The Stochastic Multi-strain Dengue Model: Analysis of the Dynamics

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Abstract. Dengue dynamics is well known to be particularly complex with large fluctuations of disease incidences. An epidemic multi-strain model motivated by dengue fever epidemiology shows deterministic chaos in wide parameter regions. The addition of seasonal forcing, mimicking the vectorial dynamics, and a low import of infected individuals, which is realistic in the dynamics of infectious diseases epidemics show complex dynamics and qualitatively a good agreement between empirical DHF monitoring data and the obtained model simulation. The addition of noise can explain the fluctuations observed in the empirical data and for large enough population size, the stochastic system can be well described by the deterministic skeleton.

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INTRODUCTION

In many countries in Asia and South-America dengue fever (DF) and dengue hemorrhagic fever (DHF) has become a substantial public health concern leading to serious socio-economical costs.

Dengue is a viral mosquito-borne infection which in recent years has become a major international public health concern, a leading cause of illness and death in the tropics and subtropics. It is estimated that every year, there are 70 – 500 million dengue infections, 36 million cases of dengue fever (DF) and 2.1 million cases of dengue hemorrhagic fever (DHF), with more than 20,000 deaths per year [1, 2]. Dengue is caused by four antigenically distinct but closely related viruses, designated by dengue types 1,2,3, and 4, where infection by one serotype confers life-long immunity to only that serotype and a short period of temporary cross-immunity to other serotypes [1, 3, 4, 5, 6, 7, 8]. Two variants of the disease exist: dengue fever (DF), a non-fatal form of illness, and dengue hemorrhagic fever (DHF), which may evolve towards a severe form known as dengue shock syndrome (DSS). Epidemiological studies support the association of DHF with secondary dengue infection [9, 10, 11, 12, 13], and there is good evidence that sequential infection increases the risk of developing DHF, due to a process described as antibody-dependent enhancement (ADE) [1, 7, 8]. There is no specific treatment for dengue, and a vaccine is not yet available. So far, prevention of exposure and vector control remain the only alternatives to prevent dengue transmission.

Mathematical models describing the transmission of dengue viruses appeared in the literature as early as 1970 [14]. In the literature the multi-strain interaction leading to deterministic chaos via ADE has been described previously, e.g. [15, 16, 17] but neglecting temporary cross immunity. Consideration of temporary cross immunity is rather complicated and up to now not in detail analyzed. In [18, 19, 20] by including temporary cross immunity into dengue models with ADE, a rich dynamic structure including deterministic chaos was found in wider and more biologically realistic parameter regions. However, in order to be able to reproduce the yearly cycle in dengue incidence seasonal forcing has to be included in the models. The combination of seasonal forcing and a low import of infected individuals into our previous model [19] shows already a qualitatively very good result when comparing empirical DHF data and simulation results [21], suggesting that this parameter set could be the starting set for a more detailed parameter estimation procedure.

In this work, we compare the obtained results for the deterministic multi-strain model described in [21] with the results obtained with the stochastic model.
THE BASIC EPIDEMIC MODEL

In the simple SIR epidemics without strain structure of the pathogens we have the following reaction scheme for the possible transitions from one to another disease related state, susceptibles $S$, infected $I$ and recovered $R$,

\[ S + I \xrightarrow{\beta} I + I \]
\[ I \xrightarrow{\gamma} R \]
\[ R \xrightarrow{\alpha} S \] (1)

for a host population of $N$ individuals, with contact and infection rate $\beta$, recovery rate $\gamma$ and temporary immunity rate $\alpha$. The deterministic ODE model

\[ \dot{S} = \alpha R - \frac{\beta}{N} I \cdot S \]
\[ \dot{I} = \frac{\beta}{N} I \cdot S - \gamma I \]
\[ \dot{R} = \gamma I - \alpha R \] (2)

describes in mean field approximation $\langle S \cdot I \rangle \approx \langle S \rangle \cdot \langle I \rangle$ the dynamics of the mean values, e.g. $\langle I \rangle := \sum_{S=0}^N \sum_{I=0}^N I \cdot p(S,I,t)$, where the initial values determin the time course of the system for all times.

The stochastic process

For the SIR-model, the master equation [22] reads

\[ \frac{dp(S,I,t)}{dt} = \frac{\beta}{N} (S+1)(I-1) \cdot p(S+1,I-1,t) + \gamma (I+1) \cdot p(S,I+1,t) \]
\[ + \alpha (N-S-I) \cdot p(S-1,I,t) - \left( \frac{\beta}{N} + \gamma I + \alpha (N-S-I) \right) \cdot p(S,I,t) \]

This process can be simulated by the Gilpie algorithm giving stochastic realizations. Only few stochastic processes can be solved explicitly, however, the mean field approximation is a good approximation to be used in order to understand better the behaviour of the stochastic systems in certain parameter regions.

THE MULTI-STRAIN DENGUE MODEL

Multi-strain dynamics are generally modelled with SIR-type models, dividing the host population into susceptible, infected and recovered individuals with subscripts for the respective strains. The stochastic version is now in complete analogy to the previously described SIR model, and the mean field ODE system for the multi-strain dengue model can be can be read from the following reaction scheme

\[ S + I_1 \xrightarrow{\beta_1} I_1 + I_1 \]
\[ S + I_{21} \xrightarrow{\phi \beta_2} I_1 + I_{21} \]
\[ I_1 \xrightarrow{\gamma} R_1 \]
\[ R_1 \xrightarrow{\alpha} S_1 \]
\[ S_1 + I_2 \xrightarrow{\beta_2} I_{12} + I_2 \]
\[ S_1 + I_{12} \xrightarrow{\phi \beta_2} I_{12} + I_{12} \]
\[ I_{12} \xrightarrow{\gamma} R \]
describing the transitions for first infection with strain 1 and secondary infection with strain 2. The same reaction scheme can be used to describe the transitions for first infection with strain 2 and secondary infection with strain 1. The demographic transitions are $S, I_1, I_2, S_1, S_2, I_1, I_2, R \xrightarrow{\mu} S$ defining the system of two strains completely.

The parameter $\beta$ takes the seasonal forcing into account as a cosine function, $\beta(t) = \beta_0(1 + \eta \cos(\omega t))$, and a low import factor is included ($S \xrightarrow{\rho} I$) where $S$ can be any susceptible like $S, S_1$ or $S_2$ respectively $I_1, I_2, I_{12}$ or $I_{21}$.

**EMPIRICAL DATA AND NUMERICAL SIMULATIONS**

The inspection of the available DHF incidence data in Thailand shows a smooth behaviour with a well defined maximum each year of irregular height, for the North Provinces for example, whereas for the Central, East, and South Provinces the data is very noisy linked with a low endemicity of DHF cases (see Fig. 1a) and Fig. 1 b)).

In Fig. 1 c) we show the deterministic model simulation and in Fig. 1 d) one realization of the stochastic model. The deterministic system shows only a limit cycle whereas the stochastic model shows a much more realistic pattern of dengue fever epidemics, with irregular, yearly and smooth outbreaks.

**FIGURE 2.** Bifurcation diagram on the import parameter. We fixed the parameter as before and vary the import factor $\rho$ from $\ln(\rho) = -20$ to $\ln(\rho) = -10$. In red we show the maxima of the deterministic model and in black the maxima of one realization of the correspondent stochastic model. In a) numerical simulation for a population size compatible with Chiang Rai $N = 1130000$ and in b) numerical simulation for a population size compatible with North, North-East and East of Thailand and Cambodia (as an example of surrounding country) $N = 42940000$. 
The bifurcation diagrams in Fig. 2, show the interplay between noise and deterministic skeleton. The introduction of stochasticity is needed to get even better agreement for some of the available data sets. We show that the addition of noise can explain the fluctuations observed in the empirical data and that for large enough population size, the stochastic system can be well described by the deterministic skeleton and therefore gaining insights on dengue practical predictability under noise.

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