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A continuous stochastic maturation model

Djalil CHAFAÏ and Didier CONCORDET

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Abstract

We present a continuous time model of maturation and survival, obtained as the limit of a compartmental evolution model when the number of compartments tends to infinity. We establish in particular an explicit formula for the law of the system output under inhomogeneous killing and when the input follows a time-inhomogeneous Poisson process. Identifiability issues are discussed, and an application to the modelling of the toxicity of anti-cancer drugs is given. Such models can be seen in particular as generalisations of previous works of Jacquez & Simon and Schuhmacher & Thieme.

Keywords: Compartmental systems; time lags; maturation models; stochastic modelling; Markov processes; inhomogeneous Markov processes; birth and death processes; queueing systems; point processes; Feynman-Kac formulæ, jump processes.

MSC-2000 : 92B05 ; 60G07 ; 60K25 ; 60K20 ; 60J80 ; 60J85 ; 47D08 ; 60J25 ; 60J75 .

Introduction

As presented by John. A. Jacquez and Carl P. Simon in their joint paper [JS02], dynamical models of many biological processes give rise to systems of ordinary differential equations called “compartmental systems”. Such compartmental systems can be interpreted as birth and death processes. They can also be seen as particular queueing systems. The reader may find an introduction to compartmental systems in for example [JS93] and references therein. For birth and death and queueing processes, one can find recent introductions in [Bor03] and [Rob03] for example.

Catenary chain of compartments with one-way flow can be used to generate time lags, see for example [Gou86], [Gyó89], [ST88], [JS02] and references therein. The compartments that belong to the chain correspond to hidden states ; the last compartment being the only observed. In biology, these states are often used to describe the different stages of maturation of cells. Their number is generally not precisely known but it is likely to be large. Such hidden states are interpreted as position in the chain. The particles (cells) are transported from position 0 to n and can be killed during transport. The observed effect in the last compartment is thus a lag for the surviving particles. Roughly speaking, the catenary chain thus corresponds to a one-way drift with possible killing.

We first consider a compartmental model as the one shown in Figure 1. The dynamic of the maturation process of a single particle from position 0 to n is described. This description allows to deduce the maturation dynamics for the continuous model by letting

the number of compartments goes to infinity. This first step is quite similar to the results given in [JS02] but it allows to introduce the general probabilistic formalism used in the subsequent steps of the study.

A random number of independent particles enter in this system. We chose an inhomogeneous Poisson process to describe their apparition at the first stage of maturity. The law of the number of particles that reach the last stage of maturity is then deduced. In a way, our approach can be seen as a complement and extension of the boxcartrain models considered for example in [ST88], the novelty being mainly the space-time inhomogeneous killing, the stochastic interpretation in terms of Feynman-Kac's formulæ, and the computation of the output occupation law when the input follows a time-inhomogeneous Poisson process.

This work was initially motivated by a Pharmacokinetics/Pharmacodynamics study of the toxicity of an anti-cancer drug. The observed effect is the number of circulating neutrophils (in blood) while the drug action occurred during their maturation stages, cf. figure 3. The continuous model we study can be interpreted as a limit model of most models used to describe toxicity of anti-cancer drugs. *It enables to show that despite the apparent variety of models with different physiological meaning, most of them are indistinguishable in certain situations discussed in Section 2.2.*

Outline of the paper. In section 1, we derive a continuous maturation model for a single particle, from a finite compartmental model by letting the number of compartments tends to ∞ . In section 2, we consider the occupation law of the output when the input is a Poisson process, we also discuss identifiability issues, and applications to anti-cancer drugs models in pharmacology. Finally, Section 3 gathers various postponed Lemmas and proofs.

Notations and conventions. In the sequel, we denote by \mathbb{R}_+ the non negative half line $[0, +\infty)$. For a set A , we denote by I_A the indicator function defined by $I_A(x) = 1$ if $x \in A$ and $I_A(x) = 0$ otherwise. For two real numbers a and b , we denote by $a \wedge b$ and by $a \vee b$ the minimum and the maximum of a and b . We denote by $\mathcal{L}(X)$ the law of the random variable X , by $\mathcal{L}(X|Y)$ the conditional law of X given Y , and by $\mathbf{E}(X|Y)$ the conditional expectation of X given Y . We use in addition the classical associated maps $\mathcal{L}(X|Y = y)$ and $\mathbf{E}(X|Y = y)$. We denote by $\mathcal{P}(\lambda)$, the Poisson distribution with intensity $\lambda \geq 0$ defined by

$$\mathcal{P}(\lambda) := e^{-\lambda} \sum_{n=0}^{+\infty} \frac{\lambda^n}{n!} \delta_n.$$

We denote by $\mathcal{B}(n, p)$ the binomial distribution of size $n \in \mathbb{N}$ and parameter $p \in [0, 1]$ defined by

$$\mathcal{B}(n, p) := \sum_{k=0}^n \binom{n}{k} p^k (1-p)^{n-k} \delta_k,$$

where $\binom{n}{k} := n!/(k!(n-k)!)$ is the binomial coefficient. In particular, $\mathcal{B}(1, p)$ is the Bernoulli distribution $p\delta_1 + (1-p)\delta_0$ and $\mathcal{B}(n, p) = \mathcal{B}(1, p)^{*n}$ where $*$ denotes the convolution. We denote by $\mathcal{NB}(n, p)$ the negative-binomial distribution of size $n \in \mathbb{N}^*$ and parameter $p \in [0, 1]$ defined by

$$\mathcal{NB}(n, p) := \sum_{k=n}^{+\infty} \binom{k-1}{n-1} p^n (1-p)^{k-n} \delta_k.$$

In particular, $\mathcal{NB}(1, p)$ is the Geometric distribution $\mathcal{G}(p)$ and $\mathcal{NB}(n, p) = \mathcal{G}(p)^{*n}$. Finally, we denote by $\Gamma(n, \lambda)$ the Gamma distribution of shape parameter $n \in \mathbb{N}^*$ and scale parameter $\lambda \in \mathbb{R}_+^*$ which is absolutely continuous with respect to Lebesgue's measure on \mathbb{R} with probability density function

$$t \in \mathbb{R} \mapsto \frac{\lambda^n}{(n-1)!} t^{n-1} e^{-\lambda t} \mathbf{I}_{\mathbb{R}_+}(t).$$

In particular, $\Gamma(1, \lambda)$ is the exponential distribution $\mathcal{E}(\lambda)$ and $\Gamma(n, \lambda) = \mathcal{E}(\lambda)^{*n}$.

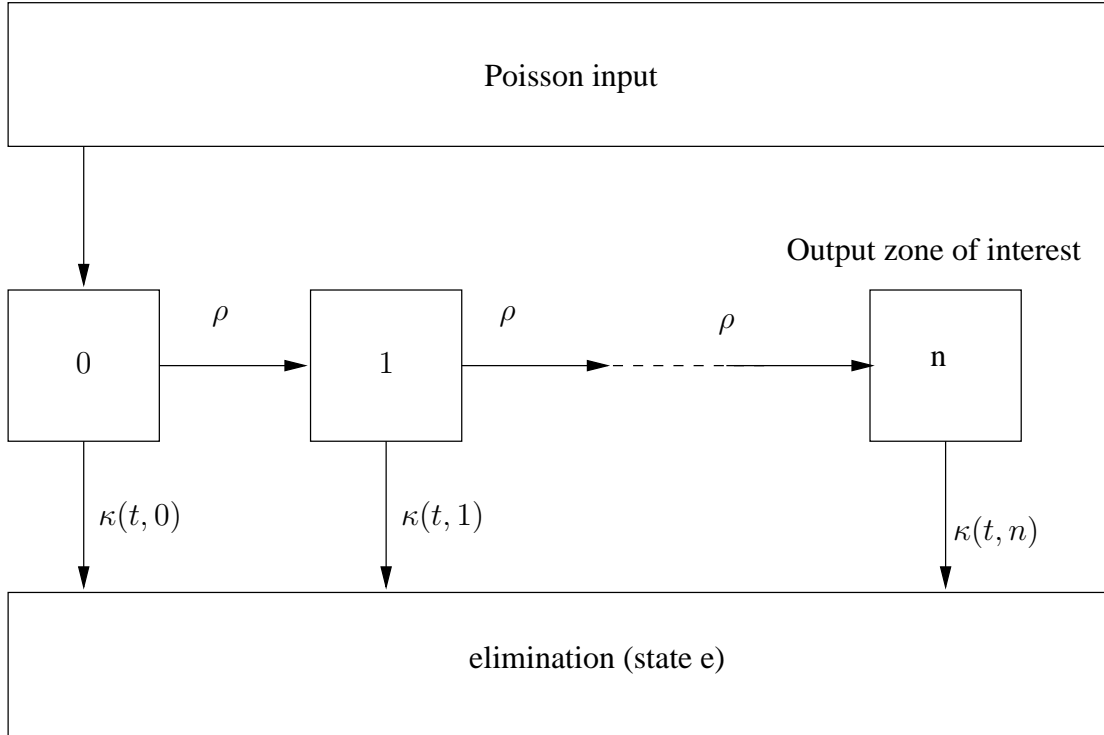


Figure 1: A particular compartmental model: catenary chain of compartments with Poisson input, one-way flow (ρ), and space-time-inhomogeneous killing (κ).

1 The continuous position model for a single particle

Let us recall briefly the Markovian formalism on a finite set. Let $\mathcal{S}^{(n)}$ be a finite set indexed by a positive integer n . Let $(X_t^{(n)})_{t \geq 0}$ be the continuous time Markov process with state space $\mathcal{S}^{(n)}$ which encodes the position of a particle in $\mathcal{S}^{(n)}$ at time t . Such a process is entirely described by the associated Markov semi-group of conditional laws $\mathcal{L}(X_t^{(n)} | X_s^{(n)} = x)$ for any $x \in \mathcal{S}^{(n)}$ and any $0 \leq s \leq t$. The discrete topology on $\mathcal{S}^{(n)}$ makes continuous any function $f : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$. For any (continuous) function $f : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$, any $x \in \mathcal{S}^{(n)}$ and any $0 \leq s \leq t$, one can define $\mathbf{P}_{s,t}^{(n)}(f) : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$ by

$$\mathbf{P}_{s,t}^{(n)}(f)(x) = \mathbf{E}\left(f(X_t^{(n)}) | X_s^{(n)} = x\right).$$

Since $\mathbf{P}_{s,t}^{(n)}$ is linear and $\mathcal{S}^{(n)}$ is finite, $\mathbf{P}_{s,t}^{(n)}$ can be seen as a stochastic matrix. Namely, for any i and j in $\mathcal{S}^{(n)}$,

$$\mathbf{P}_{s,t}^{(n)}(i, j) = \mathbb{P}(X_t^{(n)} = j \mid X_s^{(n)} = i) = \mathbf{P}_{s,t}^{(n)}(\mathbf{I}_{\{j\}})(i),$$

where $\mathbf{I}_{\{j\}}$ is the indicator function of the set $\{j\}$. In particular, functions from $\mathcal{S}^{(n)}$ to \mathbb{R} can be seen as vectors and one has

$$\mathbf{P}_{s,t}^{(n)}(f)(i) = \sum_{j \in \mathcal{S}^{(n)}} \mathbf{P}_{s,t}^{(n)}(i, j) f(j).$$

The family of linear operators $(\mathbf{P}_{s,t}^{(n)})_{0 \leq s \leq t}$ acting on functions $f : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$ forms a Markov semi-group. In other words,

1. If $f \geq 0$ then $\mathbf{P}_{s,t}^{(n)}(f) \geq 0$;
2. $\mathbf{P}_{s,t}^{(n)}(1) = 1$ where 1 is the constant function which is equal to 1;
3. For any $0 \leq s \leq u \leq t$

$$\mathbf{P}_{u,t}^{(n)} \circ \mathbf{P}_{s,u}^{(n)} = \mathbf{P}_{s,t}^{(n)}.$$

The infinitesimal generators $(\mathbf{L}_t^{(n)})_{t \geq 0}$ of the Markov semi-group $(\mathbf{P}_{s,t}^{(n)})_{0 \leq s \leq t}$ are by definition the operators defined for any $s \geq 0$, any $f : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$ and any $x \in \mathcal{S}^{(n)}$ by

$$\mathbf{L}_s^{(n)}(f)(x) := \partial_{t=s} \left[t \mapsto \mathbf{P}_{s,t}^{(n)} f(x) \right].$$

Here again, one can see $\mathbf{L}_s^{(n)}$ as a matrix defined for any i, j in $\mathcal{S}^{(n)}$ by

$$(\mathbf{L}_s^{(n)})_{i,j} = \partial_{t=s} [t \mapsto \mathbf{P}_{s,t}(i, j)].$$

In the literature related to compartmental systems, the matrix \mathbf{L}_s is known as the “transfer matrix”. The reader may find an excellent reference for Markov processes and related topics in the book [EK86] by N. Ethier and G. Kurtz.

1.1 The maturation with killing model

Let us consider now the special case where $\mathcal{S}^{(n)} := \{0, 1, \dots, n\} \cup \{e\}$. Each value from 0 to n corresponds to a maturation stage (or position) of a particle, the final value n being the final maturation stage. As we will see, the state e will serve as an absorbing state from which the particle cannot escape (cemetery point). Let

$$\kappa^{(n)} : \mathbb{R}_+ \times \{0, \dots, n\} \rightarrow \mathbb{R}_+$$

be a function which is smooth in the first variable, and $\rho^{(n)}$ be a positive real number. Let $(X_t^{(n)})_{t \geq 0}$ be the Markov process with infinitesimal generators $(\mathbf{L}_t^{(n)})_{t \geq 0}$ given for any i and j in $\mathcal{S}^{(n)}$ and any $t \geq 0$ by

$$(\mathbf{L}_t^{(n)})_{i,j} = \begin{cases} \rho^{(n)} & \text{if } i \neq e \text{ and } j = i + 1 \\ \kappa^{(n)}(t, i) & \text{if } i \neq e \text{ and } j = e \\ -(\rho^{(n)} + \kappa^{(n)}(t, i)) & \text{if } i = j \notin \{n, e\} \\ -\kappa^{(n)}(t, n) & \text{if } i = j = n \\ 0 & \text{otherwise.} \end{cases} \quad (1)$$

The dynamics of the associated process can be read directly on the expression of the infinitesimal generator (1) above. Namely, at time t and from position i , the particle can only move to position $i + 1$ with rate $\rho^{(n)}$, or die (being killed) with rate $\kappa(i, t)$ and placed in the special state e from which it cannot escape. Instead of expressing the infinitesimal generators in matrix form as in (1), one can alternatively adopt an equivalent functional point of view which consists in writing that for any $f : \mathcal{S}^{(n)} \rightarrow \mathbb{R}$, and any $i \in \mathcal{S}^{(n)}$,

$$\mathbf{L}_t^{(n)}(f)(i) = \sum_{j \in \mathcal{S}^{(n)}} (\mathbf{L}_t^{(n)})_{i,j} f(j).$$

This gives $\mathbf{L}_t^{(n)}(f)(e) = 0$ and for any $i \in \{0, \dots, n\}$

$$\mathbf{L}_t^{(n)}(f)(i) = \rho^{(n)}(f(i+1) - f(i)) + \kappa^{(n)}(t, i)(f(e) - f(i)),$$

where we have taken the convention $f(n+1) := f(n)$.

1.2 The continuous limit

Let $\mathcal{S} := [0, 1] \cup \{e\}$ and consider the natural inclusion $\pi_n : \mathcal{S}^{(n)} \rightarrow \mathcal{S}$ defined by $\pi_n(i) = i/n$ for any $i \in \{0, \dots, n\}$ and $\pi_n(e) = e$. Assume now that $\rho^{(n)} = n\rho$ for some positive constant ρ and that $\kappa^{(n)}(t, i) = \kappa(t, i/n)$ for some bounded piecewise continuous function

$$\kappa : \mathbb{R}_+ \times [0, 1] \rightarrow \mathbb{R}_+.$$

By this way, any function $f : \mathcal{S} \rightarrow \mathbb{R}$ induces naturally a function $f(\pi_n)$ from $\mathcal{S}^{(n)}$ to \mathbb{R} , and one has

$$\mathbf{L}_t^{(n)}(f(\pi_n))(i) = n\rho \left(f\left(\frac{i+1}{n}\right) - f\left(\frac{i}{n}\right) \right) + \kappa\left(t, \frac{i}{n}\right) \left(f(e) - f\left(\frac{i}{n}\right) \right).$$

By using suitable continuity arguments based on Taylor's formulas, one can show that the Markov process $(n^{-1} X_t^{(n)})_{t \geq 0}$ converges in law when n goes to ∞ toward the Markov process $(X_t)_{t \geq 0}$ with state space $\mathcal{S} := [0, 1] \cup \{e\}$ and infinitesimal generators

$$\mathbf{L}_t(f)(x) = \begin{cases} \rho f'(x) + \kappa(t, x)(f(e) - f(x)) & \text{if } x \neq e \\ 0 & \text{if } x = e \end{cases} \quad (2)$$

defined for continuous functions $f : \mathcal{S} \rightarrow \mathbb{R}$ which are smooth on $[0, 1]$ and vanish at the boundaries. One can find detailed techniques of such limiting procedures in [EK86] for example. The obtained generator \mathbf{L}_t above is the addition of a deterministic constant drift term $\rho f'(x)$ together with a random space-time inhomogeneous killing term $\kappa(t, x)(f(e) - f(x))$. The interpretation in terms of the position X_t of the particle is quite clear: the particle is moving from left to right on $[0, 1]$ with a constant speed ρ . At any time t , it can be killed (and thus placed in state e) with rate $\kappa(x, t)$ where x is the current position.

Actually, one can always explicitly translate on the semi-group the effect of the addition of a killing term to a Markov generator, by mean of a Feynman-Kac formulae, cf. Lemma 3.4. In some ways, our case (2) is the simplest one since we add a killing term to

a deterministic generator (constant drift). Lemma 3.4 or even a direct check shows that the Markov semi-group associated to (2) is given for any $0 \leq s \leq t$ and any $x \in \mathcal{S}$ by

$$\mathbf{P}_{s,t}(f)(x) = \begin{cases} p(s,t,x)f(x + \rho t) + (1 - p(s,t,x))f(e) & \text{if } x \neq e \\ f(e) & \text{if } x = e \end{cases}$$

where $p(u,v,e) = 0$ and for any $x \neq e$

$$p(u,v,x) := \exp\left(-\int_u^v \kappa(w, x + \rho(w-u)) dw\right). \quad (3)$$

As we will see, function p corresponds to a survival probability. It is sometimes more convenient to write

$$p(u,v,x) = \exp\left(-\int_0^{v-u} \kappa(u+w, x + \rho w) dw\right).$$

One can check that for any $x \in \mathcal{S}$ and any $s \geq 0$

$$\partial_{t=s} [t \mapsto \mathbf{P}_{s,t}(f)(x)] = \mathbf{L}_s(f)(x),$$

where \mathbf{L}_s is defined by (2). Recall that by definition of the semi-group, for any $x \in \mathcal{S}$, any bounded continuous function $f : \mathcal{S} \rightarrow \mathbb{R}$ and any $0 \leq s \leq t$ one has

$$\mathbf{P}_{s,t}(f)(x) := \mathbf{E}(f(X_t) | X_s = x).$$

In particular, for any Borel set A

$$\mathbb{P}(X_t \in A | X_s = x) = \mathbf{P}_{s,t}(\mathbf{1}_A)(x).$$

The corresponding conditional law is given for any $0 \leq s \leq t$ and any $x \in \mathcal{S}$ by

$$\mathcal{L}(X_t | X_s = x) = \begin{cases} p(s,t,x) \delta_{x+\rho(t-s)} + (1 - p(s,t,x)) \delta_e & \text{if } x \neq e \\ \delta_e & \text{if } x = e \end{cases}$$

The conditional law $\mathcal{L}(X_t | X_s = x)$ is thus a Dirac or a Bernoulli measure. Recall that it corresponds to the law of the position of a particle at time t given its position x at time s . Namely, the particle is killed between time s and t with probability $1 - p(s,t,x)$. At time t , it is either at position $x + \rho(t-s)$ with probability $p(s,t,x)$, or at position e (killed) with probability $1 - p(s,t,x)$. The quantity $p(s,t,x)$ is exactly the ‘‘survival probability’’ of the particle at time t given that it was in position x at time s . One can define the ‘‘maturation time’’ τ by

$$\tau := \frac{1}{\rho}. \quad (4)$$

In this definition, τ is a time and 1 is a position, in such a way that $\rho = 1/\tau$ is a speed.

$$\begin{aligned} \text{position in } [0,1] &= \text{stage of maturity} \\ \text{position } 1 &= \text{maturity} \end{aligned}$$

The term “maturation time” is justified by the fact that in absence of killing (i.e. $\kappa \equiv 0$), one has $p(s, t, 0) = 1$ and τ is exactly the deterministic time taken by a particle to reach position 1 from position 0 (at constant speed ρ).

Conclusion. If one views position 0 as an input and position 1 as an output, the whole dynamics corresponds to a lag and killing. Namely, if one puts a particle at the input at time s , then either this particle will be killed and never see the output with probability $1 - p(s, s + \tau, 0)$, or will reach the output at time $s + \tau$ with probability $p(s, s + \tau, 0)$. The maturation time τ corresponds to a time lag. The whole picture is given by Figure 2.

Extension. The dynamics can be extended from $\mathcal{S} = [0, 1] \cup \{e\}$ to the whole right side half line $\mathcal{S} = \mathbb{R}_+ \cup \{e\}$, provided that one consider a suitable killing function

$$\kappa : (t, x) \in \mathbb{R}_+ \times \mathbb{R}_+ \mapsto \kappa(t, x) \in \mathbb{R}_+.$$

We will always consider this extension in the sequel.

$$\begin{aligned} \text{position in } [0, 1] &= \text{stage of maturity} \\ \text{position in } (1, +\infty) &= \text{maturity} \end{aligned}$$

In this extended model, a particle evolves from left to right at constant speed ρ . At time t , it can be killed (and placed in position e) with rate $\kappa(t, x)$ where x is its position on \mathbb{R}_+ . The particle is *mature* when its position exceeds position 1. Hence, in term of maturity, we consider here that the output is the whole interval $(1, +\infty)$ instead of position 1; and by this way, the killing action of κ on the position interval $(1, +\infty)$ corresponds to an extinction after the arrival at maturity. In Figure 2, the box labelled “Lag τ ” corresponds to the interval of position $[0, 1]$, whereas the box labelled “Maturity” corresponds to the interval of positions $(1, +\infty)$.

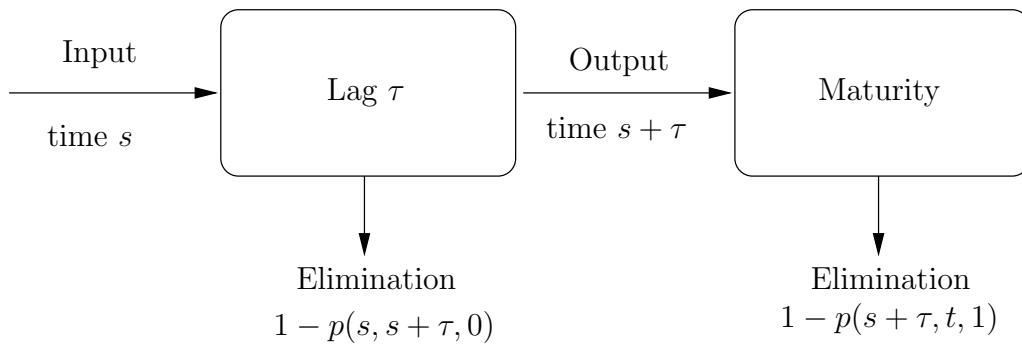


Figure 2: Schematic view of the system. Recall that τ is the maturation time. The quantity $p(s, s + \tau, 0)$ is the survival probability of a particle up to maturity given the fact that it was at the input of the system at time s . The quantity $p(s + \tau, t, 1)$ is the survival probability at time t of a mature particle given the fact that it was at the input of the system at time s (makes sense for $t \geq s + \tau$).

2 Output occupation law when the input is Poisson

We consider a system describing the maturation of particles, as in the conclusion of Section 1. We assume that independent particles enter into the system at random times.

We denote by T_n the arrival time of the n^{th} particle at the system input. These particles evolve independently according to the maturation dynamics described in Section 1. This dynamics depends on some positive constant ρ and some piecewise continuous function $\kappa : \mathbb{R}_+ \times \mathbb{R}_+ \rightarrow \mathbb{R}_+$. Let $(M_t)_{t \geq 0}$ be the output occupation process, in other words the number of mature particles still present at time t . The stochastic process $(M_t)_{t \geq 0}$ is a Markov process. Let $Z_{t,n}$ be the Bernoulli random variable corresponding to the presence in the output at time t of the n^{th} particle. On the event $\{M_0 = 0\}$, one has for any $t \geq 0$

$$M_t := \begin{cases} 0 & \text{if } t < \tau \\ C_{t-\tau} & \\ \sum_{n=1} Z_{t,n} & \text{if } t \geq \tau, \end{cases} \quad (5)$$

where τ is the maturation time as in (4), and where the process $(C_t)_{t \geq 0}$ is defined by

$$C_t := \sum_{n=1}^{+\infty} \mathbf{I}_{\{T_n \leq t\}} = \inf \{n \in \mathbb{N}, \text{ such that } T_{n+1} > t\}.$$

The random variable T_n is the n^{th} jump time of the counting process $(C_t)_{t \geq 0}$, and C_t is the number of particles that have entered the system before time t . In the sequel, we consider exclusively the case where $(C_t)_{t \geq 0}$ is a time-inhomogeneous Poisson process starting from 0 with locally integrable intensity function $\lambda : \mathbb{R}_+ \rightarrow \mathbb{R}_+$. The infinitesimal generators $(\mathbf{L}_t^C)_{t \geq 0}$ of $(C_t)_{t \geq 0}$ are given for any $t \geq 0$, any $n \in \mathbb{N}$ and any $f : \mathbb{N} \rightarrow \mathbb{R}$ by

$$\mathbf{L}_t^C(f)(n) := \lambda(t)(f(n+1) - f(n)). \quad (6)$$

When the intensity function $\lambda : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is constant, the process $(C_t)_{t \geq 0}$ reduces to a homogeneous simple Poisson process.

Theorem 2.1 below gives the law of the Markov process $(M_t)_{t \geq 0}$, by mean of its semi-group, and Corollary 2.2 gives the associated infinitesimal generators. Finally, Remark 2.3 provides the expression of the parameters of the semi-group in terms of the coefficients of the infinitesimal generators.

Theorem 2.1 (Semi-group). *Let $(M_t)_{t \geq 0}$ be the output occupation process defined by (5) where the input counting process $(C_t)_{t \geq 0}$ is as in (6). Assume that there exists bounded piecewise continuous functions $g : \mathbb{R}_+ \times [0, 1] \rightarrow \mathbb{R}_+$ and $\mu : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ such that for any $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$*

$$\kappa(t, x) = g(t, x)\mathbf{I}_{[0,1]}(x) + \mu(t)\mathbf{I}_{(1,+\infty)}(x). \quad (7)$$

Then, for any s, t with $0 \leq s \leq t$ and any $n \in \mathbb{N}$

$$\mathcal{L}(M_t | M_s = n) = \mathcal{B}(n, p(s, t, 1)) * \mathcal{P}(r(s, t)), \quad (8)$$

where

$$r(s, t) := \int_{(s-\tau) \vee 0}^{(t-\tau) \vee 0} \lambda(u) p(u, t, 0) du, \quad (9)$$

where p is defined by (3) and τ by (4). In particular, for any $0 \leq s \leq t$ and any $n \in \mathbb{N}$

$$\mathbf{E}(M_t | M_s = n) = np(s, t, 1) + r(s, t). \quad (10)$$

Proof. The proof is postponed to Section 3 page 15. \square

Corollary 2.2 (Infinitesimal generators). *Under the hypotheses of Theorem 2.1, the infinitesimal generators $(\mathbf{L}_s)_{s \geq 0}$ of the Markov process $(M_t)_{t \geq 0}$ are given for any $s \geq 0$, any $f : \mathbb{N} \rightarrow \mathbb{R}$ and any $n \in \mathbb{N}^*$ by*

$$\mathbf{L}_s(f)(n) = n\mu(s)(f(n-1) - f(n)) + \lambda_g(s - \tau)(f(n+1) - f(n)) I_{[\tau, +\infty)}(s), \quad (11)$$

where by notational convention $f(-1) = f(0)$ and where for any $t \geq 0$

$$\lambda_g(t) := \lambda(t) p(t, t + \tau, 0) = \lambda(t) \exp\left(-\int_0^\tau g(t+w, \rho w) dw\right). \quad (12)$$

Proof. The proof is postponed to Section 3 page 17. \square

Remark 2.3 (Expression of $p(s, t, 1)$ and $r(s, t)$). *Assume that the hypotheses of Theorem 2.1 are fulfilled. One has for any $0 \leq s \leq t$*

$$p(s, t, 1) = \exp\left(-\int_s^t \mu(w) dw\right). \quad (13)$$

In the other hand, $p(u, t, 0) = p(u, u + \tau, 0)p(u + \tau, t, 1)$ for any u and t with $0 \leq u \leq t - \tau$. Therefore, the coefficient $r(s, t)$ defined by (9) can be rewritten by virtue of the expressions (13) and (12) for any $\tau \leq s \leq t$ as

$$r(s, t) = \int_s^t \lambda_g(u - \tau) \exp\left(-\int_u^t \mu(w) dw\right) du, \quad (14)$$

where λ_g is as in (12). The formulas (13) and (14) allow to express the conditional law (8) in terms of the coefficients of the infinitesimal generators (11). It makes clear the fact that the knowledge of $(\mathbf{L}_s)_{0 \leq s \leq t}$ is equivalent to the knowledge of the law of the process $(M_s)_{0 \leq s \leq t}$ given M_0 .

Remark 2.4 (Negative values of κ and input rate amplification). *The direct use of Feynman-Kac's formulae of Lemma 3.4 and a careful reading of the proof shows that Theorem 2.1 still makes sense even when g in (7) takes negative values. In that case, the quantity $p(s - \tau, s, 0)$ may exceed 1, and thus cannot be interpreted as a "survival probability". In view of (14), such negative values of g correspond to an "amplification" of the input rate instead of a killing. Notice that one can always write $g = g_+ - g_-$ where $g_- := \sup(-g, 0) \geq 0$ and $g_+ := \sup(g, 0) \geq 0$. By this way, the negative values of g are gathered in g_- and can be incorporated into λ . The two models corresponding to (λ, g) and (λ_{g_-}, g_+) are indistinguishable since they give rise to the same function r via (14). Functions g with negative values are considered in the discussion about identifiability in Section 2.1.*

Remark 2.5 (Simulation of the sample paths). *The simulation of the sample paths of the process $(M_t)_{t \geq 0}$ can be done via the law of the jumps of the process, which can be obtained from the expression of the infinitesimal generators given by Corollary 2.2. Namely, assume that the process is at position n at time s , and let*

$$T := \min\{t > s : M_t \neq M_s\} - s$$

be the next “waiting time”. Then, by using the matrix notation $\mathbf{L}_u(i, j) := \mathbf{L}_u(\mathbf{I}_{\{j\}})(i)$, one has for any $t \geq 0$

$$\mathbb{P}(T \leq t) = 1 - \exp\left(\int_s^{s+t} \mathbf{L}_u(n, n) du\right).$$

Moreover, given that the jump occurs at time t , the process moves to $n+1$ with probability $\mathbf{L}_t(n, n+1)/\mathbf{L}_t(n, n)$ and to $n-1$ with probability $\mathbf{L}_t(n, n-1)/\mathbf{L}_t(n, n)$, cf. [Bor03, pp. 179-180]. This leads, by using (11), to the following schematic algorithm to simulate a sample path. Assume that the process is in state $n \in \mathbb{N}$ at time $s \geq \tau$.

- Generate an exponential random variable U with law $\mathcal{E}(1)$;
- Compute $T := F^{-1}(U)$ where $F(t) := n \int_0^t \mu(s+u) du + \int_0^t \lambda_g(s-\tau+u) du$;
- Compute $P := \lambda_g(s+T-\tau)/(n\mu(s+T) + \lambda_g(s+T-\tau))$;
- Generate a Bernoulli random variable J with law $\mathcal{B}(1, P)$, independent of U .

The next jump will occur at time $s+T$, from state n to state $n+2J-1$.

As one can see clearly on the infinitesimal generators (11), $(M_t)_{t \geq 0}$ is a particular inhomogeneous birth and death process, cf. for example [Bor03]. Process $(M_t)_{t \geq 0}$ can also be seen as an inhomogeneous queueing system with infinite number of servers in parallel. The literature on similar queueing systems is enormous, cf. for example [Zei88] and [ZC85] and references therein. In an M/M/ ∞ queue, each client is immediately served by an independent dedicated server. Recall that the infinitesimal generators of a time-inhomogeneous M/M/ ζ queue (i.e. ζ servers in parallel) is given by

$$(\mathbf{L}_s)_{i,j} = \begin{cases} \lambda(s) & \text{if } j = i + 1 \\ (i \wedge \zeta)\mu(s) & \text{if } j = i - 1 \\ -(\lambda(s) + (i \wedge \zeta)\mu(s)) & \text{if } j = i. \end{cases}$$

In other words, for any function $f : \mathbb{N} \rightarrow \mathbb{R}$ and any $n \in \mathbb{N}$

$$\mathbf{L}_s(f)(n) = (n \wedge \zeta)\mu(s)(f(n-1) - f(n)) + \lambda(s)(f(n+1) - f(n)),$$

where by notational convention $f(-1) = f(0)$. When $g \equiv 0$ and μ is constant in (7), one has $p(s-\tau, s, 0) = 1$ for any $s \geq 0$. Consequently, the process $(M_t)_{t \geq 0}$ is in that case an M/M/ ∞ queue with input intensity λ and constant output intensity μ . When λ is constant, the invariant measure of this queue is the Poisson law $\mathcal{P}(\lambda/\mu)$. In a way, the M/M/ ∞ queue with constant intensities is for the Poisson process what the Ornstein-Uhlenbeck process is for Brownian motion, cf. [Rob03, Theorem 6.14].

The role played by the M/M/ ∞ queueing processes in our model is due to the independency of the particles in the definition of $(M_t)_{t \geq 0}$. One can alternatively consider a non independent killing after maturation, which can lead for example to an M/M/1 type queueing process. Unfortunately, the law at fixed time of such a process, even for the homogeneous case, is far more complex than the simple formula obtained in the M/M/ ∞ case, cf. [Tar02] and [Rob03].

Assume that the input rate function λ is constant. When $\mu \equiv 0$ in (7), i.e. when there is no killing after maturation, the formula (9) for $r(s, t)$ when $0 \leq s \leq t$ boils down to

$$r(s, t) = \lambda \int_{(s-\tau) \vee 0}^{(t-\tau) \vee 0} \exp \left(- \int_0^\tau g(w+u, \rho w) dw \right) du.$$

In that case, $t \in \mathbb{R}_+ \mapsto r(s, t)$ is non decreasing since the main integrand does not depend on t . This is not surprising since the particles are never killed after maturation. Hence, on $\{M_s = 0\}$, the process $t \in \mathbb{R}_+ \mapsto M_t$ is non decreasing, and in particular its expected value $r(s, t)$ is non decreasing too.

Let us consider now the particular case in (7) where κ is of the form

$$k(t, x) = g(t)I_{[0, \alpha]}(x) + \mu I_{(1, +\infty)}(x), \quad (15)$$

where $\alpha \in [0, 1]$, where $\mu \in \mathbb{R}_+$, and where $g : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is a smooth function. It corresponds to a time dependent killing before the maturation stage α and to a constant killing after maturation. No killing is made between maturation stage α and full maturation. The formula (9) for $r(s, t)$ when $\tau \leq s \leq t$ boils down to

$$r(s, t) = \lambda e^{-\mu(t-\tau)} \int_{s-\tau}^{t-\tau} \exp \left(u\mu - \int_0^{\alpha\tau} g(u+w) dw \right) du. \quad (16)$$

When $g \equiv 0$, this formula reduces to the classical M/M/ ∞ average queue length

$$r(s, t) = \frac{\lambda}{\mu} (1 - e^{-\mu(t-s)}). \quad (17)$$

Assume that function g in (15) vanishes at infinity, then the two formulas (16) and (17) are equivalent when t goes to $+\infty$. In particular, the Poisson measure $\mathcal{P}(\lambda/\mu)$ is a stationary distribution of $(M_t)_{t \geq 0}$ in that case. One can see on figure 3 that this Poisson equilibrium is quickly reached. It is possible to quantify the speed of convergence in total variation norm, cf. [Rob03].

2.1 Identifiability of the parameters

According to Theorem 2.1, the law of $(M_t)_{t \geq 0}$ is parametrised by the positive real number ρ and the three functions $\lambda : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ and $g : \mathbb{R}_+ \times [0, 1] \rightarrow \mathbb{R}_+$ and $\mu : \mathbb{R}_+ \rightarrow \mathbb{R}_+$.

$$(\lambda, \rho, \mu, g) \mapsto \mathcal{L}((M_t)_{t \geq 0} | M_0).$$

It is then natural to ask about the identifiability of these parameters, in other words, about the injectivity of this parametrisation. According to Corollary 2.2 and Remark 2.3, the dynamics is fully described by τ and by the two functions μ and λ_g where λ_g is defined by (12). Function μ is always identifiable. In the other hand, function $\lambda_g(\cdot - \tau)$ is identifiable but the couple (λ, g) is not. The action of g can be compensated by λ and vice versa. Namely, and in the spirit of Remark 2.4, suppose that g can be written $g = g_1 + g_2$, where g_1 and g_2 are non-negative functions. Then, according to (14), the two models corresponding respectively to (λ, g) and (λ_{g_1}, g_2) are indistinguishable. The extreme case corresponds to $(\lambda_g, 0)$, for which the entire killing function g is merged into the input rate function λ .

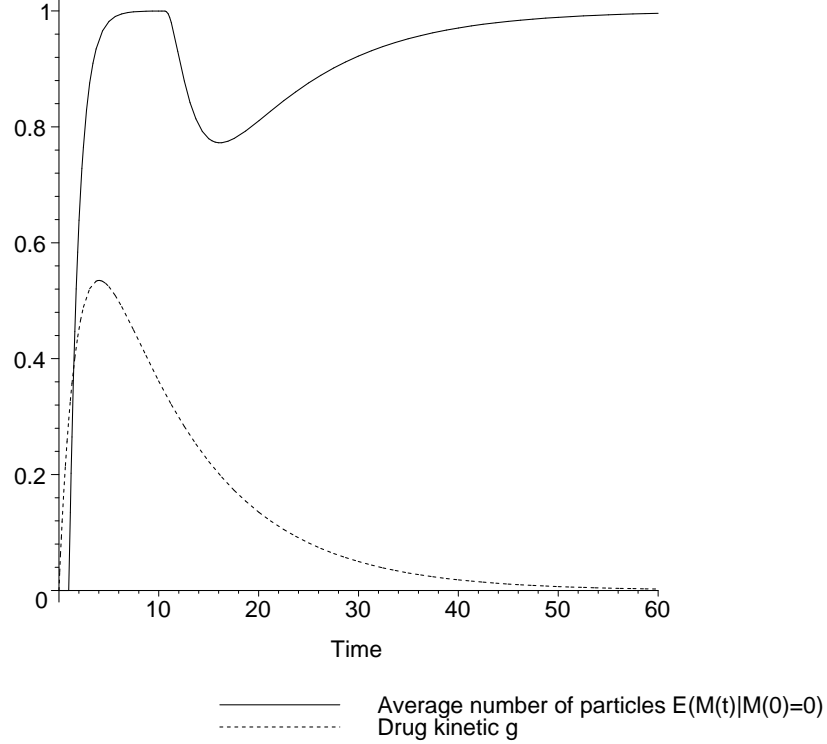


Figure 3: This example corresponds to the case (15) with $\lambda \equiv 1$, $\alpha = \frac{1}{2}$, $\mu \equiv 1$, $\rho = 1$, and $g(t - 10) = e^{-t/10} - e^{-t/2}$. Are plotted the average number $\mathbf{E}(M_t | M_0 = 0)$ of circulating neutrophils (particles), and the “drug kinetic” g . One can observe on the plot of the average number of particles three main time phases. The first phase corresponds to an ascendancy to a Poisson equilibrium before the action of the drug via g . The second phase corresponds to a decrease due to the action of the drug via function g (delayed by the time lag is $\tau = \rho^{-1} = 1$). In the third phase, the drug action decreases and the Poisson equilibrium is reached again.

Let us analyse some special cases. For any $\theta > 0$, let us consider the transformation which replaces (λ, g) by $(\lambda^\theta, g^\theta)$ defined by

$$\lambda^\theta := \theta\lambda \quad \text{and} \quad g^\theta := g + \rho \log \theta.$$

Notice that g^θ may become negative when $\theta < 1$, cf. Remark 2.4. Function μ and parameter ρ are left unchanged, and one can check that $\lambda_{g^\theta}^\theta = \lambda_g$. Therefore, the dynamics is invariant by this transformation: the models corresponding to (λ, ρ, μ, g) and $(\lambda^\theta, \rho, \mu, g^\theta)$ are indistinguishable. A multiplicative perturbation of the input intensity λ corresponds to an additive perturbation of the killing function g before maturation. Hence, one can decide to normalise the parametrisation by taking for example $\lambda \equiv 1$.

Similarly, when λ is constant, and for any $\theta > 0$, let us consider the transformation which replaces (ρ, g) by (ρ_θ, g_θ) defined by

$$\rho_\theta := \theta\rho \quad \text{and} \quad g_\theta := \theta g.$$

Notice that by (4), one has $\tau_\theta = \tau/\theta$. Here again, μ is left unchanged and for any

$$s \geq \tau_{\text{critical}}(\rho, \theta) := \max(\tau, \tau_\theta)$$

$$\exp\left(-\int_{s-\tau_\theta}^s \kappa_\theta(w, \rho_\theta(w-s+\tau_\theta)) dw\right) = \exp\left(-\int_{s-\tau}^s \kappa(w', \rho(w'-s+\tau)) dw'\right),$$

where we used the change of variable $w = s + (w' - s)\theta$. Therefore, the dynamics is invariant by this transformation: the models corresponding to (λ, ρ, μ, g) and $(\lambda, \rho_\theta, \mu, g_\theta)$ are indistinguishable after the critical time $t_{\text{critical}}(\rho, \theta)$. A multiplicative perturbation of the maturation time τ corresponds, after some critical time, to a multiplicative perturbation of the killing function g before maturation.

Remark 2.6 (Estimation of the parameters). *Suppose that one observes a finite sequence $((t_1, M_{t_1} + \varepsilon_1), \dots, (t_n, M_{t_n} + \varepsilon_n))$ where $t_1 < \dots < t_n$ are random times and where $(\varepsilon_1, \dots, \varepsilon_n)$ is some unobserved noise. A natural question is to ask about the estimation of the parameters τ, μ, λ_g of the dynamics from such observations. In absence of noise, one can provide at least some heuristic graphical methods in the case corresponding to (17). However, a more general answer is out of the scope of this paper and will be hopefully the subject of a forthcoming article.*

2.2 Application to anti-cancer drugs models

Myelosuppression is the dominating toxicity for most anti-cancer drugs, cf. [FK03]. The circulating leukocytes in blood comprise neutrophils (approximately 60-70% in humans), lymphocytes (30%), monocytes (5%), eosinophils (2%) and basophils (< 1%). Maturation of eosinophils, basophils and monocytes basically follows the same maturation steps in the bone marrow as that of neutrophils. For this reason the neutrophils profiles are usually used as marker of toxicity.

All blood cells originate from a common type of cell, the pluripotent haematopoietic stem cell (PHSC), which has a high capacity for selfrenewal, i.e. such cells can give rise to “identical” daughter cells. PHSCs can also differentiate to form lymphoid stem cells or myeloid multipotent stem cells (CFU-GEMMs), which give rise to granulocytes, erythrocytes, monocytes and platelets. During maturation, the cells remain at a certain stage for a while, and then move to the next stage, as shown in Figure 4. Most cells in the bone marrow are lineage specific precursors with little self-renewal capacity and high mitotic activity. Non-mitotic cells include metamyelocytes, band cells and segmented neutrophils that are released into the blood. Neutrophils disappear from the blood in a random (first-order) process. Thereafter, the neutrophils enter the tissues, where they undergo apoptosis. Regulation of leukocyte levels is still only partly understood.

There is a huge literature on Pharmacokinetics/Pharmacodynamics models that describe the link between the drug concentration profiles and their effect (neutrophils cells counts for toxicity of anti-cancer drugs). Among the authors, Jusko described in [DGJ93, GJ01] the properties of a large number of indirect models while others, cf. for example [FFSK00, HSS⁺98], specialised on the study of models for anti-cancer drugs. These empirico-physiologic models macroscopically mimic the action of drugs on cells and share two properties. Firstly, they allow to describe the whole time course of neutrophils. Secondly, there is an intrinsic delay between the drug administration and the effect. Cancer drugs models can be roughly classified into three families.

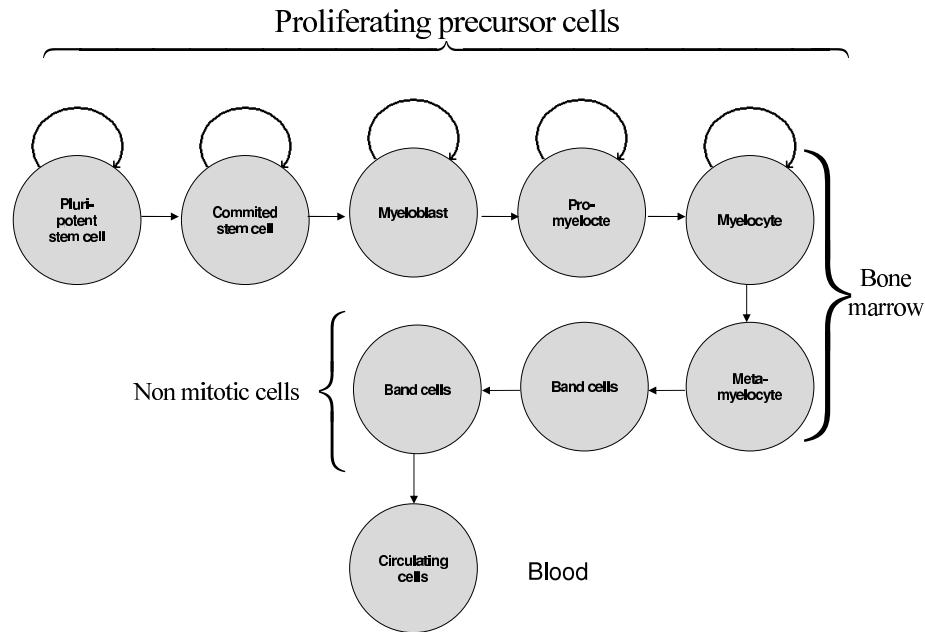


Figure 4: Cell evolution diagram

1. In the first family of models, cells are created at constant rate and they transit to compartments to mimic leukocyte maturation. A number of compartments with replicating cells are connected in series with a number of compartments of non-replicating cells and a compartment of circulating leukocytes. Only compartments with replicating cells are sensitive to the drug action. From a macroscopic point of view, the bone marrow produces progenitor stem cells that divide rapidly that can be killed. If these cells survive, they continue their maturation without “obstacle” in the bone marrow. Finally, they migrate into blood, the observed pool, as white blood cells, cf. Figure 4.
2. In models from the second family, all compartments with replicating cells are concatenated to give the input of a number of compartments of non replicating cells, cf. Figure 5. At equilibrium, (without drug) there is a constant rate production of non-replicating cells that continue their maturation until they reach blood. The drug action only concentrates on the production of non replicating cells.
3. The third family of models has only two compartments. The first one represents the replicating cells which are sensitive to the drug. The second compartment represents the blood, from which the cells are excreted. The transit compartments are substituted by a lag time which mimics the delay between the actual drug action and its observed effect in blood. The picture corresponds roughly to Figure 2.

The continuous model we studied can adapt to compartments with replicating cells by a careful adjustment of the functions g and λ , cf. Section 2.1.

Conclusion. Most kineticists use mainly the first family of models to describe the myelosuppression toxicity of anticancer drugs. Friberg summarized in [FK03] the current kineticists preferences : “transit compartments are more attractive than lag times (third family of models) since they actually mimic the different cell stages within the bone marrow and since the maturation is a gradual process contrarily to lag-time”. The same author suggested that increasing the number of transit compartments is a good way to increase the delay without adding any extra parameters since the same transit rate is used. In light of our work, these two assertions seem contradictory and penalizing for numerical purpose. Actually, adding transit compartments in models from family 1 or 2 to adjust for a long delay makes these models close to a lag-time model (family 3). Moreover, the first and second families of models lead to high dimensional systems of differentials equations which are mainly solved numerically while the dimension of the system given by the third family of models is always 2. We argue that a preliminary analysis of the system, leading to a fine choice of the κ function, should save computer time and minimize numerical errors without lost in interpretation.

Non replicating cells

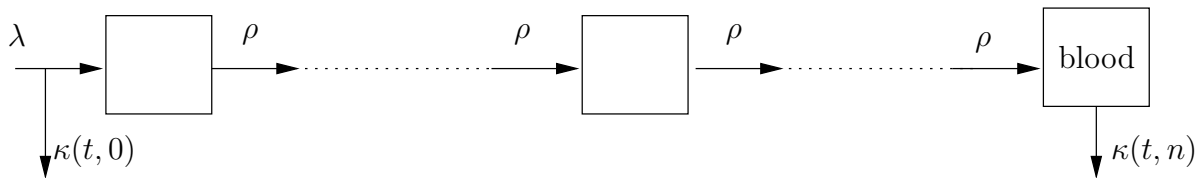


Figure 5: Cell maturation model. Second family.

3 Proofs and Lemmas

Proof of Theorem 2.1. The process $(C_t)_{t \geq 0}$ can be constructed as a simple Poisson process starting from 0 and changed in time. Namely,

$$(C_t)_{t \geq 0} := (N_{F(t)})_{t \geq 0} \quad (18)$$

where $(N_t)_{t \geq 0}$ is a homogeneous simple Poisson process starting from 0 with intensity 1 and where the “time change function” F is defined by

$$F(t) := \int_0^t \lambda(u) du. \quad (19)$$

Notice that the jump times of $(C_t)_{t \geq 0}$ are $(T_n)_{n \in \mathbb{N}^*} := (G(U_n))_{n \in \mathbb{N}^*}$ where $(U_n)_{n \in \mathbb{N}^*}$ are the jump times of $(N_t)_{t \geq 0}$ and where $G := F^{-1}$ is the generalised inverse of F defined by

$$G(u) := \inf\{v \in \mathbb{R}_+ \text{ such that } F(v) \geq u\}. \quad (20)$$

Recall that $(U_{n+1} - U_n)_{n \in \mathbb{N}^*}$ is a sequence of i.i.d. exponential random variables with common law $\mathcal{E}(1)$, and in particular, $\mathcal{L}(U_n) = \Gamma(n, 1)$.

Let us establish (8). As we will see below, the binomial part $\mathcal{B}(n, p(s, t, 1))$ in (8) corresponds actually to the n particles already mature at time s . They evolve independently

of the new particles arriving at maturity on the time interval $[s, t]$. These ones correspond to the Poisson part $\mathcal{P}(r(s, t))$ in (8).

The event $\{M_s = n\}$ corresponds to the presence at time s of n independent mature particles. We do not know the position of each particle. However, since by assumption the killing function κ does not depend on the position after maturation, the survival probability at time t of each particle does not depend on the position in $(1, +\infty)$. More precisely, each particle has a probability $p(s, t, 1)$ to be still present at time t . By independence, the number of these particles still present at time t follows a binomial law $\mathcal{B}(n, p(s, t, 1))$.

To this binomial number of particles, one has to add the independent number of particles with law $\mathcal{L}(M_t | M_s = 0)$. Therefore, the problem is reduced to the computation of $\mathcal{L}(M_t | M_s = 0)$. For simplicity, we will compute $\mathcal{L}(M_t | M_\tau = 0)$ since the case $s > \tau$ is similar. More precisely, we will compute $\mathcal{L}(M_t)$ when $\mathcal{L}(M_\tau) = \delta_0$.

Recall that $Z_{t,n}$ is the Bernoulli random variable corresponding to the presence in the output $(1, +\infty)$ at time t of the particle number n . On the event $\{M_0 = 0\}$, the process $(M_t)_{t \geq 0}$ is then defined by (5). Let us consider the Markov process $(X_t)_{t \geq 0}$ with state space $\mathbb{R}_+ \cup \{e\}$ constructed in Section 1. Let $((X_t^{[n]})_{t \geq 0})_{n \in \mathbb{N}}$ be independent instances of $(X_t)_{t \geq 0}$ starting from 0, independent of $(C_t)_{t \geq 0}$. One has

$$Z_{t,n} := \begin{cases} \mathbf{I}_{(1,+\infty)}(X_{t-T_n}^{[n]}) & \text{if } t \geq T_n \\ 0 & \text{if not.} \end{cases}$$

Thus, for any $t \geq \tau$, any $n \in \mathbb{N}^*$ and any $0 \leq t_1 \leq \dots \leq t_n \leq t - \tau$

$$\mathcal{L}(Z_{t,1}, \dots, Z_{t,n} | T_1 = t_1, \dots, T_n = t_n, C_{t-\tau} = n) = Q(t_1, t) \otimes \dots \otimes Q(t_n, t),$$

where for any $0 \leq s \leq t$, $Q(s, t)$ is the probability measure on $\{0, 1\}$ defined by

$$Q(s, t) = \begin{cases} \delta_0 & \text{if } t < s + \tau \\ (1 - p(s, t, 0)) \delta_0 + p(s, t, 0) \delta_1 & \text{if } t \geq s + \tau. \end{cases}$$

Therefore, for any $\alpha \in \mathbb{R}$, any $t \geq \tau$, any $n \in \mathbb{N}^*$ and any $0 \leq t_1 \leq \dots \leq t_n \leq t - \tau$

$$\mathbf{E}(e^{\alpha M_t} | T_1 = t_1, \dots, T_n = t_n, C_{t-\tau} = n) = \prod_{i=1}^n \Psi_{t,\alpha}(t_i), \quad (21)$$

where for any s such that $0 \leq s \leq t$

$$\Psi_{t,\alpha}(s) := 1 + (e^\alpha - 1)p(s, t, 0). \quad (22)$$

Recall now that $(C_t)_{t \geq 0} = (N_{F(t)})_{t \geq 0}$ and that $(T_n)_{n \in \mathbb{N}^*} = (G(U_n))_{n \in \mathbb{N}}$. For any $t \geq \tau$, any $\alpha \in \mathbb{R}$, and any $n \in \mathbb{N}$, one can write

$$\begin{aligned} \mathbf{E}(e^{\alpha M_t} | C_{t-\tau} = n) &= \mathbf{E}(\mathbf{E}(e^{\alpha M_t} | T_1, \dots, T_n, C_{t-\tau} = n)) \\ &= \mathbf{E}(\mathbf{E}(e^{\alpha M_t} | G(U_1), \dots, G(U_n), N_{F(t-\tau)} = n)). \end{aligned} \quad (23)$$

Since $(N_t)_{t \geq 0}$ is a simple Poisson process with jump times $(U_n)_{n \in \mathbb{N}^*}$, one has

$$\mathcal{L}(U_1, \dots, U_n | N_{F(t-\tau)} = n) = \sigma_n \quad (24)$$

where σ_n is the law of the order statistics of the uniform law over the cube $K^n := [0, F(t - \tau)]^n$. The support of σ_n is the simplex $\Delta_n := \{0 \leq u_1 \leq \dots \leq u_n \leq F(t - \tau)\}$. Therefore, by virtue of (24) and (21), equation (23) gives

$$\begin{aligned} \mathbf{E}(e^{\alpha M_t} | C_{t-\tau} = n) &= \int_{\Delta_n} \Psi_{t,\alpha}(G(u_1)) \cdots \Psi_{t,\alpha}(G(u_n)) d\sigma_n(u_1, \dots, u_n) \\ &= (n!)^{-1} \sum_{\sigma \in \Sigma_n} \int_{\Delta_n} \Psi_{t,\alpha}(G(u_{\sigma(1)})) \cdots \Psi_{t,\alpha}(G(u_{\sigma(n)})) d\sigma_n(u_1, \dots, u_n) \\ &= \int_{K^n} \Psi_{t,\alpha}(G(u_1)) \cdots \Psi_{t,\alpha}(G(u_n)) |K|^{-n} du_1 \cdots du_n \\ &= \left(\frac{1}{F(t - \tau)} \int_0^{F(t-\tau)} \Psi_{t,\alpha}(G(u)) du \right)^n. \end{aligned}$$

Thus, by (19), (22) and (20) the formula above gives

$$\mathbf{E}(e^{\alpha M_t} | C_{t-\tau} = n) = \left(1 + \frac{e^\alpha - 1}{F(t - \tau)} \int_0^{t-\tau} \lambda(v) p(v, t, 0) dv \right)^n.$$

Since $\mathcal{L}(C_{t-\tau}) = \mathcal{P}(F(t - \tau))$, one obtains finally

$$\mathbf{E}(e^{\alpha M_t}) = \mathbf{E}(\mathbf{E}(e^{\alpha M_t} | N_{t-\tau})) = e^{(e^\alpha - 1)r(t)},$$

where by definition

$$\begin{aligned} r(t) &= \int_0^{t-\tau} \lambda(u) p(u, t, 0) du \\ &= \int_0^{t-\tau} \lambda(u) \exp\left(-\int_0^{t-u} \kappa(u+w, \rho w) dw\right) du. \end{aligned}$$

Therefore, M_t has the Laplace transform of a Poisson distribution with intensity $r(t)$, which concludes the proof. \square

Proof of Corollary 2.2. The formula (11) for the infinitesimal generators of $(M_t)_{t \geq 0}$ follows immediately from (8) and Lemma 3.1. Namely, one has for any $0 \leq s \leq t$ and any $x \in \mathbb{R}_+$

$$\partial_t p(s, t, x) = -\kappa(t, x + \rho(t - s)) p(s, t, x).$$

Since $p(t, t, x) = 1$ for any $t \geq 0$ and any $x \in \mathbb{R}_+$, we get that $\partial_{t=s} p(s, t, 1) = -\mu(s)$. Now, the following basic rule of calculus

$$\partial_t \int_s^t F(t, u) du = F(t, t) + \int_s^t (\partial_1 F)(t, u) du$$

gives immediately that for any s, t with $\tau \leq s \leq t$

$$\partial_t r(s, t) = \lambda(t - \tau) p(t - \tau, t, 0) - \int_{s-\tau}^{t-\tau} \kappa(t, 1 + \rho(t - u)) \lambda(u) p(u, t, 0) du.$$

Therefore one obtains $\partial_{t=s} r(s, t) = -\lambda(s - \tau) p(s - \tau, s, 0)$, and the conclusion follows from Lemma 3.1. \square

Lemma 3.1. Let $\mathcal{T} := \{(s, t) \in \mathbb{R}^2 \text{ with } 0 \leq s \leq t\}$ and let $p : \mathcal{T} \rightarrow (0, 1]$ and $b : \mathcal{T} \rightarrow \mathbb{R}_+$ be two bounded piecewise \mathcal{C}^1 functions. Let $(R_t)_{t \geq 0}$ be a continuous time stochastic process with state space \mathbb{N} such that $\mathcal{L}(R_t | R_s = n) = \mathcal{B}(n, p(s, t)) * \mathcal{P}(\lambda(s, t))$ for any $(s, t) \in \mathcal{T}$ and any $n \in \mathbb{N}$. Then the following two properties hold.

1. The process $(R_t)_{t \geq 0}$ is Markov if and only if p and λ satisfy to the following equations

- (a) $p(t, t) = 1$ and $\lambda(t, t) = 0$ for any $t \geq 0$;
- (b) $p(s, t) = p(s, u)p(u, t)$ for any $0 \leq s \leq u \leq t$;
- (c) $\lambda(s, t) = \lambda(s, u)p(u, t) + \lambda(u, t)$ for any $0 \leq s \leq u \leq t$.

2. If $(R_t)_{t \geq 0}$ is Markov, its infinitesimal generators $(\mathbf{L}_t)_{t \geq 0}$ are given for any $s \geq 0$, any function $f : \mathbb{N} \rightarrow \mathbb{R}$ and any $n \in \mathbb{N}$ by

$$\mathbf{L}_s f(n) = -n(\partial_{t=s} p(s, t))(f(n-1) - f(n)) + (\partial_{t=s} \lambda(s, t))(f(n+1) - f(n)),$$

where by notational convention $f(-1) = f(0)$.

Proof of Lemma 3.1. The process $(R_t)_{t \geq 0}$ is Markov if and only if for any $0 \leq s \leq u \leq t$ and any $n \in \mathbb{N}$, the mixture obtained by mixing the family $\{\mathcal{L}(R_t | R_u = m), m \in \mathbb{N}\}$ with the law $\mathcal{L}(R_u | R_s = n)$ is precisely $\mathcal{L}(R_t | R_s = n)$. By assertion 1 of Lemma 3.2 and assertion 1 of Lemma 3.3, this statement is equivalent to

$$\mathcal{B}(n, p(s, t)) * \mathcal{P}(\lambda(s, t)) = \mathcal{B}(n, p(s, u)p(u, t)) * \mathcal{P}(\lambda(s, u)p(u, t) + \lambda(u, t)).$$

The first part of Lemma 3.1 follows by considering the particular cases $n = 0$ and $s = u = t$ or by considering Laplace or Fourier transforms or generating functions. It remains to derive the second part of Lemma 3.1, namely the formula for the infinitesimal generators. By density, it is enough to consider functions of the form $f(n) = \exp(\alpha n)$ where $\alpha \in i\mathbb{R}$ and $i^2 = -1$. Define for any $n \in \mathbb{N}$ and any $0 \leq s \leq t$ the quantity

$$Q_n(\alpha, s, t) := \mathbf{E}(f(Z_t) | Z_s = n).$$

Since $\mathcal{L}(R_t | R_s = n) = \mathcal{B}(n, p(s, t)) * \mathcal{P}(\lambda(s, t))$, we get by denoting $\beta := e^\alpha - 1$ that

$$Q_n(\alpha, s, t) = \mathbf{E}(e^{\alpha Z_t} | Z_s = n) = (p(s, t)\beta + 1)^n \exp(\lambda(s, t)\beta).$$

Therefore, one has by taking the partial derivative in t

$$\partial_t Q_n(\alpha, s, t) = n\beta Q_{n-1}(\alpha, s, t)\partial_t p(s, t) + \beta Q_n(\alpha, s, t)\partial_t \lambda(s, t),$$

where by notational convention $Q_{-1}(\alpha, s, t) = 0$. But one has also that for any $m \in \mathbb{N}$

$$Q_{m+1}(\alpha, s, t) - Q_m(\alpha, s, t) = p(s, t)\beta Q_m(\alpha, s, t).$$

Thus, this gives by denoting $\Delta_m(\alpha, s, t) := Q_{m+1}(\alpha, s, t) - Q_m(\alpha, s, t)$

$$\partial_t Q_n(\alpha, s, t) = na(s, t)\Delta_{n-1}(\alpha, s, t) + b(s, t)\Delta_n(\alpha, s, t),$$

where $\Delta_{-1} := 0$ and where

$$a(s, t) := -\partial_t \log p(s, t) \quad \text{and} \quad b(s, t) := \frac{\partial_t \lambda(s, t)}{p(s, t)}.$$

Since $p(s, s) = 1$ by virtue of the first part of Lemma 3.1, we have actually that

$$a(s, s) = -\partial_{t=s} p(s, t) \quad \text{and} \quad b(s, s) = \partial_{t=s} \lambda(s, t).$$

In the other hand, one has that $\Delta_m(\alpha, s, s) = f(m+1) - f(m)$, and the desired formula for \mathbf{L}_s follows finally from the definition of the infinitesimal generators

$$\mathbf{L}_s f(n) := \partial_{t=s} [t \mapsto \mathbf{E}(f(Z_t) | Z_s = n)].$$

□

Lemma 3.2 (Bernoulli process and mixtures). *Let (X, Y) be a couple of random variables. Then the following statements are true for any $p, p' \in [0, 1]$, and any $n \in \mathbb{N}$.*

1. *If $\mathcal{L}(Y) = \mathcal{B}(n, p')$ and $\mathcal{L}(X | Y) = \mathcal{B}(Y, p)$, then $\mathcal{L}(X) = \mathcal{B}(n, pp')$. In other words, the binomial distribution $\mathcal{B}(n, pp')$ can be obtained by mixing the family of binomial distributions $\{\mathcal{B}(m, p), m \in \mathbb{N}\}$ with the binomial distribution $\mathcal{B}(n, p')$;*
2. *If $\mathcal{L}(Y) = \mathcal{NB}(n, p)$ and $\mathcal{L}(X | Y) = \mathcal{NB}(Y, p')$, then $\mathcal{L}(X) = \mathcal{NB}(n, pp')$. In other words, the negative-binomial distribution $\mathcal{NB}(n, pp')$ can be obtained by mixing the family of negative-binomial distributions $\{\mathcal{NB}(m, p'), m \in \mathbb{N}\}$ with the negative-binomial distribution $\mathcal{NB}(n, p)$;*
3. *Let $(A_n)_{n \in \mathbb{N}}$ and $(B_n)_{n \in \mathbb{N}}$ be two independent Bernoulli processes with parameters p and p' respectively. Then the compound $(A_{B_n})_{n \in \mathbb{N}}$ is a Bernoulli process with parameter pp' .*

Proof of Lemma 3.2. Some of the desired assertions are well known, but we will give full proofs here. Assertion 1 follows by considering generating functions, or Laplace or Fourier transforms. Namely, we simply write for any $s \in (0, 1)$

$$\mathbf{E}(s^X) = \mathbf{E}(\mathbf{E}(s^X | Y)) = \mathbf{E}((1 + p(s-1))^Y) = (1 + p'p(s-1))^n,$$

and thus $\mathcal{L}(X) = \mathcal{B}(n, pp')$. A direct computation of $\mathbb{P}(X = k)$ shows that assertion 1 is in fact a consequence of the following elementary Abel type binomial identity, cf. [Rom84]

$$\sum_{m=k}^n \binom{m}{k} \binom{n}{m} a^{m-k} b^{n-m} = \binom{n}{k} (a+b)^{n-k}.$$

Assertion 2 follows easily via generating functions since for any $s \in (0, 1)$, one has

$$\mathbf{E}(s^X) = \mathbf{E}(\mathbf{E}(s^X | Y)) = \mathbf{E}\left(\left(\frac{p's}{1 - s(1-p')}\right)^Y\right) = \left(\frac{pp's}{1 - s(1-pp')}\right)^n,$$

and thus $\mathcal{L}(X) = \mathcal{NB}(n, pp')$. Recall that the n^{th} jump time of a Bernoulli process of parameter p follows a negative-binomial distribution $\mathcal{NB}(n, p)$. Thus, assertions 1 and

2 are direct consequences of assertion 3. Conversely, the compound process $(A_{B_n})_{n \in \mathbb{N}}$ satisfies for any $m \in \mathbb{N}$

$$\mathcal{L}(A_{B_n} \mid B_n = m) = \mathcal{B}(m, p).$$

Thus, assertion 3 is a direct consequence of assertion 1 by taking $X = A_Y$ and $Y = B_n$. One can construct $(A_n)_{n \in \mathbb{N}}$ and $(B_n)_{n \in \mathbb{N}}$ by taking $A_0 = 0$, $B_0 = 0$, and

$$A_n = \zeta_1 + \cdots + \zeta_n \quad \text{and} \quad B_n = \xi_1 + \cdots + \xi_n,$$

where $(\zeta_n)_{n \in \mathbb{N}^*}$ and $(\xi_n)_{n \in \mathbb{N}^*}$ are two independent sequences of i.i.d. Bernoulli random variables with common law $\mathcal{B}(1, p)$ and $\mathcal{B}(1, p')$ respectively. Since these random variables take their values in $\{0, 1\}$, we get

$$X = A_{B_n} = \sum_{i=1}^{B_n} \zeta_i = \sum_{i=1}^{\xi_1 + \cdots + \xi_n} \zeta_i = \sum_{i=1}^n \xi_i \zeta_i.$$

The $\xi_1 \zeta_1, \dots, \xi_n \zeta_n$ are i.i.d. Bernoulli random variables with common law $\mathcal{B}(1, pp')$. The intuition is enlighten if we imagine a gamer who tosses n times independently two independent coins with probability of success p and p' .

□

Lemma 3.3 (Poisson process and mixtures). *Let (X, Y) be a couple of random variables. Then the following statements are true for any $p \in [0, 1]$, any $\lambda \in \mathbb{R}_+$, and any $n \in \mathbb{N}$.*

1. *If $\mathcal{L}(Y) = \mathcal{P}(\lambda)$ and $\mathcal{L}(X \mid Y) = \mathcal{B}(Y, p)$, then $\mathcal{L}(X) = \mathcal{P}(p\lambda)$. In other words, the Poisson distribution $\mathcal{P}(p\lambda)$ can be obtained by mixing the family of binomial distributions $\{\mathcal{B}(m, p), m \in \mathbb{N}\}$ with the Poisson distribution $\mathcal{P}(\lambda)$;*
2. *If $\mathcal{L}(Y) = \mathcal{NB}(n, p)$ and $\mathcal{L}(X \mid Y) = \Gamma(Y, \lambda)$, then $\mathcal{L}(X) = \Gamma(n, p\lambda)$. In other words, the gamma distribution $\Gamma(n, p\lambda)$ can be obtained by mixing the family of gamma distributions $\{\Gamma(m, \lambda), m \in \mathbb{N}\}$ with the negative-binomial distribution $\mathcal{NB}(n, p)$;*
3. *Let $(N_t)_{t \geq 0}$ be a simple Poisson process of intensity λ and let $(A_n)_{n \in \mathbb{N}}$ be a Bernoulli process with parameter p , independent of $(N_t)_{t \geq 0}$. Then the compound $(A_{N_t})_{t \geq 0}$ is a simple Poisson process of intensity $p\lambda$.*

Proof of Lemma 3.3. Some of the desired assertions are well known, but we will give full proofs here. Assertion 1 follows immediately via generating functions since for any $s \in (0, 1)$

$$\mathbf{E}(s^X) = \mathbf{E}(\mathbf{E}(s^X \mid Y)) = \mathbf{E}((1 + p(s - 1))^Y) = e^{p\lambda(s-1)},$$

and thus $\mathcal{L}(X) = \mathcal{P}(p\lambda)$. Alternatively, one can derive assertion 1 from assertion 1 of Lemma 3.2 by considering the Poisson limit, namely

$$\mathcal{B}(n, p_n) \xrightarrow[n \rightarrow +\infty]{} \mathcal{P}(\lambda) \text{ weakly when } np_n \xrightarrow[n \rightarrow +\infty]{} \lambda.$$

Assertion 2 follows easily by computing the density of $\mathcal{L}(X)$. Namely, for any $t \geq 0$,

$$\sum_{m=n}^{+\infty} \frac{\lambda^m}{(m-1)!} t^{m-1} e^{-\lambda t} \binom{m-1}{n-1} p^n (1-p)^{m-n} = \frac{(p\lambda)^n}{n!} t^{n-1} e^{-p\lambda t},$$

and thus $\mathcal{L}(X) = \Gamma(n, p\lambda)$. Alternatively, assertion 2 can be deduced from assertion 2 of Lemma 3.2 by considering the negative-binomial approximation of the gamma distribution. Namely, let us denote for any $\alpha \in \mathbb{R}$ and any distribution μ by $\mathcal{D}_\alpha(\mu)$ the law of αZ when $\mathcal{L}(Z) = \mu$. Then, $\mathcal{D}_{r_n}(\mathcal{NB}(m, p_n))$ converges weakly toward $\Gamma(m, \lambda)$ when

$$p_n \xrightarrow{n \rightarrow +\infty} 0 \quad \text{and} \quad \frac{r_n}{p_n} \xrightarrow{n \rightarrow +\infty} \lambda > 0.$$

In particular, the case $m = 1$ corresponds to the approximation of the exponential distribution $\mathcal{E}(\lambda) = \Gamma(1, \lambda)$ by dilations $\mathcal{D}_{r_n}(\mathcal{G}(p_n))$ of geometric distributions $\mathcal{G}(p_n)$.

Recall the the n^{th} jump time of a simple Poisson process of intensity λ follows a gamma distribution $\Gamma(n, \lambda)$. Consequently, assertions 1 and 2 follow from assertion 3. Conversely, the compound Poisson process $(A_{N_t})_{t \geq 0}$ satisfies

$$\mathcal{L}(A_{N_t} | N_t = n) = \mathcal{B}(n, p).$$

Thus, assertion 3 is a consequence of assertions 1 and 2 by taking $X = A_Y$ and $Y = N_t$.

We have also to mention for the sake of completeness the classical result which states that the negative-binomial distribution can be obtained by mixing a family of Poisson distributions with a gamma distribution. \square

Lemma 3.4 (Killed Markov process and Feynman-Kac formulæ). *Let $(X_t)_{t \geq 0}$ be a Markov process with state space \mathcal{S} and infinitesimal generators $(\mathbf{L}_t)_{t \geq 0}$. Let $\mathcal{S}^e := \mathcal{S} \cup \{e\}$ be an extended state space with $e \notin \mathcal{S}$. Let $\kappa : \mathbb{R}_+ \times \mathcal{S} \rightarrow \mathbb{R}$ be a bounded continuous function. For any $0 \leq s \leq t$, let $\mathbf{P}_{s,t}^e$ be the linear functional operator defined for any suitable $f : \mathcal{S}^e \rightarrow \mathbb{R}$ and any $x \in \mathcal{S}^e$ by*

$$\mathbf{P}_{s,t}^e(f)(x) = \begin{cases} \mathbf{E}(f(X_t)K_{s,t}|X_s = x) + (1 - \mathbf{E}(K_{s,t}|X_s = x))f(e) & \text{if } x \neq e \\ f(e) & \text{if } x = e, \end{cases}$$

where $K_{s,t} := e^{-\int_s^t \kappa(u, X_u) du}$. Then $(\mathbf{P}_{s,t}^e)_{0 \leq s \leq t}$ is a Markov semi-group and its infinitesimal generators are given for any $t \geq 0$, any suitable $f : \mathcal{S}^e \rightarrow \mathbb{R}$ and any $x \in \mathcal{S}^e$ by

$$\mathbf{L}_t^e(f)(x) = \begin{cases} \mathbf{L}_t(f)(x) + \kappa(t, x)(f(e) - f(x)) & \text{if } x \neq e \\ 0 & \text{if } x = e. \end{cases} \quad (25)$$

Proof. The proof is classical and can be based on Itô formula, cf. for example [DM04] and [KS91]. Infinitesimal generators of the form (25) are sometimes called ‘‘Schrödinger operators with potential κ ’’. In particular, when $\mathcal{S} = \mathbb{R}$ and $\mathbf{L}_t(f)(x) = \rho f'(x)$ for some real constant ρ , the process $(X_t)_{t \geq 0}$ is deterministic with $\mathcal{L}(X_t | X_s = x) = \delta_{x+\rho(t-s)}$, and we thus recover (2). \square

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