

Stochastic and Renewal Methods
Applied to
Epidemic Models

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A Dissertation submitted to
the Faculty of Graduate Studies
in Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

Graduate Program in
Mathematics & Statistics
York University
Toronto, Ontario

July 2020

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Abstract

The thesis is made up of three chapters, which analyse the disease spreads within the population in three different settings.

The second chapter analyses the effects of the adaptive vaccination strategy on the infectious disease dynamics in a closed population and a demographically open population. The analytical methods are used to show that the cumulative force of infection for the closed population and the endemic force of infection in the demographically open population can be significantly reduced by combining two factors: the vaccine effectiveness and the vaccination rate. The impact of these factors on the force of infection can transform an endemic steady state into a disease free state.

The third chapter analyses the SIS Epidemic dynamics using the Birth-Death Markov processes. The Susceptible-Infected-Susceptible (SIS) model is defined with the population of constant size (M); the susceptible population (S) and the infected population (I) have the same rate of birth and death (μ); the disease spreads with the transmission rate (β). Using a stochastic method, it is shown that the magnitude of the disease spread depends on the Reproductive Number ($R = \frac{\beta}{\alpha}$). In the long run, the stochastic equilibrium and the deterministic equilibrium yield the same infected size equilibrium ($1 - \frac{1}{R}$) in proportion. Finally, the asymptotic distribution of the infected size is shown to follow a normal distribution with mean $(1 - \frac{1}{R})M$ and variance $\frac{M}{R}$.

The fourth chapter studies the impact of the Gamma distribution of the individual lifetime on the SIS Epidemic Dynamic. The approaches are both numerical and analytical methods. The composite Newton-Cotes quadrature formulas are implemented in order to provide the best accurate estimation of the infected size equilibrium. The numerical solution of the infected size was computed and the results show that the infected size is an increasing function of the shape parameter (k) with a phase of acceleration and a phase of deceleration before reaching a stable value ($1 - \frac{1}{2R}$). The numerical solution was also compared with the analytical solution provided by the Extreme Value Theory. The results consolidate the numerical solutions of the infected size. However, the analytical approximation is not valid for shape parameters (k) less than 1.

Acknowledgments

Firstly, I would like to express my sincere gratitude to my supervisor Dr. Neal Madras for the continuous and multi-formed supports throughout my Ph.D Programme. A special thank for sharing your knowledge and for your guidance during my studies at York University.

In addition to my supervisor, I would like to extend my gratitude to the rest of my supervisory committee: Dr. Jianhong Wu and Dr. Jane Heffernan for their encouragement and insightful comments.

I also seize this opportunity to individually thank to Dr. Neal Madras, Dr. David Tanny, Dr. Emanoil Theodorescu, Dr. Alexey Kuznetsov, Dr. Tom Salisbury, Dr. Gao Xin, Dr. Thomas Defo and Dr. Ignace Kamga Tchwaket for welcoming my invitation and providing some good recommendations to support my multiple applications throughout my studies at York University.

I would like to thank the American Mathematical Society (AMS) for providing the opportunity to attend to the AMS Sectional Meeting at San Francisco State University and to be a speaker at 2020 Joint Mathematics Meetings (JMM) at the Colorado Convention Center. By the same token, I thank the Applied Mathematics, Modeling and Computational Science (AMMCS) Conference Series for providing the opportunity to speak at 2019 AMMCS conference at Waterloo, Ontario, Canada.

Finally, I would like to thank the members (both faculty and staff) of the Department of Mathematics & Statistics for the service and help during my stays at the department.

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Chapter 1

Introduction

We will investigate in chapter 2 the adaptive vaccination strategy effects on infectious disease dynamics in two types of population: in the closed population and in the demographically opened population. The dynamic of the epidemic model is captured by the force of infection, which is derived from a scalar-renewal equation. The methodology and key assumptions are based on the paper of Breda et al (2012), which our study extends and integrates the adaptive vaccination strategy. The susceptible population is divided into non-vaccinated susceptible population (S) and vaccinated susceptible population (V). The main assumptions are that the infection leads to permanent immunity (no re-infection); the force of infection occurring in vaccinated susceptible is proportional to the force of infection within the non-vaccinated susceptible; and the rate of vaccination is proportional to the force of infection in the non-vaccinated susceptible. The assumptions of no re-infection and the linearity relationships are all reasonable assumptions. Regarding the no re-infection assumption, the diseases like Varicella (chickenpox) and hepatitis A meet the assumption; but this is not the case for flu (influenza). The linearity assumptions are reasonable because, a natural feature of an adaptive vaccination policy is that the rate of vaccination should increase when the force of infection increases and decrease when the force of infection decreases.

For the age structured model, an additional assumption is that the disease has no impact on the time of death. This is also a reasonable assumption and can be applied to flu (influenza) disease.

These relations are summarized in each type of population by the following system of differential equations and scalar-renewal equation.

In the closed population epidemic model, the dynamics of both classes of susceptible ($S(t)$ and $V(t)$ at time(t)) is described by the system of differential equations.

$$\begin{aligned}\frac{dS(t)}{dt} &= -F(t)S(t) - \phi(t)S(t) \\ \frac{dV(t)}{dt} &= -\theta F(t)V(t) + \phi(t)S(t)\end{aligned}$$

where $F(t)$ is the force of infection function, $\phi(t)$ the rate of vaccination function, θ ($0 \leq \theta \leq 1$) is the vaccine effectiveness parameter.

The following scalar-renewal equation describes the dynamic of the force of infection. $A(\tau)$ is the expected contribution to the force of infection.

$$F(t) = \int_0^\infty (F(t-\tau)S(t-\tau) + \theta F(t-\tau)V(t-\tau))A(\tau)d\tau$$

In the age-structured epidemic model, the dynamics of both classes of susceptible ($S(t, a)$ and $V(t, a)$ at time(t) and at age(a)) is described by the following system of differential equations.

$$\begin{aligned}\frac{d\left(\frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}\right)}{d\sigma} &= -F(t-a+\sigma)\frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} - \phi(t-a+\sigma)\frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} \\ \frac{d\left(\frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}\right)}{d\sigma} &= -\theta F(t-a+\sigma)\frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} + \phi(t-a+\sigma)\frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}\end{aligned}$$

where $F(t)$ is the force of infection function; $\phi(t)$ the rate of vaccination function; $\mathcal{F}(a)$ is the survival function, which describes the probability that a newborn lives at least until age a . The following scalar-renewal equation¹ describes the dynamic of the force of

¹“The renewal equation (RE) was introduced by Leonhard Euler in 1767 in his work on population dynamics and was rediscovered in a modern continuous formulation by Lotka in 1907. Lotka’s formulation is usually expressed as : $B(t) = \int_0^\infty B(t-a)p(a)m(a)da$; where $B(t)$ is the number of births at time t , $p(a)$ is the probability of survival to age a , and $m(a)$ is the fertility at age a . This equation was derived for demographic studies and has been adapted to model epidemics by changing the interpretation of the variables: $B(t)$ represents the number of new infectious individuals at time t , $p(a)$ the probability to be infectious a time units after acquiring the disease, and $m(a)$ the transmission potential, that is the average number of secondary infections at infection age a .” (Champredon et al (2019),p1)

infection.

$$F(t) = \int_0^\infty F(t-\tau) \int_0^\infty (S(t-\tau, a) + \theta V(t-\tau, a)) \frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)} A(\tau) d\tau da$$

Background on the formulation of epidemic models Framework

The paper of Breda et al (2012) is reminiscent of the general epidemic theory of 1927 paper of Kermack–McKendrick. The key feature of the general theory like the per capita rate of infectivity was incorporated and Breda et al (2012) show that the force of infection can be derived from the scalar nonlinear renewal equation and the model still generates the Kermack–McKendrick threshold theorem in the close population. The summary of methodologies and results from the paper of Breda et al (2012) is provided for the closed population and the open population, where a constant birth rate B and a general survival function $\mathcal{F}(a)$ were introduced.

Epidemic in closed population

$F(t)$ is the force of infection at time t

$A(\tau)$ is the expected contribution to the force of infection by an individual that was itself infected τ units of time ago.

$S(t)$ is the number per unit area of susceptible at time t

The force of infection derived from a renewal equation type: $F(t) = \int_0^\infty (F(t-\tau)S(t-\tau)A(\tau)d\tau$.

The susceptible dynamic is obtained by: $S(t) = S(-\infty)e^{-\int_{-\infty}^t F(\sigma)d\sigma}$

The following equation was derived:

$$y(\infty) = R \left(1 - e^{-y(\infty)}\right) \quad \text{where} \quad R = \int_0^\infty S(-\infty)A(\tau)d\tau \quad \text{and} \quad y(\infty) = \int_{-\infty}^{+\infty} F(\sigma)d\sigma.$$

According to Breda et al (2012), the reproduction number $(R)^2$ is the expected number of secondary cases caused by a primary case introduced in a population with susceptible

²Even though the definition of the reproduction number (R) depends of the model being studied, many authors think that the most important role of R is to serve as a reference parameter, a threshold parameter. When $R > 1$, we have an outbreak or a steady-state endemic infection level; and when $R < 1$, we have an extinction of the infection where the disease will eventually die out.

density $S(-\infty)$ Breda et al (2012) concluded that:

1. when $R > 1$, there is an outbreak and the solution $y(\infty)$ is a strictly positive
2. when $R < 1$, the disease dies out and the solution $y(\infty)$ is zero.

Epidemic in open population

The force of infection ($F(t)$) derived from a renewal equation type:

$$F(t) = \int_0^\infty \int_0^\infty F(t-\tau) S(t-\tau, a) A(\tau) \frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)} d\tau da$$

The susceptible dynamic ($S(t, a)$) becomes: $S(t, a) = B \mathcal{F}(a) e^{-\int_0^a F(t-a+\sigma) d\sigma}$

The following equation was derived with F the unknown value:

$$1 = B \int_0^\infty \int_0^\infty e^{-aF} \mathcal{F}(a+\tau) A(\tau) d\tau da \quad \text{where} \quad R = B \int_0^\infty \int_0^\infty \mathcal{F}(a+\tau) A(\tau) d\tau da \quad \text{and} \quad F = F(\infty).$$

Breda et al (2012) concluded that:

1. when $R > 1$, there exists exactly one steady endemic force of infection
2. when $R < 1$, no such steady endemic force of infection exists
3. for $\mathcal{F}(a) = e^{-\mu a}$, $F = B\bar{A}(\mu) - \mu$.

In chapter 3, our main interest is to describe the behaviour of the SIS Epidemic Model using a class of Markov processes, called Birth-Death Markov processes³. We investigate the relationship between stochastic⁴ infection size and the reproduction number (R). The Susceptible-Infected-Susceptible (SIS) model is defined within a population of constant size (M); the susceptible population (S) and the infected population (I) have the same

³Birth-Death processes are a flexible class of continuous-time Markov chains that model the number of particles in a system, where the number of particles transitions are only two types: births, which increase the number of particles by one and deaths, which decrease the number by one. Taylor and Karlin(1975)

⁴“In deterministic models, the output of the model is fully determined by the parameter values and the initial conditions; whereas the stochastic models is characterized by the randomness. In fact, the same set of parameter values and initial conditions will lead to an ensemble of different outputs.” (Gross(2013), slide 2)

rate of birth (α) and the same rate of death (μ); the disease spread with the transmission rate (β). As methodology, we will use both numerical and analytical approaches. In the numerical approach, we firstly implemented the Stochastic Interacting Particle (IPS) methods developed by Klauß et al (2008) in order to draw some sample of infection paths. And secondly, we analyse the infection size statistics (means, variance) based on a Birth and Death equilibrium distribution $\pi_{M,\varepsilon}$ defined on the state space $\{0, 1, \dots, M\}$ for small $\varepsilon > 0$. The small ε plays a key role by allowing 0 to not be an absorbing state. We introduce an external source of disease through a small non negative parameter ($\varepsilon > 0$) in the infection transition rate.

$$\begin{aligned}\lambda_i^{[\varepsilon]} &= \beta \frac{(M-i)}{M} i + \varepsilon & (i \rightarrow i+1) \\ \mu_i &= \alpha i & (i \rightarrow i-1) \quad \text{for } i = 1, \dots, M\end{aligned}$$

As a consequence, we have an irreducible Markov Chain process. The equilibrium distribution ($\pi_M^{[\varepsilon]}$) of the process is derived as follows.

$$\pi_M^{[\varepsilon]}(i) = \begin{cases} \frac{\theta_0}{\theta_0 + \sum_{j=1}^M \theta_j^{[\varepsilon]}} & i = 0 \\ \frac{\theta_i^{[\varepsilon]}}{\theta_0 + \sum_{j=1}^M \theta_j^{[\varepsilon]}} & (i = 1, 2, \dots, M) \end{cases}$$

where

$$\begin{aligned}\theta_0 &= 1 \\ \theta_i^{[\varepsilon]} &= \frac{\lambda_0^{[\varepsilon]} \lambda_1^{[\varepsilon]} \dots \lambda_{i-1}^{[\varepsilon]}}{\mu_1 \mu_2 \dots \mu_i} \quad \text{for } i = 1, \dots, M\end{aligned}$$

And thirdly, the analytical approach will be used to demonstrate that the asymptotic behaviour of the infected size follows a normal distribution with mean $(1 - \frac{1}{R})M$ and variance $\frac{M}{R}$.

Background of some Continuous Time Markov Chain (CTMC) SIS Epidemic Models

The infected size and the equilibrium distribution were analysed by Allen (2008). The analysis was based on the infinitesimal transition probabilities, which was used to derive the infected size probability at any time. Allen (2008) used the infected size probability to simulate three sample paths as a function of time. One sample path was absorbed rapidly; and the two remaining sample paths have more time to increase and before reaching the equilibrium where the probability distribution of the infected size becomes quasi-stationary. Allen (2008) results highlight the randomness feature of the stochastic model. In the deterministic model, the three paths would have had the same characteristics. However, the impact of the reproduction number on the sample paths was not part of the analysis.

The quasi-stationary distribution⁵ was also tackled by Allen (2008). In order to find the probability distribution, the probability conditioned on non-extinction was defined because zero state is absorbing and leads to the free disease equilibrium. From the conditional probability, Allen (2008) derived two quasi-stationary distributions. The first quasi-stationary distribution was :

$$p_1 = \left[\sum_{j=1}^M \frac{(M-1)!}{j(M-j)!} \left(\frac{R}{M}\right)^{j-1} \right]^{-1}$$

$$p_i = p_1 \frac{(M-1)!}{i(M-i)!} \left(\frac{R}{M}\right)^{i-1} \quad \text{for } i = 2, \dots, M$$

and the second quasi-stationary distribution was:

$$q_1 = \left[\sum_{j=1}^M \frac{(M-1)!}{(M-j)!} \left(\frac{R}{M}\right)^{j-1} \right]^{-1}$$

$$q_i = q_1 \frac{(M-1)!}{(M-i)!} \left(\frac{R}{M}\right)^{i-1} \quad \text{for } i = 2, \dots, M$$

However, when the size of the population becomes a variable, the analysis of asymptotic

⁵“Quasi-stationary distributions (QSD) are limiting distributions conditioning on the process not being in an absorbing state” (Hernandez-Suarez et al(1997), p6)

quasi-stationary distribution becomes important in the SIS epidemic model. Nåsell(1996) is one of the pioneers in studying the quasi-stationary distribution when $M \rightarrow \infty$. Nåsell (1996) showed that as the population size become larger, the quasi-stationary distribution can be approximated by a normal distribution when the basic reproduction number is distinctly above 1 ($R \gg 1$); the quasi-stationary distribution can be approximated by a geometric distribution when the basic reproduction number is distinctly below 1; and there is a transition region when the reproduction number is near 1 where the form of the distribution is more complex.

Later, in 1999, Nåsell (1999a) suggested a slightly different asymptotic distribution for the quasi-stationary distribution in three cases as well : (1) R distinctly greater than 1, (2) R close to 1, and (3) R distinctly smaller than 1.

For R distinctly greater than 1 (1), the asymptotic distribution is a normal distribution with mean $M(1 - \frac{1}{R})$ and variance $\frac{M}{R}$;

For R distinctly smaller than 1 (3), the asymptotic distribution is a geometric distribution with parameter R .

The major critic of Nåsell (1996,1999a)'s work is that the findings are not mathematically rigorous. In fact, Ovaskainen (2001) found the approximation formula for quasi-stationary distribution provided by Nåsell (1996,1999a) to be heuristic, and his work was aiming to address the issue. Ovaskainen (2001) provides the asymptotic formula for the quasi-stationary distribution in two cases: (1) $M > 2$ fixed and $R \rightarrow \infty$, and (2) $R > 1$ fixed and $M \rightarrow \infty$.

In the second case (2), the asymptotic distribution p^M for the quasi-stationary is given by:

$$p_i^M = p^* \exp\left(-\frac{M-1}{R}\right) \left(1 - \left(\frac{1}{R}\right)^i\right) p_i^R \quad \text{for } i = 1, \dots, M$$

Weirman and Marchette (2004) also consider the SIS epidemic model as a model for computer virus spread. The aim was to better understand the spread of the computer virus in an effort to design a defensive strategy. In the model, the parameters (infection rate and cure rate) can be fixed or be a function of population size (M) and Weirman and Marchette (2004) show that the asymptotic distribution of the infection size can follow a Poisson dis-

tribution, a Normal distribution and a logarithmic distribution depending on infection rate function of population size. The literature review on the asymptotic distribution for the quasi-stationary offers many approximation distributions and some distributions are unknown like the distribution provided by Ovaskainen (2001). Clancy and Mendy (2010) provide a systematic comparison between approximations. Based on two criteria : accuracy and simplicity, Clancy and Mendy (2010) find that in the subcritical region ($R < 1$), a geometric distribution approximation is preferred; and in the supercritical region ($R > 1$) a beta-binomial distribution is preferred.

In chapter 4, we are interested in studying the impact of the Gamma distribution of the lifetime on the SIS Epidemic Dynamic. More precisely, we look into the impact of gamma distribution on the reproduction number (R) and study the effect of the gamma distribution on the equilibrium when R is greater than one. The key assumptions of the Markov SIS Epidemic Dynamic remain the same, only the lifetime exponential distribution is changed and replaced by a much broader class of Gamma distribution with shape parameter (k) and scale parameter ($\frac{1}{\alpha}$). As illustrated in the Figure (4.1), the Gamma density has a large variety of shapes. When $k < 1$, the lifetime frequency is concentrated around 0 and the individuals have shorter life. When $1 < k$, the individuals live longer. The longer or shorter lifetime have an impact on the disease spread and therefore the equilibrium when the reproduction number is more than one. As methodology, the determination of R is based on the work of Breda et al (2012). R value will be used to simulate some samples of the infection path in order to check the relationship between infection size and reproduction number.

In our study, the excess or residual lifetime variable and asymptotic distribution as defined in the Renewal Theory (Taylor and Karlin(1981)) were used as a base to provide an estimation of the equilibrium when R is greater than one. Our approaches are both numerical and analytic methods. As numerical method, the composite rule of the Newton-Cotes Algorithm scheme will be implemented in order to provide the best accurate estimation of the equilibrium as a function of the population size (M), the reproduction Number R and

the shape parameter (k) of the Gamma distribution. As analytical method, the Extreme Value Theory will be used to estimate the asymptotic behaviour of the equilibrium. By asymptotic behaviour, we mean when the population size (M) is larger and also when the shape parameter (k) is larger.

Background on the use of Gamma distribution in Epidemic Models

The Gamma distribution has been used by Park et al (2019) to model the generation interval, which is the time between when an individual is infected by an infector, and when that infector was infected. Park et al (1999) show that the statistical characteristics of the Gamma distributed generation interval provide insight into the relationship between the reproduction number and the population-level rate of spread and can be used as a robusted estimation of the reproduction number. The Gamma distribution with integer valued shape parameter called the Erlang distribution has been used also to model the latent and the infectious periods both in deterministic and stochastic frameworks. Wearing et al (2005) show that ignoring the latent period or making the common assumption of exponentially distributed latent and infectious periods always results in underestimating the basic reproductive ratio. Feng et al (2007) analyse a SEIR model with the inclusion of quarantine and isolation, they show that modeling a relatively long latent or infectious period with an exponential distribution might not be appropriate when isolation is not effective. However, the use of the Gamma distribution improves the model by providing valuable information and important insights into the disease dynamics. Champredon et al (2019) analyse a SEIR compartmental model with Erlang distribution for the latent and infectious periods, the model introduces the generation-interval distribution that links Erlang SEIR models to renewal-equation models. Champredon et al (2019) provide the exact analytical expressions for the intrinsic generation-interval distribution by solving the ordinary differential equation (ODE) system generated by the compartmental model. Yan et al (2019) in their book “Quantitative Methods for Investigating Infectious Disease Outbreaks” have highlighted some desirable features of the gamma distribution that make them a very convenient choice in infectious disease transmission models. The Erlang distribution has the important property of being the sum of independently exponentially

distributed lifetime. This property makes it the best candidate of non-exponential distributions for ordinary differential equation (ODE) models using the technique called Linear Chain Trick (LCT). The second important feature is the flexible shape of probability density function (PDF) of the Gamma distribution with the shape parameter k . The PDF varies from a highly skewed shape with a long tail when $k < 1$, to the negative exponential function as $k = 1$ and towards a bell-shape when $k > 1$. This feature is also illustrated by Figure (4.1).

Chapter 2

Epidemic Dynamics and Adaptive Vaccination Strategy : Scalar-Renewal Equation Approach

2.1 Introduction

The paper of Kermack and McKendrick (1927) is one of the best known contributions to mathematical theory of epidemic modelling. The paper provides the condition of outbreak and the final size equation in a closed population setting. One of the key features of Kermack and McKendrick (1927) was to introduce an age of infection model. In such a model, the general infectivity function ($A(\tau)$) is the expected contribution to the force of infection ($F(t)$ ¹) by an individual that was itself infected (τ) units of time ago. Kermack and McKendrick's framework encompasses a wide family of epidemic models; Breda et al (2012) have illustrated the generalisation by providing the following age infection

¹the probability per unit of time that a susceptible becomes infected

functions for standard SIR² and SEIR³ models.

$$\begin{aligned} A(\tau) &= \beta e^{-\alpha\tau} \iff SIR \\ A(\tau) &= \beta \frac{\gamma}{\gamma - \alpha} (e^{-\alpha\tau} - e^{-\gamma\tau}) \iff SEIR \end{aligned} \quad (2.1)$$

The paper of Breda et al (2012) “On the formulation of epidemic models (an appraisal of Kermack and McKendrick)” revised Kermack and McKendrick’s paper and produced the same results, but the method used was different. In fact, Breda et al (2012) considered the force of infection as a result of a nonlinear scalar-renewal equation, and they analyzed the cumulative force of infection or the simple force of infection at the disease-free equilibrium and the endemic equilibrium.

In the current chapter, we investigate the effects of an adaptive vaccination strategy on the dynamics of infectious diseases in a closed population and a demographically open population. The methodology and key assumptions are based on Breda et al (2012). The epidemic⁴ model and the vaccination process are illustrated by Figure 2.1. There is no recovered class (R) in the model, but rather, the function $A(\tau)$ can be used to indicate recovery when $A(\tau)$ drops to a very small (or zero) value. The susceptible population is divided into non-vaccinated susceptible and vaccinated susceptible.

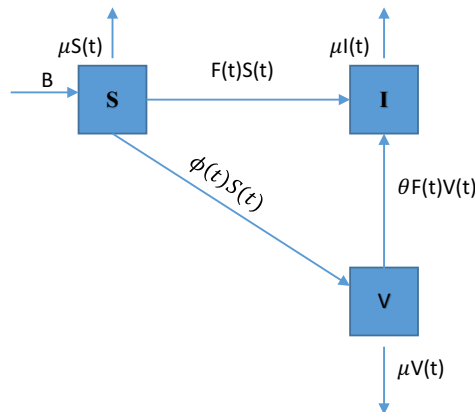


Figure 2.1: Transfer diagram of the model

²Epidemic model with the flows of people between three states: Susceptible (S), infected (I) and recovered (R)

³Epidemic model with the flows of people between four states: susceptible (S), exposed (E), infected (I), and recovered (R)

⁴In the case of closed population ($\mu = B = 0$), the model is better described as a model for an “outbreak” rather than an “epidemic”. This is because the lack of births and deaths means that we are modelling a relatively short time interval, rather than a long-run equilibrium.

In the transfer diagram of the model (Figure 2.1), $F(t)$ is the force of infection function; $\phi(t)$ is the rate of vaccination function; $S(t)$, $V(t)$, $I(t)$ are respectively the non-vaccinated susceptible, the vaccinated susceptible and the infected population; θ ($0 \leq \theta \leq 1$) is the vaccine parameter; μ is the constant per capita death rate and B is the constant birth rate. The main assumptions are that the infection leads to permanent immunity (no re-infection); there is no "waning" of the vaccine, i.e. no transition from V to S , which is reasonable over a short time horizon; the force of infection occurring in non-vaccinated susceptibles is proportional to the force of infection within the vaccinated susceptibles; and the rate of vaccination is proportional to the force of infection in the non-vaccinated susceptibles. In fact, a natural feature of an adaptive vaccination policy is that the rate of vaccination should increase when the force of infection increases and decrease when the force of infection decreases.

The closed population setting will be analysed, followed by the introduction of a survival function and the analysis of the age-structured population.

2.2 Closed Population Epidemic Model

The dynamic of infection can be described in each susceptible group as illustrated on the transfer diagram of the model. The instantaneous change in the susceptibles is determined by the number of new cases of susceptibles infected per unit of time (incidence) and the number of new vaccinated susceptibles per unit of time. In a closed population, the number of susceptibles only changes due to transmission of infection and vaccination; thus, $\mu = B = 0$ in Figure 2.1. The following system of equations can be derived.

$$\begin{aligned}\frac{dS(t)}{dt} &= -F(t)S(t) - \phi(t)S(t) \\ \frac{dV(t)}{dt} &= -\theta F(t)V(t) + \phi(t)S(t)\end{aligned}\tag{2.2}$$

The initial conditions are given by $S(-\infty) > 0$ and $V(-\infty) = 0$.

By solving the system of equations (2.2), we have the following results.

$$\begin{aligned} S(t) &= S(-\infty)e^{-(y+\Phi)(t)} \\ (S+V)(t) &= S(-\infty)C(t)e^{-\theta y(t)} \end{aligned} \quad (2.3)$$

where

$$\begin{aligned} y(t) &= \int_{-\infty}^t F(\sigma) d\sigma, \quad \Phi(t) = \int_{-\infty}^t \phi(\sigma) d\sigma, \quad \text{and} \\ C(t) &= 1 - (1 - \theta) \int_{-\infty}^t F(\sigma) e^{-(1-\theta)y(\sigma) - \Phi(\sigma)} d\sigma. \end{aligned} \quad (2.4)$$

Proof of (2.3) and (2.4):

From the first equation of the system (2.2), we have the solution: $S(t) = S(-\infty)e^{-(y+\Phi)(t)}$

By summing the two equations from the system (2.2), the new equation becomes:

$$\frac{d(S+V)(t)}{dt} = -F(t)(S + \theta V)(t) = -F(t)\theta(S+V)(t) - F(t)(1-\theta)S(t) \quad (2.5)$$

The solution of equation (2.5) has the following form : $(S+V)(t) = S(-\infty)C(t)e^{-\theta y(t)}$

with $C(t)$ solution of the equation (2.6)

$$\begin{aligned} \frac{dC(t)}{dt} &= -F(t)(1-\theta)e^{-\Phi(t) - (1-\theta)y(t)} \\ \text{and} \end{aligned} \quad (2.6)$$

$$C(-\infty) = 1$$

We have

$$C(t) = 1 - (1 - \theta) \int_{-\infty}^t F(\sigma) e^{-(1-\theta)y(\sigma) - \Phi(\sigma)} d\sigma$$

and

$$(S+V)(t) = S(-\infty)C(t)e^{-\theta y(t)}$$

□

The force of infection depends on the size of the infectious population. The rate of new

infections at time $t - \tau$ is $F(t - \tau)S(t - \tau)$ from the non-vaccinated susceptibles and $\theta F(t - \tau)V(t - \tau)$ from the vaccinated susceptibles. After τ additional units of time, these cases contribute $(F(t - \tau)S(t - \tau) + \theta F(t - \tau)V(t - \tau))A(\tau)$ to the force of infection at time t . By summing all the contributions with respect to the elapsed time τ , we obtain the scalar-renewal equation

$$F(t) = \int_0^\infty (F(t - \tau)S(t - \tau) + \theta F(t - \tau)V(t - \tau))A(\tau) d\tau \quad (2.7)$$

Taking into account the equations (2.7) and (2.2), we derive the following cumulative force of infection at each time t , denoted $y(t)$.

$$\begin{aligned} y(t) &= \int_{-\infty}^t F(\sigma) d\sigma \\ &= \int_0^\infty \int_{-\infty}^t -\frac{d(S+V)}{dt}(\sigma - \tau) A(\tau) d\tau d\sigma \\ &= \int_0^\infty S(-\infty) \left(1 - \frac{(S+V)(t - \tau)}{S(-\infty)} \right) A(\tau) d\tau \end{aligned} \quad (2.8)$$

Under the reasonable assumption that R is finite, the Dominated Convergence Theorem allows to exchange the limit inside the integral.

When $t \rightarrow \infty$, the equation (2.8) becomes

$$\begin{aligned} y(\infty) &= \left(1 - \frac{(S+V)(\infty)}{S(-\infty)} \right) \int_0^\infty S(-\infty) A(\tau) d\tau \\ &= R \left(1 - \frac{(S+V)(\infty)}{S(-\infty)} \right) \quad \text{where} \quad R = \int_0^\infty S(-\infty) A(\tau) d\tau. \end{aligned} \quad (2.9)$$

According to Breda et al (2012), the reproduction number (R) defined in (2.9) is the expected number of secondary cases caused by a primary case introduced in a population with susceptible density $S(-\infty)$.

In the expression for $C(t)$ in (2.4), the integral $\int_{-\infty}^t F(\sigma) e^{-(1-\theta)y(\sigma) - \Phi(\sigma)} d\sigma$ is generally not easy to handle, as the rate of vaccination ($\phi(t)$) is unknown. We consider a special case by assuming a linear relationship between the vaccination rate and the force of infection. Specifically, we assume $\phi(t) = pF(t)$ where p is the vaccination rate parameter.

With this assumption on $\phi(t)$, the following results can be derived.

$$\begin{aligned}
C(\infty) &= \frac{1}{1+p-\theta} \left(p + (1-\theta)e^{-(1+p-\theta)y(\infty)} \right), \\
\frac{(S+V)(\infty)}{S(-\infty)} &= C(\infty)e^{-\theta y(\infty)} \\
&= \frac{1}{1+p-\theta} \left(pe^{-\theta y(\infty)} + (1-\theta)e^{-(1+p)y(\infty)} \right).
\end{aligned} \tag{2.10}$$

Proof of (2.10):

By substitution, $C(t)$ in (2.4) becomes

$$\begin{aligned}
C(t) &= 1 - (1-\theta) \int_{-\infty}^t F(\sigma) e^{-(1-\theta+p)y(\sigma)} d\sigma \\
&= 1 - (1-\theta) \int_{-\infty}^t F(\sigma) e^{-(1-\theta+p) \int_{-\infty}^{\sigma} F(a) da} d\sigma \\
&= 1 + \frac{1-\theta}{1-\theta+p} (e^{-(1-\theta+p)y(t)} - 1) \\
&= \frac{1}{1-\theta+p} (p + (1-\theta)e^{-(1-\theta+p)y(t)})
\end{aligned}$$

We have the results

$$C(\infty) = \frac{1}{1-\theta+p} (p + (1-\theta)e^{-(1-\theta+p)y(\infty)})$$

and

$$\frac{(S+V)(\infty)}{S(-\infty)} = \frac{1}{1+p-\theta} \left(pe^{-\theta y(\infty)} + (1-\theta)e^{-(1+p)y(\infty)} \right)$$

2.2.1 Impact on the Endemic Steady State

The expression in (2.10) was replaced into the equation (2.9), which describes the asymptotic behaviour of the cumulative force of infection in the epidemic dynamic. The result is

$$y(\infty) = R \left(1 - \frac{pe^{-\theta y(\infty)} + (1-\theta)e^{-(1+p)y(\infty)}}{1+p-\theta} \right) \tag{2.11}$$

The case $R > 1$ is the interesting case to study if we want to investigate the effect of the vaccination rate parameter (p) and the vaccine parameter (θ) on the cumulative infection force ($y(\infty)$).

In order to analyse the equation (2.11) above, we have to know the classical properties of the solution of the equation $x = W(x)e^{W(x)}$, where the solution $W(x)$ is called the Lambert function.

As shown in the Figure (2.2), the solution $W(x)$ is actually a multivalued function, with

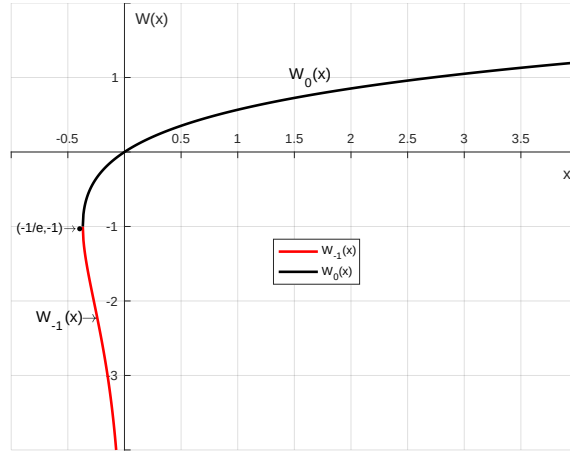


Figure 2.2: Solution of equation $x = W(x)e^{W(x)}$

two branches denoted W_0 and W_{-1} defined as follows:

$$W(x) = \begin{cases} W_0(x) & \text{if } -\frac{1}{e} \leq x \\ W_{-1}(x) & \text{if } -\frac{1}{e} \leq x < 0 \end{cases}$$

Lemma 2.2.1 *Let R be a positive real number, and consider nonnegative solutions u of the equation*

$$u = R(1 - e^{-u})$$

(a) *If $0 < R \leq 1$, then $u = 0$ is the only nonnegative solution.*

(b) *If $R > 1$, then there are two nonnegative solutions: $u = 0$ and $u = R + W_0(-Re^{-R})$.*

Proof

Part (a): $g(u) = u - R(1 - e^{-u})$ is a strictly increasing function for $0 \leq u$. Therefore the unique root is $u = 0$.

Part (b) : we have $u - R = -Re^{-R}e^{-u+R}$, which implies $(u - R)e^{u-R} = -Re^{-R}$. By using the Lambert function, we have $u = R + W(-Re^{-R})$.

For $R > 1$, using the identity property of the Lambert function, we have

$$W(-Re^{-R}) = \begin{cases} W_0(-Re^{-R}) > -1 \\ W_{-1}(-Re^{-R}) = -R \end{cases}$$

Therefore, we have two nonnegative solutions $u = 0$ and $u = R + W_0(-Re^{-R})$ for $R > 1$. $\square$

Case 1: ineffective vaccine ($\theta = 1$)

The expression in (2.11) becomes

$$y(\infty) = R \left(1 - e^{-y(\infty)} \right) \quad (2.12)$$

The quantity $y(\infty)$ is the same as the cumulative force of infection without vaccination (Breda et al (2012)). Using Lemma 2.2.1, the nonzero solution is $y(\infty) = R + W_0(-Re^{-R})$ because $R > 1$.

Case 2: 100% effective vaccine ($\theta = 0$)

The expression in (2.11) becomes

$$y(\infty) = R \left(1 - \frac{p + e^{-(1+p)y(\infty)}}{1+p} \right) \quad (2.13)$$

Using Lemma 2.2.1 with the substitution $u = (1+p)y(\infty)$, we find that Equation (2.13) has the positive solution $y(\infty) = [R + W_0(-Re^{-R})]/(1+p)$ when $R > 1$. Thus we approach a disease-free steady state as p gets larger.

Case 3: $p \rightarrow \infty$ and $\theta \neq 0$

By increasing the vaccination rate parameter (p), the expression in (2.11) becomes

$$y(\infty) = R \left(1 - e^{-\theta y(\infty)} \right) \quad (2.14)$$

Using Lemma 2.2.1 with the substitution $u = \theta y(\infty)$, we find the solution of the equation (2.14) as follows

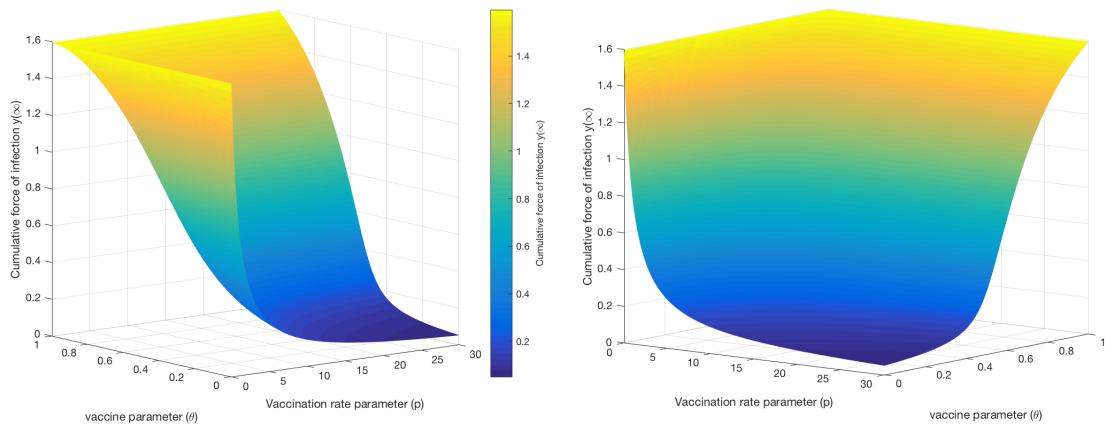
$$y(\infty) = \begin{cases} 0 & \text{if } \theta \leq \frac{1}{R} \\ R + \frac{1}{\theta} W_0(-\theta R e^{-\theta R}) & \text{if } \frac{1}{R} < \theta \leq 1 \end{cases}$$

Case 4: $0 < \theta < 1$ and $p > 0$.

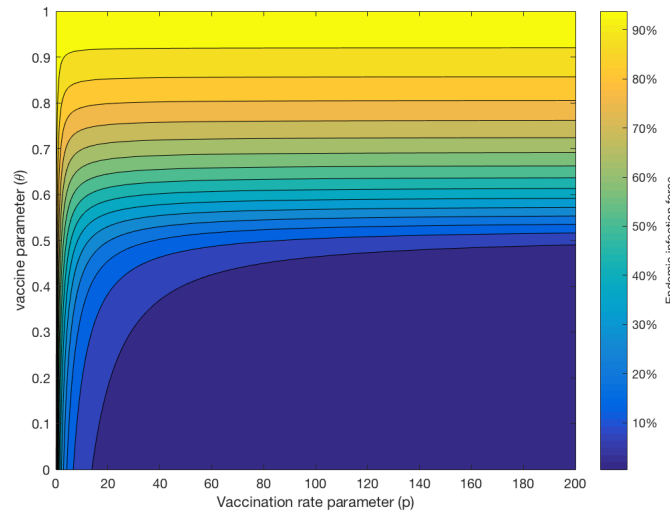
The expression in (2.11) can be transformed into the following standard equation (2.15) with one unknown variable, which is the variable of interest.

$$x - R \left(1 - \frac{pe^{-\theta x} + (1-\theta)e^{-(1+p)x}}{1+p-\theta} \right) = 0 \text{ where } x = y(\infty) \quad (2.15)$$

To consider a representative situation, we supposed the reproduction number (R) is equal to 2. As illustrated in the Figure 2.3, the result shows that the effective vaccine is the most determinant factor. In fact, when the vaccine is not effective (high vaccine parameter θ), whatever the vaccination rate parameter chosen, the effect on $y(\infty)$ is marginal (yellow area). On the other side, $y(\infty)$ is responsive to both factors when the vaccine parameter is low; the degree of $y(\infty)$ reduction depends on the vaccination rate parameter. As shown in the Figure 2.3, the color on the graph becomes quickly blue when the vaccination rate parameter increases. In Figure 2.3, the graphs 2.3a and 2.3b are two views of the same function in a three-dimensional space, whereas the graph 2.3c is a two-dimensional space.



(a) Cumulative force of infection $y(\infty)$ as a function of θ and p (b) Cumulative force of infection $y(\infty)$ as a function of θ and p



(c) Cumulative force of infection $y(\infty)$ in percentage (vaccination versus non vaccination scenario)
Figure 2.3: Impact of adaptive vaccination strategy on cumulative force of infection $y(\infty)$

2.3 Age-Structured Epidemic Model

In this section, we consider the situation whereby, at the population level, new susceptibles arise as a result of reproduction at a constant birth rate B . In addition, we consider the survival function $\mathcal{F}(a)$, which describes the probability that a newborn individual lives at least until age a . If at time t a susceptible has age a , then at time $t - a + \sigma$ this susceptible has age σ ($0 < \sigma \leq a$). For a small positive time duration h , taking into account the survival function $\mathcal{F}(a)$, the behavior of the non-vaccinated susceptibles $S(t, a)$ at time t and at age a follows the equation

$$S(t - a + \sigma + h, \sigma + h) = S(t - a + \sigma, \sigma) \frac{\mathcal{F}(\sigma + h)}{\mathcal{F}(\sigma)} (1 - F(t - a + \sigma)h - \phi(t - a + \sigma)h + o(h^2)). \quad (2.16)$$

The demographic factor $\frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)}$ represents those infectious individuals who survived the next τ unit of time given that he/she survived to age a . By re-arranging, we have the following approximation.

$$\frac{\frac{S(t-a+\sigma+h, \sigma+h)}{\mathcal{F}(\sigma+h)} - \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}}{h} = -F(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} - \phi(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} + \frac{o(h^2)}{h}$$

We can use similar reasoning for the vaccinated susceptibles $V(t, a)$ at time t and at age a , and then take the limit as h converges to 0, resulting in the system of differential equations

$$\begin{aligned} \frac{d\left(\frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}\right)}{d\sigma} &= -F(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} - \phi(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} \\ \frac{d\left(\frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)}\right)}{d\sigma} &= -\theta F(t-a+\sigma) \frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} + \phi(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} \end{aligned} \quad (2.17)$$

If there is no infection in the population, then we have a stable age distribution (Breda et al (2012)), with $S(t, a)$ and $V(t, a)$ becoming

$$S(t, a) = B\mathcal{F}(a),$$

$$V(t, a) = 0.$$

Recall from the transfer diagram of the model that B is the constant birth rate.

More generally, by solving the system of equations (2.17), we have:

$$\begin{aligned} S(t, a) &= B\mathcal{F}(a)e^{-\int_0^a (F+\phi)(t-a+\sigma)d\sigma} \\ V(t, a) &= B\mathcal{F}(a)e^{-\theta\int_0^a F(t-a+\sigma)d\sigma} \int_0^a \phi(t-a+\sigma)e^{-\int_0^\sigma ((1-\theta)F+\phi)(t-a+\tau)d\tau}d\sigma \end{aligned} \quad (2.18)$$

Proof of (2.18):

From the first equation of the system (2.17), we have the solution $S(t, a) = B\mathcal{F}(a)e^{-\int_0^a (F+\phi)(t-a+\sigma)d\sigma}$

The second equation of the system (2.17) can be re-arranged

$$\frac{d(\frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)})}{d\sigma} + \theta F(t-a+\sigma) \frac{V(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} = \phi(t-a+\sigma) \frac{S(t-a+\sigma, \sigma)}{\mathcal{F}(\sigma)} \quad (2.19)$$

The solution of equation (2.19) has the following form : $\frac{V(t, a)}{\mathcal{F}(a)} = C(t, a)e^{-\int_0^a \theta F(t-a+\sigma)d\sigma}$

with $C(t, a)$ solution of the equation (2.20)

$$\frac{dC(t-a+\sigma, \sigma)}{d\sigma} = B\phi(t-a+\sigma)e^{-\int_0^\sigma ((1-\theta)F+\phi)(t-a+\tau)d\tau} \quad (2.20)$$

We have

$$C(t, a) = B \int_0^a \phi(t-a+\sigma)e^{-\int_0^\sigma ((1-\theta)F+\phi)(t-a+\tau)d\tau}d\sigma$$

and

$$V(t, a) = B\mathcal{F}(a)e^{-\theta\int_0^a F(t-a+\sigma)d\sigma} \int_0^a \phi(t-a+\sigma)e^{-\int_0^\sigma ((1-\theta)F+\phi)(t-a+\tau)d\tau}d\sigma$$

□

The force of infection depends on the size of the infectious population and the survival function characteristics of the population. At time t from individuals who were infected at time $t - \tau$ at age a , the contribution to the force of infection is the product of $(F(t - \tau)S(t - \tau, a) + \theta F(t - \tau)V(t - \tau, a))A(\tau)$ infectious individuals and a demographic factor $\frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)}$. By summing all the contributions with respect to elapsed time τ and with respect

to age a , we get the following renewal equation.

$$\begin{aligned}
F(t) &= \int_0^\infty \int_0^\infty (F(t-\tau)S(t-\tau, a) + \theta F(t-\tau)V(t-\tau, a))A(\tau) \frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)} d\tau da \\
&= \int_0^\infty F(t-\tau) \int_0^\infty (S(t-\tau, a) + \theta V(t-\tau, a)) \frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)} A(\tau) d\tau da.
\end{aligned} \tag{2.21}$$

The integral $\int_0^a \phi(t-a+\sigma) e^{-\int_0^\sigma ((1-\theta)F+\phi)(t-a+\tau) d\tau} d\sigma$ from (2.18) is not easy to handle because the rate of vaccination function ($\phi(t)$) is unknown. As in Section 2, we assume a linear relationship between the vaccination rate and the force of infection, in the form $\phi(t) = pF(t)$ where p is the vaccination rate parameter. The solution (2.18) becomes:

$$\begin{aligned}
S(t, a) &= B\mathcal{F}(a) e^{-(1+p) \int_0^a F(t-a+\sigma) d\sigma}, \\
V(t, a) &= B\mathcal{F}(a) \frac{p}{1+p-\theta} \left(e^{-\theta \int_0^a F(t-a+\sigma) d\sigma} - e^{-(1+p) \int_0^a F(t-a+\sigma) d\sigma} \right).
\end{aligned} \tag{2.22}$$

2.3.1 Characteristic Equation and General Case

The solution (2.22) can be substituted in the renewal equation (2.21). In the endemic steady state, we assume the force of infection ($F(t)$) converges to a constant value F . When t goes to $+\infty$, the renewal equation can be rearranged, leading to the following characteristic equation of the endemic steady state.

$$1 = \frac{B}{1+p-\theta} \int_0^\infty \int_0^\infty \left(p\theta e^{-\theta aF} + (1+p)(1-\theta) e^{-(1+p)aF} \right) \mathcal{F}(a+\tau) A(\tau) d\tau da. \tag{2.23}$$

Proof of (2.23):

By substituting $S(t, a)$ and $V(t, a)$ from (2.22) in (2.21), we have

$$\begin{aligned}
F(t) &= \frac{B}{1+p-\theta} \int_0^\infty F(t-\tau) \int_0^\infty \left((1+p)(1-\theta) e^{-(1+p) \int_0^a F(t-a+\sigma) d\sigma} \theta p e^{-\theta \int_0^a F(t-a+\sigma) d\sigma} \right) \\
&\quad \times \mathcal{F}(a+\tau) A(\tau) d\tau da.
\end{aligned}$$

We assume $\lim_{t \rightarrow \infty} F(t) = F \neq 0$ and the result follows

$$1 = \frac{B}{1+p-\theta} \int_0^\infty \int_0^\infty [(1+p)(1-\theta) e^{-(1+p)aF} + \theta p e^{-\theta aF}] \mathcal{F}(a+\tau) A(\tau) d\tau da$$

□

In order to study the properties of the characteristic equation, we consider the following function.

$$f(x) = \frac{B}{1+p-\theta} \int_0^\infty \int_0^\infty \left(p\theta e^{-\theta ax} + (1+p)(1-\theta)e^{-(1+p)ax} \right) \mathcal{F}(a+\tau)A(\tau) d\tau da. \quad (2.24)$$

It is obvious that $f(x)$ is decreasing in x , and $f(0) = B \int_0^\infty \int_0^\infty \mathcal{F}(a+\tau)A(\tau) d\tau da$. The condition $f(0) > 1$ is sufficient to guarantee the existence of a solution F of equation (2.23) with $F \neq 0$. Furthermore, $f(0)$ depends only on the constant birth rate B , the survival function $\mathcal{F}$, and the expected contribution to the force of infection A , since the vaccine parameters θ and p cancel out. Indeed, as noted by Breda et al (2012), $f(0)$ is the basic reproduction number and can be interpreted as the expected number of secondary cases caused by a primary case introduced in a susceptible population with age distribution $B\mathcal{F}(a)$

$$R = f(0) = B \int_0^\infty \int_0^\infty \mathcal{F}(a+\tau)A(\tau) d\tau da. \quad (2.25)$$

Throughout this subsection, we shall assume $R = f(0) > 1$. The implicit function theorem can be used on equation (2.23) to express F as a function of two variables p and θ .

Let us define:

$$G(\theta, p, F) = \frac{B}{1+p-\theta} \int_0^\infty \int_0^\infty (p\theta e^{-\theta aF} + (1+p)(1-\theta)e^{-(1+p)aF}) \mathcal{F}(a+\tau)A(\tau) d\tau da - 1$$

G is a continuously differentiable function; $G(\theta, p, F) = 0$ if F is the solution of equation (2.23); and $\frac{dG(\theta, p, F)}{dF} < 0$.

Therefore $F(\theta, p)$ is a continuously differentiable function and the solution of the following equation.

$$1 = \frac{B}{1+p-\theta} \int_0^\infty \int_0^\infty (p\theta e^{-\theta aF(\theta, p)} + (1+p)(1-\theta)e^{-(1+p)aF(\theta, p)}) \mathcal{F}(a+\tau)A(\tau) d\tau da \quad (2.26)$$

Case 1: ineffective vaccine ($\theta = 1$)

When $\theta = 1$, the equation (2.26) becomes:

$$1 = B \int_0^\infty \int_0^\infty e^{-aF(1,p)} \mathcal{F}(a+\tau) A(\tau) d\tau da \quad (2.27)$$

We have $F(1, p) = F^*$, where F^* comes from the non vaccination case studied by Breda et al (2012). Therefore, the endemic force of infection is the same as the endemic force of infection without vaccination.

Case 2: 100% effective vaccine ($\theta = 0$)

When $\theta = 0$, the equation (2.26) becomes:

$$1 = B \int_0^\infty \int_0^\infty e^{-(1+p)aF(0,p)} \mathcal{F}(a+\tau) A(\tau) d\tau da \quad (2.28)$$

Similarly to Case 1, we have $(1+p)F(0, p) = F^*$ for $p > 0$. Thus $F(0, p) = \frac{F^*}{p+1}$, which depend on the factor $\frac{1}{p+1}$, and we see that $\lim_{p \rightarrow \infty} F(0, p) = 0$, which corresponds to the disease free steady state.

Case 3: $p \rightarrow \infty$ and $\theta \neq 0$

We assumed $\lim_{p \rightarrow \infty} F(\theta, p) = F(\theta, +\infty)$.

The solution of the equation (2.26) becomes:

$$F(\theta, +\infty) = \begin{cases} 0 & \text{if } \theta \leq \frac{1}{f(0)} \\ F(\theta, +\infty) & \text{if } \frac{1}{f(0)} < \theta < 1 \\ F^* & \text{if } \theta = 1. \end{cases} \quad (2.29)$$

In addition, for $\frac{1}{f(0)} < \theta < 1$, $F(\theta, +\infty)$ is an increasing function and $0 < F(\theta, +\infty) < F^*$.

a) For $\theta = 1$

By Case 1 above, $F(1, p) = F^*$ for all $p > 0$. Therefore, $F(1, +\infty) = F^*$.

b) For $0 < \theta \leq \frac{1}{f(0)}$.

We shall assume $F(\theta, +\infty) > 0$.

Let us take a sequence (p_n) such that $\lim_{n \rightarrow \infty} p_n = +\infty$, so that $\lim_{n \rightarrow \infty} F(\theta, p_n) = F(\theta, +\infty)$.

We consider the sequence of functions (f_n) defined by:

$$f_n(a, \tau) = \frac{B}{1 + p_n - \theta} \left(p_n \theta e^{-\theta a F(\theta, p_n)} + (1 + p_n)(1 - \theta) e^{-(1 + p_n) a F(\theta, p_n)} \right) \mathcal{F}(a + \tau) A(\tau).$$

According to the definition of $F(\theta, p_n)$ and the equation (2.26), we have $\int_0^\infty \int_0^\infty f_n(a, \tau) d\tau da =$

1. The function f_n is dominated by an integrable function $B\mathcal{F}(a + \tau)A(\tau)$. In fact, we have:

$$\begin{aligned} f_n(a, \tau) &\leq B\mathcal{F}(a + \tau)A(\tau) \\ f(0) &= \int_0^\infty \int_0^\infty B\mathcal{F}(a + \tau)A(\tau) d\tau da \end{aligned}$$

Following the Dominated Convergence Theorem (DCT), and recalling $F(\theta, +\infty) > 0$, we have:

$$1 = \int_0^\infty \int_0^\infty \lim_{n \rightarrow \infty} f_n(a, \tau) da d\tau = B\theta \int_0^\infty \int_0^\infty e^{-\theta a F(\theta, +\infty)} \mathcal{F}(a + \tau) A(\tau) d\tau da \quad (2.30)$$

and we have

$$1 = B\theta \int_0^\infty \int_0^\infty e^{-\theta a F(\theta, +\infty)} \mathcal{F}(a + \tau) A(\tau) d\tau da < \theta f(0)$$

Which means $1 < \theta f(0)$, which is a contradiction. Therefore, $F(\theta, +\infty) = 0$ for $0 < \theta \leq \frac{1}{f(0)}$.

c) For $\frac{1}{f(0)} < \theta < 1$.

Suppose $F(\theta, +\infty) = 0$.

From (2.26)

$$1 \geq B \frac{p\theta}{1 + p - \theta} \int_0^\infty \int_0^\infty e^{-\theta a F(\theta, p)} \mathcal{F}(a + \tau) A(\tau) d\tau da$$

When p goes to $+\infty$,

$$1 \geq \theta B \int_0^\infty \int_0^\infty e^{-\theta a F(\theta, +\infty)} \mathcal{F}(a + \tau) A(\tau) d\tau da = \theta f(0)$$

Which means $\theta \leq \frac{1}{f(0)}$; and we have a contradiction. Therefore, $F(\theta, +\infty) \neq 0$.

d) Finally, we show that $F(\theta, +\infty)$ is an increasing function on $]\frac{1}{f(0)}, 1[$.

Let us consider a function $\psi_\theta(x)$ defines for every $x \geq 0$ and $\theta \geq 0$ by:

$$\psi_\theta(x) = B\theta \int_0^\infty \int_0^\infty e^{-\theta ax} \mathcal{F}(a + \tau) A(\tau) d\tau da$$

$\psi_\theta(x)$ is well defined because $\psi_\theta(x) \leq f(0)$

It can be checked that $\psi_\theta(x)$ is a strictly decreasing continuous function of x

According to Dominated Convergence Theorem (DCT) in (2.30)

$$\psi_\theta(F(\theta, +\infty)) = 1$$

By changing the variable, $\psi_\theta(x)$ becomes

$$\psi_\theta(x) = B \int_0^\infty \int_0^\infty e^{-bx} \mathcal{F}\left(\frac{b}{\theta} + \tau\right) A(\tau) d\tau db$$

Which shows that $\psi_\theta(x)$ is an increasing function of θ . Let us take θ_1 and θ_2 such that $\frac{1}{f(0)} < \theta_1 < \theta_2 < 1$. Then we have:

$$\psi_{\theta_2}(F(\theta_1, +\infty)) \geq \psi_{\theta_1}(F(\theta_1, +\infty)) = 1 = \psi_{\theta_2}(F(\theta_2, +\infty)) \quad (2.31)$$

$\psi_\theta(x)$ is a strictly decreasing function of x and from the development (2.31), we conclude that $F(\theta_1, +\infty) \leq F(\theta_2, +\infty)$. This shows that $F(\theta, +\infty)$ is an increasing function.

2.3.2 Special Case of Natural Constant Per-Capita Mortality Rate (μ)

In this subsection, we assume that all individuals have a survival function $\mathcal{F}(a) = e^{-\mu a}$, which describes a constant per-capita mortality rate μ . By applying the survival function, the following basic reproduction number is derived from (2.25)

$$\begin{aligned} R = f(0) &= B \int_0^\infty \int_0^\infty e^{-\mu(a+\tau)} A(\tau) d\tau da \\ &= \frac{B}{\mu} \int_0^\infty e^{-z\tau} A(\tau) d\tau \end{aligned} \quad (2.32)$$

This expression for the reproduction number was also found by Breda et al (2012) for a constant per-capita mortality rate μ . The characteristic equation (2.23) for endemic steady state becomes a second degree equation. The coefficients depend on the parameters of

vaccination and the reproduction number.

$$\frac{\theta(1+p)}{\mu f(0)} F(\theta, p)^2 + \left(\frac{1+p+\theta}{f(0)} - \theta(1+p) \right) F(\theta, p) + \frac{\mu}{f(0)} (1-f(0)) = 0 \quad (2.33)$$

We define:

$$\begin{aligned} a &= \frac{\theta(1+p)}{\mu f(0)} \\ b &= \frac{1+p+\theta}{f(0)} - \theta(1+p) \\ c &= \frac{\mu}{f(0)} (1-f(0)) \end{aligned}$$

In an endemic steady state, $f(0) > 1$. We have $c = \frac{\mu}{f(0)} (1-f(0)) < 0$ and $b^2 - 4ac > 0$.

The solution of the equation (2.33) becomes;

$$\begin{aligned} F(\theta, p) &= \frac{-b + \sqrt{b^2 - 4ac}}{2a} \\ &= \frac{\mu}{2} \left\{ \left(f(0) - \frac{1+p+\theta}{\theta(1+p)} \right) + \sqrt{\left(\frac{1+p+\theta}{\theta(1+p)} - f(0) \right)^2 + 4 \frac{f(0)-1}{\theta(1+p)}} \right\} \quad (2.34) \end{aligned}$$

The endemic force of infection is more complex with vaccination parameters. In fact, in Breda et al (2012), with a constant per-capita mortality rate μ and no vaccination, the authors find the endemic force of infection $F^* = \mu(f(0) - 1)$.

Case 1: ineffective vaccine ($\theta = 1$)

The endemic force of infection becomes

$$\begin{aligned} F(1, p) &= \lim_{\theta \rightarrow 1} F(\theta, p) = \frac{\mu}{2} \left\{ \left(f(0) - \frac{2+p}{1+p} \right) + \sqrt{\left(\frac{2+p}{1+p} - f(0) \right)^2 + 4 \frac{f(0)-1}{1+p}} \right\} \\ &= \frac{\mu}{2} \left\{ \left(f(0) - 1 - \frac{1}{1+p} \right) + \sqrt{\left(f(0) - 1 + \frac{1}{1+p} \right)^2} \right\} \\ &= \mu(f(0) - 1) \\ &= F^* \end{aligned}$$

In the case of 100% ineffective vaccine, the endemic force of infection is the same as the endemic force of infection without vaccination (Breda et al (2012)).

Case 2: 100% effective vaccine ($\theta = 0$)

Multiplying the quadratic formula of (2.34) by $b + \sqrt{b^2 - 4ac}$ in numerator and denominator gives

$$F(\theta, p) = \frac{-b^2 + (\sqrt{b^2 - 4ac})^2}{2a(b + \sqrt{b^2 - 4ac})} = \frac{-2c}{b + \sqrt{b^2 - 4ac}}.$$

As $\theta \rightarrow 0$, we see that $a \rightarrow 0$ and $b \rightarrow (1 + p)/f(0)$, resulting in

$$\lim_{\theta \rightarrow 0} F(\theta, p) = \frac{-2\mu(1 - f(0))/f(0)}{2(1 + p)/f(0)} = \frac{\mu(f(0) - 1)}{1 + p} = \frac{F^*}{1 + p}.$$

Again, $F^* = \mu(f(0) - 1)$ is the endemic force of infection without vaccination from Breda et al (2012). Taking into account the vaccination process, we have $F = \frac{F^*}{p+1}$, which depend on the factor $\frac{1}{p+1}$, with vaccination rate parameter p . We have $\lim_{p \rightarrow \infty} \{\lim_{\theta \rightarrow 0} F(\theta, p)\} = 0$, which corresponds to the disease free steady state.

Case 3: $p \rightarrow \infty$ and $\theta \neq 0$

The vaccine is not 100% effective. By increasing the vaccination rate parameter (p), the expression in (2.34) becomes

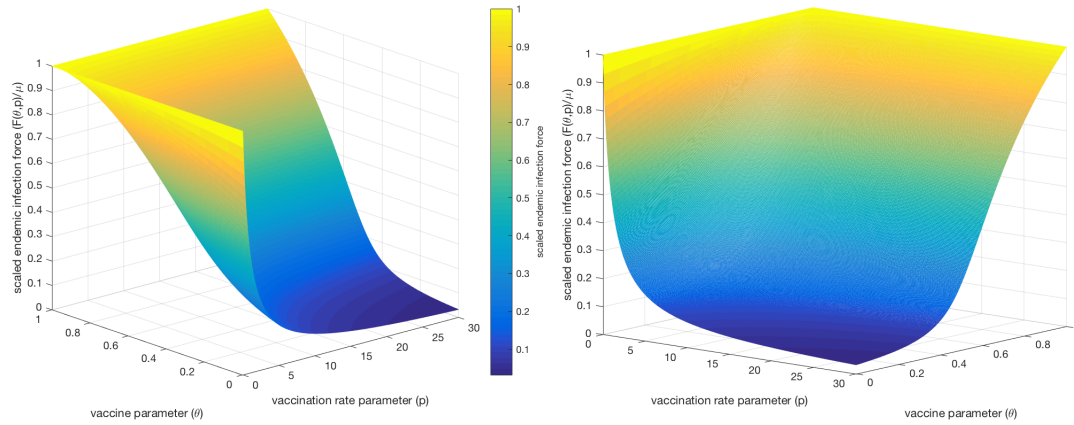
$$\begin{aligned} \lim_{p \rightarrow \infty} F(\theta, p) &= \lim_{p \rightarrow \infty} \frac{\mu}{2} \left\{ \left(f(0) - \frac{1 + p + \theta}{\theta(1 + p)} \right) + \sqrt{\left(\frac{1 + p + \theta}{\theta(1 + p)} - f(0) \right)^2 + 4 \frac{f(0) - 1}{\theta(1 + p)}} \right\} \\ &= \frac{\mu}{2} \left\{ \left(f(0) - \frac{1}{\theta} \right) + \sqrt{\left(\frac{1}{\theta} - f(0) \right)^2} \right\} \\ \lim_{p \rightarrow \infty} F(\theta, p) &= \begin{cases} 0 & \text{if } \theta \leq \frac{1}{f(0)} \\ \mu(f(0) - \frac{1}{\theta}) & \text{if } \frac{1}{f(0)} < \theta \leq 1 \end{cases} \end{aligned}$$

With a sufficiently high vaccination rate parameter (p), the disease free steady state can still be approached arbitrarily closely if the vaccine parameter (θ) is below a threshold ($\theta \leq \frac{1}{f(0)}$).

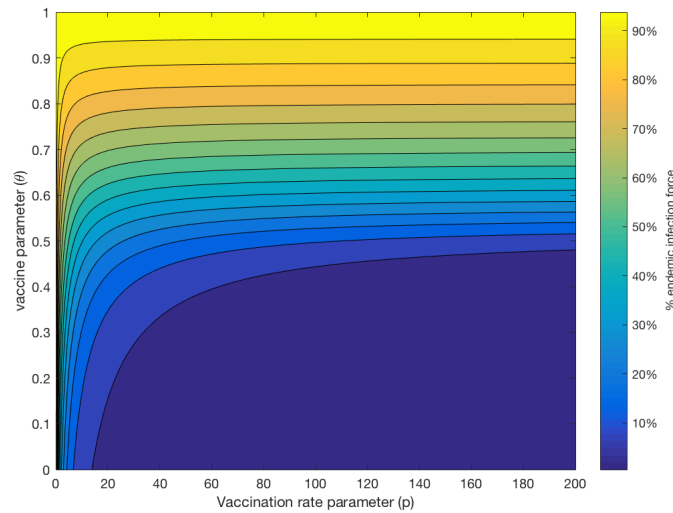
Case 4: $0 < \theta < 1$ and $p > 0$.

The endemic force of infection in the expression (2.34) was simulated as a function of vaccination rate parameter (p) and vaccine parameter (θ). Figure 2.4 below provides a summary of the findings. We supposed the reproduction number (R) is equal to 2. As illustrated by the yellow area in the Figure 2.4, the scaled endemic infection force ($\frac{F^*}{\mu}$) remains almost constant; whereas in the blue area, the reduction of the endemic force of

infection is significant. Compared to the non-vaccination scenario, the endemic force of infection is almost 0. In Figure 2.4, the graphs 2.4a and 2.4b are two views of the same function in a three-dimensional space, whereas the graph 2.4c is a two-dimensional space.



(a) Endemic force of infection as a function of θ and p (b) Endemic force of infection as a function of θ and p



(c) Endemic force of infection in percentage (vaccination versus non-vaccination scenario)

Figure 2.4: Impact of adaptive vaccination strategy on the endemic force of infection ($R = f(0) = 2$)

2.4 Conclusion

The force of infection was developed by Breda et al (2012) to study the disease spread within a closed population and a demographically open population. In the same context of disease spread, the susceptibles in each population are divided into two groups, non-vaccinated susceptible and vaccinated susceptible, in order to evaluate the combined effect of vaccine effectiveness and the vaccination rate on the dynamics of the force of

infection. The adaptive vaccination strategy is used and consists of choosing the rate of vaccination proportional to the force of infection; although, simplistic and natural, this strategy makes the model more analytically tractable. The investigation focuses on the relation between force of infection of the disease spreading, vaccine effectiveness, and adaptive vaccination rate. The vaccine parameter θ ($0 \leq \theta \leq 1$) captures the vaccine effectiveness, and the vaccination rate parameter ($p > 0$) determines the rate of vaccination. As shown by the results, the reproduction number (R) can be used to compare the model without vaccination (Breda et al (2012)) and with vaccination. In fact in each population, R is not affected by the vaccine parameter and the vaccination rate parameters. The findings show that the cumulative force of infection in a closed population and the endemic force of infection in a demographically open population have the same pattern of behavior as they can significantly be reduced by the two factors: the effective vaccine and the vaccination rate. In fact, for a given vaccination rate parameter (p), the cumulative force of infection or the endemic force of infection decreases significantly when the vaccine is effective (θ below a threshold (dark blue color in Figure 2.3 and Figure 2.4)). When p is sufficiently big, the threshold of effectiveness is $\frac{1}{R}$ ($\theta < \frac{1}{R}$) for respectively closed population and demographically open population; and the force of infection transforms an endemic steady state into to a disease free state. The study also highlights the fact that only the effective vaccine is the key for a successful reduction of the force of infection. In fact, when the vaccine is not effective ($\frac{1}{R} < \theta$), for any vaccination rate parameter chosen, the effect on the cumulative force of infection ($y(\infty)$) or the endemic force of infection ($\frac{F^*}{\mu}$) remains significantly different from 0. The results also show that θR serves as an effective Reproduction Number when p is large.

One of the limitations of the study is the linearity relationship assumptions related to the force of infection and the vaccination rate. In fact, it was assumed that the force of infection within the vaccinated susceptibles varies proportionally with the force of infection within the non-vaccinated susceptibles; and the rate of vaccination is proportional to the force of infection. In the future work, the linearity relationship assumptions might be substitute with a more complex relationship.

Chapter 3

SIS Epidemic Model : Birth-and-Death Markov Chain Approach

3.1 Introduction

The Susceptible-Infected-Susceptible (SIS) model is one of the simplest and most paradigmatic models in mathematical epidemiology. In this model, a population is divided into susceptible and infective individuals, with the functions $S(t)$ and $I(t)$ denoting respectively the susceptible individual size and the infected individual size at time t . The evolution of these quantities is described by the deterministic differential equations:

$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta}{M}SI + \alpha I \\ \frac{dI}{dt} &= \frac{\beta}{M}SI - \alpha I\end{aligned}$$

The transmission parameter β is the average number of individuals that one infected individual can infect per time unit. The parameter α is the rate of death and birth. In fact to make the population size(M) constant, each individual who dies is replaced by a susceptible individual. Figure 3.1 depicts the replacement and the infection process. The threshold value $R = \frac{\beta}{\alpha}$, which is a basic reproduction number, is an indicator that determines whether we will have extinction of the disease ($0 < R < 1$) or an outbreak of the disease ($R > 1$). One of the results of the previous deterministic differential equations is the equilibrium of the system in the long run. When $R > 1$, for $\frac{dS}{dt} = 0$ and $\frac{dI}{dt} = 0$, we

have the following equilibrium in term of the population fraction :

$$\begin{cases} \frac{I}{M} = 1 - \frac{\alpha}{\beta} = 1 - \frac{1}{R} \\ \frac{S}{M} = \frac{\alpha}{\beta} = \frac{1}{R} \end{cases}$$

In this chapter, the Markov chain method is used to describe the dynamics of the SIS model and study its features, which are well-known from the deterministic approach such as the impact of the basic reproduction number on the infected size sample paths, and the equilibrium of the sample path in the long run . One of the specific characteristics of the Markov chain is that it allows the study of the equilibrium distribution of the infected size when the population size (M) increases.

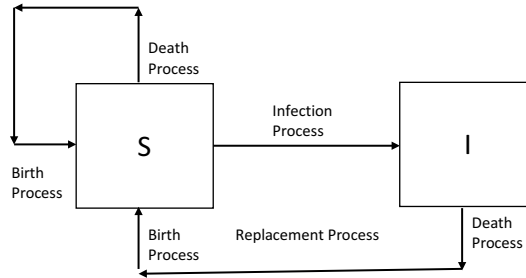


Figure 3.1: Diagram of the infection and replacement process

The chapter is organized as follows: in the next section, we will set up the methodology that will be used to perform the simulation in the subsequent sections. In section 2.3, the infected size will be analysed by simulating infected size sample paths and studying the impact of the reproduction number on these sample paths. Section 2.4 will focus on the distribution of the infected size. Finally, section 2.5 will analytically study the asymptotic infected size distribution. The symptotic distribution developed in this section was tackled by Weirman and Marchette (2004) when modelling the computer virus prevalence. However, the assumption on the infection process was different. In fact, Weirman and Marchette (2004) make use the mass action incidence $(r(M-i)i)^1$ rather than the proportional²incidence $(\beta \frac{(M-i)i}{M})$. Weirman and Marchette (2004)'s model is more general because they take into account case where the parameters are fixed and case where the parameters depend on the population size. In the latter case, they found that the infection

¹" r is the infection rate from a particular infected computer to a particular susceptible computer" Weirman and Marchette (2004,p5)

²According to Arino(2013), with the mass action incidence, all susceptibles can meet all infectious individuals (vice-versa); whereas with proportional incidence, every infectious individual(susceptible) meets the proportion of susceptibles(infectious) in the population

size can follow a Normal distribution. In section 2.5, our analysis will use the Poisson distribution properties, the equivalent function properties, the Taylor series technique and the Local Central Limit Theorem to show the asymptotic distribution of the SIS epidemic model.

3.2 Epidemic Spreading: Stochastic Interacting Particle

Approach

Stochastic Interacting Particle system (IPS) is a continuous time Markov process. It is an individual-based model, which allows us to model the interaction of spatially distributed individuals. In our study, the population can supposedly be spatially distributed, but each individual of the population is in contact with other individuals and therefore can be infected from any infected individual. The methodology developed in this section relies on the work by Klauß et al (2008) and Durrett(1988).

3.2.1 Infection Process Modelling

The size of the population (M) remains constant during all the process. The death of each individual within the population is automatically replaced by a new born. The disease has no effect on the constant death rate and each individual in the population is subjected to the same survival function. At any point in time, each individual from the population has a status of Healthy or infected; and the population can be classified in two groups: Healthy population ($\mathcal{H}$) or Infected population ($\mathcal{I}$).

In order to model the temporal evolution of the infected population ($\mathcal{I}$), we assume the population is spatially distributed and each individual interacts with each other. We consider a connected graph ($G(\mathcal{V}, \mathcal{E})$) and a configuration system ($\{0, 1\}^{\mathcal{V}}$). The connected graph ($G(\mathcal{V}, \mathcal{E})$) is defined by M vertices or nodes ($\mathcal{V}$) with $\mathcal{V} = \{v_1, v_2, \dots, v_M\}$ and the set of edges ($\mathcal{E}$) with $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$ (cartesian product). It is important to note that the structure of the edges plays no role in the dynamics of the model; in fact, every vertex can interact with every other vertex. Each vertex in $\mathcal{V}$ is either healthy individual and will be

denoted 0 or infected individual and will be denoted by 1. The configuration described the state of the whole system $\{0, 1\}^{\mathcal{V}}$ with $\text{cardinality}(\{0, 1\}^{\mathcal{V}}) = 2^M$. For a configuration $f \in \{0, 1\}^{\mathcal{V}}$, we have $f = (f(x))_{x \in \mathcal{V}}$ where f describes the state of each individual in the population, $f(x) = 0$ (healthy) or $f(x) = 1$ (infected). A snapshot of a configuration is shown in Figure 3.2 with 15 infected individuals.

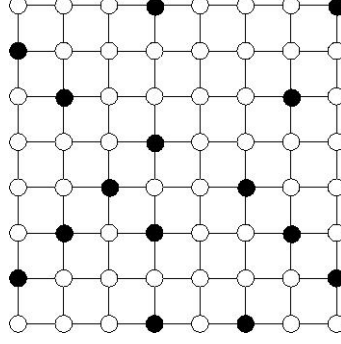


Figure 3.2: Example of configuration $(f = (f(x))_{x \in \mathcal{V}})$ with : $M = 64$, white pixel (healthy), black pixel (infected)

Given a configuration f , the transition from f to $T(f)$ takes place on a single node and can be defined as follows: with $x \in \mathcal{H} \cup \mathcal{I}$

$$T_x(f)(y) = \begin{cases} f(y) & \text{if } y \neq x \\ 1 - f(y) & \text{if } y = x \end{cases}$$

If x has susceptible status, after one transition x will become infected and the infected size will increase. Otherwise x has infected status and after one transition, x will die and will be replaced by a susceptible; the infected size will therefore decrease. Such a transition is called Spin-Flip. In fact, If the configuration f is at time t_0 , between time t_0 and t_1 we have a transition status $(T_x(f))$ for some randomly chosen x , we will have at new configuration $T(f)$ at time t_1 . The dynamic of the system is Markovian. The rate for a transition from the actual configuration f to a new configuration $T(f)$ does not depend on the temporal history of the system but on the present configuration f and the future configuration $T(f)$. In the case of infection process, the transition from f to $T(f)$ depends on three factors: the transmission rate β ; the proportion of infected $(\frac{|f|}{M})$ with $|f|$ the number of infected individuals; and the number of non infected $(M - |f|)$. Each susceptible in the population ($x \in \mathcal{H}$) has the same transition rate, which is $C(f, T_x(f)) = \beta * \frac{|f|}{M}$; and the infection

process transition rate (from f to $T(f)$) is $\sum_{x \in \mathcal{H}} C(f, T_x(f)) = \beta * \frac{(M-|f|)|f|}{M}$, which is the transition rate to $|f| + 1$.

3.2.2 Death Process Modelling

The life span of each individual is modelled by an exponential distribution with parameter α , which does not take into account the status of the individual in the population. As described in Diagram 3.1, after the death of an infected or susceptible, the individual is automatically replaced by a healthy individual. The size of the population remains constant during all the process and the transition rate of the death process ($\alpha * M$) does not change all the time for the population. However, the most interesting case is the death process within the infected population. In fact, only the death of infected population has an impact on the configuration $T(f)$. Therefore, the death transition rate is $\alpha * |f|$ with $|f|$ the number of infected individuals.

3.2.3 Some Results of the IPS Implementation

The methodology was coded into a Matlab program to simulate the infection process. In order to illustrate the results, we choose M equal to 324 individuals, and four configuration snapshots of the disease spreading were taken after 10 transitions, 100 transitions, 800 transitions and 10000 transitions, when the Matlab program was running. Figure 3.3 shown healthy individual in red and infected individual in black. As shown in Figure 3.3a, there were only 3 infected individuals after 10 transitions. Overall, the number of infected individuals increases as illustrated in Figure 3.3b and 3.3c. The infection process becomes stable in Figure 3.3d, as the number of infected individuals becomes stable and starts fluctuating very slowly. These results are consolidated by Figure 3.4 in the next subsection where the number of infected individuals is presented in real time for M equal to 200 individuals.

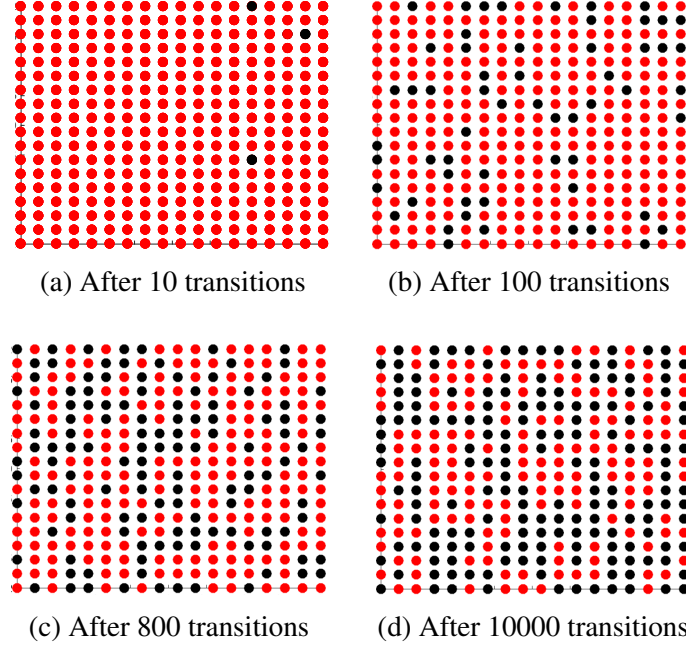


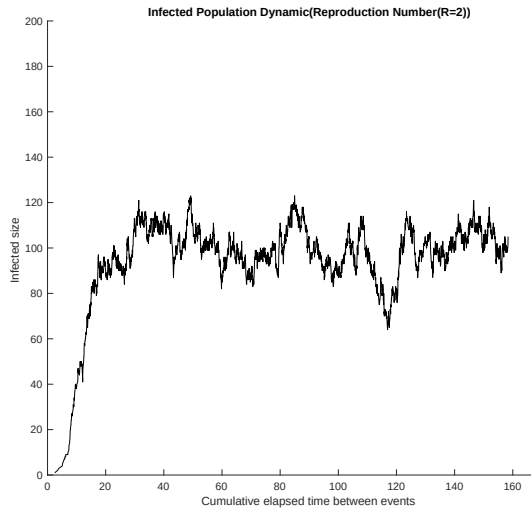
Figure 3.3: Simulation of the configuration $T(f)$ dynamic : $R=4$, $M=324$, healthy(Red) and infected(black)

3.3 Infected Size Analysis

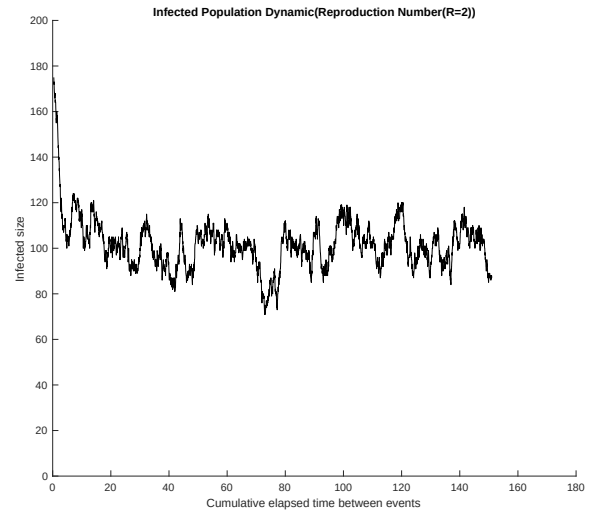
From the previous section, it was shown that the infection transition rate is $\beta * \frac{(M-|f|)|f|}{M}$ and the death transition rate is $\alpha * |f|$ with $|f|$ the number of infected individuals.

3.3.1 Infected sized dynamic and stability: $\beta = 0.6$ and $\alpha = 0.3$

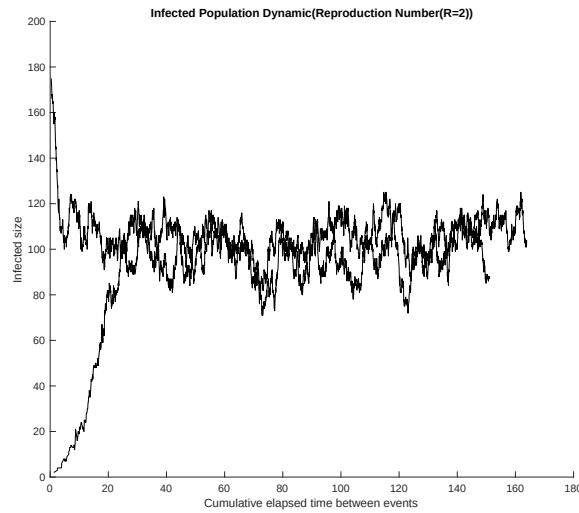
The sample path of this case is presented in Figure 3.4. Figure 3.4a illustrates the sample path where initially we have one infected; Figure 3.4b shows the sample path where initially almost all the population has been infected and Figure 3.4c combines both Graphs. As shown in these Graphs, after a period of increasing or decreasing, the infected size converges to a stable equilibrium.



(a) Only one infected individual initially



(b) Almost all population infected

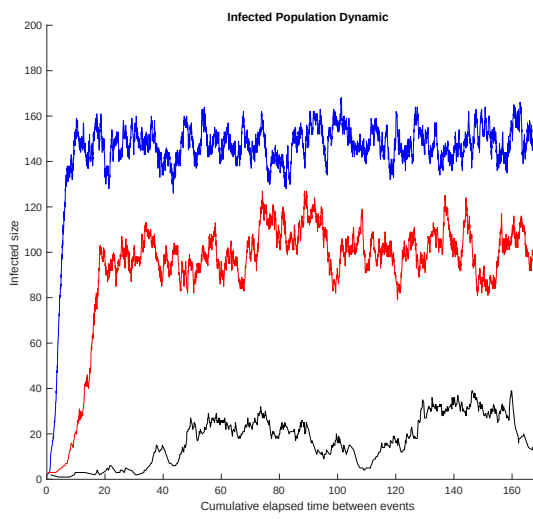


(c) Combined previous cases

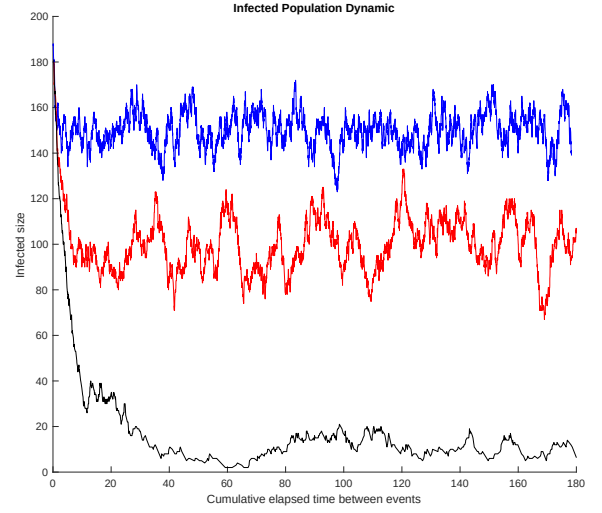
Figure 3.4: Infected sized dynamic and stability ($M=200$)

3.3.2 Impact of the Reproduction Number on Infected Size

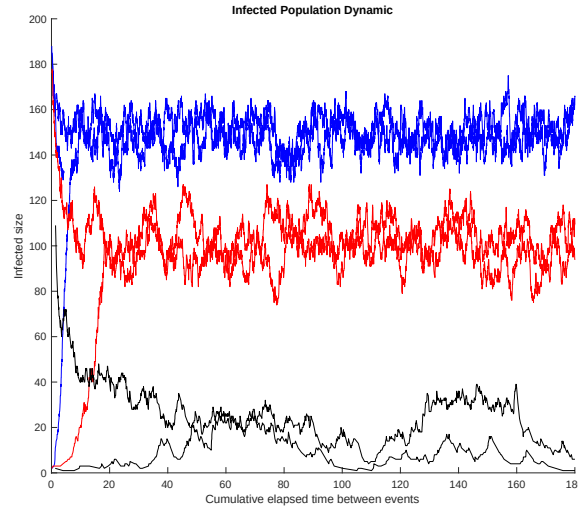
We have illustrated in Figure 3.5 how the sample path reacts to the reproduction number (R). As shown in Figure 3.5a, when the reproduction number is greater than 1, the infected size increases rapidly and plateaus at a high level of equilibrium. The same pattern is observed in Figure 3.5b but after a rapid decrease. The stability in the equilibrium is also shown in Figure 3.5c for $R = 2$ and $R = 4$. For $R = 1$, the process is unstable and the disease will eventually die out.



(a) Only one infected individual initially



(b) Almost all population infected



(c) Combined both above

Figure 3.5: Impact of reproduction number: $R=4$ (Blue), $R=2$ (Red), $R=1$ (Black), ($M=200$)

3.4 Limit Distribution: Numerical Results

The previously described continuous Markov Chain can be analyzed as a general Birth and Death process(Taylor and Karlin(1975,1998)) on the state space $\{0, 1, \dots, M\}$ with transition rates:

$$\lambda_k = \beta \left(\frac{M-k}{M} \right) k \quad (k \rightarrow k+1)$$

$$\mu_k = \alpha k \quad (k \rightarrow k-1)$$

However, $\lambda_0 = \beta \frac{(M-0)}{M} 0 = 0$ makes the Markov Process reducible. In order to have an irreducible Markov Process, we introduce an external source of disease through a small non negative parameter ($\varepsilon > 0$) in the infection transition rate. We have a new Process $P_{M,\varepsilon}$ on the state space $\{0, 1, \dots, M\}$.

$$\begin{aligned}\lambda_i^{[\varepsilon]} &= \beta \frac{(M-i)}{M} i + \varepsilon & (i \rightarrow i+1) \\ \mu_i &= \alpha i & (i \rightarrow i-1)\end{aligned}$$

We also define $\theta_0, \theta_1^{[\varepsilon]}, \dots, \theta_M^{[\varepsilon]}$ as following:

$$\begin{aligned}\theta_0 &= 1 \\ \theta_i^{[\varepsilon]} &= \frac{\lambda_0^{[\varepsilon]} \lambda_1^{[\varepsilon]} \dots \lambda_{i-1}^{[\varepsilon]}}{\mu_1 \mu_2 \dots \mu_i} \quad \text{for } i = 1, \dots, M.\end{aligned}$$

For $\varepsilon > 0$, we let $\pi_{M,\varepsilon}$ be the equilibrium distribution of $P_{M,\varepsilon}$ (Taylor and Karlin(1975,1981))

and we have

$$\pi_M^{[\varepsilon]}(i) = \begin{cases} \frac{\theta_0}{\theta_0 + \sum_{j=1}^M \theta_j^{[\varepsilon]}} & i = 0 \\ \frac{\theta_i^{[\varepsilon]}}{\theta_0 + \sum_{j=1}^M \theta_j^{[\varepsilon]}} & (i = 1, 2, \dots, M) \end{cases}$$

We will consider three case studies based on these values of the reproduction number (R): R=1.1, R=2 and R=4. As it will be shown, the patterns of the equilibrium distribution depend on the reproduction number.

3.4.1 Infected Size Equilibrium Distribution: Case with R=2

For small $\varepsilon > 0$ and R=2, Figure 3.6 illustrates the curve of the equilibrium distribution for a population size M equal to 200. The behaviour of the distribution is a symmetric bell shaped curve and the shape does not depend on ε values as shown below. In fact, we have the same Graph after changing ε values. However, when ε becomes 0, the shape of the distribution vanishes for $i \neq 0$.

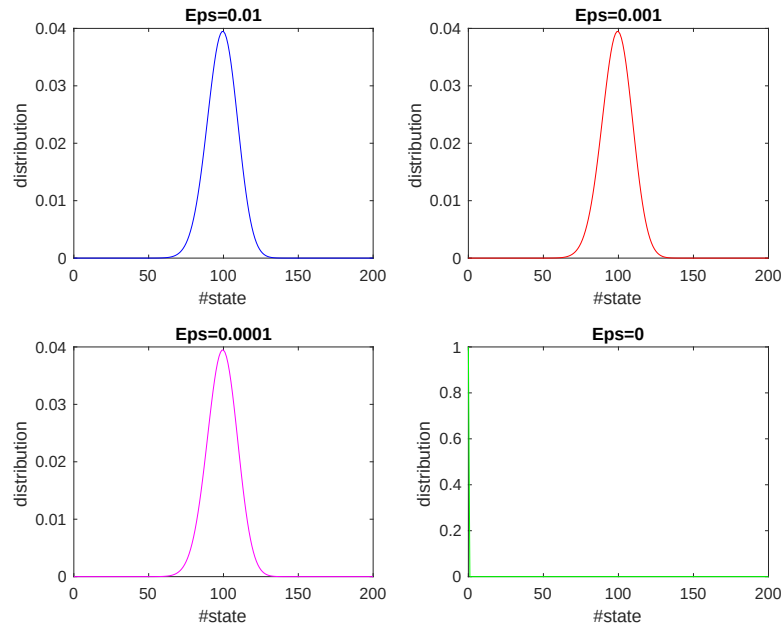


Figure 3.6: Asymptotic distribution : $R=2$, $M=200$ and $\alpha = 0.3$

In Figure 3.7, four statistic indicators (mean, variance, skewness and kurtosis) are used to summary the characteristics of the distribution above. It appears from Figure 3.7a that the mean of infected size is $M/2$. In fact, as shown in the first Graph of the Figure, the ratio of the mean of the infected size to the population size (M) is equal to the constant $1/2$ after population size (M) reaches a threshold between 50 and 100. In the next Graph 3.7b of the same Figure, it also appears that the ratio of the variance of the infected size to the population size(M) is a constant $1/2$, when the population size (M) is growing. It results that the variance of the infected size is $M/2$. The skewness³ equal to 0 (Graph 3.7c) and the kurtosis⁴ equal to 3 (Graph 3.7d) in the same Figure give more evidence that the infected size might follow a normal distribution when the population size(M) reaches a certain threshold.

³ $\sum_{j=0}^M \pi_M^{[E]}(j)(j - \bar{x})^3$ $\bar{x}$ is the mean derived from 3.7a

⁴ $\sum_{j=0}^M \pi_M^{[E]}(j)(j - \bar{x})^4$

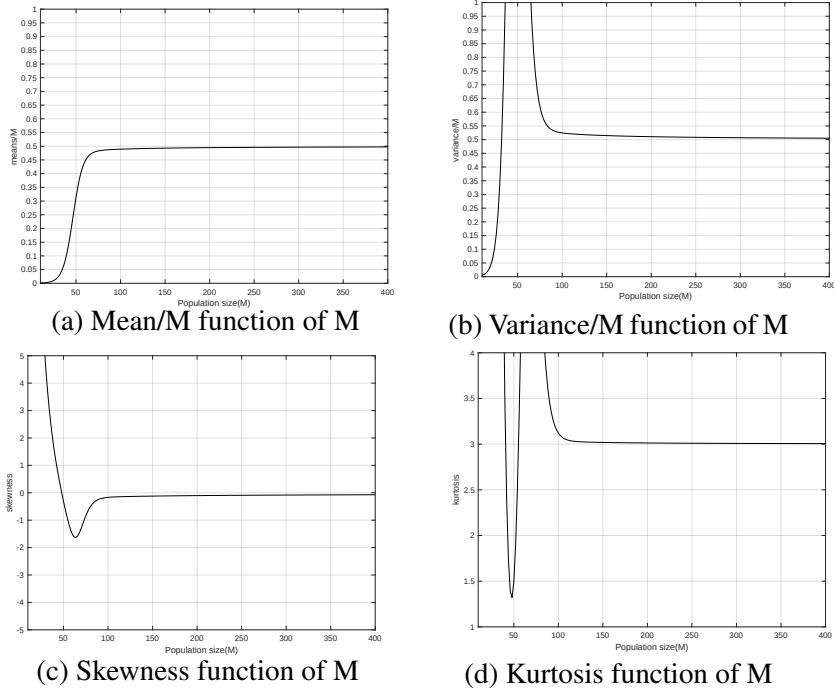


Figure 3.7: Distribution characteristics: $R=2$, $\varepsilon = 0.0001$ and $\alpha = 0.3$

3.4.2 Infected Size Equilibrium Distribution: Case with $R=1.1$

For $R=1.1$, as illustrated in Figure 3.8, the symmetric bell shaped curve of the equilibrium distribution shifts to the left. The distribution needs a high value of M because the reproduction number is near 1, which is the threshold of the disease extinction. In the case shown in Figure 3.8, the population size(M) is 6000. The equilibrium distribution shape does not depend on ε values as shown below.

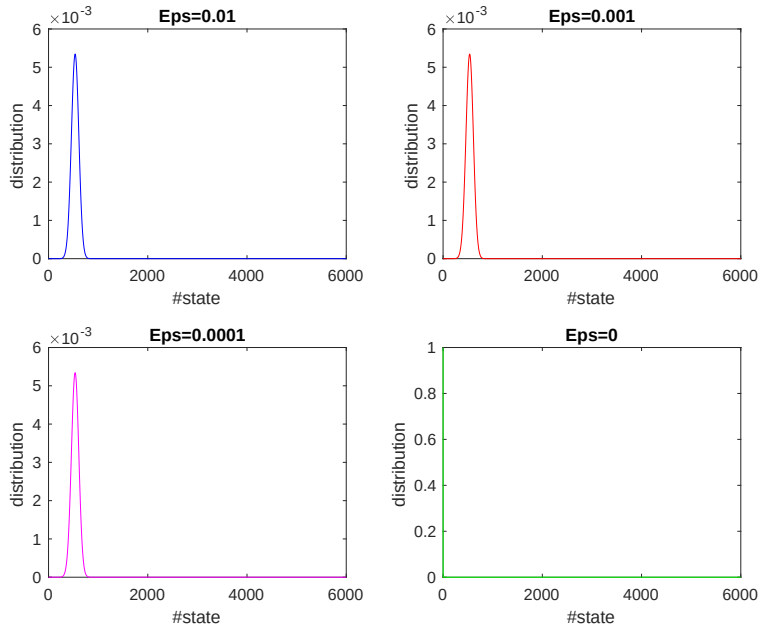


Figure 3.8: Asymptotic distribution : $R=1.1$, $M=6000$ and $\alpha = 0.3$

It appears from Figure 3.9a that the mean of infected size is $(1/11)M$. In fact, as shown in the first Graph of the Figure, the ratio of the mean of the infected size to the population size (M) is $1/11$ after population size (M) reaches a threshold. In the next Graph 3.9b of the same Figure, when the population size (M) grows, the ratio of the variance of the infected size to the population size(M) is a constant $10/11$. It results that the variance of the infected size is $(10/11)M$. The skewness equal 0 (Graph 3.9c) and the kurtosis equal 3 (Graph 3.9d) in the same Figure give more evidence that the infected size might follow a normal distribution, when the population size(M) grows.

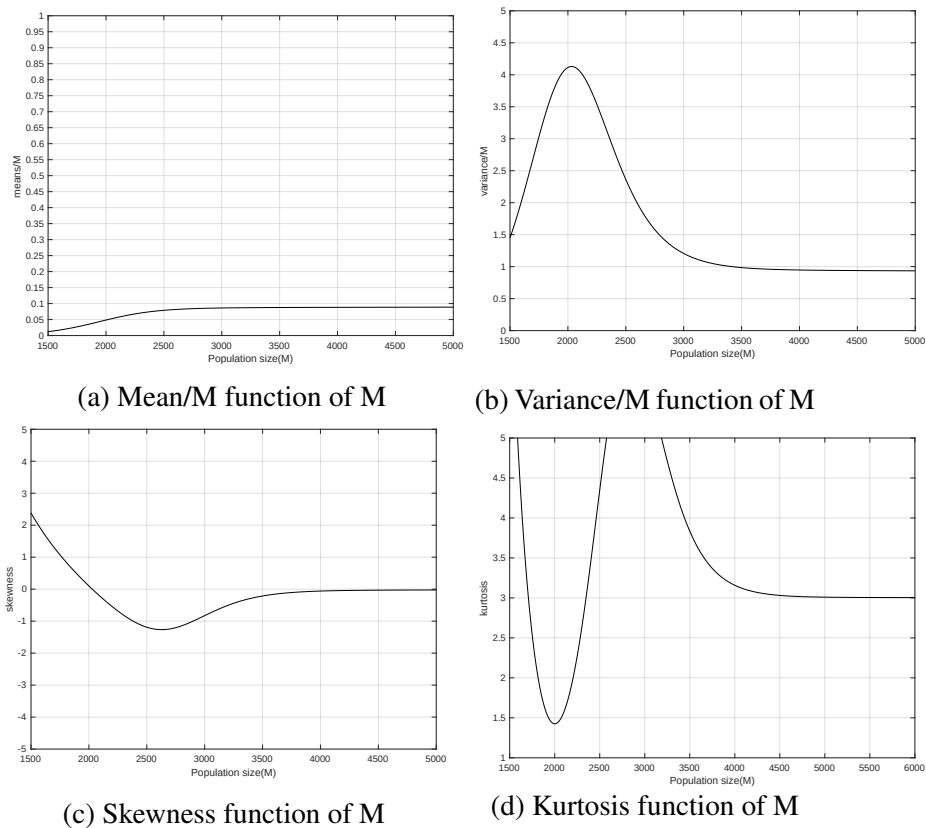


Figure 3.9: Asymptotic distribution : $R=1.1$, $\varepsilon = 0.0001$ and $\alpha = 0.3$

3.4.3 Infected Size Equilibrium Distribution: Case with $R=4$

For $R=4$, the equilibrium distribution (Figure 3.10) shifts to the right and always has the symmetric bell shaped curve. The distribution shape does not depend on ε values as shown below.

It appears from Figure 3.11a that the mean of infected size is $(3/4)M$. In the next Graph 3.11b of the same Figure, it also appears that when the population size (M) grows, the ratio of the variance of the infected size to the population size(M) is a constant $1/4$.

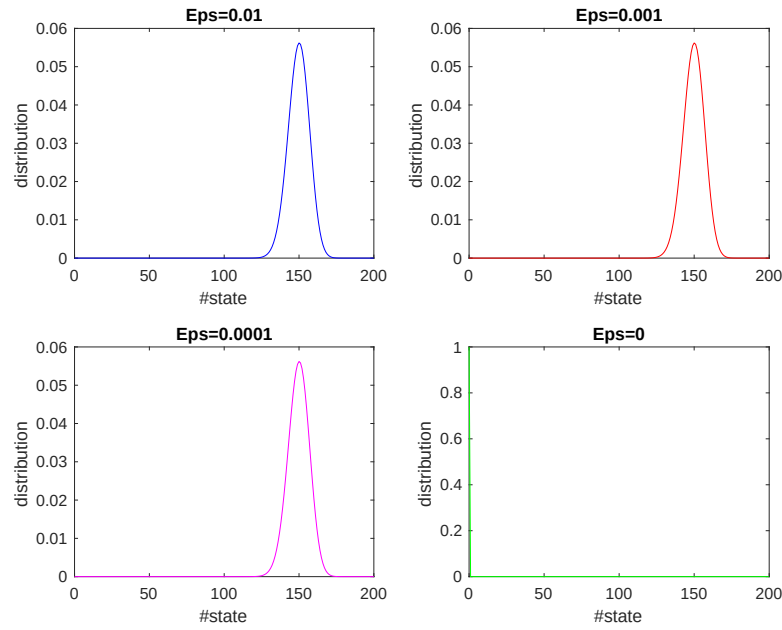


Figure 3.10: Asymptotic distribution : $R=4$, $M=200$ and $\alpha = 0.3$

It results that the variance of the infected size is $(1/4)M$. The skewness equal 0 (Graph 3.11c) and the kurtosis equal 3 (Graph 3.11d) give evidence of the normal distribution.

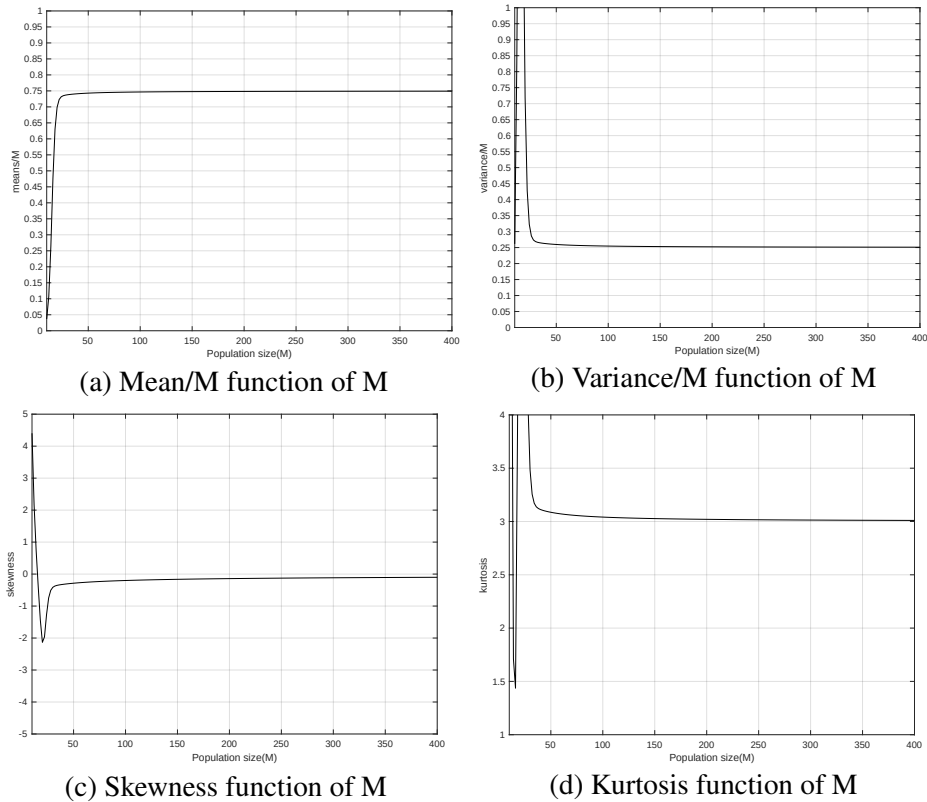


Figure 3.11: Distribution characteristics: $R=4$, $\epsilon = 0.0001$, $M=400$ and $\alpha = 0.3$

3.5 Limit Distribution: Analytical Results

We consider the continuous-time Markov chain on the state space $\{0, 1, \dots, M\}$ with transition rates.

$$\lambda_k = \begin{cases} \beta \left(\frac{M-k}{M}\right) k & \text{for } k = 1 \dots M-1 \\ \varepsilon & \text{for } k = 0 \end{cases} \quad (k \rightarrow k+1)$$

$$\mu_k = \alpha k \quad (k \rightarrow k-1)$$

On the contrary to the previous section, the external factor $\varepsilon > 0$ is used only for λ_0 because it simplifies the analysis giving that 0 is the only absorbing state. Here α and β are strictly positive parameters, and ε is a non negative parameter. We define $\theta_0, \theta_1^{[\varepsilon]}, \dots, \theta_M^{[\varepsilon]}$ by

$$\theta_0 = 1$$

$$\theta_i^{[\varepsilon]} = \frac{\lambda_0 \lambda_1 \dots \lambda_{i-1}}{\mu_1 \mu_2 \dots \mu_i} \quad \text{for } i = 1, \dots, M.$$

The equilibrium distribution of $P_{M,\varepsilon}$ is derived as follows:

$$\pi_M^{[\varepsilon]}(i) = \begin{cases} \frac{\theta_0}{\theta_0 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}} & i = 0 \\ \frac{\theta_i^{[\varepsilon]}}{\theta_0 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}} & (i = 1, 2, \dots, M) \end{cases}$$

Lemma 3.5.1 Assume $\beta > 0$, $\alpha > 0$, $\varepsilon > 0$, $M > 0$ and $R = \frac{\beta}{\alpha}$. We have :

$$\theta_0 = 1$$

$$\theta_{M-k}^{[\varepsilon]} = \frac{\varepsilon}{R\alpha(M-k)} \left(\frac{R}{M}\right)^{M-k} \frac{M!}{k!} \quad \text{for } k = 0, \dots, M-1$$

Proof:

$$\begin{aligned} \theta_{M-k}^{[\varepsilon]} &= \frac{\lambda_0 \lambda_1 \dots \lambda_{(M-k-1)}}{\mu_1 \mu_2 \dots \mu_{(M-k)}} = \frac{\lambda_0}{\mu_{(M-k)}} \prod_{j=1}^{M-k-1} \frac{\lambda_j}{\mu_j} = \frac{\varepsilon}{\alpha(M-k)} \prod_{j=1}^{M-k-1} \left[\frac{\beta}{\alpha} \left(\frac{M-j}{M}\right) \right] \\ &= \frac{\varepsilon}{\alpha(M-k)} \prod_{j=1}^{M-k-1} R \left(\frac{M-j}{M}\right) = \frac{\varepsilon}{R\alpha(M-k)} \left(\frac{R}{M}\right)^{M-k} \frac{M!}{k!} \end{aligned}$$

3.5.1 Some Properties of the Poisson Distribution

Some properties of Poisson distribution will be stated with proof and the results will be applied in the next subsection.

Lemma 3.5.2 Suppose X follows a Poisson distribution with parameter λ and $\mu(d) = E[X|X \leq d] \quad \forall d \in \mathbb{N}^*$

Then:

$$\mu(d) = \lambda \frac{g(d-1)}{g(d)} \quad \text{where } g(d) = \sum_{i=0}^d \frac{\lambda^i}{i!} \quad \text{and} \quad \lim_{d \rightarrow \infty} \frac{g(d-1)}{g(d)} = 1$$

Proof:

Let us define the following function $p(x, \lambda, d) = P(X = x|X \leq d) = \frac{p(X=x)}{p(X \leq d)}$ for $x = 0, \dots, d$

$$p(x, \lambda, d) = \frac{\frac{\lambda^x}{x!} e^{-\lambda}}{\sum_{i=0}^d \frac{\lambda^i}{i!} e^{-\lambda}} = \frac{\frac{\lambda^x}{x!}}{\sum_{i=0}^d \frac{\lambda^i}{i!}} = \frac{\lambda^x}{x!} \frac{1}{g(d)}$$

$$p(x, \lambda, d) = \frac{\lambda^x}{x!} \frac{1}{g(d)} = \frac{g(d-1)}{g(d)} \frac{\lambda^x}{x!} = \frac{g(d-1)}{g(d)} p(x, \lambda, d-1) \quad \text{with} \quad \frac{g(d-1)}{g(d)} = \frac{\sum_{i=0}^{d-1} \frac{\lambda^i}{i!}}{\sum_{i=0}^d \frac{\lambda^i}{i!}} = 1 - \frac{\frac{\lambda^d}{d!}}{\sum_{i=0}^d \frac{\lambda^i}{i!}}$$

$$\lim_{d \rightarrow \infty} \frac{g(d-1)}{g(d)} = 1 - \frac{\lim_{d \rightarrow \infty} \frac{\lambda^d}{d!}}{\lim_{d \rightarrow \infty} \sum_{i=0}^d \frac{\lambda^i}{i!}} = 1 \quad \frac{dg}{d\lambda}(d) = \sum_{j=1}^d j \frac{\lambda^{j-1}}{j!} = \sum_{j=1}^d \frac{\lambda^{j-1}}{(j-1)!} = \sum_{j=0}^{d-1} \frac{\lambda^j}{j!} = g(d-1)$$

$$\lambda \frac{dg}{d\lambda}(d) = \sum_{j=1}^d j \frac{\lambda^j}{j!} = \lambda g(d-1)$$

We have the result

$$\mu(d) = E[X|X \leq d] = \sum_{j=0}^d j p(j, \lambda, d) = \frac{\sum_{j=1}^d j \frac{\lambda^j}{j!}}{g(d)} = \frac{\lambda \frac{dg}{d\lambda}(d)}{g(d)} = \lambda \frac{g(d-1)}{g(d)} \quad \square$$

Corollary 3.5.3 Assume $R > 1$, $M > 0$, and X follows a Poisson distribution with parameter $\frac{M}{R}$. Then : $E[\frac{X}{M}|X < M] = \frac{1}{R} \frac{g(M-2)}{g(M-1)}$ with $\lim_{M \rightarrow \infty} \frac{g(M-2)}{g(M-1)} = 1$

Proof:

From lemma 3.5.2 for $\lambda = \frac{M}{R}$ and $d = M-1$

we have $\mu(M-1) = E[X|X \leq M-1] = \frac{M}{R} \frac{g(M-2)}{g(M-1)}$

$$\begin{aligned} E\left[\frac{X}{M}|X < M\right] &= E\left[\frac{X}{M}|X \leq M-1\right] = \frac{1}{M} E[X|X \leq M-1] = \frac{1}{M} \mu(M-1) \\ &= \frac{1}{M} \frac{M}{R} \frac{g(M-2)}{g(M-1)} \\ &= \frac{1}{R} \frac{g(M-2)}{g(M-1)} \end{aligned}$$

and we have $E\left[\frac{X}{M}|X < M\right] = \frac{1}{R} \frac{g(M-2)}{g(M-1)} \square$

Lemma 3.5.4 (Chernoff bound) Assume X follows a Poisson distribution with parameter λ and let $a > \lambda$. We have : $P(X > a) \leq e^{-\lambda+a-a\log(\frac{a}{\lambda})}$

Proof:

$M(\theta) = e^{\lambda(e^\theta-1)}$ is the moment generating function of the Poisson distribution.

$$M(\theta) = E(e^{\theta X}) = \sum_{i=0}^{k \rightarrow \infty} e^{k\theta} P(X = k) > e^{a\theta} P(X > a)$$

$$\forall \theta \in \mathbb{R} \quad P(X > a) < \frac{M(\theta)}{e^{a\theta}} = e^{\lambda(e^\theta-1)-a\theta}$$

Therefore, $P(X > a) \leq \inf_{\theta \in \mathbb{R}} \{e^{\lambda(e^\theta-1)-a\theta}\}$ and we define a function $\psi(\theta) = e^{\lambda(e^\theta-1)-a\theta}$.

The function $\psi(\theta)$ reaches its minimum at $\theta^* = \log(\frac{a}{\lambda})$ and we have :

$$P(X > a) \leq \inf_{\theta \in \mathbb{R}} (e^{\lambda(e^\theta-1)-a\theta}) = \psi(\theta^*) = e^{-\lambda+a-a\log(\frac{a}{\lambda})} \square$$

Lemma 3.5.5 Assume X follows a Poisson distribution with parameter $\lambda = \frac{M}{R}$. Then

$$P(X > \frac{M}{R} + \delta M) \leq e^{\frac{\phi(\delta R)}{R} M} \quad \forall \delta > 0 \quad \text{where } \phi() \text{ is a function and } \phi(\delta R) < 0$$

Proof:

Let us define the function $\phi(x) = x - (1+x)\log(1+x)$ and it can be shown that : $\phi(x) < 0 \quad \forall x > 0$

For $x = \delta R$, we have $\phi(\delta R) = \delta R - (1 + \delta R)\log(1 + \delta R) < 0$

For $a = \frac{M}{R} + \delta M$ and $\lambda = \frac{M}{R}$, we apply Lemma 3.5.4 and we have :

$$\begin{aligned} P(X > \frac{M}{R} + \delta M) &\leq e^{-\lambda + \frac{M}{R} + \delta M - (\frac{M}{R} + \delta M)\log(\frac{\frac{M}{R} + \delta M}{\lambda})} = e^{-\frac{M}{R} + \frac{M}{R} + \delta M - (\frac{M}{R} + \delta M)\log(\frac{\frac{M}{R} + \delta M}{\frac{M}{R}})} \\ &\leq e^{\frac{M}{R}(\delta R - (1 + \delta R)\log(1 + \delta R))} = e^{\frac{M}{R}\phi(\delta R)} = e^{\frac{\phi(\delta R)}{R} M} \end{aligned}$$

Lemma 3.5.6 Assume $R > 1$, $M > 0$, X follows a Poisson distribution with parameter

$\lambda = \frac{M}{R}$. Then

$$\limsup_{M \rightarrow \infty} E\left(\frac{M}{M-X} | X < M\right) \leq \frac{1}{1 - \frac{1}{R}}$$

Proof:

$$E\left[\frac{M}{M-X} | X < M\right] = \frac{E\left[\frac{M}{M-X} I(X < M)\right]}{P(X < M)} \quad \text{where } I(X < M) \text{ is an indicator function}$$

$$E\left[\frac{M}{M-X} I(X < M)\right] = E\left[\frac{M}{M-X} I(X \leq M^*)\right] + E\left[\frac{M}{M-X} I(M^* < X < M)\right]$$

where $M^* = \frac{M}{R} + \delta M$, for $\delta > 0$. Moreover, we assume that $M^* < M$ which is equivalent

to $0 < \delta < \frac{R-1}{R}$

$$E\left[\frac{M}{M-X} I(X \leq M^*)\right] = E\left[\frac{M}{M-X} I(X \leq \frac{M}{R} + \delta M)\right] \leq \frac{1}{1 - \frac{1}{R} - \delta} P(X \leq \frac{M}{R} + \delta M)$$

$$E\left[\frac{M}{M-X} I(M^* < X < M)\right] = E\left[\frac{M}{M-X} I(\frac{M}{R} + \delta M < X < M)\right] \leq \frac{M}{M - (M-1)} P(\frac{M}{R} + \delta M < X) \leq MP(\frac{M}{R} + \delta M < X)$$

By applying Lemma 3.5.5, $E\left[\frac{M}{M-X} I(M^* < X < M)\right] \leq Me^{\frac{\phi(\delta R)}{R}M}$ where $\phi(\delta R) < 0$.

$$\begin{aligned} E\left[\frac{M}{M-X} | X < M\right] &= \frac{E\left[\frac{M}{M-X} I(X < M)\right]}{P(X < M)} = \frac{E\left[\frac{M}{M-X} I(X \leq M^*)\right] + E\left[\frac{M}{M-X} I(M^* < X < M)\right]}{P(X < M)} \\ &= \frac{E\left[\frac{M}{M-X} I(X \leq M^*)\right]}{P(X < M)} + \frac{E\left[\frac{M}{M-X} I(M^* < X < M)\right]}{P(X < M)} \\ &\leq \frac{P(X \leq \frac{M}{R} + \delta M)}{P(X < M)} \frac{1}{1 - \frac{1}{R} - \delta} + \frac{1}{P(X < M)} Me^{\frac{\phi(\delta R)}{R}M} \\ &\leq \frac{1}{1 - \frac{1}{R} - \delta} + \frac{1}{P(X < M)} Me^{\frac{\phi(\delta R)}{R}M} \end{aligned}$$

By applying Lemma 3.5.5 with $\delta^* = 1 - \frac{1}{R}$

$$P[X > M] = P[X > \frac{M}{R} + (1 - \frac{1}{R})M] \leq e^{\frac{\phi(R\delta^*)}{R}M} \quad \text{and} \quad \lim_{M \rightarrow \infty} P[X > M] = 0$$

Therefore, we have $\lim_{M \rightarrow \infty} \frac{1}{P(X < M)} Me^{\frac{\phi(\delta R)}{R}M} = 0$

And the result follows:

$$\begin{aligned} \limsup_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] &\leq \frac{1}{1 - \frac{1}{R} - \delta} \quad \text{for } 0 < \delta < \frac{R-1}{R} \\ \lim_{\delta \rightarrow 0} \limsup_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] &\leq \lim_{\delta \rightarrow 0} \frac{1}{1 - \frac{1}{R} - \delta} \\ \limsup_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] &\leq \frac{1}{1 - \frac{1}{R}} \end{aligned}$$

3.5.2 Approximation of the Asymptotic Distribution of $P_{M,\varepsilon}$

Lemma 3.5.7 Assume $\beta > 0$, $\alpha > 0$, $\varepsilon > 0$, $M > 0$ with $R = \frac{\beta}{\alpha} > 1$.

$$\sum_{k=0}^M \theta_{(M-k)}^{[\varepsilon]} = 1 + \sum_{k=0}^{M-1} \theta_{(M-k)}^{[\varepsilon]} \sim C(M) \frac{R}{R-1} e^{\left(\frac{M}{R}\right)} \quad \text{As } M \rightarrow \infty \text{ and } C(M) = \frac{M! \varepsilon}{MR\alpha} \left(\frac{R}{M}\right)^M$$

Proof:

$$\begin{aligned} \sum_{k=0}^{M-1} \theta_{M-k}^{[\varepsilon]} &= \sum_{k=0}^{M-1} \frac{\varepsilon}{R\alpha(M-k)} \left(\frac{R}{M}\right)^{M-k} \frac{M!}{k!} \quad (\theta_{M-k}^{[\varepsilon]} \text{ from Lemma 3.5.1}) \\ &= \frac{M! \varepsilon}{MR\alpha} \left(\frac{R}{M}\right)^M \sum_{k=0}^{M-1} \frac{M}{M-k} \frac{1}{k!} \left(\frac{M}{R}\right)^k \\ &= C(M) e^{\left(\frac{M}{R}\right)} \sum_{k=0}^{M-1} \frac{M}{M-k} \frac{1}{k!} \left(\frac{M}{R}\right)^k e^{-\left(\frac{M}{R}\right)} \quad \text{with } C(M) = \frac{M! \varepsilon}{MR\alpha} \left(\frac{R}{M}\right)^M \\ &= C(M) e^{\left(\frac{M}{R}\right)} \sum_{k=0}^{M-1} \frac{M}{M-k} P[X = k] \quad \text{with } X \sim \text{Poisson}\left(\frac{M}{R}\right) \\ &= C(M) e^{\left(\frac{M}{R}\right)} E\left[\frac{M}{M-X} I(X < M)\right] \quad (I(X < M) \text{ indicator function}) \end{aligned}$$

We have the following conditional expectation

$$E\left[\frac{M}{(M-X)} I(X < M)\right] = P[X < M] E\left[\frac{M}{M-X} | X < M\right] \quad (3.1)$$

By applying Lemma 3.5.5 with $\delta = 1 - \frac{1}{R}$

$$P[X > M] = P\left[X > \frac{M}{R} + \left(1 - \frac{1}{R}\right)M\right] \leq e^{\frac{\phi\left((1-\frac{1}{R})R\right)}{R}M} \quad \text{and} \quad \lim_{M \rightarrow \infty} P[X > M] = 0$$

We have $\lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} I(X < M)\right] = \lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right]$

We need to show that $\lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right]$ exists and $\lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] = \frac{1}{1-\frac{1}{R}}$. In fact, the restriction on $0 \leq x < M$ of the function $f_M(x) = \frac{M}{M-x}$ is convex.

By using the Jensen Inequality property, $f_M(E[X | X < M]) \leq E[f_M(X) | X < M]$

From corollary 3.5.3 $E[X | X < M] = \frac{M}{R} \frac{g(M-2)}{g(M-1)}$

By substitution in the Jensen Inequality, we have :

$$E\left[\frac{M}{(M-X)} | X < M\right] \geq \frac{M}{M - E[X | X < M]} = \frac{M}{M - \frac{M}{R} \left(\frac{g(M-2)}{g(M-1)}\right)} \quad \forall M > 0$$

We take the limit inferior

$$\liminf_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] \geq \liminf_{M \rightarrow \infty} \frac{1}{\left(1 - \frac{1}{R} \left(\frac{g(M-2)}{g(M-1)}\right)\right)} = \frac{1}{\left(1 - \frac{1}{R}\right)}$$

The upper bound results from lemma 3.5.6 $\limsup_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] \leq \frac{1}{1 - \frac{1}{R}}$

We have :

$$\frac{1}{1 - \frac{1}{R}} \leq \liminf_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] \leq \lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] \leq \limsup_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] \leq \frac{1}{1 - \frac{1}{R}}$$

Therefore, $\lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right]$ exists and

$$\lim_{M \rightarrow \infty} E\left[\frac{M}{M-X} | X < M\right] = \frac{1}{1 - \frac{1}{R}} \quad (3.2)$$

Previously, we have shown that

$$\sum_{k=0}^{M-1} \theta_{(M-k)}^{[\varepsilon]} = C(M) e^{\left(\frac{M}{R}\right)} E\left[\frac{M}{M-X} I(X < M)\right] \quad \text{with } C(M) = \frac{M! \varepsilon}{M R \alpha} \left(\frac{R}{M}\right)^M$$

$$\frac{1 + \sum_{k=0}^{M-1} \theta_{(M-k)}^{[\varepsilon]}}{C(M) e^{\left(\frac{M}{R}\right)} \left(\frac{R}{R-1}\right)} = \left(1 - \frac{1}{R}\right) E\left[\frac{M}{M-X} I(X < M)\right] + \frac{1}{C(M) e^{\left(\frac{M}{R}\right)} \left(\frac{R}{R-1}\right)} \quad (3.3)$$

$\lim_{M \rightarrow \infty} \left(1 - \frac{1}{R}\right) E\left[\frac{M}{M-X} I(X < M)\right] = 1$ comes from the result (3.2).

We need to show that

$$\lim_{M \rightarrow \infty} \frac{1}{C(M) e^{\left(\frac{M}{R}\right)} \left(\frac{R}{R-1}\right)} = 0 \quad \forall R > 1 \quad (3.4)$$

And we know that

$$\begin{aligned} M! &\sim \sqrt{2\pi} e^{-M} M^{M+\frac{1}{2}} \\ C(M) &\sim \sqrt{2\pi} \frac{\varepsilon}{R\alpha} \frac{1}{\sqrt{M}} e^{M(-1+\log(R))} \\ C(M) e^{\left(\frac{M}{R}\right)} \left(\frac{R}{R-1}\right) &\sim \sqrt{2\pi} \frac{\varepsilon}{(R-1)\alpha} \frac{1}{\sqrt{M}} e^{M(-1+\log(R)+\frac{1}{R})} \end{aligned}$$

We define the function $\psi(R) = -1 + \log(R) + \frac{1}{R}$. $\psi(R)$ is an increasing function for $R > 1$

and $\psi(1) = 0$. Therefore, we have: $\psi(R) > 0$ for $\forall R > 1$.

We have (3.4) (proved)

$$\lim_{M \rightarrow \infty} \frac{1}{C(M)e^{\left(\frac{M}{R}\right)\left(\frac{R}{R-1}\right)}} = \lim_{M \rightarrow \infty} \frac{1}{\sqrt{2\pi} \frac{\varepsilon}{(R-1)\alpha}} \sqrt{M} e^{-M\psi(R)} = 0$$

From (3.3), we have : $\lim_{M \rightarrow \infty} \frac{1 + \sum_{k=0}^{M-1} \theta_{(M-k)}^{[\varepsilon]}}{C(M)e^{\left(\frac{M}{R}\right)\left(\frac{R}{R-1}\right)}} = 1$

This proves the lemma $\square$

Theorem 3.5.8 Assume $\beta > 0$, $\alpha > 0$, $\varepsilon > 0$, $M > 0$ with $R = \frac{\beta}{\alpha} > 1$. The infected size has the following equilibrium distribution.

$$\pi_M^{[\varepsilon]}(k) \sim \pi(k) \quad \text{As } M \rightarrow \infty$$

with

$$\pi(k) = \frac{R-1}{R} \frac{M}{(M-k)!k} \left(\frac{M}{R}\right)^{M-k} e^{-\left(\frac{M}{R}\right)} \quad (k = 1, 2, \dots, M)$$

Proof: for $k = 1, 2, \dots, M$

$$\begin{aligned} \pi_M^{[\varepsilon]}(k) &= \frac{\theta_k^{[\varepsilon]}}{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}} = \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}} \frac{\theta_k^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}} \\ &= \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}} \frac{\frac{\varepsilon}{R\alpha k} \left(\frac{R}{M}\right)^k \frac{M!}{(M-k)!}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}} = \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}} \frac{\frac{\varepsilon}{R\alpha k} \left(\frac{R}{M}\right)^k \frac{M!}{(M-k)!}}{\frac{M!\varepsilon}{M\alpha(R-1)} \left(\frac{R}{M}\right)^M e^{\left(\frac{M}{R}\right)}} \\ &= \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}} \frac{R-1}{R} \frac{M}{(M-k)!k} \left(\frac{M}{R}\right)^{M-k} e^{-\left(\frac{M}{R}\right)} = \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}} \pi(k) \end{aligned}$$

We have the following quotient :

$$\frac{\pi_M^{[\varepsilon]}(k)}{\pi(k)} = \frac{1}{\frac{1 + \sum_{j=0}^{M-1} \theta_{(M-j)}^{[\varepsilon]}}{C(M)\left(\frac{R}{R-1}\right)e^{\left(\frac{M}{R}\right)}}}$$

Now the result follows from lemma 3.5.7 $\square$

3.5.3 Normal Distribution and Asymptotic Distribution of $P_{M,\varepsilon}$

Theorem 3.5.9 Assume $\beta > 0$, $\alpha > 0$, $M \gg 1$ with $R = \frac{\beta}{\alpha} > 1$. The infected size follows asymptotically⁵ a normal distribution with mean $\mu = (1 - \frac{1}{R})M$ and variance $\sigma^2 = \frac{M}{R}$.

Proof:

Let us take

$$\psi(k) = \frac{R-1}{R\sqrt{2\pi}} \frac{M}{k(M-k)^{\frac{1}{2}}} \left(\frac{M}{(M-k)R} \right)^{M-k} e^{-\left(\frac{M}{R}\right) + (M-k)} \quad (3.5)$$

We want to show that

$$\lim_{M \rightarrow \infty} \frac{\psi(k)}{\pi(k)} = 1 \quad (3.6)$$

We know that $k! \sim \sqrt{2\pi} e^{-k} k^{k+\frac{1}{2}}$ and $(M-k)! \sim \sqrt{2\pi} e^{-(M-k)} (M-k)^{(M-k)+\frac{1}{2}}$

Therefore,

$$\begin{aligned} \pi(k) &= \frac{R-1}{R} \frac{M}{(M-k)!k} \left(\frac{M}{R} \right)^{M-k} e^{-\left(\frac{M}{R}\right)} \sim \frac{R-1}{R} \frac{M}{k\sqrt{2\pi} e^{-(M-k)} (M-k)^{(M-k)+\frac{1}{2}}} \left(\frac{M}{R} \right)^{M-k} e^{-\left(\frac{M}{R}\right)} \\ &= \frac{R-1}{R\sqrt{2\pi}} \frac{M}{k(M-k)^{\frac{1}{2}}} \left(\frac{M}{(M-k)R} \right)^{M-k} e^{-\left(\frac{M}{R}\right) + (M-k)} \\ &= \psi(k) \end{aligned}$$

We apply the Taylor's expansion theory to these functions

Supposed that $x = k = (1 - \frac{1}{R})M(1 + \delta)$, we have also $M - k = \frac{1}{R}M - (1 - \frac{1}{R})M\delta$

$$\log(M - k) = \log\left(\frac{M}{R}\right) + \log(1 - (R-1)\delta) \quad (3.7)$$

$$\log(1 - (R-1)\delta) = -(R-1)\delta - \frac{1}{2}(R-1)^2\delta^2 + O_2(\delta^3) \quad \text{with } \frac{1}{R-1} > |\delta| \quad (3.8)$$

$$\begin{aligned} \log(k) &= \log\left(\left(1 - \frac{1}{R}\right)M(1 + \delta)\right) = \log\left(1 - \frac{1}{R}\right) + \log(M) + \log(1 + \delta) \\ &= \log\left(1 - \frac{1}{R}\right) + \log(M) + \delta - \frac{1}{2}\delta^2 + O_1(\delta^3) \quad \text{with } 1 > |\delta| \quad (3.9) \end{aligned}$$

⁵As $M \rightarrow \infty$

From (3.8), it results the following development.

$$\begin{aligned}
(M-k+\frac{1}{2})\log(1-(R-1)\delta) &= (\frac{M}{R} - (1-\frac{1}{R})M\delta + \frac{1}{2})(-(R-1)\delta - \frac{1}{2}(R-1)^2\delta^2 + O_2(\delta^3)) \\
&= -(\frac{M}{R} + \frac{1}{2})(R-1)\delta - \frac{1}{2}(\frac{M}{R} + \frac{1}{2})(R-1)^2\delta^2 + \frac{(R-1)^2}{R}M\delta^2 \\
&\quad + \frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 + (M-k+\frac{1}{2})O_2(\delta^3) \\
&= -\frac{(R-1)}{R}M\delta - \frac{(R-1)}{2}\delta - \frac{1}{4}(R-1)^2\delta^2 + \frac{1}{2}\frac{(R-1)^2}{R}M\delta^2 \\
&\quad + \frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 + (M-k+\frac{1}{2})O_2(\delta^3) \\
&= -\frac{(R-1)}{2}\delta - \frac{1}{4}(R-1)^2\delta^2 - \frac{(R-1)}{R}M\delta + \frac{1}{2}\frac{(R-1)^2}{R}M\delta^2 \\
&\quad + \frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 + (\frac{M}{R} - (1-\frac{1}{R})M\delta + \frac{1}{2})O_2(\delta^3)
\end{aligned}$$

From (3.5) and (3.7)...(3.9), we have:

$$\begin{aligned}
\log(\psi(k)) &= \log(\frac{R-1}{R\sqrt{2\pi}}) + \log(\frac{M}{k}) - \frac{1}{2}\log(M-k) + (M-k)\log(\frac{M}{(M-k)R}) - \frac{M}{R} + (M-k) \\
&= \log(\frac{R-1}{R\sqrt{2\pi}}) + \log(M) - \log(k) - \frac{1}{2}\log(M-k) + (M-k)\log(\frac{M}{(M-k)R}) - \frac{M}{R} + (M-k) \\
&= \log(\frac{R-1}{R\sqrt{2\pi}}) - \frac{M}{R} - \log(1-\frac{1}{R}) - \delta + \frac{1}{2}\delta^2 + O_1(\delta^3) + (M-k) - \frac{1}{2}\log(\frac{M}{R}) \\
&\quad - (M-k+\frac{1}{2})\log(1-(R-1)\delta) \\
&= -\frac{1}{2}\log(2\pi\frac{M}{R}) - \delta + \frac{1}{2}\delta^2 + O_1(\delta^3) - (1-\frac{1}{R})M\delta + \frac{(R-1)}{2}\delta + \frac{1}{4}(R-1)^2\delta^2 \\
&\quad + \frac{(R-1)}{R}M\delta - \frac{1}{2}\frac{(R-1)^2}{R}M\delta^2 - \frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 - (\frac{M}{R} - (1-\frac{1}{R})M\delta + \frac{1}{2})O_2(\delta^3) \\
&= -\frac{1}{2}\log(2\pi\frac{M}{R}) - \frac{1}{2}\frac{(R-1)^2}{R}M\delta^2 + [\frac{(R-3)}{2}\delta + \frac{1}{4}((R-1)^2+2)\delta^2 + O_1(\delta^3)] \\
&\quad + [-\frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 - (\frac{1-(R-1)\delta}{R}M + \frac{1}{2})O_2(\delta^3)]
\end{aligned}$$

$$\psi(k) = \frac{1}{\sqrt{2\pi\frac{M}{R}}} e^{\left\{-\frac{1}{2}\frac{(R-1)^2}{R}M\delta^2\right\}} e^{\left\{\frac{(R-3)}{2}\delta + \frac{1}{4}((R-1)^2+2)\delta^2 + O_1(\delta^3)\right\}} e^{\left\{-\frac{1}{2}\frac{(R-1)^3}{R}M\delta^3 - (\frac{1-(R-1)\delta}{R}M + \frac{1}{2})O_2(\delta^3)\right\}}$$

(3.10)

We will prove the Local Central Limit Theorem. For k integer, to get a convenient limit,

we will choose m_M , σ_M and k as a function of M ($k = k(M)$) that satisfy the following properties:

$$\lim_{M \rightarrow \infty} \frac{k - m_M}{\sigma_M} = s \quad \text{for some real number } s.$$

and

$$\Pr(X_M = k(M)) \sim \frac{1}{\sqrt{2\pi}\sigma_M} e^{-s^2/2} \quad \text{as } M \rightarrow \infty$$

In our case (theorem 3.5.7), we will choose $m_M = (1 - \frac{1}{R})M$ and $\sigma_M = \sqrt{M/R}$. Fix a real number s , we choose the sequence $k(M)$ such as

$$\lim_{M \rightarrow \infty} \frac{k - m_M}{\sigma_M} = s \tag{3.11}$$

$k(M)$ is provided by the previous Taylor's expansion condition $k(M) = (1 - \frac{1}{R})M(1 + \delta)$ with $\text{Min}(\frac{1}{R-1}, 1) > \delta$.

The limit (3.11) holds if $\delta = \delta(M) = \frac{s\sqrt{R}}{(R-1)\sqrt{M}}$. In addition, we have the following property

$$\lim_{M \rightarrow \infty} \delta = 0 \qquad \lim_{M \rightarrow \infty} M\delta^3 = \lim_{M \rightarrow \infty} \frac{s^3 R^{\frac{3}{2}}}{(R-1)^3 \sqrt{M}} = 0$$

From the function (3.10) and the equivalent function (3.6), as $M \rightarrow \infty$, we have :

$$\pi(k) \sim \frac{1}{\sqrt{2\pi}\sigma_M} e^{\{-\frac{1}{2}s^2\}} \tag{3.12}$$

3.6 Conclusion

The SIS epidemic model is analysed through the dynamic of the infected size over time and the equilibrium distribution of the infected size at the equilibrium. The study of the infected size over time is based on the Stochastic Interacting Particle System (*IPS*) approach, which is used to simulate the spread of the disease within the population. The stability and the equilibrium convergence of the resulting infected size was shown through

the sample path simulations. The impact of the reproduction number (R) on the infected size sample paths was studied as well. The stochastic simulations show that when the reproduction number increases, the level of infected size increases as well and the infected size sample path increases as a whole. These results are not different from the findings derived from the deterministic approach.

The study of the equilibrium distribution of infected size is based on the Birth and Death Markov chain approach. In fact, this approach was made possible by transforming a reducible Markov chain process to an irreducible Markov chain process by introducing a small $\varepsilon > 0$ that allows 0 not to be an absorbing state. It results from the numerical method that the equilibrium distribution of the infected size is a symmetric-bell shaped curve and the mean and the variance are functions of the reproduction number (R). An in-depth analysis of the equilibrium distribution of the infected size was performed with the size of the population (M) large. The analysis relies on the Poisson distribution properties, the Taylor development series techniques and the local Central Limit theorem. It results that asymptotic distribution of the infected size follows a Normal distribution with mean $(1 - \frac{1}{R})M$ and variance $\frac{M}{R}$.

Chapter 4

SIS Epidemic Model : Non - Markov Chain Approach

4.1 Introduction

In the non-markovian case, we are interested in studying the impact of the Gamma distribution of the individual lifetime on the SIS Epidemic Dynamic. In this context, we will determine the new the reproduction number (R) and study the effect of the gamma distribution on the infected size equilibrium which is the equilibrium where the disease spread converges when the reproduction number (R) is greater than one. The key assumptions of the Markov SIS Epidemic Dynamic remain the same, only the lifetime exponential distribution is changed and replaced by a much broader class of Gamma distribution with shape parameter (k) and scale parameter (α). As illustrated in the Figure (4.1), the Gamma density has a large variety of shapes.

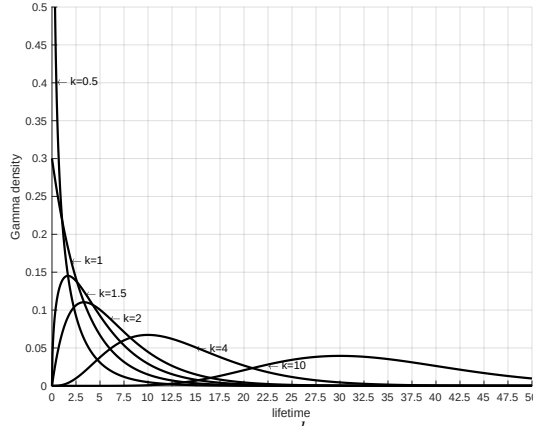


Figure 4.1: Some Gamma density ($f(x) = \frac{\alpha^k}{\Gamma(k)} x^{k-1} e^{-\alpha x}$) of the lifetime with shape parameter k and scale parameter $\alpha = 0.3$

As shown in Figure (4.1), when $k \leq 1$, the lifetime frequency is concentrated around 0 and the population has shorter lifetime; in fact, this is true on average because the mean of the Gamma distribution is $\frac{k}{\alpha}$. On the other hand, when $1 < k$, the population lives longer. The longer or shorter lifetime has an impact on the disease spread dynamic and the convergence of the disease spread to the infected size equilibrium. As a methodology, the determination of reproduction number (R) is based on the work of Breda et al (2012). R values will be used to simulate some samples of the infection path in order to check the relationship between infection size and reproduction number. In the remaining analysis, the limit of excess or residual lifetime variable and its asymptotic distribution as defined in the Renewal Theory (Karlin and Taylor (1975)) will be used as a basis to provide an estimation of the infected size equilibrium. The approaches are both numerical and analytical methods. As numerical method, the composite Newton-Cotes quadrature formulas will be implemented in order to provide the best accurate estimation of the infected size equilibrium. As analytical method, the Extreme Value Theory will be used to determine analytically the asymptotic behaviour of the infected size equilibrium.

4.2 Reproduction Number Analysis

Determining the reproduction number (R) of the Gamma distribution lifetime relies on the work of Breda et al (2012). The reproduction number formulas will be used to simulate some samples of the infection path when the R value changes. In the subsequent section, reproduction number formula will be used to estimate and analyse the infected

size equilibrium.

4.2.1 Non-Markovian Reproduction Number

According to Breda et al (2012), in a general case where per capita rate of infectivity ($A(\tau)$) depends on the time (τ) elapsed since the infection took place, the reproduction number is defined by:

$$R = B \int_0^\infty \int_0^\infty \mathcal{F}(a + \tau) A(\tau) d\tau da \quad (4.1)$$

B is the constant birth rate; $\mathcal{F}(a) = \int_a^\infty f(y) dy$ the survival probability; the incomplete gamma function $\Gamma(s, x) = \int_x^\infty t^{s-1} e^{-t} dt$.

Proposition 4.2.1 *We assume the per capita rate of infectivity $A(\tau)$ is a constant $\beta > 0$, and the life time of individual follows a gamma distribution with the shape parameter (k) and the scale parameter (α). The reproduction number R for the SIS model becomes:*

$$R = \frac{\beta}{\alpha} \frac{k+1}{2} \quad (4.2)$$

Proof:

By replacing $A(\tau) = \beta$, the formula (4.1) becomes

$$R = B\beta \int_0^\infty \int_0^\infty \mathcal{F}(a + \tau) d\tau da$$

$\mathcal{F}(a)$ is the gamma survival probability and we change the variable $y = a + \tau$.

$$\int_0^\infty \int_0^\infty \mathcal{F}(a + \tau) d\tau da = \int_0^\infty \int_\tau^\infty \mathcal{F}(y) dy d\tau \quad (4.3)$$

By integration by parts, we have:

$$\int_\tau^\infty \mathcal{F}(y) dy = \{y\mathcal{F}(y)\}_\tau^{+\infty} + \int_\tau^\infty y f(y) dy = -\tau \mathcal{F}(\tau) + \int_\tau^\infty y f(y) dy$$

$\lim_{y \rightarrow +\infty} y \mathcal{F}(y) = 0$ (exponential function dominates the polynomial function)

We have

$$\mathcal{F}(a) = \frac{\Gamma(k, \alpha a)}{\Gamma(k)}$$

$$\int_{\tau}^{\infty} y f(y) dy = \frac{1}{\alpha} \frac{\Gamma(k+1, \alpha \tau)}{\Gamma(k)}$$

We can also show that for $a > 0$ and $b > 0$, we have the following formula

$$\int_0^{\infty} \tau^{a-1} \Gamma(b, \tau) d\tau = \Gamma(a+b)/a \quad (4.4)$$

In fact,

$$\begin{aligned} \int_0^{\infty} \tau^{a-1} \Gamma(b, \tau) d\tau &= \left\{ \frac{\tau^a}{a} \Gamma(b, \tau) \right\}_0^{+\infty} + \int_0^{\infty} \frac{1}{a} \tau^{a+b-1} e^{-\tau} d\tau \\ &= \left\{ \frac{\tau^a}{a} \Gamma(b, \tau) \right\}_0^{+\infty} + \frac{1}{a} \Gamma(a+b, \tau) \\ &= \frac{1}{a} \Gamma(a+b) \end{aligned}$$

Now, we come back on the expression (4.3)

$$\begin{aligned} \int_0^{\infty} \int_0^{\infty} \mathcal{F}(a+\tau) d\tau da &= \int_0^{\infty} \int_{\tau}^{\infty} \mathcal{F}(y) dy d\tau \\ &= - \int_0^{\infty} \tau \mathcal{F}(\tau) d\tau + \int_0^{\infty} \frac{1}{\alpha} \frac{\Gamma(k+1, \alpha \tau)}{\Gamma(k)} d\tau \\ &= - \frac{1}{\alpha^2} \int_0^{\infty} y \frac{\Gamma(k, y)}{\Gamma(k)} dy + \frac{1}{\alpha^2} \int_0^{\infty} \frac{\Gamma(k+1, y)}{\Gamma(k)} dy \\ &= - \frac{1}{\alpha^2} \frac{\Gamma(k+2)}{2\Gamma(k)} + \frac{1}{\alpha^2} \frac{\Gamma(k+2)}{\Gamma(k)} \quad (\text{applying 4.4}) \\ &= \frac{1}{\alpha^2} \frac{\Gamma(k+2)}{2\Gamma(k)} \\ &= \frac{1}{\alpha^2} \frac{k(k+1)}{2} \quad (\text{in fact } \Gamma(k+2) = (k+1)k\Gamma(k)) \end{aligned}$$

The reproduction number becomes

$$R = B\beta \int_0^{\infty} \int_0^{\infty} \mathcal{F}(a+\tau) d\tau da = B\beta \frac{1}{\alpha^2} \frac{k(k+1)}{2} \quad (4.5)$$

In this case, $B = \frac{\alpha}{k}$ is the birth intensity, which is the inverse of the mean of $Gamma(k, \frac{1}{\alpha})$. By replacing (4.5), we have

$$R = \frac{\beta}{\alpha} \frac{k+1}{2}$$

□

As a consequence, for $k = 1$ we have by replacement

$$R = \frac{\beta}{\alpha}$$

which is the reproduction number for the Markovian case where the lifetime follows the exponential distribution.

The result of the proposition is interesting because we would have had an overestimation if we had computed the reproduction number as follows: $R_1 = \beta \int_0^\infty \mathcal{F}(a) da = \beta \frac{k}{\alpha}$.

Even though, R_1 remains correct for $k = 1$; for the general case of Gamma distribution, Breda et al(2012)'s formula is the weighted average of reproduction number ($\beta \frac{k}{\alpha}$) and the Markovian reproduction number ($\frac{\beta}{\alpha}$), with equal weight.

4.2.2 Impact of the Lifetime Distribution on Epidemic Dynamic

For $k \neq 1$ positive value, we have the non-Markov case . The reproduction number formula (4.2) is used to simulate the disease spread process and the Gamma lifetime with parameter k and α to simulate the death process in the population.

As shown in Figure (4.2) for $k = 12$ and $\alpha = 0.3$, the disease dies out when the reproduction number (R) is less than one. When the reproduction number is more than one, the disease spread reaches an equilibrium infected size. As illustrated in the Figure, the infected size dynamic has two phases: the increasing or decreasing phase where the number of infected population increases or decreases considerably and the stable phase where the number of infected population reaches a plateau and remains at that stable level.

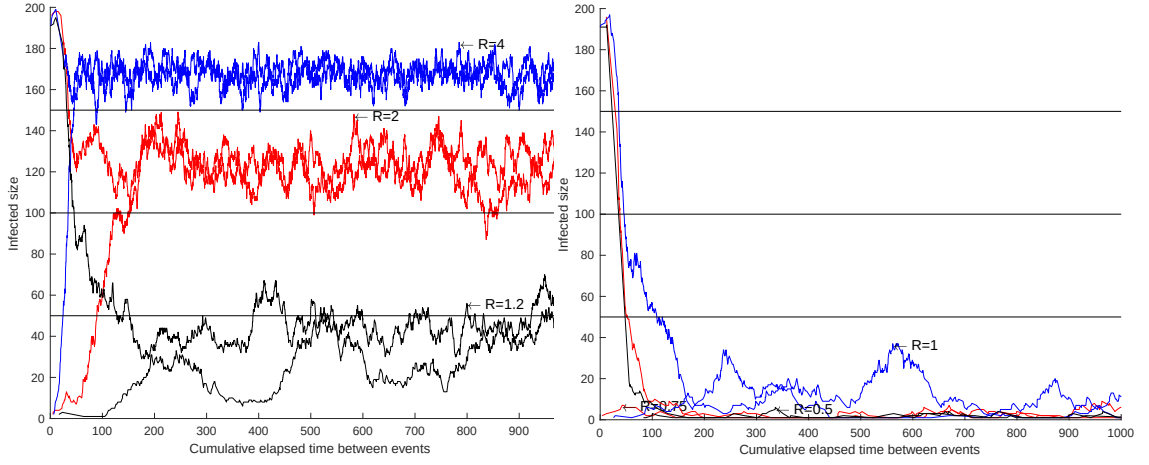


Figure 4.2: Some SIS disease spread samples with population size ($M = 200$) and lifetime following a Gamma($k = 12, \alpha = 0.3$)

In addition, for $R \geq 1$, there is a positive relation between the equilibrium infected size and the reproduction number. As illustrated the Figure (4.2), the equilibrium infected size increases when the reproduction number increases. In the next section, we will focus on determining the equilibrium infected size using some mathematical tools developed in the Renewal Theory (Taylor and Karlin(1975,1981,1998)).

4.3 Analysis of the Infection and Death Process

The SIS model combines three processes : infection process, death process and birth process. But in our case, the death of each individual is replaced by a healthy individual. The dynamic of these processes yields the equilibrium infected size at the equilibrium when reproduction number is more than one. We will develop some mathematical tools that will help to estimate the equilibrium infected size. In our study, M is the population size, n is the population infected size and S is the susceptible population size.

4.3.1 Infection Process

One of the key assumption is that the disease transmission coefficient (β) is constant. The proportional incidence function $f(S, n) = \beta \frac{S}{M} n$ is a common assumption as the population size becomes big; in this case, each susceptible will rather meet the proportion ($\frac{n}{M}$) of infectious in the population. In addition, as Ovaskainen (2001) points it out, the

scaled $f(S, n) = \beta \frac{S}{M} n$ assumes more generally that the number of contact per person is independent of the population size (M). Suppose n individuals are infected at time t in the model, and the rate of infectivity of each healthy individual is $\beta \frac{n}{M}$. For the i^{th} susceptible individual at time t ($i = 1, \dots, M - n$), let I_i be an independent random variable that is exponentially distributed with parameter $\beta \frac{n}{M}$. We view I_i as an idealized time until infection, meaning the amount of time from t until the i^{th} individual gets infected under the assumption that the infection status of the other $M-1$ individuals does not change. Then the smallest of the $I_1, \dots, I_{M-n}$ is the amount of time from t until the first new infection occurs (assuming that none of the n infected individuals die before then).

Proposition 4.3.1 *Let us consider the following Independent and Identically Distributed (IID) idealized times until infection of $M - n$ susceptibles: $I_1, I_2, \dots, I_{M-n}$. We have the expectation of the first time of infection among the $M - n$ susceptibles in the absence of deaths :*

$$E(\text{Min}(I_1, I_2, \dots, I_{M-n})) = \frac{1}{\beta \frac{n}{M} (M - n)} \quad (4.6)$$

Proof:

Each I_i follows an exponential distribution with parameter $\beta \frac{n}{M}$. $P(I_i > a) = e^{-\beta \frac{n}{M} a}$

We have:

$$\begin{aligned} P(\text{Min}(I_1, I_2, \dots, I_{M-n}) > a) &= P(I_1 > a, I_2 > a, \dots, I_{M-n} > a) = P(I_1 > a)P(I_2 > a) \dots P(I_{M-n} > a) \\ &= \prod_{i=1}^{M-n} P(I_i > a) = \prod_{i=1}^{M-n} e^{-\beta \frac{n}{M} a} = e^{-\beta \frac{n}{M} (M-n)a} \end{aligned}$$

We can now have the expectation

$$E(\text{Min}(I_1, I_2, \dots, I_n)) = \int_0^\infty P(\text{Min}(I_1, I_2, \dots, I_{M-n}) > a) da = \int_0^\infty e^{-\beta \frac{n}{M} (M-n)a} da = \frac{1}{\beta \frac{n}{M} (M - n)}$$

4.3.2 Death Process

The lifetime of each individual in the SIS model follows an independent and identically distributed (iid) variable X with $E(X) = \mu < \infty$. After dying, the individual is replaced by another individual with the same lifetime distribution. This process makes the lifetime of each individual and all of that individual's successors follows a renewal process $(N(t), T_n)$ with $T_{n+1} - T_n$ having the distribution as X ; where $N(t)$ is the number of occurrences of death, T_n is the time of the n^{th} arrival and $T_{n+1} - T_n$ the interarrival time of N . At each time t , for each individual, we define the variable excess lifetime at t : $E(t) = T_{N(t)+1} - t$. It was shown by Taylor and Karlin (1975,1981), that when $t = \infty$, $E(\infty)$ has a distribution defined by

$$P(E(\infty) \leq y) = \frac{1}{\mu} \int_0^y \mathcal{F}(a) da \quad (4.7)$$

Proposition 4.3.2 *Let us consider the following Independent and Identically Distributed (IID) random variables: $E_1(\infty), E_2(\infty), \dots, E_n(\infty)$, which is the excess lifetime of n individuals. we have:*

$$E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) = \frac{1}{\mu^n} \int_0^\infty \left(\int_y^\infty \mathcal{F}(a) da \right)^n dy \quad (4.8)$$

Proof:

$$\begin{aligned} P(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) > y) &= P(E_1(\infty) > y, E_2(\infty) > y, \dots, E_n(\infty) > y) \\ &= P(E_1(\infty) > y) P(E_2(\infty) > y) \dots P(E_n(\infty) > y) \quad (\text{iid}) \\ &= \prod_{i=1}^n P(E_i(\infty) > y) = \prod_{i=1}^n (1 - P(E_i(\infty) \leq y)) \\ &= \prod_{i=1}^n \left(1 - \frac{1}{\mu} \int_0^y \mathcal{F}(a) da \right) = \prod_{i=1}^n \frac{1}{\mu} \int_y^\infty \mathcal{F}(a) da \\ &= \frac{1}{\mu^n} \left(\int_y^\infty \mathcal{F}(a) da \right)^n \end{aligned}$$

We have the expectation

$$\begin{aligned} E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) &= \int_0^\infty P(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) > y) dy \\ &= \frac{1}{\mu^n} \int_0^\infty \left(\int_y^\infty \mathcal{F}(a) da \right)^n dy \end{aligned}$$

4.3.3 Equilibrium Equation with Gamma Distribution Lifetime

We consider the following function $g(p)$ with $p = \frac{n}{M}$, which is the expectation of the difference between the first time infection random variable and the first time death random variable.

$$\begin{aligned} g(p) &= E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) - E(\text{Min}(I_1, I_2, \dots, I_{M-n})) \\ &= \int_0^\infty \left(\frac{\int_y^\infty \mathcal{F}(a) da}{\mu} \right)^{Mp} dy - \frac{1}{p(1-p)M\beta} \end{aligned} \quad (4.9)$$

The goal in analysing the function $g(p)$ is to determine the value and properties of the root of the function $g(p)$ for different parameters: $M > 0, k \geq 0, \alpha > 0, R > 0$.

In fact, if there exists a $p > 0$ such that $g(p) = 0$, we have a disease equilibrium with

$$E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) = E(\text{Min}(I_1, I_2, \dots, I_{M-n})) \quad (4.10)$$

In the case of Gamma distribution with k and α , we have $\mathcal{F}(a) = \frac{1}{\Gamma(k)} \Gamma(k, \alpha a)$, $\mu = \frac{k}{\alpha}$ and $\Gamma(k+1, \alpha y) = k\Gamma(k, \alpha y) + (\alpha y)^k e^{-\alpha y}$ (derived from integration by parts), which help to derive the following expression:

$$\begin{aligned} \int_y^\infty \mathcal{F}(a) da &= \frac{1}{\Gamma(k)} \int_y^\infty \Gamma(k, \alpha a) da = \frac{1}{\alpha \Gamma(k)} \int_{\alpha y}^\infty \Gamma(k, x) dx \\ &= \frac{1}{\alpha \Gamma(k)} (-\alpha y \Gamma(k, \alpha y) + \Gamma(k+1, \alpha y)) \quad (\text{integration by parts: } U = \Gamma(k, x) \text{ and } V = x) \\ &= \frac{1}{\alpha \Gamma(k)} ((-\alpha y + k) \Gamma(k, \alpha y) + (\alpha y)^k e^{-\alpha y}) \end{aligned}$$

The expectation of $\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))$ in (4.8) becomes

$$\begin{aligned} \frac{1}{\mu^n} \int_0^\infty \left(\int_y^\infty \mathcal{F}(a) da \right)^n dy &= \frac{1}{\mu^n} \int_0^\infty \left(\int_y^\infty \frac{1}{\alpha \Gamma(k)} \Gamma(k, \alpha a) da \right)^n dy \\ &= \frac{1}{\mu^n} \int_0^\infty \left(\frac{(-\alpha y + k) \Gamma(k, \alpha y) + (\alpha y)^k e^{-\alpha y}}{\alpha \Gamma(k)} \right)^n dy \\ &= \frac{1}{\alpha} \int_0^\infty \left(\frac{(-z + k) \Gamma(k, z) + z^k e^{-z}}{k \Gamma(k)} \right)^n dz \end{aligned}$$

We know from (4.2) that $\beta = \frac{2R\alpha}{k+1}$ and the function $g(p)$ defined in (4.9) becomes:

$$g(p) = \frac{1}{\alpha} \left(\int_0^\infty \left(\frac{(-z + k) \Gamma(k, z) + z^k e^{-z}}{k \Gamma(k)} \right)^{pM} dz - \frac{k+1}{2Rp(1-p)M} \right)$$

For $g(p) = 0$, we have the equation:

$$\int_0^\infty \left(\frac{(-z + k) \Gamma(k, z) + z^k e^{-z}}{k \Gamma(k)} \right)^{pM} dz - \frac{k+1}{2Rp(1-p)M} = 0 \quad (4.11)$$

It results from (4.11) that the equilibrium infected size p depends on the reproduction number (R); it does not depend explicitly on the scale parameter α . In the subsequent section, we will develop a numerical method to compute p with a high level of accuracy.

4.4 Computation of the Expectation of the First Excess

Lifetime

As shown in the previous section, the analytics computation of the infected size equilibrium is cumbersome and complicated in equation (4.11) because of incomplete gamma function $\frac{\Gamma(k, \alpha a)}{\Gamma(k)}$ and the power pM function that make the integrand difficulty to handle analytically in the following integral expression. for every $k \geq 0$, $M > 0$ and $0 \leq p \leq 1$

$$\int_0^\infty \left(\frac{(-z + k) \Gamma(k, z) + z^k e^{-z}}{k \Gamma(k)} \right)^{pM} dz$$

In order to overcome the problem, we will construct an underlying function using Composite Newton-Cotes Quadrature Formulas (Shampine et al (1997)). And the subsequent subsection will compare the numerical results in the case when $k = 1$ with the analytical results.

4.4.1 Composite Newton-Cotes Quadrature Formulas

The Newton - Cotes rules values the integrand f at equally spaced points x_i over the interval $[a, b]$; where $x_i = a + i\frac{b-a}{n} = a + ih$ with $h = \frac{b-a}{n}$; $n = Qn_0$ and $x_{Qp+Q} = x_{Q(p+1)}$ where Q is the number of h within the subinterval $[x_{Qp}, x_{Qp+Q}]$ of the interval $[a, b]$.

4.4.1.1 Composite Rules

To have a greater accuracy, the idea of the composite rule will be to subdivide the interval $[a, b]$ into smaller intervals like $[x_{Qp}, x_{Qp+Q}]$, applying the quadrature formulas in each of these smaller intervals and add up the results to obtain more accurate approximations.

$$\int_a^b f(x)dx = \sum_{p=0}^{n_0-1} \int_{x_{Qp}}^{x_{Qp+Q}} f(x)dx$$

We define the Lagrange basis polynomials over the sub-interval $[x_{Qp}, x_{Qp+Q}]$.

$$l_{Qp+j}(x) = \prod_{\substack{i=0 \\ i \neq j}}^Q \frac{x - x_{Qp+i}}{x_{Qp+j} - x_{Qp+i}} \quad (4.12)$$

such that

$$l_j(x_i) = \delta_{ij} = \begin{cases} 0 & \text{if } i \neq j \\ 1 & \text{if } i = j \end{cases}$$

The Lagrange Interpolating Polynomial can be derived

$$\tilde{f}(x) = \sum_{j=0}^Q f(x_{Qp+j}) l_{Qp+j}(x)$$

The integration of the Lagrange Interpolating becomes

$$\int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx = \sum_{j=0}^Q f(x_{Qp+j}) \int_{x_{Qp}}^{x_{Qp+Q}} l_{Qp+j}(x) dx \quad (4.13)$$

Weight of the Lagrange Interpolating integration is obtained by the integration of Lagrange basis polynomials. We have firstly

$$\begin{aligned} \int_{x_{Qp}}^{x_{Qp+Q}} l_{Qp+j}(x) dx &= \int_{x_{Qp}}^{x_{Qp+Q}} \prod_{\substack{i=0 \\ i \neq j}}^Q \frac{x - x_{Qp+i}}{x_{Qp+j} - x_{Qp+i}} dx = \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q \frac{y-i}{j-i} dy \\ &= \frac{h}{\prod_{\substack{i=0 \\ i \neq j}}^Q (j-i)} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy = \frac{b-a}{n} \frac{(-1)^{(Q-j)}}{j!(Q-j)!} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy \end{aligned}$$

And the expression (4.13) becomes

$$\int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx = \frac{b-a}{n} \sum_{j=0}^Q \left(\frac{(-1)^{(Q-j)}}{j!(Q-j)!} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy \right) f(x_{Qp+j}) = \frac{b-a}{n} \sum_{j=0}^Q W_j f(x_{Qp+j}) \quad (4.14)$$

with

$$W_j = \frac{(-1)^{(Q-j)}}{j!(Q-j)!} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy \quad (4.15)$$

4.4.2 Error Analysis of the High Order Newton Cotes Formulas

Regarding the error related to the Lagrange Interpolating Polynomial, Shampine et al (1997) and Heath(2002) show that for $f \in \mathcal{C}^{Q+1}([x_{Qp}, x_{Qp+Q}])$, $x \in [x_{Qp}, x_{Qp+Q}]$, there exists $\eta(x) \in]x_{Qp}, x_{Qp+Q}[$

such that

$$f(x) - \tilde{f}(x) = \frac{1}{(Q+1)!} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i})$$

By integration, we have:

$$\int_{x_{Qp}}^{x_{Qp+Q}} f(x)dx - \int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x)dx = \frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i})dx \quad (4.16)$$

For Q odd, The same as Al-Sammarraie(2015), Qrylov(1962) has shown in section 6.2 (theorem 3) that for $f \in \mathcal{C}^{Q+1}([x_{Qp}, x_{Qp+Q}])$, there exists $\eta_p \in]x_{Qp}, x_{Qp+Q}[$ such that

$$\frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i})dx = \frac{f^{(Q+1)}(\eta_p)}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} \prod_{i=0}^Q (x - x_{Qp+i})dx \quad (4.17)$$

By variable changed $x = x_{Qp} + hy$, the expression (4.17) becomes

$$\frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i})dx = h^{Q+2} \frac{f^{(Q+1)}(\eta_p)}{Q+1!} \int_0^Q \prod_{i=0}^Q (y - i)dy \quad (4.18)$$

For Q even, Hayes and Rubin(1970) has shown in theorem 1.1 that for $f \in \mathcal{C}^{Q+2}([x_{Qp}, x_{Qp+Q}])$, there exists $\eta_p \in [x_{Qp}, x_{Qp+Q}]$ such that

$$\frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i})dx = \frac{f^{(Q+2)}(\eta_p)}{Q+2!} \int_{x_{Qp}}^{x_{Qp+Q}} A^*(t)dt \quad (4.19)$$

with

$$A^*(t) = \int_{x_{Qp}}^t A(x)dx \quad (4.20)$$

$$A(x) = \prod_{i=0}^Q (x - x_{Qp+i})$$

By variable changed $t = x_{Qp} + hy$ and $x = x_{Qp} + ha$, the expression (4.20) becomes

$$\begin{aligned} \int_{x_{Qp}}^{x_{Qp+Q}} A^*(t)dt &= h \int_0^Q A^*(x_{Qp} + hy)dy \\ A^*(x_{Qp} + hy) &= \int_{x_{Qp}}^{x_{Qp} + hy} A(x)dx = h \int_0^y A(x_{Qp} + ha)da \\ A(x_{Qp} + ha) &= \prod_{i=0}^Q (x_{Qp} + ha - x_{Qp+i}) = h^{(Q+1)} \prod_{i=0}^Q (a - i) \end{aligned} \quad (4.21)$$

Therefore, for Q even, the expression (4.19) becomes

$$\frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i}) dx = h^{Q+3} \frac{f^{(Q+2)}(\eta_p)}{Q+2!} \int_0^Q \int_0^y \prod_{i=0}^Q (a-i) dady \quad (4.22)$$

The error analysis of the Newton-Cotes formulas of degree Q shows that the level of accuracy is greater when Q is even. In fact, we have $O(h^{(Q+3)})$ for Q even, against $O(h^{(Q+2)})$ for Q odd. That is why the estimation will be carried out with Q even.

From (4.16) and (4.22), we have on $[x_{Qp}, x_{Qp+Q}]$

$$\begin{aligned} \int_{x_{Qp}}^{x_{Qp+Q}} f(x) dx &= \int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx + \frac{1}{Q+1!} \int_{x_{Qp}}^{x_{Qp+Q}} f^{(Q+1)}(\eta(x)) \prod_{i=0}^Q (x - x_{Qp+i}) dx \\ &= \int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx + h^{Q+3} \frac{f^{(Q+2)}(\eta_p)}{Q+2!} \int_0^Q \int_0^y \prod_{i=0}^Q (a-i) dady \end{aligned}$$

On $[a, b]$, the integral becomes

$$\begin{aligned} \int_a^b f(x) dx &= \sum_{p=0}^{n_0-1} \int_{x_{Qp}}^{x_{Qp+Q}} f(x) dx \\ &= \sum_{p=0}^{n_0-1} \int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx + \frac{h^{Q+3}}{Q+2!} \left(\sum_{p=0}^{n_0-1} f^{(Q+2)}(\eta_p) \right) \int_0^Q \int_0^y \prod_{i=0}^Q (a-i) dady \\ &= \sum_{p=0}^{n_0-1} \int_{x_{Qp}}^{x_{Qp+Q}} \tilde{f}(x) dx + h^{Q+3} \frac{n_0 f^{(Q+2)}(\eta)}{Q+2!} \int_0^Q \int_0^y \prod_{i=0}^Q (a-i) dady \end{aligned}$$

where $\frac{1}{n_0} \sum_{p=0}^{n_0-1} f^{(Q+2)}(\eta_p) = f^{(Q+2)}(\eta)$ and $\eta \in [a, b]$ (Intermediate Value Theorem)

With $n_0 = \frac{n}{Q}$, the final expression of the integral can be written:

$$\int_a^b f(x) dx = \frac{b-a}{n} \sum_{p=0}^{\frac{n}{Q}-1} \sum_{j=0}^Q W_j f(x_{Qp+j}) + h^{Q+3} \frac{(\frac{n}{Q}) f^{(Q+2)}(\eta)}{Q+2!} \int_0^Q \int_0^y \prod_{i=0}^Q (a-i) dady$$

with

$$W_j = \frac{(-1)^{(Q-j)}}{j!(Q-j)!} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy$$

(4.23)

4.4.3 Weights Computation

Before using the formulas (4.23), we need to compute the weight $\{W_j\}_{0 \leq j \leq Q}$ developed previously.

$$W_j = \frac{(-1)^{(Q-j)}}{j!(Q-j)!} \int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy$$

For $j \in \{0, 1, 2, \dots, Q\}$, each polynomial function $\prod_{\substack{i=0 \\ i \neq j}}^Q (y-i)$ can be developed as follows

$$\prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) = \sum_{i=0}^Q C_i^j y^i \quad (4.24)$$

The coefficients $(C_i^j)_{\substack{0 \leq i \leq Q \\ 0 \leq j \leq Q}}$ of the polynomial function (4.24) will be determined by resolving the equations with Vandermonde matrix. The results of the computation are summarised in table 4.1 below.

The weights $\{W_j\}_{0 \leq j \leq Q}$ can be derived from the coefficients $(C_i^j)_{\substack{0 \leq i \leq Q \\ 0 \leq j \leq Q}}$ as follows.

$$\int_0^Q \prod_{\substack{i=0 \\ i \neq j}}^Q (y-i) dy = \sum_{i=0}^Q C_i^j \frac{Q^{i+1}}{i+1}$$

We finally have the computable weight formulas

$$W_j = \sum_{i=0}^Q C_i^j \frac{Q^{i+1}}{i+1} \frac{(-1)^{(Q-j)}}{j!(Q-j)!} \quad (4.25)$$

For $Q = 12$, the Lagrange polynomial is polynomial function of degree 12. The results of the weight $\{W_j\}_{0 \leq j \leq Q}$ computations are summarized in the table 4.1.

The formula (4.23) will be used to compute the integral

$$\int_0^\infty \left(\frac{(-z+k)\Gamma(k, z) + z^k e^{-z}}{k\Gamma(k)} \right)^{pM} dz$$

In this case, $f(x) = \left(\frac{(-x+k)\Gamma(k, x) + x^k e^{-x}}{k\Gamma(k)} \right)^{pM}$ and $f(x_i)_{0 \leq i \leq n}$ with $x_i = a + ih$. In order to

Table 4.1: Weights $\{W_j\}_{0 \leq j \leq Q}$ and coefficients $\{C_i^j\}_{0 \leq i \leq Q}^{0 \leq j \leq Q}$ from Lagrange interpolating polynomial

weight		Coefficients of the Lagrange basis Polynomial													
		constant	X	X ²	X ³	X ⁴	X ⁵	X ⁶	X ⁷	X ⁸	X ⁹	X ¹⁰	X ¹¹	X ¹²	
		j	C ₀ ^j	C ₁ ^j	C ₂ ^j	C ₃ ^j	C ₄ ^j	C ₅ ^j	C ₆ ^j	C ₇ ^j	C ₈ ^j	C ₉ ^j	C ₁₀ ^j	C ₁₁ ^j	C ₁₂ ^j
W ₀	20/77	0	479001600	-1486442883	1931559560	-1414014898	657206842	-206070153	44990232	-6926634	749463	-55770	2717	-78	1
W ₁	375/199	1	0	-479001603	1007441288	-924118282	489896622	-167310223	38759931	-6230301	696333	-53130	2640	-77	1
W ₂	-270/187	2	0	-239500803	623471048	-654044266	379985322	-138610763	33729696	-5630268	648183	-50640	2565	-76	1
W ₃	673/99	3	0	-159667203	442258568	-496433674	305860414	-117115478	29651559	-5112891	604581	-48294	2492	-75	1
W ₄	-1019/104	4	0	-119750403	341673128	-397471617	254135826	-100767756	26325600	-4666158	565119	-46086	2421	-74	1
W ₅	816/49	5	0	-95800323	278128520	-330686217	216665742	-88108222	23592387	-4279569	529413	-44010	2352	-73	1
W ₆	-1537/92	6	0	-79833603	234434888	-282854121	188526802	-78113342	21326136	-3944016	497103	-42060	2285	-72	1
W ₇	816/49	7	0	-68428803	202573447	-246998025	166716702	-70070022	19428591	-3651663	467853	-40230	2220	-71	1
W ₈	-1019/104	8	0	-59875203	178320967	-219154832	149357513	-63481168	17823624	-3395826	441351	-38514	2157	-70	1
W ₉	673/99	9	0	-53222402	159246727	-196923656	135232365	-57997166	16452555	-3170853	417309	-36906	2096	-69	1
W ₁₀	-270/187	10	0	-47900162	143854279	-178770536	123524441	-53368242	15270192	-2972004	395463	-35400	2037	-68	1
W ₁₁	375/199	11	0	-43545602	131172487	-163671560	113667581	-49412662	14241591	-2795331	375573	-33990	1980	-67	1
W ₁₂	20/77	12	0	-39916802	120543846	-150917983	105258081	-45995732	13339536	-2637558	357423	-32670	1925	-66	1

compute the integral, the following parameter values are used : $a = 0$, $b = 50$, $Q = 12$, $n = 30000$, $n_0 = 2500$ and the weight $\{W_j\}_{0 \leq j \leq Q}$ value in the table 4.1. The upper bound $b = 50$ was chosen by simulations. In fact a sample of upper bounds with value more that 50 was chosen. By comparing the estimations of the integral (4.23) on the sample and the estimation of integral with upper bound ($b = 50$), it results that the upper bound ($b = 50$) yields good approximation result and is also efficient in term of computing time.

4.5 Equilibrium Infected Size Analysis

4.5.1 Reproduction Number less than One

The equation (4.11) does not always have a solution when the reproduction number (R) is less than one. As shown in the following Figures, for different shape parameters, each expected first infection time curves (with R is less than 1 in black color) does not meet the expected first death time curve (in red color) when p spans from 0 to 1.

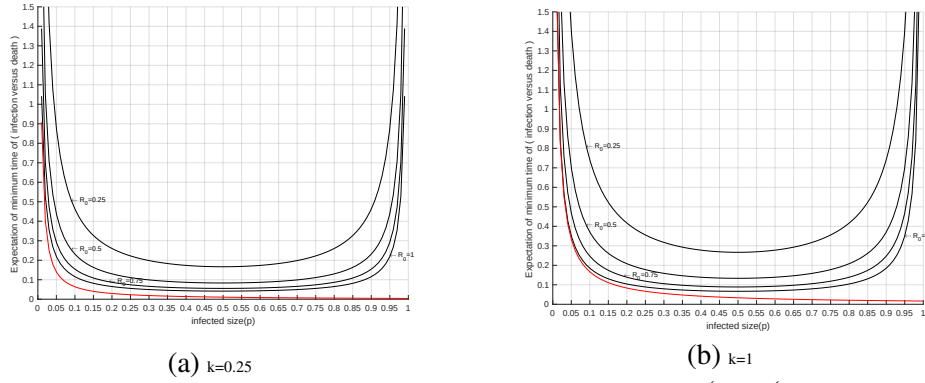


Figure 4.3: Expectation of the minimum infection time ($E(\text{Min}(I_1, I_2, \dots, I_{M-n}))$ in black color) versus expectation of the minimum death time ($E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)))$ in red color): parameters $\alpha = 0.03$, $M = 200$, $R \leq 1$, $p = \frac{n}{M}$

Studying a disease equilibrium is interesting when the reproduction number is more than one. In the subsequent section, we will focus on this case.

4.5.2 Compare Numerical and Analytical Solution for $k=1$

For $k = 1$, the lifetime follows an exponential distribution and the analytical solution of the equation (4.11) is

$$p = 1 - \frac{1}{R} \quad (4.26)$$

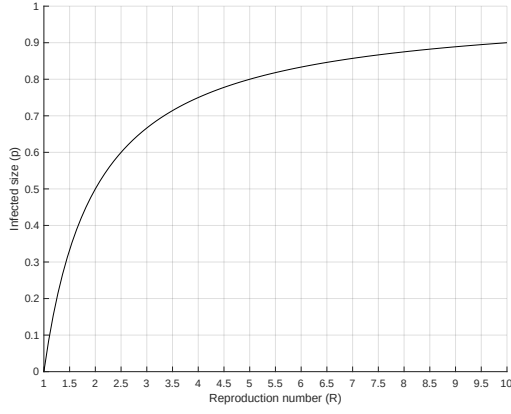
Proof for $k = 1$

$$\begin{aligned} \int_0^\infty \left(\frac{(-z+k)\Gamma(k, z) + z^k e^{-z}}{k\Gamma(k)} \right)^{pM} dz &= \int_0^\infty \left(\frac{(-z+1)e^{-z} + ze^{-z}}{1} \right)^{(1-\frac{1}{R})M} dz = \int_0^\infty e^{-(1-\frac{1}{R})Mz} dz \\ &= \frac{1}{(1-\frac{1}{R})M} = \frac{1}{R(1-\frac{1}{R})\frac{1}{R}M} = \frac{1}{Rp(1-p)M} \end{aligned}$$

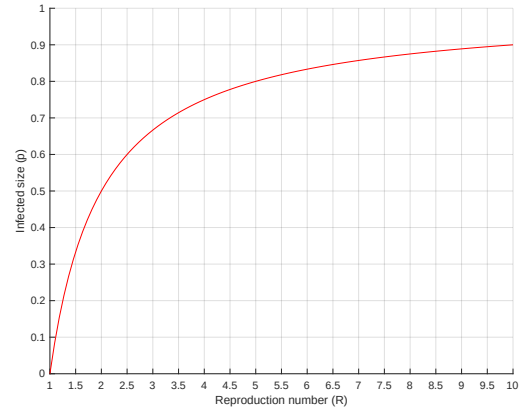
Which is the equation (4.11).

The numerical solution of the equation (4.11) was computed with reproduction number (R) as input. Newton-Cotes formulas (4.23) was applied to yield the numerical solution in Figure (4.4a).

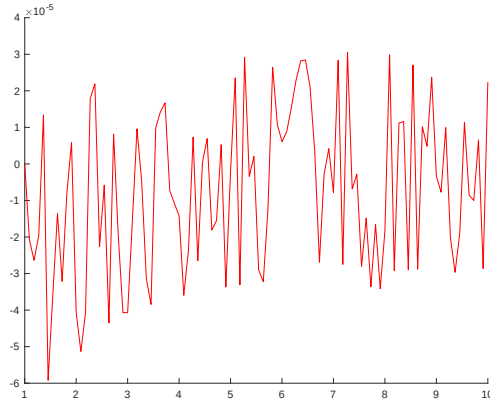
As shown in Figure (4.4), the numerical and analytical solutions yield the same values at four decimal places. The Figure (4.4c) shows a difference between the two solutions when the solution values are rounded at more than four decimal places.



(a) Numerical solution



(b) Analytical solution ($p = 1 - \frac{1}{R}$)



(c) Error between numerical and analytical solution

Figure 4.4: Numerical solution versus analytical solution of the equation (4.11) for $k = 1$

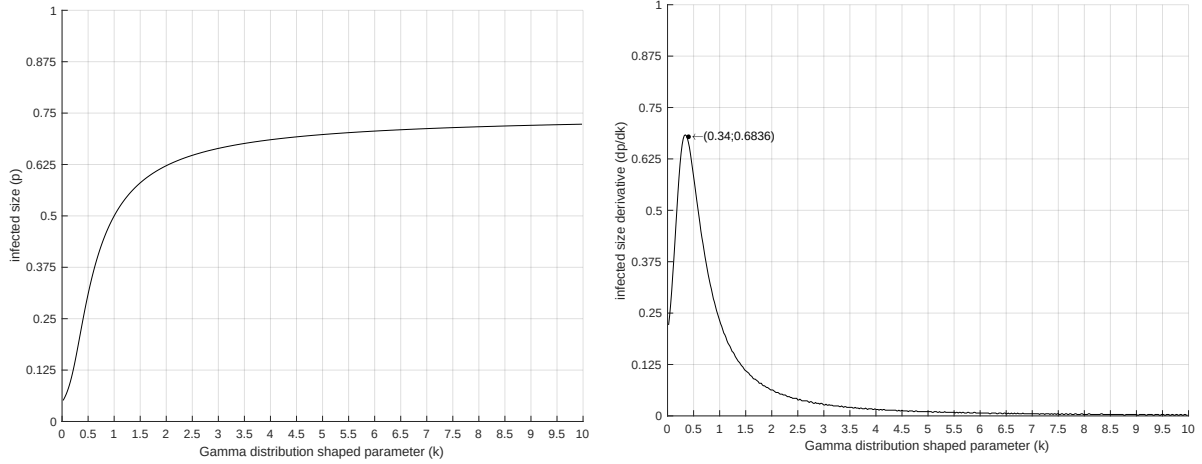
4.5.3 Parameter Shape, Reproduction Number and Infected Size

For $R = 2$, the equation (4.11) becomes

$$\int_0^\infty \left(\frac{(-z+k)\Gamma(k,z) + z^k e^{-z}}{k\Gamma(k)} \right)^{pM} dz - \frac{k+1}{4p(1-p)M} = 0$$

by choosing the shape parameter k as input, the Newton-Cotes formulas of 12 degrees was applied and the equation (4.11) was solved numerically. As shown in Figure 4.5(a), the infected size (p) increases along with the shape parameter (k). But the increase has two phases: a convex phase and a concave phase.

A convex phase ($0 \leq k \leq 0.34$): the population lives longer as k increases; the infected size increases as fewer infected die and the new infected out weights the number of infected deaths. As shown in Figure 4.5(b), the infected size increases rapidly.



(a) Infected size proportion (p) as a function of the parameter shape k (b) Derivative of the infected size proportion ($\frac{dp}{dk} = \frac{p(i+h) - p(i-h)}{2h}$)

Figure 4.5: Numerical solution of the equation (4.11) using Newton-Cotes formulas with degree 12 and the reproduction number $R = 2$

A concave phase ($k \geq 0.34$). As shown in Figure 4.5(b), the infected size slowly increases, before converging to a stable level when the shape parameter k becomes high. In fact, the population already has a longer lifetime and only a few infected die when the shape parameter k increases; in this case, the infected size can not continue increasing significantly because the infection process has reached its saturation state, which is defined by the reproduction number (R). Therefore, the proportion of infected size increases slowly and approaches its limit $(1 - \frac{1}{2R})$ as k goes to $+\infty$.

Given the critical role of the reproduction number (R) in the disease dynamic, it was added as a new variable in the equation (4.11). The solution of the equation (4.11) as a function of two independent variables (shape parameter and reproduction number) is represented in the Figure (4.6). As illustrated below (Figure (4.6)), for R constant, the infected size increases rapidly and slowly as the shape parameter k increases. We have the same pattern for k constant except that the infected size increasing is only slow throughout the reproduction number values. As the reproduction number (R) increases, the limit of the infected size (changes to yellow color in the Figure (4.6)) increases and the saturation state vanishes progressively. As a consequence, the infection size can reach 100% as the reproduction number goes to $+\infty$.

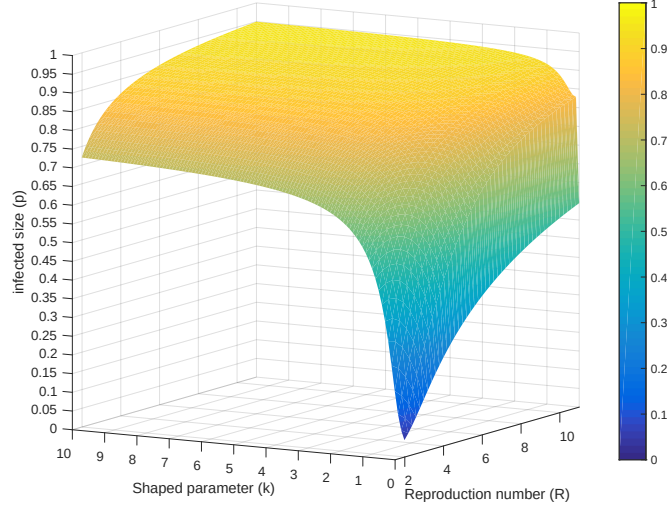


Figure 4.6: Numerical solution of the equation (4.11) as a function of shape parameter k and reproduction number R

4.5.4 Contribution of the Extreme Value Theory

The Extreme Value Theory will consolidate the numerical solutions previously developed by providing an analytical formula of the equilibrium infected sized. However, the analytical solution is not valid for all the shape parameters k .

Proposition 4.5.1 *Let $E_1(\infty), E_2(\infty), \dots, E_n(\infty)$ be Independent and Identically Distributed (iid) positive random variables with cumulative distribution function $G(y) = \frac{1}{\mu} \int_0^y \mathcal{F}(a) da$ and survival function $\mathcal{F}(a) = \int_a^\infty f(y) dy$.*

we have:

$n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))$ converges in distribution to an exponential distribution with parameter $\frac{1}{\mu}$.

Proof:

$$\begin{aligned}
 P(n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) \leq y) &= P(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) \leq \frac{y}{n}) \\
 &= 1 - P(\text{Max}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) > \frac{y}{n}) \\
 &= 1 - \prod_{i=1}^n P(E_i(\infty) > \frac{y}{n}) = 1 - \prod_{i=1}^n (1 - G(\frac{y}{n})) \\
 &= 1 - (1 - G(\frac{y}{n}))^n
 \end{aligned}$$

$$G(\frac{y}{n}) = \frac{1}{\mu} \int_0^{\frac{y}{n}} \mathcal{F}(a) da = \frac{1}{\mu} \frac{y}{n} \mathcal{F}(\eta) \text{ with } 0 \leq \eta \leq \frac{y}{n} \text{ (Mean Value Theorem for Integrals)}$$

$$P(n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) \leq y) = 1 - (1 - G(\frac{y}{n}))^n = 1 - (1 - \frac{1}{\mu} \frac{y}{n} \mathcal{F}(\eta))^n$$

when n goes to $+\infty$, we have

$$\lim_{n \rightarrow +\infty} P(n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty)) \leq y) = 1 - e^{-\frac{1}{\mu} y} \quad (4.27)$$

□

We can conclude that $\lim_{n \rightarrow +\infty} E(n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) = \mu$

Previously, we used equation (4.10): $E(\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) = E(\text{Min}(I_1, I_2, \dots, I_{M-n}))$

in order to determine the equilibrium infected size. By applying the same equation, we have the following expression

$$\begin{aligned} \mu &= \lim_{n \rightarrow +\infty} E(n\text{Min}(E_1(\infty), E_2(\infty), \dots, E_n(\infty))) \\ &= \lim_{n \rightarrow +\infty} nE(\text{Min}(I_1, I_2, \dots, I_{M-n})) \\ &= \lim_{n \rightarrow +\infty} \frac{n}{\beta \frac{n}{M}(M-n)} \quad (\text{From (4.6)}) \\ &= \frac{k+1}{2R(1-p)\alpha} \quad \text{From (4.2)} \end{aligned}$$

Recall that $\mu = \frac{k}{\alpha}$ and the solution of the equation becomes

$$p = 1 - \left\{ \frac{k+1}{k} \frac{1}{2R} \right\} \quad (4.28)$$

As shown in Figure (4.7), the analytical solution is the same as the numerical solution in the concave phase ($k > 1$) which features the slow increase of the infected size before converging to the stable value ($p = 1 - \frac{1}{2R}$). In this case $R = 2$ and the infected size converges to 0.75.

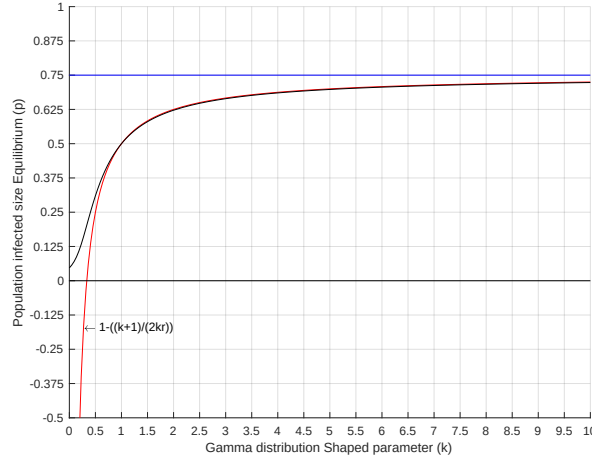


Figure 4.7: Numerical solution versus analytical solution of the equation (4.11) for $R = 2$

On the contrary, when $0 \leq k \leq 1$, the analytical solution does not match the numerical solution. In this case, the infected size (p) is negative and can not be the solution of the equation (4.11); whereas, the numerical solution gives a better result. The analytical solution yield wrong result because $n = pM$ is not large enough for the Extreme Value Theory to work.

4.6 Conclusion

SIS model with Gamma distribution lifetime is broader than the usual Markov case with exponential distribution lifetime. In the study, we focus on the case where the reproduction number (R) is greater than one and analyse the properties and values of the equilibrium infected size. The challenge was to find the reproduction number formula that works for the Non-Markov case; and to find the numerical method with high order of accuracy to compute the integral with complex integrand. Breda et al (2012) was used to find the reproduction number; and we develop the composite Newton-Cotes Quadrature formulas of 12 degree; and implement the results to estimate the integral after computing the weights. As results, in the case of exponential lifetime distribution ($k = 1$), the numerical solution of the infected size yields the same values at four decimal places as the analytical solution. In the case of $k \neq 1$, the numerical solution of the infected size was computed through the integral. The results show that the infected size is an increasing function of the shape parameter with two phases of acceleration and deceleration before reaching a stable value $(1 - \frac{1}{2R})$. This numerical solution was also compared with the analytical solution derived

from the Extreme Value Theory. The results consolidate the numerical solutions of the infected size. However, this analytical solution is not valid for shape parameters (k) less than 1.

In our study, the population is homogeneous regarding the lifetime distribution, which follows a gamma distribution with parameters k and μ . In the future research, the population might be heterogeneous by modelling the scale parameter (μ) with a distribution like exponential distribution or a generalized Beta distribution. In the future research, the non Markovian lifetime Gamma distribution might be changed to Log-Normal distribution as well.

References

- [1] D. Breda, O. Diekmann, W. F. de Graaf, A. Pugliese, and R. Vermiglio. On the formulation of epidemic models (an appraisal of Kermack and Mckendrick). *Journal of Biological Dynamics*, 6(sup2):103–117, 2012. PMID: 22897721.
- [2] David Champredon, Jonathan Dushoff, and David JD Earn. Equivalence of the erlang-distributed SEIR epidemic model and the renewal equation. *SIAM Journal on Applied Mathematics*, 78(6):3258–3278, 2018.
- [3] John C Wierman and David J Marchette. Modeling computer virus prevalence with a susceptible-infected-susceptible model with reintroduction. *Computational Statistics & Data Analysis*, 45(1):3–23, 2004.
- [4] Ingemar Nåsell. On the quasi-stationary distribution of the stochastic logistic epidemic. *Mathematical Biosciences*, 156(1-2):21–40, 1999.
- [5] Jane M Heffernan, Robert J Smith, and Lindi M Wahl. Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, 2(4):281–293, 2005.
- [6] Samuel Karlin and Howard M Taylor. *A First Course in Stochastic Processes*, volume 1. New York : Academic Press, 1975.
- [7] Kevin Gross. Unbounded population growth: stochastic models. class lecture, Population Ecology, North Carolina State University, 2013.
- [8] Linda JS Allen. An introduction to stochastic epidemic models. In *Mathematical epidemiology*, pages 81–130. Springer, 2008.
- [9] Carlos M Hernandez-Suarez and Carlos Castillo-Chavez. Approximations to the quasistationary distributions of the SIS and SEIS epidemic models for general distribution of the duration of the infectious state. 1997. Preprint.
- [10] Ingemar Nåsell. The quasi-stationary distribution of the closed endemic SIS model. *Advances in Applied Probability*, 28(3):895–932, 1996.
- [11] Otso Ovaskainen. The quasistationary distribution of the stochastic logistic model. *Journal of Applied Probability*, 38(4):898–907, 2001.

- [12] Damian Clancy and Sang Taphou Mendy. Approximating the quasi-stationary distribution of the SIS model for endemic infection. *Methodology and Computing in Applied Probability*, 13(3):603–618, 2011.
- [13] Samuel Karlin and Howard M Taylor. *A Second Course in Stochastic Processes*. Elsevier, 2nd edition, 1981.
- [14] Howard M Taylor and Samuel Karlin. *An Introduction to Stochastic Modeling*. Academic Press, New York, 1998.
- [15] Sang Woo Park, David Champredon, Joshua S Weitz, and Jonathan Dushoff. A practical generation-interval-based approach to inferring the strength of epidemics from their speed. *Epidemics*, 27:12–18, 2019.
- [16] Helen J Wearing, Pejman Rohani, and Matt J Keeling. Appropriate models for the management of infectious diseases. *PLoS medicine*, 2(7), 2005.
- [17] Zhilan Feng, Dashun Xu, and Haiyun Zhao. Epidemiological models with non-exponentially distributed disease stages and applications to disease control. *Bulletin of Mathematical Biology*, 69(5):1511–1536, 2007.
- [18] Ping Yan and Gerardo Chowell. *Quantitative methods for investigating infectious disease outbreaks*. Springer, 2019.
- [19] William Ogilvy Kermack and Anderson G McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London*, 115(772):700–721, 1927.
- [20] William Ogilvy Kermack and Anderson G McKendrick. Contributions to the mathematical theory of epidemics. ii.—the problem of endemicity. *Proceedings of the Royal Society of London*, 138(834):55–83, 1932.
- [21] Michael T Meehan, Daniel G Cocks, and Emma S McBryde. Global stability of a general, scalar-renewal epidemic model. *arXiv preprint arXiv:1707.03489*, 2017.
- [22] Amit Huppert and G Katriel. Mathematical modelling and prediction in infectious disease epidemiology. *Clinical Microbiology and Infection*, 19(11):999–1005, 2013.
- [23] Odo Diekmann, Hans Heesterbeek, and Tom Britton. *Mathematical Tools for Understanding Infectious Disease Dynamics*. ISBN 978-0-691-15539-5. New Jersey: Princeton University Press, 2013.
- [24] H Andersson and T Britton. *Lecture notes in statistics: Stochastic Epidemic Models and their Statistical Analysis*. Springer, 2000.

- [25] Tobias Klauß and Anja Voß Böhme. Modelling and simulation by stochastic interacting particle systems. In *Mathematical Modeling of Biological Systems, Volume II*, pages 353–367. Springer, 2008.
- [26] Richard Durrett. *Lecture Notes on Particle Systems and Percolation*. Wadsworth & Brooks/Cole, Advanced Books & Software, Pacific Grove, Calif, 1988.
- [27] Jeremy. J. Collis-Bird. *The Poisson Distribution*. PhD thesis, Doctoral dissertation, McGill University Libraries, 1963.
- [28] A Dembo and O. Zeitouni. *Large Deviations Techniques and Applications. Applications of Mathematics*, volume 38. 1998.
- [29] Marian Boguna, Luis F Lafuerza, Raul Toral, and M Serrano. Simulating non-Markovian stochastic processes. *arXiv preprint arXiv:1310.0926*, 2013.
- [30] Lawrence F Shampine, Richard C Allen, and Steven Pruess. *Fundamentals of Numerical Computing*, volume 1. Wiley New York, 2nd edition, 1997.
- [31] Michael T Heath. *Scientific Computing: An Introductory Survey*. New York : Academic Press, 2nd edition, 2002.
- [32] Omar A AL-Sammarraie and Mohammed Ali Bashir. Error analysis of the high order Newton Cotes formulas. *International Journal of Scientific and Research Publications*, 5, 2015.
- [33] V.I. Krylov and A.H. Stroud. *Approximate Calculation of Integrals*. Dover Books on Mathematics. New York, NY : Macmillan, 1962.
- [34] D. R. Hayes and L. Rubin. A proof of the Newton Cotes quadrature formulas with error term. *The American Mathematical Monthly*, 77(10):1065–1072, 1970.