Quantifying the effect of synchrony on the persistence of infectious diseases in a metapopulation

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1 INTRODUCTION

2 MATERIAL AND METHODS

2.1 MATERIAL

2.1.1 Deterministic model for many subpopulations

The standard SEIR model (susceptible-exposed-infective-recovered) has been strongly developed for the dynamics of directly infectious disease [3]. For disease-based metapopulation models, we give here a suitable new version of the SEIR equation that would be as follows:

Consider a metapopulation of n sub-populations. In a subpopulation i of size N_i, disease dynamics can be deterministically described by the following set of differential equations [2]:

$$\frac{dS_i}{dt} = \mu N_i - \lambda_i S_i - \mu S_i \tag{2.1}$$

$$\frac{dE_i}{dt} = \lambda_i S_i - \mu E_i - \sigma E_i \tag{2.2}$$

$$\frac{dI_i}{dt} = \sigma E_i - \mu I_i - \gamma I_i \tag{2.3}$$

$$\frac{dR_i}{dt} = \gamma I_i - \mu R_i \tag{2.4}$$

where S_i, E_i, I_i et R_i are the numbers of susceptible, exposed, infectious and recovered in this sub-population i respectively. Individuals are born susceptible, die at a rate μ, become infected with the force of infection λ_i, infectious after a latency period of an average duration of $1/\sigma$ and recover at the rate γ. In a case the infectious contact rate is constant, the equilibrium values of the variables S, E, I and R can be expressed analytically (see appendix). The force of infection depends not only on the total population size N_i and the number of infected I_i in subpopulation i, but also in other sub-populations [16] :

$$\lambda_i = \sum_j \rho_{ij}\kappa_j \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right] \tag{2.5}$$

where $c_{i,k}$ $(0 \leqslant c_{ij} \leqslant 1)$ is the probability that a susceptible individual native from i being in contact with another infected individual native from k gets infected. ξ_{jk} $(0 \leqslant \xi_{ij} \leqslant 1)$ refers to the probability that an individual y meeting x in the subpopulation C_j comes from the subpopulation C_k. κ_j is the average number of contacts per unit of time a susceptible will have when visiting city j. $\rho_{i,j}$ $(0 \leqslant \rho_{ij} \leqslant 1)$ is denoted as the probability that an individual from subpopulation i visits subpopulation j, of course, $\sum_{j=1}^{M} \rho_{ij} = 1$. See appendix for detail on the construction of this equation. We can verify that in the limit case on one single subpopulation in the metapopulation ($i = j$ and $n = 1$) we have

$$\lambda_i = -\kappa_i \log(1 - \frac{I_i}{N_i} \times c_{ii}) \tag{2.6}$$

Consider that the average number of contacts per unit of time κ_i is seasonally forced [1] and seasonality is an annually periodic function of time [9]. As a result, for the subpopulation i :

$$\kappa_i(t) = \kappa_{i0}\left[1 + \kappa_{i1}\cos\left(\frac{2\pi t}{T} + \varphi_i\right)\right] \tag{2.7}$$

where t is the time, κ_{i0} and κ_{i1} are the mean value and amplitude of the average contact rate κ_i at which a susceptible will have when visiting city i per unit of time, T and φ_i are the period and the phase of the forcing. With the annual sinusoidal form of the average contact rate, we really have the sinusoidally forced SEIR metapopulation model.

2.1.2 Stochastic model for many subpopulations

In order to study the extinction ability of an infectious disease in a metapopulation, we must consider a stochastic version of the model [15, 19, 20]. We use for that a population-based time-to-next-event model based on Gillespie's algorithm [8]. Table 1 lists all the events of the model, occurring in subpopulation i.

Table 1: Events of the stochastic version of the model of equations 2.1-2.4, occuring in subpopulation i.

Events	Rates	Transitions
birth	μN_i	$S_i \leftarrow S_i + 1$ and $N_i \leftarrow N_i + 1$
death of a susceptible	μS_i	$S_i \leftarrow S_i - 1$
death of an exposed	μE_i	$E_i \leftarrow E_i - 1$
death of an infected	μI_i	$I_i \leftarrow I_i - 1$
death of an immune	μR_i	$I_i \leftarrow I_i - 1$
infection	$\lambda_i S_i$	$S_i \leftarrow S_i - 1$ and $E_i \leftarrow E_i + 1$
becoming infectious	σE_i	$E_i \leftarrow E_i - 1$ and $I_i \leftarrow I_i + 1$
recovery	γI_i	$I_i \leftarrow I_i - 1$ and $R_i \leftarrow R_i + 1$

2.1.3 Spatial structures

A metapopulation is a population of populations (subpopulations). Such a structure implies an heterogeneity in the sense where the probability of contact (or contact rate) between individuals from a same subpopulation is higher than the probability of contact between individuals of different subpopulations [7]. Such heterogeneity is actually the result of the interaction between two phenomena that are often difficult to disentangle in nature. The first one relates to the granularity of the metapopulation (as rendered by the number of and sizes of subpopulations) and the second one relates to the isolation between subpopulations (as can be rendered, among others, by physical distances separating each pair of subpopulations). Moreover, according to the findings of Benjamin Bolker (1995) [3], there is no coexistence between periodicity and disease persistence in non-spatial measles models, and spatial structure is an important factor to both enhance persistence and create new types of dynamic behaviour.

In order to identify clearly the causes of observed phenomena, these two aspects will be modeled distinctly. In this article, our null model (model 0) will be a metapopulation without any explicit spatial distance (all the subpopulations are at the same distance from each other) and where all the metapopulation have the same population size N. Like the original Levins's model [18], this model considers that all the subpopulations are at equal distance from each other:

$$\rho_{ij} = \rho, \qquad 0 \leqslant \rho \leqslant 1, \qquad \forall i, \forall j. \tag{2.8}$$

The structure of this metapopulation is thus characterized by 3 parameters: (i) the number n of sub-populations, (ii) the population size N ($N_i = N$, $\forall i$) of all these subpopulations and, (iii) the coupling (or distance) ρ_{ij} between two subpopulations i and j that refers to the the probability that an individual from subpopulation i visits subpopulation j.

2.2 METHOD

2.2.1 Stationary distribution in metapopulation

Here we show some assumptions for the stationary distribution model as follows :

- Assumption 1. For each city V_i, there exists a markov chain M_i describing where (i.e. in which city) individuals native from V_i travel at each time step.
- Assumption 2. Each M_i has a stationary distribution $\rho(M_i)$.
- Assumption 3. At time t=0, each agent is located in a city randomly drawn from $\rho(M_i)$.

When we consider a simplified model in which the dynamics of the agents is stationary: each agent native from V_i no more follows a markov chain, but is relocated at each time step on a city randomly drawn from $\rho(M_i)$.

Then, under assumptions 1,2,3, at any time t, when the total number of agents grows to infinity, the size of the populations under the markovian dynamics converges towards the size of the populations under stationary dynamics.

Hence, any statistics computed on the densities of agents from the same population in various cities will not distinguish the markovian from the stationary dynamics.

Based on this conclusion, we will deploy a stationary distribution in a metapopulation. First of all, we choose a population size N for the metapopulation. Then, we compute the After that, the transition matrix converge towards a stationary distribution matrix. Finally, we apply the stationary distribution matrix in the metapopulation of n subpopulations.

2.2.2 Global persistence in a metapopulation

In order to examine questions of interaction between disease transmissibility and phase of seasonal forcing, we start in this section by studing the stochastic SEIR model in a metapopualtion of n subpopulations. For this metapopulation, we observe the disease extinction in time due to spatial synchrony/asynchrony that are influenced by phase difference in seasonal forcing. To create the phase difference, we change the value of the forcing phase for each subpopulation. In this experience, we use a parameter φ_{max} in radian that runs in the interval from zero to π. With each value of φ_{max}, based on n the number of subpopulations in the metapopulation, we divide the interval [0, φ_{max}] into a set of $(n-1)$ equal samples, so the value of the forcing phase of the i^{th} subpopulation is correspondent to i^{th} value in the set. We call φ_{max} asynchrony parameter.

The persistence of disease in the metapopulation was characterized by fitting an exponential survival model [5, 17] on a data simulated by a stochastic model. To measure the persistence in ecology and epidemiology, so many methods we can use [5, 10, 15]. For example, Keeling et al.(2002) [15] gave two methods. One method was for an isolated metapopulation without migration by calculating the expected extinction time or the extinction rate during a given period. This was a theoretical measure as no real data exists to compare with model results. The other method for a population with migration was found by calculating the number or the total duration of extinctions. Then in 2010, "mean annual fade-out" and "fade-outs post epidemic" methods proposed by Conlan [5] were used to quantify persistence by basing on the proportion or on the frequency of zero reports in a given reporting interval. For our metapopulation of n subpopulations, to do so we run first m independent simulations of our stochastic model. We calculate then the average metapopulation size by summing subpopulations at each sample time and averaging across the entire time series for each metapopulation. Lastly, we record the dates t of global disease extinction in all these m metapopulations. These dates allow to draw Kaplan-Meier survival curves from which we estimate the global extinction rates χ:

$$M(t) = \exp(-\chi t) \tag{2.9}$$

where $M(t)$ $(0 \leqslant M(t) \leqslant m)$ is the number of metapopulations in which the disease is not extinct at time t.

To assess global extinction rate as well as global persistence level in metapopulation, here, we use the parametric survival model for the exponential distribution (R package '*survival*' [22]). Due to that, we can capture one of the most important features of stochastic systems in spatial structure : its global extinction characteristics of disease.

Besides, to compute local extinction rate that illustrates the probability of local extinction event in the duration of fluctuations in incidence. We save up all disease duration in all subpopulations of the metapopulation. We consider the data array like a Poisson process and we estimate local extinction rate from this data.

2.2.3 Characterization of synchrony

Call $\delta_{ij} = \delta_{ji}$ $(0 \leqslant \delta_{ij} < 2\pi)$ the phase difference between subpopulations i and j :

$$\delta_{ij} = |\varphi_i - \varphi_j| \bmod 2\pi \tag{2.10}$$

where φ_i and φ_j are the phases of the contact rates (equation 2.7) in subpopulations i et j. Populations i and j are perfectly in phase if $\delta_{ij} = \delta_{ji} = 0$ or 2π and in opposition of phase if $\delta_{ij} = \delta_{ji} = \pi$. We can thus define the degree of synchrony $\xi_{ij} = \xi_{ji}$ $(0 \leqslant \xi_{ij} \leqslant 1)$ between populations i and j as

$$\xi_{ij} = \left| 1 - \frac{\delta_{ij}}{\pi} \right|. \tag{2.11}$$

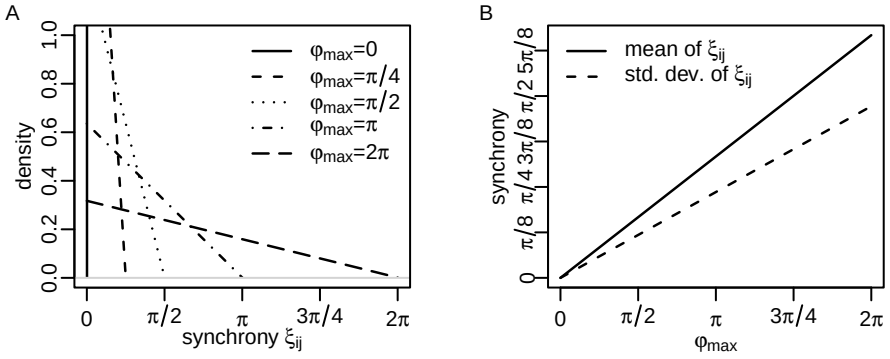

Figure 2.1: Synchrony in the case of model 0. (A) distribution of synchrony ξ_{ij} for various values of φ_{max}. (B) mean and standard deviation of the distribution of ξ_{ij} as functions of $\varphi_{\max}$.

Consider that in the metapopulation the phases φ_i of the contact rates in the n subpopulations are evenly distributed between 0 and $\varphi_{\max}$ $(0 \leqslant \varphi_{\max} \leqslant \pi)$. We can express the mean of the pairwise phase differences $\delta_{ij} = \delta_{ji}$ as

$$<\delta_{ij}> = <\delta_{ji}> = 2\varphi_{\max} \sum_{k=1}^{n-1} \frac{(n-k)k}{(n-1)n^2} = \frac{n+1}{3n}\varphi_{\max} \tag{2.12}$$

and thus the mean of the synchronies $\xi_{ij} = \xi_{ji}$ as

$$<\xi_{ij}> = <\xi_{ji}> = 1 - \frac{n+1}{3n}\frac{\varphi_{\max}}{\pi} \tag{2.13}$$

and thus

$$\lim_{n\to\infty} <\xi_{ij}> = 1 - \frac{\varphi_{\max}}{3\pi} \tag{2.14}$$

This last result shows that, for a high enough number n of subpopulations, the mean value of the ξ_{ij} does not depend on the number of subpopulation.

The values of φ_i are chosen so that they are uniformly distributed between $\varphi_{\min} = 0$ and $\varphi_{\max}$. The distribution of ξ_{ij} doesn't depend on n the number of subpopulation, but only depends $\varphi_{\max}$ and may be is characterized by one single parameter (we choose the average value of all ξ_{ij}), view figure 2.1.

3 RESULT

3.1 Influence of the number of subpopulations on the local extinction rate in the coupled model

As shown in Fig 3.1, there is a good agreement between simulations and analytic results for the synchronization and phase lag between subpopulations in the metapopulation. We implemented the simulation for the SEIR metapopulation model of subpopulations coupled by individual movement with time-varying periodic contact rate. The result shows that the local extinction rate of the synchronization is larger than the one of the asynchronization, and the number of subpopulations in the metapopulation strongly affects the local extinction rate.

In order to investigate the dependence among subpopulations, we set the coupling interaction $\rho \neq 0$. Besides, $\varphi_{\max}$ is an important parameter which clearly reflects the difference between subpopulation's phases. With the decreasing of $\varphi_{\max}$, we increase the similarity between sub-populations, but we limit the chances of re-colonizations

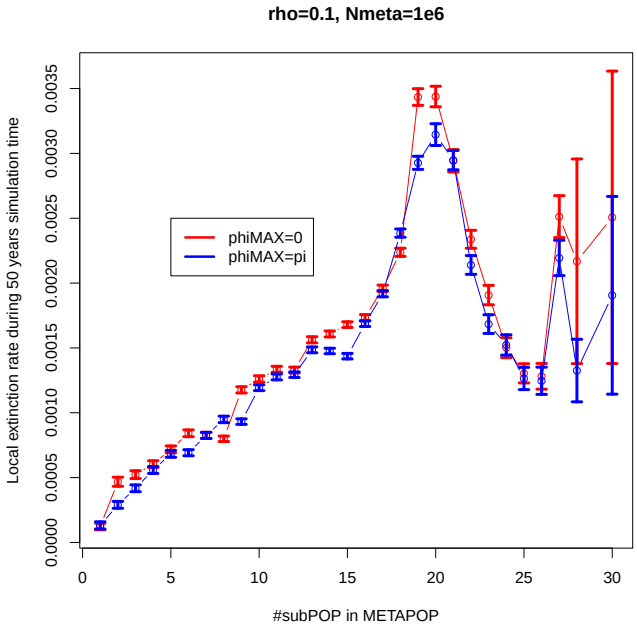

Figure 3.1: Influence of the number of subpopulations on the local extinction rate in the coupled model. The number of subpopulations n from 1 to 30, the coupling rate $\rho = 0.1$, the fixed metapopulation size $N = 1e6$, and $\varphi_{\max} = 0$ or π.

within subpopulations. The reason for this adjustment is that there is more chance that a small number of incidences may occur in nearby subpopulations when the focal subpopulation has reached extinction.

To obtain the synchrony in the metapopulation, we set $\varphi_{\max} = 0$. The subpopulations are grouped into pairs based on their interactions, and particularly their disease phases are in-phase. All the subpopulations are in synchrony. So the ability of rescue effect among subpopulations are small, they simply get extinct. Consequently, the local extinction rate when $\varphi_{\max}$ equal 0 is higher than the rest. On the other hand, the asynchrony is presented by $\varphi_{\max} \neq 0$. The disease phases in the coupled subpopulations are out of phase, the synchrony is interrupted. With $\varphi_{\max} = \pi$, the decreased similarity between sub-populations leads an increase of the chance of recolonization among sub-populations. A sub-population has even reached the local extinction, but the disease comes easily back due to the recolonization among sub-populations. Hence, the local extinction rate in the case $\varphi_{\max} \neq 0$ is lower. Briefly, the local extinction rate of the synchrony is better than that of the asynchrony.

In addition, in order to study the influence of the number of subpopulation on the extinction rate. In our experience, the number of subpopulations is modified from 1 to 30. In the case of Fig 3.1, the local extinction rate significantly increases when subpopulations are asynchronous as well as synchronous. This extinction rate increases with the number of subpopulations. However, it seems that this increase is stagnating after it reaches the peak of extinction, and even it starts decreasing after this peak. To explain this change of these curves, we known that the parameters (the metapopulation size N, the number of subpopulation n and the phase difference $\varphi_{\max}$), are three important factors that make the local extinction curve be divided into 3 parts.

For the first part, the curves are climbed. As, we fixed the values of the metapopulation and $\varphi_{\max}$. Hence, when the number of subpopulation is small (less than 20). For the fixed metapopulation size, the increase of the number of subpopulation from 1 to 20 leads a decrease of the subpopulation size. The size of each subpopulation is reduced, but this reduce is negligible, the number of native individual in any subpopulation is much larger than that of tourists, so we do not regard the effect of the decreased subpopulation size on the extinction rate. It is the reason for why $\varphi_{\max}$ clearly demonstrates its influence on the local extinction of the metapopulation. Thus, we increase the number of subpopulations in the metapopulation, we increase the chance of displacement and recolonization among subpopulations. In addition, for a given $\varphi_{\max}$, the increase of the number of subpopulations makes subpopulations be more similar. The result is that the local extinction rate has the tendency to augment.

On the other hand, when the number of subpopulation is large (larger than 20). With the fixed value $\varphi_{\max}$, the increase of the the number of subpopulation makes the subpopulations have the tendency to resemble. Then, the subpopulations are in phase of disease. It is the reason why in this case the size of subpopulations strongly

affects the local extinction rate. The number of subpopulation is large. The size of each subpopulation is small. According to a sub-population, its size is small, but the sum of the size of the neighbors is large, the number of tourists visiting this subpopulation is high. So when the number of subpopulation is big from 20 to 26, the local extinction rate decreases. In the final part of the curve, when the number of sub-population is too large, then both the sub-populations are in synchrony, and the subpopulation size is very small. Therefore, the local extinction rate increases.

3.2 Influence of the number of subpopulations on the local extinction rate in the island model

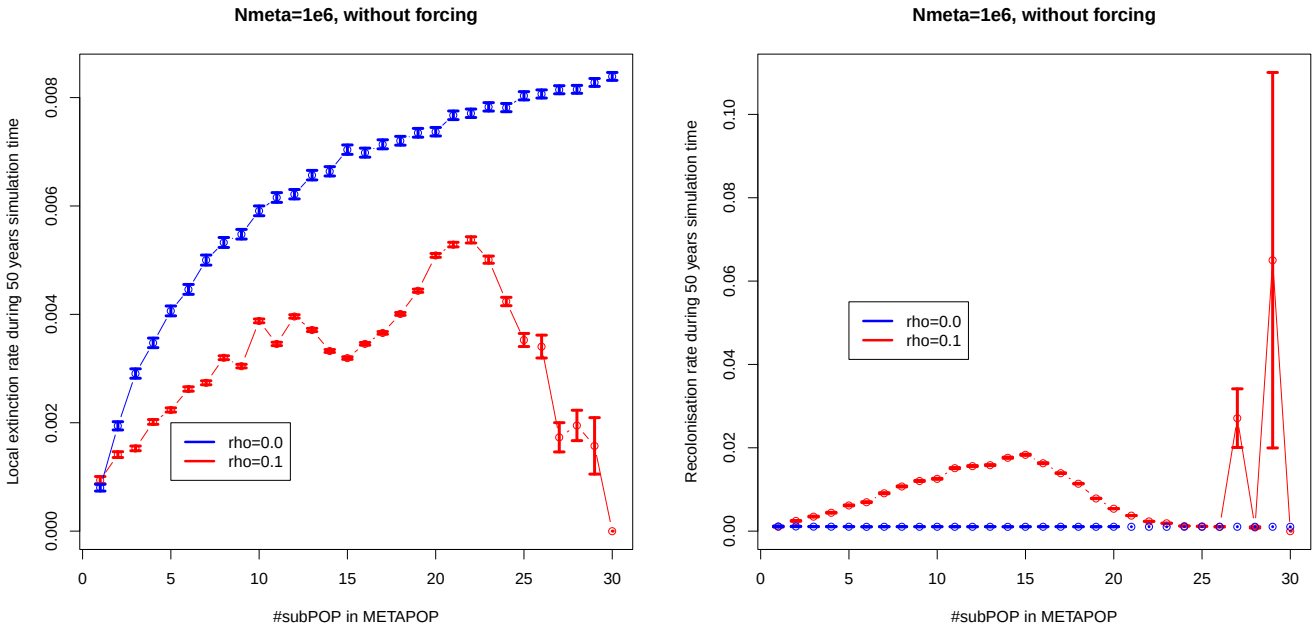

Figure 3.2: Influence of the number of subpopulations on the local extinction rate in the island model

In this experience, we are interested in the influence of the number of subpopulations on the the local extinction rate for the standard SEIR model without forcing. This simple metapopulation model just investigates subpopulations connected by individual movement without environmental transmission. The average number of contacts per unit of time of a susceptible when visiting another subpopulation is fixed as a constant. The strength of connection ρ is set to 0 for the model of isolated subpopulations (island model) and different from 0 for the model of coupled subpopulations (coupling model). Hence, in this case, the main factor affecting the extinction rate is the migration of individuals rather any environmental factor.

The result shown in the Fig 3.2 points out that in the isolation model with the fixed metapopulation size, the increased number of subpopulations leads to a decrease of the subpopulation size. This limits the ability of the rescue effect to ensure locally extinct subpopulations become recolonized. Hence the local extinction rate rises significantly. Besides that, due to the disjunction among subpopulations in the metapopulation, a subpopulation will obtain the global extinction immediately after it get the first local extinction, so any there won't be any recolonization occurs in this island model. The recolonization rate is zero in all cases as shown in the Fig 3.2.

Inverse to the coupled model, the strength of interaction between the two subpopulations have clearly demonstrated its influence on the extinction ability in metapopulation. The curve of the coupled case will be increased notably when the number of subpopulation extends in the range from 1 to 20. As explained in above obtained results of the Fig 3.1, although the number of subpopulation augments but is still small, the number of native individuals in a subpopulation is much larger than the number of tourists in any specific time. Thus, for the fixed metapopulation size, the increased number of subpopulations draws a decline of the subpopulation size. The disease of subpopulation easily get extinct, whenever the local extinction rate augments. However, when the number of subpopulation becomes a large number, then the subpopulation size becomes really small, but the number of neighbours is big. Therefore, the number of native individuals is much smaller than that of tourists, so the tourists

arrive and continue to transmit disease within the subpopulation. Hence, the local extinction rate has a significant decline. As pointed out in the Fig 3.2, the recolonization rate has the same form to the local extinction rate.

3.3 Influence of the coupling strength on the local extinction rate

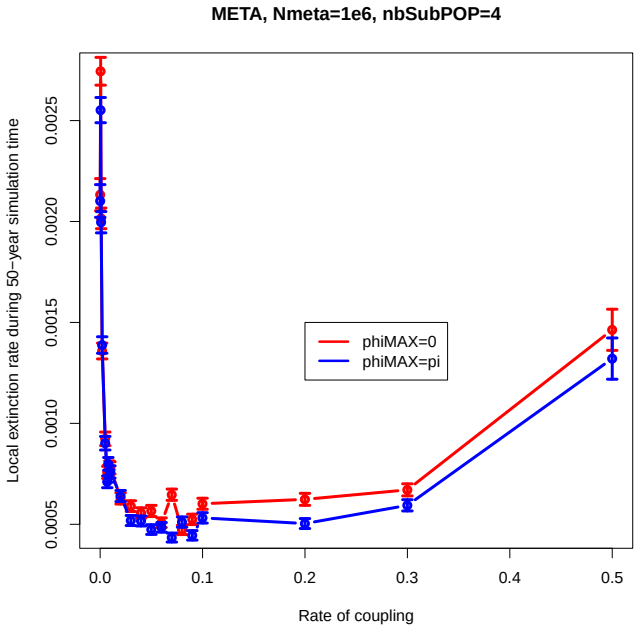

Figure 3.3: Influence of the coupling strength on the local extinction rate of the metapopulation of 4 subpopulations with the metapopulation size $N = 1e6$

One more factor that was pointed in the introduction part is coupling strength between subpopulations. Here, the coupling rate or the dispersal rate ρ can be considered as migration strength. The disease transmission speed grows fast when coupling rate goes up in metapopulations. Similar to that, global disease persistence surges also. In this part, we permit coupling rate change from weak to strong in a metapopulation of five subpopulations with the population size $N = 1e6$ for each subpopulation. The dispersal rate ρ is divided into three intervals. These are low, intermediate and high coupling rate intervals. In each interval, we chose some coupling rates that highlight the coupling strength among subpopulations in a metapopulation. With each value of coupling rate, we estimated local extinction rate that presents the extinction probability of disease in a subpopulation. We have result as following figure Fig 3.3.

When the coupling rate is small from 0.0 to 0.001, the locale extinction rate significantly decreases. However, this rate is minimum when the coupling rate has medium values from0.001 to 0.1. Lastly, the extinction rate augments back when the coupling rate is very strong from 0.1 to 0.5. As shown in the Fig 3.3, the local extinction rate in a metapopulation is one humped function for the coupling rate. The medium coupling rate (from 0.01 to 0.1) minimises the extinction rate of disease in metapopulation. Because in the case of the small and medium coupling rates, the coupling rate and the speed of migration among subpopulations are directly proportional. The dispersal speed increases. Thereby the local recolonization speed rises, the duration of persistence grows, the local extinction rate goes down. However, this trend of local extinction with decreasing coupling rate, is not right any more when the dispersal rate is strong. The metapopulation has tendency to become one big population. In this case, the phase difference or the recolonization among subpopulations are no longer significant. Hence, the local extinction rate rises.

4 DISCUSSION

We successfully have built a version for the susceptible-infected-recovered stochastic metapopulation model (subpopulations connected by individual movement), which describes both movement-based and environmental transmission.

The infection rate λ_i for $subpopulation_i$ has portrayed all effects inside as well as outside of the disease tranmission chain between individuals in the same subpopulation or in other subpopulations. Moreover, our metapopulation model became more detailed when we brought seasonality in metapopulation model to create periodic transmission in year that highlighted seasonal changes as well as school period of children [4, 3, 6, 15]. We have metapopulation model with different contact rates for each subpopulation. This is a more complex model than any used metapopulation model. We have sketched successfully in-phase and sometime out-of-phase ("antiphase") models across suburbs of He's 2003 [11].

This complex metapopulation model is also an expected result of Rozhnova(2012) [21]. It's a good result for scientists wanting to use the SEIR metapopulation model for simulating dynamics of infectious diseases. Our results roughly support those of Rozhnova's 2012. The authors gave different values of the contact rates β of each subpopulation. However, the rates β here are fixed by constants and the number of subpopulations in experiences are maximum of three. Comparing this result with our's, in a coupling metapopulation, the degree of synchorny is maintained when the coupling rate between subpopulations is weak.

Moreover, our stochastic SEIR metapopulation model with subpopulations connected to each other, we have quantified disease extinction of seasonality as well as spatial synchrony. With our model, we can easily create level of seasonality in year and at the same time, phase difference in seasonality between subpopulations. It's the reason why we have model quite close to the metapopulation model in reality.

Due to the phase difference between infection coefficient β, we can change by an increase or a decrease in level of synchrony. We want to decrease level of synchrony, by simply increasing the phase difference between forcing phase coefficients in the formulas of contact rate β. Clearly, the level of synchrony between two subpopulations are the worst when the two fluctuations are in antiphase (as figure 3.1). When the phase difference between oscillations increases, the desynchronizing effect on population dynamics of the subpopulations augments. This declines the ability of disease extinction.

Moreover, as the result above (figure 3.2) and the global extinction rate below (figure 4.1), our results, along with those of Bolker (1995) [3] and Heino (1997) [12], stress the local extinction rate being inversely proportionnel with the global extinction rate in a metapopulation. When the level of synchrony is at a reduction and the global persistence time gets an increase, the global extinction rate of metapopulation goes down and the local extinction rate goes up. Due to the result about local extinction, we also affirm that disease is always available in metapopulation if and only if at least one subpopulaiton is not extinct.

Our finding has specified the two main factors influencing the persistence ability of an infectious disease. One factor is transmission characteristics of the infectious disease and the other is interplay between mixing subpopulations in metapopulation. The interaction between the disease persistence and the spatial heterogeneity becomes a major key to unlock questions about infectious disease in epidemiology. This result takes a large part in epidemic disease persistence domain that has being exploited in scientific epidemically research works. We gained a robust understanding of how disease extinction is affected by local factors such as spatial heterogeneity, demographic asynchrony and seasonality, as well as mixing factors such as migration, disease transmission between hosts and pathogens. Lastly, we also highlighted recolonization effects. It is like rescue for disease. Because of connection between subpopulation, individuals can go everywhere. Subpopulation is quickly re-infected althought the disease has became extinct. Thus, the disease rescus makes local extintions difficult to extend into global extinctions.

As a matter of the fact of coupling strength among subpopulations in metapopulation, we proved that the extinction of the disease in the metapopulation is not only computed by a exponential survival function over time, but also a concave function for the coupling rate. In addition, the disease extinction in metapopulation is minimum when the coupling rate between subpopulations is just medium. This finding is similar to those of Huffaker(1958) [14], Holyoak and Lawler(1996) [13], and Yaari et al. (2012) [23] when they exhaustively explored the disease persistence behavior of many different metapopulation models. And our result one more time affirms that the disease persistence and the interaction in metapopulation models are significant when the interaction strength ρ is from 10^{-3} to 0.1 [16].

To summarize, we have built successfully a sinusoidally forced SEIR stochastic metapopulation model. This model is like a physical system of coupled oscillators. We have pointed out that spatial synchronization consistently and predictably makes extinction risk increase by using the model 0 where all the subpopulations have the same population size N and there is no explicit spatial distance. So, it's good for the future, we can continue this work with different population size of each subpopulation and different spatial distance between subpopulations and then, create synchronous metapopulations that optimize vaccination policies.

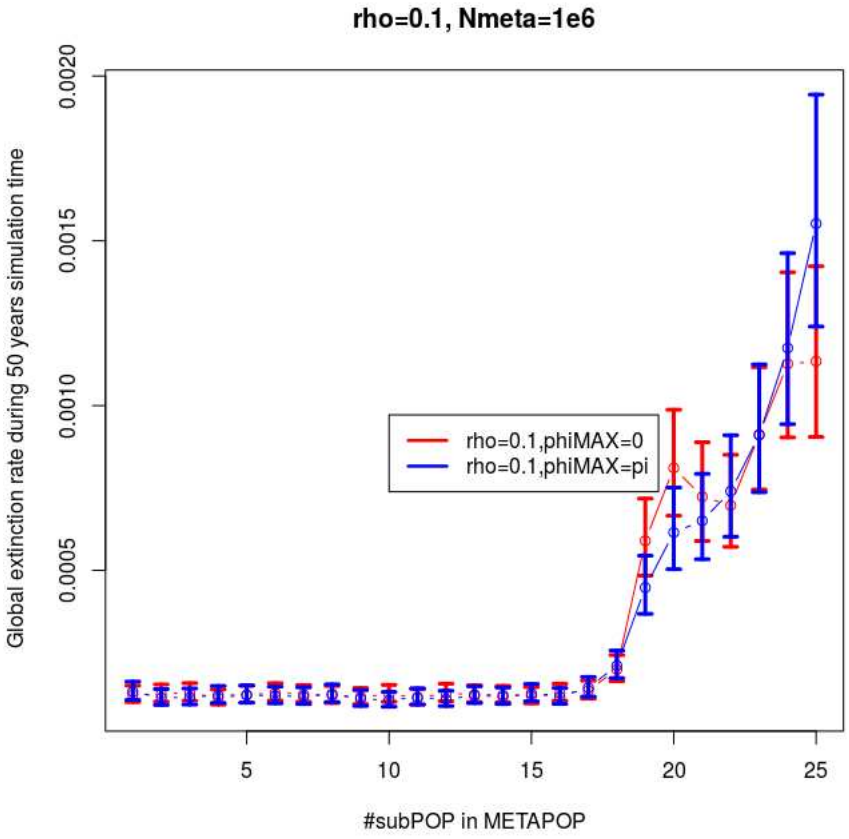

Figure 4.1: Quantifing the global extinction rate in the metapopulation. The number of subpopulation n from 1 to 25, the metapopulation size $N = 1e6$ and the coupling rate $\rho = 0.1$. As this result, the global extinction rate of the synchrony with $\varphi_{\max} = 0$ has the tendance to be larger than that of the asynchrony with $\varphi_{\max} = \pi$. Besides, when the number of subpopulation slowly increases from 1 to 15, the subpopulation size has a decrease, but this decrease is very small, the subpopulation size is still very big. Hence, the red curve of the synchrony and the blue curve of the asynchrony have a quite near resemblance. Inversely, the global extinction rate strongly augments when the number of subpopulation is quite big from 20. The increased number of subpopulation leads to strongly decline the subpopulation size. This drives quite the decrease global persitence time of the metapopualtion, so the mass extinction rate of the metapopulation increases significantly.

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5 Appendix : equilibrium values of the system 2.1–2.4

We start with ordinary differential equations for a *subpopulation*$_i$ in a metapopulation as follows:

$$\frac{dS_i}{dt} = \mu N_i - \lambda_i S_i - \mu S_i \tag{5.1}$$
$$\frac{dE_i}{dt} = \lambda_i S_i - \mu E_i - \sigma E_i \tag{5.2}$$
$$\frac{dI_i}{dt} = \sigma E_i - \mu I_i - \gamma I_i \tag{5.3}$$
$$\frac{dR_i}{dt} = \gamma I_i - \mu R_i \tag{5.4}$$

In simulation, we know that the equilibrium state allow a disease to persist in a population for a long time. So, an infectious disease in the *subpopulation*$_i$ is available in long term this system is at equilibrium. It means that at which $\frac{dS_i}{dt} = \frac{dE_i}{dt} = \frac{dI_i}{dt} = \frac{dR_i}{dt} = 0$ (*). Thus, we let all equations (equations 15 - 18) in the system be equal to zero, then calculate the values of the variables (now denoted by S_i^*, E_i^*, I_i^* , and R_i^*) that satisfy this condition (*). We have these values as folllows:

$$S_i^* = N_i \frac{(\gamma+\mu)(\sigma+\mu)}{\beta\sigma} \tag{5.5}$$
$$E_i^* = N_i\mu\left(\frac{1}{\sigma+\mu} - \frac{\gamma+\mu}{\beta\sigma}\right) \tag{5.6}$$
$$I_i^* = N_i\mu\frac{\beta\sigma - (\sigma+\mu)(\gamma+\mu)}{\beta(\sigma+\mu)(\gamma+\mu)} \tag{5.7}$$
$$R_i^* = N_i - S_i^* - E_i^* - I_i^* \tag{5.8}$$

Here, if we set $R_0 = \frac{\beta\sigma}{(\gamma+\mu)(\sigma+\mu)}$, so we have

$$S_i^* = N_i\frac{1}{R_0} \tag{5.9}$$
$$E_i^* = N_i\frac{\mu\sigma}{R_0}(R_0-1) \tag{5.10}$$
$$I_i^* = N_i\frac{\mu}{\beta}(R_0-1) \tag{5.11}$$
$$R_i^* = N_i - S_i^* - E_i^* - I_i^* \tag{5.12}$$

One nomal conditions for all population availabes is that the equilibrium values cannot be negative. Therefore, an infectious disease is available in the *subpopulation*$_i$ if $R_0 > 1$. Now, the endemic equilibrium in the system is given by $(S_i^*, E_i^*, I_i^*, R_i^*) = (N_i\frac{1}{R_0}, N_i\frac{\mu\sigma}{R_0}(R_0-1), N_i\frac{\mu}{\beta}(R_0-1), N_i(1-\frac{1}{R_0}-\frac{\mu\sigma}{R_0}(R_0-1)-\frac{\mu}{\beta}(R_0-1))$.

6 Appendix: derivation of the equation 2.5

Here, we will point out that the contact rate β is a function of the average contact number per unit of time and the probability of successful disease transmission following a contact.

Definition 1. During the small time interval δt, each individual native of the city i visits one single city j (with the probability ρ_{ij}) and will see in average κ_j individuals. These individuals come from all the cities.

6.1 Notation :

Here, we present list of sets and events describing the state of the system at time t :

- C_i is the set of all individuals born in subpopulation i.

- $V_{i,t}$ is the set of all individuals physically located in subpopulation i from time t to time $t+\delta t$. This includes foreigners traveling in subpopulation i at time t, and all natives from subpopulation i which are not traveling abroad at time t.
- S_t, E_t, I_t, R_t are the sets of all individuals respectively susceptible, exposed, infected and recovered at time t. Note that these set include individuals from all subpopulations.
- $S_{i,t}, E_{i,t}, I_{i,t}, R_{i,t}$ are the same sets, restricted to natives of subpopulation i. So formally, $S_{i,t} = S_t \cap C_i$, $E_{i,t} = E_t \cap C_i$, $I_{i,t} = I_t \cap C_i$, and $R_{i,t} = R_t \cap C_i$.
- $Transmit(y, x)$ is an event indicating that individual x gets infected by individual y which was already infected
- $c_{i,k}$ is the probability that a susceptible individual native from i being in contact with another infected individual native from k gets infected.
- κ_j is the average number of contacts per unit of time a susceptible will have when visiting city j.
- ξ_{jk} refers to the probability that an individual y meeting x in C_j comes from C_k.
- $\rho_{i,j}$, the probability that an individual from subpopulation i visits subpopulation j. Of course, $\sum_{j=1}^{M} \rho_{ij} = 1$.

Proposition 2. *The coefficient κ should also depend on i, because an individual native from city i meets more people in his own city than abroad ($\kappa_{i,i} > \kappa_{i,j}$).*

6.2 The background

One general question is always posed "how does the population of exposed individuals of subpopulation i evolve ?". For the sake of simplicity, in the process of transmission of the SEIR model, we focus on the incidence and we assume for now that the latent period and the recovery rate, repectively $\mu = \sigma = 0$. Thus, we write a probabilistic formulation of $\frac{dE_i}{dt}$. Assuming the time is discrete, we have $\frac{dE_i}{dt} \approx \mathbb{E}\left[E_{i,t+1} \setminus E_{i,t}\right]$. Then,

$$\begin{aligned}
\mathbb{E}\left[E_{i,t+1} \setminus E_{i,t}\right] &= \mathbb{E}\left[E_{i,t+1} \cap S_{i,t}\right] \\
&= \sum_{x \in C_i} Pr\left[x \in E_{t+1} \wedge x \in S_t\right] \\
&= \sum_{x \in C_i} Pr\left[x \in S_t\right] * Pr\left[x \in E_{t+1} \mid x \in S_t\right] \\
&= Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+1} \mid x \in S_t\right] * \sum_{x \in C_i} Pr\left[x \in S_t\right] \\
&= |S_{i,t}| \times Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+1} \mid x \in S_t\right]
\end{aligned}$$

Assume there are M cities. An individual x of the subpopulation i may be visiting another subpopulation, or staying in its own subpopulation. Applying the law of total probabilities, we get:

$$\begin{aligned}
Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+dt} \mid x \in S_t\right] &= \sum_{j=1}^{M} Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+dt} \wedge x \in V_{j,t} \mid x \in S_t\right] \\
&= \sum_{j=1}^{M} Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+dt} \mid x \in S_t \wedge x \in V_{j,t}\right] . Pr_{x \sim \mathcal{X}_i}\left[x \in V_{j,t}\right] \\
&\quad \sum_{j=1}^{M} Pr_{x \sim \mathcal{X}_i}\left[x \in E_{t+dt} \mid x \in S_t \wedge x \in V_{j,t}\right] \times \rho_{ij}
\end{aligned}$$

Where $\rho_{i,j} = Pr_{x \sim \mathcal{X}_i}\left[x \in V_{j,t}\right]$, the probability that an individual from subpopulation i visits subpopulation j. Of course, $\sum_{j=1}^{M} \rho_{ij} = 1$.

6.3 Study of case where agent x native from city i visits city j

Here, we look at the probability that a susceptible $x \sim \mathcal{X}_i$ visiting j gets infected or not after δt time steps. Let $\mathcal{Y}$ be the uniform distribution over $V_{j,t}$. The correct mathematical approach for this would be to assume that for each city k, the number of people native from k that we meet during δt follows a Poisson process. So both the number of people we meet and the number of infected people we meet during δt should be random variables.

In the approach described in [16], the authors did not do this. They assumed that both the number of people we meet and the number of infected people we meet *are fixed* (otherwise the maths they write would have been different). We will call this the "Keeling & Rohani" interpretation that we will present it in the following parts.

We introduce an alternative approximation, where we assume that the number κ of people we meet during δt is *fixed*, but each of these people has *some probability* to be infected. This is an *in-between interpretation*, easier than the Poisson process maths, but better than Keeling&Rohani's one. We will call this the "Yann-Giang" interpretation.

6.3.1 The "Yann-Giang" interpretation

Proposition 3. *Agent x meets* exactly κ_j *other individuals, and each of these individuals has a probability $\frac{|I_{k,t}|}{N_k}$ of being infected, where k is its native city. Let $y_1 \dots y_{\kappa_j}$ be the individuals that x meets. We get:*

$$\begin{aligned} & Pr_{x\sim\mathcal{X}_i}\left[x \in S_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \\ = \; & Pr_{x\sim\mathcal{X}_i, y_1\dots,y_{\kappa_j}\sim\mathcal{Y}}\left[\bigwedge_{p=1}^{\kappa_j} \neg\left(y_p \in I_t \wedge Transmit(y_p, x)\right) \mid x \in S_t \wedge x \in V_{j,t}\right] \end{aligned}$$

So we have:

$$\begin{aligned} & Pr_{x\sim\mathcal{X}_i}\left[x \in S_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \\ = \; & Pr_{x\sim\mathcal{X}_i, y\sim\mathcal{Y}}\left[\neg\left(y \in I_t \wedge Transmit(y, x)\right) \mid x \in S_t \wedge x \in V_{j,t}\right]^{\kappa_j \delta t} \end{aligned}$$

Moreover, we have:

- the probability so that a susceptible individual x is infected by an infected individual y :

$$\begin{aligned} & Pr_{x\sim\mathcal{X}_i, y\sim\mathcal{Y}}\left[y \in I_t \wedge Transmit(y, x) \mid x \in S_t \wedge x \in V_{j,t}\right] \\ = \; & \sum_{k=1}^{M} Pr_{x\sim\mathcal{X}_i, y\sim\mathcal{Y}}\left[y \in I_t \wedge Transmit(y, x) \mid x \in S_t \wedge x \in V_{j,t} \wedge y \in C_k\right] . Pr_{y\sim\mathcal{Y}}\left(y \in C_k\right) \\ = \; & \sum_{k=1}^{M} \{Pr_{x\sim\mathcal{X}_i, y\sim\mathcal{X}_k}\left[y \in I_t \mid x \in S_t \wedge x \in V_{j,t}\right] \\ & \quad \times Pr_{x\sim\mathcal{X}_i, y\sim\mathcal{X}_k}\left[Transmit(y, x) \mid y \in I_t \wedge x \in S_t \wedge x \in V_{j,t} \wedge y \in C_k\right] \times Pr_{y\sim\mathcal{Y}}\left(y \in C_k\right)\} \\ = \; & \sum_{k=1}^{M} \left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right) \end{aligned}$$

$\xi_{jk} = \frac{N_k \rho_{kj}}{\sum_{v=1}^{M} N_v \rho_{vj}}$ refers to the probability that an individual y meeting x in C_j comes from C_k.

- hence, the probability so that a susceptible individual x is not infected by an infected individual y :

$$1 - \sum_{k=1}^{M} \left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)$$

- thereby, the probability so that a susceptible individual x is not infected after κ_j contacts per unit time δt.

$$\left[1 - \sum_{k=1}^{M} \left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]^{\kappa_j \delta t}$$

- thus, the probability so that a susceptible individual x becomes infected after κ_j contacts per unit time δt.

$$Pr_{x\sim\mathcal{X}_i}\left[x \in E_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \quad = \quad \left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]^{\kappa_j \delta t}$$

We now apply the *log* approximation which consists in approximating $1-(1-u)^v$ by $v\log(1-u)$:

$$Pr_{x\sim\mathcal{X}_i}\left[x \in E_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \quad = \quad -\kappa_j \delta t \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]$$

So, the transmission rate per susceptible individual is as follows :

$$\frac{dPr_{x\sim\mathcal{X}_i}\left[x \in E_{t+dt} \mid x \in S_t \wedge x \in V_{j,t}\right]}{dt} \simeq -\kappa_j \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]$$

In fact, we use the parameter λ to present this quantity, and it is denoted as the "force of infection" :

$$\lambda_i = \sum_j \rho_{ij}\kappa_j \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]$$

If there is only one city i, then

$$\lambda_i = \kappa_j log(1 - \frac{|I_i|}{N_i} \times c_{ii})$$

6.3.2 "Keeling & Rohani" Interpretation

Proposition 4. *Agent x meets* exactly $\kappa_j \delta t \xi_{jk} \frac{|I_{k,t}|}{N_k}$ *other infected individuals native from city k.*
Let $l_k = \kappa_j \delta t \xi_{jk} \frac{|I_{k,t}|}{N_k}$.
Let $y_1^k \ldots y_{l_k}^k$ be the infected individuals native from k that our individual x meets between t and $t+\delta t$.

We have the probability so that a susceptible individual x is not infected after having seen l_k individuals between t and $t+\delta t$:

$$\begin{aligned}
& Pr_{x\sim\mathcal{X}_i}\left[x \in S_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \\
= \quad & Pr_{x\sim\mathcal{X}_i}\left[\bigwedge_{\substack{k=1\ldots M \\ p=1\ldots l_k}} \neg\left(Transmit(y_p^k, x)\right) \mid x \in S_t \wedge x \in V_{j,t}\right] \\
= \quad & \prod_{k=1}^{M} Pr_{x\sim\mathcal{X}_i}\left[\bigwedge_{p=1\ldots l_k} \neg\left(Transmit(y_p^k, x)\right) \mid x \in S_t \wedge x \in V_{j,t}\right] \\
= \quad & \prod_{k=1}^{M} (1 - c_{ik})^{\kappa_j \delta t \xi_{jk} \frac{|I_{k,t}|}{N_k}}
\end{aligned}$$

Then, we plug this back into the previous formula, and we get:

$$Pr_{x\sim\mathcal{X}_i}\left[x \in E_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \quad = \quad 1 - \prod_{k=1}^{M} (1 - c_{ik})^{\kappa_j \xi_{jk} \frac{|I_{k,t}|}{N_k} \delta t}$$

The first order approximation of $1 - \prod_{k=1}^{M}(1-c_{ik})^{v_k}$ is $\sum_{k=1}^{M} -v_k \log(1-c_{ik})$. Applying this approximation here, we get:

$$Pr_{x\sim\mathcal{X}_i}\left[x \in E_{t+\delta t} \mid x \in S_t \wedge x \in V_{j,t}\right] \quad \simeq \quad \delta t \sum_{k=1}^{M}\left(-\kappa_j \xi_{jk} \frac{|I_{k,t}|}{N_k} \log\left(1-c_{ik}\right)\right)$$

Define $\beta_{ijk} = -\kappa_j \log\left(1-c_{ik}\right)$, let δt converge to zero, and we get:

$$\frac{dPr_{x\sim\mathcal{X}_i}\left[x \in E_{t+dt} \mid x \in S_t \wedge x \in V_{j,t}\right]}{dt} \simeq \sum_{k=1}^{M}\left(\xi_{jk}\frac{|I_{k,t}|}{N_k}\beta_{ijk}\right)$$

If there is only one city i, then we fall back to the formula of [16]. We have :

$$\beta_i = -\kappa_i \log\left(1-c_i\right)$$

$$\frac{d}{dt}\mathbb{E}\left[|E_{i,t+dt} - E_{i,t}|\right] \simeq -\left|S_{i,t}\right|\left(\frac{|I_i|}{N_i}\beta_i\right)$$

and the force of infection as follows :

$$\lambda_i = \beta_i \frac{|I_i|}{N_i}$$

6.4 Final Formula

We simply have to plug in the probability ρ_{ij} that i visits j.

We get, for the "Yann-Giang" interpretation :

$$\frac{d}{dt}\mathbb{E}\left[|E_{i,t+dt} - E_{i,t}|\right] \simeq -\left|S_{i,t}\right| \sum_j \rho_{ij}\kappa_j \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right]$$

And for the "Keeling & Rohani" Interpretation :

$$\frac{d}{dt}\mathbb{E}\left[|E_{i,t+dt} - E_{i,t}|\right] \simeq -\left|S_{i,t}\right| \sum_j \rho_{ij} \sum_{k=1}^{M}\left(\xi_{jk}\frac{|I_{k,t}|}{N_k}\beta_{ijk}\right)$$

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