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Analysis of an asymmetric two-strain dengue model

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ABSTRACT

In this paper we analyse a two-strain compartmental dengue fever model that allows us to study the behaviour of a Dengue fever epidemic. Dengue fever is the most common mosquito-borne viral disease of humans that in recent years has become a major international public health concern. The model is an extension of the classical compartmental susceptible–infected–recovered (SIR) model where the exchange between the compartments is described by ordinary differential equations (ODE). Two-strains of the virus exist so that a primary infection with one strain and secondary infection by the other strain can occur. There is life-long immunity to the primary infection strain, temporary cross-immunity and after the secondary infection followed by life-long immunity, to the secondary infection strains. Newborns are assumed susceptible. Antibody Dependent Enhancement (ADE) is a mechanism where the pre-existing antibodies to the previous dengue infection do not neutralize but rather enhance replication of the secondary strain. In the previously studied models the two strains are identical with respect to their epidemiological functioning: that is the epidemiological process parameters of the two strains were assumed equal. As a result the mathematical model possesses a mathematical symmetry property. In this manuscript we study a variant with epidemiological asymmetry between the strains: the force of infection rates differ while all other epidemiological parameters are equal. Comparison with the results for the epidemiologically symmetric model gives insight into its robustness. Numerical bifurcation analysis and simulation techniques including Lyapunov exponent calculation will be used to study the long-term dynamical behaviour of the model. For the single strain system stable endemic equilibria exist and for the two-strain system endemic equilibria, periodic solutions and also chaotic behaviour.

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1. Introduction

Dengue is a human disease common in tropical and subtropical regions of the world. It is a vector-born disease transmitted via specific mosquitoes. 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). Antibody Dependent Enhancement (ADE) occurs when cross-reactive antibodies generated by a previous exposure to a heterologous strain facilitate the within-host replication of a second invading strain. Epidemiological studies support the association of DHF with secondary dengue infection due to ADE. The dynamics multi-strain epidemic models for dengue fever were analysed in [13,10,1,30,9,4,26,8,3,20]. In all of these models the dynamics of the vector is not included. These multi-strain models are extensions of the classical SIR-model. The population is divided into classes (or compartments) concerning the disease related stages (susceptibles, infected and recovered). The fraction or percentage of the different classes are the state variables of the set of ordinary differential equations (ODE)'s which describe the temporal exchange between the compartments. In order to describe differences between primary infections, which are often asymptomatic, and secondary infection, associated with the severe form of the disease (DHF or DSS) either of which may be life-threatening, compartments for at least two different strains were needed. In the models formulated and analysed in these papers ADE is always taken into account in combination with co-infection in [13] and with temporary cross-immunity in [30,4,8,4,3,17].

The ADE-factor ϕ is defined as the ratio of the secondary infection contribution to the force of infection. Then for $\phi > 1$ there is an enhancement of the infectiousness by the secondary infection strain with respect to the infectiousness of the primary infection strain and reduction when $\phi < 1$. In the majority of the papers enhancement of viral replication due to ADE is modeled as also an enhancement of mass action contacts in the secondary infectious rate. And therefore ADE-effects on the long-term dynamics are only studied for $\phi \geqslant 1$. Much of this work has suggested that the dynamics resulting from incorporating enhancement are inconsistent with observed patterns of incidence, with oscillation amplitudes in incidence that are much too large and periods that are much too long (see [24]) while large amplitudes entail stochastic

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extinction. Hospitalization of individuals (DHF cases) will lead to a smaller contribution to the force of infection see [4,3] and not a larger contribution. In [4,5,3,6] is was shown that for $\phi \leqslant 1$ there is complex dynamics behaviour that is consistent with observed patterns of incidence and that the origin of complex structure is a torus bifurcation of a stable limit cycle where no large amplitudes occur. Therefore we focus here on the interval $\phi \in [0, 1.3]$.

The mathematical models described by ODE's are analysed using bifurcation theory (see [16,32,21] and references therein). The equilibrium equations are analysed using the symbolic computation program Maple [22]. For the study of the long-term dynamics of these high-dimensional, complicated models we use numerical bifurcation analysis using computer-packages such as AUTO [12] and MatCont [11]. With these computer-packages one can calculate and continue bifurcation points for equilibria and periodic solutions, but not when the solution is aperiodic (quasi-periodic or chaotic). Bifurcation points are critical parameter values where the long-term dynamics changes qualitatively, for instance from a stable equilibrium to a limit cycle. To study aperiodic solutions, simulations followed by Lyapunov exponent calculations are needed. The maximum Lyapunov exponent measures the rate of convergence or divergence of nearby trajectories and quantify chaos. The algorithm we use is described in [3].

To be able to perform the numerical analysis we have to assign values to the parameters. We use parameter values which are realistic for dengue fever [4,5,3,6] given in Table 1, if not otherwise explicitly stated. To assess the sensitivity of the long-term dynamics with respect to the parameters, the results are presented in bifurcation diagrams where model parameters are varied along the axes. In a one parameter diagram the long-term solution of one state variable is plotted as a function of a free (bifurcation) parameter. Observe that since the dimension of the system is high (9 in our case) this plot is a projection onto the coordinate plane of the state space belonging to the specific state variable. In a two parameter diagram two parameters are varied simultaneously and no quantitative information about the state variables is provided, only a qualitative characterization of the long-term dynamic behaviour, such as steady state, periodic solution, quasi-periodic solution or chaotic dynamics. Since the dimension of the system is high, multiple solutions occur and this complicates the analysis since then also the initial conditions become important because they fix to which attractor the system converges.

When all parameters are equal for all strains, the model is epidemiologically symmetric. The main aim of this paper is to study the effects of asymmetry. To that end we introduce a perturbation parameter that describes the difference between the strains, namely difference in the infection rates, while all other parameters are still the same. In the past effects of asymmetry in transmission rates between the strains has been not been studied systematically. Recently this was done in [24] in conjunction with the value of the ADE-factor $\phi \geqslant 1$.

Only in [4,3,20] and other papers by Aguiar and collaborators, it was recognized that with epidemiological symmetry with exact equal parameter values for all strains, implies that the mathematical model possesses $\mathbb{Z}_2$ symmetry properties. These properties allow for a classification of the possible long-term dynamical behaviours, see for instance [21,4,3,20].

The $\mathbb{Z}_2$ symmetry leads to specific properties of equilibria and limit cycles with relationships between the state variables related to the two strains, but also to a pair of conjugate limit cycles and moreover to specific bifurcations such as a pitchfork bifurcation (see [21]). It is, however, well know that a pitchfork bifurcation is structurally unstable, that is, small perturbations imposing asymmetry, alter abruptly the qualitative behaviour of the bifurcation pattern. Therefore, it is interesting to study the robustness of this epidemiological symmetric dynamics with respect to an introduction of asymmetry.

It turns out that from an application point of view, the bifurcation pattern is robust for small values of the symmetry perturbation parameter except in the parameter region very close to a pitchfork bifurcation. For larger asymmetries the change in the pattern increases drastically in some situations leading to extinction of one of the strains while with identical epidemiological strains there is always coexistence for the reference parameter values given in Table 1.

Table 1
Parameter set, rates given in units per year, ratio's without units. Since we take $N = 100$, the fractions of the classes are expressed in percentages. In [13,9] enhancement of mass action contacts in the secondarily infected: $\phi > 1$ and in [4,5,3], decrease of the infectivity of secondarily infected due to hospitalization: $\phi < 1$. Perturbation parameter $0 \leqslant \varepsilon \leqslant 2\gamma$ is used to study the effects of asymmetry of the infection rates $\beta_i : \beta_i = \beta \pm \varepsilon, i = 1, 2$.

Par.	Description	Values	Ref
N	Population size	100	–
α	Temporary cross-immunity rate	2 y^{-1}	[25]
β	Ref. infection rate	2γ	[13]
γ	Recovery rate	52 y^{-1}	[31,15]
μ	New born susceptible rate	$1/65$ y^{-1}	–
ϕ	Ratio of contrib. to force of inf.	Variable	–
ε	Asymmetry perturbation parameter	Variable	–

2. Formulation of the two-strain epidemic model with temporary cross-immunity

Starting point for our study is the model formulated in [4] and analysed in [4,3,20]. The model divides the host population into susceptible, infected and recovered classes denoted by S, I and R with subscripts for respective the primary and secondary infection. The population size is constant because the birth and death rates of the human host population are assumed to be equal and furthermore newborns are susceptibles. There is life-long immunity for the strain of the primary infection. After a cross-immunity period individuals get infected for the second time by a different strain and thereafter there is life-long immunity to all strains. In this model the two virus strains are, from the epidemiologically point of view, identical: all parameters have the same values for the different strains. This allows for two different interpretations of the classes (susceptible, infected and recovered) associated with the two strains.

In the first framework there are only two strains (as was for dengue fever the case in the past and nowadays still in some regions of the world). So, either the individuals are infected by one specific strain and life-long immune for this strain or are infected thereafter by the other strain. We label the infected classes by those strains the individuals have previously been infected.

In the second framework, there are four strains (as is often the case now for dengue fever) and the individuals are primarily infected by one of the four strains or are secondarily infected by one of the other three strains. Only two classes are distinguished. We label classes as first infected by one of the four strains. Individuals in the secondary infected class are those that were first infected by one of the other three strains. In this formulation an additional assumption is that tertiary and quaternary infections do not occur. Epidemiological data shows them to be quite rare, [14].

The latter framework was used in [4,3]. When the four strains are epidemiological identical it is reasonable that primarily and secondarily infected are lumped separately. Here the same interpretation is also valid when one strain differs considerably from

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