

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

TRAN THI CAM GIANG, JEAN DANIEL ZUCKER, MARC CHOISY, YANN CHEVALEYRE

Un plan pour ton mémoire de thèse pourrait être:

## 1. ÉTAT DE L'ART:

### 1.1. épidémiologie (et contrôle).

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

This thesis is proposed in 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, in the start of the 2014, the World Health Organization (WHO) had officially to state global measles epidemic outbreak. In the first three months of the year 2014, there were about 56,000 cases of measles 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 works proposed by the WHO<sup>2</sup>, the Institute Pasteur<sup>3</sup> and the Inserm<sup>4</sup> 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*. As we know, 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. For the directly infectious diseases, it means to directly transmit 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 vaccinated, it means that we transport microorganisms in the weakened or killed forms of the microbe into our body. The body's immune system produces the right antibodies to recognize the germs as a threat, destroy it and keep a record of it. Due to that, when the disease occurs, our immune system can more recognize and destroy any of these germs that it later encounters. The administration of vaccines is called vaccination. The human world has thanked a lot the vaccination. The results of vaccination have been appreciated such as in the vaccination of the influenza, HPV and chicken pox diseases. Smallpox is a particular example. This disease was a terror of the human during the closing years of the 18th century. Smallpox killed an estimated 400,000 Europeans annually and the people were lucky to be survival, a third of all were blind. However, the World Health Organization (WHO) officially 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 of infectious diseases. In order to answer to this question, first of all, we have to answer to some following small questions :

---

Date: 03/04/2015.

Question	Answer	Why?
Are vaccines safe?	YES	Vaccines are generally quite safe
Have all infectious diseases vaccines?	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 four answers above, we can say that the human still faces up to infectious diseases. In order to implement proper infection control measures and prevention campaigns with large scale, knowing well the features of the disease is quite important. Clear that the disease transmission methods depend on the characteristics of each disease and the nature of the microorganism that causes it. In the shape of 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 secretions, or contact with body lesions. Therefore, these diseases usually occur between members of the same household or close friends and family. In particular, measles will be mainly studied throughout this thesis. Because measles is a highly contagious, serious disease caused by a virus. It is a typical disease for the infectious diseases with the direct transmission. In 1980, it killed an estimated 2.6 million deaths each year before we had the widespread vaccination policies. It is spread 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, especially in developing countries, 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 up about 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 measles vaccines safe and always available.

The mass policy (or the routine measles vaccination policy for measles) that vaccinates the maximum number of children before 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 in the way where it has gotten a clear decrease of the incidence in most of countries. However, the problem of this vaccination policy is too expensive, 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 is 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 need still very much 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 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 bacterias, 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 population 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 researches 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 the differential equations to control its models. At the "intra-city level" (or 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 account of the resident population as well as the current population of individuals [?]. A population may be considered in the simple way 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 among cities), it is the main reason for that why diseases can be 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

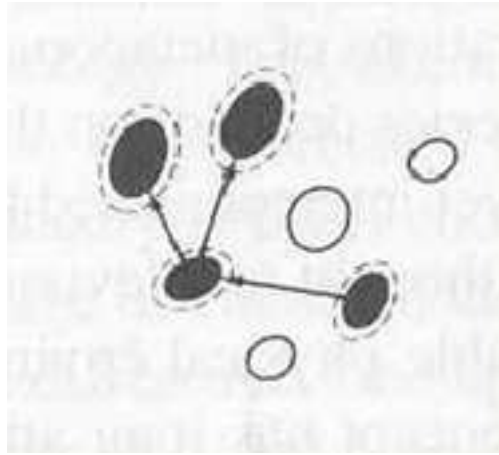


FIGURE 1.1. Classic Levins Metapopulation Model [?]

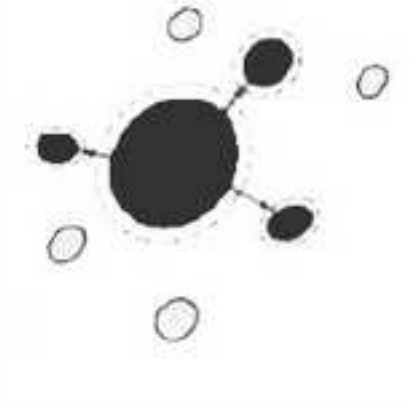


FIGURE 1.2. Mainland-Island Metapopulation [?]

extinction [?, ?, ?] and migration between subpopulations is significantly restricted. In a metapopulation, if recolonization rates are smaller than extinction rates, then the metapopulation is easy to obtain the extinction of all local populations. 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 metapopulation, 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 being white or filled, but is propagule for the islands connected. Therefore, if mainland population has a low individual density and without immigration, then population growth rate is positive. Inversely, if island populations are in the same conditions of the mainland, then its population growth rate is negative. Thus, the islands would go down to extinction if there isn’t any emigrants.
- The third model is the patchy population. The local populations exist in a big habitat population and the dispersal rate between subpopulations is high.

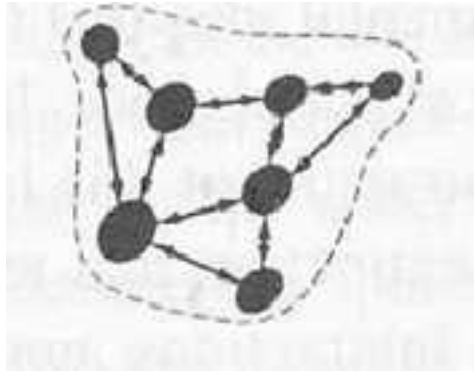


FIGURE 1.3. Patchy population [?]

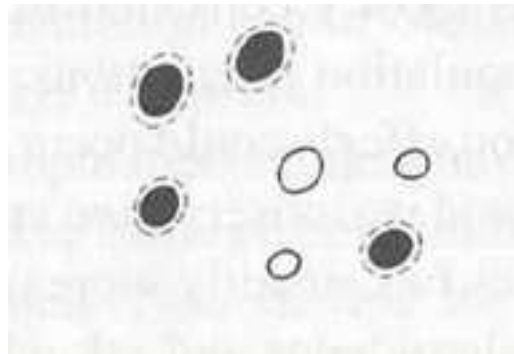


FIGURE 1.4. Non-equilibrium population [?]

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 metapopulation too.

- The final model is the non-equilibrium population. The local populations are patches, its local extinctions are much great 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 model. In order to model the metapopulations 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 don't care distance between them and population size of each subpopulation. The advantages of this model are easy mathematically and conceptually. 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, spatially-explicit model is more complex than the first model. Subpopulations may be filled or vacant. Local populations only have interactions with nearest neighbours. 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 can not simply describe the state of the metapopulation through filled subpopulations. Finally, the spatially-realistic model uses GIS to realize attributes, georeferenced 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. The advantage of 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 exist any more in this model.

- Cai nay can cho bai cua “Socially Optimal Vaccination Policies” by Louis Boguchwal.

1.3. algorithmes de simulation stochastique.

1.4. reinforcement learning.

## 2. DESCRIPTION DU MODÈLE (CE QUI CORRESPOND 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 se 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 nouveaux login et mot de passe de Bibliovie (<http://bibliovie.inist.fr>) sont 15SCBUMR5290 et 4NX9E5. Ou, on peut utiliser l’account de Giang à UPMC selon les conseils du site : [http://www.jubil.upmc.fr/fr/ressources\\_en\\_ligne2/mode\\_acces\\_ressour](http://www.jubil.upmc.fr/fr/ressources_en_ligne2/mode_acces_ressour)