Comment

Thresholds, bifurcation and chaos in biological phenomena Comment on "Mathematical models for Dengue fever epidemiology: A 10-year systematic review" by M. Aguiar et al.

Hyun Mo Yang

UNICAMP – IMECC, Departamento de Matemática Aplicada, Praça Sérgio Buarque de Holanda, 651, CEP: 13083-859, Campinas, SP, Brazil

Aguiar et al. reviewed systematically 10-years of mathematical models for multi-stains dengue transmission [1]. They described mathematical modelings addressing the hemorrhagic dengue fever caused by antibody dependent enhancement (ADE), selecting autonomous (encompassing or not the mosquito population) and non-autonomous (seasonality) approaches. They considered the estimation of the basic reproduction number R_0 in simple models, and discussed the bifurcation and chaotic behaviors originated from the ADE phenomenon enhancing the secondary dengue infection by different serotype. They analyzed the severity of dengue epidemic in communities vaccinated with tetravalent dengue vaccine. Due to ADE phenomenon, in a low efficient tetravalent dengue vaccine, it is preferable the control of mosquito population. They also analyzed a possible ADE occurring in the dengue virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) co-infection.

Dengue virus is transmitted to humans by the biting of infected female mosquitoes. Mosquitoes are hugely dependent on the environment conditions, especially temperature and rain [2], [3]. For this reason, it is not reasonable the assumption that mosquito population can be incorporated in a transmission parameter (or, in a quasi-steady state assumption due to a very short life-span in comparison to human population). Non-autonomous model considering mosquito population must be preferable [4]; however, autonomous model can be dealt with aiming at the obtention of R_0. The reason behind this approach is the definition of the effective reproduction number R_e in non-autonomous model. The wide spread and accepted characterization of the basic reproduction number is the spectral radius ρ evaluated from the characteristic equation $\Lambda(\lambda) = \sum_{i=0}^{n} a_i \lambda^i$ corresponding to the next generation matrix (NGM). However, there are different ways to construct NGM, with each construction of NGM providing different expression for ρ. Besides, in more elaborated modelings, the evaluation of ρ from $\Lambda(\lambda)$ does not have an explicit formulae, or it does not provide a biological meaning.

Usually, the spectral radius characterizes the basic reproduction number ($R_0 = \rho$), which is true in SIR (susceptible, infectious and recovered) or SEIR (exposed) models. Nevertheless, the spectral radius can be interpreted as the geometric mean of the partial reproduction numbers, arising a new methodology which avoids a particular choice of NGM [5] neither the calculation of ρ. The new approach was proposed in [6] and proved in [7]:

1. The characterization of R_0 – (A) if $\Lambda_n(\lambda) = \lambda^n - \sum_{i=0}^{n-1} a_i \lambda^i$, with $a_i \geq 0$, then $R_0 = \sum_{i=0}^{n} a_i$; and (B) if $\Lambda(\lambda) = \Lambda_n(\lambda)\Lambda_m(\lambda) - \Lambda_p(\lambda)$, with $\Lambda_n(\lambda) = \lambda^n - \sum_{i=0}^{n-1} a_i \lambda^i$, $\Lambda_m(\lambda) = \lambda^m - \sum_{i=0}^{m-1} b_i \lambda^i$, and $\Lambda_p(\lambda) = \sum_{i=0}^{p} c_i \lambda^i$, with $\Omega_n = \sum_{i=0}^{n-1} a_i$, $\Omega_m = \sum_{i=0}^{m-1} b_i$ and $\Omega_p = \sum_{i=0}^{p} c_i$, then $R_0 = \max\left\{\Omega_n, \Omega_m, \frac{\Omega_p}{(1-\Omega_n)(1-\Omega_m)}\right\}$.

2. The characterization of χ – All different ways to obtain NGM result in the same basic reproduction number R_0, except one, which provides the fraction of susceptible individuals at the steady-state χ: (A) if $\Lambda_n(\lambda) = \lambda^n - \sum_{i=0}^{n-1} a_i \lambda^i$, with $a_i \geq 0$, then $1/\chi = \sum_{i=0}^{n} a_i$; and (B) if $\Lambda(\lambda) = \Lambda_n(\lambda)\Lambda_m(\lambda) - \Lambda_p(\lambda)$, then ρ evaluated from $\Lambda(\lambda)$ is the reciprocal of the fraction of susceptible individuals at the steady-state, that is, $\rho = 1/\chi$. Notice that χ can also be obtained by solving the equations of the model at the steady-state.

3. Relationship between R_0 and χ – (A) a unique threshold if $\chi = 1/R_0$; and (B) two distinct thresholds R_0 and χ if $\chi \neq 1/R_0$. It is worth stressing that the NGM approach characterizes both initial and ending phases of an epidemic.

Let us illustrate above approach. In a simple dengue modeling [6], $R_0 = R_0^h R_0^m$, where R_0^h and R_0^m are the partial reproduction numbers corresponding to human and mosquito populations (a particular spectral radius is $\rho = \sqrt{R_0}$, a geometric mean of the partial numbers R_0^h and R_0^m), and $\chi = \bar{s}^h \bar{s}^m = 1/R_0$ (this result can also be obtained from the steady-state solutions), where $\bar{s}^h$ and $\bar{s}^m$ are the time-varying fractions of humans (s^h) and mosquitoes (s^m) at the steady-state. Based on this result provided by the corresponding autonomous modeling, the effective reproduction number should be defined as $R_e = R_0^h s^h R_0^m s^m$ [4]. The assumption that a fraction of j eggs is infected by dengue virus resulted in two distinct thresholds R_o and χ: the overall transmission number $R_o = R_0 + R_t$, and $\chi = \bar{s}^h \bar{s}^m = \frac{1}{R_0} - \frac{R_t}{R_0}$, where $R_0 = R_0^h R_0^m$ is the basic reproduction number and $R_t = j$ is the additional (transovarial) reproduction number [8]. In a drug sensitive and resistant tuberculosis transmission model [9], the fraction of susceptible individuals at the steady-state was obtained by both the spectral radius ($\chi = 1/\rho$) and by solving the model equations at the steady-state.

The mathematical results must be confronted with biological meanings. The backward bifurcation and other behaviors are observed in many models, however may occur in a non-biological range of parameters. For instance, backward bifurcation occurs when the period of latency is much higher than the life-span of humans in tuberculosis [10], and when the period of time of vaccine protection is much higher than the natural infection [11]. In cancer model [12], the limit-cycle occurs in a very strong competition between cancer and healthy cells: a cycle allowing the recovery of healthy cells from a quasi-complete depletion, that is, the alive-death cycles. In regularly separated pulses vaccination model [13], bifurcations similar than those observed in a discrete logistic map [14] resulting from unstable dynamics. Notice that when perfect periodical forced systems are considered, the transient dynamic, which lasts for long time as the amplitude of the forced input increases, is followed by the period doubling bifurcation, eventually arising irregular and chaotic behaviors [15].

Notice that ADE can occur in any confections involving viruses sharing immunogenetic similarity; however ADE phenomenon was not observed in dengue and SARS-CoV-2 co-infection [1], which was described by SIR and SAIR (asymptomatic) models. However, the epidemic of coronavirus disease 2019 (Covid-19) caused by SARS-CoV-2 can not be described by SEIR-type of model [16]. A realistic model must consider asymptomatic, pre-symptomatic and mild Covid-19 cases [17]. To control Covid-19 epidemic, quarantine was implemented to avoid the collapse of the health care system [18]. Additionally, the partial (São Paulo State, Brazil) and rigid (Spain) quarantines were assessed [19], as well as the appearance of variants of concern [20].

The main idea behind ADE phenomenon is the increased viral load [21] [22] [23], which could enhance the hemorrhagic cases in a secondary dengue infection if a low efficient tetravalent vaccine is administrated. In this case, biological control of mosquito population must be applied [24] [25] [26]. However, the quiescence eggs [27] and heterogeneous distribution of breeding sites [28] may difficult the controlling efforts. However, in a successive vector-borne different serotype dengue infections, an alternative risk factor of severe dengue may be the temperature. In an optimal temperature, the increasing in mosquito size and life-span, as well as a shortening in the incubation period, could result in a huge virus load among infected mosquitoes surviving long period [2] [3]. It is an open question whether the temperature, or ADE, or joint action, contributes to increase the risk of severe dengue; however higher the temperature, higher the occurrence of hemorrhagic dengue fever [11]. Severe dengue is usually correlated with ADE phenomenon; nevertheless severe diseases are not common in co-infections among myriads of infections threatening humans, especially in re-infections with SARS-CoV-2 variants of concern, which are directly transmitted (air-borne)

infections in which the temperature is irrelevant in the viral load. (However, health care professionals were under high risk due to huge amount of virus released by hospitalized Covid-19 patients [18]).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hyun Mo Yang reports a relationship with UNICAMP - University of Campinas that includes: employment.

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