Prescriptive, descriptive or predictive models: what approach should be taken when empirical data is limited? Reply to comments on “Mathematical models for dengue fever epidemiology: A 10-year systematic review”

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Mathematical modeling has become an important tool for the understanding of epidemiological systems, addressing ideas about the components of pathogen-environment-host interactions and acting as a guiding tool to predict disease spreading and to evaluate the introduction of control strategies. Models incorporate factors focusing on several different aspects of the disease (duration of infectivity, infection rate, waning immunity rate), the biological properties of a vector (vector biting rate, vector spreading capacity), and climatic information (influencing disease seasonal trends), which can imply rich dynamic behavior even in the most basic dynamical models.
Aimed to identify a consensus on dengue modeling aspects that can contribute to public health authorities’ capacity to implement intervention measures to control the disease spreading, our review \cite{1} describes the most recent mathematical models applied to dengue fever epidemiology - the most important viral mosquito-borne disease worldwide.

The insightful commentaries by Codeço et al. \cite{2}, Yang \cite{3}, Roster \cite{4}, Pinho \cite{5} and Banarjee et al. \cite{6} bring up interesting considerations that complement our review, enhancing the debate and encouraging further research on the epidemiological dynamics of dengue fever.

**Complex dynamics in multi-strain models**

In our review, we focused on three structural dengue modeling approaches. The within-host, the vector-host, and the host-to-host transmission models were described. While the within-host framework is built to describe viral replication and immunological responses during the infection process, see e.g. \cite{7, 8}, the other two approaches aim to describe disease transmission at population level. On the one hand, the simplified host-host transmission model includes the effect of seasonality to mimic the abundance of mosquitoes, see e.g. \cite{9, 10, 11, 12, 13, 14, 15, 16, 17, 18}, on the other hand, the vector-host approach considers the explicit dynamics for the mosquito population, see e.g. \cite{15, 19, 20}. Only frameworks able to capture differences between primary and secondary infections were included in our review.

Codeço et al. \cite{2} refers to the short prediction horizon of multi-strain models, in which deterministic chaos was found in wide parameter regions \cite{9, 10, 21, 22}. Although the authors recognize the ability of these models to describe well the irregular yearly dengue outbreaks occurring in endemic countries, they argue that the multi-serotype framework would not be of appropriate use for policymaking due to its intrinsic complexity, and claim that simple models would be more adequate, considering that “epidemics tend to be dominated by a single strain”.

We appreciate the perspective of the authors, however, it is important to mention that the co-circulation of different serotypes in the same region has long been identified \cite{23, 24, 25}. While the coexistence of serotypes is the key feature to explain disease severity outcomes via the Antibody-Dependent Enhancement (ADE) process, a well-known immunological process occurring during secondary heterologous infection, the rather simplified single-strain host-to-host models cannot describe the irregular yearly dengue outbreaks occurring in endemic countries \cite{26, 27, 28, 29, 30}. To be predictive, models must at first be descriptive.

Following a rigorous analysis, multi-strain dengue models have shown to be good models for understanding dengue transmission in endemic regions \cite{9, 21, 22}. Their extensions have been effectively used to evaluate the impact of the up-to-now only licensed dengue vaccine \cite{11, 31, 32, 33, 34, 35, 36}, giving important public health recommendations for administration of this vaccine \cite{37, 38}. Beyond these important contributions, we note that finding wide ranges of complex dynamical behavior in multi-strain dengue models has opened new ways to analyze the existing empirical data worldwide, indicating that complex behavior (including deterministic chaos) is much more important in public health epidemiological systems than previously thought.
On the author’s statement “similarities between COVID and dengue dynamics should be considered only in very broad terms”: it is clear that the spread path of epidemics differs from one disease to another, and therefore, specific epidemiological information must be considered during the modeling development, as stated in Section 5.3 of our review [1]. We would like to clarify, however, that rather than comparing pathogen dynamics and suggesting straightforward generalization of the existing models, our intention was to highlight common features to be considered during modeling development. To cite one, the contribution of asymptomatic individuals to the overall force of infection is observed in both epidemiological dynamics, dengue and COVID-19 [39, 40, 41, 42]. While many real life epidemiological systems are characterized by chaotic dynamics, modeling insights for epidemiological scenarios characterized by chaotic dynamics have been largely unexplored. Especially for systems considering multiple disease variants, such as strains or serotypes, this is, without a doubt, a very promising research area.

The role of vector dynamics and the other biological mechanisms in dengue epidemiological models

Transmitted by the bite of infected mosquitoes, dengue transmission dynamics have been modeled in different ways. While some authors have incorporated the effects of the vector dynamics by the effective transmission parameters in the model, others have included the mosquito dynamics explicitly into the framework.

As included in our review, besides the population-based and the within-host models, multi-scale modelling approaches [43, 44], and individual-based or agent-based modelling [45], have also been used to understand the dynamics of dengue fever. However, our search across four repositories only yielded one agent-based modelling study, indicating limited use of this approach during the period we examined. In agreement with Pinho [5], we believe that both multi-scale and individual-based modelling approaches hold great potential for advancing the modelling of dengue.

Multiple factors influence the dynamics of dengue fever, such as its multi-strain nature, antigen-dependent enhancement (ADE), seasonal variations, and vector control. Pinho [5] has noted that host-to-host models may not fully capture the complexities of dengue transmission, while Yang [3] states that the non-autonomous model considering mosquito population explicitly should be the preferable approach since the dynamics of the vectors are dependent on environmental factors such as temperature and precipitation. However, the lack of data to parameterize such detailed models might lead to a flawed interpretation of the system, which indeed, must be confronted with biological meaning and empirical data.

We maintain that host-to-host models including pathogen structure, while simplified like all models, are well-founded for two main reasons. Firstly, explicit modelling of vector dynamics may not significantly contribute to the accuracy of a dengue model, as demonstrated in Rocha et al. [15]. Secondly, the difference in generation time between mosquitoes and humans, and the necessity to capture decades-long dynamics of dengue transmission beg for some compromises in modelling. For example, using days as the unit of time to capture multi-decade dynamics of dengue can lead to a redundant computational burden that may be
avoided by implicitly modelling vector dynamics. While we recognize the concerns raised, we believe that host-to-host models have a valuable role to play in advancing our understanding of dengue transmission. We agree on the importance of including realistic environmental features in a vector-host modeling framework, however, we also understand that to avoid getting lost in unnecessary components of a model, parsimony is needed. Overall, we believe that host-to-host models have a valuable role to play in advancing our understanding of dengue transmission.

In the comment by Yang [3], much attention was paid to the calculation of the basic ($R_0$) and effective reproduction numbers ($R_e$). The $R_0$ plays a vital role in the analysis of infectious disease modeling and analysis. It is defined as the expected number of cases directly generated by one case in a population where all individuals are susceptible (disease-free steady-state). The threshold criterion $R_0 = 1$ marks the situation where the disease-free steady-state transfers into the endemic state where $R_e$ is the number of cases generated in the current state of a population. There are several methods that can be used to obtain this well-known $R_0$ measure. The next generation matrix method, as defined and described in [46], with the method for the decomposition in the transmission and transition parts given in [47]. However, unfortunately, sometimes this is not only based on new infections, as explained in [48]. Another possible approach is to use the centre manifold analysis as proposed in [49]. The existence of sub-threshold equilibria can be shown by analysing the dynamics close to the threshold value $R_0 = 1$, where the forward or backward bifurcation can occur. In [50], both approaches are used for the analysis of dengue host-vector model where the vector life stages (eggs, larva, pupa and adult) are modelled explicitly.

The aim for modelling and analysis is to verify whether the validity holds in general. However, in applications it is restricted to specific parameter ranges above those always made such as: the numbers of individuals in the population must be non-negative. The aim is to classify under which circumstances dynamical behaviour such as steady-state, oscillatory or chaotic occur. Non-linear dynamical systems theory, especially bifurcation analysis, [51] [49] can be performed where computer packages for symbolic analysis as well as numerical calculations can be used. The starting point is the Jacobian matrix evaluated at disease-free equilibrium and when an eigenvalue of the Jacobian at a transcritical bifurcation point is zero. Hence the calculation of $R_0$ is not necessary in general, for instance the transition between forward and backward bifurcations mentioned by the author, is fixed by a so-called cusp bifurcation described recently in [26]. Another important point is that no separation into transmission and transition processes is required. This allows the application in more complex eco-epidemiological models. Note that often the ecological model is very simple where the birth-rate of the susceptible host individuals equals the death rate of all individuals such that the total number of individuals is constant in which cases $R_0$ is a very useful measurement.

Yang has also discussed the modelling of the antibody-dependent enhancement phenomenon. By proposing additional compartments for the host and vector with enhanced viral load [52], the system does not include extra compartments for the within-host dynamics itself. It is essentially a one-strain model because the dynamics of infection is for one serotype to individuals already infected by another serotype. Nevertheless, this is an interesting modelling approach, that is different from the assumption of disease enhancement
of secondary heterologous dengue infection proposed in [9, 53]. Note that the Antibody-Dependent Enhancement (ADE) leads to a disease augmentation phenomenon where pre-existing antibodies do not neutralize but rather enhance the new infection. And this does not occur within the vector but is restricted to the human immune response during the infection process. While there is no evidence that mosquitoes biting individuals experiencing ADE would acquire and transmit higher concentrations of the virus as compared to mosquitoes biting individuals in a primary infection with mild or no symptoms at all, it is well known that individuals experiencing a secondary infection with an heterologous serotype have higher risk of developing severe disease needing hospitalization (decreasing their contact rate with mosquitoes), contributing less to the overall force of infection than those mild/asymptomatic individuals (with higher mobility as transmission capacity). Besides being well-documented in the immunological literature, this effect was recently confirmed with a within-host modelling approach, see [8]. A more realistic epidemiological system to describe the ADE factor and its impact on disease transmission at population level would eventually need to couple the within-host and the vector-host frameworks. We agree with Pinho that the estimation of model parameters is a critical step towards validating models, and it is evident that techniques for parameter estimation have undergone significant improvements over time. We appreciate the insightful comment on the potential benefits of incorporating new machine-learning methods into the calibration of models to enhance identification of parameters. Indeed, a technical parameter estimation is notoriously difficult for chaotic time series, however, advances based on Deep Learning and on Bayesian techniques have been recently proposed [54, 55, 56, 57, 58, 59, 60]. While this is a fascinating research question, the lack of good immunological and entomological data would give rise to important uncertainties during the modeling parametrization.

Further possible approaches to model dengue spreading and data availability

Beyond the modeling strategies already examined in our review and commented on above, there are, of course, many other approaches to model dengue epidemiology. Due to the well-defined scope of our review, approaches related to behavioral features of the host population were not included, which are very important as described by Banerjee and Ghosh in [6]. In particular, a great deal of attention is devoted to:

(1) the use of game theory to analyze the effect of pharmaceutical and non-pharmaceutical interventions taken individually (regardless of existing health control policies) by each inhabitant (e.g., use of mosquito nets, spray of insecticides, garbage collection, avoiding accumulation of waterlogged areas, etc.) which may lead to a reduction in the vector population and, consequently, in the spread of the disease [61, 62]. We consider that these individual actions, which can eventually become collective, play a major role against disease propagation, in some cases getting over potential (and usually delayed) actions initiated by the public health authorities.

(2) the application of neural networks and machine learning techniques for epidemic forecasting (see e.g., reviews [63, 64, 65]), and, as cited above, for parameter estimation of complex systems.

Banerjee et al. [6] have suggested to model the behavioral change of human
individuals during dengue outbreaks by means of game-theoretical approaches, considering that individual actions could maximize personal payoffs. Undoubtedly, some of the preliminary results are worthy of consideration. The basic idea is to merge a simplified epidemiological model with an evolutionary game, where “agents” can rationally choose their individual actions (assuming that individuals are driven by self-interest rather than by the interest of the group). In these models, in general, the infection rates will be affected by the chosen strategy, whereas the risk perception and payoff of each strategy depend on the number of infected individuals. To mention a few practical applications, the use of this game-theoretical framework allows to explore the effect of the individual-based quarantine/social distancing strategies [66], of the decision of using bed-nets (and how often) [67], or of voluntary vaccination [68, 69, 70]. Aligned to the latter, Kabir et al. [71] have considered the case where a primary and secondary vaccines scheme is suitable, like those intended for immunological multi-serotype illnesses (such as dengue). For a broader perspective of this modelling strategy, please refer to Chang’s review [72]. Lastly, some recent contributions on how tools of game theory can be used to model human interactions regarding disease contamination can be found in [73, 74, 75] for an airborne transmitted disease and in [76] for contagion within a crowd, where cooperative and competitive interactions are taken into account. We believe that some of the therein proposed ideas can be extended to the case of a vector-borne disease like dengue to model the so-called effect of individual’s decision making on global regulation [77]. In consensus with Banerjee and Ghosh [6], we share their view that game theory-based approaches and neural networks, are promising frontier areas which merit further investigation. Especially now that new data on dengue fever epidemiology are becoming increasingly available, allowing to validate models that were developed on the basis of previously known information.

As pointed out by Roster in [4], the 2019 dengue outbreak in Brazil, which some might believe to have been driven by a newly imported strain, was most probably caused by a dengue serotype circulating at low transmission levels for many years, as hypothesized in the study by Brito Anderson et al. [78], where genomic, epidemiological, and ecological data were combined to investigate the resurgence of dengue across the country.

Such slow replacement of one strain by another is to be expected, given the dynamics observed in multi-strain models. These models suggest, at least for the serotype replacement, that the yearly outbreaks are not caused by a single strain, but often by mixtures of at least two co-circulating strains. While one serotype is causing the outbreak, given that the population susceptibility is affected by temporary cross-immunity, the dominant strain is observed to be slowly replaced by another serotype over time (several years), as predicted by the above mentioned multi-strain models (e.g. in [9, 10, 53]). It should be noted that, when these models were proposed to explain dengue transmission dynamics, genomic sequencing of serotypes was rare, if performed at all. Two exceptions were data sets from Puerto Rico and Vietnam, where a large proportion of the dengue cases was sequenced, clearly showing the replacement of serotypes over several outbreak seasons, as well as the presence of more than one serotype in each season [79, 80].

Climatic factors also influence disease dynamics, especially vector-borne diseases, with weather fluctuations shifting the warm season or rainy season by days or weeks, allowing disease outbreaks to happen earlier or later in the year.
However, the availability of susceptible humans to one or another serotype will rather determine the size of a yearly outbreak, depending on previous seasons’ burn out and replacement of serotypes. While the time scale of several years or decade long immunological status of the human host population might override the short fluctuations of weather and rapid replacement of mosquito populations, which just follow the longer term immunological dynamics, as mentioned above, longer term climatic changes, such as the slow increase of mean temperatures in various regions of the world, can cause gradual shifts of parameters in mid scale multi-strain dynamical models of dengue fever. Among other effects, this may lead to new introduction scenarios in up to now non-endemic world regions. In this respect, new data and observations can lead the future research, as sketched by Roster [4].

Finally, at microscopic scale, we note the relevance of human immunological processes in shaping our view on fluctuations in epidemiological systems. Dengue fever dynamics, driven by the interplay between antibody dependent enhancement (ADE), which affects individual transmissibility, and temporary cross immunity (TCI), which generates waning cross-protection, is still a prime example, that may even be considered paradigmatic. Applied to the more recent COVID-19 pandemic scenario, the growing availability of polymerase chain reaction (PCR) testing, as well as variant sequencing, have highlighted a few aspects which could be inferred from previous multi-strain dengue modeling experience. Firstly, the role of asymptomatic/mild infections versus hospitalized/severe disease, which has become common knowledge by now due to the large increase in testing capacity during the first year of the pandemic (a fact that has been known in dengue fever epidemiology for a long time, since primary infection is often milder than secondary infection with a heterologous serotype virus, which leads to most hospitalizations). And secondly, the emergence of new variants and its capacity for undermining previously gained resistance, either by natural infection or by vaccination with vaccines developed to target the already existing wild type or first variants. This became clearly noticeable during the second year of the pandemic, when wider sequencing of variants started (again, a fact previously known from other respiratory diseases, like influenza, where vaccines have to be renewed every new season due to rapid mutations of the virus). Consequently, with the significant increase in epidemiological knowledge and data from the past few years of COVID-19 pandemic - justified by its vast economic impact - we now expect the availability of new public epidemiological data to shed light on other infectious diseases of public health concern, such as dengue fever, for example.

In conclusion, we also believe that the gathered knowledge of already existing epidemiological models can really set the stage for increasingly complex questions that may be answered by interdisciplinary studies [4]. Provided, of course, that such empirical data become widely accessible for studies in several directions. We should always bear in mind that mathematical models are only good to the extent that in applications they can describe certain data on certain time scales [81]. Being a simplification of reality, parsimony is key to identifying the extent to which the modelling of biological mechanisms can replicate the realistic dynamical behavior observed in the available empirical data, and provide a straightforward interpretation of real world epidemiological systems.
Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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