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Infectious Disease Modeling

A Hybrid System Approach

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Preface

Human life expectancy has increased over the past three centuries, from approximately 30 years in 1700 to approximately 70 years in 1970 [4]; one of the main factors of this improvement is a result of the decline in deaths caused by infectious diseases. In contrast to this decline in mortality, both the magnitude and frequency of epidemics increased during the eighteenth and nineteenth centuries, principally as a result of an increase of large population centers in industrialized societies [4]. This trend then reversed in the twentieth century, mainly due to the development and widespread use of vaccines to immunize susceptible populations [4]. The human invasion of new ecosystems, global warming, increased international travel, and changes in economic patterns will continue to provide opportunities for the spread of new and existing infectious diseases [65].

New infectious diseases have emerged in the twentieth century and some existing diseases have reemerged [65]: Measles, a serious disease of childhood, still causes approximately one million deaths each year worldwide. Type A influenza led to the 1918 pandemic (a worldwide epidemic) that killed over 20 million people. Examples of newly emerging infectious diseases include Lyme disease (1975), Legionnaire's disease (1976), hepatitis C (1989), hepatitis E (1990), and hantavirus (1993). The appearance of the human immunodeficiency virus (HIV) in 1981, which leads to acquired immunodeficiency syndrome (AIDS), has become a significant sexually transmitted disease throughout the world. New antibiotic-resistant strains of tuberculosis, pneumonia, and gonorrhea have emerged. Malaria, dengue, and yellow fever have reemerged and, as a result of climate changes, are spreading into new regions. Plague, cholera, and hemorrhagic fevers (e.g., Ebola) continue to erupt occasionally.

In 1796, an English country doctor, Edward Jenner, observed that milkmaids who had been infected with cowpox did not get smallpox, and so he began inoculating people with cowpox to protect them from getting smallpox (this was the world's first vaccine, taken from the Latin word vacca for cow) [65]. Mathematical models have become important tools in analyzing both the spread and control of infectious diseases. The first known mathematical epidemiology model was formulated and solved by Daniel Bernoulli in 1760 [92]. The pioneering work on infectious

disease modeling by Kermack and McKendrick has had a major influence in the development of mathematical models of infectious diseases [116]. These authors were the first to obtain a threshold result that showed the density of susceptibles must exceed a critical value for an outbreak to occur [65]. In the early twentieth century, the foundations of modern mathematical epidemiology based on compartment models were laid, and mathematical epidemiology has grown exponentially since the middle of the previous century [92]. An extensive number of models have been formulated, analyzed, and applied to a variety of infectious diseases, including measles, rubella, chickenpox, whooping cough, smallpox, malaria, rabies, gonorrhea, herpes, syphillis, and HIV/AIDS [64].

Studying these somewhat simple mathematical epidemiology models is crucial in order to gain important knowledge of the underlying aspects of the spread of infectious diseases [64]; one such purpose of analyzing epidemiology models is to get a clear understanding of the similarities and differences in the behavior of solutions of the models, as this allows us to make decisions in choosing models for certain applications. Mathematical models and computer simulations are extremely useful tools for building and testing theories, assessing quantitative conjectures, answering qualitative questions, and estimating key parameters from data; epidemic modeling can help to identify trends, suggest crucial data that should be collected, make general forecasts, and estimate the uncertainty in forecasts [65].

The transmission of a disease, which depends on its intrinsic infectiousity as well as population behavior, is a crucial part in the medical and statistical study of an epidemic [38]. In mathematical modeling, these two aspects are summarized in the contact rate and the incidence rate of a disease, which are the average number of contacts between individuals that would be sufficient for transmitting the disease and the number of new cases of a disease per unit time, respectively [65]. Empirical studies have shown that there are seasonal variations in the transmission of many infections [69]. Examples include differences in the abundance of vectors due to weather changes (e.g., dry season vs rainy season), changes in the survivability of pathogens (outside hosts), differences in host immunity, and variations in host behavior (e.g., increased contacts between individuals in the winter season from being indoors) [39, 53]. For childhood infections such as measles, chickenpox, and rubella, it has been observed that the rates of transmission peak at the start of the school year and decline significantly during the summer months [69]. An analysis of measles data in New York demonstrates that sufficiently large seasonal variations in transmission can generate a biennial-looking cycle [134]. Data from England and Wales displays a four-year cycle in poliomyelitis incidence, while measles has been observed to have a biennial cycle for the same countries [134]. Reports have found that many diseases show periodicity in their transmission, such as measles, chickenpox, mumps, rubella, poliomyelitis, diphtheria, pertussis, and influenza [66]. Depending on the particular disease of interest and population behavior, an appropriate model of the disease's spread may require term-time forcing where the model parameters change abruptly in time.

The recent increase in seaborne trade and air travel has removed many geographic barriers to insect disease vectors [26]. For example, the vector responsible in part

for transmitting diseases such as chikungunya and, more recently, Zika virus, *Aedes albopictus*, has developed capabilities to adapt to nontropical regions and is now found in Southeast Asia, the Pacific and Indian Ocean islands, Europe, the USA, and Australia [41, 113, 114]. Consequently, studying mathematical models on the spread of vector-borne diseases has become a large focus in the literature, for example, the dengue virus [165, 166] and the chikungunya virus [7, 40–43, 113, 114]. Seasonal changes are an important factor in how these vector-borne diseases spread in a population and relate to changes in the abundance of vectors and the host population behavior. For example, Bacaër [7] noted that seasonality plays an important role in the spread of the chikungunya virus. The 2005 outbreak of chikungunya virus in Réunion occurred when the mosquito population was at its highest, the end of the hot season and beginning of the winter season [42]. The transmission of dengue fever is higher during wet and humid periods with high temperatures ideal for mosquitoes and lower when the temperature is low [126, 165].

One of the most important aspects of epidemic modeling is the application of control schemes to eradicate, or at least suppress, an impending epidemic. Infectious disease models are a vital component of comparing, implementing, evaluating, and optimizing various detection, prevention, and control programs [65]; epidemic models are useful in approximating vaccination levels needed for the control of a disease [116]. For example, in 1967, there were approximately 15 million cases of smallpox per year which led the World Health Organization (WHO) to develop an initiative against smallpox. The WHO strategy involved extensive vaccination programs, surveillance for outbreaks, and containment of these outbreaks by local vaccination programs [65]. This has been considered the most spectacular success of a vaccination program [101]; smallpox was eventually eradicated worldwide by 1977, and the WHO estimates that the elimination of smallpox worldwide saves over two billion dollars per year [65]. There are now vaccines that are effective in preventing rabies, yellow fever, poliovirus, hepatitis B, parotitis, and encephalitis B, among others [83].

Aside from seasonal changes in population behavior, the conduct of the population can shift due to, for example, psychological effects (widespread panic of an impending outbreak) or from public health campaigns to prevent a disease spread. The aim of this study is to mathematically model infectious diseases, which take these important factors into account, using a switched and hybrid systems framework. The scope of coverage includes background on mathematical epidemiology, including classical formulations and results; a motivation for seasonal effects and changes in population behavior; an investigation into term-time forced epidemic models with switching parameters; and a detailed account of several different control strategies. The main goal is to study these models theoretically and to establish conditions under which eradication or persistence of the disease is guaranteed. In doing so, the long-term behavior of the models is determined through mathematical techniques from switched systems theory. Numerical simulations are also given to augment and illustrate the theoretical results and to help study the efficacy of the control schemes.

The objective of this monograph is to formulate new epidemiology models with time-varying contact rates or time-varying incidence rate structures, and to study the long-time behavior of diseases. More specifically, we look to extend epidemiology models in the literature by the addition of switching, which is the abrupt change of the dynamics governing the systems at certain switching times. This switching framework allows the contact rate to be approximated by a piecewise constant function. Since relatively modest variations in the contact rate can result in large amplitude fluctuations in the transmission of a disease [69], this is an important phenomenon that requires attention. Switching is a new approach to this problem that has not been studied before as an application to epidemiology models. A specific incidence rate must be chosen appropriately based on the scenario and disease being modeled for any given infectious disease model. There are numerous incidence rates which have been used in models in the literature, for example, the standard incidence, psychological-effect incidences, saturation incidences, media coverage incidences, and more general nonlinear forms (see [38, 64, 73, 122]). With regard to different forms of the incidence rate, one of the possible causes of unexpected failures of a vaccination campaign may be the nonlinearity of the incidence rate not being properly modeled [38], which gives extra motivation in studying switching incidence rate structures. The focus of this monograph is to present new methods for formulating and analyzing epidemic models with time-varying model parameters and function forms, which are easily extendable to many different models, as will be shown.

The area of hybrid dynamical systems (HDS) is a new discipline which bridges applied mathematics, control engineering, and theoretical computer science [45]. HDS frameworks provide a natural fit for many problems scientists face as they seek to control complex physical systems using computers [45]. Indeed, there is a growing demand in industry for methods to model, analyze, and understand systems that combine continuous components with logic-based switching [136]. Practical examples of switched systems, a type of HDS, include areas as diverse as mechanical systems, the automotive industry, air traffic control, robotics, intelligent vehicle/highway systems, chaos generators, integrated circuit design, multimedia, manufacturing, high-level flexible manufacturing systems, power electronics, interconnected power systems, switched-capacitor networks, computer disk drives, automotive engine management, chemical processes, and job scheduling [31, 45, 54, 85]. Examples of systems which can be described by switching systems with abrupt changes at the switching instances include biological neural networks, optimal control modes in economics, flying object motions, bursting rhythm models in pathology, and frequency-modulated signal processing systems [54]. Impulsive systems will be important when we look to add pulse control to the switched models. As mentioned, switched systems are described using a mixture of continuous dynamics and logic-based switching, in that they evolve according to mode-dependent continuous dynamics and experience transitions between modes that are triggered by certain events [136]. There are typically two cases in which a switched system arises [31]: One is when there are abrupt changes in the structure or the

parameters of a dynamical system, which can be due to, for example, environmental factors (i.e., outside forces). The second is when a continuous system is controlled using a switched controller.

This monograph is not meant to be a comprehensive analysis of every modeling choice possible for mathematical models of infectious diseases. Rather, its aim is to provide theoretical tools which are applicable to a wide variety of problems in epidemic modeling. The mathematical methods are revealed one at a time as this monograph progresses. Aside from modeling the spread of an infectious disease using a hybrid and switched system, a new approach to mathematical disease modeling, the unique features of this monograph can be summarized as follows: (1) using techniques from switched systems theory to study the stability of epidemic models, (2) focusing on the role seasonality plays in the spread of infectious diseases, and (3) investigating how abrupt changes in model parameters or function forms affect control schemes. Accessible to individuals with a background in dynamical systems theory or mathematical modeling of epidemics, this work is intended as a graduate-level book for individuals with an interest in mathematical biology, epidemic models, and, more generally, physical problems exhibiting a mixture of continuous and discrete dynamics (i.e., hybrid behavior).

The reader gains the fundamentals of compartmental infectious disease modeling, as well as the necessary mathematical background (e.g., stability theory of ordinary and functional differential equations). The reader learns techniques from switched and hybrid systems, which are applicable to a variety of applications in engineering and computer science. Knowledge is gained regarding the roles seasonality and population behavior play in the spread of a disease, including the formulation and theoretical tools for analysis of epidemic models and infectious disease control strategies. In doing so, the reader learns about the concept of threshold conditions in epidemic modeling, such as the basic reproduction number, used to prove eradication or persistence of the disease based on model parameters. Numerical simulations are also given, to help illustrate the results to the reader.

The structure of the monograph is outlined as follows: In Part I, the theoretical framework is established for the remainder of the monograph. Chapter 2 details the necessary foundational material. Switching epidemic models are formalized and studied in Part II: The classic SIR model is investigated in Chap. 3 while extensions are studied in Chap. 4. Control methods to achieve eradication of the disease are presented and thoroughly analyzed in Part III. Switching control schemes are investigated in Chap. 5 while impulsive strategies are studied in Chap. 6. A case study is given in Chap. 7 detailing an outbreak of chikungunya virus and possible control strategies for its containment and eradication. Conclusions and future directions are given in Part IV.

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Contents

List of Symbols

$\mathbb{R}^n$	Euclidean space of n-dimensions
$\mathbb{R}_+$	Set of nonnegative real numbers
$\mathbb{R}^{m \times n}$	Vector space of $m \times n$ real-valued matrices
$\mathbb{N}$	Set of positive integers
$\|\cdot\|$	Euclidean norm: $\|x\| = \sqrt{x_1^2 + \ldots + x_n^2}$ for $x \in \mathbb{R}^n$
cl A	Closure of a set $A \subset \mathbb{R}^n$
int A	Interior of a set $A \subset \mathbb{R}^n$
∂A	Boundary of a set $A \subset \mathbb{R}^n$
conv A	Convex hull of a set $A \subset \mathbb{R}^n$
$B_r(x)$	Open ball of radius $r > 0$ centered at $x \in \mathbb{R}^n$
$\lambda_{\min}(Q)$	Minimum eigenvalue of a symmetric matrix Q
$\lambda_{\max}(Q)$	Maximum eigenvalue of a symmetric matrix Q
$Df(x)$	Jacobian matrix of f evaluated at x
$C(D, \mathbb{R}^m)$	Continuous functions mapping $D \subset \mathbb{R}^n$ to $\mathbb{R}^m$
$C^1(D, \mathbb{R}^m)$	Continuously differentiable functions mapping $D \subset \mathbb{R}^n$ to $\mathbb{R}^m$
$C^k(D, \mathbb{R}^m)$	Continuously differentiable functions of order k
$\delta(\cdot)$	Dirac delta generalized function
$\mathscr{K}_0$	$\{w \in C(\mathbb{R}_+, \mathbb{R}_+) : w(0) = 0, w(s) > 0 \text{ for } s > 0\}$
$\mathscr{K}_1$	$\{w \in \mathscr{K}_0 : w \text{ is nondecreasing in } s\}$
$\mathscr{K}$	$\{w \in C(\mathbb{R}_+, \mathbb{R}_+) : w(0) = 0 \text{ and } w \text{ is strictly increasing}\}$
$\mathscr{K}_\infty$	$\{w \in \mathscr{K} : w(s) \to \infty \text{ as } s \to \infty\}$
C_τ	Continuous functions mapping $[-\tau, 0] \subset \mathbb{R}$ to $\mathbb{R}^m$
$\mathrm{PC}(D, \mathbb{R}^m)$	Piecewise continuous functions mapping D to $\mathbb{R}^m$
PC_τ	$\mathrm{PC}([-\tau, 0], \mathbb{R}^m)$
$\|\cdot\|_\tau$	Usual sup norm: $\|\psi\|_\tau = \sup_{-\tau \le s \le 0} \|\psi(s)\|$ for $\psi \in \mathrm{PC}$
$\mathscr{S}$	Set of all admissible switching rules
σ	Switching rule associated with a switched system
$\mathscr{S}_{\text{periodic}}$	Subset of $\mathscr{S}$ that are periodic
$\mathscr{S}_{\text{dwell}}$	Subset of $\mathscr{S}$ that admit a dwell-time
$\mathscr{S}_{\text{avg}}$	Subset of $\mathscr{S}$ that admit an average dwell-time

$\mathscr{P}$	Finite index set of modes of switched system: $\mathscr{P} \equiv \{1, \dots, p\}$
$\mathscr{M}$	Finite index set of modes of switched system: $\mathscr{M} \equiv \{1, \dots, m\}$
$\mathscr{N}$	Finite index set of modes of switched system: $\mathscr{N} \equiv \{1, \dots, n\}$
$\mathscr{F}$	Finite index set of vector fields: $\mathscr{F} \equiv \{f_1, \dots, f_m\}$
$T_i(t^1, t^2)$	Total activation time of the ith mode on $[t^1, t^2]$
$T^+(t^1, t^2)$	Total activation time of the modes $\mathscr{M}^+ \subset \mathscr{M}$ on $[t^1, t^2]$
$T^-(t^1, t^2)$	Total activation time of the modes $\mathscr{M}^- \subset \mathscr{M}$ on $[t^1, t^2]$
$N(t^1, t^2)$	Number of switches activating the ith mode on $[t^1, t_1^2)$
$N^-(t^1, t^2)$	Number of switches activating modes in $\mathscr{M}^-$ on $[t^1, t^2)$
$R_0^{(*)}$	Basic reproduction number of the infectious disease model $(*)$
$D_{(*)}$	Physical domain associated with epidemic model $(*)$
$Q_{\mathrm{DFS}}^{(*)}$	Disease-free solution associated with epidemic model $(*)$
$Q_{\mathrm{ES}}^{(*)}$	Endemic solution associated with epidemic model $(*)$
C_H^c	Cumulative number of infected humans with control
C_H^0	Cumulative number of infected humans without control
F_0	Control strategy efficacy rating ($F_0 \equiv 100 C_H^c / C_H^0$)
Ψ	Total number of vaccinations administered during a campaign
χ	Cost-benefit rating of a control scheme ($\chi \equiv \Psi/(C_H^0 - C_H^c)$)