A Markov model for the spread of hepatitis C virus

Nicolas Scotto Di Perto and Raphaël Teboul

July 1, 2018

This was made for the class MACS207a on stochastic calculus at Telecom Paristech. All the data and calculations are from "A Markov model for the spread of hepatitis C virus" by L.Coutin, L.Decreusefond and J.S. Dhersin

Objectives: We propose here a Markov model for the spread of HCV among drug users who use injections (IDU) and would like to find its stationary regim after proving it exists. We also propose a deterministic differential system to describe the situation in order to prove that its solution describes the Markov chain asymptotically, using a mean field approximation, i.e. for large populations. We would like to know then if the limit of the differential system is also the limit of the stationary distributions for the mean field approximation, meaning the diagram of convergence commutes. We establish a central limit theorem for our system so that we can estimate error of approximations. Finally, our simulations illustrates the rapidity of convergence of the system to it's stationary regime, and how important the parameter p plays a role in the prevalence obtained. The conclusion is that we need to minimize this parameter to limit the prevalence of HCV among IDU.

1. The Markov model

We denote by $X_1(t)$, resp. by $X_2(t)$, the number of anti-body positive (AP), resp. anti-body negative (AN), among a local population of (IDU). We assume that the continuous arrival of an AP, resp. AN, is best described by a Poisson process of intensity r, resp. λ. At t, an IDU has $q(t) = X_1(t)(X_1(t) + X_2(t))$ chance of being AP. For medical reasons, the probability of being infected even in such case is denoted by p_I. Thus, the global probability of being infected is $pq(t)$ with p another parameter to be estimated. We call α the rate at which a drug user injects, and we consider that in each population (AN or AP) an individual exits by death or self - healing under an exponentially distributed time of parameter μ_1, respectively μ_2. To sum it up, we have these transitions :

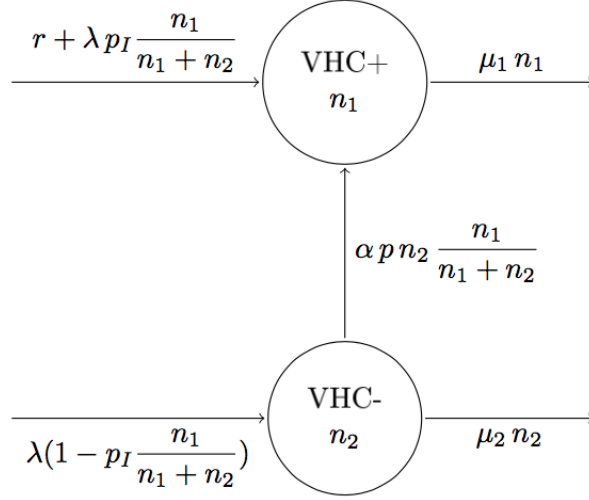- $q_1(n_1, n_2) = r + \lambda p_I \frac{n_1}{n_1 + n_2}$
- $q_2(n_1, n_2) = \mu_1 n_1$

Figure 1: Transitions of the Markov model

- $q_3(n_1, n_2) = \alpha p n_2 \frac{n_1}{n_1+n_2}$

- $q_4(n_1, n_2) = \lambda(1 - p_I \frac{n_1}{n_1+n_2})$

- $q_5(n_1, n_2) = \mu_2 n_2.$

2. A deterministic differential system

According to the model, the situation can be described by this system :

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

Thus we can deduce from this system that for any non zero initial conditions, there exists a unique solution with the following invariant points we can find via the standard method used to solve differential equations :

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

With $a = \alpha p - \mu_1 + \mu_2$, $b = r + \lambda$,and $c = r\mu_1 + \lambda(1 - p_I)\mu_2$.

3. Mean Field Approximation

We would like to find the stationary regime for our Markov Process, but the non linearities in the transition Matrix make it hard to compute... To bypass that difficulty we will study the Markov Process asymptotically on an increasing population and show that it converges to the solution of our differential system. So We are now considering the sequence $(X^N)_N = (X_1^N, X_2^N)_N$ of Markov process with same transitions as defined previously, except that parameters are now depending on N :

- $q_1^N(n_1, n_2) = r_N + \lambda p_I \frac{n_1}{n_1 + n_2}$

- $q_2^N(n_1, n_2) = \mu_1 n_1$

- $q_3^N(n_1, n_2) = \alpha p n_2 \frac{n_1}{n_1 + n_2}$

- $q_4^N(n_1, n_2) = \lambda_N (1 - p_I \frac{n_1}{n_1 + n_2})$

- $q_5^N(n_1, n_2) = \mu_2 n_2$.

For any $t > 0$, assuming the hypothesis that $\frac{1}{N} X^N(0)$ converges in L^2 towards x^0, and the normalized parameters $\frac{1}{N} r_N$ and $\frac{1}{N} \lambda_N$ converges respectively to the parameters r and λ used in the differential system, we have that for any $T > 0$:

$$E\big[\sup_{t \leq T} \|\frac{1}{N} X^N(t) - \psi(x^0, t)\|^2\big]$$

where $\psi(x^0, t)$ is the solution of the differential system with initial condition x^0. This is sort of a L^2 convergence on our process and it is one of the most important result of this article because it relates the solution of the differential system to an asymptotic behavior of our Markov Chain, it has good applications for computations because it is a lot faster to approach this solution than to simulate a Markov chain. As usual, to prove that a positive quantity converges toward zero we can find a majorant of it which converges toward zero. For that, thanks to Dynkin's lemma we can get the decomposition of X^N as a vector-valued semi-martingale, and compute its square bracket, using Ito's formula in both cases with appropriate problems. We then use that decomposition and simple analysis to get a useful majoration which is a start for Gronwall's lemma :

$$\|\frac{1}{N} X^N(t) - \psi(x^0, t)\|^2 \leq$$

$$C\big(\|\frac{1}{N} X^N(0) - \psi(x^0, 0)\|^2 + T^2 |r - \frac{r_N}{N}|^2 + T^2 |\lambda - \frac{\lambda_N}{N}|^2$$

$$+T \int_0^t (1 + \frac{1}{\|\psi(x^0, s)\|})^2 \|\frac{1}{N} X^N(s) - \psi(x^0, s)\|^2 ds + \frac{1}{N^2} \|M^N(t)\|^2\big)$$

where M^N is the martingale part of X^N. In order to apply Gronwall's lemma we need to prove that some of the variable terms right member of the inequality

can be majored by some constants. For this we use Burkholder-Davis-Gundy inequality, we get :

$$E[\sup_{t\in[0,T]} \|M^N(t)\|^2|\sigma(X^M(0), M \in N)] \leq$$

$$CE[| < M_1 >_T + < M_2 >_T ||\sigma(X^M(0), M \in N)]$$

 we can then majorate the right member using some previous results on our process, we obtain the majorant $CT(E[\|X^N(0)\|]) + (r_N + \lambda_N)T)$. We can now apply Gronwall's lemma, giving us a majorant for the "L^2 distance" of X with *psi* that tends to zero when N goes to infinity. Hence the result of that section.

4. Commutativity of the diagram

We increased the population and found a deterministic process which have a vector valued limit. We want to know now if we would have gotten the same results increasing first the time, then the population, meaning that the sequence of stationary distributions converges towards a Dirac in ψ_∞. Otherwise said, we would like to know if the diagram of convergence is commutative. It is the case, the results comes with weakly convergence of initial distributions.

5. Central limit theorem

We like the central limit theorem in the random variable case to estimate some errors of approximation. In this section we give a sort of central limit theorem for this process. Using hypothesis of section 3. we have that the process $W^N = \sqrt{N}(N^{-1}X^N - \psi)$ tends in distribution in $D([0,T]nR^2)$ to a centered Gaussian process with covariance depending on t and the solution of the differential system and its parameters. The premise of the result comes from *Markov processes : Characterizations and convergence, Wiley, 1986, p. 339*, according to which it suffices to prove that

$$E[\sup_{t\leq T} \|W^N(t) - W^N(t_-)\|] \xrightarrow{N\to\infty} 0$$

and that

$$<< W^N >>_t$$

converges, then we have that the limit of the square brackets is the variance of the centered gaussian process. The first point comes from the simple fact that the jumps of W^N are bouded by $N^{-1/2}$, and the second point comes from the result of section 3 remarking that

$$<< W^N >>_t = N^{-1} << M^N >>_t$$
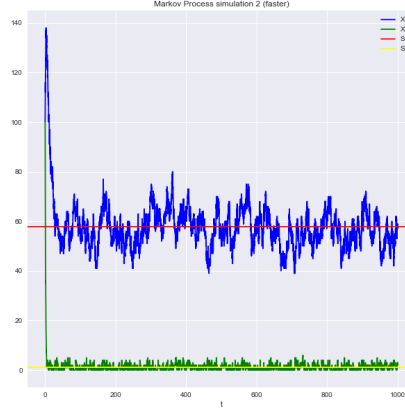
with M the martingale associated to X^N.

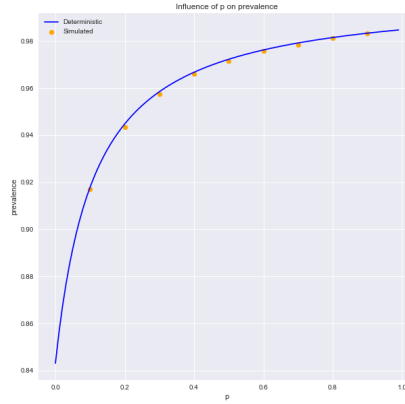Figure 2: Trajectories according to the differential system

Figure 3: Prevalence with respect to p

6. Simulation

We first simulated the trajectories of the markov simulations and then to compare them to the differential system we computed the prevalence with respect to p with a Monte - Carlo simulation for N = 100 on 10 000 trajectories for the following parameters : $\alpha = 1$, $\mu_1 = 0.1$, $\mu_2 = 0.2$, $r = 1$, $\lambda = 5$ and $p_I = 0.8$. We find that the results of the Markov model are really close to those of the differential system which proves the quick convergence of the model !

As a conclusion we have to state that, while it is hard to measure the parameters of the model, we cannot have an influence on every one of them in the real world. Regardless of their values, we have seen than the system will find an equilibrium for which the prevalence depends greatly on p. Parameter p modeled the probability of a new IDU initiated by an infected one to get infected, in the real world we can decrease this probability distributing clean syringe to IDUs.