MODÉLISATION, SIMULATION MULTI-NIVEAU POUR L'OPTIMISATION DE POLITIQUES DE VACCINATION

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1. State of the art:

1.1. Epidemiology (and monitoring).

1.1.1. *Epidemiology.* As we know that public health problems are one of the emerging troubles in the entire world. They directly influence human heath, the health of one person, the health of a community. In particular, any news about infectious diseases for children has always been a subject of concern to parents as well as everyone. Hence, in the world, a discipline "epidemiology" has risen to study the factors, causes, and effects of infectious diseases.

This thesis is proposed in a context in which many public health serious events have occurred in the world : SRAS in 2003, avian influenza in 2004 or swine flu in 2009, etc. In particular, at the start of 2014, the World Health Organization (WHO) officially stated global measles epidemic outbreak. In the first three months of the year 2014, there were about 56,000 cases of measle infections in 75 countries [**?**], particularly in southeast Asia and in Vietnam [**?**]. This has pointed out the important role of the epidemiological phenomena anticipation when diseases occur. Many studies proposed by the WHO, the Pasteur Institute and the Inserm in the field of "environmental security" try to understand disease phenomena and spread of disease over a territory, to better manage when diseases occur. These researches consist of mathematical or statistical studies via surveillance networks [**?**]. This is one of the axes of the UMMISCO laboratory's research themes (IRD UMI 209).

1.1.2. *Control.* Pathogenic microorganisms such as bacteria, viruses, parasites or fungi are key factors causing infectious diseases. The diseases can be spread directly or indirectly from one person to another, through a mediate environment or contaminated tools. As far as directly infectious diseases are concerned, meaninf diseases directly transmitted from one person to another, we have some normal policies to prevent the spread of diseases such as vaccines, anti-viral medications, and quarantine. In this thesis, we focus on vaccines in the human community. A vaccine is understood as a biological preparation that provides active acquired immunity to a particular disease for our body. After having been vaccinated, we transport microorganisms in weakened or killed form of the microbe into our body. The body's immune system produces the right antibodies to recognize the germs as a threat, destroy them and keep a record of them. Because of that, when the disease occurs, our immune system can recognize and destroy with a better chance of success any of these germs that it later encounters. The administration of vaccines is called vaccination. Vaccination has greatly helped human beings. The vaccination of influenza, Human Papillomavirus (HPV) and chicken pox have been particularly appreciated. Smallpox is a particular example. This disease was filled people with terror during the closing years of the 18th century. Smallpox killed an estimated 400,000 Europeans annually and among the people that luckily survived, a third had been blinded by the disease. However, the World Health Organization (WHO) offcially stated the eradication of smallpox in 2011 [**?**, **?**, **?**]. In addition, many infectious diseases are clearly restricted such as influenza, polio, measles and tetanus from much of the world. Thus, one big question proposed is why many infectious diseases still exist in the world though we have produced vaccines for most infectious diseases. In order to answer this question, first of all, we have to answer to some following small questions :

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Question	Answer	Why?
Are vaccines safe?	YES	Vaccines are generally quite safe
Are there vaccines for all infectious?	NO	For example: dengue
Are all vaccines free?	NO	Funding problem
Are all people vaccinated before a requested age for each disease?	NO	Funding/geographic/cultural problems

Table 1. Vaccine state

With the four answers above, we can say that the human still faces up to infectious diseases. A thorough knowledge of the disease is essential in order to implement large-scale proper infection control measures and prevention campaigns. Granted that the disease transmission methods depend on the characteristics of each disease and the nature of the microorganism that causes it. In this thesis, we will investigate popular infectious diseases with transmission by direct contact. This transmission requires a close contact between an infected person and a susceptible person, such as touching an infected individual, kissing, sexual contact with oral saliva, or contact with body lesions. Therefore, these diseases usually occur between members of the same household or close friends and family. In particular, this thesis will mostly focus on measles. Because measles is a highly contagious, serious disease caused by a virus. It is a typical infectiuous disease with direct transmission. In 1980, approximate 2.6 milion people was killed each year before we had the widespread vaccination policies. It spreads very fast by coughing and sneezing in human communities via close interpersonal contact or direct contact with secretions. Its main symptoms consist of high fever, cough, runny nose and red eyes. These first symptoms usually take from 10 to 12 days after exposure to an infectious person, and lasts 4 to 7 days [**?**]. In fact, now there is no proper treatment for measles to totally prevent the spread of measles except routine measles vaccination policy for children. According to the report by the World Health Organization (WHO), since 2002 measles was eradicated from U.S. However, today measles vaccination has not been extensively popularized in the entire world. Beside the obtained results, for example, in 2013, there was about 84% of the world's children having received one dose of measles vaccine, and during 2000-2013, measles vaccination prevented an estimated 15.6 million deaths; we have had to face upabout 145700 measles deaths globally- estimated 400 deaths every day or 16 deaths every hour in 2013. Measles becomes one of the leading causes of death among young children in the world, although now we are having a big stock of safe and readily available measles vaccines.

Mass policy (or the routine measles vaccination policy for measlses) that vaccinates the maximum number of children before a certain age, is the oldest (started from the 1950s in the rich countries) and is now the most used. The policy has obtained clear results : a clear decrease of the incidence in most countries. However, the problem of this vaccination policy is too expensive, really ineffective and quite impossible to implement in poor countries, especially in Africa because of both financial and logistical problems. (e.g. the WHO project "Extended Program on Immunization" in Vietnam for the measles extinction before 2012 failed [**?**]). In addition, when a vaccination policy is performed in a country, there is only one policy deployed, but in modeling, we can realize many policies and assess their results.

In short, measles is still a common and often fatal disease in the world. We still very much need to model the transmission dynamics of measles and investigate the effect of vaccination on the spread of measles in the entire world. More largely, we need to give new optimal vaccination policies in artificial intelligence in order that these policies may become more effective, less expensive, and take into account the spatial dimension for all popular infectious diseases.

1.2. **dynamiques/structures spatiales (théorie métapopulations, réseaux, etc. . .)**

- For directly transmitted infectious diseases by virus and bacteria, susceptible individuals are not only infected by infected individuals in the same location, but also by other infected individuals due to the movement of individuals between populated regions. This is one very important part in the domain studying the geographical spread of infectious diseases. We care for host population characteristics, then characteristics of spatial spread of an infectious disease among populations. Through these characteristics, we find optimal policies to minimize the number of infected individuals in a community. In fact, there are many studies about the interactions among populations. However, we can divide the spatial structure of populations into two main levels: "inter-city level" and "intra-city level". At the inter-city level (or called "micro-level"), we use differential equations to control its models. At the "intra-city level" (also called "macro-level") in which we provide connections between the populations, simulate the intra-city traffic. We consider the effect of travel through the connections between population regions as a means of spreading a virus [**?**].
- We have two basic models considered in the "macro-level", the model has no explicit movement of individuals and the models describes enough travels and movements of individuals among populations and even takes into account the resident population as well as the current population of individuals [**?**]. A population may be simplified as a city, community, or some other geographical region. Population travel (e.g. among animals and among people by foot, birds, mosquitoes and in particular, people travel by air from one city to another), is the main reason why diseases can spread quickly among very distant cities such as SARS disease in 2003. Therefore, the term "metapopulation" arrived in the ecological literature in 1969 by Levins [**?**, **?**]. A metapopulation is a population of a set of spatially discrete local populations (or subpopulations in short) with mutual interaction [**?**]. In the metapopulation in which a subpopulation can only go extinct locally and be recolonized by another after it is emptied by extinction [**?**, **?**, **?**] and migration between subpopulaitons is

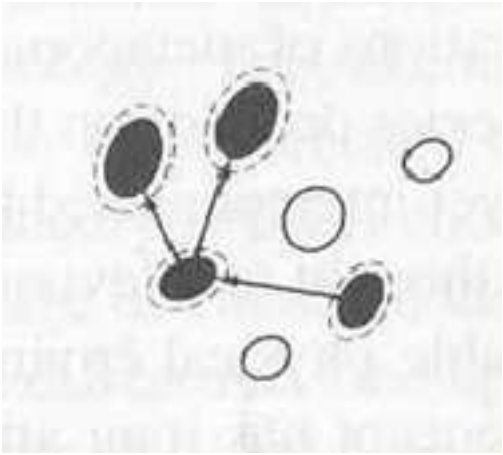

FIGURE 1.1. Classic Levins Metapopulation Model [?]

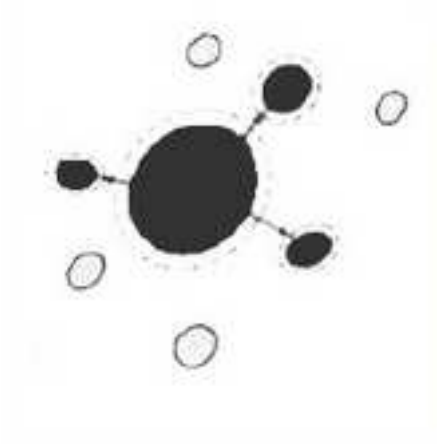

FIGURE 1.2. Mainland-Island Metapopulation [?]

significantly restricted. In a metapopulation, if recolonization rates are smaller than extinction rates, then total extinction of all local population will easily be reached. The persistence time of the metapopulation is measured as the time until all subpopulations go extinct. According to Harrison (1991) [?] there are four types of spatially dynamic populations : classic Levins metapopulation, mainland-island metapopualtion, patchy population and non-equilibrium populations.

- The first metapopulation model was proposed in 1969 by Levins. It is called the classic Levins Metapopulation [?]. Wilson in 1980 [?] stated that in this classic model "A nexus of patches, each patch winking into life as a population colonizes it, and winking out again as extinction occurs."
  All subpopulations in this classic model are relatively small. The levels of interaction among individuals within a subpopulation is much higher than between subpopulations.
- The second model is the mainland-island metapopulation in which there are some small "island" subpopulations within dispersal distance of a much larger "mainland" subpopulation.
  It is evident that smaller subpopulations have a high probability of local extinction, but the mainland population will hardly become extinct. The migration from the mainland to the islands is independent of the islands white or filled, but is propagated for the connected islands. Therefore, if the mainland population has a low individual density and there is no immigration, then population growth rate is positive. Inversely, if island populations are in the same conditions as the mainland, then its population growth rate is negative. Thus, the islands would go down to extinction if there are no imemigrants.
- The third model is patchy population. The local populations exist in a big habitat population and the dispersal rate between subpopulations is high.

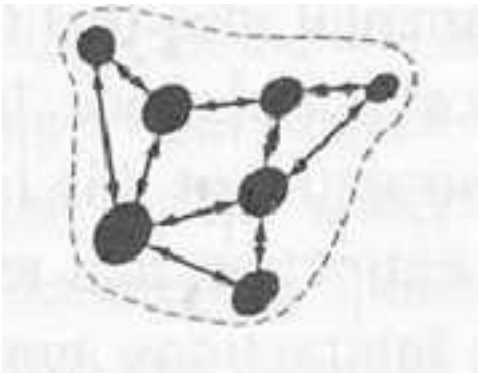

FIGURE 1.3. Patchy population [?]

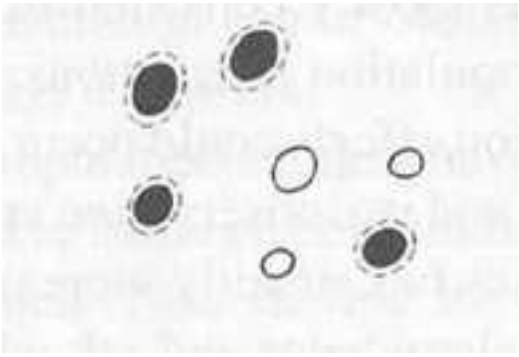

FIGURE 1.4. Non-equilibrium population [?]

Here we can find that the population structure is grouped and the interaction among them is frequent. However, this model is not referred as a concept for metapopulation and most researchers do not consider this a meta-population either.

– The final model is the non-equilibrium population. The local populations are patches, its local extinctions are much greater than its recolonisation.
It is obvious that white patches are rarely or never recolonized. Therefore, this model is not considered as a functional metapopulation. We can find this model in forested agricultural fields.

We already have four metapopulation models. In order to model the metapopulations mentioned above, we have three main model to implement : spatially-implicit model, spatially-explicit model and spatially-realistic model. For the first model, this is the type of model used in Levins (1969) [?] in which supposing that all local populations are connected with each other and they have independent local fluctuations. At any one time, we save track of the proportion of local populations and we do not take care the distance between them and the population size of each subpopulation. This model are mathematically and conceptually easy to implement. But this model can only answer some metapopulation problems because it ignores so many variables of a metapopulation. This model should be used for metapopulation close to a steady state.

For the second model, the spatially-explicit model is more complex than the first model. Subpopulations may be filled or vacant. Local populations only have interactions with the nearest neighbors. Subpopulations are organized as cells on a grid and migration among them depends on population density. We also only consider presence or absence of a species in each subpopulation. The advantage of this model is easy to model because of same local behaviors from subpopulation to subpopulation. However, we cannot simply describe the state of the metapopulation through filled subpopulations. Finally, the spatially-realistic model uses GIS to realize attributes, geometric coordinates, etc ... to a metapopulation. The first author using this model is Hanski in 1994 [?]. His model was defined as the incidence function (IF) model. This model is more realistic, and we can estimate quantitative predictions about metapopulation fluctuation. However, in fact, this model is very complicated, and many geographic data have to be estimated. Hence, the metapopulation concept start to no longer exist.

In the scope of this thesis, we focus on a metapopulation model that is result of combination between the spatially-explicit model and the patchy population. In general, this a simple spatial model, but is one of the most

applicable model to descrire spread of diseases in human communities. This metapopulation consists of distinct "subpopulation, each of which fluctuates independently, together with interaction limited by a coupling parameter ρ. These subpopulations may be filled or empty and contact with any neighbours.

1.3. **Epidemiologic models.** It is known that, there are many current models that are used to model complex systems in nature, in ecology system and in epidemiology. Mathematical models in epidemiology are a typical exemple. These models permit us to present behavior of diseases and disease process in mathematics. However, explaining the transmission of infectious diseases is a difficult problem for an epidemiologist. Because there are many different interacting factors causing the outbreak of diseases such as the environment, the climate, the geography, the culture,...Hence, the role of the epidemiologist is how to model the characteristics and the transmission process of an infectious disease. Researchers have proposed compartmental models in epidemiology by dividing the population into "compartments" that illustrate health states of human through individuals. These compartmental models are called the epidemic models too. The first benefit of these models is to model the transmission process of a communicable disease through compartments. Then, we can predict the properties of the disease dynamics such as the estimated number of infected individual, the time of persistence of disease, further that where and when we can implement vaccination policies to have both a minimum number of vaccined individuals and the minimum number of infected individuals in a given population. Let image that now in your country, there is an infectious disease as measles, a baby can be infected. According to the process of infection of disease, firstly this baby was born, he is fine and he is not infected yet by the measles but he may be infected in the future. We say that he belongs to the susceptible group (in short, S). Then, his mother takes him to a supermaket, there he see so many people, he is really infected through any way. He starts having a high fever, he may have to pass this state from 3 days to 5 days. In this period, he is really infected but he cannot infecte others. We say that he belong to the exposed group (in short, E). After that, he start decreasing the temperature, but at the same time, he begins having red rashs on the back of the ears, after a few hours, on the head, on the neck and finally most of the body. This period appears from five to eight days after the exposed step. This duration is very sensible. The baby is completely infected and he can infecte others if they see him. He belongs to the infected group (in short, I). Finally, he passes to the final period, he comes back good state. We say that he belongs to the recovered group with immunity (in short, R).

Around these four main health groups presenting the process of infection propagation in community, there are many epidemic models proposed. We give here the development of epidemic models by focusing on acute infections, assuming the pathogen causes illness for a periods of time followed by (typically lifelong) immunity. The first simplest model is the S-I-R model created by W. O. Kermack and A. G. McKendrick in 1927. The authors categorized hosts within groups as described above **S**usceptible (if not yet exposed to the pathogen), **I**nfected (if currenly infected by the pathogen) and **R**ecovered (if they have successfully cleared the infection). From the simplest SIR model, in order to accord each infectious disease and real property of disease, scientists have modified it, made it different multiforme. However, in shape of this thesis, we concentrate on the SEIR model (as the figure 1.5) that fit many currently infectious diseases in the world. Each patient must pass four health steps : susceptible stage, incubation stage, infectious stage and recovered stage.

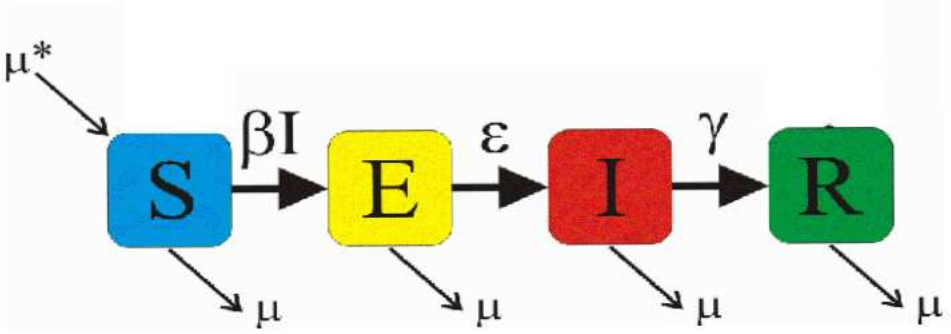

FIGURE 1.5. SEIR model

In this model, the host population (N) is divided into four classes : susceptible S(t), exposed E(t), infected I(t) and recovered R(t). We have :
$N(t) = S(t) + E(t) + I(t) + R(t)$

- Classe S(t) : contains the number of individuals not yet with the disease at time t, or those susceptible to the disease.
- Classe E(t) : contains the number of individuals who are in the exposed or latent period of the disease.
- Classe I(t) : contains the number of individuals who have been infected with the disease and are capable of spreading the disease to those in the susceptible category.
- Classe R(t) : contains the number of individuals who have been infected and then removed from the disease, either due to immunization or due to death. Individuals of this classe are not able to be infected again or to transmit the disease infection to others.

The conceptual descriptions of the model can be represented by a flow diagram above. The flow diagram for the SEIR model uses arrows to present the movement between the S and I classes, the E and I classes and the I and R classses. Here, individuals are born susceptible, die at a rate μ, become infected with the force of infection λ that is a function among the contact rate β, the number of infected invidual I and the population size N, infectious after a latency period of an average duration of $1/\sigma$ and recover at the rate γ.

The SEIR model is investigated by ordinary differential equations (ODE) that are deterministic [**?**]. The value of variable states is only determined by parameters in the model and by sets of previous states of these variables. Moreover, the epidemic models are often proposed for one single population [**?**]. In the scope of this thesis, we propose a deterministic model for many subpopulations in a metapopulation. The standard SEIR model (susceptible-exposed-infective-recovered) has been strongly developed for the dynamics of directly infectious disease [**?**]. 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 [**?**]:

$$\frac{dS_i}{dt} = \mu N_i - \lambda_i S_i - \mu S_i \tag{1.1}$$

$$\frac{dE_i}{dt} = \lambda_i S_i - \mu E_i - \sigma E_i \tag{1.2}$$

$$\frac{dI_i}{dt} = \sigma E_i - \mu I_i - \gamma I_i \tag{1.3}$$

$$\frac{dR_i}{dt} = \gamma I_i - \mu R_i \tag{1.4}$$

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 [**?**] **:**

$$\lambda_i = \sum_j \rho_{ij}\kappa_j \log\left[1 - \sum_{k=1}^{M}\left(\frac{|I_{k,t}|}{N_k} \times c_{ik} \times \xi_{jk}\right)\right] \tag{1.5}$$

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 C_j comes from C_k. κ_j is the average number of contacts per unit of time a susceptible will have when visiting subpopulation 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

$$\lambda_i = -\kappa_i \log(1 - \frac{I_i}{N_i} \times c_{ii}) \tag{1.6}$$

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

$$\kappa_i(t) = \kappa_{i0}\left[1 + \kappa_{i1}\cos\left(\frac{2\pi t}{T} + \varphi_i\right)\right] \tag{1.7}$$

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 subpopulation 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.

In detail, the deterministic model performs the same way for a given set of initial conditions. It doesn't have randomness, dynamics, and don't present dynamic of diseases in nature. Thus, stochastic models have been proposed. A stochastic model is always more realistic than a deterministic one. These models have stochastic and variable states are not described by unique values, but by probability distributions. It is why we will use the stochastic models to predict extinction propability of disease in spatial context[?].

1.4. **Algorithmes de simulation stochastique.** Stochastic simulation works on variables that both are random and can be changed with certain probability. Today, these stochastic models have been used widely in many domain because of some reasons as following : before, in order to model chemically reacting systems, in simple way, we solved a set of coupled ordinary differential equations (ODEs) [?]of deterministic approches. Basically, these approches use the law of mass action that shows a simple relation between reaction rate and molecular component concentrations. We start with a given set of initial molecular concentrations, the law of mass action permits us to see the component concentrations over time. The states of a reaction are a homogeneous, free medium. The reaction rate will be directly scaled with the concentrations of the elements. Most systems can use the traditional deterministic approches to simulate. It is evident that many systems such as some biochemical systems consist of random, discreate interactions between individual elements. However, in the case, these systems becomes smaller and smaller, the traditional deterministic models may not be accurate. It is the reason for that the fluctuations of these systems can be simulated exactly by applying stochastic models, particularly as well as the Stochastic Simulation Algorithms (SSA) [?, ?].

The SSA uses Monte Carlo (MC) methods to study the time evolution of the jump process. Because the basis feature of the Monte Carlo simulation is insensitive to the dimensionality of the problem, and the work grows linearly with the number of reaction channels in the model. The SSA describes time-evolution statistically correct trajectories of finite populations in continuous time by solving the corresponding stochastic differential equations. Using the stochastic models can solve three questions. (1) These models take account the discrete character of the number of elements and the evidently random character of collision among elements. (2) They coincide with the theories of thermodynalics and stochastic processes. (3) They are a good idea to describe "small systems" and "instable systems". The main idea of the stochastic models is that element reactions are essentially random processes. We don't know certainly how a reaction occur at a moment. We also call it the process stochasticity. In particular, in the process stochasticity, we talk about demographic and environmental stochasticities in epidemic models. The demographic stochasticity is strongly controlled by population size such as the birth and death rates, contamination,etc. But, the environmental stochasticity is just affected by environmental factors what we can not govern. Therefore, there are many epidemic models that forcus on exploration of demographic stochasticity. Demographic stochasticity is considered as fluctuation in population processes that are based the random nature of events at the level of the individual. Each event is related to one baseline probability fixed, individuals are presented in differing fates due to chance. In addition to the demographic stochasticity, the number of infectious, susceptible, exposed and recovered individuals is now required to be an interger. Modeling approches that incorporate demographic stochasticity are called event-driven methods. These methods require explicit consideration of events. The first aprroach published by Daniel T.Gillespie in 1976 [?] is an exact stochastic simulation approach for chemical kinetics. The Gillespie stochastic simulation algorithm (SSA) has become the standard procedure of the discrete-event modelling by taking proper value of the available randomness in such a system. The methods modelling the event-driven model demands explicit presentation of events. For the santard SEIR model, we have to consider the nine events that can occur, each causing the numbers in the relative groups to go up or down by one. Table 2 lists all the events of the model, occurring in subpopulation i of a metapopulation:

To implement this SEIR stochastic model, there are many different methods, thought most researchers often use the method of Gillespie in 1977. Starting from the initial states, the stochastic simulation algorithms simulate the trajectory in population processes by repeatedly answering the following two questions and updating the states.

- When (time τ) will the next reaction fire?
- Which (reaction channel index μ) reaction will fire next?

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 $R_i \leftarrow R_i + 1$

TABLE 2. Events of the stochastic version of the model of equations, occuring in subpopulation i.

So the key parameters in the SSA model are τ and μ. To calculate these distributions, we set $a_0(x) = \sum_{j=1}^{M} a_j(x)$. The time τ, given $X(t) = x$, that the reaction will fire at $t + \tau$, is the exponentially distributied random variable with mean $\frac{1}{a_0(x)}$,

$$P(\tau = s) = a_0(x) exp(-a_0(x)s),$$

and the index μ is the integer random variable of that firing reaction with probability :

$$P(\mu = j) = \frac{a_j(x)}{a_0(x)}$$

In each step, the SSA generates random bumbers and calculates τ and μ according to the probability distribution 1.4 and 1.4. Below we will show some methods that simulate exactly stochastic models. In this part, we will review the variant formulations of Gillespie's stochastic simulation algorithm (SSA) about the overview and the computational cost of each algorithm, then approximate simulation methods, and finally hybrid and multi-scale methods. We will also point out which algorithm that is most efficient, which algorithm that we have used in this thesis.

1.4.1. *Exact stochastic simulation.* The key property for a discrete event simulation of a Markovian system basically samples a time for the next event from this distribution and selecting the reaction that occurs at that time. The Markovian simulation methods have the basic steps of the widely used kinetic Monte Carlo (KMC) method. First persons introduced the method (also known as the KBL algorithm) are Young and Elcock in 1966 [**?**]and independently Lebowitz, Bortz and Kalos in 1975 [**?**]. However, Gillespie really is the person who made kinetic Monte Carlo popular in the chemical and biochemical domains, calling the algorithm the Stochastic Simulation Algorithm (SSA) in his seminal articles [**?**, **?**]. Below we will review his two papers.

(1) First reaction method (FRM) [GILLESPIE 1976] [**?**]:

The first reaction method was proposed by Gillespie in 1976. It models demographic stochasticity in the more intuitive and slower way to the deterministic model. The obtained result is "fluctuations in population processes that arise from the random nature of events at the level of the individual" [**?**] The following pseudo-code provides a clean implementation of Gillespie's first reaction method :

If supposing that generate one random number takes C_{rand} time. Then the FRM takes nC_{rand} time per step. It is a big problem for that Gillespie proposed a new improved algorithm in 1976. The FRM has three main disadvantages : (1) generating random numbers is relatively slow, (2) the FRM generates a cycle too many random numbers in the case where the simulation time is big and the random number generator will have tend on saturation when it generates too many numbers, (3) the FRM is difficult for indexing the events to effectively implement the update step.

(2) Direct method (DM) [GILLESPIE 1977] [**?**] :

The Direct Method was proposed by Gillespie in 1977. The main objective is to present the stochastic simulation for chemically reacting systems. The following pseudo-code of this method is :

We can find that on each step, the Direct Method has to generate two random numbers. Supposing that generate one random number takes C_{rand} time. Hense, on each step, the DM takes $(2C_{rand} + O(n))$ where

Algorithm 1 Gillespie's first reaction method in 1976 - MONOPOPULATION

0. Labell all species $X_1, ..., X_k$.
1. Label all possible events E_1,...,E_n.
2. For each event determine the rate at which it occurs, R_1,...,R_n.
3. **While** ($t < t_{end}$ and $R_N = \sum_{v=1}^{n} R_v \neq 0$) **then**
4. **For** $m = 1, n$ **do**
5. Generate one random number $U(0, 1) : RAND_m$
6. At the event m calculate the time until the next event is $\delta t_m = \frac{-1}{R_m} log(RAND_m)$
7. **end for**
8. Find the event, p , that happens first (has the smallest δt)
9. The time is now updated, $t \rightarrow \delta t_p$
10. Update $\{X_i\}$ following the event p.
11. Return to Step 3.

Algorithm 2 Direct method of Gillespie in 1977 - MONOPOPULATION [**?**]

0. Labell all species $X_1, ..., X_k$.
1. Label all possible events E_1,...,E_n.
2. For each event determine the rate at which it occurs, R_1,...,R_n.
3. **While** ($t < t_{end}$ and $R_N = \sum_{v=1}^{n} R_v \neq 0$) **then**
4. **For** $m = 1, n$ **do**
5. Calculate R_m and $R_m = \sum_{v=1}^{m} R_v$
6. **end for**
7. Generate uniformly distributed random numbers (r_1, r_2)
8. Determine when ($\tau = ln(1/r_1)/R_N$ and which ($min\{p|R_p \geq r_2 R_N\}$) reaction will occur
9. Set $t = t + \tau$
10. Update $\{X_i\}$
11. Return to step 3

$O(n)$ is time to search the index p of the next reaction channel. For this reason, the DM is more efficient than the FRM.

The Gillespie algorithm plays an very important role and has become a fundamental method in computational systems biology. Hence, many efforts have been proposed to improve its efficiency. The key step in the DM is to choose the next reaction channel to implement. This step applies a linear search with a complexity $O(n)$ where n is the number of occurred event in the system. Many methods have focused on this step to improve and give more efficient formulations. For example, Maksym in 1988 [**?**] separated the set of reactions into subsets with a complexity of $O(n^{1/2})$. In 1995, Blue et al. [**?**] extended the division approach of Maksym, where a $K - level$ method results in a search time proportional to $n^{1/K}$. Then, in taking K to the limit, they applied a binary tree structure and obtained the complexity $O(logR)$. Don't stop improving, the Next Reaction Method (NRM) by Gibson and Bruck is more known to the systems biology domain [**?**].

(3) Next Reaction Method (NRM) [GIBSON2000] [**?**]

In 2000, Gibson and Bruck successful tranformed the algorithm FRM into an equivalent but more efficient new structure. The Next Reaction Method applies just a sigle random number per iteration. Moreover, the initiation times of the reactions can be set as the firing times of independent, unit rate Poisson processes with internal times given by integrated propensity functions. It is evaluated steady faster than the FRM and more efficient than DM in special cases as the system includes many species and loosely coupled reaction channels. The NRM is presented as follows :

The data structure presented in the NRM is a dependency graph. Because a propensity function R_j should be modified when a given reaction is implemented. A node in the graph is correspondent to a reaction channel. A directed edge of the reactions A_i and A_j points out that the execution of A_i really affects the molecules in A_j. Due to the the dependency graph, in step 4, the number of propensity functions recalculated is minimal.

In addition, the indexed priority queue is similar to a heap tree in computer science. It is a tree that includes ordered pairs of the form (i, τ_i), where i is both the reaction channel index and the position in the tree, τ_i is the corresponding time when the new A_i reaction is expected to occur. In the tree, the value τ

Algorithm 3 Next Reaction Method (NRM) [GIBSON2000]

1. Initialize

(a) set initial numbers of species, set $t = 0$, generate a dependency graph G
(b) calculate the propensity function $R_j(x)$, for all j
(c) for each j, generate a putative time τ_j according to an exponential distribution with parameter $R_j(x)$
(d) store the τ_j values in an indexed priority queue P

2. Let μ be the reaction whose putative time τ_μ stored in P is least. Set $\tau = \tau_\mu$

3. Update the states of the species to reflect execution of reaction μ. Set $t = \tau$

4. For each edge (μ, α) in the dependency graph G

(a) update R_α
(b) if $\alpha \neq \mu$, set
$\tau_\alpha = R_{\alpha,old}/R_{\alpha,new}(\tau_\alpha - t) + t$
(c) if $\alpha = \mu$, generate a random number r and compute τ_α according to an equation similar to Step 8 of the DM
$\tau_\alpha = \frac{1}{R_\alpha(x)} log(\frac{1}{r}) + t$
(d) replace the old $R_\alpha$value in P with the new value.

Go to step 2.

of each parent is a smaller than that of its children. The top node of the tree is always the minimum value of τ and the order is only vertical. In each step, the nodes of the tree will change its positions according to its value to get the new prority queue.

In short, the NRM solved two additional optimizations : (1) by switching to absolute time, Gibson and Bruck reduced the number of random numbers needed in each step from two to one; (2) because of the use of a dependency graph, the number of propensities needing to be recomputed for every timestep is minimum. In estimating the computation time of the NRM, we find that, for every reaction channel, the time until that reaction occurs is computed, maintained in an indexed priority queue, and efficiently implemented as a binary heap. However, the cost for maintaining the priority queue is relatively high. The time to select the next event is done in constant time, but the time to update the propensities is done in logarithmic time. Hence, the NRM is commonly used for systems with many reaction channels and where relatively few propensities change with each reaction. The disadvantage of the NRM is that diffusion is added to the models and the reaction-diffusion master equation is simulated, so systems arise. For such models, in 2004, Elf et al. [**?**] proposed a variant of the NRM that is called the Next Subvolume Method (NSM). This method can be referred as a clever association of the ideas of NRM and Maksym's method for intracellular 3D chemical reaction systems.

(4) Compare the direct method (DM) to the next reaction method (NRM), which algorithm is most efficient?

We find that in the NRM, after the executed first initial step, all sequent timesteps only ask one random number to be generated while the DM requests two. Even, the search step for the index μ of the next reaction channel takes $O(M)$ time for DM, but the corresponding task of updating the indexed priority queue takes $log(M)$. It is the reason for that the NRM is always evaluated more efficient for large scale problems. To evaluate the real cost of two methods (NRM and DM) based on the total simulation time, Yang Cao et al. [**?**] made experiments for both formulations of SSA on a 1.4 GHz Pentium IV Linux workstation. The problem used in their experiments is a stochastic model of the heat shock response of E. Coli [**?**], which includes 28 variables and 61 reactions. The experimental resultats pointed out that the average simulation time for DM is larger than that for NRM due to its data structure maintenance. In particular, for the loose coupling system where the components (or elements) in a system are interconnected and dependant on each other to the least extent practicable, NRM works better than DM. Yang et al. found that three main factors that strongly affect the CPU cost, are the costs, C_p to calculate M propensities, $C_{a_0}$to calculate the sum of all propensity probabilities, and C_s to search for a event μ. Hence, to reduce these costs, Yang et al. [**?**] suggested that a new optimization called the Optimized Directed Method (ODM). They found that in a reaction set of a system, some reactions fire much more frequently than others. To reduce the search time C_s, they arranged the index of the reaction ordering, placing the most frequently occurring events first based on how often they fire, combined with a dependency graph, achieves better results than the NRM for moderately large systems. Their optimized direct method (ODM) gives a new search depth smaller than the original method DM. The obtained result is that C_s can be significantly declined. In the next step to reduce the costs C_{a_0} and C_p, the authors used an idea from the method NRM. The ODM only recomputes the propensities for those reaction channels affected by the last reaction. Because of an extra cost used for accessing the dependency graph, so this approach applies only to loose-coupling systems. In conclusion,

the obtained results of Yang et al. have shown that the ODM is faster than NRM, in particular, unless the system is very nearly uncoupled. This result broken the held belief for a long time that NRM was the fastest.

Through this result, we can say that the efficience of the ODM, currently is evaluated to be the fastest known algorithm for stochastic simulation for most biological problems. This method can be negatively impacted by transient shifts in the frequency at which reactions occur, and commonly used in biochemical reaction networks because of the inductive and repressive nature of genetic regulation. Due to these shifts, the ODM defeats the pre-simulation strategy employed within the ODM to decrease the time complexity of the SSA's reaction selection step and thus degrade performance. In order to decrease this degradation, in 2005, McCollum et al. [**?**] introduced the sorting direct method (SDM) that improves on ODM. This method eliminates the pre-simulations required by the ODM and permits the simulator to adapt to sharp changes in reaction execution frequencies. The common point of these two methods is to focus on the optimization of the system instead of the method itself by reducing the average number of operations required to obtain the index of the next reaction to fire. This average number of operations is called the search depth that is hightly dependent on the biochemical system. For these two methods, the search depth us $O(M)$. Besides, within the paper of McCollum et al. [**?**], the authors also gave a detailed overview of the difference in the implementation of DM, NRM, ODM and SDM. In 2006, Li and Petzold introduced an alternative formulation of the SSA, named the Logarithmic Direct Method (LDM). In this method, the computational cost is independent of the ordering of the reactions and no need for a pre-simulation. The LDM declined the search depth to $O(logM)$, and pointed out the efficiency of the logarithmic method.

Two years later, in 2008, a different approach is proposed by Hellander [**?**] where the authors used the uniformization and quasi-Monte Carlo to reduce the number of trajectories needed to compute an approximation of the probability density function (PDF) at the price of a higher cost per trajectory. Another is also found to reduce the number of simulation in [**?**].

A new search direction is very beneficial to generate ensembles of trajectories in parallel. Because the parallelization of a single trajectory is very hard. Apply clusters to implement SSA is proposed by Li [**?**]. Then, Li et al. continued executing SSA on the graphics processing unit [**?**, **?**].

1.4.2. *Approximate methods.* As mentioned above, the methods Direct, First Reaction and Next Reaction are all exact stochastic approaches of the underlying ordinary differential equations. Their advantage give us a really mathematically exact approach to simulate time-to-event model (in condition that the definition of the propensity functions accurately reflects the dynamics of the system). But, their disavantages are 1) noise in exact simulations only affects the probabilities associated with fates of individuals and the updating of each consecutive event is independent – there is no assumption concerning environmental stochasticity; 2) these exact solutions become too slow and impractical when any one transition rate is large, when there is a big number of subpopulations or one a big number of event in a metapopulation; because the exact algorithms SSA must proceed one reaction at a time and take the task of explicitly simulating each and every reaction event, hence they are much too slow for most practical problems. It is the reason for that, approximate models have been proposed instead of the exact stochastic methods. The approximate approaches ask the question : "How many times does each action channel fire in each subinterval?"

These approaches could be used in larger systems, and made much faster than the exact methods. However, the exact structure of the Markov chain is no logner simulated in the approximate approaches, hence the validity of the approximations become a main issue. Now we will show some mostly used approximate methods.

(1) $\tau - leaping$ method

Gillespie (2001) [**?**] has proposed a new method that decreases the simulation accuracy, but speeds up the stochastic simulation. This is the explicit Poisson $\tau - leap$ method known as an approximate method reduces the number of iterations by treating transition rates as constant over time periods for which this approximation leads to little error [**?**]. The $\tau - leap$ method applies a Poisson approximation to can "leap over" many fast reactions and approximate the stochastic behavior of the system very well. The $\tau - leap$ method is described as follows :

The main problem in the $\tau - leap$ method is relative to the value of the time increment between steps, δt. How do we choose the value fixed of δt? δt must satisfy two conditions, large enough so that many reaction events occur in that time and small enough of the leap condition. The leap condition is pointed out that [**?**]: For the current state x, the value of δt is asked to be small enought that the modification in the state during $[t, t + \delta t]$ will be so small that no propensity function will suffer an appreciable change in its value. Thus, the key to the success of this technique is to choose a leap size large enough to allow many reactions to occur during the leap (reducing computation) and small enough that none of the propensity functions

Algorithm 4 $\tau - leap$ method proposed by Gillespie (2001)[?]

1. Let δt be the time increment between steps, δt is fixed as a constant.
2. Let $M_T(t)$ and $M_R(t)$ be the number of transmission and recovery events by time t.
3. Setting $\delta M_i = M_i(t+\delta t) - M_i(t)\ i = T, R)$, then

$$\begin{aligned} P(\delta M_T = 1|X,Y) &= \frac{\beta XY}{N}\delta t + o(\delta t) \\ P(\delta M_R = 1|Y) &= \gamma Y \delta t + o(\delta t) \end{aligned}$$

These two equations represent the transition probabilities for transmission and recovery events occurring in the time interval δt.

4. For small δt, the increments δM_i are approximately Poisson, such that:

$$\begin{aligned} \delta M_T &\approx Poisson(\frac{\beta XY}{N}\delta t) \\ \delta M_R &\approx Poisson(\gamma Y \delta t) \end{aligned}$$

5. Updating the values of the variables :

$$\begin{aligned} X(t+\delta t) &= X(t) - \delta M_T + \delta M_R \\ Y(t+\delta t) &= Y(t) + \delta M_T - \delta M_R \end{aligned}$$

6. Updating the time, $t = t + \delta t$.
7. Return to Step 4.

will change significantly in value (causing an error). Cao et al. [?] pointed also out a method to estimating the largest value of δt, the expected change in each propensity function during a leap be limited by $\epsilon a_0(x)$, where ϵ $(0 < \epsilon \ll 1)$ is the error control parameter. In short, the best advantage of the $\tau - leap$ method is to speed up the stochastic simulation for many "not-too-stiff" systems −i.e., systems in which the difference between the characteristic time scales of the fastest and slowest dynamical modes is not too large. However, the number of firings of each reaction channels during a fixed time step δt is approximated as a Poisson random varibale. This Poisson variable can have arbitrarily large sample values. Hence, there exists the possibility that this $\tau - leap$ method will cause one or more reaction channels to fire so many times during δt that number of reactants in each population will be became negative, in particular in systems with multiple timescales (for short the stiff systems). Due its obtained advantage, so this technique has continued to mature, specially in the area of leap-size selection, through the work of a variety of researchers : procedure for determining the maximum leap size for a specified degree of accuracy [?]; a binomial leaping method developed independently Tian et al.[?] and Chatterjee et al. [?]; based on the multinominal distribution by Pettigrew et al. in [?]; the post-leap checks of Anderson [?]; and a further work in this area can be expected. In detail for the binomial leaping method, this method replaces the Poisson random variables with binominal random variables, whose values are naturally bounded. However, the disadvantage of this method appeared when the system is in the state : there are multiple reactions with common consumed reactants, so the issues of the binomial tau-leaping stratery have not yet been fully resolved, and to write a general binominal tau-leaping program that reliably handles all situations that could possibly arise, this task would seem to be a very challenging task. It is the reason for that, Yang et al. (2005) [?] is introduced a modified Poisson tau-leaping procedure that also avoids negative populations and these particular issues, but is easier to implement than the binomial procedure.

1.4.3. *Hybrid and multiscale methods.*

- Key word : Langevin equation, a Langevin equation is a stochastic differential equation that could present the time advance of a subset pf the degrees of freedom. In the epidemiology, the Langevin equations are the equation that describe of the dynamics of the individuals between the different compartments depends on the specific disease considered.

Here, we show an other kind of approximation methods that are based on the validity of different approximations, and are the combination of the deterministic equations and the Langevin equations for subsets of the reactions, the chemical species or both. The results of these methods have pointed out that the speedup obtained applying this hybrid idea can be substantly. For example, Adalsteinsson et al. combine the deterministic and stochastic

approaches in order to develop the software package Biochemical Network Stochastic Simulator (BioNetS) for efficiently and accurately simulating stochastic models of biochemical networks in [**?**]; the method that applies chemical Langevin equations in [**?**] and in [**?**, **?**]; Poisson-Runge-Kutta methods [**?**]; multiscale algorithms like the slow-scale stochastic simulation algorithm [**?**] and use of the quasi-steady state assumption [**?**]. Besides, there are many varieties of others, for exemple : Haseltine and Rawlings associate deterministic or Langevin equations for fast reactions with SSA for slow channels.

These method

1.5. **reinforcement learning.**

2. Description du modèle (ce qui corretspond au package R)

- comparaison avec ce qui existe déjà en termes de (1) possibilité (ce que l'on peut faire) et de (2) rapidité. En gros il y a un compromis entre flexibilité et rapidité. Il faut que tu montres où ce situe ton package. Par exemple, sous R, à comparer avec "adaptivetau" et "GillespieSSA". Voir aussi les autres outils qu'il existe (par exemple ceux développés par Petzold http://www.cs.ucsb.edu/~cse/index2.php?publications.php)
- **Kullback-Leibler Divergence or Kolmogorov–Smirnov test to compare the simulation results.**

3. Relation structure/dynamique spatiale et persistence

C'est ce que tu es en train d'explorer pour le moment. Plusieurs questions à explorer. Chaque question constitue un sous-chapitre. A toi de développer et structurer cette partie plus en détails.

4. Contrôle par reinforcement learning:

- comment utiliser ton simulateur pour faire du reinforcement learning. Partie qui reste à développer.

5. Conclusion et discussion générales.

Commence donc à écrire certaines parties dès que tu peux (un peu chaque semaine et de plus en plus au fur et à fur que le temps avance). Pense aussi à bien faire la bibliographie (il faut que tu sois incollable sur le sujet). Les nouveau login et mot de passe de Bibliovie (http://bibliovie.inist.fr) sont 15SCBUMR5290 et 4NX9E5. Ou, on peux utiliser l'account de Giang à UPMC selon les conseil de la site : http://www.jubil.upmc.fr/fr/ressources_en_ligne2/mode_acces_ressour