Rich dynamics in multi-strain models: Non-linear dynamics and deterministic chaos in dengue fever epidemiology

Aguiar Freire dos Santos, M.

2012

document version
Publisher's PDF, also known as Version of record

English summary

Throughout human history, infectious diseases have caused debilitation and premature death to large portions of the human population, leading to serious social-economic concerns. Many factors have contributed to the persistence and increase in the occurrence of infectious disease (such as demographic factors, political, social and economic changes, environmental change, public health care and infrastructure, microbial adaptation, etc.). According to the World Health Organization (WHO), are the second leading cause of death globally after cardiovascular diseases (WHO, 2010). In recent years, mathematical modeling became an important tool for the understanding of infectious disease epidemiology and has led to great advances in conceiving disease control strategies, including vaccination programs.

One of the most important infectious diseases is dengue, a major international public health concern with more than 55% of world population at risk of acquiring the infection. Dengue is a viral mosquito-borne infection, a leading cause of illness and death in the tropics and subtropics. Dengue fever is caused by four antigenically distinct viruses, designated dengue types 1, 2, 3 and 4. Infection by one serotype confers life-long immunity to only that serotype, and temporary cross-immunity to other related serotypes. The temporary cross-immunity period lasts from three to nine months and it is related to antibody levels created during the immune response to a previous dengue infection. It is stated that such high antibody levels would be enough to protect the individual against an immediately new dengue infection caused by a different but related serotype.

Two variants of the disease exist: dengue fever (DF), a non-fatal form of illness, and dengue hemorrhagic fever (DHF), which may evolve toward a severe form known as dengue shock syndrome (DSS). Epidemiological studies support the association of DHF with secondary dengue infection. There is good evidence that sequential infection increases the risk of developing DHF due to a process described as antibody-dependent enhancement (ADE), where the pre-existing antibodies to previous dengue infection cannot neutralize but

rather enhance the new infection.

Treatment of uncomplicated dengue cases is only supportive, and severe dengue cases requires careful attention to fluid management and proactive treatment of hemorrhagic symptoms. A vaccine against dengue is not yet available, since it would have to simulate a protective immune response to all four serotypes, although several candidates of tetravalent vaccines are at various stages of development. So far, prevention of exposure and vector control remain the only alternatives to prevent dengue transmission.

In recent years, mathematical modeling became an interesting tool for the understanding of infectious diseases epidemiology and dynamics. A series of deterministic compartment models such as Susceptible-Infected (SI) and Susceptible-Infected-Recovered (SIR) for example, have been proposed based on the flow patterns between compartments of hosts. The SIR epidemic model divides the population into three classes concerning the disease stages: susceptible (S), Infected (I) and Recovered (R). This model framework can represent infectious diseases where waning immunity can happen. Assuming that the transmission of the disease is contagious from person to person, the susceptibles become infected and infectious, are cured and become recovered. After a waning immunity period, the recovered individual can become susceptible again to reinfection.

Multi-strain dynamics, such as dengue epidemiology, are generally modeled with extended SIR-type models. Dengue fever dynamic is well known to be particularly complex with large fluctuations of disease incidences. To capture differences in primary and secondary dengue infections, a two-strain SIR-type model for the host population has to be considered. Dengue models including multi-strain interactions via ADE, but without temporary cross-immunity, have shown already deterministic chaos when strong infectivity on secondary infection was assumed. The addition of the temporary cross-immunity period in such models brings a new chaotic attractor in wider and unexpected parameter region.

In this thesis we present different extensions of the classical single-strain SIR model motivated by modeling dengue fever epidemiology with its peculiar ADE phenomenology. We focus on a minimalistic model, where the notion of at least two different strains is needed to describe differences between primary and secondary dengue infections. The models divide the host population into susceptible, infected and recovered individuals with subscripts for the respective strains. The individuals can be (1) susceptibles without a previous dengue infection; (2) infected and recovered for the first time; (3) susceptible with an experienced previous dengue infection and (4) infected for the second time with a different strain, more likely to be hospitalized due to the ADE effect leading to severe disease. Our analysis shows a rich dynamic structure, including deterministic chaos in wider and more biologically realistic parame-

ter regions, just by adding temporary cross-immunity to previously existing dengue models.

In Chapter 1 we present the properties of the basic SIR epidemic model applied to infectious diseases. A summary of the analysis of the dynamics identifying the thresholds and equilibrium points in order to introduce notation and terminology are presented. These results were then generalized to a more advanced models motivated by dengue fever epidemiology. In Chapter 2 the basic two-strain SIR-type model motivated by modeling dengue fever epidemiology is presented. In this chapter we focused on the multi-strain aspect and its effects on the host population. The effects of the vector dynamics or seasonality is taken in account only by the effective parameters of the SIR-type model, but these mechanisms are not modeled explicitly. In Chapter 3 a detailed bifurcation analysis for the basic multi-strain dengue model is presented where the ADE parameter ϕ and the temporary cross-immunity parameter α are studied.

In Chapter 4 the seasonally forced system with temporary cross-immunity and possible secondary infection is analyzed. This study was motivated by dengue hemorrhagic fever monitoring data. The role of seasonality and import of infected individuals are now considered as biologically relevant effects to determine the dynamical behavior of the system. A comparative study between three different scenarios (non-seasonal, low seasonal and high seasonal with a low import of infected individuals) is presented. The extended models show complex dynamics and qualitatively a good agreement between empirical DHF monitoring data and the obtained model simulation.

At the moment only such minimalistic models have a chance to be qualitatively understood well and eventually tested against existing data. The simplicity of the model (low number of parameters and state variables) offer a promising perspective on parameter values inference from the DHF case notifications. Such a technical parameter estimation is notoriously difficult for chaotic time series due to the long term unpredictability versus short term predictability. Recently, this short term predictability has been used for temporally local approaches in statistical inference on the cost of difficulty in obtaining a final definite best answer to the parameter estimation problem.

Being able to predict future outbreaks of dengue in the absence of human interventions is a major goal if one wants to understand the effects of control measures. Even after a dengue virus vaccine has become accessible or available, this holds true for the implementation of a vaccination program. For example, to perform a vaccine trial in a year where the disease epidemic generate a low number of cases, would make the statistical tests of vaccine efficacy much more difficult compared with the information provided by a vaccine trial performed in a epidemic year with much higher numbers of cases. Thus predictability of the next season's height of the dengue peak, on the basis of deterministic

balance of infected and susceptible, would be of major practical use.

Although the fact that disease propagation is an inherently stochastic phenomenon, dengue models are mainly expressed mathematically as a set of deterministic differential equations, which are easier to analyze. The mean field approximation, an approximation of stochastic processes leading to deterministic dynamics, is a good approximation to be used in order to understand better the behavior of the stochastic systems in certain parameter regions, where the dynamics of the mean quantities are approximated by neglecting correlations. However, it is only stochastic, as opposed to deterministic, models that can capture the fluctuations observed in some of the available time series data. In Chapter 5 the stochastic version of the minimalistic multi-strain model is presented. In this chapter we investigate the interplay between stochasticity, seasonality and imported cases of the disease. The introduction of stochasticity reveal a scenario where noise and complex deterministic skeleton strongly interact. For large enough population size, the stochastic system could be well described by the deterministic skeleton, where the essential dynamics are captured, gaining insight into the relevant parameter values purely on topological information of the dynamics.

The two-strain dengue model is a 9 dimensional system and therefore, future statistical inference can still attempt to estimate all initial conditions as well as the few model parameters. Concerning data availability, long term epidemiological data consist on monthly incidences of hospitalized DHF cases. For such a data scenario, models that are able to generate both primary and secondary infection cases (with a different strain, without the need of considering differences on the dynamics of different co-circulating dengue serotypes), have shown a good qualitative agreement between empirical data and model output (see Chapter 4 and Chapter 5). These results were obtained just by combining the ADE effect, generating difference in transmissibility on primary and secondary infections, with the temporary cross-immunity aspect. Differently from the minimalistic dengue model, the four-strain model is mathematically represented by a system of 26 ODE' s. It becomes a very high dimensional system and obviously very difficult to be used for parameter inference due to the high number of initial conditions. In Chapter 6 we present the multi-strain dengue model for the four existing serotypes. For four different strains, 1, 2, 3 and 4, we now label the SIR classes for the hosts that have seen each one of the possible strains. Again, without epidemiological asymmetry between strains, once the serotype data are recent and very short to give any realistic information concerning difference in biological parameters (such as infection and recovery rates) for a given strain. In this chapter we present the bifurcation diagram comparison for both two-strain and four-strain model. In the relevant parameter region of $\phi < 1$, when dengue patients in a secondary infection evolving to severe disease due to the ADE phenomenon contribute

less to the force of infection, the bifurcation points appear to happen at similar parameter regions, well below the region of interest $\phi \approx 1$.

We conclude that the two-strain model in its simplicity is a good model to be analyzed giving the expected complex behavior to explain the fluctuations observed in empirical data. Statistical inference to estimate the basic parameters of transmission, infectivity, disease severity (ADE parameter) and temporary cross-immunity period using empirical data of incidence of severe disease is needed to identify eventual deviations from the simplest symmetric case investigated here. Further work on the parameter estimation using the minimalistic dengue model is in progress.

The vector dynamics might also play a role in understanding the final picture when comparing the model output with the available empirical data. Following the investigations described in this thesis, a number of research directions could be addressed, involving the minimalistic dengue model. Future work would be to investigate extensions of the multi-strain model to address the following questions and issues: (1) How much (more or less than first infection) does secondary infection contribute to the force of infection? (2) Does there exist a difference between the forces of infection for the different strains and to what extent can the bifurcation structure explain the viral diversity contribution? (3) Formulate hypotheses using the mechanism of temporary cross-immunity suitable to recurrent infections protection. (4) Model the vaccine trials based on short term predictability of chaotic systems to be applied when tetravalent vaccines will become available. And (5) propose targets for intervention and control design according to the expected impact of the disease. My special interest would be to get the model fully parametrized on data referring to incidence of severe disease and prevalence of infection. With such a model framework we would be able to give an insight into the predictability of upcoming dengue outbreaks. This epidemiological tool would help to understand the effects of control measures and therefore to guide the policies of prevention and control of the dengue virus transmission.