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# A MARKOV MODEL FOR THE SPREAD OF HEPATITIS C VIRUS

L. COUTIN, L. DECREUSEFOND, AND J.S. DHERSIN

**ABSTRACT.** We propose a Markov model for the spread of Hepatitis C virus (HCV) among drug users who use injections. We then proceed to an asymptotic analysis (large initial population) and show that the Markov process is close to the solution of a non linear autonomous differential system. We prove both a law of large numbers and functional central limit theorem to precise the speed of convergence towards the limiting system. The deterministic system itself converges, as time goes to infinity, to an equilibrium point. This corroborates the empirical observations about the prevalence of HCV.

## 1. MOTIVATIONS

Hepatitis C virus (HCV) infects 170 million people in the world (3 % of the population) and 9 million in Europe (1 % of the population) [16]. More than 75 % of newly infected patients progress to develop chronic infection. Then, Cirrhosis develops in about 10 % to 20 %, and liver cancer develops in 1 % to 5 % over a period of 20 to 30 years. These long-term consequences, which suggest an increased mortality due to HCV infection, make the prevention of spread of hepatitis C a major public health concern.

HCV is spread primarily by direct contact with human blood. In developed countries that have safe blood supplies, the population infected by HCV is closely related to injecting drug users (IDU). It is estimated that 90 % of infectious are due to IDU [11]. In order to reduce the numbers of new hepatitis C cases, preventing infections in IDU is then a priority. Programs exist all over the world which try to reduce the prevalence of many infectious diseases like HIV or hepatitis C, among injecting drug users. They are mainly based on needle exchanges. It turns out that after several years of such programs, the HIV prevalence seems to be now rather low whereas the percentage of IDU who are HCV positive remains about 60 % [9, 11]. We were asked by epidemiologists to provide them a mathematical model which could quantitatively evaluate the differences between the two diseases.

It is always a challenge to analyze an epidemic problem because there are so many real-life situations that should be incorporated while keeping the mathematical model tractable. Moreover, epidemic field studies are expensive and hard to organize so that parameter estimates are rare and often imprecise. It is thus necessary to deal with parsimonious models whose parameters have clear and visible meaning. To the best of our knowledge, the only models which have been developed for the dynamics of HCV transmission are found in the references [14, 4]. It is a deterministic model with more than twenty-five parameters, for which the authors do not have explicit results for the asymptotics and only estimate them by simulations. In our paper, we propose a parsimonious Markovian model for the spread of HCV

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in a local population of IDU. It should be noted that our model bears some resemblance to a random SIR (Susceptible-Infected-Recovered) model but differs from it by some essential characteristics. Our Susceptible (respectively Infected) are IDU who are sero-negative (respectively sero-positive). There is no Recovered category in our model since we can't measure their number (when they are no longer IDU, they can't be counted in studies focused on drugs users). Moreover, our population is not closed (there are new susceptible all the time) and a new drug user may be infected at his first injection. This means that there is an exogeneous flow to the Infected category, a feature which is not included in usual SIR models.

To keep the Markovian character of our model, we made the following usual and reasonable hypothesis. Exogenous antibody-positive and antibody-negative individuals arrive in this local population according to Poisson processes. If initiated by an antibody-positive drug addict, a new IDU acquires the virus very rapidly after the initiation [1, 6]. HCV then spreads in the population by sharing syringe, needles and other accessories (cotton, boilers, etc.). Each individual of the population stays in his state (infected/non infected) for an exponentially distributed time. We present the model in Section 3. If we denote by  $X_1(t)$  (resp.  $X_2(t)$ ) the number of antibody-positive (resp. antibody-negative) individuals in the local population at time  $t$ , we prove that the process  $X = (X_1, X_2)$  is an ergodic Markov process. In Section 4., we give a related deterministic differential system connected with this Markov process. We study its asymptotic behaviour and give an explicit expression of the limit of the solution. In Section 5., we give a mean-field approximation of the process  $X$ : For large populations, we prove that the process  $X$  is close to the solution  $\psi$  of the deterministic differential system. In Section 6., we prove that, for large populations, the invariant distribution for the Markov process  $X$  can be approximated by the Dirac measure which only charges  $\psi(\infty)$ . Hence we can give an explicit limit of the prevalence of HCV in the population. In Section 7, we give a central limit theorem for the approximation of  $X$  by  $\psi$  when the population tends to infinity. In Section 8, we show that even for a small value of  $N$ , there is a good accordance between the prevalence computed on the deterministic limit and the prevalence observed on the stochastic model. We also show that this can be extended to the sensitivity of the model with respect to slight variations of some parameters.

## 2. PRELIMINARIES

Let us denote by  $\mathbb{D}([0, T], \mathbf{R}^2)$  the set of cadlag functions equipped with its usual topology. In this Section, we recall some results about cadlag semi-martingales; for details we refer to [10]. We assume that we are given  $(\Omega, (\mathcal{F}_t, t \geq 0), \mathbf{P})$  a filtered probability space satisfying the so-called usual hypothesis. On  $(\Omega, (\mathcal{F}_t, t \geq 0), \mathbf{P})$ , let  $X$  and  $Y$  be two real-valued cadlag square integrable semi-martingales. The mutual variation of  $X$  and  $Y$ , denoted by  $[X, Y]$ , is the right continuous process with finite variation such that the following integration by parts formula is satisfied:

$$X(t)Y(t) - X(0)Y(0) = \int_{(0, t]} X(s_-) dY(s) + \int_{(0, t]} Y(s_-) dX(s) + [X, Y]_t.$$

The Meyer process of the couple  $(X, Y)$ , or its square bracket, is denoted by  $\langle X, Y \rangle$  is the unique right continuous with finite variation predictable process such that

$$X(t)Y(t) - X(0)Y(0) - \langle X, Y \rangle_t$$

is a martingale. Alternatively,  $\langle X, Y \rangle$  and is the unique right continuous, predictable with finite variation, process such that  $[X, Y] - \langle X, Y \rangle$  is a martingale. For a vector valued semi-martingale  $X = (X_1, X_2)$  where  $X_1$  and  $X_2$  are real valued

martingales, we denote by  $\langle\langle X \rangle\rangle$ , its square bracket, defined by

$$\langle\langle X \rangle\rangle_t = \begin{pmatrix} \langle X_1 \rangle_t & \langle X_1, X_2 \rangle_t \\ \langle X_1, X_2 \rangle_t & \langle X_2 \rangle_t \end{pmatrix}.$$

In the sequel, if  $x$  is a vector (resp.  $M$  a matrix) we denote by  $\|x\|$  (resp.  $\|M\|$ ) its  $\mathbf{L}^1$ -norm.

Let  $E$  be a discrete denumerable space. Let  $(X(t), t \geq 0)$  be an  $E$ -valued, pure jump Markov process, with infinitesimal generator  $Q = (q_{xy}, (x, y) \in E \times E)$ . For any  $F : E \rightarrow \mathbf{R}$ , Dynkin's Lemma states that the process:

$$F(X(t)) - F(X(0)) - \int_0^t QF(X_s) ds$$

is a local martingale, where

$$QF(x) = \sum_{y \neq x} (F(y) - F(x))q_{xy}.$$

Here and hereafter, we identify the matrix  $Q$  and the operator  $Q$  defined as above.

### 3. MARKOV MODEL

We consider the dynamics of HCV among a local population which suffers a continuous arrival of exogenous antibody-positive individuals, described by a Poisson process of intensity  $r$ . We let  $X_1(t)$  and  $X_2(t)$  denote the number of antibody-positive, respectively antibody-negative, users at time  $t$  in the population under consideration. The new susceptible drug users arrive as a Poisson process of intensity  $\lambda$ . We assume that for their first injection, they are initiated by an older IDU who has a probability  $q(t) = X_1(t)(X_1(t) + X_2(t))^{-1}$  of being infected. For different reasons, even in this situation, the probability of being infected, is not exactly one and is denoted by  $p_I$ . Each time, an antibody-negative IDU has an injection, he may share some of his paraphernalia and may become infected if the sharing occurs with an infected IDU. We summarize all these probabilities by saying that at each injection, the probability of becoming infected is  $pq(t)$ , where  $p$  is a parameter to be estimated, as is  $p_I$ . If we denote by  $\alpha$  the rate at which an IDU injects, and if  $\alpha p$  is small, we can assume that the rate at which a sane IDU in the population is infected, is given by  $\alpha pq(t)$ . Once infected, an IDU may exit from the population under consideration either by a death, self healing or stopping drug usage. The whole of these situations is modeled by an exponentially distributed duration with parameter  $\mu_1$ . For antibody-negative IDU, the only way to exit the population is by stopping drug injection, supposed to happen after an exponentially distributed duration with parameter  $\mu_2$ . In summary, the transitions are described in Figure 1.

For further references, we set

$$\begin{aligned} q_1(n_1, n_2) &= r + \lambda p_I \frac{n_1}{n_1 + n_2} \\ q_2(n_1, n_2) &= \mu_1 n_1 \\ q_3(n_1, n_2) &= \alpha p n_2 \frac{n_1}{n_1 + n_2} \\ q_4(n_1, n_2) &= \lambda \left(1 - p_I \frac{n_1}{n_1 + n_2}\right) \\ q_5(n_1, n_2) &= \mu_2 n_2. \end{aligned}$$

**Lemma 3.1.** *Let  $x^0 = (x_1^0, x_2^0)$ . Conditionally on  $X(0) = x^0$ , the process  $W(t) = X_1(t) + X_2(t) - (x_1 + x_2)$  is dominated (for the strong stochastic order of processes)*

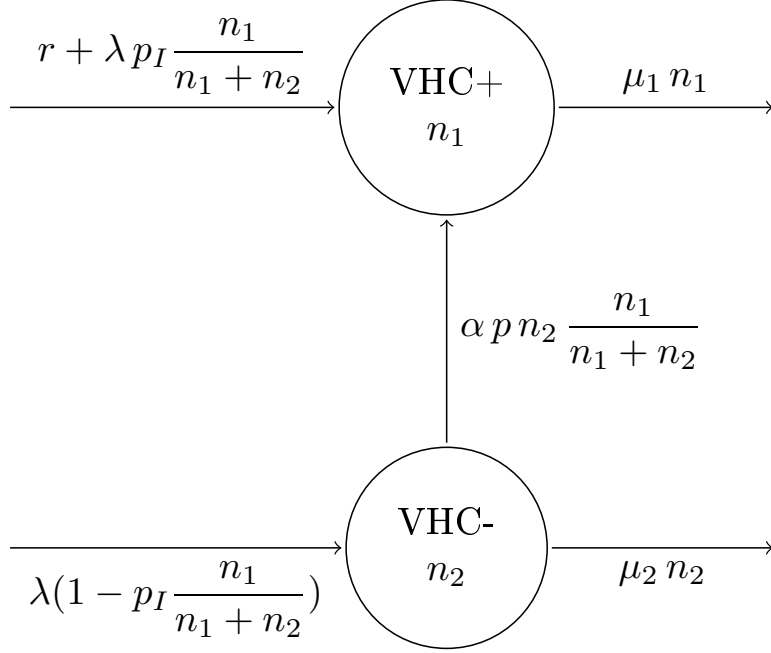


FIGURE 1. Transitions of the Markov model.

by a Poisson process of intensity  $r + \lambda$ . In particular, for any  $t \in [0, T]$ ,

$$\mathbf{E} \left[ \sup_{t \leq T} \|X(t)\|^p \mid X(0) = x^0 \right] \leq (\|x^0\| + (r + \lambda)T)^p,$$

for any  $p \geq 1$ .

*Proof.* It suffices to say that by suppressing all the departures, we get another system with a population larger than that of the system under consideration, at any time, for any trajectory. Then,  $X_1^N(t) + X_2^N(t) - (x_1 + x_2)$  is less than the number of arrivals of a Poisson process of intensity  $r + \lambda$ . Since a Poisson process has increasing path, its supremum over  $[0, T]$  is its value at time  $T$ . The second assertion follows.  $\square$

**Theorem 3.1.** *The Markov process  $X = (X_1, X_2)$  is ergodic. For  $r > 0$ , the process  $X$  is irreducible. For  $r = 0$ , the set  $\{(n_1, n_2) \in \mathbf{N} \times \mathbf{N}, n_1 = 0\}$  is a proper closed subset.*

*Proof.* Let  $S$  be the function defined on  $\mathbf{N} \times \mathbf{N}$  by

$$S(n_1, n_2) = \|(n_1, n_2)\| = n_1 + n_2.$$

If we denote by  $Q$  the infinitesimal generator of  $X$ , we have

$$QS(n_1, n_2) = \lambda + r - \mu_1 n_1 - \mu_2 n_2.$$

Let  $K$  be a real strictly greater than  $(\lambda + r + 1)/\mu_-$  where  $\mu_- = \mu_1 \wedge \mu_2$  and consider the following finite subset of the state space:

$$D_K = \{(n_1, n_2) \in \mathbf{N} \times \mathbf{N}, n_1 + n_2 \leq K\}.$$

If  $(n_1, n_2)$  belongs to  $D_K^c$ , then

$$QS(n_1, n_2) \leq \lambda + r - \mu_-(n_1 + n_2) < -1.$$

Lemma 3.1 implies that both

$$\mathbf{E} \left[ \sup_{s \in [0, 1]} S(X(s)) \right] \text{ and } \mathbf{E} \left[ \int_0^1 |QS(X(s))| ds \right]$$

are finite. Then according to [12, Proposition 8.14],  $X$  is ergodic.

The second and third assertions are immediate through inspection of the transition rates.  $\square$

With the non-linearity appearing in the transitions, it seems hopeless to find an exact expression for the stationary probability of the Markov process  $(X_1, X_2)$ . As usual in queueing theory [12], we then resort to asymptotic analysis in order to gain some insights on the evolution of this system. This means that we let the initial population becoming larger and larger. For keeping other quantities of the same order of magnitude, one are thus led to increase  $r$  and  $\lambda$  at the same speed, i.e., keeping the ratio  $i = (r + \lambda)/(x_1 + x_2)$  constant. Note that in epidemiological language,  $i$  is the incidence of new susceptible. It is measured in percentage of individuals per unit of year.

#### 4. A DETERMINISTIC DIFFERENTIAL SYSTEM

The mean field approximation will lead us to investigate the solutions of the following differential system with initial condition  $x^0 = (x_1^0, x_2^0) \in (\mathbf{R}_+ \times \mathbf{R}_+) \setminus \{(0, 0)\}$ :

$$(S_r(x^0)) \quad \begin{cases} \psi_1'(t) &= r + \lambda p_I \frac{\psi_1(t)}{\psi_1(t) + \psi_2(t)} - \mu_1 \psi_1(t) + \alpha p \frac{\psi_1(t)\psi_2(t)}{\psi_1(t) + \psi_2(t)}, \\ \psi_1(0) &= x_1^0, \\ \psi_2'(t) &= \lambda(1 - p_I \frac{\psi_1(t)}{\psi_1(t) + \psi_2(t)}) - \mu_2 \psi_2(t) - \alpha p \frac{\psi_1(t)\psi_2(t)}{\psi_1(t) + \psi_2(t)}, \\ \psi_2(0) &= x_2^0. \end{cases}$$

**Theorem 4.1.** *For any  $x^0 = (x_1^0, x_2^0) \in (\mathbf{R}_+ \times \mathbf{R}_+) \setminus \{(0, 0)\}$ , there exists a unique solution to  $(S_r(x^0))$ . Furthermore, this solution is defined on  $\mathbf{R}$ . For  $r > 0$ , the differential system has a unique fixed point  $(\xi_1, \xi_2)$  in  $\mathbf{R}_+ \times \mathbf{R}_+$ , defined by the equations*

$$(1) \quad \xi_2 = \frac{1}{\mu_2}(r + \lambda - \mu_1 \xi_1) \text{ and } \xi_1 = \frac{ab - c + \text{sgn}(a)\sqrt{(ab - c)^2 + 4abr\mu_1}}{2a\mu_1},$$

where  $a = \alpha p - \mu_1 + \mu_2$ ,  $b = r + \lambda$  and  $c = r\mu_1 + \lambda(1 - p_I)\mu_2$ . Moreover, for  $r > 0$  and any  $x^0 \in \mathbf{R}_+^2 \setminus \{0, 0\}$ ,

$$\lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (\xi_1, \xi_2).$$

If  $r = 0$  and  $x_1^0 = 0$  then

$$\psi_1(t) = 0 \text{ for all } t \text{ and } \lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (0, \lambda/\mu_2).$$

If  $r = 0$  and  $\rho = \alpha p + \mu_2 p_I - \mu_1 > 0$ , then there exists two equilibrium points: one is  $(0, \lambda/\mu_2)$  and the other is the unique solution with positive first coordinate of (1). If  $x_1^0 > 0$  then

$$\lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (\xi_1, \xi_2).$$

If  $r = 0$  and  $\rho \leq 0$ , then for any  $x^0$  with positive  $x_1^0$ ,

$$\lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (0, \lambda/\mu_2).$$

For further references, we denote by  $\psi^\infty$  the unique point to which the system converges in each case. We denote by  $\Psi$  the measurable function such that  $\Psi(x^0, t)$  is the value of the solution of  $(S_r(x^0))$  at time  $t$ .

*Proof.* We denote by  $f_1$  and  $f_2$  the functions such that  $(S_r(x^0))$  is written

$$(2) \quad \psi'_1(t) = f_1(\psi_1(t), \psi_2(t)) \text{ and } \psi'_2(t) = f_2(\psi_1(t), \psi_2(t)).$$

Since  $f_1$  and  $f_2$  are locally Lipschitz, there exists a local solution for any starting point  $x^0$  belonging to  $(\mathbf{R}_+ \times \mathbf{R}_+) \setminus \{(0, 0)\}$ . Moreover, for any  $(x_1, x_2) \in (\mathbf{R}_+ \times \mathbf{R}_+) \setminus \{(0, 0)\}$ ,

$$r - \mu_1 x_1 \leq f_1(x_1, x_2) \leq r + \lambda p_I + \alpha p x_1 \text{ and } \lambda(1 - p_I) - \mu_2 x_2 \leq f_2(x_1, x_2) \leq \lambda.$$

By standard theorems about comparison of solutions of differential equations, one can then show that every local solution  $\psi$  can be extended to  $\mathbf{R}$  and that for any  $t \in \mathbf{R}$ ,  $\psi(t) = (\psi_1(t), \psi_2(t))$  belongs to  $(\mathbf{R}_+ \times \mathbf{R}_+) \setminus \{(0, 0)\}$ . Furthermore, with direct calculations, we have

$$(3) \quad \frac{d}{dt}(\psi_1(t) + \psi_2(t)) = r + \lambda - \mu_1 \psi_1(t) - \mu_2 \psi_2(t).$$

For  $\varepsilon > 0$ , consider

$$\begin{aligned} A_\pm^\varepsilon &= \{(x_1, x_2) \in \mathbf{R}_+ \times \mathbf{R}_+, 0 \leq \pm(r + \lambda - \mu_1 x_1 - \mu_2 x_2) < \varepsilon\}, \\ B_+^\varepsilon &= \{(x_1, x_2) \in \mathbf{R}_+ \times \mathbf{R}_+, r + \lambda - \mu_1 x_1 - \mu_2 x_2 \geq \varepsilon\}, \\ B_-^\varepsilon &= \{(x_1, x_2) \in \mathbf{R}_+ \times \mathbf{R}_+, r + \lambda - \mu_1 x_1 - \mu_2 x_2 \leq -\varepsilon\}, \end{aligned}$$

and

$$A^0 = \{(x_1, x_2) \in \mathbf{R}_+ \times \mathbf{R}_+, r + \lambda - \mu_1 x_1 - \mu_2 x_2 = 0\}.$$

According to (3), on  $B_+^\varepsilon$ , the derivative of  $\psi_1 + \psi_2 = \|(\psi_1, \psi_2)\|$  is greater than  $\varepsilon$ , hence for a starting point in  $A_+^\varepsilon$ , the trajectory has an  $\mathbf{L}^1$  increasing norm. Reasoning along the same lines on  $B_-^\varepsilon$ , we see that for any  $\eta > 0$ , for any starting point outside  $A^0$ , the trajectory of the differential system enters, in a finite time, one of the set  $A_+^\eta$  or  $A_-^\eta$ . Moreover, upon this time, the orbit stays in the compact  $A_+^\eta \cup A_-^\eta$  forever. It follows that (see for instance [13])

$$\lim_{t \rightarrow +\infty} \text{dist}((\psi_1(t), \psi_2(t)), A^0) = 0.$$

This implies that any invariant set  $M$  must be included in  $A^0$ . We then seek for a maximal invariant set. It is given by the intersection of the sets  $Z_i = \{(x_1, x_2), f_i(x_1, x_2) = 0\}$ ,  $i = 1, 2$ . We then remark that this system of equation is equivalent to the system  $f_1 + f_2 = 0$  and  $f_2 = 0$ . It turns out that

$$(f_1 + f_2)(x_1, x_2) = r + \lambda - \mu_1 x_1 - \mu_2 x_2 = 0.$$

The equation  $f_2(x_1, x_2) = 0$  yields to

$$x_1 = \frac{\mu_2 x_2^2 - \lambda x_2}{\lambda(1 - p_I) - (\alpha p + \mu_2)x_2} = h(x_2).$$

The variations of  $h$  shows that  $h$  is a strictly decreasing diffeomorphism from  $I = [\lambda(1 - p_I)/(\alpha p + \mu_2), \lambda/\mu_2]$  onto  $\mathbf{R}_+$ . Hence its reciprocal function is a decreasing diffeomorphism from  $\mathbf{R}_+$  onto  $I$ .

Assume first that  $r > 0$ . Then  $(\lambda + r)/\mu_2 > \lambda/\mu_2$  and there exists one and only one equilibrium point whose coordinates  $(\xi_1, \xi_2)$  are thus given by the solution of (1) – see Figure 2 for an illustration.

Consider the two distinct situations where  $\mu_1 = \mu_2$  and  $\mu_1 \neq \mu_2$ . If  $\mu_1 \neq \mu_2$ , then for any starting point  $(x_1, x_2) \neq (\xi_1, \xi_2)$  belonging to  $A^0$ ,  $\psi'_1(x_1, x_2) + \psi'_2(x_1, x_2) = 0$  but  $\mu_1 \psi'_1(x_1, x_2) + \mu_2 \psi'_2(x_1, x_2) \neq 0$ . Hence for  $t$  sufficiently close to 0,  $\psi(t)$  does

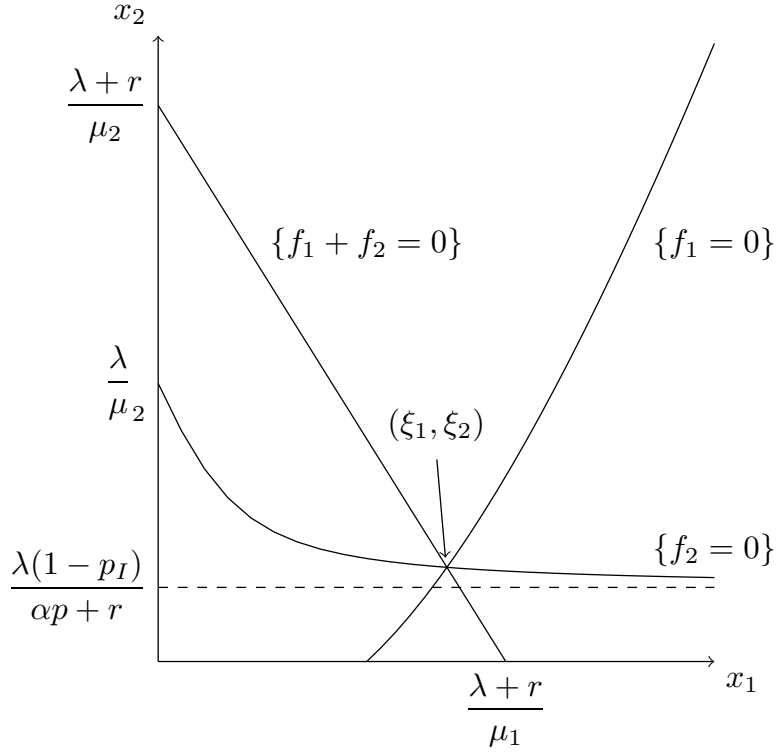


FIGURE 2. Determination of the fixed point.

not belong to  $A^0$  and then  $(x_1, x_2)$  does not belong to  $M$ . Thus,  $M = \{(\xi_1, \xi_2)\}$  and according to the Poincaré-Bendixson theorem (see [13] for example),

$$(4) \quad \lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (\xi_1, \xi_2).$$

If  $\mu_1 = \mu_2$  then  $\psi_1 + \psi_2$  is solution of the differential equation

$$v'(t) = r + \lambda - \mu_1 v(t), \quad v(0) = x_1 + x_2.$$

By direct integration, this yields to

$$(\psi_1 + \psi_2)(t) = (x_1 + x_2)e^{-\mu_1 t} + \frac{r + \lambda}{\mu_1}(1 - e^{-\mu_1 t}).$$

This entails that  $A^0$  is invariant. Since  $A^0$  is compact, there exists a minimum invariant set, say  $M$ . According to the Poincaré-Bendixson theorem,  $M$  is either a periodic orbit or a critical point. Since  $\psi_1 + \psi_2$  is not periodic,  $M$  is also reduced to  $(\xi_1, \xi_2)$  and we have (4).

For  $r = 0$ , the point  $(0, \lambda/\mu_2)$  is a fixed point. Due to the concavity of  $h^{-1}$ , the sets  $A^0$  and  $\{f_2 = 0\}$  have at most one point of intersection with positive abscissa. The existence of it depends on the slope of  $h^{-1}$  at the origin. By direct computations, we find that

$$(h^{-1})'(0) = -\left(\frac{\alpha p}{\mu_2} + p_I\right).$$

Hence there exists another equilibrium point if and only if  $(h^{-1})'(0) > \mu_1/\mu_2$ , i.e.,  $\rho = \alpha p + \mu_2 p_I - \mu_1 > 0$ . We still denote by  $(\xi_1, \xi_2)$  the unique solution of (1) with a strictly positive first coordinate. Note first that if  $x_1 = 0$  then  $\psi_1(t) = 0$  for any  $t$



thus the vertical axis is an invariant set. Moreover, for  $x_1 = 0$ , a direct integration of  $(S_r(x^0))$  shows that

$$\lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (0, \lambda/\mu_2).$$

We hereafter assume that  $x_1 \neq 0$ . If  $\alpha p + \mu_2 p_I - \mu_1 \leq 0$ , the same reasoning as above shows that

$$\lim_{t \rightarrow +\infty} (\psi_1(t), \psi_2(t)) = (0, \lambda/\mu_2).$$

Assume now that  $\alpha p + \mu_2 p_I - \mu_1 > 0$ . At  $(0, \lambda/\mu_2)$ , the linearization of  $(S_r(x^0))$  gives a matrix whose determinant is given by

$$d = -\rho\mu_2.$$

Then, according to the hypothesis,  $d < 0$  thus  $(0, \lambda/\mu_2)$  is a saddle point and cannot be an attractor. Reasoning as above again yields to the conclusion that every orbit converges to  $(\xi_1, \xi_2)$  for any  $(x_1, x_2)$  such that  $x_1 \neq 0$ .  $\square$

## 5. MEAN FIELD APPROXIMATION

We now consider a sequence  $(X^N(t) = (X_1^N(t), X_2^N(t)), t \geq 0)$  of Markov processes with the same transitions as above but with different rates given by (with self evident notations):

$$\begin{aligned} q_1^N(n_1, n_2) &= r_N + \lambda_N p_I \frac{n_1}{n_1 + n_2} \\ q_2^N(n_1, n_2) &= \mu_1 n_1 \\ q_3^N(n_1, n_2) &= \alpha p n_2 \frac{n_1}{n_1 + n_2} \\ q_4^N(n_1, n_2) &= \lambda_N (1 - p_I \frac{n_1}{n_1 + n_2}) \\ q_5^N(n_1, n_2) &= \mu_2 n_2. \end{aligned}$$

The main result of this Section is the following mean field approximation of the system  $X^N$ .

**Theorem 5.1.** *Assume that*

$$\mathbf{E} \left[ \left\| \frac{1}{N} X^N(0) - x^0 \right\|^2 \right] \xrightarrow{N \rightarrow +\infty} 0, \quad \frac{1}{N} r_N \xrightarrow{N \rightarrow +\infty} r \geq 0, \quad \frac{1}{N} \lambda_N \xrightarrow{N \rightarrow +\infty} \lambda.$$

Let  $\psi(x^0, \cdot) = (\psi_1(x^0, \cdot), \psi_2(x^0, \cdot))$  be the solution of the differential system  $(S_r(x^0))$ . Then, for any  $T > 0$ ,

$$\mathbf{E} \left[ \sup_{t \leq T} \left\| \frac{1}{N} X^N(t) - \psi(x^0, t) \right\|^2 \right] \xrightarrow{N \rightarrow +\infty} 0.$$

Before turning into the proof of Theorem 5.1, let us give the martingale problem satisfied by the process  $X^N$ .

**Theorem 5.2.** *For any  $N > 0$ , the process  $X^N$  is a vector-valued semi-martingale with decomposition:*

$$\begin{aligned} X_1^N(t) &= X_1^N(0) + \int_0^t (q_1^N + q_3^N - q_2^N)(X^N(s)) ds + M_1^N(t) \\ X_2^N(t) &= X_2^N(0) + \int_0^t (q_4^N - q_3^N - q_5^N)(X^N(s)) ds + M_2^N(t), \end{aligned}$$

where  $M^N = (M_1^N, M_2^N)$  is a local martingale vanishing at zero with square bracket given by:

$$\langle\langle M^N \rangle\rangle_t = \begin{pmatrix} \int_0^t (q_1^N + q_3^N + q_2^N)(X^N(s)) ds & - \int_0^t q_3^N(X^N(s)) ds \\ - \int_0^t q_3^N(X^N(s)) ds & \int_0^t (q_4^N + q_3^N + q_5^N)(X^N(s)) ds \end{pmatrix}.$$

*Proof.* Using the martingale problem associated with the Markov process  $X^N$ , we get that, for  $t \geq 0$ ,

$$X^N(t) = X^N(0) + \begin{pmatrix} \int_0^t (q_1^N + q_3^N - q_2^N)(X^N(s)) ds \\ \int_0^t (q_4^N - q_3^N - q_5^N)(X^N(s)) ds \end{pmatrix} + M^N(t),$$

where  $M^N = (M_1^N, M_2^N)$  is a 2-dimensional local martingale vanishing at zero.

Let us now compute its square bracket. First of all, we consider  $\langle M_1^N, M_2^N \rangle$ . By integration by parts, we get that, for  $t \geq 0$ ,

$$\begin{aligned} X_1^N(t)X_2^N(t) &= X_1^N(0)X_2^N(0) + \int_{(0,t]} X_1^N(s_-) dX_2^N(s) \\ &\quad + \int_{(0,t]} X_2^N(s_-) dX_1^N(s) + [X_1^N, X_2^N]_t, \end{aligned}$$

where  $[X_1^N, X_2^N]$  denotes the mutual variation of  $X_1^N$  and  $X_2^N$ . Hence

$$\begin{aligned} X_1^N(t)X_2^N(t) &= X_1^N(0)X_2^N(0) + \int_0^t X_1^N(s)(q_4^N - q_3^N - q_5^N)(X^N(s)) ds \\ &\quad + \int_0^t X_2^N(s)(q_1^N + q_3^N - q_2^N)(X^N(s)) ds \\ &\quad + [X_1^N, X_2^N]_t \\ &\quad + \text{local martingale.} \end{aligned}$$

Now, writing the martingale problem associated with the process  $X_1^N X_2^N$ , we have

$$\begin{aligned} X_1^N(t)X_2^N(t) &= X_1^N(0)X_2^N(0) + \int_0^t X_1^N(s)(q_4^N - q_5^N)(X^N(s)) ds \\ &\quad + \int_0^t X_2^N(s)(q_1^N - q_2^N)(X^N(s)) ds \\ &\quad + \int_0^t (X_2^N(s) - X_1^N(s) - 1)q_3^N(X^N(s)) ds \\ &\quad + \text{local martingale.} \end{aligned}$$

We conclude that

$$\langle X_1^N, X_2^N \rangle_t = - \int_0^t q_3^N(X^N(s)) ds.$$

Similar arguments show that

$$\langle X_1^N \rangle_t = \int_0^t (q_1^N + q_3^N + q_2^N)(X^N(s)) ds \text{ and } \langle X_2^N \rangle_t = \int_0^t (q_4^N + q_3^N + q_5^N)(X^N(s)) ds$$

which ends the proof.  $\square$

*Proof of Theorem 5.1.* According to Theorem 4.1, for any  $x^0 \in \mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$   $\inf_{s \in \mathbf{R}_+} \|\psi(x^0, s)\| > 0$ . Then, the theorem 5.1 is a consequence of the following Lemma.  $\square$

**Lemma 5.1.** *There exists a constant  $C$  depending only on  $r, \lambda, P_I, \mu_1, \mu_2$  and  $\alpha p$  such that for any  $x^0 \in \mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$ , any  $(X^M(0))_{M \in \mathbf{N}}$  sequence of random variables taking its values in  $\mathbf{R} \times \mathbf{R} \setminus \{(0, 0)\}$ , for any  $N \in \mathbf{N}^*$ , and for any  $T > 0$*

$$\begin{aligned} \mathbf{E} \left[ \sup_{t \leq T} \left\| \frac{1}{N} X^N(t) - \psi(x^0, t) \right\| \middle| \sigma(X^M(0), M \in \mathbf{N}) \right] \\ \leq \left( \left\| \frac{1}{N} X^N(0) - x^0 \right\|^2 + \frac{1}{N} \left( T + T^2 \frac{1}{N} \|X^N(0)\| \right) \right) \\ \times \exp \left( T \int_0^T \left( 1 + \frac{1}{\|\psi(x^0, s)\|} \right)^2 ds \right). \end{aligned}$$

*Proof of Lemma 5.1.* Let us fix  $T > 0$ . Using Theorem 5.2, we have

$$\begin{aligned} \frac{1}{N} X_1^N(t) &= \frac{1}{N} X_1^N(0) + \int_0^t \frac{1}{N} (q_1^N + q_3^N - q_2^N)(X^N(s)) ds + \frac{1}{N} M_1^N(t), \\ \frac{1}{N} X_2^N(t) &= \frac{1}{N} X_2^N(0) + \int_0^t \frac{1}{N} (q_4^N - q_3^N - q_5^N)(X^N(s)) ds + \frac{1}{N} M_2^N(t). \end{aligned}$$

Moreover,

$$\begin{aligned} \psi_1(t) &= \int_0^t (q_1 + q_3 - q_2)(\psi(s)) ds, \\ \psi_2(t) &= \int_0^t (q_4 - q_3 - q_5)(\psi(s)) ds. \end{aligned}$$

Note that for  $x = (x^1, x^2)$  and  $y = (y_1, y_2)$  in  $\mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$ , then

$$\begin{aligned} \left| \frac{x_1}{x_1 + x_2} - \frac{y_1}{y_1 + y_2} \right| &\leq \left| \frac{x_1 - y_1}{y_1 + y_2} \right| + \left| \frac{x_1}{x_1 + x_2} - \frac{y_1}{y_1 + y_2} \right| \\ &= \left| \frac{x_1 - y_1}{y_1 + y_2} \right| + \left| \frac{x_1}{x_1 + x_2} \frac{y_1 - x_1 + y_2 - x_2}{y_1 + y_2} \right| \\ &\leq 2 \frac{\|x - y\|}{\|y\|}. \end{aligned}$$

We also have

$$\left| \frac{x_1 x_2}{x_1 + x_2} - \frac{y_1 y_2}{y_1 + y_2} \right| \leq 2 \|x - y\|.$$

From now on, we use  $C$  for positive constants which depend only on  $r, \lambda, p_I, \mu_1, \mu_2$  and  $\alpha p$ , and which may vary from line to line. For  $0 \leq t \leq T$ ,

$$\begin{aligned} &\left\| \frac{1}{N} X^N(t) - \psi(x^0, t) \right\|^2 \\ (5) \quad &\leq C \left( \left\| \frac{1}{N} X^N(0) - \psi(x^0, 0) \right\|^2 + T^2 \left| r - \frac{r_N}{N} \right|^2 + T^2 \left| \lambda - \frac{\lambda_N}{N} \right|^2 \right. \\ &\quad \left. + T \int_0^t \left( 1 + \frac{1}{\|\psi(x^0, s)\|} \right)^2 \left\| \frac{1}{N} X^N(s) - \psi(x^0, s) \right\|^2 ds + \frac{1}{N^2} \|M^N(t)\|^2 \right). \end{aligned}$$

Using Burkholder-Davis-Gundy inequality, we get that

$$\mathbb{E}[\sup_{t \in [0, T]} \|M^N(t)\|^2 | \sigma(X^M(0), M \in \mathbf{N})] \leq C\mathbb{E}[\|\langle M^N \rangle_T | \sigma(X^M(0), M \in \mathbf{N})].$$

As a consequence of Lemma 3.1 we get that for  $i \in \{1, 2, 3, 4, 5\}$ ,

$$(6) \quad \mathbf{E} \left[ \sup_{t \leq T} q_i^N(X_s) \right] \leq C(\|X^N(0)\| + (r_N + \lambda_N)T),$$

and

$$\mathbb{E}[\|\langle M^N \rangle_T | \sigma(X^M(0), M \in \mathbf{N})] \leq CT(\mathbf{E}[\|X^N(0)\|] + (r_N + \lambda_N)T).$$

Hence, using Gronwall's lemma, (5) implies that

$$\begin{aligned} & \mathbf{E} \left[ \sup_{t \leq T} \left\| \frac{1}{N} X^N(t) - \psi(x^0, t) \right\| \middle| \sigma(X^M(0), M \in \mathbf{N}) \right] \\ & \leq \left( \left\| \frac{1}{N} X^N(0) - x^0 \right\|^2 + \frac{1}{N} \left( T + T^2 \frac{1}{N} \|X^N(0)\| \right) \right) \\ & \quad \times \exp \left( T \int_0^T \left( 1 + \frac{1}{\|\psi(x^0, s)\|} \right)^2 ds \right). \end{aligned}$$

□

## 6. STATIONARY REGIME

We have proved so far that the process  $N^{-1}X^N$  converges, as  $N$  goes to infinity, to a deterministic  $\mathbf{R}^2$ -valued function. This function converges, as  $t$  goes to infinity, to a fixed point  $\psi^\infty$ . On the other hand, for each  $N$ , the Markov process  $X^N$  is ergodic thus has a limiting distribution as  $t$  goes to infinity. This raises the natural question to know whether this limiting distribution converges to the Dirac mass at  $\psi^\infty$  when  $N$  goes to infinity. Let us denote by  $\mathbf{P}_{Y^N, \nu}$  the distribution of the process  $Y^N = N^{-1}X^N$  under initial distribution  $\nu$ . We denote by  $\mathbf{P}_{\psi, \nu}$  the distribution of the process whose initial state is chosen according to  $\nu$  and whose deterministic evolution is then given by the differential system  $(S_r(x^0))$ . According to Theorem 3.1, we know that  $X^N$  has a stationary probability whose value is irrespective of the initial distribution of  $X^N$ . We denote by  $Y^N(\infty)$  a random variable whose distribution is the stationary measure of  $Y^N$ . We already know that

$$\begin{array}{ccc} \mathbf{P}_{Y^N(t), \delta_{x^0}} & \xrightarrow{N \rightarrow \infty} & \mathbf{P}_{\psi(t), \delta_{x^0}} \\ t \rightarrow \infty \downarrow & & \downarrow t \rightarrow \infty \\ \mathbf{P}_{Y^N(\infty)} & \xrightarrow[N \rightarrow \infty]{?} & \delta_{\psi^\infty} \end{array}$$

The question is then to prove that this is a commutative diagram, i.e., that  $Y^N(\infty)$  converges in distribution to the Dirac measure at the equilibrium point of the system  $(S_r(x^0))$ . We borrow the proof from [15] and [7] but we need to take into consideration the special role of the point  $(0, 0)$  which is a singular point for some of the  $q_j$ .

**Definition 1.** *We say that a probability measure  $\nu$  on  $\mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$  belongs to  $\mathcal{P}_0$  when  $\nu(\{0, 0\}) = 0$ .*

We will show that 1) for any sequence of initial distribution  $\nu^N$  converging weakly to  $\nu$  with  $\nu \in \mathcal{P}_0$  then  $\mathbf{P}_{Y^N, \nu^N}$  converges weakly to  $\mathbf{P}_{\psi, \nu}$ , 2) that for any probability measure  $\nu \in \mathcal{P}_0$ ,  $\mathbf{P}_{\psi(t), \nu}$  converges weakly to  $\delta_{\psi^\infty}$ , 3) that the

sequence  $(Y^N(\infty), N \geq 1)$  is tight and 4) that any possible accumulation point of  $(Y^N(\infty), N \geq 1)$  belongs to  $\mathcal{P}_0$ .

The proof is then short and elegant: since  $(Y^N(\infty), n \geq 1)$  is tight, it is sufficient to prove that there is a unique possible limit to any convergent sub-sequence of  $(Y^N(\infty))$ . We still denote by  $Y^N(\infty)$  such a converging sub-sequence (as  $N$  goes to infinity). Its limit is denoted by  $\nu$ , known to belong to  $\mathcal{P}_0$ . According to Point 1. above,  $\mathbf{P}_{Y^N, \mathbf{P}_{Y^N(\infty)}}$  converges weakly to  $\mathbf{P}_{\psi, \nu}$ . Moreover by the properties of Markov processes,  $\mathbf{P}_{Y^N, \mathbf{P}_{Y^N(\infty)}}$  is the distribution of a stationary process, hence  $\psi$  is also a stationary process when started from  $\nu$ . This means that the distribution of  $\psi(t)$  is  $\nu$  for any  $t$ . Then, by Point 2. above,  $\nu = \delta_{\psi^\infty}$ . We have thus proved that any convergent sub-sequence of  $Y^N(\infty)$  converges to  $\delta_{\psi^\infty}$ , hence the result. We now turn to the proof of the three necessary lemmas.

**Theorem 6.1.** *For any sequence of initial distribution  $\nu^N$  converging weakly to  $\nu \in \mathcal{P}_0$ , then  $\mathbf{P}_{Y^N, \nu^N}$  converges weakly to  $\mathbf{P}_{\psi, \nu}$ .*

*Proof.* We will proceed in two steps: First prove the tightness in  $\mathbb{D}([0, T], \mathbf{R}^2)$  and then identify the limit. Actually, we will prove the slightly stronger result that  $\mathbf{P}_{Y^N, \nu^N}$  is tight and that the limiting process is continuous. According to [2], we need to show that for each positive  $\epsilon$  and  $\eta$ , there exists  $\delta > 0$  and  $n_0$  such that for any  $N \geq n_0$ ,

$$\mathbf{P} \left( \sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} \|Y^N(v) - Y^N(u)\| \geq \epsilon \right) \leq \eta.$$

We denote by

$$\begin{aligned} A_1^N(t) &= \frac{1}{N} \int_0^t (q_1^N + q_3^N - q_2^N)(X^N(s)) \, ds \\ A_2^N(t) &= \frac{1}{N} \int_0^t (q_4^N - q_3^N - q_5^N)(X^N(s)) \, ds. \end{aligned}$$

From Theorem 5.2, we know that

$$Y_i^N(v) = A_i^N(v) + \frac{1}{N} M_i^N(v), \quad i = 1, 2.$$

Hence, for any positive  $a$ ,

$$\begin{aligned} (7) \quad \mathbf{P} \left( \sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} \|Y^N(v) - Y^N(u)\| \geq \epsilon \right) &\leq \mathbf{P}(\|Y^N(0)\| \geq a) \\ &+ \mathbf{P} \left( \sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} \|A^N(v) - A^N(u)\| \geq \epsilon/2; \|Y^N(0)\| \leq a \right) \\ &+ \mathbf{P} \left( \sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} \frac{1}{N} \|M^N(v) - M^N(u)\| \geq \epsilon/2; \|Y^N(0)\| \leq a \right). \end{aligned}$$

Eqn. (6) implies that

$$\mathbf{E} \left[ \sup_{s \leq T} \frac{1}{N^2} \|M^N(s)\|^2 \mid \|Y^N(0)\| \leq a \right] \leq \frac{C(a+1)}{N}.$$

This means that  $(N^{-1}M^N, N \geq 1)$  converges to 0 in  $L^2(\Omega; \mathbb{D}([0, T], \mathbf{R}^2), \mathbf{P}_{\cdot, \|Y^N(0)\| \leq a})$ . Hence it converges in distribution in  $\mathbb{D}([0, T], \mathbf{R}^2)$  and thus it is tight. This means

that the last summand of (7) can be made as small as needed for large  $N$ . Furthermore,

$$\begin{aligned} \|A^N(v) - A^N(u)\| &\leq \frac{2}{N} \int_u^v \sum_{i=1}^5 q_i(X^N(s)) ds \\ &\leq 2|v - u| \left( \frac{r_N + \lambda_N}{N} + \frac{C}{N} \sup_{s \leq T} \|X^N(s)\| \right). \end{aligned}$$

It follows from Lemma 3.1 that

$$\begin{aligned} \mathbf{E} \left[ \sup_{\substack{|v-u| \leq \delta, \\ v, u \leq T}} \|A^N(v) - A^N(u)\| \mid \|Y^N(0)\| \leq a \right] &\leq C\delta \left( \frac{r_N + \lambda_N}{N} T + a \right) \\ &\leq C((r + \lambda)T + a)\delta. \end{aligned}$$

This means that the second summand of (7) can also be made as small as wanted. The hypothesis on the initial condition exactly means that this also holds for the first summand of (7). Thus we have proved so far that  $\mathbf{P}_{Y^N, \nu^N}$  is tight and that its limit belongs to the space of continuous functions.

We now prove that the only possible limit is  $\mathbf{P}_{\psi, \nu}$ . Assume that  $\nu^N$  tends to  $\nu$  and that  $\mathbf{P}_{Y^N, \nu^N}$  tends to some  $\mathbf{P}_{Z, \nu}$ . We suppose that the initial conditions  $X^N(0)$  of the Markov processes are distributed as  $\nu_N$  and we introduce a random variable  $x^0$  distributed as  $\nu$ . Recall that  $Y^N = N^{-1}X^N$ . We fix  $M \in \mathbf{N}^*$ ,  $(\alpha^k = (\alpha_1^k, \alpha_2^k))_{0 \leq k \leq M} \in \mathbf{R}^{2M+2}$  and  $0 = t_0 \leq t_1 \leq \dots \leq t_M$ . We introduce

$$\begin{aligned} G^N &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, Y^N(t_k) \rangle \right] \right), \\ \tilde{G}^N &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, \psi\left(\frac{X^N(0)}{N}, t_k\right) \rangle \right] \right), \\ G &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, \psi(x^0, t_k) \rangle \right] \right), \end{aligned}$$

where  $Y^N(-1) = 0$ , and  $Y^N = N^{-1}X^N$ , with initial condition  $X^N(0)$  distributed as  $\nu_N$  and  $X^0$  as  $\nu$ .

Let  $\varepsilon > 0$ . The sequence  $(\nu_N)_{N \in \mathbf{N}}$  is tight, hence there exists a compact set  $K \subset \mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$  such that  $\nu(K^c) + \sup_N \nu_N(K^c) \leq \varepsilon$ . We also introduce

$$\begin{aligned} G_K^N &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, Y^N(t_k) \rangle \right] \mathbf{1}_K\left(\frac{X^N(0)}{N}\right) \right), \\ \tilde{G}_K^N &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, \psi\left(\frac{X^N(0)}{N}, t_k\right) \rangle \right] \mathbf{1}_K\left(\frac{X^N(0)}{N}\right) \right), \\ G_K &= \mathbf{E} \left( \exp i \left[ \sum_{k=0}^M \langle \alpha_k, \psi(x^0, t_k) \rangle \right] \mathbf{1}_K(x^0) \right). \end{aligned}$$

Then,

$$\limsup_N |G - G^N| \leq 2\varepsilon + \limsup_N |\tilde{G}_K^N - G_K^N| + \limsup_N |\tilde{G}_K^N - G_K^N|.$$

From Theorem 4.1, the map  $(x, s) \mapsto \psi(x, s)$  is continuous on  $(\mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}) \times [0, T]$  and  $\inf_{(x, s) \in K \times [0, T]} \|\psi(x, s)\| > 0$ . Since  $\frac{X^N}{N}(0)$  takes its value in

the compact set  $K$ , then from Lemma 5.1,  $\limsup_N |\tilde{G}_K^N - G_K^N| = 0$ . Since the sequence of measures  $(\nu_N)$  converges weakly to  $\nu$ , then  $\limsup_N |\tilde{G}_K^N - G_K^N| = 0$ . Hence,

$$\limsup_N |G - G^N| \leq 2\varepsilon$$

for all  $\varepsilon > 0$ .

That means for any  $t_0, \dots, t_M$ ,

$$\mathbf{P}_{(Y^N(t_0), \dots, Y^N(t_M)), \nu_N} \xrightarrow{N \rightarrow \infty} \mathbf{P}_{(\psi(x^0, t_0), \dots, \psi(x^0, t_M)), \nu},$$

Hence all the accumulation points are the same and the convergence of  $\mathbf{P}_{Y^N, \nu_N}$  follows.  $\square$

**Theorem 6.2.** *For any probability measure  $\nu \in \mathcal{P}_0$ ,  $\mathbf{P}_{\psi(t), \nu}$  converges weakly to  $\delta_{\psi^\infty}$  as  $t \rightarrow \infty$ .*

*Proof.* For any  $f$  continuous bounded on  $\mathbf{R}^2$ , we have

$$\int f d\mathbf{P}_{\psi(t), \nu} = \int_{\mathbf{R}^2} \mathbf{E}[f(\psi(t)) | \psi(0) = x] d\nu(x).$$

Theorem 4.1 says that for any  $x \in \mathbf{R}_+ \times \mathbf{R}_+ \setminus \{(0, 0)\}$ ,

$$\mathbf{E}[f(\psi(t)) | \psi(0) = x] \xrightarrow{t \rightarrow \infty} f(\psi^\infty).$$

The result follows by dominated convergence.  $\square$

**Theorem 6.3.** *The sequence  $(Y^N(\infty), N \geq 1)$  is tight and any accumulation point belongs to  $\mathcal{P}_0$ .*

We need a preliminary lemma which relies on the observation that when  $\mu_1 = \mu_2$ , the process  $X_1 + X_2$  has the dynamics of the process counting the number of customers in an M/M/ $\infty$  queue. Recall that  $\mu_- = \min(\mu_1, \mu_2)$  and set  $\zeta = (r + \lambda p_I) / \mu_-$ . For any  $c \in \mathbf{R}_+$ , any  $x \in \mathbf{N}$ , define the function

$$h_c(t, x) = (1 + ce^{\mu_- t})^x e^{-\zeta c \exp(\mu_- t)}.$$

Note that  $h_c$  is increasing with respect to  $x$ . Moreover, according to [12, Chapter 6],

$$(8) \quad \frac{\partial h_c}{\partial t}(t, x) + R(h_c(t, \cdot))(x) = 0,$$

where, for any  $w : \mathbf{N} \rightarrow \mathbf{R}$ ,

$$Rw(x) = (w(x+1) - w(x))(r + \lambda p_I) + (w(x-1) - w(x))\mu_- x.$$

**Lemma 6.1.** *For any non negative real  $c$ , the process  $H_c = (h_c(t, X_1(t) + X_2(t)), t \geq 0)$  is a positive supermartingale.*

*Proof.* According to Dynkin formula (see [12, Proposition C.5]), for any  $0 \leq s < t$ , we have

$$\begin{aligned}
0 &= \mathbf{E} \left[ h_c(t, \|X(t)\|) - h_c(s, \|X(s)\|) - \int_s^t \frac{\partial h_c}{\partial t}(r, \|X(r)\|) \right. \\
&\quad - (r + \lambda p_I) \int_s^t \left( h_c(r, \|X(r)\| + 1) - h_c(r, \|X(r)\|) \right) dr \\
&\quad \left. - \int_s^t \left( h_c(r, \|X(r)\| - 1) - h_c(r, \|X(r)\|) \right) (\mu_1 X_1(r) + \mu_2 X_2(r)) dr \middle| \mathcal{F}_s \right] \\
&\geq \mathbf{E} \left[ h_c(t, \|X(t)\|) - h_c(s, \|X(s)\|) - \int_s^t \frac{\partial h_c}{\partial t}(r, \|X(r)\|) \right. \\
&\quad - (r + \lambda p_I) \int_s^t \left( h_c(r, \|X(r)\| + 1) - h_c(r, \|X(r)\|) \right) dr \\
&\quad \left. - \int_s^t \left( h_c(r, \|X(r)\| - 1) - h_c(r, \|X(r)\|) \right) \mu_-(X_1(r) + X_2(r)) dr \middle| \mathcal{F}_s \right],
\end{aligned}$$

where the inequality follows from the monotony of  $h_c$  and the definition of  $\mu_-$ . Hence we get that

$$\begin{aligned}
0 &\geq \mathbf{E} \left[ h_c(t, \|X(t)\|) - h_c(s, \|X(s)\|) \right. \\
&\quad \left. - \int_s^t \frac{\partial h_c}{\partial t}(r, \|X(r)\|) + R(h_c(r, \cdot))(\|X(r)\|) dr \middle| \mathcal{F}_s \right].
\end{aligned}$$

In view of Eqn. (8), we get

$$0 \geq \mathbf{E} [h_c(t, \|X(t)\|) - h_c(s, \|X(s)\|) | \mathcal{F}_s],$$

i.e.,  $H_c$  is a supermartingale.

Now, let  $(Y^N(\infty), N \geq 1)$  be a subsequence which converge to  $\nu$ . Since  $X^N(\infty)$  is a random variable distributed according to the stationary law of the process  $X^N$ ,

$$\mathbf{E} \left[ Q e^{-\|\cdot\|} (X^N(\infty)) \right] = 0.$$

By a direct calculation, we have

$$Q e^{-\|\cdot\|}(x) = e^{-\|x\|} [(\lambda + r)(e^{-1} - 1) + (\mu_1 x_1 + \mu_2 x_2)(e - 1)],$$

then

$$\begin{aligned}
&(\lambda_N + r_N)(1 - e^{-1}) \mathbf{E} \left[ e^{-N \|Y^N(\infty)\|} \right] \\
&= N(e - 1) \mathbf{E} \left[ e^{-N \|Y^N(\infty)\|} (\mu_1 Y_1^N(\infty) + \mu_2 X_2^N(\infty)) \right].
\end{aligned}$$

Hence,  $(1 - e^{-1})(r + \lambda)\nu(\{(0, 0)\}) = 0$ , i.e.,  $\nu$  belongs to  $\mathcal{P}_0$ .  $\square$

*Proof of Theorem 6.3.* Let  $K$  be real, for any positive real  $\theta$ , we have

$$\mathbf{P}(\|Y^N(t)\| > K) = \mathbf{P}(\|X^N(t)\| > NK) \leq e^{-\theta NK} \mathbf{E} \left[ \exp(\theta \|X^N(t)\|) \right].$$

Lemma 6.1 entails that

$$\mathbf{E} \left[ \exp(\theta \|X^N(t)\|) \right] \leq (1 + (e^\theta - 1)e^{-\mu-t})^{N \|X^N(0)\|} \exp\left(N\zeta(e^\theta - 1)(1 - e^{-\mu-t})\right).$$



Hence,

$$\begin{aligned}
\mathbf{P}(\|Y^N(\infty)\| > K) &= \lim_{t \rightarrow \infty} \mathbf{P}(\|Y^N(t)\| > K) \\
&\leq \inf_{\theta > 0} \lim_{t \rightarrow \infty} (1 + (e^\theta - 1)e^{-\mu-t})^{N\|X^N(0)\|} \exp\left(-\theta NK + N\zeta(e^\theta - 1)(1 - e^{-\mu-t})\right) \\
&= \inf_{\theta > 0} \exp\left(N(-\theta K + \zeta(e^\theta - 1))\right) \\
&\leq \exp\left(-\frac{1}{2}NK \ln K\right),
\end{aligned}$$

for  $K$  large enough. The tightness follows.  $\square$

## 7. CENTRAL LIMIT THEOREM

It turns out that we can also evaluate the order of the approximation when we replace  $X^N$  by  $\psi$ . This is given by CLT like theorem.

**Theorem 7.1.** *Assume that the hypothesis of Theorem 5.1 holds. Then, for any  $T > 0$ , the process*

$$W^N = \sqrt{N}(Y^N - \psi)$$

*tends in distribution in  $\mathbb{D}([0, T], \mathbf{R}^2)$  to a centered Gaussian process with covariance matrix  $\Gamma(t)$  given by:*

$$\Gamma(t) = \begin{pmatrix} \Gamma_1(t) & -\alpha p \int_0^t \frac{\psi_1(s)\psi_2(s)}{\psi_1(s) + \psi_2(s)} ds \\ -\alpha p \int_0^t \frac{\psi_1(s)\psi_2(s)}{\psi_1(s) + \psi_2(s)} ds & \Gamma_2(t) \end{pmatrix},$$

where

$$\begin{aligned}
\Gamma_1(t) &= rt + \int_0^t \lambda p_I \frac{\psi_1(s)}{\psi_1(s) + \psi_2(s)} + \mu_1 \psi_1(s) + \alpha p \frac{\psi_1(s)\psi_2(s)}{\psi_1(s) + \psi_2(s)} ds \\
\Gamma_2(t) &= \int_0^t \lambda(1 - p_I \frac{\psi_1(s)}{\psi_1(s) + \psi_2(s)}) + \mu_2 \psi_2(s) + \alpha p \frac{\psi_1(s)\psi_2(s)}{\psi_1(s) + \psi_2(s)} ds.
\end{aligned}$$

*Proof.* According to [5, p. 339], it suffices to prove that

$$\mathbf{E} \left[ \sup_{t \leq T} |W^N(t) - W^N(t_-)| \right] \xrightarrow{N \rightarrow +\infty} 0$$

and that

$$\langle\langle W^N \rangle\rangle_t \xrightarrow{N \rightarrow +\infty} \Gamma(t).$$

Since the jumps of  $Y^N$  are bounded by  $1/N$ , those of  $W^N$  are bounded by  $N^{-1/2}$ , hence the first point is proved. As to the second point, remark that

$$\langle\langle W^N \rangle\rangle_t = N^{-1} \langle\langle M^N \rangle\rangle_t$$

and then use Theorem 5.1.  $\square$

## 8. NUMERICAL INVESTIGATION

Another approach to evaluate the order of approximation can be made by computer simulation. We simulated the Markov process for  $N = 100$  and compute the estimate of the prevalence by a simple Monte-Carlo method on 10,000 trajectories. For the parameters we chose,  $\alpha = 1$ ,  $\mu_1 = 0.1$ ,  $\mu_2 = 0.2$ ,  $r = 1$ ,  $\lambda = 5$  and  $p_I = 0.8$ , the results are strikingly good as shown in Figure 3. Note that the choice of parameters is here very delicate since biological parameters are not very well known (i.e.,  $\mu_1$ ,  $\mu_2$ ,  $p$ , ...) and population dependant quantities are even more obscure to

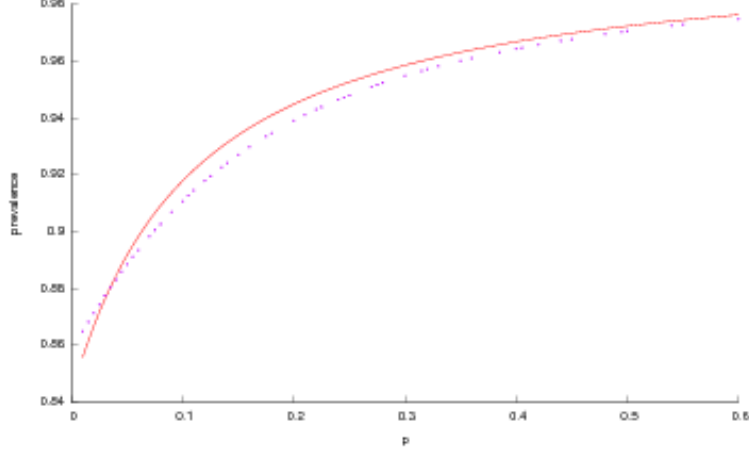


FIGURE 3. Prevalence with respect to  $p$ . The solid line represents the value as computed by Equations 1. The dots represents the simulated values. The 95% confidence interval are so small, they can't be displayed.

determine. We here chose parameters which seems reasonable and fit the observed prevalence.

In such models, another quantity of interest is the relative importance of each parameters: what does affect most the prevalence ? On the deterministic system, this question is easily solved by computing the derivative of the prevalence with respect to each of the parameters. We now explain how to compute the sensitivity of the prevalence on the stochastic model. Say we have a function  $F$  bounded which depends on the sample-paths of  $X$ , we aim to compute:

$$\frac{d}{dp} \mathbf{E}_p[F],$$

where we put a  $p$  under the expectation symbol to emphasize the dependence of the underlying probability with respect to  $p$ . Other “greeks”, as these quantities are called in mathematical finance, can be derived analogously. We assume that we observe the Markov process on a time window of size  $T$ , i.e., any functional is implicitly assumed to belong to  $\mathcal{F}_T = \sigma\{X(s), 0 \leq s \leq T\}$ .

**Theorem 8.1.** *For any bounded  $F$ ,  $F \in \mathcal{F}_T$ , we have:*

$$\begin{aligned} \frac{d}{dp} \mathbf{E}_p[F] &= \frac{1}{p} \mathbf{E}_p \left[ F \left( \sum_{s \leq T} \mathbf{1}_{\{(1, -1)\}}(\Delta X(s)) - \int_0^T q_3(X(s_-)) ds \right) \right] \\ &= \frac{1}{p} \text{cov}_p \left( F, \sum_{s \leq T} \mathbf{1}_{\{(1, -1)\}}(\Delta X(s)) \right), \end{aligned}$$

where  $\Delta X(s) = X(s) - X(s_-)$ .

*Proof.* The proof relies on the Girsanov theorem which is more easily expressed in the framework of multivariate point measures. Since there are only five kind of jumps, we can represent the dynamics of  $X$  as a point measures on  $\mathbf{R}^+ \times \{1, \dots, 5\}$ :

$$\mu([0, t] \times \{i\}) = \sum_{s \leq t} \mathbf{1}_{\{\Delta X(s)=i\}},$$

where

$$l_1 = (1, 0), l_2 = (-1, 0), l_3 = (1, -1), l_4 = (0, 1) \text{ and } l_5 = (0, -1).$$

In the reverse direction,

$$X(t) = X(0) + \sum_{i=1}^5 \mu([0, t] \times \{i\}) l_i.$$

It is immediate from the preceding results that  $\nu^p$ , the  $\mathbf{P}_p$ -predictable compensator of  $\mu$  is given by

$$d\nu^p(t, i) = q_i(X(t_-)) dt.$$

To compute  $d/dp \mathbf{E}_p[F]$  means to compute

$$\lim_{\varepsilon \rightarrow 0} \frac{1}{\varepsilon} (\mathbf{E}_{p+\varepsilon}[F] - \mathbf{E}_p[F]).$$

Under  $\mathbf{P}_{p+\varepsilon}$ ,

$$d\nu^{p+\varepsilon}(t, i) = d\nu^p(t, i) \text{ for } i \neq 3 \text{ and } d\nu^{p+\varepsilon}(t, 3) = (1 + \frac{\varepsilon}{p}) d\nu^p(t, 3).$$

Let

$$U(t, i) = \begin{cases} 0 & \text{if } i \neq 3, \\ \frac{\varepsilon}{p} & \text{if } i = 3. \end{cases}$$

According to the Girsanov theorem (see [3, 8]), this means that

$$\begin{aligned} \mathbf{E}_{p+\varepsilon}[F] &= \mathbf{E}_p \left[ F \mathcal{E} \left( \int_0^t U(s, i) (d\mu(s, i) - d\nu^p(s, i)) \right) \right] \\ &= \mathbf{E}_p \left[ F \mathcal{E} \left( \frac{\varepsilon}{p} (\mu([0, T] \times \{3\}) - \nu^p([0, T] \times \{3\})) \right) \right], \end{aligned}$$

where  $\mathcal{E}$  denotes the Doléans-Dade exponential. It is known (see [3]) that a Doléans-Dade exponential follows the same rule of derivation as a usual exponential, hence the result.  $\square$

With the parameters above, the simulated greek coincides pretty well with the sensitivity computed by differentiating the expression of the stationary prevalence in the deterministic system, see Figure 4. However, as usual with this method, the confidence interval are rather large.

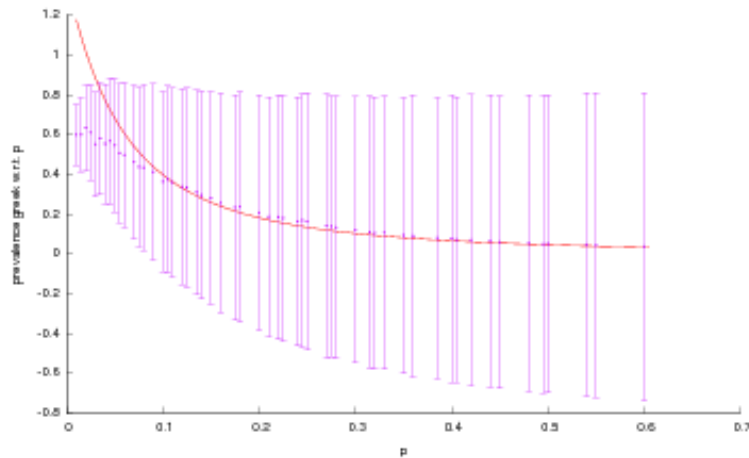


FIGURE 4. Prevalence greek with respect to  $p$ . Same conventions as above. The error bars represent the 95% confidence interval.

#### REFERENCES

- [1] J. Bell, R.G. Batey, G.C. Farrell, E.B. Crewe, Cunningham A.L., and K. Byth, *Hepatitis C virus in intravenous drug users*, Med. J. Aust. **153** (1990), 274-276.
- [2] P. Billingsley, *Convergence of probability measures*, second ed., Wiley Series in Probability and Statistics: Probability and Statistics, John Wiley & Sons Inc., New York, 1999, A Wiley-Interscience Publication.
- [3] L. Decreusefond, *Perturbation analysis and Malliavin calculus*, Annals of Applied Probability **8** (1998), no. 2, 496-523.
- [4] N. Esposito and C. Rossi, *A nested-epidemic model for the spread of hepatitis C among injecting drug users*, Mathematical Biosciences **188** (2004), no. 1-2, 29-45.
- [5] S.N. Ethier and T.G. Kurtz, *Markov processes : Characterizations and convergence*, Wiley, 1986.
- [6] R.S. Garfein, D. Vlahov, N. Galai, M.C. Doherty, and K.E. Nelson, *Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses*, Am. J. Public Health **86** (1996), 655-661.
- [7] C. Graham, *Kinetic limits for large communication networks*, Modeling in applied sciences, Model. Simul. Sci. Eng. Technol., Boston, MA, 2000, pp. 317-370. MR MR1763158 (2001f:60109)
- [8] J. Jacod, *Calcul stochastique et problèmes de martingales*, Springer-Verlag, 1979.
- [9] M. Jauffret-Roustide, J. Emanuelli, M. Quaglia, P. Arduin, and J-C. Desenclos, *Impact of harm-reduction policy on HIV and hepatitis C virus transmission among drug users: Recent french data-the ANRS-Coquelicot study*, Substance Use and Misuse **41** (2006), 1603-1621.
- [10] P. Métivier, *Stochastic partial differential equations in infinite-dimensional spaces*, Scuola Normale Superiore di Pisa. Quaderni. [Publications of the Scuola Normale Superiore of Pisa], Scuola Normale Superiore, Pisa, 1988, With a preface by G. Da Prato.
- [11] Health protection agency, *Shooting up. infection among injecting drug users in the united kingdom 2003*, Tech. report, London, 2004.
- [12] P. Robert, *Stochastic networks and queues*, french ed., Applications of Mathematics, vol. 52, Springer-Verlag, Berlin, 2003, Stochastic Modelling and Applied Probability.
- [13] F. Verhulst, *Nonlinear differential equations and dynamical systems*, second ed., Universitext, Springer-Verlag, Berlin, 1996, Translated from the 1985 Dutch original.
- [14] P. Vickerman, M. Hickman, and A. Judd, *Modelling the impact on hepatitis C transmission of reducing syringe sharing: London case study*, Epidemiology ; **36** (2007), no. 2, 396-405.
- [15] W. Whitt, *Blocking when service is required from several facilities simultaneously*, AT&T Tech. J. **64** (1985), no. 8, 1807-1856.
- [16] WHO, *Hepatitis C fact sheet*, <http://www.who.int/mediacentre/factsheets/fs164/en/> (2000).

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