




ORIGINAL RESEARCH ARTICLE

Managing Infectious Diseases Under Quiescence

Usman Sanusi¹ , Saratu Abdulfatah², Sulaiman Sani³  and Sani Abba¹ ¹Department of Mathematics and Statistics, Umaru Musa Yar'adua University, Katsina, Nigeria²Physics Department, Umaru Musa Yar'adua University, Katsina, Nigeria³Department of Mathematics, University of Eswatini, Kwaluseni Campus, Kingdom of Eswatini

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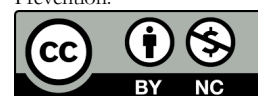
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ABSTRACT

Quiescence is added to the Susceptible-Infectious-Recovered (SIR) model with demography in this work. To investigate the consequences of Quiescence in the infection process in more depth, we use stochastic simulations on the stochastic version of the model we built. This method provides a more accurate picture of the dynamics of infectious diseases by considering the inherent randomness in the disease processes. We examine the effects of Quiescence on the number of infected people using simulations. The results, presented in histograms depicting the distribution of infected individuals, reveal a notable trend: the mean number of infected individuals is higher when Quiescence is incorporated into the dynamics. These findings emphasize the dynamic influence of Quiescence on infectious disease spread. The higher mean number of infections during periods of Quiescence highlights the need for public health strategies that are flexible enough to focus interventions during these times to reduce the possibility of an increase in infections.

KEYWORDS

Parasite quiescence;
Managing; Model;
stochasticity; Public Health;
Prevention.



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INTRODUCTION

Around the world, effective disease management is an essential part of public health and healthcare systems. In order to decrease the negative consequences infections have on patients, communities, and society at large, it encompasses a wide spectrum of prevention, management, and treatment methods. Enhancing health outcomes and reducing the burden of illness, from infectious diseases that can spread fast through populations to chronic illnesses that require ongoing care, depends on effective disease management (Keeling and Pejman, 2011). Disease management attempts to take preventive measures to stop the emergence and spread of diseases and attend to the immediate medical needs of afflicted individuals. Disease management tries to reduce healthcare costs, enhance quality of life, and promote overall well-being by focusing on prevention, early detection, and evidence-based treatments. Contact tracing, isolation, vaccination, and quarantine are routinely used to manage infectious diseases effectively (Okolie and Müller, 2020; Linda, 2010; Lindberg *et al.*, 2006). By isolating sick people and monitoring their contacts, the disease's spread can be managed, limiting further transmission within the population. A set of therapeutic suggestions based on empirical research and clinical investigations also forms

the basis for disease management. Healthcare practitioners follow set standards to guarantee that patients receive the most effective and appropriate care for their condition. Antibiotic stewardship is also emphasized to address the expanding problem of antibiotic resistance, which is the genetic change within the bacteria that enables them to survive the application of antibiotics (Figure 2) (National Institute, 2023) and maintain the effectiveness of crucial medicines. Recent advances in science and technology have accelerated efforts to treat illnesses. The introduction of novel drugs, preventative measures, and diagnostic tools facilitates the improvement of disease diagnosis accuracy and therapeutic efficacy. Strategies for managing diseases must be flexible and adaptable since diseases might evolve and new issues might surface. When healthcare systems can quickly adapt to changing situations, they can successfully manage both present and emerging health issues. We now explain in more depth what is Quiescence state is.

QUIESCENCE STATE

Quiescence can be defined as a state of inactivity/dormancy in which certain microorganisms,

Correspondence: Usman Sanusi. Department of Mathematics and Statistics, Umaru Musa Yar'adua University, Katsina, Nigeria. ✉ usman.sanusi@umyu.edu.ng.

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including viruses and bacteria, enter the body under some conditions. In this state, these microorganisms may be insensitive to antibiotics, making them difficult to eradicate. This dormancy has significant implications for effectively managing infectious diseases, as it can lead to persistent infections, recurrences, and treatment failures (Blath *et al.*, 2021; Lennon *et al.*, 2011). Quiescence in viral infections happens when the virus becomes inactive after integrating its genetic material into the host cell's Deoxyribonucleic acid (DNA) (Balaban *et al.*, 2004; Joachim *et al.*, 2021). A virus can persist in this state for long periods of time (weeks, months, or even years), reactivating on some occasions and leading to disease relapses (Nil *et al.*, 2018; Sung-Hee *et al.*, 2019; Pintu and Stefan, 2013), see also (Figure 1). (Please note that the *Quiescence* is different from *Drug Resistance*) in the case of drug resistance, the bacteria are active while the quiescent are not. The herpes simplex virus, HIV, and the hepatitis B virus are some viruses that can enter Quiescence. Similarly, some bacteria, like Mycobacterium TB, can enter a phase called Quiescence, during which they become less vulnerable to medications and the host immune system. The persistence of tuberculosis infections and the formation of drug-resistant strains are thought to be caused by this condition of dormancy.

Additionally, millions of people die from the fatal disease of malaria each year (Nil *et al.*, 2018). One of the five malaria parasites that cause the disease, Plasmodium, has a complicated life cycle that involves both mosquito and human hosts; weeks, months, or even years may pass before the parasite reactivates and causes malaria symptoms in the liver cells (Shigeharu, 2021; Robert *et al.*, 2005). It has been suggested that the characteristic of Quiescence may be a means by which Plasmodium parasites elude the host immune response and survive in the liver cells (Cindy *et al.*, 2018; Aimee *et al.*, 2019). Similarly, developing successful treatment plans requires understanding the mechanisms underlying Quiescence in viral disorders. Researchers are studying Quiescence in different microorganisms to find strategies to prevent or disrupt this state and enhance the effectiveness of treatments (Sanusi *et al.*, 2022). Quiescence can help maintain population stability by building up a reservoir of dormant parasites among the host population (Jochen *et al.*, 2021; Tellier, 2019); it also raises the risk of a significant epidemic outbreak (Sanusi and Tasiu, 2023). There may be a mixture of parasites that are reproducing actively and dormant parasites

In a typical parasite population (Sanusi *et al.*, 2022). This variety of states ensures the parasite population's longevity over time, especially in unfavorable circumstances such as when receiving antibiotic therapy. Some members of the parasite population may go into a quiescent state when exposed to harmful conditions, such as antibiotic use (Duolong *et al.*, 2018). The active reproducing parasites may be killed or inhibited by the antibiotic, but the quiescent parasites are left in a dormant, non-replicating state. When the antibiotic therapy is stopped or when circumstances are more conducive to reproduction, these dormant parasites may become active again. This reservoir of dormant parasites supports the parasite's overall population size and genetic diversity (Nathalie *et al.*, 2004). Quiescent parasites are less susceptible to the deadly effects of antibiotics than actively proliferating parasites are, even though medications may still have some impact on them. This is due to their decreased metabolic activity and replication rate. Due to this resistance, dormant parasites can endure antibiotic therapy and possibly reawaken when conditions are better. By assuming a quiescent condition, parasites can avoid the immediate threat of antibiotics and create long-term plans to combat them. It's crucial to remember that the specific mechanisms and tactics used by parasites might change based on the host environment and the species of the parasite. One method parasites may use to increase their chances of survival and drug resistance is Quiescence (Ian *et al.*, 2009). The general insensitivity of parasite populations to antibiotics can also be caused by other causes, including genetic changes or the acquisition of resistance genes, as defined above and shown in (Figure 2). Quiescence can be a tactic parasites use to increase population stability and build up drug resistance. Some parasites enter Quiescence, characterized by decreased metabolic activity or a state of dormancy, when unfavorable conditions are present, such as when antibiotics are present, or the host immune system is actively attacking them.

DISEASE MECHANISMS

Mathematical models are useful tools to comprehend the dynamics of quiescent parasites and foresee its effects for effective disease management measures. The mechanisms driving parasite quiescence, however, are not well known, and the potential use of mathematical

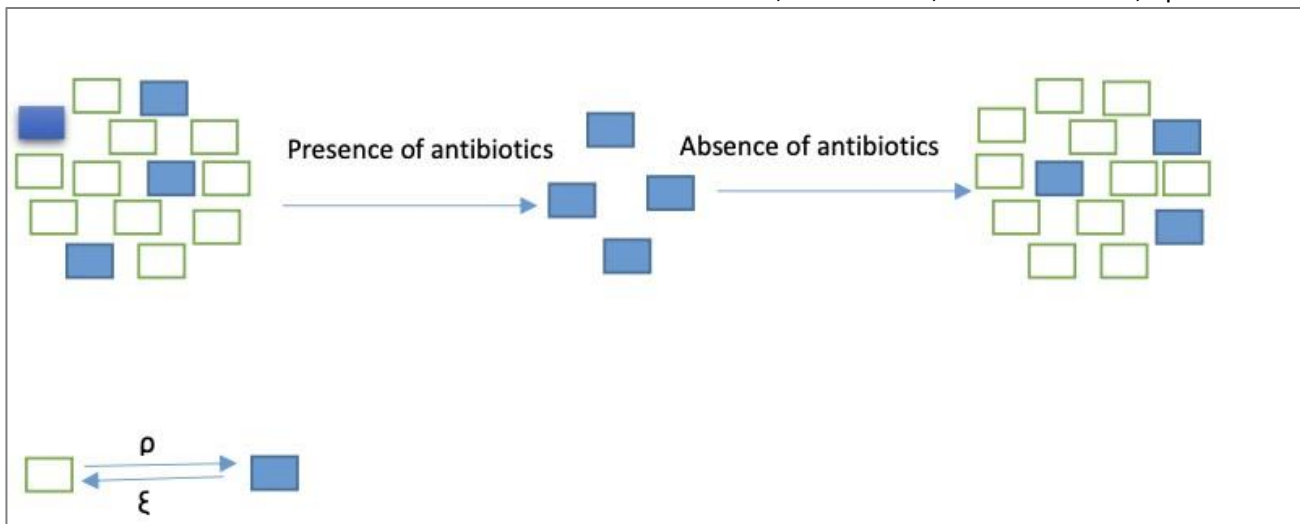


Figure 1: Population of bacteria that started from one comprising of active (white) and quiescent (blue).

After applying antibiotics, the active cells died, while those in quiescent phase remained alive. The quiescent cells wake up and grow when the antibiotic is taken away. As one can see, some proportion of the bacteria became

quiescent again, ρ is the rate at which the bacteria population becomes Quiescence, and ξ is the rate of exiting Quiescence; this stochastic process continues in this pattern.

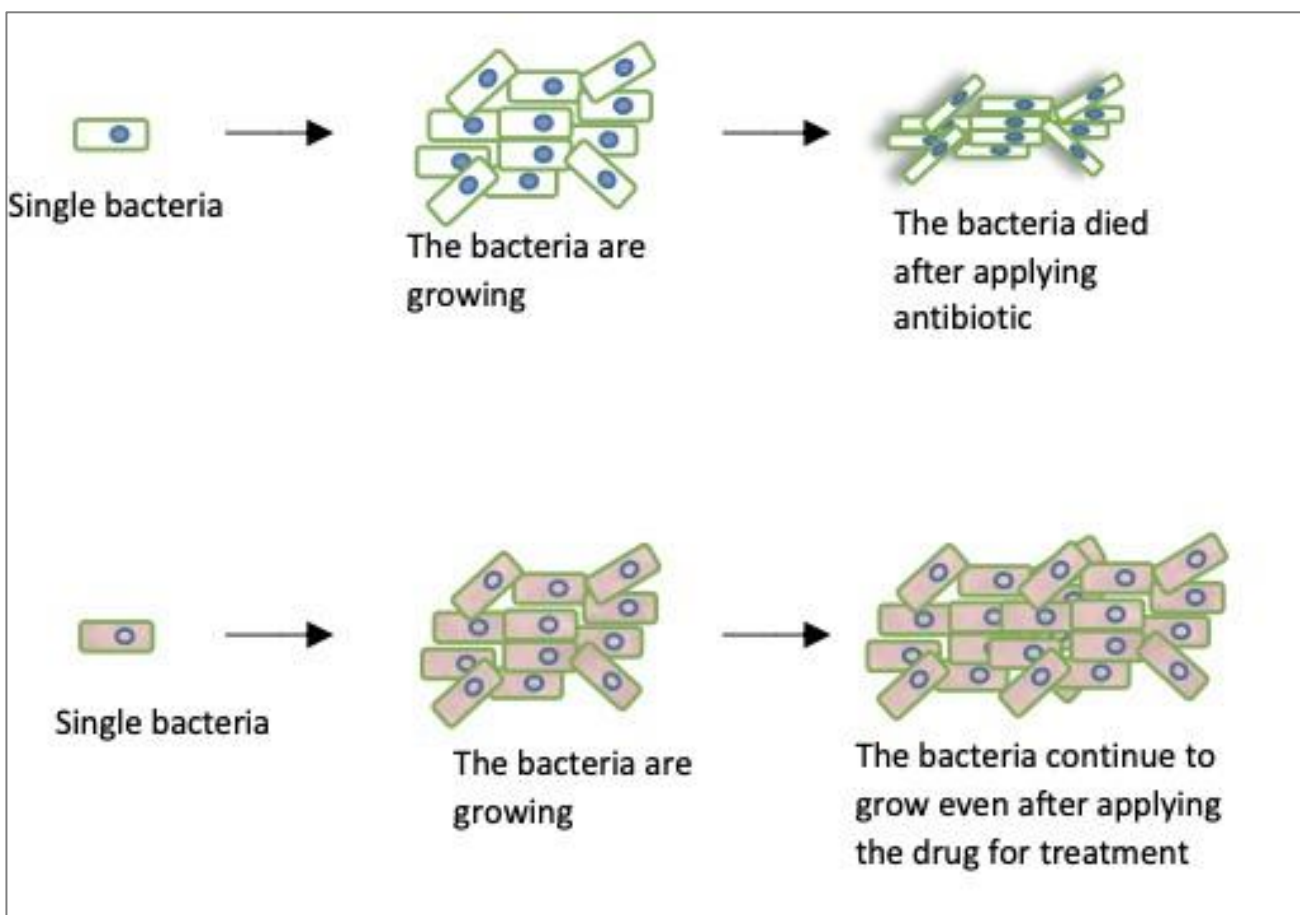


Figure 2: Resistant and non-resistant populations of bacteria; the non-resistant bacteria died after applying antibiotics, while the resistant population did not.

Models for the study of Quiescence have not been substantially investigated. Investigating the importance of mathematical models in comprehending the influence

of Quiescence in the co-infection model has been studied (Bendix et al., 2017; Sellinger et al., 2019).

The SIQR Model with Demography

$$\begin{aligned}
 \frac{dS}{dt} &= \Lambda - \beta \frac{SI}{N} - \mu S \\
 \frac{dI}{dt} &= \beta \frac{SI}{N} - \sigma I - \rho I + \zeta Q - \mu I \\
 \frac{dQ}{dt} &= \rho I - \zeta Q - \mu Q, \\
 \frac{dR}{dt} &= \sigma I - \mu R
 \end{aligned}
 \tag{1}$$

When the third compartment of model 1 is deleted, one gets a mathematical model called the Susceptible-Infectious-Recovered (SIR) model with demography studied (Bartlett, 1956; Maurice, 1960), which is used to analyze how infectious diseases propagate throughout a community. When adding demographic elements, the SIR model becomes a more realistic and detailed representation of disease dynamics. In this Research work, we incorporate the quiescence phase into the SIR model using demographics and build up the SIQR model with Demography.

Four compartments are created within a population by the SIQR model:

Susceptible (S): People who are not afflicted with the illness but are at risk of contracting it.

Infectious (I): Those who have the illness and have the potential to transfer it to others.

Quiescence (Q): Those with the disease but the parasites are inactive within a host.

Recovered (R): People who are immune after recovering from the illness.

System of Ordinary Differential Equations 1 describes the rates of change people in each compartment over time and keeps a record of transitions between these compartments. Within a population, demographic parameters consider the rates of births and deaths. When incorporating the Quiescence stage, we add one more compartment to the SIR model. The parameters of the models are: Λ representing the birth rate at which new

individuals enter the population, β is the transmission rate, σ is the recovery rate, μ is the death rate, ρ is the rate of entering Quiescence, ζ is the rate of exiting the quiescence phase, and N is the total population size. Considering the effects of diseases, births, and deaths, the first equation shows the rate of change in the susceptible population. Taking infections, recoveries, and deaths into account, the second equation shows the rate of change in the infectious population. When the quiescence phase is considered, the third equation shows the rate of change of the quiescent population. The fourth equation shows the rate of change in the recovered population.

THE EQUILIBRIUM SOLUTIONS

The equilibrium solution of a mathematical model represents a steady state where the system’s variables no longer change over time. The SIQR model has two equilibrium solutions. The first equilibrium solution occurs when the number of infectious, Quiescence, and recovered individuals is zero, and the number of susceptible individuals is given as the ratio of birth and death rates, that is *disease free equilibrium*.

$$I^* = Q^* = R^* = 0, S^* = \frac{\Lambda}{\mu}$$

The second equilibrium solution is the endemic equilibrium, where the disease persists in the population, in the SIQR model, this happens when the individual in each compartment coexist and the equilibrium solution is given by

$$\begin{aligned}
 S^* &= \frac{N(\sigma\zeta + \sigma\mu + \mu\zeta + \mu^2 + \rho\mu)}{\beta(\zeta + \mu)} \\
 I^* &= \frac{\Lambda\beta\zeta + (\Lambda\beta - \sigma N\zeta)\mu - N(\sigma + \zeta + \rho)\mu^2 - N\mu^3}{\beta(\mu^2 + (\sigma + \zeta + \rho)\mu + \sigma\zeta)}, \\
 Q^* &= \frac{\rho(\Lambda\beta\mu + \Lambda\beta\zeta - \rho N\mu^2 - N\mu^3 - N\mu^2\zeta - N\mu^2\sigma - N\mu\sigma\zeta)}{\beta(\zeta + \mu)(\sigma\zeta + \sigma\mu + \mu\zeta + \mu^2 + \rho\mu)} \\
 R^* &= \frac{\sigma(\Lambda\beta\mu + \Lambda\beta\zeta - \rho N\mu^2 - N\mu^3 - N\mu^2\zeta - N\mu^2\sigma - N\mu\sigma\zeta)}{\beta\mu(\sigma\zeta + \sigma\mu + \mu\zeta + \mu^2 + \rho\mu)}
 \end{aligned}
 \tag{2}$$

STOCHASTICITY

Since we aim to find the effect of Quiescence on the mean number of infected individuals, we now transform model 1 into a stochastic process (birth and death process). We first find the transition probabilities given in Table 1. The likelihood of changing from one state to another within a specified time frame (very small) is referred to as a transition probability. These transitions capture the dynamics of people moving over time between the four compartments (Susceptible, Infectious, Quiescence and Recovered). The continuous time Markov Chain of SIQR model has the following transitions: from susceptible to infectious (caused by disease transmission), from contagious to recovered (caused by immunity or recovery), from communicable

to quiescent stage (caused by parasite entering quiescence phase), from quiescent stage to infectious (caused by parasite exiting quiescence phase), the birth of susceptible into the population (caused by giving birth) and the death of an individual from each compartment (caused by natural death or disease-induced death). In this research, we find that the Quiescence increases the mean number of infected individuals.

DISCUSSION

Impact on Transmission: Since Quiescence raises the average number of infected people, it stands to reason that this period accelerates the disease’s spread

Table 1: Transitions rates for the SEIQR model

Type	Transition	Probability
Birth of Healthy	$(S_b, I_b, Q_b, R_t) \rightarrow (S_t + 1, I_t + Q_b, R_t)$	$\Lambda\Delta t + o(\Delta t)$
Infection	$(S_b, I_b, Q_b, R_t) \rightarrow (S_t - 1, I_t + 1, Q_b, R_t)$	$\frac{\beta \cdot S I}{N} \Delta t + o(\Delta t)$
Natural Death of S	$(S_b, I_b, Q_b, R_t) \rightarrow (S_t, I_t + 1, Q_t - 1, R_t)$	$\mu S \Delta t + o(\Delta t)$
Recovery of I	$(S_b, I_b, Q_b, R_t) \rightarrow (S_b, I_t - 1, Q_b, R_t + 1)$	$\sigma I \Delta t + o(\Delta t)$
Go quiescent of I	$(S_b, E_b, I_b, Q_b, R_t) \rightarrow (S_b, I_t - 1, Q_t + 1, R_t)$	$\rho I \Delta t + o(\Delta t)$
Wake-up of Q	$(S_b, I_b, Q_b, R_t) \rightarrow (S_b, I_t + 1, Q_t - 1, R_t)$	$\zeta Q \Delta t + o(\Delta t)$
Natural Death of I	$(S_b, I_b, Q_b, R_t) \rightarrow (S_b, I_t + 1, Q_t - 1, R_t)$	$\mu I \Delta t + o(\Delta t)$
Natural Death of R	$(S_b, I_b, Q_b, R_t) \rightarrow (S_b, I_t + 1, Q_t - 1, R_t)$	$\mu R \Delta t + o(\Delta t)$

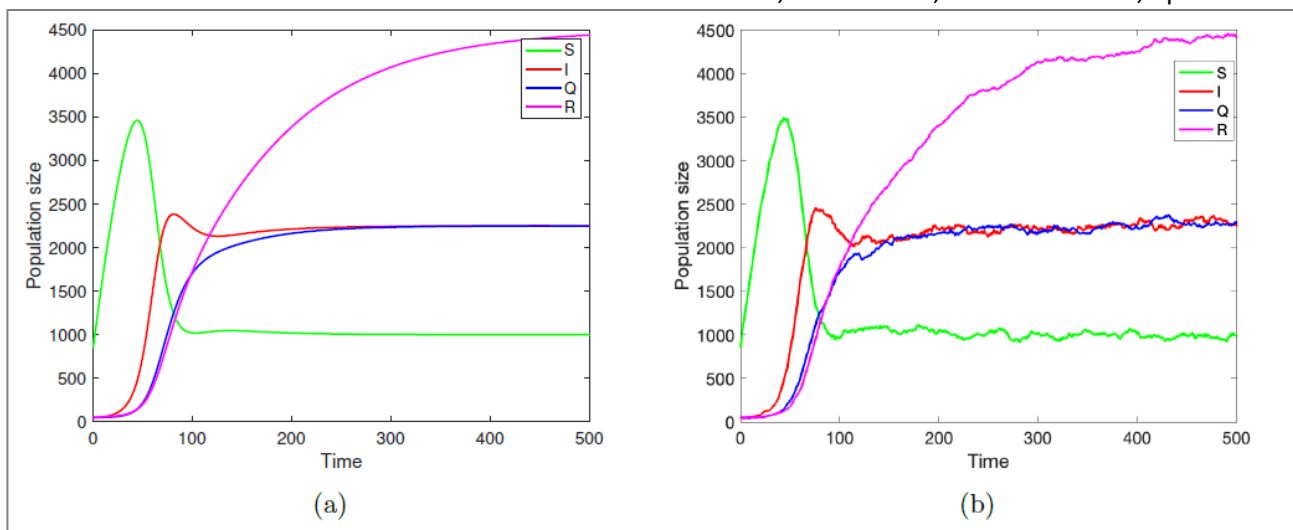


Figure 3: a) Numerical simulation of the deterministic SIQR model 1 with $S(0) = 850, I(0) = Q(0) = R(0) = 50$ and the parameter values $\Lambda = 100, \beta = 0.02, \mu = 0.01, \sigma = 0.02, \rho = 0.03, \zeta = 0.02$ b) Stochastic simulation of SIQR model using Gillespie’s algorithm; initial population size is $S(0) = 850, I(0) = Q(0) = R(0) = 50$ the parameters are 1 with the parameter values $\Lambda = 100, \beta = 0.02, \mu = 0.01, \sigma = 0.02, \rho = 0.03, \zeta = 0.02$. Please observe that the stochastic and deterministic solutions are in good agreement.

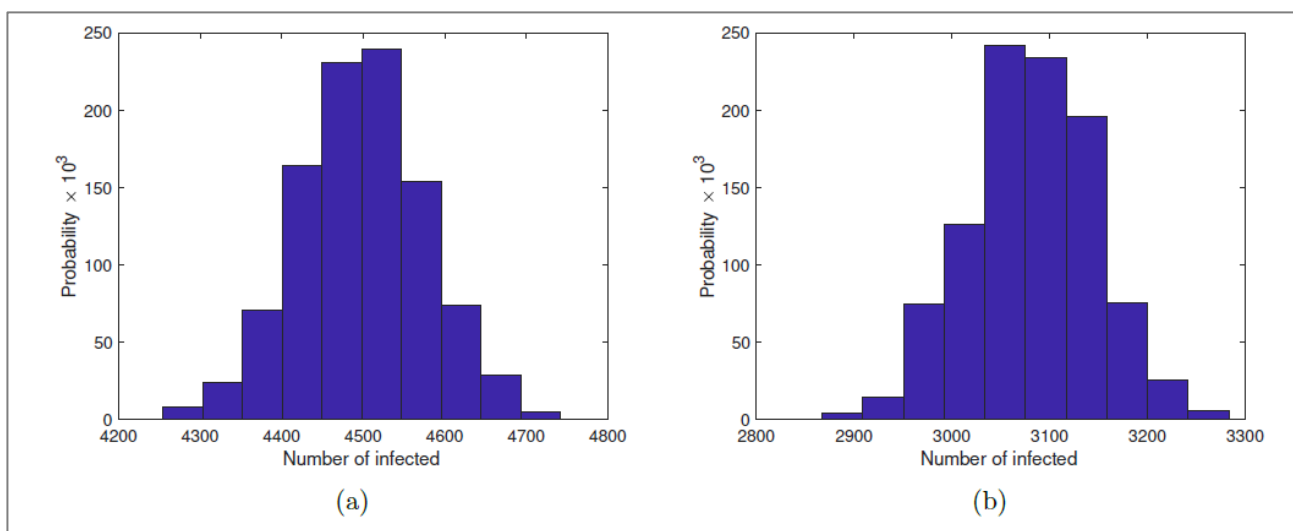


Figure 4: a) Probability distribution of the number of infected of the stochastic SIQR model (1000 repetitions of Gillespie’s algorithm) with $S(0) = 850, I(0) = Q(0) = R(0) = 50$ and the parameter values $\Lambda = 100, \beta = 0.02, \mu = 0.01, \sigma = 0.02, \rho = 0.03, \zeta = 0.02$ b) Probability distribution of the number of infected of the stochastic SIR model (1000 repetitions of Gillespie’s algorithm) with $S(0) = 900, I(0) = R(0) = 50$, and the parameter values $\Lambda = 100, \beta = 0.02, \mu = 0.01, \sigma = 0.02$. Please observe that the Quiescence shifted the mean number of infected to the right. Due to:

Reservoir Effect: Infectious agents may persist in spreading throughout a population when they are not active during the quiescent phase, which could result in a higher rate of infections when they wake up again at the proper time.

CONCLUSION

As dormant organisms might contribute to the survival and return of the disease, managing infectious diseases under the influence of pathogen quiescent can be difficult. However, a prolonged treatment period, that is, to

extend the time that antibiotics are administered to target both quiescent and actively proliferating parasites. Treating quiescence parasites for a longer time is necessary to completely eradicate them. If you stick with the antibiotic prescription for a long time, there is a better chance of getting rid of dormant parasites and keeping the infectious disease from re-emerging.

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