each $x \in E$.

From these standard conditions, a right-continuous sample path $\{x_t : t > 0\}$ starting at $x = (y, \nu) \in E$ may be constructed as follows. Define

$$x_t(\omega) := \phi_\nu(t, y), \quad \text{for } 0 \leq t < T_1(\omega),$$

where $T_1(\omega)$ is the realization of the first jump time T_1 , with the following distribution :

$$\mathbb{P}_x(T_1 > t) = \exp\left(-\int_0^t \lambda(\phi_\nu(s, y), \nu) ds\right) =: H(t, x), \quad t \in \mathbb{R}^+.$$

We have then $x_{T_1^-}(\omega) = (\phi_\nu(T_1(\omega), y), \nu)$, and the post-jump state $x_{T_1(\omega)}(\omega)$ has the distribution given by :

$$\mathbb{P}_x(x_{T_1} \in A | T_1 = t) = Q(A; (\phi_\nu(t, y), \nu))$$

on the Borel sets A of E .

We then restart the process at $x_{T_1(\omega)}(\omega)$ and proceed recursively according to the same procedure to obtain a sequence of jump-time realizations $T_1(\omega), T_2(\omega), \dots$. Between each of two consecutive jumps, $x_t(\omega)$ follows a deterministic motion, given by the flow corresponding to the vector field F .

Such a process x_t is called a PDP. The number of jumps that occur between the times 0 and t is denoted by

$$N_t(\omega) = \sum_k \mathbb{1}_{t \geq T_k}(\omega).$$

It can be shown that x_t is a strong Markov process with right-continuous, left-limited sample paths (see Davis (1993)). The generator \mathcal{A} of the process is formally given by

$$\mathcal{A}f(x) = F_\nu(x) \cdot \nabla_y f(x) + \lambda(x) \int_E (f(z) - f(x)) Q(dz; x) \quad (1)$$

for each $x = (y, \nu) \in E$, we have denoted by ∇_y the gradient with respect to the variable $y \in \mathbb{R}^n$. The domain of \mathcal{A} is described precisely in Davis (1993). We do not need such a precise description and just note that \mathcal{A} is well defined for $f \in \mathcal{E}$, the set of functions $f : E \rightarrow \mathbb{R}$ such that :

- E1. f is bounded,
- E2. for all $\nu \in \mathbb{N}^d$, $f(\cdot, \nu) \in C^1(\mathbb{R}^n)$,
- E3. its derivatives are bounded uniformly in E .

For $f \in \mathcal{E}$, we denote by

$$L_f = \sup_{y \in \mathbb{R}^n} \|D_y f\|_\infty = \sup_{(y, \nu) \in E} \|D_y f(y, \nu)\|, \quad (2)$$

the Lipschitz constant of f with respect to the variable y .

The space \mathcal{E} is a Banach space when endowed with the norm

$$\|f\|_{\mathcal{E}} = \|f\|_\infty + L_f. \quad (3)$$

If Z is a Banach space, $\mathcal{B}_b(Z)$ is the set of bounded Borel measurable functions on Z ; $C_b^k(Z)$ is the set of C^k -differentiable functions on Z , such that the derivatives, until the k -th order, are bounded; $\mathcal{C}_b(Z)$ is the set of bounded continuous functions on Z . Also $D(\mathbb{R}^+; Z)$ is the set of process defined on \mathbb{R}^+ with right-continuous, left-limited sample paths defined on \mathbb{R}^+ and taking values in Z and $C(\mathbb{R}^+; Z)$ is the set of continuous process defined on \mathbb{R}^+ and taking values in Z .

The PDPs considered in this paper will always satisfy the following property :

Hypothesis 2.1 *The three local characteristics of the PDP satisfy the standard conditions given above. The jump rate λ is C^1 -differentiable with respect to the variable $y \in \mathbb{R}^n$. For every starting point $x = (y, \nu) \in E$ and $t \in \mathbb{R}^+$, we suppose $\mathbb{E}(N_t) < \infty$.*

Remark 2.2 $\mathbb{E}(N_t) < \infty$ implies in particular that $T_k(\omega) \rightarrow \infty$ almost surely. This assumption is usually quite easy to check in applications, but it is hard to formulate general conditions under which it holds, because of the complicated interaction between F, λ and Q . It can be shown for instance that if λ is bounded, then $\mathbb{E}(N_t) < \infty$ (cf. Davis (1993)).

For some results, we need the following stronger property :

Hypothesis 2.3 *The functions F, λ and $x \mapsto \lambda(x) \int_E f(z) Q(dz; x)$, with $f \in \mathcal{E}$, are bounded on E , C^1 -differentiable with respect to the variable $y \in \mathbb{R}^n$ and their derivatives with respect to y are also bounded.*

When Hypothesis 2.3 is satisfied, we set

$$M_F = \|F\|_\infty, \quad L_F = \sup_{y \in \mathbb{R}^n} \|D_y F\|_\infty,$$

$$M_\lambda = \|\lambda\|_\infty, \quad L_\lambda = \sup_{y \in \mathbb{R}^n} \|D_y \lambda\|_\infty.$$

and L_Q a constant such that, for all $f \in \mathcal{E}$ and $x = (y, \nu) \in E$:

$$\left\| D_y \left(\lambda(x) \int_E f(z) Q(dz; x) \right) \right\|_\infty \leq L_Q \|f\|_{\mathcal{E}}$$

Denote by $(P_t)_{t \geq 0}$ the transition semigroup associated to the PDP constructed above and by P_x the law of the PDP starting from $x \in E$. Then, P_x is a solution of the martingale problem associated to \mathcal{A} in the following sense:

$$f(x_t) - f(x) - \int_0^t \mathcal{A}f(x_s) ds$$

is a local martingale for any $f \in \mathcal{E}$ (see Davis (1993)). Moreover, if Hypothesis 2.3 holds, it is a bounded martingale. As usual, we have denoted by $(x_t)_{t \geq 0}$ the canonical process on $D(\mathbb{R}^+; E)$.

The following results gives a uniqueness property for this martingale problem. It will enable us to characterize the asymptotic behavior of our stochastic regulatory networks.

Theorem 2.4 *If Hypothesis 2.3 is satisfied, then the law of the PDP determined by F , λ , and Q is the unique solution of the martingale problem associated to the generator \mathcal{A} .*

The proof of the theorem is given in the appendix.

Markov jump model for stochastic regulatory networks: known results

We consider a set of chemical reactions R_r , $r \in \mathcal{R}$; \mathcal{R} is supposed to be finite. These reactions involve species indexed by a set $S = 1, \dots, M$, the number of molecules of the specie i is denoted by n_i and $X \in \mathbb{N}^M$ is the vector consisting of the n_i 's. Each reaction R_r has a rate $\lambda_r(X)$ which depends on the state of the system, described by X and corresponds to a change $X \rightarrow X + \gamma_r$, $\gamma_r \in \mathbb{Z}^M$.

Mathematically, this evolution can be described by the following Markov jump process. It is based on a sequence $(\tau_k)_{k \geq 1}$ of random waiting times with exponential distribution. Setting $T_0 = 0$, $T_i = \tau_1 + \dots + \tau_i$, X is constant on $[T_{i-1}, T_i)$ and has a jump at T_i . The parameter of τ_i is given by $\sum_{r \in \mathcal{R}} \lambda_r(X(T_{i-1}))$:

$$\mathbb{P}(\tau_i > t) = \exp\left(-\sum_{r \in \mathcal{R}} \lambda_r(X(T_{i-1}))t\right).$$

At time T_i , a reaction $r \in \mathcal{R}$ is chosen with probability $\lambda_r(X(T_{i-1})) / \sum_{r \in \mathcal{R}} \lambda_r(X(T_{i-1}))$ and the state changes according to $X \rightarrow X + \gamma_r$:

$$X(T_i) = X(T_{i-1}) + \gamma_r.$$

This Markov process has the following generator (see Ethier and Kurtz (1986)):

$$Af(X) = \sum_{r \in \mathcal{R}} [f(X + \gamma_r) - f(X)] \lambda_r(X).$$

We do not need a precise description of the domain of A , the above definition holds for instance for functions in $C_b(\mathbb{R}^M)$.

In the applications we have in mind, the numbers of molecules have different scales. Some of the molecules are in small numbers and some are in large numbers. Accordingly, we split the set of species into two sets C and D with cardinals M_C and M_D . This induces the decomposition $X = (X_C, X_D)$, $\gamma_r = (\gamma_r^C, \gamma_r^D)$. For $i \in D$, n_i is of order 1 while for $i \in C$, n_i is proportional to N where N is a large number. For $i \in C$, setting $\tilde{n}_i = n_i/N$, \tilde{n}_i is of order 1. We define $x_C = \frac{1}{N}X_C$ and $x = (x_C, X_D)$.

We also decompose the set of reactions according to the species involved. We set $\mathcal{R} = \mathcal{R}_D \cup \mathcal{R}_C \cup \mathcal{R}_{DC}$. A reaction in \mathcal{R}_D (resp. \mathcal{R}_C) produces or consumes only species in D (resp. C). Also, the rate of a reaction in \mathcal{R}_D (resp. \mathcal{R}_C) depends only on X_D (resp. x_C). A reaction in \mathcal{R}_{DC} has a rate depending on both x_C and X_D and produces or consumes, among others, species from C or D .

The rate of a reaction in $r \in \mathcal{R}_C$ is also large and of order N and we set $\tilde{\lambda}_r = \frac{\lambda_r}{N}$. In general, reactions in \mathcal{R}_D or \mathcal{R}_{DC} have a rate of order 1.

Introducing the new scaled variables, the generator has the form:

$$\begin{aligned} \tilde{A}f(x_C, X_D) &= \sum_{r \in \mathcal{R}_C} \left[f\left(x_C + \frac{1}{N}\gamma_r^C, X_D\right) - f(x_C, X_D) \right] N\tilde{\lambda}_r(x_C) \\ &+ \sum_{r \in \mathcal{R}_{DC}} \left[f\left(x_C + \frac{1}{N}\gamma_r^C, X_D + \gamma_r^D\right) - f(x_C, X_D) \right] \lambda_r(x_C, X_D) \\ &+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(X_D). \end{aligned}$$

Assuming that the scaled rates $\tilde{\lambda}_r$ are C^1 with respect to x_C , it is not difficult to see that if $N \rightarrow \infty$, the two sets of species decouple. Indeed, reactions in \mathcal{R}_{DC} do not

happen sufficiently often and they do not change x_C in a sufficiently large manner. The limit would simply give a set of differential equations for the continuous variable x_C , which evolves without influence of X_D . The discrete variable would have its own dynamic made of jumps. These results have been shown by Kurtz (1971) and Kurtz (1978).

In the following sections, we consider more general systems where other types of reactions may happen and which yield different limiting systems

3 Continuous piecewise deterministic process

In this section, we assume that some of the reactions in a subset S_1 of \mathcal{R}_{DC} are such that their rate is large and scales with N . We again set $\tilde{\lambda}_r = \frac{1}{N}\lambda_r$ for $r \in S_1$. We assume that these equations do not change X_D , in other words

$$\gamma_r^D = 0, \quad r \in S_1. \quad (4)$$

However, the rate λ_r depends on X_D . Note that this is possible and even frequent in molecular biology, meaning that reactions of the type S_1 recover the reactant, like in the reaction $A \rightarrow A + B$, with A and B discrete and continuous species, respectively. The more complicated case $\gamma_r^D \neq 0$ is treated in section 5.

The scaled generator has now the form

$$\begin{aligned} \tilde{\mathcal{A}}_N f(x_C, X_D) &= \sum_{r \in \mathcal{R}_C} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D) - f(x_C, X_D) \right] N\tilde{\lambda}_r(x_C) \\ &+ \sum_{r \in S_1} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D) - f(x_C, X_D) \right] N\tilde{\lambda}_r(x_C, X_D) \\ &+ \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D + \gamma_r^D) - f(x_C, X_D) \right] \lambda_r(x_C, X_D) \\ &+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(X_D). \end{aligned} \quad (5)$$

For $f \in C_b^1(E)$, we may let $N \rightarrow \infty$ and obtain the limit generator

$$\begin{aligned} \mathcal{A}_\infty f(x_C, X_D) &= \left(\sum_{r \in \mathcal{R}_C} \tilde{\lambda}_r(x_C)\gamma_r^C + \sum_{r \in S_1} \tilde{\lambda}_r(x_C, X_D)\gamma_r^C \right) \cdot \nabla_{x_C} f(x_C, X_D) \\ &+ \sum_{r \in \mathcal{R}_{DC} \setminus S_1} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(x_C, X_D) \\ &+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(X_D). \end{aligned}$$

This formal argument indicates that, as $N \rightarrow \infty$, the process converges to a continuous PDP (see (1)). The state is described by a continuous variable x_C and a discrete variable X_D . The discrete variable is a jump process and is piecewise constant. The continuous variable evolves according to differential equations depending on X_D . It is continuous but the vector field describing its evolution changes when X_D jumps.

This is rigorously justified by the following theorem.

Theorem 3.1 *Let $x^N = (x_C^N, X_D^N)$ be a jump Markov process as above, starting at $x^N(0) = (x_C^N(0), X_D^N(0))$. Assume that the jump rates $\tilde{\lambda}_r$, $r \in \mathcal{R}_C \cup S_1$ and λ_r ,*

$r \in \mathcal{R}_{DC} \setminus S_1$ are C^1 functions of $x_C \in \mathbb{R}^{M_C}$. We define P_{x_0} the law of the PDP starting at $x_0 = (x_{C,0}, X_{D,0})$ whose jump intensities are:

$$\lambda(x) = \sum_{r \in \mathcal{R}_D \cup \mathcal{R}_{DC} \setminus S_1} \lambda_r(x),$$

the transition measure is defined by:

$$\begin{aligned} & \int_E f(z) Q(dz; x) \\ &= \frac{1}{\lambda(x)} \left(\sum_{r \in \mathcal{R}_{DC} \setminus S_1} f(x_C, X_D + \gamma_r^D) \lambda_r(x_C, X_D) + \sum_{r \in \mathcal{R}_D} f(x_C, X_D + \gamma_r^D) \lambda_r(x_C, X_D) \right), \end{aligned}$$

for $x = (x_C, X_D)$, and the vectors fields are given by:

$$F_{X_D}(x_C) = \sum_{r \in \mathcal{R}_C} \gamma_r^C \tilde{\lambda}_r(x_C) + \sum_{r \in S_1} \gamma_r^C \tilde{\lambda}_r(x_C, X_D).$$

Assume that Hypothesis 2.1 is satisfied and $x^N(0)$ converges in distribution to x_0 , then x^N converges in distribution to the PDP whose law is P_{x_0} .

Proof:

In the following, we work only with scaled variables and simplify the notation by omitting the tildes. In other words, we use λ_r to denote the rate of all reactions.

The proof is divided into three steps. We begin our proof by supposing that the jump rates and their derivatives with respect to x_C are bounded. Hypothesis 2.3 is then satisfied. We then prove Theorem 3.1 by a truncation argument.

Step 1: Tightness for bounded reaction rates.

We first assume that all rates λ_r are bounded as well as their derivatives with respect to x_C .

Let x^N be a Markov jump process whose generator is given by $\tilde{\mathcal{A}}_N$.

Without loss of generality, we assume that the initial value of the process is deterministic: $x^N(0) = (x_C^N(0), X_D^N(0))$ and converges to $x_0 = (x_{C,0}, X_{D,0})$ in $\mathbb{R}^{M_C} \times \mathbb{N}^{M_D}$.

Let $(Y_r)_{r \in \mathcal{R}}$ be a sequence of independent standard Poisson processes. By Proposition 1.7, Part 4, and Theorem 4.1, Part 6, of Ethier and Kurtz (1986) we know that there exists stochastic processes $(\tilde{x}^N)_{N \in \mathbb{N}}$ in $D(\mathbb{R}^+; E)$ such that

$$\tilde{x}^N(t) = x^N(0) + \sum_{r \in \mathcal{R}} \gamma_r Y_r \left(\int_0^t \lambda_r(\tilde{x}^N(s)) ds \right), \quad t \geq 0.$$

Moreover, for each N , x^N and \tilde{x}^N have the same distribution. Since we consider only the distributions of the processes, we only consider \tilde{x}^N in the following and use the same notation for both processes.

Using the decomposition $x^N = (x_C^N, X_D^N)$, we have

$$\begin{aligned} x_C^N(t) &= x_C^N(0) + \sum_{r \in \mathcal{R}_C} \frac{1}{N} \gamma_r^C Y_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s)) ds \right) \\ &+ \sum_{r \in S_1} \frac{1}{N} \gamma_r^C Y_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s), X_D^N(s)) ds \right) \\ &+ \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \frac{1}{N} \gamma_r^C Y_r \left(\int_0^t \lambda_r(x_C^N(s), X_D^N(s)) ds \right) \end{aligned}$$

and

$$\begin{aligned} X_D^N(t) &= X_D^N(0) + \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \gamma_r^D Y_r \left(\int_0^t \lambda_r(x_C^N(s), X_D^N(s)) ds \right) \\ &\quad + \sum_{r \in \mathcal{R}_D} \gamma_r^D Y_r \left(\int_0^t \lambda_r(X_D^N(s)) ds \right) \end{aligned}$$

We easily prove tightness in $D(\mathbb{R}^+; \mathbb{R}^{M_D})$ of the laws of $(X_D^N)_{N \in \mathbb{N}}$ by the same proof as for Proposition 3.1 in chapter 6 of Ethier and Kurtz (1986) and by using the fact that the law of Y_r is tight in $D(\mathbb{R}^+; \mathbb{N})$, for every $r \in \mathcal{R}$, according to Theorem 1.4 of Billingsley (1999).

To prove that the laws of $(x_C^N)_{N \in \mathbb{N}}$ are tight in $C(\mathbb{R}^+; \mathbb{R}^{M_C})$, we adapt the argument of section 2 chapter 11 in Ethier and Kurtz (1986).

Let $\tilde{Y}_r(u) = Y_r(u) - u$ be the standard Poisson process centered at its expectation, we have:

$$\begin{aligned} x_C^N(t) &= x_C^N(0) + \sum_{r \in \mathcal{R}_C} \frac{1}{N} \gamma_r^C \tilde{Y}_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s)) ds \right) \\ &\quad + \sum_{r \in S_1} \frac{1}{N} \gamma_r^C \tilde{Y}_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s), X_D^N(s)) ds \right) \\ &\quad + \int_0^t F(x_C^N(s), X_D^N(s)) ds \\ &\quad + \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \frac{1}{N} \gamma_r^C Y_r \left(\int_0^t \lambda_r(x_C^N(s), X_D^N(s)) ds \right) \end{aligned}$$

Observe that

$$\sup_{u \in [0, A]} \frac{1}{N} \tilde{Y}_r(Nu) \rightarrow 0, \text{ a.s.}$$

for any $A \geq 0$. Since λ_r are bounded, it follows that, for all $T > 0$,

$$\sup_{t \in [0, T]} \left| \sum_{r \in \mathcal{R}_C} \frac{1}{N} \gamma_r^C \tilde{Y}_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s)) ds \right) + \sum_{r \in S_1} \frac{1}{N} \gamma_r^C \tilde{Y}_r \left(N \int_0^t \tilde{\lambda}_r(x_C^N(s), X_D^N(s)) ds \right) \right|$$

$\rightarrow 0$, a.s. when $N \rightarrow \infty$.

Clearly

$$\sup_{t \in [0, T]} \left| \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \frac{1}{N} \gamma_r^C Y_r \left(\int_0^t \lambda_r(x_C^N(s), X_D^N(s)) ds \right) \right| \rightarrow 0, \text{ a.s.}$$

It follows that there exists a random constant K_N going to zero such that, for $t, t_1, t_2 \in [0, T]$, and $\|F\|_\infty = \sup_{x \in \mathbb{R}^{M_C} \times \mathbb{N}^{M_D}} |F(x)|$.

$$|x_C^N(t)| \leq |x_C^N(0)| + \|F\|_\infty t + K_N, \text{ a.s.}$$

and

$$|x_C^N(t_1) - x_C^N(t_2)| \leq \|F\|_\infty |t_1 - t_2| + 2K_N, \text{ a.s.}$$

Tightness of $(x_C^N)_{N \in \mathbb{N}}$ in $C(\mathbb{R}^+; \mathbb{R}^{M_C})$ follows by classical criteria (see for instance Jacod and Shiryaev (1987), chapter 6, section 3b).

We conclude, from Jacod and Shiryaev (1987) (chapter 6, section 3b), that $\{x^N\}_N = \{(x_C^N, X_D^N)\}_N$ is tight in $D(\mathbb{R}^+; E)$.

Step 2: Identification of limit points for bounded reaction rates.

Let $x = (x_t)_{t \geq 0}$ be the canonical process on $D(\mathbb{R}^+; E)$, and P_N the law of $(x_t^N)_{t \geq 0}$ on this space, for each $N \in \mathbb{N}$.

We know that for each $N \in \mathbb{N}$ and $\varphi \in \mathcal{E}$.

$$\varphi(x_t) - \varphi(x_0) - \int_0^t \tilde{\mathcal{A}}_N \varphi(x_s) ds$$

is a P_N -martingale. Equivalently, for each $n \in \mathbb{N}$, $t_1, \dots, t_n \in [0, r]$, $t \geq r \geq 0$, $\psi \in (C_b(E))^n$ and $\varphi \in \mathcal{E}$

$$\begin{aligned} & \mathbb{E}_{P_N} \left(\left(\varphi(x_t) - \varphi(x_0) - \int_0^t \tilde{\mathcal{A}}_N \varphi(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right) \\ &= \mathbb{E}_{P_N} \left(\left(\varphi(x_r) - \varphi(x_0) - \int_0^r \tilde{\mathcal{A}}_N \varphi(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right). \end{aligned} \quad (6)$$

Let $(P_{N_k})_k$ be a subsequence which converges weakly to a measure P on $D(\mathbb{R}^+; E)$. We know that x is P almost surely continuous at every t except for a countable set D_P and that for t_1, \dots, t_n outside D_P , $P_{N_k} \pi_{t_1, \dots, t_n}^{-1}$ converges weakly to $P \pi_{t_1, \dots, t_n}^{-1}$ where π_{t_1, \dots, t_n} is the projection that carries the point $x \in D(\mathbb{R}^+; E)$ to the point $(x_{t_1}, \dots, x_{t_n})$ of \mathbb{R}^n .

Therefore, it is easy, using dominated convergence theorem and weak convergence properties, to let $k \rightarrow \infty$ in (6) and obtain for t, t_1, \dots, t_n, r outside D_P :

$$\begin{aligned} & \mathbb{E}_P \left(\left(\varphi(x_t) - \varphi(x_0) - \int_0^t \mathcal{A}_\infty \varphi(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right) \\ &= \mathbb{E}_P \left(\left(\varphi(x_r) - \varphi(x_0) - \int_0^r \mathcal{A}_\infty \varphi(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right). \end{aligned} \quad (7)$$

If $t \in D_P$, we choose a sequence (t^k) outside D_P such that $t^k \rightarrow t$ with $t^k > t$. Then $P \pi_{t^k}^{-1}$ converges weakly to $P \pi_t^{-1}$ since x is P -a.s. right continuous in t and x_{t^k} converges almost surely to x_t . Then, we use (7) with t^k instead of t , let $k \rightarrow \infty$ and deduce that (7) also holds for $t \in D_P$. Similarly, we show that t_1, \dots, t_n, r may be taken in D_P .

This shows that the measure P is a solution of the martingale problem associated to the generator \mathcal{A}_∞ on the domain \mathcal{E} .

Hypothesis 2.3 enables us to apply Theorem 2.4. The martingale problem has then a unique solution. It follows that the limit P is equal to P_{x_0} , the law of the PDP, and that the whole sequence $(P_N)_N$ converges weakly to P_{x_0} .

Step 3: Conclusion

Now, we prove Theorem 3.1 with a truncation argument.

Let $\theta \in C^\infty(\mathbb{R}^+)$ such that

$$\begin{cases} \theta(x) = 1, & x \in [0, 1], \\ \theta(x) = 0, & x \in [2, \infty), \end{cases}$$

and, for $k \geq 1$ and $r \in \mathcal{R}$, define

$$\theta_k(x) = \theta \left(\frac{|x|^2}{k^2} \right), \quad x \in E,$$

and

$$\lambda_r^k(x) = \theta_k(x) \lambda_r(x).$$

Then, the problem with λ_r^k instead of λ_r fulfills Hypothesis 2.3. We define $x_k^N = (x_{C,k}^N, X_{D,k}^N)$ the jump Markov process associated to the jump intensities λ_r^k , starting at $x^N(0)$. By the preceding result, we know that, for all $k \in \mathbb{N}$, $(x_k^N)_{N \in \mathbb{N}}$ converges weakly to the PDP x_k in $D(\mathbb{R}^+; E)$, whose characteristics are the jump intensities

λ_r^k , with corresponding transition measure, and vector fields (obvious definitions as in Theorem 3.1).

Then, $((x_k^N)_{k \in \mathbb{N}})_{N \in \mathbb{N}}$ converges weakly to $(x_k)_{k \in \mathbb{N}}$ in $D(\mathbb{R}^+; E)^{\mathbb{N}}$.

By Skorohod representation Theorem (see Billingsley (1971), Theorem 3.3), up to a change of probability space, we may assume that that for all $k \in \mathbb{N}$ $(x_k^N)_N$ converges a.s. to x_k in $D(\mathbb{R}^+; E)$.

Let $T > 0$ and the stopping times

$$\tau^k = \inf\{t \in [0, T], |x_k(t)| \geq k\},$$

with $\tau^k = T$ if $\{t \in [0, T], |x_k(t)| \geq k\} = \emptyset$.

Then, for $k, l \in \mathbb{N}$

$$x_k(t) = x_l(t), \quad t \in [0, \tau^l \wedge \tau^k], \quad a.s.$$

so that τ^k is a.s. non-decreasing.

Moreover, if x (resp. x^N) are the PDP associated to \mathcal{A}_∞ (resp. the Markov jump process associated to \mathcal{A}_N), then

$$x_k(t) = x_t, \quad t \in [0, \tau^k), \quad a.s.$$

and if

$$\tau_N^k = \inf\{t \in [0, T], |x_k^N(t)| \geq k\},$$

with $\tau_N^k = T$ if $\{t \in [0, T], |x_k^N(t)| \geq k\} = \emptyset$, then

$$x_k^N(t) = x^N(t), \quad t \in [0, \tau_N^k), \quad a.s.$$

Let $\delta > 0$. Observing that if $\tau^{k-1} > T - \delta$ and $d_{T-\delta}(x_k^N, x_k) < \epsilon$, where $d_{T-\delta}$ is the distance on $D([0, T - \delta]; E)$, then, for enough small ϵ :

$$\sup_{t \in [0, T-\delta]} |x_k^N(t)| \leq k, \quad a.s.$$

then a.s., $\tau_N^k \geq T - \delta$ and $x_k^N = x^N$ in $[0, T - \delta]$. Since $\tau^k \geq \tau^{k-1} > T - \delta$; we have also, a.s., $x_k = x$ in $[0, T - \delta]$ and

$$d_{T-\delta}(x^N, x) < \epsilon.$$

We deduce that

$$\forall \delta > 0, \quad \mathbb{P}(d_{T-\delta}(x^N, x) \geq \epsilon) \leq \mathbb{P}(\tau^{k-1} \leq T - \delta) + \mathbb{P}(d_{T-\delta}(x_k^N, x_k) \geq \epsilon).$$

Finally, we have

$$\mathbb{P}(\tau^{k-1} \leq T - \delta) = \mathbb{P}\left(\sup_{t \in [0, \tau^k]} |x_k(t)| \geq k - 1\right) \leq \mathbb{P}\left(\sup_{t \in [0, T-\delta]} |x(t)| \geq k - 1\right).$$

By Hypothesis 2.1, the PDP x can not explode in finite time. Thus for k large, this term is small. Then for large N , the second is small. We deduce that x^N converges in probability to x in the new probability space. Returning in the original probability space, we obtain that x^N converges in distribution to x .

4 Piecewise deterministic process with jumps

In this section, we assume that some of the reactions in a subset S_2 of \mathcal{R}_{DC} are such that γ_r^C is large and scales with N . We set $\tilde{\gamma}_r^C = \frac{1}{N}\gamma_r^C$ for $r \in S_2$. We define $S = S_1 \cup S_2$.

The scaled generator has now the form

$$\begin{aligned}
\tilde{\mathcal{A}}_N f(x_C, X_D) &= \sum_{r \in \mathcal{R}_C} \left[f(x_C + \frac{1}{N} \gamma_r^C, X_D) - f(x_C, X_D) \right] N \tilde{\lambda}_r(x_C) \\
&+ \sum_{r \in S_2} [f(x_C + \tilde{\gamma}_r^C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(x_C, X_D) \\
&+ \sum_{r \in S_1} \left[f(x_C + \frac{1}{N} \gamma_r^C, X_D) - f(x_C, X_D) \right] N \tilde{\lambda}_r(x_C, X_D) \\
&+ \sum_{r \in \mathcal{R}_{DC} \setminus S} \left[f(x_C + \frac{1}{N} \gamma_r^C, X_D + \gamma_r^D) - f(x_C, X_D) \right] \lambda_r(x_C, X_D) \\
&+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(X_D).
\end{aligned} \tag{8}$$

For $f \in C_b^1(E)$, we may let $N \rightarrow \infty$ and obtain the limit generator

$$\begin{aligned}
\tilde{\mathcal{A}}_\infty f(x_C, X_D) &= \left(\sum_{r \in \mathcal{R}_C} \tilde{\lambda}_r(x_C) \gamma_r^C + \sum_{r \in S_1} \tilde{\lambda}_r(x_C, X_D) \gamma_r^C \right) \cdot \nabla_{x_C} f(x_C, X_D) \\
&+ \sum_{r \in S_2} [f(x_C + \tilde{\gamma}_r^C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(x_C, X_D) \\
&+ \sum_{r \in \mathcal{R}_{DC} \setminus S} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(x_C, X_D) \\
&+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D + \gamma_r^D) - f(x_C, X_D)] \lambda_r(X_D).
\end{aligned}$$

This formal argument indicates that if $N \rightarrow \infty$, the process is a piecewise deterministic process with jumps both in x_C and X_D . In fact, the proof of this can be done easily thanks to the result of section 3.

Indeed, let us introduce the following auxiliary system of reactions involving the variable $(x_C^{1,N}, x_C^{2,N}, X_D^N) \in \mathbb{R}^{M_C} \times \mathbb{R}^{M_C} \times \mathbb{N}^{M_D}$:

- If $r \in \mathcal{R}_C$, $(x_C^{1,N}, x_C^{2,N}, X_D^N) \rightarrow (x_C^{1,N} + \frac{1}{N} \gamma_r^C, x_C^{2,N}, X_D^N)$
- If $r \in S_2$, $(x_C^{1,N}, x_C^{2,N}, X_D^N) \rightarrow (x_C^{1,N}, x_C^{2,N} + \tilde{\gamma}_r^C, X_D^N + \gamma_r^D)$
- If $r \in \mathcal{R}_{DC} \setminus S_2$, $(x_C^{1,N}, x_C^{2,N}, X_D^N) \rightarrow (x_C^{1,N} + \frac{1}{N} \gamma_r^C, x_C^{2,N}, X_D^N + \gamma_r^D)$
- If $r \in \mathcal{R}_D$, $(x_C^{1,N}, x_C^{2,N}, X_D^N) \rightarrow (x_C^{1,N}, x_C^{2,N}, X_D^N + \gamma_r^D)$

The rates of these reactions are $\lambda_r(x_C^{1,N}, x_C^{2,N}, X_D^N) = \lambda_r(x_C^{1,N} + x_C^{2,N}, X_D^N)$.

If we choose the initial data $(x_C^N(0), 0, X_D^N(0))$ then this system and the original system are equivalent. Indeed, we recover the value of the original system by the relation:

$$(x_C^N, X_D^N) = (x_C^{1,N} + x_C^{2,N}, X_D^N).$$

Conversely, notice that x_C^N is a sum of a pure jump part and of a continuous one so that given (x_C^N, X_D^N) , $(x_C^{1,N}, x_C^{2,N}, X_D^N)$ can be recovered by isolating from x_C^N the small jumps to obtain $x_C^{1,N}$ and the jump of order one (from S_2) to obtain $x_C^{2,N}$.

The auxiliary system corresponds to the following generator:

$$\begin{aligned}
& \mathcal{A}_{aux} f(x_C^1, x_C^2, X^D) \\
&= \sum_{r \in \mathcal{R}_C} \left[f(x_C^1 + \frac{1}{N} \gamma_r^C, x_C^2, X^D) - f(x_C^1, x_C^2, X^D) \right] N \tilde{\lambda}_r(x_C^1 + x_C^2) \\
&+ \sum_{r \in S_2} [f(x_C^1, x_C^2 + \tilde{\gamma}_r^C, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D)] \lambda_r(x_C^1 + x_C^2, X^D) \\
&+ \sum_{r \in S_1} \left[f(x_C^1 + \frac{1}{N} \gamma_r^C, x_C^2, X^D) - f(x_C^1, x_C^2, X^D) \right] N \tilde{\lambda}_r(x_C^1 + x_C^2, X^D) \tag{9} \\
&+ \sum_{r \in \mathcal{R}_{DC} \setminus S} \left[f(x_C^1 + \frac{1}{N} \gamma_r^C, x_C^2, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D) \right] \lambda_r(x_C^1 + x_C^2, X^D) \\
&+ \sum_{r \in \mathcal{R}_D} [f(x_C^1, x_C^2, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D)] \lambda_r(X^D).
\end{aligned}$$

This generator is of the form as in section 3 but the discrete variable is now (x_C^2, X^D) . Using the results proved in this section we thus obtain that this auxiliary system of reaction converges in distribution to the piecewise continuous deterministic process given by the generator

$$\begin{aligned}
& \mathcal{A}_{aux, \infty} f(x_C^1, x_C^2, X^D) \\
&= \left(\sum_{r \in \mathcal{R}_C} \tilde{\lambda}_r(x_C^1 + x_C^2, X^D) \gamma_r^C + \sum_{r \in S_1} \tilde{\lambda}_r(x_C^1 + x_C^2, X^D) \gamma_r^C \right) \cdot \nabla_{x_C^1} f(x_C^1, x_C^2, X^D) \\
&+ \sum_{r \in S_2} [f(x_C^1, x_C^2 + \tilde{\gamma}_r^C, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D)] \lambda_r(x_C^1 + x_C^2, X^D) \\
&+ \sum_{r \in \mathcal{R}_{DC} \setminus S} [f(x_C^1, x_C^2, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D)] \lambda_r(x_C^1 + x_C^2, X^D) \\
&+ \sum_{r \in \mathcal{R}_D} [f(x_C^1, x_C^2, X^D + \gamma_r^D) - f(x_C^1, x_C^2, X^D)] \lambda_r(X^D).
\end{aligned}$$

Going back to the original variables, i.e. setting $x_C = x_C^1 + x_C^2$, we deduce that the original system converges in distributions to the piecewise deterministic process with generator $\tilde{\mathcal{A}}_\infty$.

To obtain this convergence, we suppose that the jump intensities are C^1 -differentiable with respect to the variable x_C^1 and that the limit PDP satisfies Hypothesis 2.1.

5 Averaging

In this section, we examine the case when (4) is not satisfied by all the discrete variables. In this case, the previous results are not valid. We introduce the decomposition $X^D = (X_D^1, X_D^2) \in \mathbb{N}^{M_{D,1}} \times \mathbb{N}^{M_{D,2}}$ and $\gamma_r^D = (\gamma_r^{D,1}, \gamma_r^{D,2})$ such that

$$\gamma_r^{D,1} = 0, \quad r \in S_1.$$

This replaces (4). The continuous variable x_C follows the same characteristics as in section 3.

In the set of the reactions S_1 , the discrete variable X_D^2 has fast motion, its jumps rates are of order N and its jumps are of order 1.

More precisely, for $r \in S_1$, the state changes according to

$$(x_C, X_D^1, X_D^2) \rightarrow (x_C + \frac{1}{N}\gamma_r^C, X_D^1, X_D^2 + \gamma_r^{D,2})$$

with the rate $N\tilde{\lambda}_r(x_C, X_D^1, X_D^2)$.

We now have the following generator for the process :

$$\begin{aligned} & \tilde{A}_N f(x_C, X_D^1, X_D^2) \\ &= \sum_{r \in \mathcal{R}_C} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D^1, X_D^2) - f(x_C, X_D^1, X_D^2) \right] N\tilde{\lambda}_r(x_C) \\ &+ \sum_{r \in S_1} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D^1, X_D^2 + \gamma_r^{D,2}) - f(x_C, X_D^1, X_D^2) \right] N\tilde{\lambda}_r(x_C, X_D^1, X_D^2) \\ &+ \sum_{r \in \mathcal{R}_{DC} \setminus S_1} \left[f(x_C + \frac{1}{N}\gamma_r^C, X_D^1 + \gamma_r^{D,1}, X_D^2 + \gamma_r^{D,2}) - f(x_C, X_D^1, X_D^2) \right] \lambda_r(x_C, X_D^1, X_D^2) \\ &+ \sum_{r \in \mathcal{R}_D} \left[f(x_C, X_D^1 + \gamma_r^{D,1}, X_D^2 + \gamma_r^{D,2}) - f(x_C, X_D^1, X_D^2) \right] \lambda_r(X_D^1, X_D^2). \end{aligned} \tag{10}$$

This new model combines slow and fast motions. This leads to double time scale evolution which can be further simplified. Contrary to the previous sections, we can not take the formal limit of this generator. The idea is to average in fast discrete variables X_D^2 , and focus on the slow variables (x_C, X_D^1) , in order to obtain a much simpler averaged generator. We assume that X_D^2 takes only a finite number of values: there exists a finite set K in $\mathbb{N}^{M_{D,2}}$ such that $X_D^2 \in K$.

To this aim, we introduce the following generator depending on (x_C, X_D^1) :

$$\mathcal{A}_{x_C, X_D^1} h(X_D^2) = \sum_{r \in S_1} [h(X_D^2 + \gamma_r^{D,2}) - h(X_D^2)] \tilde{\lambda}_r(x_C, X_D^1, X_D^2).$$

We assume that for all (x_C, X_D^1) , the process associated to the generator \mathcal{A}_{x_C, X_D^1} is uniquely ergodic, and we denote by ν_{x_C, X_D^1} its unique invariant measure.

Then we define the averaged jump rates:

$$\begin{aligned} \bar{\lambda}_r(x_C, X_D^1) &= \int_{\mathbb{N}^{M_{D,2}}} \tilde{\lambda}_r(x_C, X_D^1, X_D^2) \nu_{x_C, X_D^1}(dX_D^2), \quad r \in S_1, \\ \bar{\lambda}_r(x_C, X_D^1) &= \int_{\mathbb{N}^{M_{D,2}}} \lambda_r(x_C, X_D^1, X_D^2) \nu_{x_C, X_D^1}(dX_D^2), \quad r \in \mathcal{R}_{DC} \setminus S_1, \\ \bar{\lambda}_r(x_C, X_D^1) &= \int_{\mathbb{N}^{M_{D,2}}} \lambda_r(X_D^1, X_D^2) \nu_{x_C, X_D^1}(dX_D^2), \quad r \in \mathcal{R}_D. \end{aligned} \tag{11}$$

We present now the main result of this section.

Theorem 5.1 *Let $x^N = (x_C^N, X_{D,1}^N, X_{D,2}^N)$ be a jump Markov process with generator \tilde{A}_N , starting at $x^N(0) = (x_C^N(0), X_{D,1}^N(0), X_{D,2}^N(0))$. Assume that the set of values of $X_{D,2}$ is finite and that for all (x_C, X_D^1) , the process associated to the generator \mathcal{A}_{x_C, X_D^1} is uniquely ergodic. Assume also that the jump rate $\tilde{\lambda}_r$, $r \in \mathcal{R}_C \cap S_1$, and λ_r , $r \in \mathcal{R}_{DC} \setminus S_1$ and $\bar{\lambda}_r$, $r \in \mathcal{R}_{DC} \cup \mathcal{R}_D$, are C^1 with respect to x_C . Define P_{x_0} the law of the PDP starting at $x_0 = (x_{C,0}, X_{D,0}^1)$ whose jump intensities are:*

$$\lambda(x_C, X_D^1) = \sum_{r \in (\mathcal{R}_{DC} \setminus S_1) \cup \mathcal{R}_D} \bar{\lambda}_r(x_C, X_D^1),$$

with transition measure:

$$\int_E f(z)Q(dz; x_C, X_D^1) = \frac{1}{\lambda(x_C, X_D^1)} \sum_{r \in (\mathcal{R}_{DC} \setminus S_1) \cup \mathcal{R}_D} f(x_C, X_D^1 + \gamma_r^{D,1}) \bar{\lambda}_r(x_C, X_D^1),$$

and vectors fields:

$$F_{X_D^1}(x_C) = \sum_{r \in \mathcal{R}_C} \gamma_r^C \tilde{\lambda}_r(x_C) + \sum_{r \in S_1} \gamma_r^C \bar{\lambda}_r(x_C, X_D^1).$$

Assume that

1. λ, Q and F satisfy Hypothesis 2.1.
2. $(x_C^N(0), X_D^{1,N}(0))$ converges in distribution to x_0 in $\mathbb{R}^{M_C} \times \mathbb{N}^{M_{D,1}}$.
3. there exists $K_1 > 0$ and $K_2 > 0$ such that, for every $s \in \mathbb{R}^+$, $(x_C, X_D^1, X_D^2) \in E$, and for every bounded function g satisfying the centering condition

$$\int_{\mathbb{N}^{M_{D,2}}} g(X_D^2) \nu_{x_C, X_D^1}(dX_D^2) = 0 \quad (12)$$

we have

$$P_s^{x_C, X_D^1} g(X_D^2) < K_1 e^{-K_2 s} \|g\|_\infty$$

where $(P_s^{x_C, X_D^1})_s$ is the semigroup associated to \mathcal{A}_{x_C, X_D^1} .

4. if g is a bounded function satisfying the centering condition (12), the Poisson equation

$$\sum_{r \in S_1} [h(x_C, X_D^1, X_D^2 + \gamma_r^{D,2}) - h(x_C, X_D^1, X_D^2)] \tilde{\lambda}_r(x_C, X_D^1, X_D^2) = g(X_D^2)$$

has a solution given by

$$h(x_C, X_D^1, X_D^2) = - \int_0^\infty P_s^{x_C, X_D^1} g(X_D^2) ds$$

and this solution is Lipschitz with respect to x_C , uniformly in X_D^1 .

Then $(x_C^N, X_D^{1,N})$ converges in distribution in $D(\mathbb{R}^+; \mathbb{R}^{M_C} \times \mathbb{N}^{M_{D,1}})$ to the PDP whose law is P_{x_0} .

Remark 5.2 Assumptions 1. and 2. are similar to those made previously. Assumptions 3. and 4. guaranty that it is possible to average with respect to the variable X_D^2 . Assumption 3. states that the dynamic associated to the generator \mathcal{A}_{x_C, X_D^1} is exponentially mixing, uniformly with respect to (x_C, X_D^1) , assumption 4. then follows if \mathcal{A}_{x_C, X_D^1} depends smoothly on x_C .

Proof

The steps of the proof are similar to the proof of the Theorem 3.1. We begin by supposing that all the jump rates are bounded as well as their derivatives. This Hypothesis will be removed at the end of the proof. We take $E = \mathbb{R}^{M_C} \times \mathbb{N}^{M_{D,1}}$.

Step 1: Tightness.

The proof of the tightness of the laws of $(x_C^N, X_{D,1}^N)$ is similar as in section 3, and is left to the reader.

Step 2: Identification of limit points.

Since we are interested by the evolution of (x_C, X_D^1) , it is natural to consider, for the generator $\tilde{\mathcal{A}}_N$, test functions $f(x_C, X_D^1)$ depending only on those variables. Unfortunately, it remains some terms of order 1 depending on the variable X_D^2 . To

overcome this problem, we introduce 'perturbed test functions' (see Papanicolaou et al. (1976), Kushner (1994), Fouque et al. (2007)) :

$$f_N(x_C, X_D^1, X_D^2) = f(x_C, X_D^1) + \frac{1}{N} f^1(x_C, X_D^1, X_D^2),$$

with $f \in \mathcal{E}$ and f independent of X_D^2 . We temporarily need that f is also C^2 with bounded second derivatives with respect to x_C . The function f^1 is chosen such that the formal limit of $\tilde{\mathcal{A}}_N f_N(x_C, X_D^1, X_D^2)$ does not depend on X_D^2 .

This can be done by taking f^1 such that

$$\sum_{r \in S_1} [f^1(x_C, X_D^1, X_D^2 + \gamma_r^{D,2}) - f^1(x_C, X_D^1, X_D^2)] \tilde{\lambda}_r(x_C, X_D^1, X_D^2) = g_{x_C, X_D^1}(X_D^2) \quad (13)$$

with

$$\begin{aligned} & g_{x_C, X_D^1}(X_D^2) \\ &= \left(\sum_{r \in S_1} \gamma_r^C \bar{\lambda}_r(x_C, X_D^1) - \gamma_r^C \tilde{\lambda}_r(x_C, X_D^1, X_D^2) \right) \cdot \nabla_{x_C} f(x_C, X_D^1) \\ &+ \sum_{r \in \mathcal{R}_{DC} \setminus S_1} [f(x_C, X_D^1 + \gamma_r^{D,1}) - f(x_C, X_D^1)] (\bar{\lambda}_r(x_C, X_D^1) - \lambda_r(x_C, X_D^1, X_D^2)) \\ &+ \sum_{r \in \mathcal{R}_D} [f(x_C, X_D^1 + \gamma_r^{D,1}) - f(x_C, X_D^1)] (\bar{\lambda}_r(x_C, X_D^1) - \lambda_r(X_D^1, X_D^2)) \end{aligned} \quad (14)$$

Since the jump rates are assumed to be bounded, g_{x_C, X_D^1} is clearly bounded. Also, the function g_{x_C, X_D^1} is zero mean with respect to the invariant distribution, i.e. g_{x_C, X_D^1} satisfy (12).

Then, the function f^1 satisfying (13) exists under our assumptions. Moreover, it is not difficult to check that f^1 is Lipschitz with respect to x_C , uniformly with respect to X_D^1 .

Limiting infinitesimal generator.

We now return to the analysis of the limiting problem. We denote by $P_{x,N}$ the law of $(x_C^N, X_{D,1}^N, X_{D,2}^N)$, then

$$\begin{aligned} & f_N(x_C(t), X_D^1(t), X_D^2(t)) - f_N(x_C(0), X_D^1(0), X_D^2(0)) \\ & - \int_0^t \tilde{\mathcal{A}}_N f_N(x_C(s), X_D^1(s), X_D^2(s)) ds \end{aligned}$$

is a $P_{x,N}$ martingale. Equivalently, for each $n \in \mathbb{N}$, $t_1, \dots, t_n \in [0, r]$, $t \geq r \geq 0$, $\psi \in (C_b(\mathbf{E}))^n$

$$\begin{aligned} & \mathbb{E}_{P_{x,N}} \left(\left(f_N(x_t) - f_N(x_0) - \int_0^t \tilde{\mathcal{A}}_N f_N(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right) \\ &= \mathbb{E}_{P_{x,N}} \left(\left(f_N(x_r) - f_N(x_0) - \int_0^r \tilde{\mathcal{A}}_N f_N(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right) \end{aligned} \quad (15)$$

Let us now consider a subsequence $(\tilde{P}_{x, N_k})_k$ of $(\tilde{P}_{x, N})_N$, the laws of $(x_C^N, X_{D,1}^N)$ which weakly converges to a measure \tilde{P}_x on $D(\mathbb{R}^+; \mathbb{R}^{M_C} \times \mathbb{N}^{M_{D,1}})$.

It is clear that f_N converges to f , uniformly on E . Moreover, the continuity and boundedness properties of f^1 ensure that $\tilde{A}_N f_N$ converges on E towards $\tilde{A}_\infty f$, where

$$\begin{aligned} & \tilde{A}_\infty f(x_C, X_D^1) \\ &= \left(\sum_{r \in \mathcal{R}_C} \gamma_r^C \tilde{\lambda}_r(x_C) + \sum_{r \in \mathcal{S}_1} \gamma_r^C \tilde{\lambda}_r(x_C, X_D^1) \right) \cdot \nabla_{x_C} f(x_C, X_D^1) \\ &+ \sum_{r \in (\mathcal{R}_{DC} \setminus \mathcal{S}_1) \cup \mathcal{R}_D} [f(x_C, X_D^1 + \gamma_r^{D,1}) - f(x_C, X_D^1)] \tilde{\lambda}_r(x_C, X_D^1). \end{aligned} \quad (16)$$

It is the generator of a PDP whose characteristics have been averaged in fast variable X_D^2 .

Equation (15) gives, as $N_k \rightarrow \infty$:

$$\begin{aligned} & \mathbb{E}_{\tilde{P}_x} \left(\left(f(x_t) - f(x_0) - \int_0^t \tilde{A}_\infty f(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right) \\ &= \mathbb{E}_{\tilde{P}_x} \left(\left(f(x_r) - f(x_0) - \int_0^r \tilde{A}_\infty f(x_s) ds \right) \psi(x_{t_1}, \dots, x_{t_n}) \right). \end{aligned} \quad (17)$$

Recall that we have assumed that f is C^2 with respect to x_C . It is easy to prove that (17) holds for any $f \in \mathcal{E}$ by choosing a sequence (f_n) in \mathcal{E} such that, for all n , f_n is C^2 with bounded second derivatives and f_n and ∇f_n are uniformly bounded and converge pointwise to f and ∇f .

The measure \tilde{P}_x is then a solution of the martingale problem associated to the generator \tilde{A}_∞ on the domain of the functions in \mathcal{E} independent of X_D^2 .

By the Theorem 2.4, the martingale problem has then a unique solution. We can then deduce that $(\tilde{P}_{x,N})_N$ converges weakly to P_{x_0} , the law of the PDP defined in the Theorem 5.1.

Step 3: Conclusion.

Since X_D^2 is assumed to live in a finite set, we can remove the boundedness assumption on the jumps rates as in section 3. We then conclude as in section 3. Theorem 5.1 is proved.

6 Discontinuous PDP and singular switching

In this section, our system has two time scales. The switching between fast and slow dynamics is governed by the state of a discrete variable. For simplicity, we suppose now that there is no other discrete variable and denote by θ , taking values in $\{0, 1\}$, this unique discrete variable which governs the time scale of the continuous variables.

The number of molecules belonging to species C are again supposed to be of order N , and we continue to write $x_C = \frac{X_C}{N}$.

When $\theta = 0$, the rates of all reactions from $\mathcal{R}_C \cup \mathcal{R}_{DC}$ is of order N . When $\theta = 1$, some reactions (inactive for $\theta = 0$) become active with much faster rates of order $\frac{N}{\epsilon}$, where ϵ is a new parameter, supposed to be small. For simplicity we consider that there are no \mathcal{R}_C type reactions. This would cause only slightly more complicated notations. Then for $r \in \mathcal{R}_{DC}$, we introduce the rescaled reaction rates

$$\begin{aligned} \tilde{\lambda}_r(x_C, 0) &= \frac{1}{N} \lambda_r(x_C, 0) \\ \tilde{\lambda}_r(x_C, 1) &= \frac{\epsilon}{N} \lambda_r(x_C, 1). \end{aligned}$$

This system will not have a limit if θ stays for too long time in the state 1. The rate of the reaction changing θ from state 1 to state 0 is supposed to be of order $\frac{1}{\epsilon}$ and we also set:

$$\tilde{\lambda}_\theta(x_C, 1) = \epsilon \lambda_\theta(x_C, 1).$$

The opposite reaction changing θ from state 0 to state 1 is written $\lambda_\theta(x_C, 0)$.

In these conditions, the generator of the process has the following form:

$$\begin{aligned} & \tilde{\mathcal{A}}_{N,\epsilon} f(x_C, 0) \\ &= \sum_{r \in \mathcal{R}_{DC}} \left[f(x_C + \frac{1}{N} \gamma_r^C, 0) - f(x_C, 0) \right] N \tilde{\lambda}_r(x_C, 0) + [f(x_C, 1) - f(x_C, 0)] \lambda_\theta(x_C, 0), \end{aligned}$$

and

$$\begin{aligned} & \tilde{\mathcal{A}}_{N,\epsilon} f(x_C, 1) \\ &= \frac{1}{\epsilon} \sum_{r \in \mathcal{R}_{DC}} \left[f(x_C + \frac{1}{N} \gamma_r^C, 1) - f(x_C, 1) \right] N \tilde{\lambda}_r(x_C, 1) + \frac{1}{\epsilon} [f(x_C, 0) - f(x_C, 1)] \tilde{\lambda}_\theta(x_C, 1). \end{aligned}$$

At the limit (for high N and small ϵ), we will show that the discrete process θ inducing kicks in the continuous variable x_C is almost surely equal to 0. We are interested in the limit distribution of the process x_C .

We introduce the flow $\phi_1(t, x_C)$, associated to the vector fields

$$F_1(x_C) = \sum_{r \in \mathcal{R}_{DC}} \gamma_r^C \tilde{\lambda}_r(x_C, 1).$$

We now state the main result of this section.

Theorem 6.1 *Let $x^{N,\epsilon} = (x_C^{N,\epsilon}, \theta^{N,\epsilon})$ be a jump Markov process with values in $\mathbb{R}^{M_C} \times \{0, 1\}$, with generator $\tilde{\mathcal{A}}_{N,\epsilon}$, starting at $x^{N,\epsilon}(0) = (x_C^{N,\epsilon}(0), \theta^{N,\epsilon}(0))$. Assume that the following assumptions hold:*

- $x_C^{N,\epsilon}(0)$ converges in distribution to $x_C(0)$ in \mathbb{R}^{M_C} as $N \rightarrow \infty$ and $\epsilon \rightarrow 0$.
- $\theta^{N,\epsilon}(0)$ converges in distribution to 0 as $N \rightarrow \infty$ and $\epsilon \rightarrow 0$.
- The jump rates $\tilde{\lambda}_r$, for $r \in \mathcal{R}_{DC}$, $\tilde{\lambda}_\theta(\cdot, 1)$ and $\lambda_\theta(\cdot, 0)$ are uniformly bounded, C^1 with respect to x_C , and their derivatives are uniformly bounded. Moreover, there exists $\alpha > 0$, such that

$$\tilde{\lambda}_\theta(x_C, 1) \geq \alpha, \quad \forall x_C \in \mathbb{R}^{M_C}.$$

Then $(x_C^{N,\epsilon})$ converges in distribution in $L^p([0, T]; \mathbb{R}^{M_C})$, for any $\infty > p \geq 1$, to the PDP whose generator is given by

$$\begin{aligned} \tilde{\mathcal{A}}_\infty \varphi(x_C) &= \left(\sum_{r \in \mathcal{R}_{DC}} \gamma_r^C \tilde{\lambda}_r(x_C, 0) \right) \cdot \nabla_{x_C} \varphi(x_C) \\ &+ \lambda_\theta(x_C, 0) \int_0^\infty (\varphi(\phi_1(t, x_C)) - \varphi(x_C)) \tilde{\lambda}_\theta(\phi_1(t, x_C), 1) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(s, x_C), 1) ds} dt \end{aligned}$$

for every $\varphi \in C_b^1(\mathbb{R}^{M_C})$.

Remark 6.2 *The PDP associated to the generator $\tilde{\mathcal{A}}_\infty$ has discontinuities which are not present for the process $x_C^{N,\epsilon}$. They only appear at the limit $\epsilon \rightarrow 0$. Therefore, the convergence does not occur in $D(\mathbb{R}^+; [0, T])$, indeed creation of discontinuities can not occur in $D(\mathbb{R}^+; [0, T])$. As shown below, it is possible to show tightness, then weak convergence of the process $x_C^{N,\epsilon}$ in $L^p([0, T])$. Unfortunately, this topology does not imply a uniform bound on the processes and we cannot get rid of the boundedness assumptions on the reaction rates as was done in the preceding sections.*

Proof: The proof is divided into four steps.

Step 1: Limit of $\theta^{N,\epsilon}$

We begin with the test-function

$$f(x_C, 0) = 0, \quad f(x_C, 1) = 1, \quad \forall x_C \in \mathbb{R}^{Mc}$$

Then, $\tilde{A}_{N,\epsilon} f(x_C, \theta) = \lambda_\theta(x_C, 0) \mathbb{1}_{\theta=0} - \frac{1}{\epsilon} \tilde{\lambda}_\theta(x_C, 1) \mathbb{1}_{\theta=1}$, and

$$\mathbb{1}_{\theta^{N,\epsilon}(t)=1} - \mathbb{1}_{\theta^{N,\epsilon}(0)=1} - \int_0^t \lambda_\theta(x_C^{N,\epsilon}(s), 0) \mathbb{1}_{\theta^{N,\epsilon}(s)=0} - \frac{1}{\epsilon} \tilde{\lambda}_\theta(x_C^{N,\epsilon}(s), 1) \mathbb{1}_{\theta^{N,\epsilon}(s)=1} ds$$

is a martingale. We then deduce, for every $T > 0$ and $t \in [0, T]$,

$$\frac{\alpha}{\epsilon} \mathbb{E} \left(\int_0^t \mathbb{1}_{\theta^{N,\epsilon}(s)=1} ds \right) \leq M_\lambda T + 1 \quad (18)$$

where M_λ is the superior bound of $\lambda_\theta(\cdot, 0)$. Then, $\theta^{N,\epsilon} \rightarrow 0$ in $L^1(\Omega \times [0, T]; \{0, 1\})$ when $\epsilon \rightarrow 0$ and $N \rightarrow \infty$.

Step 2: Tightness of $x_C^{N,\epsilon}$

For all $t \in [0, T]$, we write

$$x_C^{N,\epsilon}(t) = x_C^{N,\epsilon}(0) + \sum_{r \in \mathcal{R}_{DC}} \frac{\gamma_r^C}{N} Y_r \left(\int_0^t N \tilde{\lambda}_r(x_C^{N,\epsilon}(s), 0) \mathbb{1}_{\theta^{N,\epsilon}(s)=0} + \frac{N}{\epsilon} \tilde{\lambda}_r(x_C^{N,\epsilon}(s), 1) \mathbb{1}_{\theta^{N,\epsilon}(s)=1} ds \right)$$

where $(Y_r)_{r \in \mathcal{R}_{DC}}$ are independent standard Poisson processes. Then

$$\left| x_C^{N,\epsilon}(t) \right| \leq \left| x_C^{N,\epsilon}(0) \right| + \sum_{r \in \mathcal{R}_{DC}} \frac{|\gamma_r^C|}{N} Y_r \left(NM \left(T + \frac{1}{\epsilon} \int_0^T \mathbb{1}_{\theta^{\epsilon,N}(s)=1} ds \right) \right) \quad (19)$$

where M is the superior bound of $\tilde{\lambda}_r, r \in \mathcal{R}_{DC}$. Since $\sup_{t \in [0, T]} \frac{1}{N} Y_r(Nt)$ is almost surely bounded, using (18) and (19), we have for all $K > 0$, for N large enough and ϵ small enough:

$$\mathbb{P}(\sup_{[0, T]} |x_C^{\epsilon, N}(t)| \geq K) \leq \varepsilon(K)$$

where $\varepsilon(K) \rightarrow 0$ if $K \rightarrow \infty$.

We introduce $BV(0, T)$ the space of functions of bounded variations on $[0, T]$, with its norm, defined for $f \in BV(0, T)$ by

$$\|f\|_{BV(0, T)} = \|f\|_{L^1([0, T])} + \sup \left\{ \sum_i |f(t_{i+1}) - f(t_i)|, \text{ for } (t_i)_i \text{ a finite subdivision of } [0, T] \right\}$$

Since the processes Y_r are non decreasing, we obtain for a subdivision of $[0, T]$, denoted by $0 = t_0 < t_1 < \dots < t_n = T$,

$$\begin{aligned} & \sum_{i=0}^{n-1} |x_C^{\epsilon, N}(t_{i+1}) - x_C^{\epsilon, N}(t_i)| \\ & \leq \sum_{i=0}^{n-1} \sum_{r \in \mathcal{R}_{DC}} \frac{|\gamma_r^C|}{N} \left[Y_r \left(\int_0^{t_{i+1}} N \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 0) \mathbb{1}_{\theta^{\epsilon, N}(s)=0} + \frac{N}{\epsilon} \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 1) \mathbb{1}_{\theta^{\epsilon, N}(s)=1} ds \right) \right. \\ & \quad \left. - Y_r \left(\int_0^{t_i} N \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 0) \mathbb{1}_{\theta^{\epsilon, N}(s)=0} + \frac{N}{\epsilon} \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 1) \mathbb{1}_{\theta^{\epsilon, N}(s)=1} ds \right) \right] \\ & = \sum_{r \in \mathcal{R}_{DC}} \frac{|\gamma_r^C|}{N} Y_r \left(\int_0^T N \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 0) \mathbb{1}_{\theta^{\epsilon, N}(s)=0} + \frac{N}{\epsilon} \tilde{\lambda}_r(x_C^{\epsilon, N}(s), 1) \mathbb{1}_{\theta^{\epsilon, N}(s)=1} ds \right) \end{aligned}$$

It is then easy to prove that for all $K > 0$, for N large enough and ϵ small enough:

$$\mathbb{P}(\|x_C^{N,\epsilon}\|_{BV(0,T)} \geq K) \leq \varepsilon(K)$$

where $\varepsilon(K) \rightarrow 0$ if $K \rightarrow \infty$.

The set $\{f \in BV(0,T), \text{ such that } \|f\|_{BV(0,T)} \leq K\}$ is relatively compact in $L^1([0,T])$ (see for instance Giusti (1984)), and the set

$$\{f \in BV(0,T), \text{ such that } \|f\|_\infty \leq K \text{ and } \|f\|_{BV(0,T)} \leq K\}$$

is relatively compact in $L^p([0,T])$ for $1 < p < \infty$. We then conclude that the family of processes $(x_C^{N,\epsilon})_{N,\epsilon}$ is tight in $L^p([0,T])$, $1 \leq p < \infty$.

Step 3: Identification of the limit distribution of $x_C^{N,\epsilon}$

Since we are interested by the limit distribution of $x_C^{N,\epsilon}$, we introduce test-functions depending only on the continuous variable $x_C \in \mathbb{R}^{M_C}$. We then define

$$f(x_C, 0) = \varphi(x_C), \quad x_C \in \mathbb{R}^{M_C}$$

where $\varphi \in C_b^1(\mathbb{R}^{M_C})$.

We want to define $f(\cdot, 1)$ such that

$$\begin{aligned} & \sum_{r \in \mathcal{R}_{DC}} \left[f(x_C + \frac{1}{N} \gamma_r^C, 1) - f(x_C, 1) \right] N \tilde{\lambda}_r(x_C, 1) - \tilde{\lambda}_\theta(x_C, 1) f(x_C, 1) \\ & = -\tilde{\lambda}_\theta(x_C, 1) \varphi(x_C). \end{aligned} \tag{20}$$

Drawing inspiration from the preceding section, we introduce the process $y_N(\cdot, x)$ starting from x , and whose generator is

$$A_N \psi(y) = \sum_{r \in \mathcal{R}_{DC}} \left[\psi(y + \frac{1}{N} \gamma_r^C) - \psi(y) \right] N \tilde{\lambda}_r(y, 1).$$

Since F_1 is Lipschitz on \mathbb{R}^{M_C} , a result of Kurtz (1971) states that for all $x \in \mathbb{R}^{M_C}$, $T > 0$ and $\delta > 0$,

$$\mathbb{P} \left(\sup_{s \leq T} |y_N(s, x) - \phi_1(s, x)| > \delta \right) \xrightarrow{N \rightarrow \infty} 0. \tag{21}$$

Remember that $\phi_1(\cdot, x)$ is the flow associated to the vector field $F_1(x) = \sum_{r \in \mathcal{R}_{DC}} \gamma_r^C \tilde{\lambda}_r(x, 1)$ and starting at x .

We also introduce the semigroup $(P_t^N)_{t \geq 0}$ defined on $\mathcal{B}_b(\mathbb{R}^{M_C})$ by

$$P_t^N \psi(x) := \mathbb{E} \left(\psi(y_N(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(s, x), 1) ds} \right).$$

It is classical that $(P_t^N)_{t \geq 0}$ satisfies the semigroup property and that

$$\frac{d}{dt} P_t^N \psi(x) = A_N P_t^N \psi(x) - \tilde{\lambda}_\theta(x, 1) P_t^N \psi(x), \quad x \in \mathbb{R}^{M_C}, \quad \psi \in \mathcal{C}_b(\mathbb{R}^{M_C}), t \in \mathbb{R}^+.$$

Then we propose:

$$f(x_C, 1) := \int_0^\infty P_s^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) ds.$$

Since $\tilde{\lambda}_\theta(\cdot, 1)$ is bounded below by $\alpha > 0$, $f(\cdot, 1)$ is well defined. Moreover $f(\cdot, 1)$ satisfies (20). Indeed,

$$\begin{aligned} & A_N f(x_C, 1) - \tilde{\lambda}_\theta(x_C, 1) f(x_C, 1) \\ & = \int_0^\infty A_N P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) - \tilde{\lambda}_\theta(x_C, 1) P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) dt \\ & = \int_0^\infty \frac{d}{dt} P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) dt \\ & = \lim_{t \rightarrow \infty} P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) - \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) \\ & = - \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C) \end{aligned}$$

This test-function f satisfies:

$$\tilde{\mathcal{A}}_{N,\epsilon} f(x_C, 1) = 0$$

and

$$\begin{aligned} \tilde{\mathcal{A}}_{N,\epsilon} f(x_C, 0) &= \sum_{r \in \mathcal{R}_{DC}} \left[f(x_C + \frac{1}{N} \gamma_r^C, 0) - f(x_C, 0) \right] N \tilde{\lambda}_r(x_C, 0) \\ &+ \left[\int_0^\infty P_t^N (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(x_C) dt - \varphi(x_C) \right] \lambda_\theta(x_C, 0). \end{aligned}$$

Since $f \in C_b(E)$, f is in the domain of $\tilde{\mathcal{A}}_{N,\epsilon}$, for all N, ϵ . Then, for all $0 \leq t_1, \dots, t_\ell \leq t$ and $\psi \in C_b(\mathbb{R}^{M_C \times \ell})$

$$\begin{aligned} &\mathbb{E} \left(\left[f(x_C^{N,\epsilon}(t), \theta^{N,\epsilon}(t)) - f(x_C^{N,\epsilon}(0), \theta^{N,\epsilon}(0)) \right. \right. \\ &\left. \left. - \int_0^t \tilde{\mathcal{A}}_{N,\epsilon} f(x_C^{N,\epsilon}(s), 0) \mathbb{1}_{\theta^{N,\epsilon}(s)=0} ds \right] \psi(x_C^{N,\epsilon}(t_1), \dots, x_C^{N,\epsilon}(t_\ell)) \right) = 0. \end{aligned} \quad (22)$$

We now are searching a possible formulation for the limit generator. For all $x \in \mathbb{R}^{M_C}$ and uniformly in $t \in [0, T]$, for all $T > 0$, we have

$$P_t^N (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(x) \xrightarrow{N \rightarrow \infty} (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(\phi_1(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(s, x), 1) ds}.$$

Indeed,

$$\begin{aligned} &P_t^N (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(x) - (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(\phi_1(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(s, x), 1) ds} \\ &= \mathbb{E} \left((\tilde{\lambda}_\theta(\cdot, 1) \varphi)(y_N(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(s, x), 1) ds} - (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(\phi_1(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(s, x), 1) ds} \right) \\ &+ \mathbb{E} \left((\tilde{\lambda}_\theta(\cdot, 1) \varphi)(\phi_1(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(s, x), 1) ds} - (\tilde{\lambda}_\theta(\cdot, 1) \varphi)(\phi_1(t, x)) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(s, x), 1) ds} \right) \\ &= a + b \end{aligned}$$

and it can be shown that for all $\delta > 0$, and $t \leq T$,

$$|a| \leq \delta L_{\tilde{\lambda}_\theta(\cdot, 1) \varphi} + 2 \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty \mathbb{P}(\sup_{s \leq T} |y_N(s, x) - \phi_1(s, x)| > \delta)$$

and

$$|b| \leq \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty \left(T \delta L_{\tilde{\lambda}_\theta(\cdot, 1)} + 2 \mathbb{P}(\sup_{s \leq T} |y_N(s, x) - \phi_1(s, x)| > \delta) \right)$$

where $L_{\tilde{\lambda}_\theta(\cdot, 1) \varphi}$ and $L_{\tilde{\lambda}_\theta(\cdot, 1)}$ are the Lipschitz constants of the functions $\tilde{\lambda}_\theta(\cdot, 1) \varphi$ and $\tilde{\lambda}_\theta(\cdot, 1)$.

By (21) and the dominated convergence theorem, we deduce that

$$\tilde{\mathcal{A}}_N f(x_C, 0) \xrightarrow{N \rightarrow \infty} \tilde{\mathcal{A}}_\infty \varphi(x_C).$$

The tightness in $L^p([0, T]) \times L^1(\Omega \times [0, T]; \{0, 1\})$ of the family of processes $(x_C^{N,\epsilon}, \theta^{N,\epsilon})_{N,\epsilon}$, and the Skorohod representation theorem imply the existence of a subsequence which converges almost surely in $L^p([0, T]) \times L^1(\Omega \times [0, T]; \{0, 1\})$ to $(x_C(t), 0)_t \in L^p([0, T]) \times L^1(\Omega \times [0, T]; \{0, 1\})$. This almost surely convergence implies that a new subsequence can be extracted such that

$$(x_C^{N_k, \epsilon_k}(t), \theta^{N_k, \epsilon_k}) \xrightarrow{k \rightarrow \infty} (x_C(t), 0)$$

almost surely, and for almost all $t \in [0, T]$. To simplify notations, this subsequence is still noted $x_C^{N,\epsilon}$.

Taking $N \rightarrow \infty$ and $\epsilon \rightarrow 0$ in (22), we deduce by the dominated convergence theorem, the boundedness of f and ψ , and the hypothesis on $x_C^{N,\epsilon}(0)$ and $\theta^{N,\epsilon}(0)$:

$$\begin{aligned} & \mathbb{E} \left(\left[f(x_C^{N,\epsilon}(t), \theta^{N,\epsilon}(t)) - f(x_C^{N,\epsilon}(0), \theta^{N,\epsilon}(0)) \right] \psi(x_C^{N,\epsilon}(t_1), \dots, x_C^{N,\epsilon}(t_\ell)) \right) \\ & \xrightarrow{N \rightarrow \infty, \epsilon \rightarrow 0} \mathbb{E} \left(\left[\varphi(x_C(t)) - \varphi(x_C(0)) \right] \psi(x_C(t_1), \dots, x_C(t_\ell)) \right) \end{aligned}$$

for almost all $t \in [0, T]$ and almost all $0 \leq t_1, \dots, t_\ell \leq t$. We now prove that

$$\tilde{\mathcal{A}}_{N,\epsilon} f(x_C^{N,\epsilon}(s), 0) \mathbb{1}_{\theta^{N,\epsilon}(s)=0} \xrightarrow{N \rightarrow \infty, \epsilon \rightarrow 0} \tilde{\mathcal{A}}_\infty \varphi(x_C(s)) \quad (23)$$

almost surely, and for almost all $s \in [0, T]$.

First, for $s \in [0, T]$, $t \in \mathbb{R}^+$, we write

$$\begin{aligned} & P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C^{N,\epsilon}(s)) - \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(u, x_C(s)), 1) du} \\ & = \mathbb{E} \left[\left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (y_N(t, x_C^{N,\epsilon}(s))) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(u, x_C^{N,\epsilon}(s)), 1) du} \right] \\ & \quad - \mathbb{E} \left[\left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(u, x_C^{N,\epsilon}(s)), 1) du} \right] \\ & \quad + \mathbb{E} \left[\left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(y_N(u, x_C^{N,\epsilon}(s)), 1) du} \right] \\ & \quad - \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(u, x_C(s)), 1) du} \\ & = a_1 + b_1 \end{aligned}$$

For all $\delta > 0$, $T_1 > 0$, and $0 \leq t \leq T_1$,

$$|a_1| \leq \delta L_{\tilde{\lambda}_\theta(\cdot, 1) \varphi} + 2 \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty \mathbb{P} \left(\sup_{u \leq T_1} |y_N(u, x_C^{N,\epsilon}(s)) - \phi_1(u, x_C(s))| > \delta \right),$$

and if $t \geq T_1$,

$$|a_1| \leq 2 \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty e^{-\alpha T_1}.$$

Similarly, for $0 \leq t \leq T_1$,

$$|b_1| \leq \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty \left(T_1 \delta L_{\tilde{\lambda}_\theta(\cdot, 1)} + 2 \mathbb{P} \left(\sup_{u \leq T_1} |y_N(s, x_C^{N,\epsilon}(s)) - \phi_1(s, x_C(s))| > \delta \right) \right)$$

and if $t \geq T_1$,

$$|b_1| \leq 2 \|\tilde{\lambda}_\theta(\cdot, 1) \varphi\|_\infty e^{-\alpha T_1}.$$

We choose T_1 sufficiently large and then δ small enough and have almost surely, for all $s \in [0, T]$, $t \in \mathbb{R}^+$:

$$P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C^{N,\epsilon}(s)) - \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(u, x_C(s)), 1) du} \xrightarrow{N \rightarrow \infty, \epsilon \rightarrow 0} 0.$$

By the dominated convergence theorem, we have almost surely, for almost all $s \in [0, T]$,

$$\int_0^\infty P_t^N \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (x_C^{N,\epsilon}(s)) dt \xrightarrow{N \rightarrow \infty, \epsilon \rightarrow 0} \int_0^\infty \left(\tilde{\lambda}_\theta(\cdot, 1) \varphi \right) (\phi_1(t, x_C(s))) e^{-\int_0^t \tilde{\lambda}_\theta(\phi_1(u, x_C(s)), 1) du} dt.$$

Since $\varphi \in C_b^1(\mathbb{R}^{M_C})$, we obtain (23).

By the dominated convergence theorem, we conclude finally that

$$\mathbb{E} \left(\left[\varphi(x_C(t)) - \varphi(x_C(0)) - \int_0^t \tilde{\mathcal{A}}_\infty \varphi(x_C(s)) ds \right] \psi(x_C(t_1), \dots, x_C(t_\ell)) \right) = 0$$

for almost all t, t_1, \dots, t_ℓ such that $t \in [0, T]$ and $0 \leq t_1 \dots t_\ell \leq t$.

Step 4: Uniqueness of the solution of the martingale problem

By Theorem 2.4, proved in a weaker sense in the Appendix, we conclude that the limit x_C , more exactly a version of x_C , is the PDP whose generator is given by $\tilde{\mathcal{A}}_\infty$.

A Appendix

Proof of theorem 2.4

Let $x = (x_t)_{t \geq 0}$ denote the canonical process on $D(\mathbb{R}^+; E)$. Recall that we say that a probability measure P on $D(\mathbb{R}^+; E)$ is solution of the martingale problem associated to the generator \mathcal{A} if, for all $f \in \mathcal{E}$,

$$f(x_t) - f(x_0) - \int_0^t \mathcal{A}f(x_s) ds$$

is a P -martingale.

Let $(P_t)_{t \geq 0}$, P_x and $\bar{\mathcal{A}}$ denote the semigroup, the probability measure and the infinitesimal generator associated to the PDP whose characteristics are F , λ , Q , and starting from $x \in E$.

We need the following

Proposition A.1 *Assume that Hypothesis 2.3 holds, then, for all $t \in \mathbb{R}^+$, $f \in \mathcal{E}$, $P_t f$ is also in \mathcal{E} and*

$$\|P_t f\|_\infty \leq \|f\|_\infty, \quad (24)$$

$$|P_t f(y_1, \nu) - P_t f(y_2, \nu)| \leq c \|f\|_\infty e^{Kt} |y_1 - y_2|, \quad y_1, y_2 \in \mathbb{R}^n, \nu \in \mathbb{N}^d, \quad (25)$$

for some constants c and K depending only on the characteristics of the PDP.

Proof : Equation (24) is clear. Let us define, for $f \in \mathcal{E}$ and $\psi \in \mathcal{B}_b(\mathbb{R}^+ \times E)$:

$$\begin{aligned} G_f \psi(t, x) &= \mathbb{E}_x (f(x_t) \mathbb{1}_{t < T_1} + \psi(t - T_1, x_{T_1}) \mathbb{1}_{t \geq T_1}) \\ &= f(\phi_\nu(t, y), \nu) H(t, x) \\ &\quad + \int_0^t \int_E \psi(t - s, z) Q(dz; \phi_\nu(s, y), \nu) \lambda(\phi_\nu(s, y), \nu) H(s, x) ds \end{aligned}$$

for $(t, x) \in \mathbb{R}^+ \times E$, with $x = (y, \nu)$. Then, according to Lemma 27.3 of Davis (1993),

$$G_f^n \psi(t, x) = \mathbb{E}_x (f(x_t) \mathbb{1}_{t < T_n} + \psi(t - T_n, x_{T_n}) \mathbb{1}_{t \geq T_n})$$

and

$$\lim_{n \rightarrow \infty} G_f^n \psi(t, x) = P_t f(x).$$

We then deduce by dominated convergence and the strong Markov property:

$$\begin{aligned} P_t f(x) &= f(\phi_\nu(t, y), \nu) H(t, x) \\ &\quad + \int_0^t \int_E P_{t-s} f(z) Q(dz; \phi_\nu(s, y), \nu) \lambda(\phi_\nu(s, y), \nu) H(s, x) ds. \end{aligned} \quad (26)$$

That is, $P.f : t \mapsto P_t f$ is a fixed point of G_f .

For $T > 0$, we introduce the Banach space $\mathcal{E}_T = L^\infty([0, T], \mathcal{E})$, with the norm

$$\|\psi\|_{\mathcal{E}_T} = \sup_{t \in [0, T]} e^{-\alpha t} (\|\psi(t, \cdot)\|_\infty + L_{\psi(t, \cdot)})$$

where α will be fixed hereafter.

For $t \in [0, T]$, $(y, \nu) \in E$, we set $q_t(y, \nu) = f(\phi_\nu(t, y), \nu)H(t, y, \nu)$. Then $q : t \mapsto q_t$ is in \mathcal{E}_T . Indeed,

$$|H(t, y, \nu)| \leq 1, \quad (y, \nu) \in E, \quad t \in [0, T].$$

Also, from the Gronwall Lemma, we have that ϕ_ν is differentiable with respect to y and

$$|D_y \phi_\nu(t, y)| \leq e^{Lt}, \quad (y, \nu) \in E, \quad t \in [0, T].$$

Then we have, for $(y, \nu) \in E$, $t \in [0, T]$,

$$|D_y H(t, y, \nu)| \leq \int_0^t |D_y \{\lambda(\phi_\nu(s, y), \nu)\}| ds \leq L_\lambda \int_0^t |D_y \phi_\nu(s, y)| ds \leq \frac{L_\lambda}{L} (e^{Lt} - 1).$$

Hence if $\alpha > L$

$$\|q\|_{\mathcal{E}_T} \leq \left(L_f + \frac{L_\lambda}{L} \|f\|_\infty \right) + \|f\|_\infty.$$

If $\psi \in \mathcal{E}_T$, we then easily show that $G_f \psi \in \mathcal{E}_T$. Moreover, if $\psi_1, \psi_2 \in \mathcal{E}_T$, we have

$$\|G_f \psi_1(t, \cdot) - G_f \psi_2(t, \cdot)\|_\infty \leq M_\lambda \int_0^t \|\psi_1(t-s, \cdot) - \psi_2(t-s, \cdot)\|_\infty ds. \quad (27)$$

Also, it is easy to see that

$$\|D_y G_f \psi_1(t, \cdot) - D_y G_f \psi_2(t, \cdot)\|_\infty \leq \kappa \int_0^t e^{Ls} \|\psi_1(t-s, \cdot) - \psi_2(t-s, \cdot)\|_{\mathcal{E}} ds$$

where κ is a constant depending only on the characteristics of the PDP.

Then we easily deduce that

$$\begin{aligned} \|G_f \psi_1 - G_f \psi_2\|_{\mathcal{E}_T} &\leq \kappa_1 \sup_{t \in [0, T]} e^{-\alpha t} \left(\int_0^t e^{\alpha(t-s)} ds + \int_0^t e^{\alpha(t-s)} e^{Ls} ds \right) \|\psi_1 - \psi_2\|_{\mathcal{E}_T} \\ &\leq \kappa_1 \left(\frac{1}{\alpha} + \frac{1}{\alpha - L} \right) \|\psi_1 - \psi_2\|_{\mathcal{E}_T} \end{aligned}$$

where κ_1 is a constant depending only on the characteristics of the PDP. We now choose α sufficiently large and deduce from Picard theorem that G_f has a unique fixed point in \mathcal{E}_T . This fixed point is the limit $G_f^n \psi$ for any $\psi \in \mathcal{E}_T$. Thus $P_t f : t \mapsto P_t f$ is that fixed point, and is then in \mathcal{E}_T .

The Lipschitz constant $L_{P_t f}$ of $P_t f$ can easily be found with the preceding results and Gronwall Lemma.

□

The infinitesimal generator $\bar{\mathcal{A}}$ of P_t is characterized by (cf. for instance Ethier and Kurtz (1986), part 1, chapter 2):

$$(\mu - \bar{\mathcal{A}})^{-1} f = \int_0^\infty e^{-\mu t} P_t f dt, \quad \mu > 0, \quad f \in C_b(E). \quad (28)$$

Let $f \in \mathcal{E}$, $\mu > K$ and $\varphi = (\mu - \bar{\mathcal{A}})^{-1} f$, then $\varphi \in \mathcal{D}(\bar{\mathcal{A}})$ and

$$\frac{P_t \varphi(x) - \varphi(x)}{t} \xrightarrow[t \rightarrow 0]{} \bar{\mathcal{A}} \varphi(x), \quad x \in E.$$

By Proposition A.1, it is easy to see that if Hypothesis 2.3 is satisfied, $(\mu - \bar{\mathcal{A}})^{-1}$ maps \mathcal{E} into itself if $\mu > K$. In particular, $\varphi \in \mathcal{E}$ and for all $x \in E$:

$$\varphi(x_t) - \varphi(x) - \int_0^t \mathcal{A} \varphi(x_s) ds \quad (29)$$

is a P_x -martingale.

It follows that, for all $x \in E$, and $t \in \mathbb{R}^+$,

$$\frac{P_t \varphi(x) - \varphi(x)}{t} = \frac{1}{t} \int_0^t \mathbb{E}_x(\mathcal{A}\varphi(x_s)) ds.$$

Since $\mathcal{A}\varphi(x_s)$ is P_x -a.s. bounded and continuous on $[0, T_1[$, we deduce that

$$\frac{P_t \varphi(x) - \varphi(x)}{t} \xrightarrow[t \rightarrow 0]{} \mathcal{A}\varphi(x), \quad x \in E.$$

It follows that

$$\mathcal{A}\varphi(x) = \bar{\mathcal{A}}\varphi(x), \quad x \in E.$$

Remark A.2 *In fact, we do not need that (29) defines a P_x martingale. This can be weakened and replaced by the following:*

For all $x \in E$, $\varphi \in \mathcal{E}$ and for $t \in \mathbb{T}$, where \mathbb{T} is a dense subset of \mathbb{R}^+ :

$$P_t \varphi(x) - \varphi(x) = \int_0^t \mathbb{E}_x(\mathcal{A}\varphi(x_s)) ds \quad (30)$$

In that case, we can define a sequence $(t_n)_n$ such that $t_n \in \mathbb{T}$ for all n and $t_n \rightarrow 0$ as $n \rightarrow \infty$. Taking $n \rightarrow \infty$ in the equality

$$\frac{P_{t_n} \varphi(x) - \varphi(x)}{t_n} = \frac{1}{t_n} \int_0^{t_n} \mathbb{E}_x(\mathcal{A}\varphi(x_s)) ds,$$

we obtain, since $\mathcal{A}\varphi(x_s)$ is P_x -a.s. bounded and continuous on $[0, T_1[$,

$$\bar{\mathcal{A}}\varphi(x) = \mathcal{A}\varphi(x), \quad x \in E.$$

We now use a classical argument (see for instance Ethier and Kurtz (1986), part 4, chapter 4). Let \tilde{P}_x be another solution of the martingale problem. By the same reasoning as before, let $f \in \mathcal{E}$, $\mu > K$ and $\varphi = (\mu - \bar{\mathcal{A}})^{-1} f$, then

$$\varphi(x_t) - \varphi(x) - \int_0^t \mathcal{A}\varphi(x_s) ds$$

is a \tilde{P}_x -martingale.

Let us write

$$\tilde{\mathbb{E}}_x(\varphi(x_t) - \int_0^t \mathcal{A}\varphi(x_s) ds) = \varphi(x).$$

Multiply this identity by $\mu e^{-\mu t}$ and integrate on $[0, \infty)$ to obtain

$$\tilde{\mathbb{E}}_x \left(\int_0^\infty e^{-\mu t} (\mu \varphi(x_t) - \mathcal{A}\varphi(x_t)) dt \right) = \varphi(x).$$

Since $\bar{\mathcal{A}}\varphi = \mathcal{A}\varphi$, we deduce, from (28)

$$\tilde{\mathbb{E}}_x \left(\int_0^\infty e^{-\mu t} f(x_t) dt \right) = \varphi(x) = \int_0^\infty e^{-\mu t} P_t f(x) dt, \quad \mu > K,$$

By injectivity of the Laplace transform, this implies

$$\tilde{\mathbb{E}}_x(f(x_t)) = P_t f(x), \text{ for almost all } t \geq 0, \text{ for all } x \in E.$$

We have proved that the law of a solution of the martingale problem at a fixed time t in a dense set of \mathbb{R}^+ , is uniquely determined. This implies uniqueness for the martingale problem (see Billingsley (1999) section 14).

Remark A.3 *Again, the hypothesis that \tilde{P}_x is a solution of the martingale problem can be weakened and replaced by the following:*

$$\tilde{E}_x \left(\varphi(x_t) - \varphi(x) - \int_0^t \mathcal{A}\varphi(x_s) ds \right) = 0,$$

for $x \in E$ and almost all $t \in \mathbb{R}^+$. The previous calculus are similar, since the Lebesgue integral is null over a negligible set.

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