Dynamics of Coinfection: Complexity and Implications

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Linköping Studies in Science and Technology.

Dissertations No. 2011

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Linköping 2019

Linköping Studies in Science and Technology. Dissertations No. 2011

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Typeset by the author in L^AT_EX2e documentation system.

ISSN 0345-7524

ISBN 978-91-7519-016-7

Printed by LiU-Tryck, Linköping, Sweden 2019

To my parents

Abstract

Living beings are always on risk from multiple infectious agents in individual or in groups. Though multiple pathogens' interactions have widely been studied in epidemiology. Despite being well known, the coexistence of these pathogens and their coinfection remained a mystery to be uncovered. Coinfection is one of the important and interesting phenomenon in multiple interactions when two infectious agents coexist at a time in a host. The aim of this thesis is to understand the complete dynamics of coinfection and the role of different factors affecting these interactions.

Mathematical modelling is one of the tools to study the coinfection dynamics. Each model has its own limitations and choice of the model depends on the questions to be addressed. There is always a crosstalk between the choice of model and limitation of their solvability. The complexity of the problem defines the restriction in analytical possibilities.

In this thesis we formulate and analyse the mathematical models of coinfection with different level of complexities. Since viral infections are a major class of infectious diseases, in the first three papers we formulated a susceptible, infected, recovered (SIR) model for coinfection of the two viral strains in a single host population introducing carrying capacity as limited growth factor in susceptible class. In the first study, we made some assumptions for the transmission of coinfection in the model. In the following papers, the analysis is expanded by relaxing these assumptions which has generated the complexity in dynamics. We showed that the dynamics of stable equilibrium points depends on the fundamental parameters including carrying capacity K . A parameter dependent transition dynamics exists starting from disease free state to a level where coinfection can persist only with susceptible class. A disease-free equilibrium point is stable only when K is small. With increase in carrying capacity to a level where only single infection can invade and persists. Further increase in carrying capacity becomes large enough for the existence and persistence of coinfection due to the high density of susceptible class. In paper I, we proved the existence of a globally stable equilibrium point for any set of parameter values, revealing persistence of disease in a population. This shows a close relationship between the intensity of infection and carrying capacity as a crucial parameter of the population. So there is always a positive correlation between risk of infection and carrying capacity which leads to destabilization of the population.

In paper IV, we formulated mathematical models using different assumptions and multiple level of complexities to capture the effect of additional phenomena such as partial cross immunity, density dependence in each class and a role of recovered population in the dynamics. We found the basic reproduction number for each model which is the threshold

that describes the invasion of disease in population. The basic reproduction number in each model shows that the persistence of disease or strains depends on the carrying capacity K . In the first model of this paper, we have also shown the local stability analysis of the boundary equilibrium points and showed that the recovered population is not uniformly bounded with respect to K .

Paper V uses simulations to analyse the dynamics and specifically studies how temporal variation in the carrying capacity of the population affects its dynamics. The degree of autocorrelation in variability of carrying capacity influences whether the different classes exhibit temporal variation or not. The fact that the different classes respond differently to the variation depends in itself on whether their equilibrium densities show a dependence on the carrying capacity or not. An important result is that at high autocorrelation, the healthy part of the population is not affected by the external variation and at the same time the infected part of the population exhibits high variation. A transition to lower autocorrelation, more randomness, means that the healthy population varies over time and the size of the infected population decreases in variation.

Populärvetenskaplig sammanfattning

Djur och människor riskerar alltid att utsättas för flera smittämnen samtidigt från andra individer eller från grupper av individer. Denna typ av patogen-interaktioner har studerats i epidemiologi och flera olika sjukdomsbeskrivningar för hur olika infektioner samverkar är gjorda. Trots att de är välkända, är dessa patogeners samexistens och dynamiska system inte kartlagda. Att tvåsmittämnen existerar samtidigt hos en individ, en coinfektion, är ett viktigt och ofta allvarligt sjukdomsfenomen. Målet med denna avhandling är att förstå olika möjliga dynamiska system som kan uppträda vid coinfektion och den roll olika faktorer har på hur dessa dynamiska system uppträder. Matematisk modellering av coinfektion och dess interaktioner används för att beskriva interaktionerna och matematisk analys används för att förstå och beskriva dess dynamik. Varje modell har sina egna begränsningar och valet av modell beror på de frågor som ska besvaras. En ökad komplexitet av interaktioner och funktionella svar kan ge ett mer välbeskrivet system men också ett system som är betydligt svårare att analysera och kartläggning av dessa dynamiska system kan vara mycket begränsade.

I denna avhandling formuleras och analyseras matematiska modeller för coinfektion med olika nivåer av komplexitet vilka alla skall avspejla coinfektion för virusinfektioner. Alla modellerna är SIR- modeller med mottagliga-smittade-återställda för coinfektion av två infektionssjukdomar, eller tvåstammar av samma sjukdom, i en värdpopulation. Modellerna har även tagit hänsyn till begränsning av tillväxt för populationen genom att introducera en maximal populationsstorlek via en såkallad bärförmåga. För varje modell gjorde vi specifika antaganden för överföring av infektion och i den fjärde artikeln studerar vi hela systemet med alla smittvägar och alla klasser är dock så begränsade av bärförmågan.

I avhandlingen visas att dynamiken vid stabila jämvikter beror på de grundläggande parametrarna för smittspridning inklusive bärförmågan. En parameterberoende övergång för olika typer av dynamik existerar från sjukdomsfria tillstånd till en nivå där coinfektion kan existera. En sjukdomsfri jämviktspunkt är stabil bara när bärförmågan är låg. Ökar bärförmågan, storlek på populationens maximala storlek, förbi denna nivå uppkommer ett område där endast en enda infektion kan invadera och existera. Ytterligare ökning av bärförmågan medför förekomst och existens av coinfektion på grund av den höga populationstätheten av mottagliga individer. I avhandlingen bevisas att det finns en globalt stabil jämviktspunkt för alla uppsättningar av parametervärden, vilka avgör persistensen av sjukdomar i en population. Detta visar att det finns ett nära samband mellan smittsamhet, alltså infektionsrisk, och befolkningens bärförmåga, alltså dess storlek, som bestämmer hur coinfektion kan utvecklas i en befolkning. Det finns en positiv korrelation mellan infektion-

srisk och bärformåga som leder till ökad smittspridning och sjukdom inom befolkningen.

I papper IV använder vi de matematiska modeller som utvecklats i papper I-III och lägger till flera komplexitetsnivåer för att fånga upp effekten av ytterligare fenomen som partiell korsimmunitet, begränsad tillväxt i varje klass och en interaktion med den återhämtad befolkning.

Papper V använder simuleringar för att analysera dynamiken och studerar speciellt hur temporal variation i bärformågan för populationen påverkar dess dynamik. Graden av autokorrelation i variation av bärformåga påverkar huruvida de olika klasserna uppvisar temporal variation eller ej. Att de olika klasserna svara olika på variationen beror i sig på huruvida deras jämviktstättigheter uppvisar ett beroende av bärformågan eller ej.

Acknowledgement

First of all, I am very grateful to my main supervisor, Vladimir Kozlov, for his guidance, continuous support, sharing great ideas. It was encouraging for me to have the opportunity to think and explore this area of science to become an independent researcher. I would like to express my deep gratitude to my co-supervisor Uno Wennergren, for sharing great ideas, inspiring discussions, endless support, encouragements and feedback to improve my work. I am also very thankful to my co-supervisor Vladimir Tkachev, your help during my studies and having the eye that detects what went wrong where. You always had the time for my drop-in questions. Special thanks goes to Dietrich von Rosen for his guidance and help.

The institutions playing role in my academic career are LiU, SBKWU and Higher education Commission, Pakistan. I would highly acknowledge these respectable institutes for financial support during my Ph.D studies. It would not have been possible to reach my academic goals without the support that I have received during my Ph.D. I would like to extend my thanks to all the people working in the Department of Mathematics at Linköping University for their support and help during my Ph.D studies. I am really thankful for your precious time you had for me whenever I needed.

I am really grateful to my friends and colleagues. Most importantly, Hanifa and Budor, for the all fun time we had together, discussions and making me laugh out loud. Special thanks to my siblings for their love, care and encouragement during each and every pace of my life. My biggest appreciation and love goes to my precious daughter Alina, whose cute smile at the end of the day is always enough to take away all the worries and my husband, Shah, for his love, care and always being there for me.

List of Papers

- I. S. Gherseen, V. A. Kozlov, V. G. Tkachev, and U. Wennergren. *Dynamical behavior of SIR model with coinfection: the case of finite carrying capacity*. Mathematical Methods in the Applied Sciences. 42(8), 2019.
Author's contribution: Contribution to the model development and its analysis, writing of the paper draft.

- II. S. Gherseen, V. A. Kozlov, V. G. Tkachev, and U. Wennergren. *Mathematical analysis of complex SIR model with coinfection and density dependence*. Computational and Mathematical Methods. 2019 May 13:e1042.
Author's contribution: Model formulation and its analysis, writing of the paper draft.

- III. S. Gherseen, J. Andersson, V. A. Kozlov, V. G. Tkachev, and U. Wennergren. *Specifics of coinfection and its dynamics*, manuscript.
Author's contribution: Contribution to the model development, local stability analysis, writing of part of paper.

- IV. S. Gherseen, V. A. Kozlov, and U. Wennergren. *Effects of density dependence, partial cross immunity and standard incidence rates on coinfection dynamics*, manuscript.
Author's contribution: Contribution to the models development and their analysis, writing the manuscript.

- V. S. Gherseen, V. A. Kozlov, V. G. Tkachev, and U. Wennergren. *Effects of environmental variation on coinfection dynamics*, manuscript.
Author's contribution: Model formulation, numerical simulations, writing the manuscript.

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Introduction

Infectious diseases have always been a great threat to humans and animals. The complete insight of the dynamics of diseases is the biggest concern of public health policy makers. The evolution of pathogens has made this phenomenon more complex. The important mechanisms in this situation are virulence of disease and reasons of coexistence of multiple pathogens. The factors that can influence the virulence of pathogens has also been focused by different epidemiologist to understand the infection age and the factors that can affect positively or negatively the pathogenicity. This can provide a better understanding of the disease to public health policy makers and also helps to design the best possible controlling strategies. The continuous eradication of communicable diseases on global scale and their interaction brought many challenges including the understanding of complete dynamics and controlling factors of epidemics. One of the major problem in this context is coexistence of two different pathogens in a single host which is commonly known as coinfection. Coinfection is very common globally. It not only involves multiple strains but also multiple disease (viral and bacterial) [9, 24]. Most of the studies [29, 16] report negative effects of coinfection on human health. However, existing coinfection research rarely focuses on pathogens with highest global mortality. Understanding of coinfection dynamics is also important to investigate the pathogen-pathogen interaction and also their interaction with host immune system. Since coinfection involves the coexistence of many pathogens, these pathogens and there interactions can have various effects on hosts which can change the transmission, treatment and clinical progression of infectious diseases. Understanding the nature of coinfection and its effects on host population needs integrated evaluation strategies and research but such data is very rare. [29, 33, 16]. The studies available in this regard are often narrowly focused. Therefore to understand the dynamics completely one must know the effect of interactions and various transmission levels on hosts. Mathematical modelling is one of the effective tools to understand biological processes. It has been widely used in epidemiology to understand not only the dynamics of disease, but it is also helpful to design practical controlling strategies. The two major challenges in the mathematical modelling of infectious disease are: the demand of realistic model in the most applicable sense to predict the disease spread and for mathematical analysis to provide the analytical solution. Therefore in order to deal with both challenges, the main objective of this thesis is to go from simple to more complex models step by step. This helps to understand the role of each parameter in the dynamics of coinfection and also can help to take controlling measure by controlling crucial parameter. Many mathematical studies

are performed on the single pathogen and multiple pathogen interaction and their effect on the host population. Different mathematical models have been developed and analysed [1, 3, 26, 18, 25, 23, 7, 38] to study the specific multiple pathogen, their counteractions and also for general diseases.

The next chapter gives a brief introduction about the models and main analytical tools used in the analysis of models. In chapter 3, we discuss papers I-III which concern with the role of different parameters in coinfection dynamics. This is done by using a new approach *transition dynamics*. Chapter 4 is devoted to paper IV which deals with the study of individual level effects: density dependence, partial cross immunity and standard incidences on coinfection dynamics. In chapter 5 gives a brief overview of paper V where effect of environmental variation on coinfection dynamics is discussed. Chapter 6 contains discussion.

1.1 Aims

The aims of the thesis are

- To develop mathematical models and analytical tools that describe role of density dependence and other parameters in coinfection dynamics. (Papers I, II, III, IV)
- To study the individual level effects such as partial cross immunity and standard incidences on coinfection dynamics, density dependence on coinfection dynamics. (Paper IV)
- The effect of environmental variation on coinfection dynamics. (Paper V)

Compartmental models in epidemiology

Most of the epidemiological modelling is based on continuous models where non-linear differential equations are used. A classical way of such modelling is to divide population into different non overlapping classes. The way individuals change over time is described by the flows through different compartments. This approach is relatively simple and very useful in disease modelling. The objective of this section is to introduce the basics for better understanding of the models used in this thesis rather than summarizing the overview of the analytical results. For the interested readers we refer to the studies [21, 6, 8, 20] for further details. The simple models have two or three compartments which are SI and SIS, SIR models and can be extended to multiple compartments depending on the nature of disease. Compartmental models were first developed by Kermack and McKendrick (1927) [21]. The results are basic to infectious disease modelling. They have found a threshold for the invasion and persistence of disease in population, commonly known as basic reproduction number R_0 . This is the most important quantity in mathematical epidemiology which illustrates the invasion of infection or disease in population. It is the average number of secondary cases of infection induced by a primary case in a completely susceptible population [13]. If $R_0 < 1$ then disease will go extinct after some time in the population. Mathematically in that case disease free equilibrium must be stable and if $R_0 > 1$ then disease will persist in population and the endemic equilibrium is stable. In the models presented in this thesis, we use SIR models to model coinfection dynamics. These models consist of system of ordinary differential equations.

The model suggested by Kermick-MacKendric, birth and the death rates are not considered. Later as an extension of their model, there are many studies [14, 6, 37] which allows vital dynamics by considering birth and death rates. Generally, in SIR models the birth rate is always constant and some times equal to the death rate specifically for human related diseases. In contrast to the previous studies, we considered the density dependence in the host population's growth in the first three papers and in fourth paper we examined the density dependence effect on each class of population. The aim is to illustrate the effect of density restricted population on disease dynamics.

2.1 Density dependence in ecology and epidemiology

One of the important characters used in all the models in this thesis is density dependence population regulation. In ecology, the idea of density dependence has widely been used for ecological population since exponential growth in natural populations is rare. There are several factors that can influence the growth of population such as resource limitation, disease, predation and competition. In ecology, density dependence means that the growth rate of population always varies with respect to time as a function of population density. This process is often linked to the idea of carrying capacity [28]. The density dependence has also been used in epidemiological models mostly dealing with animals or other species. In [32], Sharp et al proposed a model with density dependence and time delay in wild life population and observed that more frequent outbreak of disease can be caused by the increased carrying capacity. Allen et al in paper [4, 2] have used density dependence mortality for SIR model of multiple pathogens and density dependence growth in SI model of coinfection.

Traditionally, the idea of density dependence has been used for all species except humans. The question of using this idea of limited growth by multiple factors for human population is still under debate but it is not completely unrealistic. In a study [15], analysis of the data has reveal that, contrary to previous literature, the world population is probably growing in this century. In 2100 it will increase from 7.2 billion to between 9.6 billion and 12.3 billion with a probability level of 80%. In another study on 44 developing countries [11], it is revealed that the population density is negatively affecting the fertility rates. In that context it is obvious to have the population density affecting disease dynamics and progression. In papers I - IV we have used density dependence in epidemiological context for coinfection. The aim is to investigate not only the effect of density dependence but also different other parameter on coinfection progression.

2.2 Transition dynamics

Traditionally, the methods used for analysis of infectious disease models involve the analysis of existence and local stability of equilibrium points, global stability analysis, and numerical simulations. However, the rigorous techniques do not work in the case of more complex situation. In papers I-III, we introduced a new problem setup to investigate how local stable equilibrium points depend on carrying capacity, transmission rates and other fundamental parameters. This is a difficult question in general because it is not easy to establish the uniqueness of a stable equilibrium point. Also in more complex models when more than one pathogens and more interactions are involved, it is difficult to get even the local stability of equilibrium points. In these papers we develop a concept of *transition dynamics* which means that any family of local stable equilibrium points depends continuously on parameters (usually on K). More precisely, we consider an equilibrium point as a member

of a certain family of stable equilibrium points, called an equilibrium branch and study all possible types of these branches. It allows us to approach the local stability as by the global analysis point of view. As a by product this framework also allows us to understand the role of each parameter, its impact on dynamics and the disease invasion in population. This also gives the description of all possible transition scenarios in the case of different fundamental parameters.

Modelling coinfection and role of parameters

In this section we discuss the models considered in paper I, II, III and their significance. The mathematical models formulated in these studies assumed the limited susceptible population growth by making the per capita reproduction rate dependent on carrying capacity. In other words, the susceptible population is regulated by the carrying capacity while the infected populations are regulated by their death rates. In each paper we assumed vital dynamics and also the recovered class is completely immune. The SIR model in paper I-III are described by system of five ordinary differential equations and each model has its own limitation, most of these limitations are related to the transmission of disease. The most general model is discussed in paper II and it is given as follows:

$$\begin{aligned}
 S' &= (b(1 - \frac{S}{K}) - \alpha_1 I_1 - \alpha_2 I_2 - (\beta_1 + \beta_2 + \alpha_3) I_{12} - \mu_0) S, \\
 I_1' &= (\alpha_1 S - \eta_1 I_{12} - \gamma_1 I_2 - \mu_1) I_1 + \beta_1 S I_{12}, \\
 I_2' &= (\alpha_2 S - \eta_2 I_{12} - \gamma_2 I_1 - \mu_2) I_2 + \beta_2 S I_{12}, \\
 I_{12}' &= (\alpha_3 S + \eta_1 I_1 + \eta_2 I_2 - \mu_3) I_{12} + (\gamma_1 + \gamma_2) I_1 I_2, \\
 R' &= \rho_1 I_1 + \rho_2 I_2 + \rho_3 I_{12} - \mu_4 R.
 \end{aligned} \tag{3.1}$$

Here S represents the susceptible class, I_1 and I_2 are infected classes from strain 1 and strain 2 respectively, I_{12} represents co-infected class, R represents the recovered class and

$$N = S + I_1 + I_2 + I_{12} + R$$

is the total population. The parameters in this model are

- b is the birthrate of susceptible class;
- K is carrying capacity;
- ρ_i is recovery rate from each infected class ($i = 1, 2, 3$);
- β_i is the rate of transmission of a single infection from coinfecting class ($i = 1, 2$);
- γ_i is the rate at which infected with one strain get infected with the other strain and move to coinfecting class ($i = 1, 2$);

- μ_0 is death rate of susceptible class;
- μ'_i is death rate of infected and recovered classes, ($i = 1, 2, 3, 4$);
- α_i , are rates of transmission of infection 1, infection 2 and coinfection ($i = 1, 2, 3$) ;
- η_i is rate at which infected from one strain or disease get other infection from co-infected class ($i = 1, 2$) and $\mu_i = \rho_i + \mu'_i, i = 1, 2, 3$.

It is assumed that the reproduction rate of susceptible is greater than their death rate:

$$b > \mu_0.$$

Otherwise population will die out quickly. Also the system is considered under the natural initial conditions

$$S(0) > 0, \quad I_1(0) \geq 0, \quad I_2(0) \geq 0, \quad I_{12}(0) \geq 0, \quad R(0) \geq 0. \quad (3.2)$$

One can easily show that $\mathbb{R}_+^5$ is an invariant subset of (3.1). Note that since variable R is not present in the first four equations, we may consider only the first four equations of system (3.1). We assume in first three studies that the infection 1 and infection 2 are different and also the transmission rate of coinfection is always less than the transmission rates of other two infections and used the following hypothesis throughout this analysis

$$\sigma_1 < \sigma_2 < \sigma_3, \quad (3.3)$$

where

$$\sigma_i = \frac{\mu_i}{\alpha_i}, \quad 1 \leq i \leq 3.$$

In Paper I-III, we have different assumptions on the transmission of infections, from relatively simple case to more complex case. Such studies mostly rely on computer simulations, and therefore we regard it as important to fully understand the simple cases first. This helps from public health management and control prospective, to identify the crucial parameters in the spread of diseases. Below each case has been discussed explicitly.

3.1 The case of zero transmission parameters

This special case of (3.1) is considered in paper I. It is assumed that the coinfection can occur only in the case of contact between coinfecting class and other classes. The coinfection can not occur when two single infected individual come in contact. Moreover, it is also assumed that the coinfecting individual can only transmit two infection simultaneously to a susceptible individual. These assumptions vanish parameters β_i, γ_j i.e.

$$\beta_1 = \beta_2 = \gamma_1 = \gamma_2 = 0. \quad (3.4)$$

These assumptions simplified the model and the resulting system corresponds to the Lotka-Volterra type model. The system (3.1), when (3.4) holds, can be written in the form

$$\frac{dY_k}{dt} = F_k(Y) \cdot Y_k, \quad k = 0, 1, 2, 3, \quad (3.5)$$

where we denote

$$F(Y) = -q + AY \quad (3.6)$$

with

$$Y^T = (Y_0, Y_1, Y_2, Y_3) = (S, I_1, I_2, I_{12}),$$

$$F(Y) = \begin{pmatrix} F_0(Y) \\ F_1(Y) \\ F_2(Y) \\ F_3(Y) \end{pmatrix}, \quad q = \begin{pmatrix} -b + \mu_0 \\ \mu_1 \\ \mu_2 \\ \mu_3 \end{pmatrix}, \quad A = \begin{pmatrix} -\frac{b}{K} & -\alpha_1 & -\alpha_2 & -\alpha_3 \\ \alpha_1 & 0 & 0 & -\eta_1 \\ \alpha_2 & 0 & 0 & -\eta_2 \\ \alpha_3 & \eta_1 & \eta_2 & 0 \end{pmatrix}. \quad (3.7)$$

The fact that $A + A^T \leq 0$ is semi definite plays a crucial role. The system (3.5) has the basic reproduction number

$$R_0 = \frac{S^{**}}{\sigma_1}, \quad \text{where} \quad S^{**} = \frac{K}{b} (b - \mu_0).$$

Therefore, when $S^{**} < \sigma_1$, the disease can not persist in population. The quantity S^{**} , which is the *modified carrying capacity*, is very important in all of the studies presented here. Note that this quantity is always less than K , which shows susceptible population size in the absence of any infection.

3.1.1 On F -stable equilibrium points

The system (3.5) has eight equilibrium points listed below

$$E_1 = (0, 0, 0, 0), E_2 = (S^{**}, 0, 0, 0), E_3 = (S^*, I_1^*, 0, 0), E_4 = (S^*, 0, I_2^*, 0),$$

$$E_5 = (S^*, 0, 0, I_{12}^*), E_6 = (S^*, I_1^*, 0, I_{12}^*), E_7 = (S^*, 0, I_2^*, I_{12}^*), E_8 = (S^*, I_1^*, I_2^*, I_{12}^*).$$

The trivial equilibrium point E_1 is always unstable. An equilibrium point Y is said to be F -stable for admissible set of parameters if $F_i(Y) \leq 0$ for all $0 \leq i \leq 3$. In paper I, we have used the Linear Complementary Problem (LCP) for the analysis of equilibrium points and to prove the existence and uniqueness. We recommend interested reader references [10], [35] for details of LCP. An application of the LCP to the Lotka-Volterra systems is not new and was firstly used by Takeuchi and Adachi [36], see also [35]. However, some challenges are by the semi definite property of our matrix A . Our aim is to study how F -stable points depends on the fundamental parameters of the system. Due to the special structure of the matrix A in (3.7), we have always a unique stable equilibrium point for each admissible set of parameters.

3.1.2 Boundedness of solutions

In epidemiology, it is important to know the boundedness for different classes in the population. In this section, we discuss the estimates for susceptible population and the total population. The boundedness of the the susceptible class can be obtain from the first equation of (3.5)

$$S(t) \leq \max\{S^{**}, S(0)\}. \quad (3.8)$$

Furthermore, there holds the limit relation

$$\limsup_{t \rightarrow \infty} S(t) \leq S^{**}. \quad (3.9)$$

This shows that the susceptible class is always bounded.

Next, the total estimate for population is given

$$\sum_{i=0}^3 Y_i(t) \leq \max\left\{\sum_{i=0}^3 Y_i(0), \frac{Kb}{4\hat{\mu}}\right\} \quad (3.10)$$

for $t \geq 0$, where $\hat{\mu} := \min\{\mu_0, \mu_1, \mu_2, \mu_3\}$. In particular, any solution of (3.5) with initial data (3.2) is bounded. This boundedness allows us to describe an invariant set such that all trajectories are attracted towards that set. It rises a natural question about the existence of a globally stable point there.

3.1.3 The global stability analysis

The concept of F -stable points is related to the Lyapunov stability. For global stability analysis, we use the generalized Volterra function [27]

$$V_{Y^*}(y_0, y_1, y_2, y_3) = \sum_{i=0}^3 (y_i - Y_i^* \ln y_i).$$

The time derivative of V_{Y^*} along any integral trajectory of (3.5) is given by

$$\frac{d}{dt} V_{Y^*} := (\nabla V_{Y^*}) \cdot \frac{dy}{dt} = -\frac{b}{K}(y_0 - Y_0^*)^2 + \sum_{i=0}^3 F_i(Y^*)y_i, \quad (3.11)$$

which gives the sign of the derivative for F -stable points. It is important to consider those equilibrium points for which F is negative and it appears also in LCP. Since the first part of above equation is negative, we have

$$\frac{d}{dt} V_{Y^*}(y(t)) \leq 0 \quad (3.12)$$

and the equilibrium point is stable in this case. Another important issue is the transition dynamics. We study dependence of stable equilibrium points on parameters. We found different branches of such points which can be parametrized by $K \in (0, \infty)$. These branches depend on other parameters of the problem and describe progression of disease with the increasing carrying capacity. The important point is that each of this progression scenario depends on the choice of parameters $(\alpha_i, \mu_i, \eta_i)$.

3.1.4 Main results

The main results for this model contain the three properties, transition, monotonicity, uniqueness. By using the LCP, we are able to establish the existence of a unique equilibrium point of (3.5) for any set of fundamental parameters. A natural question is to study how this point depends on the carrying capacity K . In this context, transition dynamics of equilibrium points is one of the striking result in this study. This dynamics strongly depends on parameter K and it turns out that the only possible scenarios are the following:

- (i) $E_2 \rightarrow E_3$;
- (ii) $E_2 \rightarrow E_3 \rightarrow E_6 \rightarrow E_5$;
- (iii) $E_2 \rightarrow E_3 \rightarrow E_6 \rightarrow E_8$;
- (iv) $E_2 \rightarrow E_3 \rightarrow E_6 \rightarrow E_8 \rightarrow E_7 \rightarrow E_5$.

In all these scenarios, varying the value of parameters gives a new transition branch which is parametrized by the carrying capacity K . Some of these scenarios are simple. For example in the first scenario for small K , disease can not invade in population due to the small size of population, but after crossing the first threshold the population size increases and it supports the invasion of dominant infection. One possibility is that, for certain combination of the fundamental parameters, the system will remain in this state forever. But it is also possible, for further large K and different set of parameters, as in third scenario, it will transition into E_6 and end up at E_8 which is the coexistence state. This can happen when, due to the effect of coinfection on single infection, the second infection starts to spread. In the second scenarios, one can show that if E_5 is F -stable for some value of S^{**} then it remains F -stable for the larger values of K which means that the system equilibrium bifurcates to equilibrium point E_5 after some threshold and remain in this state for large carrying capacity. In the case of very large K the possible final equilibrium states are E_3, E_5, E_8 .

Next, the monotonic non-decreasing dependence of susceptible class on parameter K is observed. It is also important to point out that the density of susceptible class stabilizes when K is greater than a certain threshold value. In other words, after a threshold, the equilibrium point still depends on K except for the susceptible class which becomes

constant. Furthermore, in all scenarios, the susceptible class behave as increasing (non degenerate) function of the carrying capacity which is also biologically reasonable. The corresponding graphs of the susceptible class are pictured in Figure 3.1.

Figure 3.1: The possible scenarios of the transition dynamics

3.2 The case of zero β -parameters

In paper III, we assume that coinfection can also occur as a result of contact between two single infected individuals but the assumption of transmission of single infection from coinfecting individual still remain, i.e. $\beta_i = 0$, $\gamma_j \neq 0$, $i, j = 1, 2$. This perturbs the system (3.5) into a system which is different from the Lotka-Volterra system. Therefore the use of Linear Complementary Problem (LCP) for analysis of stable equilibrium points is not possible in this case because of an extra term in fourth equation of the model. The local stability, bifurcation and transition dynamics is studied in this paper.

3.2.1 Equilibrium point analysis

In this case we have also eight equilibrium points and similar to previous case trivial equilibrium point is unstable. The local stability of all other equilibrium points depends on the carrying capacity K . The disease free equilibrium point is globally stable for small

K . This shows that when the susceptible population is small disease can not invade in the population and go extinct. As carrying capacity increases and population becomes larger then the other infections can invade in population. As K crosses the first threshold, the first infection, which is assumed to be dominant, can invade and persist in the population. For relatively low carrying capacity the coinfection can only exist in the presence of single infections. Coinfection can invade in population alone only if the value of K is large. The stability of coexistence equilibrium point has revealed that all infections can coexist in the population. We have shown that for small γ_1, γ_2 the transition dynamics is similar to that revealed in paper I.

3.2.2 Bifurcation analysis

In comparison with paper I, the system considered in paper II is very different from that previous Lotka-Volterra type system. Therefore LCP approach can not be used for this new model. We developed a new technique based on bifurcation analysis. We construct continuous branches of stable equilibrium points which are parametrized by carrying capacity $K \in (0, \infty)$. For each branch we identify thresholds equilibrium points where its type is changed. The most difficult part is the study of coexistence equilibrium points. The starting point here is the identification of thresholds for the equilibrium points E_6 and E_7 where coinfection can coexist with infection 1 or infection 2 and the bifurcation analysis around them. This allows to describe two branches of equilibrium points near these thresholds. In paper III, the transition dynamics of the equilibriums states is also observed in the similar way. we observed that if all parameter are fixed with sufficiently small γ_i , $i = 1, 2$, then there is exactly one locally stable non negative equilibrium point. Furthermore, changing the carrying capacity K the possible scenarios of the transition dynamics are similar as in the case of $\gamma_1 = \gamma_2 = 0$. But monotonicity on the other hand is different for some cases is shown in the Figure 3.2.

3.3 The case of non-zero transmission parameters

In paper II we discussed the case when parameter $\beta_i \neq 0$, $\gamma_j \neq 0$, $i, j = 1, 2$. In this case we relax all the assumptions discussed before. The model (3.1) is more realistic but analytically more complex and we consider it as a perturbation of the Lotka-Volterra system.

3.3.1 Equilibrium points and stability analysis

Comparing to paper I and paper III, allowing all transmissions in paper III, reduced the number of equilibrium points from eight to five. Similar to the previous models the disease

Figure 3.2: The possible scenarios of the transition dynamics

free equilibrium point is always unstable. The stability of other equilibrium points depends on the parameter K which is crucial in the analysis of all papers. The local stability analysis is done in the case of disease free equilibrium point and equilibrium point $G_3(S^*, I_1^*, 0, 0)$ and $G_4 = (S^*, 0, I_2^*, 0)$. Due to the complexity of the model it was difficult to find the coordinates of the coexistence equilibrium point explicitly and determine its local analysis. But it is plausible to expect if such point is stable then the equilibrium point with strain one will bifurcates to such point. The global behaviour of equilibrium points comes from the Lyapunov function as before but the derivation of that function is slightly different from the previous cases due to the existence of some addition terms. Similar to previous models, one of the important parameter here is K which can influence the dynamics of disease. Although this model is realistic but it is more complicated from analytical prospective. Due to its complexity, the transition dynamics for the system (3.1) exist only for small positive K , β_i and γ_j , $i, j = 1, 2$, as a perturbation of (3.4). The only possible transition scenario in this case are $G_2 \rightarrow G_3$. It is also observed that for small β_1, β_2 and γ_1, γ_2 , when the equilibrium point G_3 loses its stability then the coexistence equilibrium point appears near G_3 and it is stable.

On the role of external factors in coinfection dynamics

In this section we discuss four different model to address the effect of density dependence in each class, influence of immunity and partial cross immunity on the dynamics of coinfection. This allows the deep understanding of the factors that can influence the disease progression.

4.0.1 Density dependence

This model is an extension of models discussed in paper I-III. We consider here the growth of all classes of the population (susceptible to recovered) is restricted by carrying capacity. We assume that they are sharing the same resource. It is also assumed that a susceptible individual can be infected with both pathogens or a single pathogen as a result of contact with coinfecting person. Moreover coinfection can occur as a result of contact between two single infection individuals or coinfecting and single infected individuals. However, to make model analytically solvable, the life long immunity of recovered class has been assumed. Similar to previous models, pseudo-mass action incident rates or bilinear incident rate are considered and model then is given by the following system of differential equations

$$\begin{aligned}
 S' &= \left(b \left(1 - \frac{N}{K} \right) - \alpha_1 I_1 - \alpha_2 I_2 - (\beta_1 + \beta_2 + \alpha_3) I_{12} - \mu_0 \right) S, \\
 I_1' &= \left(b \left(1 - \frac{N}{K} \right) + \alpha_1 S - \eta_1 I_{12} - \gamma_1 I_2 - \mu_1 \right) I_1 + \beta_1 S I_{12}, \\
 I_2' &= \left(b \left(1 - \frac{N}{K} \right) + \alpha_2 S - \eta_2 I_{12} - \gamma_2 I_1 - \mu_2 \right) I_2 + \beta_2 S I_{12}, \\
 I_{12}' &= \left(b \left(1 - \frac{N}{K} \right) + \alpha_3 S + \eta_1 I_1 + \eta_2 I_2 - \mu_3 \right) I_{12} + (\gamma_1 + \gamma_2) I_1 I_2, \\
 R' &= \left(b \left(1 - \frac{N}{K} \right) - \mu_4' \right) R + \rho_1 I_1 + \rho_2 I_2 + \rho_3 I_{12},
 \end{aligned} \tag{4.1}$$

where S represents the susceptible class, I_1 and I_2 are infected classes from pathogen 1 and pathogen 2 respectively, I_{12} represents co-infected class, R represents the recovered class.

Also,

$$N = S + I_1 + I_2 + I_{12} + R$$

is the total population. The parameters are given as

- b is the birthrate of each class;
- K is carrying capacity of class;
- ρ_i is recovery rate from each infected class ($i = 1, 2, 3$);
- β_i is the rate of transmission of single infection from coinfecting class ($i = 1, 2$);
- γ_i is the rate at which infected with one strain get infected with the other strain and move to coinfecting class ($i = 1, 2$);
- μ_0 is death rate of susceptible class;
- μ'_i is death rate of each class, ($i = 1, 2, 3, 4$) and $\mu_i = \rho_i + \mu'_i, i = 1, 2, 3$;
- $\alpha_1, \alpha_2, \alpha_3$ are rates of transmission of pathogen 1, pathogen 2 and both strains (in the case of coinfection);
- η_i is rate at which infected from one strain getting infection from co-infected class ($i = 1, 2$).

The possibility of simultaneous transmission from a single contact with a dually infected individual, which we model according to the assumption $\alpha_3 > 0$. An underlying assumption in the model is that individuals in all disease states have the same contact rate. Moreover, it is reasonable to assume that birth rate $b > \mu_j, j = 1, 2, 3, 4$, otherwise population dies out quickly. It is assumed that the death rate of recovered population is greater than the death rate of susceptible population, i.e

$$\mu_0 < \mu'_4 < \mu'_j, j = 1, 2, 3. \quad (4.2)$$

Since, in this model we assume the complete cross immunity therefore, the death rate of recovered class is relatively lower than other infected classes. It is also reasonable to assume that the death rates due to coinfection are greater than the death rate due to single infection due to the severity of coinfection. Moreover, we assume that

$$\sigma_1 < \sigma_2 < \sigma_3, \quad (4.3)$$

where

$$\sigma_k = \frac{\mu_k - \mu_0}{\alpha_k}, \quad k = 1, 2, 3.$$

4.0.2 Equilibrium point analysis

This system has only four non zero equilibrium points and one trivial equilibrium point. In this model the recovered population is taking part in the dynamics. Similar to the models discussed in the previous chapter the disease free equilibrium point is globally stable for small K which guarantees the extinction of disease from population. When the carrying capacity increases then the disease takeover in the population and started to spread. Since our assumption about the dominance of infection 1 is the same in this model as well, therefore it is observed that the next stable equilibrium point is the point when infection 1 exist along with susceptible population. Due to that assumption strain or disease 1 can exclude the other infections. Two infections can coexist only with coinfection and vice versa. The coexistence equilibrium point can also exist. Although the density dependence factor gives sufficient control on the population growth but it has been observed that the recovered population is not uniformly bounded by K .

4.0.3 Transition scenarios with increasing K

The transition from disease free states to the states with disease is observed in this case. That transition depends on the carrying capacity which indicate that the invasion of of pathogens increases with growing K . In this study we have the following two possible scenarios for stable equilibrium states

- (i) $G_2 \longrightarrow G_3$,
- (ii) $G_2 \longrightarrow G_3 \longrightarrow \text{Coexistence state}$.

The choice of scenario depends on the sign of following expression.

$$\left(\frac{\delta_1}{\alpha_1}(\mu'_4 - \mu_0) + \alpha_2(\sigma_1 - \sigma_2) \right) \left(\frac{\delta_2}{\alpha_1}(\mu'_4 - \mu_0) + \alpha_3(\sigma_1 - \sigma_3) \right) - \frac{\beta_2(\gamma_1 + \gamma_2)}{\alpha_1^2}(\mu'_4 - \mu_0)(\mu_1 - \mu'_4).$$

In the case of small K , there is a stable disease free equilibrium point but after a threshold, when K continue to increase, that equilibrium point become unstable and the other equilibrium point G_3 , which corresponds to the existence of infection 1, becomes stable. In next case we start with stable disease free equilibrium point for small K and as K increases it bifurcates from G_3 to a coexistence equilibrium point.

4.1 Effect of standard incidence rate, partial cross immunity and no immunity in new born of R

Models discussed in this section are formulated to understand how incidence rates, immunity and susceptibility in reproduction can effect the disease dynamics when multiple

pathogens are involved. The basic reproduction number for each model is calculated which gives the threshold for progression of disease in population.

4.1.1 Model 1: No immunity in recovered class new born

An epidemic model is considered here and susceptibility in the new born of recovered class is assumed. This assumption is true in the case of many disease when the new born can not acquire life long immunity from disease. The model then is given as follows

$$\begin{aligned}
 S' &= \left(b_1 \left(1 - \frac{N}{K} \right) - \alpha_1 I_1 - \alpha_2 I_2 - (\beta_1 + \beta_2 + \alpha_3) I_{12} - \mu_0 \right) S + \left(b_2 \left(1 - \frac{N}{K} \right) \right) R, \\
 I_1' &= (\alpha_1 S - \eta_1 I_{12} - \gamma_1 I_2 - \mu_1) I_1 + \beta_1 S I_{12}, \\
 I_2' &= (\alpha_2 S - \eta_2 I_{12} - \gamma_2 I_1 - \mu_2) I_2 + \beta_2 S I_{12}, \\
 I_{12}' &= (\alpha_3 S + \eta_1 I_1 + \eta_2 I_2 - \mu_3) I_{12} + (\gamma_1 + \gamma_2) I_1 I_2, \\
 R' &= \rho_1 I_1 + \rho_2 I_2 + \rho_3 I_{12} - \mu_4' R.
 \end{aligned} \tag{4.4}$$

b_1, b_2 are birthrates of susceptible and recovered classes and all the other transmission parameters are similar to the previous model (4.1). The basic reproduction number calculated in this case, by following the method given in [12], is

$$R_0 = \frac{S^{**}}{\sigma_1}.$$

The system (4.4) always has an unstable trivial equilibrium state. The non-trivial disease-free equilibrium point is stable if $S^{**} < \sigma_1$.

4.1.2 Model 2: On the standard incidence rates

The standard incidence rate is more realistic approach in disease modelling. This is always a better approximation for large susceptible population because in that case it is unlikely to have more contacts than needed. In the coinfection model below, the standard incident rate is considered as follows

$$\begin{aligned}
 S' &= \left(b \left(1 - \frac{S}{K} \right) - \alpha_1 \frac{I_1}{N} - \alpha_2 \frac{I_2}{N} - (\beta_1 + \beta_2 + \alpha_3) \frac{I_{12}}{N} - \mu_0 \right) S, \\
 I_1' &= \left(\alpha_1 \frac{S}{N} - \eta_1 \frac{I_{12}}{N} - \gamma_1 \frac{I_2}{N} - \mu_1 \right) I_1 + \beta_1 \frac{S I_{12}}{N}, \\
 I_2' &= \left(\alpha_2 \frac{S}{N} - \eta_2 \frac{I_{12}}{N} - \gamma_2 \frac{I_1}{N} - \mu_2 \right) I_2 + \beta_2 \frac{S I_{12}}{N}, \\
 I_{12}' &= \left(\alpha_3 \frac{S}{N} + \eta_1 \frac{I_1}{N} + \eta_2 \frac{I_2}{N} - \mu_3 \right) I_{12} + (\gamma_1 + \gamma_2) \frac{I_1 I_2}{N}, \\
 R' &= \rho_1 I_1 + \rho_2 I_2 + \rho_3 I_{12} - \mu_4' R.
 \end{aligned} \tag{4.5}$$

All the transmission parameter are similar to the model given in paper I. It is convenient to assume that

$$\sigma_1 < \sigma_2 < \sigma_3.$$

The basic reproduction number in this case is

$$R_0 = \frac{1}{\sigma_1}.$$

Moreover, the disease free equilibrium point is stable if $\sigma_1 > 1$.

4.1.3 Model 3: Partial cross immunity

Cross immunity allows infection by one strain to induce partial or complete protection against other strains. The effect of partial cross immunity has not been observed yet in the case of coinfection. The model in the case of partial cross immunity is given below

$$\begin{aligned} S' &= \left(b \left(1 - \frac{S}{K} \right) - \alpha_1 I_1 - \alpha_2 I_2 - (\beta_1 + \beta_2 + \alpha_3) I_{12} - \mu_S \right) S, \\ I_1' &= (\alpha_1 S - \eta_1 I_{12} - \gamma_1 I_2 - \xi_1 R_1 - \mu_1) I_1 + \beta_1 S I_{12}, \\ R_1' &= \xi_1 R_1 I_1 - \delta_1 R_1 I_{2R} - \mu_{R_1} R_1, \\ I_{1R}' &= \delta_2 R_2 I_{1R} - \rho_1 I_{1R} - \mu_4 I_{1R}, \\ I_2' &= (\alpha_2 S - \eta_2 I_{12} - \gamma_2 I_1 - \xi_2 R_2 - \mu_2) I_2 + \beta_2 S I_{12}, \\ R_2' &= \xi_2 R_2 I_2 - \delta_2 R_2 I_{1R} - \mu_{R_2} R_2, \\ I_{2R}' &= \delta_1 R_1 I_{2R} - \rho_2 I_{2R} - \mu_5 I_{2R}, \\ I_{12}' &= (\alpha_3 S + \eta_1 I_1 + \eta_2 I_2 - \mu_3 - \rho_3) I_{12} + (\gamma_1 + \gamma_2) I_1 I_2, \\ R' &= \rho_1 I_{1R} + \rho_2 I_{2R} + \rho_3 I_{12} - \mu_R R. \end{aligned} \tag{4.6}$$

There are eight classes where S is susceptible class, I_1, I_2 are infected classes from two different strains, I_{12} is coinfecting class, R_1 is recovered from an infection by the first strain but susceptible for strain 2, R_2 is recovered from an infection by the second strain but susceptible for strain 1, I_{1R} is recovered from strain 2 but infected with strain 1, I_{2R} is recovered from strain 1 but infected with strain 2, R class represents completely recovered individuals. This model has one disease free equilibrium point which is stable if $S^{**} < \sigma_1$.

Environmental variation

5.1 Impact of environmental fluctuation on epidemics

The environmental fluctuation can effect species population dynamics and as a result of that there is always a risk of extinction. In ecology, it is important to understand these responses due to the changes in mean and variability of climate conditions [34]. Temporal variability of two main indicators: temperature and precipitation in an environment affects the population dynamics of its inhabitants. Usually in modelling of population dynamics external noise is uncorrelated and is termed as white noise where each and every random value of noise is not dependent on its previous value. The noise values dependent of previous value is termed as red noise. Red noise is always positively autocorrelated. Red noise results slower change as compared to white noise. Redness increases with the increase in positive autocorrelation [30]. Although response to environmental fluctuation is extensively studied in ecology, this phenomenon is not addressed yet in epidemiology. Mathematical theory of infectious diseases has been mostly centred on pathogens and their direct transmission [5]. Particularly mathematical modelling has been focusing on explaining different outbreak patterns. Since environmental variation affects all natural systems. It is natural to expect their effect on pathogens indirectly within the host or during transmission. In this chapter, using simulations, I discuss how temporal variation in the carrying capacity of the population affects the dynamics of disease in the case of coexistence of two pathogens. The degree of autocorrelation in variability of carrying capacity influences whether the different classes exhibit temporal variation or not.

5.1.1 A model of coinfection

A coinfection model presented in paper I is considered. The model is described by the system of five ordinary differential equations as follows

$$\begin{aligned}
 S' &= (b(1 - \frac{S}{K}) - \alpha_1 I_1 - \alpha_2 I_2 - \alpha_3 I_{12} - \mu_0)S, \\
 I_1' &= (\alpha_1 S - \eta_1 I_{12} - \mu_1)I_1, \\
 I_2' &= (\alpha_2 S - \eta_2 I_{12} - \mu_2)I_2, \\
 I_{12}' &= (\alpha_3 S + \eta_1 I_1 + \eta_2 I_2 - \mu_3)I_{12}, \\
 R' &= \rho_1 I_1 + \rho_2 I_2 + \rho_3 I_{12} - \mu_4' R.
 \end{aligned} \tag{5.1}$$

The parameters are

- b is the birthrate of susceptible class;
- K is carrying capacity;
- μ_0 is death rate of susceptible class;
- ρ_i is recovery rate from each infected class ($i = 1, 2, 3$);
- μ_i' is death rate of each class, ($i = 1, 2, 3, 4$);
- α_i , ($i = 1, 2, 3$) are rates of transmission of infection 1, infection 2 and coinfection;
- η_i is rate at which infected from one strain getting infection from co-infected class ($i = 1, 2$) and $\mu_i = \rho_i + \mu_i'$, $i = 1, 2, 3$.

Three stable equilibrium points which consists of more than one classes are considered and analysed in different degrees of autocorrelation. In order to increase the generality of the results, five different set of parameters for each equilibrium point has been developed according to the predefined conditions on parameters. Environmental variation influence the carrying capacity K is given by

$$K_{env(t)} = 1 + env(t) \tag{5.2}$$

Here $K_{env(t)}$ is the carrying capacity affected by environmental variation at time t , and $env(t)$ is the environmental variation at time t of different classes. Natural variation is considered to be best represented by 1/f noise where the relationship between amplitudes and frequencies does not change dependent on the time scale [19], [30]. Therefore $\frac{1}{f}$ noise method used in [22, 17], is applied to create time series with different degree of autocorrelation, γ_{env} . $\gamma_{env} = 0$ is white, $0 < \gamma_{env} \leq 1$ is light red, $1 < \gamma_{env} \leq 2$ is red noise.

5.1.2 Response of classes to environmental fluctuation

All simulations are done in MATLAB. The stability of population, measured as $\frac{1}{CV_i} = \frac{\mu_i}{\sigma_i}$ where μ_i is the means and σ_i is the standard deviation of different classes' time series at three equilibrium states under different environmental fluctuation. Stability here is not related to equilibrium points but it is actually the stability of the trajectories. The less variable trajectory, the more stable it is. The equilibrium points E_3, E_5, E_7 , are considered in this analysis are given explicitly in paper I. The susceptible class has higher stability in red environment then in white environment typically in the case of equilibrium point E_5 due to its independence on carrying capacity. The figures below show the density of different classes in different equilibrium states under environmental fluctuations.

Figure 5.1: Equilibrium point E_3

Figure 5.2: Equilibrium point E_5

Figure 5.3: Equilibrium point E_7

5.1.3 Conclusion

In white environment the environment shift to fast and hence the classes cannot track their equilibriums. The consequence of this non-tracking is a variation around the mean of equilibrium density that can be characterized as a vibration. For those classes with equilibriums dependent on K the vibration is often less intense than the actual equilibrium variation. This implies that the class is less variable, more stable, in white noise than in red. While the opposite is true for classes, as often the susceptible one, that have equilibrium densities not dependent on carrying capacities. They are more stable in red than in white noise.

Discussion

This thesis contributes to the mathematical theory of epidemiology and the results discussed here unravel the complex dynamics of coexisting pathogens. This helps to understand several aspects of this convoluted phenomenon step by step. The parameters involved in the dynamics of the disease have a great significance and to understand the role of each parameter and its effects on the pathogen virulence has always been a challenge in epidemiology. In this thesis, different models are formulated to capture the effect of each increasing complexity in terms of parameters. In first step, in paper I, an SIR model for coinfection is developed and analysed and the coinfection dynamics is studied in more restricted setting. The growth of susceptible population is considered to be restricted by its carrying capacity. It is unrealistic to consider the exponential growth in human and animal populations. There are numerous factors that can limit a population growth for example food, competition, disease, predation. Considering density dependent growth of healthy population in paper I, leads to very interesting results. It is observed that the parameter, K , which is the carrying capacity of population, plays an important role in disease dynamics. The basic reproduction number shows that disease will extinct from population only in the case of small K . The pathogen invasion occurs with growing K . The existence and uniqueness of a stable equilibrium point for any admissible set of parameters guarantees the persistence of the disease with a possible future threat of any outbreak in the population. The competitive exclusion phenomena is also observed in the absence of coinfection which is natural due our assumption on infection 1 to be more dominant. The transition from one equilibrium state to another state is observed which is depending on K . Furthermore, as a result of significantly high carrying capacity oscillation in different classes is observed, and these oscillations dampen to equilibrium point, but it approaches the equilibrium point very slowly. Also the healthy population stabilizes after a certain threshold value which becomes especially interesting in the limit case when carrying capacity is very large. In that case, the susceptible population remains constant for very large K . Instead, the infected population increases as it depends on carrying capacity yet may reach a limit for infinitely large K . That shows the increased carrying capacity can increase the risk of infection, which leads to a destabilization of a healthy population. In the limit case, when $K = \infty$, the periodic behaviour of solution trajectories is observed, which becomes even more complex for coexistence equilibrium point, indicate that this system has dynamics closely related to the Rosenzweigs [31] famous paradox of enrichment for predator prey models. In the next step, more transmission are allowed as compared to

the model (3.5), by assuming that coinfection can occur due to the contact between two single infected individuals and coinfecting individual can transmit single infection to the susceptible class. This brings a new level of mathematical complexity in the dynamics. But the additional parameters do not affect the K dependence dynamics of population. The invasion and persistence of disease occurs with growing carrying capacity in these cases as well. The bifurcation analysis is done by construction of continuous branches of stable equilibrium states which also depends on carrying capacity. The type of equilibrium state changed after a threshold for each branch. The existence of stable equilibrium after each threshold confirms the disease persistence in population. An obvious improvement of these models is, first, to consider the density dependence on broad level, secondly, to check the effect of other phenomena on dynamics. The first was done by considering the density dependence in each class by assuming that all classes share the same resource. The role of parameter K is also noticeable in the dynamics. Considering recovered population in dynamics revealed that recovered population is also affected by carrying capacity and grows as the carrying capacity increases. The second improvement is done by considering models with different phenomena such as partial cross immunity, mass action type incident rates and susceptibility of newborns in recovered class. The role of parameter K is also observed in the case of partial cross immunity and susceptibility in newborn of recovered class by observing the stability of disease free equilibrium point. But the dynamics of disease free equilibrium is independent of K when mass action type incidence rates are considered. Therefore, it is worthwhile to explore these models more to understand the individual level effects of all these phenomena and compare their dynamics to the previous limit cases.

Another interesting but not very well explored fact is the effect of environmental fluctuation on the dynamics and stability of all classes (susceptible to infected). To understand that the model in paper I is considered and examined under three different noise colours. Three equilibrium points are tested at low to high degree of autocorrelation. Under slow variation each class track their equilibrium densities for a given time dependent carrying capacity. The effect of carrying capacity is different for different classes. Classes which are dependent on K are less variable and more stable in white environment while the class which does not depend on carrying capacity, which is susceptible population in most cases, is more stable in red environment than white.

The last step in infectious disease modelling is the application of model to specific disease. The presence of disease specific features such as temporary immunity, different transmission dynamics, incubation period are necessary in order to make it possible. The aim of this thesis is not to design a model for specific disease but to actually be able to see how this kind of dynamics changes as a result of added complexity. The complexity in our case is addition of different parameters due to different assumption. It helps to understand the role of each parameter in a better way. However, due to controlling strategies, system will move from complex to a simple system. For example, if there is a treatment focusing only coinfecting class or being used to separate each single infected class, such treatments can move the system from realistic condition to a condition similar to our system in paper I.

In that situation we will be able to know at least how to manage the disease.

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Department of Mathematics.

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