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A MARKOV MODEL FOR THE SPREAD OF HEPATITIS C

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) [13]. 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 [8]. 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 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 % [6, 8]. 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 parameters estimates are rare and often imprecise. It is thus necessary to deal with parcimonious models whose parameters have clear and visible meaning. To the best of our knowledge, the only model which has been developed for the dynamics of HCV transmission is found in the reference [11]. 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 parcimonious Markovian model for the spread of HCV 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

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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 (they 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 Poisson processes. If initiated by an antibody-positive drug addict, a new IDU acquires the virus very rapidly after the initiation [1, 4]. 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 ψ 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. Finally, in Section 7., we give a central limit theorem for the approximation of X by ψ when the population tends to infinity.

2. PRELIMINARIES

Let us denote by $\mathbb{D}([0, T], \mathbf{R}^2)$ the set of cadlag processes equipped with its usual topology. In this Section, we remind some results about cadlag semi-martingales; for details we refer to [7]. 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 $\langle X, Y \rangle$ and 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 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 $F : E \rightarrow \mathbf{R}$, the Dynkin's Lemma stands 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 and sane drug users arrive as a Poisson process of intensity λ . 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 α the rate at which an IDU injects, and if αp 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 decease, self healing or stopping drug usage. The whole of these situations is modeled by an exponentially distributed duration with parameter μ_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 μ_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) 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

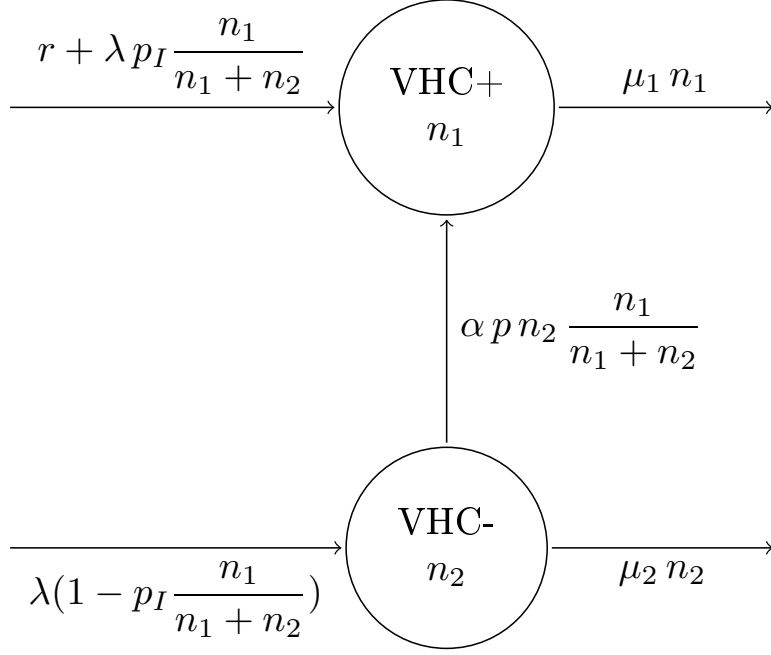


FIGURE 1. Transitions of the Markov model.

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 [9, 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 [9], 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 λ 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 (ξ_1, ξ_2) in $\mathbf{R}^+ \times \mathbf{R}^+$, defined by the equations*

$$(1) \quad r + \lambda - \mu_1 \xi_1 - \mu_2 \xi_2 = 0 \text{ and } \left(\lambda(1 - p_I) - (\alpha p + \mu_2) \xi_2 \right) \xi_1 = \mu_2 \xi_2^2 - \lambda \xi_2.$$

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 ψ^∞ the unique point to which the system converges in each case. We denote by Ψ 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 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

$$A_{\pm}^{\varepsilon} = \{(x_1, x_2) \in \mathbf{R}^+ \times \mathbf{R}^+, 0 \leq \pm(r + \lambda - \mu_1x_1 - \mu_2x_2) < \varepsilon\},$$

and

$$A^0 = \{(x_1, x_2) \in \mathbf{R}^+ \times \mathbf{R}^+, r + \lambda - \mu_1x_1 - \mu_2x_2 = 0\}.$$

According to (3), on $(A_+^{\varepsilon})^c$, the derivative of $\psi_1 + \psi_2 = \|(\psi_1, \psi_2)\|$ is greater than ε , hence for a starting point in A_+^{ε} , the trajectory has an \mathbf{L}^1 increasing norm. Reasoning along the same lines on $(A_-^{\varepsilon})^c$, 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_+^{η} or A_-^{η} . Moreover, upon this time, the orbit stays in the compact $A_+^{\eta} \cup A_-^{\eta}$ forever. It follows that (see for instance [10])

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

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

$$(f_1 + f_2)(x_1, x_2) = r + \lambda - \mu_1x_1 - \mu_2x_2 = 0.$$

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

$$x_1 = \frac{\mu_2x_2^2 - \lambda x_2}{\lambda(1 - p_I) - (\alpha p + \mu_2)x_2} = h(x_2).$$

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 (ξ_1, ξ_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 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 [10] 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

$$v'(t) = r + \lambda - \mu_1v(t), \quad v(0) = x_1 + x_2.$$

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 (ξ_1, ξ_2) and we have (4).

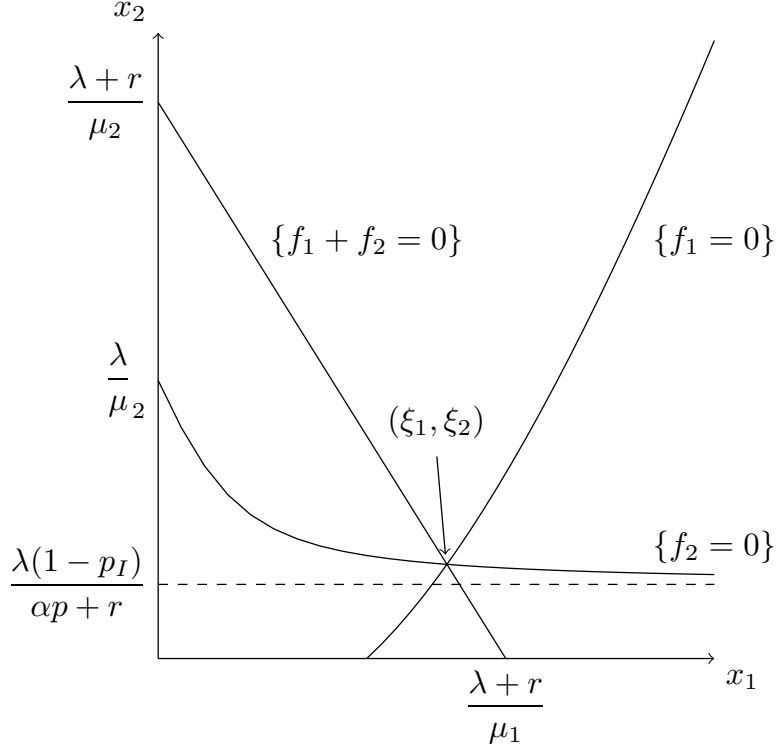


FIGURE 2. Determination of the fixed point.

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 (ξ_1, ξ_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 (ξ_1, ξ_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*

$$\frac{1}{N} X^N(0) \xrightarrow{N \rightarrow +\infty} x^0, \quad \frac{1}{N} r_N \xrightarrow{N \rightarrow +\infty} r \geq 0, \quad \frac{1}{N} \lambda_N \xrightarrow{N \rightarrow +\infty} \lambda.$$

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

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

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:

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

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. 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,

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

We have the following lemma, immediate by computing partial derivatives.

Lemma 5.1. *For any $N > 0$, for any $L > 0$, the functions q_1 and q_4 are $\lambda p_I/L$ -Lipschitz on $D_L^c = \{(x_1, x_2) \in \mathbf{R}_+^2, x_1 + x_2 > L\}$. The functions q_2, q_5 and q_3 are respectively μ_1, μ_2 and αp -Lipschitz on \mathbf{R}_+^2 .*

We fix $L > 0$ small enough so that $\psi(t) \in D_L^c$ for all $t \in [0, T]$. We introduce the stopping time

$$\tau_L^N = \inf\{t > 0, X_1^N(t) + X_2^N(t) \leq NL\} = \inf\{t > 0, X_1^N(t) + X_2^N(t) \in D_L\}.$$

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

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

Using Burkholder-Davis-Gundy inequality, we get that

$$\mathbf{E} \left[\sup_{t \in [0, T \wedge \tau_L^N]} \|M^N(t)\|^2 \right] \leq C \mathbf{E}[\langle M^N \rangle_{T \wedge \tau_L^N}].$$

As a consequence of Lemma 3.1 and Lemma 5.1, we get that for $i \in \{1, 2, 3, 4, 5\}$,

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

It is then easy to see that

$$\mathbf{E}[\langle M^N \rangle_{T \wedge \tau_L^N}] \leq CT(\|x^0\| + (r + \lambda)T)N.$$

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

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

In order to bound $\mathbf{E} \left[\sup_{t \in [T \wedge \tau_L^N, T]} \left\| \frac{1}{N} X^N(t) - \psi(t) \right\|^2 \right]$, we need the following lemma.

Lemma 5.2. *Assume that hypothesis of Theorem 5.1 holds. Then, for any $T > 0$, for $L < (x_1 + x_2) \exp(-(\mu_1 \vee \mu_2)T)$*

$$\mathbf{P}(\tau_L^N \leq T) \xrightarrow{N \rightarrow +\infty} 0.$$

Proof. By stopping fresh arrivals, one sees that $X_1^N(t) + X_2^N(t)$ is greater than the population remaining from the initial state without new arrivals. If we replace μ_1 and μ_2 by their supremum, we accelerate the exit rate thus $X_1^N(t) + X_2^N(t)$ is greater for the strong stochastic order, than the population of an M/M/ ∞ queue without arrivals, at time t . In such a system, the probability that a customer present at time 0 is still in the server at time t is given by $\exp(-(\mu_1 \vee \mu_2)t)$. Thus, $X_1^N(t) + X_2^N(t)$ is greater for the strong stochastic order, than a Binomial random variable with parameters $x_1^N + x_2^N$ and $\exp(-(\mu_1 \vee \mu_2)T)$. It follows that

$$\mathbf{P}(\tau_L^N \leq T) \leq \mathbf{P}(B(x_1^N + x_2^N, \exp(-(\mu_1 \vee \mu_2)T)) \leq NL).$$

According to the hypothesis,

$$\frac{1}{N}(x_1^N + x_2^N) \exp(-(\mu_1 \vee \mu_2)T) \xrightarrow{N \rightarrow +\infty} (x_1 + x_2) \exp(-(\mu_1 \vee \mu_2)T) > L,$$

hence the result by the Law of Large Numbers. \square

We have

$$\begin{aligned}
& \mathbf{E} \left[\sup_{t \in [T \wedge \tau_L^N, T]} \left\| \frac{1}{N} X^N(t) - \psi(t) \right\|^2 \right] \\
& \leq 2 \sup_{t \in [0, T]} \|\psi(t)\|^2 \mathbf{P}(\tau_L^N \leq T) + 2 \mathbf{E} \left[\sup_{t \in [0, T]} \left\| \frac{1}{N} X^N(t) \right\|^2 \mathbf{1}_{\tau_L^N \leq T} \right] \\
& \leq 2 \sup_{t \in [0, T]} \|\psi(t)\|^2 \mathbf{P}(\tau_L^N \leq T) + 2 \mathbf{E} \left[\sup_{t \in [0, T]} \left\| \frac{1}{N} X^N(t) \right\|^4 \right]^{1/2} \mathbf{P}(\tau_L^N \leq T)^{1/2},
\end{aligned}$$

which tends to 0 by Lemma 3.1 and Lemma 5.2. \square

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 ψ^∞ . 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 ψ^∞ 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 ν . We denote by $\mathbf{P}_{\psi, \nu}$ the distribution of the process whose initial state is chosen according to ν 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 [12] and [5]. It consists in showing that 1) for any sequence of initial distribution ν^N converging to ν , then \mathbf{P}_{Y^N, ν^N} converges weakly to $\mathbf{P}_{\psi, \nu}$, 2) that for any probability measure ν on \mathbf{R}^2 , $\mathbf{P}_{\psi(t), \nu}$ converges vaguely to δ_{ψ^∞} and 3) that the sequence $(Y^N(\infty), N \geq 1)$ is tight.

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 ν . 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 ψ is also a stationary process when started from ν . This means that the distribution of $\psi(t)$ is ν 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 δ_{ψ^∞} , hence the result. We now turn to the proof of the three necessary lemmas. We need to take into account 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 ν on \mathbf{R}^2 belongs to \mathcal{P}_0 when $\nu(\{0, 0\}) = 0$.

Theorem 6.1. *For any sequence of initial distribution ν^N converging to $\nu \in \mathcal{P}_0$, then \mathbf{P}_{Y^N, ν^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, ν^N} is tight and that the limiting process is continuous. According to [2], we need to show that for each positive ϵ and η , 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

$$A_1^N(t) = \frac{1}{N} \int_0^t (q_1^N + q_3^N - q_2^N)(X^N(s)) \, ds$$

$$A_2^N(t) = \frac{1}{N} \int_0^t (q_4^N - q_3^N - q_5^N)(X^N(s)) \, ds.$$

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 ,

$$(7) \quad \mathbf{P} \left(\sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} |Y^N(v) - Y^N(u)| \geq \epsilon \right) \leq \mathbf{P}(|Y^N(0)| \geq a)$$

$$+ \mathbf{P} \left(\sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} |A^N(v) - A^N(u)| \geq \epsilon/2; |Y^N(0)| \leq a \right)$$

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

Eqn. (6) implies that

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

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,

$$|A^N(v) - A^N(u)| \leq \frac{1}{N} \int_u^v \sum_{i=1}^5 q_i(X^N(s))$$

$$\leq |v - u| \left(\frac{r_N + \lambda_N}{N} + \frac{c}{N} \sup_{s \leq T} |X^N(s)| \right).$$

It follows from Lemma 3.1 that

$$\mathbf{E} \left[\sup_{\substack{|v-u| \leq \delta \\ v, u \leq T}} |A^N(v) - A^N(u)| \mid |Y^N(0)| \leq a \right] \leq 2\delta \left(\frac{r_N + \lambda_N}{N} T + a \right) \leq C((r + \lambda)T + a)\delta.$$

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, ν^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 ν^N tends to ν and that \mathbf{P}_{Y^N, ν^N} tends to some $\mathbf{P}_{Z, \nu}$. Let F be a \mathcal{C}_b^2 function on \mathbf{R}^2 , let

$$G^N(\omega, t) = F(\omega(t)) - F(\omega(0)) - \sum_{j=1}^5 \int_0^t q_j^N(\omega(u))(F(\omega(u) + N^{-1}e_j) - F(\omega(u))) du,$$

where ω is the generic element of $\mathbb{D}([0, T], \mathbf{R}^2)$ and

$$e_1 = -e_2 = (1, 0), \quad e_4 = -e_5 = (0, 1) \quad \text{and} \quad e_3 = e_1 + e_5.$$

Let us also introduce G by

$$G(\omega, t) = F(\omega(t)) - F(\omega(0)) - \sum_{k=1}^2 \int_0^t \frac{\partial F}{\partial x_k}(\omega(u)) f_k(\omega(u)) du,$$

where f_1 and f_2 are defined in (2). Note that for any $t > 0$, any ω , $G^N(\omega, t)$ tends to $G(\omega, t)$. Note that neither G nor G^N are continuous on $\mathbb{D}([0, T], \mathbf{R}^2)$ but only on $\mathbb{D}([0, T], D_L^c)$ for any $L > 0$. We denote by $Y^{N,L}$ the process $Y^N(\tau_L^N \wedge \cdot)$ and we define the initial distribution accordingly: $\nu^{N,L}(C) = \nu^N(C \cap D_L^c) / \nu(D_L^c)$. Since ν belongs to \mathcal{P}_0 , the first part of this proof entails that $\mathbf{P}_{Y^{N,L}, \nu^{N,L}}$ is tight in $\mathbb{D}([0, T], D_L^c)$. Let \mathbf{P}_{Z_L, ν_L} be an accumulation point of $\mathbf{P}_{Y^{N,L}, \nu^{N,L}}$. We still index the converging subsequence by N . We also know that

$$R^{N,L}(t) = G^N(Y^{N,L}(t))$$

is a local martingale and proceeding along the same lines as above, one can show that its square bracket tends to 0.

$$(8) \quad \mathbf{E} \left[(R^N(t) - R^N(s))^2 \right] \xrightarrow{N \rightarrow +\infty} 0.$$

According to Fatou's Lemma, we have

$$\begin{aligned} 0 &\leq \int G^2 d\mathbf{P}_{Z_L, \nu_L} \leq \liminf_N \int (G^N)^2 d\mathbf{P}_{Z_L, \nu_L} \\ &\leq \liminf_N \liminf_K \int (G^N)^2 d\mathbf{P}_{Y^{K,L}, \nu^{K,L}} \leq \liminf_N \int (G^N)^2 d\mathbf{P}_{Y^{N,L}, \nu^{N,L}} = 0, \end{aligned}$$

in view of (8). Hence,

$$\mathbf{E} [(G(Z_L(t)) - G(Z_L(s)))^2] = 0$$

and for any s and t , $G(Z_L(t)) = G(Z_L(s))$ almost surely. Unfortunately, the null space on which this property does not hold depends on s and t . We fix s and construct classically a full measure set on which $G(Z_L(t)) = G(Z_L(s))$ for all $t \geq s$ and t rational. Since Z_L is known to be continuous, the equality holds for all $t \geq s$. Choose now $K > 0$ and $F \in \mathcal{C}_b^2$ such that $F(x) = x_1$ for $|x_1| \leq K$ and $F(x) = (K+1)\text{sgn}(x_1)$ for $|x_1| \geq K+1$. Since $Z_L(s)$ is finite, there exists $\epsilon > 0$ such that

$$|(Z_L)_1(r)| < K \quad \text{and} \quad Z_L(r) \in D_L^c, \quad \text{for } r \in [s - \epsilon, s + \epsilon].$$

Then by differentiation, we get

$$(Z_L)_1'(t) = f_1(Z_L(t)) \quad \text{for } t \in [s - \epsilon, s + \epsilon].$$

Since the same holds for Z_2 and s is arbitrary, we have proved that

$$Z_L(t) = \Psi(Z_L(s), t - s),$$

for any s and t . Moreover, by continuity, $Z_L(0)$ is distributed as $\nu_L = \nu(D_L^c \cap \cdot) / \nu(D_L^c)$. Since $\nu \in \mathcal{P}_0$, ν_L tends to ν as L goes to 0. Moreover, for any h bounded and continuous, we have

$$\begin{aligned} \int h(Z(t_1)) d\mathbf{P}_\nu &= \int h(\Psi(y, t_1)) d\nu(y) \\ &= \lim_{L \rightarrow 0} \int h(\Psi(y, t_1)) d\nu_L(y) = \int h(Z_L(t_1)) d\mathbf{P}_{\nu_L}, \end{aligned}$$

since Ψ is continuous. By induction on k , one proves that for any t_1, \dots, t_k ,

$$\mathbf{P}_{(Z_L(t_1), \dots, Z_L(t_k)), \nu_L} \xrightarrow{L \rightarrow 0} \mathbf{P}_{(\psi(t_1), \dots, \psi(t_n)), \nu},$$

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

Theorem 6.2. *For any probability measure $\nu \in \mathcal{P}_0$, $\mathbf{P}_{\psi(t), \nu}$ converges vaguely to δ_{ψ^∞} .*

Proof. For any f with compact support 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 $x \in \mathbf{R}^2$,

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

The result follows by dominated convergence. \square

Theorem 6.3. *The sequence $(Y^N(\infty), N \geq 1)$ is tight.*

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/ ∞ 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 [9, Chapter 6],

$$(9) \quad \frac{\partial h_c}{\partial t}(t, x) + R(h_c(t, \cdot))(x) = 0,$$

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 [9, Proposition C.5]), for any $0 \leq s < t$, we have

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

where the inequality follows from the monotony of h_c and the definition of μ_- . We then recognize that this amounts to say

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

In view of Eqn. (9), 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. \square

Proof of Theorem 6.3. Let K be real, for any positive real θ , we have

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

Lemma 6.1 entails that

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

Hence,

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

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 ψ . 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 [3], 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

$$\langle\langle W^N \rangle\rangle_t = N \langle\langle M^N \rangle\rangle_t$$

and then use Theorem 5.1. \square

8. CONCLUSION

We provided epidemiologists with a comprehensive and insightful model for the dissemination of the Hepatitis C among injecting drug users. With the estimated values of the different parameters, we found that the most effective policies to be used are first to strictly reduce r , i.e., the contamination by external to the population antibody-positive. This amounts to put the local drug users into quarantine. Since this is hardly feasible, the second most efficient way to reduce the prevalence is to insist on not sharing the paraphernalia (syringe, cotton, boiler).

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), 274276.
- [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. MR **MR1700749** (2000e:60008)
- [3] S.N. Ethier and T.G. Kurtz, *Markov processes : Characterizations and convergence*, Wiley, 1986.
- [4] 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), 655661.
- [5] 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)
- [6] 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.
- [7] P. Mtivier, *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.
- [8] Health protection agency, *Shooting up. infection among injecting drug users in the united kingdom 2003*, Tech. report, London, 2004.

- [9] P. Robert, *Stochastic networks and queues*, french ed., Applications of Mathematics, vol. 52, Springer-Verlag, Berlin, 2003, Stochastic Modelling and Applied Probability.
- [10] F. Verhulst, *Nonlinear differential equations and dynamical systems*, second ed., Universitext, Springer-Verlag, Berlin, 1996, Translated from the 1985 Dutch original.
- [11] 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.
- [12] W. Whitt, *Blocking when service is required from several facilities simultaneously*, *AT&T Tech. J.* **64** (1985), no. 8, 1807–1856.
- [13] WHO, *Hepatitis C fact sheet*, <http://www.who.int/mediacentre/factsheets/fs164/en/> (2000).

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