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Migration rate estimation in an epidemic network

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ABSTRACT

Most of the recent epidemic outbreaks in the world have as a trigger, a strong migratory component as has been evident in the recent Covid–19 pandemic. In this work we address the problem of migration of human populations and its effect on pathogen reinfections in the case of Dengue, using a Markov-chain susceptible-infected-susceptible (SIS) metapopulation model over a network. Our model postulates a general contact rate that represents a local measure of several factors: the population size of infected hosts that arrive at a given location as a function of total population size, the current incidence at neighboring locations, and the connectivity of the network where the disease spreads. This parameter can be interpreted as an indicator of outbreak risk at a given location. This parameter is tied to the fraction of individuals that move across boundaries (migration). To illustrate our model capabilities, we estimate from epidemic Dengue data in Mexico the dynamics of migration at a regional scale incorporating climate variability represented by an index based on precipitation data.

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1. Introduction

A typical disease outbreak taking place in a completely susceptible population strongly depends on the number of secondary cases generated by a primary case and on the time it takes to infect those secondary cases (see, for example, [1]). However, in all infectious diseases transportation and movement of human groups and also of vectors of disease have for ever contributed to its spread by bringing into contact populations that are regionally or geographically separated from the focal point of the first outbreak. This interplay has been addressed from a variety of perspectives in the literature (see [2–7]). We particularly center in this work on the role of mobility on Dengue. Dengue has become the most prevalent arthropod-borne viral disease (arboviruses) of humans over the last few decades [8]; it has recently been estimated that there are 390 million human dengue infections each year, [9]. Dengue is mainly transmitted to humans through the bite of infected female mosquitoes of the Aedes genus especially in tropical and subtropical countries. Arboviruses are naturally maintained in a transmission cycle between vertebrate and arthropod hosts referred to as vectors (blood-feeding mosquitoes) [10]. Connectivity between population centers and travel and seasonality—weather and environmental factors as well as in sociological or anthropological ones—, are closely related to the import/export of infectious diseases both in directly as well as in vector-transmitted diseases [11]. Climatic conditions vary seasonally affecting habitat suitability for
reservoirs, vectors and pathogens and their entire life cycles; likewise seasonal human migrations induced by cultural or economic reasons importantly move susceptible and infectious individuals over a wide range of distances. Dengue fever is a re-emerging mosquito-borne infectious disease that is of concern as human travel, migratory patterns and expanding mosquito ranges increase the risk of spread [11–15]. Martínez-Vega et. al. [13] assessed the association between the peridomestic dengue infection and the exposure to a dengue index case to a dengue in two Mexican endemic communities. The evidence suggests that dengue endemic transmission in these locations is initially peridomestic, around an infected subject and it is influenced by characteristics of the individual, the neighborhood and the location. Once the transmission chain has been established, dengue spreads in the community probably by the adults who, despite being the group with lower infection frequency, mostly suffer asymptomatic infections and have higher mobility. They also constitute a large fraction of the economically active segment of the population that moves daily to destinations where they remain long enough as to be bitten by local vectors. These in turn transmit the virus to other subjects contributing thus to the spread the disease, initiating a new transmission cluster in a different location, in another city or segment of the urban landscape. In summary human movement may results in the regional or even global spread of infectious diseases [15,16], including vector-borne diseases [17].

The effect of mobility on Dengue has been studied by many authors, e.g., [18–23]. Dengue has caused illness in millions of people over the last several years [24] and concerns have been expressed about the increased risk it poses on the general population due to the impact of climate change [25]. Dengue is only one of the vector-borne diseases that has had major outbreaks in several countries around the globe; recently the Caribbean, several Indean Ocean islands and LatinAmerica have suffered from outbreaks of Chikungunya [26–28], Zika, another vector-borne disease transmitted by Aedes aegypti, had in 2016 a major epidemic in the American continent where its introduction into Florida has been a cause of major concern in the USA [18]. In both of these diseases, human migratory patterns –one of them travel to an international sports event–, are a major factor associated with disease spread. Mobility and Dengue have received varied and intense attention in the last decade. Dengue moves with the human population along roads and highways in many parts of the world and, being transmitted by Aedes aegypti a highly adapted vector to urban environments [29–32], prevention and control constitute a major aim in many countries [12,33–38].

The primary vector of Dengue is, as said before, Aedes aegypti but Ae. albopictus could become an important secondary vector. Both mosquito species are diurnal, biting mostly in the morning and evening rather than at night [39]. Dengue produces acute immunizing infections in humans ranging from clinically inapparent to severe and fatal hemorrhagic disease. Dengue is in itself a complex disease with multiplicity of lineages [40]. Classical dengue fever is generally observed in older children and adults and is characterized by sudden onset of fever, frontal headache, nausea, vomiting among other symptoms [41].

Mitigation strategies for Dengue include reduction of the mosquito population via indoors spraying (adulticides) larvae, lethal ovitraps, removing man-made oviposition sites and reduction of human exposure to mosquito bites via the use of screens, mosquito repellent, etc., but so far these have not being effective and, as a consequence, the absolute numbers of Dengue infection have increased worldwide during the last 40 years [42]. Vaccines are in development and currently at least two are undergoing clinical trials [35].

For Dengue, modeling has been applied to delucidate transmission as well as used as a tool to help in its control and prevention [38,43–45], but there is still much to do. In recent years, spreading processes on complex networks, like computer viruses, epidemics in human populations, rumors or information in social networks, have been modeled and described. In general, each node of the network represents a location in the system and the links represent the pathways through which the interaction among nodes takes place. Recently, Markov-chain models for susceptible-infected susceptible (SIS) dynamics over complex networks have been used to describe the dynamics of individual nodes and the macroscopic properties of the system [16,46–49]. One important result coming out from this set of works, is the existence of an infection threshold that depends on the spectral radius of the adjacency matrix [50].

In line with ideas introduced by [46,50] and [49], we present a mathematical model that relates human mobility and Dengue transmission using a Markov-chain for a susceptible-infected-susceptible (SIS) dynamics over a network. Immigration processes in deterministic models render $R_0$, the basic reproductive number, ineffective as a threshold and invasion parameter [18] with the model analysis becoming substantially more difficult compared to the no-immigration (standard) case. We propose in this work an strategy to address this problem in the context of a reinfection process of whole geographical regions. We use the classical framework of patch-dynamics adapted to Dengue colonization-extinction (eradication-outbreak) of the disease in certain sites which represent geographical regions. In a given network of sites, we assume that each site can be reinfected (recolonized) through the movement of infectious individuals from neighboring patches and, also, that the disease in any given patch may disappear because of the natural disease life cycle or because of emigration. We illustrate our model in a network of four nodes that correspond to populations in four different states of the Mexican Republic: Veracruz, Guerrero, Oaxaca and Chiapas. Links in the network and the interaction among the nodes, take place through shared borders across which migration occurs. Additionally, the model incorporates external forcing as a way to explore the effects of variability on the spread of dengue. We attempt to estimate or quantify a measure of the migratory flow that is consistent with the observed patterns of epidemic behavior (data). Parameters of the model are fitted to the data and simulations are performed to compare the model behavior with the observed patterns of incidence.
The paper is organized as follows. In Section 2 we present the general framework. In Section 3 we present the discrete mathematical model and parameter estimation. In Section 4 we present the numerical results for each region. In Section 5 we discuss the network model. Finally, in Section 6 we present some conclusions about this work.

2. General framework

The classical Levins metapopulation model [51] has been generalized to many contexts, in particular to spatially explicit settings where it has shown that landscape structure and patch dynamics can affect the persistence of metapopulations (for example [52]). Landscape structure, characterized by spatial and temporal heterogeneities determines the nature and impact of all of these effects [52]. Here, we formulate a mathematical model following the classic work of Levins [51,53]. It is a patch dynamics model with time-dependent contact (infection) rates associated to climatic variability, particularly rain. We are interested in defining a general contact rate as a local measure of several factors: the population size of infected hosts that arrive at a given location as a function of total population size, the current incidence at neighboring locations, and the connectivity of the network where the disease spreads. Once constructed, we assess its validity applying it to the specific example of Dengue infection for the years 2004 to 2009 in Mexico, as the infection moves through four patches. Migration occurs across a common border between neighboring states.

In Mexico population mobility is essentially carried out on buses through the road network of the country. Unfortunately, due to the lack of information on transportation statistics, we have no data to parametrize this factor and, therefore, one of our specific objectives is the quantification of the migration rate from the observed incidence patterns. We concentrate in a relatively simple system constituted by large regions, in this case political subdivisions known as States. Our data base comprises weekly incidence data reported to regional health centers in each of four states of Oaxaca, Guerrero, Veracruz and Chiapas (see map Fig. 1).

We have aggregated our data by state. There certainly are alternatives to the choice of spatial aggregation done here. For example, we could have chosen to identify regions by hydrological basins since this subdivision could be associated to mosquito data in a more natural way. However, lacking information on vector abundance and distribution our choice was to look at aggregated data following state boundaries. However, we are currently preparing a forthcoming work where we look at hydrological basins and roads associated to epidemic outbreaks.

3. The mathematical model

The general idea supporting our model is that Dengue dynamics can be approximated by a discrete model with nonlinear dynamics of the kind

$$M_{t+1} = g(M_t)$$
where $g$ is some non-linear function operating on a vector $\mathbf{M}_t$ that specifies the state of the system at time $t$.

In general, suppose that the model has $k$ states (for example $k = 2$ for the SIS model and $k = 3$, for the SIR) and it operates on a graph of $N$ nodes, therefore we have a $k \cdot N \times 1$ vector $\mathbf{M}_t$ that captures the probability of each node to be in any of these $k$ states at a given time $t$, specifically

$$\mathbf{M}_t = [M_{s1,1.t}, M_{s1,2.t}, \ldots, M_{s1,N.t}, M_{s2,1.t}, \ldots, M_{s2,N.t}]^T$$

where, $M_{sj,i,t} =$ the probability of node $i$ being in state $s_j$ at time $t$. Following [49] we take each federal state (Oaxaca, Veracruz, Guerrero, Chiapas) as a node of the network that can be in either of two (epidemiological) states in analogy to an SIS epidemic model. We use the following assumptions:

- Each node represents the population of each state (hereafter renamed as location or site) of the Mexican Republic: Chiapas, Guerrero, Oaxaca and Veracruz. The connection between locations is defined by adjacency: having a common border; see Fig. 2.
- Each location can be in either of two epidemiological states: $S$ susceptible (uncolonized or empty of infection) or $I$ (presenting an outbreak). The probability of an outbreak in location $i$ at time $t$, is defined as $p_i(t) \in [0, 1]$, with $i \in E = \{\text{Chiapas, Guerrero, Oaxaca and Veracruz}\}$. Therefore, each location at each time $t$ is in state $S$ with probability $s_i(t) = 1 - p_i(t)$ (without outbreaks), and with probability $p_i(t)$ in state $I$ (with outbreaks).
- Dengue infections are sensitive to the mosquito life cycle, besides, climatic conditions vary seasonally affecting habitat suitability for vectors and their entire life cycles [54], so we assume that dengue infections are climate-sensitive. Dengue outbreaks vary over characteristic periods longer than a year and the seasonal variability drives these cycles [55–58]. We have chosen precipitation as a general “approach” of an external factor affecting the probability of contagion [59].

Our model has fundamentally two types of transition drivers: the first one, changes induced by the neighbors represented by a connectivity matrix in which population flow changes as a function of climatic variability and total population size of connected sites (exogenous) and the second one, caused by the node itself that has some probability of being in a given state at every time step (endogenous). For example, the transition from $S$ to $I$ in the SIS model is an exogenous transition while the transition from $I$ to $S$ is an endogenous transition. It is the presence of the graph-based transitions that makes our model not a simple Markov chain and brings in the topology of the graph into play. In our model only one class of transitions is graph-based, all others are endogenous transitions. See Fig. 3.

We construct an undirected network with nodes that represent the locations that, in principle does not have any particular topology. The model is set up with discrete time-steps of size $\Delta t = 7$ days, corresponding to an epidemiological week, transitions between states ($S$ and $I$) depend on the probability of infection $\eta_i(P(t))$, a function of the interaction among locations, and the recovery probability $\mu$. Fig. 4 shows the state transition diagram for each node.

Our main tool is the construction of $\eta_i(P(t))$ (the interaction function) and its associated parameters that we use to estimate the probability of occurrence of an outbreak. Following [26,27] this interaction function represents the probability that a site in the network is infected or colonized after interaction with its neighbors.

Any site in state $I$ passes to state $S$ with probability $\mu$ (clearance or recovery rate), but it is reinfected with probability $\eta_i(P(t))$, where

$$P(t) = [p_{\text{chis}}(t), p_{\text{cro}}(t), p_{\text{oxa}}(t), p_{\text{ver}}(t)]^T$$

is a vector with entries $p_i(t)$ that represents the probability of outbreaks (state $I$) in location $i$ at time $t$. We are modeling the transmission by function $\eta_i(P(t))$ that quantifies the probability that in the $i$th location, an outbreak will occur due to three factors: a) the probability $\beta_i$ of location $i$ becoming infected, defined as a per-node probability of infection, b) the probability that an outbreak occurs at node $i$ given the occurrence of an outbreak in location $j$ and c) the average monthly
Although by give the each graph the replication number, epidemic (described below).

The epidemic threshold on a graph depends fundamentally on the graph itself. Wang et al. describe a general theory for epidemic thresholds for arbitrary graphs where the epidemic threshold is a condition linking the infection and recovery rates to the adjacency matrix of the graph i.e., a condition between $R_0 = \beta / \mu$, the basic reproduction number of the standard SIS model, and the largest eigenvalue $\lambda_A$ of the adjacency matrix. This relation is given by (see Theorem 1, [49])

$$R = \lambda_A \frac{\beta}{\mu}$$  \hspace{1cm} (1)

where $R$ is the reproduction number on the graph (accounting for disease severity and network topology) and the adjacency matrix of the network (see Fig. (2)) is given by

$$A = \begin{pmatrix} 1 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 \\ 1 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 \end{pmatrix}.$$  \hspace{1cm} (2)

Note that from (Eq. 1), by knowing $R_i$ with $i \in E = \{Chiapas, Guerrero, Oaxaca and Veracruz\}$ we can determine $\beta_i$ for each year during the period 2004–2009. We next look at the probability that any given node $i$ is infected. We denote by $r_{ij}$ the probability that there is an interaction between node $j$ and node $i$ (that means, node $j$ is connected to node $i$ but that does not imply that there is an interaction). Note that $r_{ij}$ is directly linked to the probability of an outbreak. These numbers give the probabilities that, given a link between $j$ and $i$, the transmission of infection can occur [47]. In summary, the term $f_j(t)\beta_j(t)r_{ij}(t)p_j(t)$ represents the probability that an outbreak will occur in location $i$ given the occurrence of an outbreak in location $j$; we call this the probability of transmission from location $j$ to location $i$. We are assuming that the interaction between node $i$ and node $j$ is independent of the interaction of node $i$ with node $k$, therefore each of the events quantified by the above probabilities are independent, i.e., $\prod_{j=1}^{N} (1 - f_j(t)\beta_j(t)a_{ij}r_{ij}(t)p_j(t))$ the probability of not being infected the location $i$, is the product of not being infected by its neighbors. With this statements in mind, we define the probability of being infected by

$$\eta_i(P(t)) = 1 - \prod_{j=1}^{N} (1 - f_j(t)\beta_j(t)a_{ij}r_{ij}(t)p_j(t))$$  \hspace{1cm} (3)

Although the graph is not directed, there is interaction from state $j$ to state $i$ and from state $i$ to state $j$, given that immigration customs are different ([2]), one would expect $r_{ij} \neq r_{ji}$.
As for the climatological factors, monthly precipitation data were obtained from Sistema Nacional de Información del Agua (SINA) [60], Mexico, from 2004 to 2009 for each location. Each monthly precipitation data is normalized concerning the maximum value of the corresponding year, so, is possible that the selection of this maximum can affect the transmission. These normalized monthly precipitation represents the climate variability \( f_i(t) \), see Fig. 5.

\( f_i(t) \) acts as a forcing periodic function affecting the outbreaks. This climatological factor together with human migration, determine the occurrence of outbreaks. The rate of leaving the infectious stage is denoted by \( \mu \), and this rate is assumed constant, we consider the average infection time of 7 days [61,62], therefore, in the model we consider \( \mu = 1/7 \).

Since the state of any node at time-step \( t + 1 \) depends only on its state at time-step \( t \); we have a Markov chain described as

\[
p_i(t + 1) = (1 - \mu)p_i(t) + \eta_i(P(t))(1 - p_i(t)),
\]

where \( i \in E = \{ \text{Chiapas}, \text{Guerrero}, \text{Oaxaca}, \text{Veracruz} \} \) and \( 0 \leq p_i(t) \leq 1 \), where each time step corresponds to an epidemiological week. The first term on the right-hand side of Eq. (4) is the probability that node \( i \) is has an outbreak at time \( t \) and is not eradicated, and the second term is the probability that node \( i \) is free of outbreaks with probability \( (1 - p_i(t)) \) but can get one with probability \( \eta_i(P(t)) \) if at least one nearest neighbor has an outbreak.

Eq. (4) represents our non-linear dynamical system (see Fig. 4). Given the topology of our network and the values of the characteristic parameters of the dynamics of dengue infection, we will adjust the probabilities \( r_{ji} \) using a heuristic approach that consists of an estimate \( R_0 \) in each location per year, and later perform several simulations of the system given by Eq. (4) for a given set of \( r_{ji} \). The set of graphs generated by simulations is compared with the data in order to establish those \( r_{ji} \) set that best matches. In a future work, this heuristic procedure will be replaced by an estimating method that approximates the parameters in a better way, and the approach proposed in this work could you give us hints of the initial conditions for the approximation method.

### 3.1. Model parametrization

Our information from the National System of Epidemiological Surveillance covers the history of epidemic events for several years in different municipalities of South Eastern Mexico. The recorded cases are provided by Regional Hospitals that are in charge of reporting infectious diseases to the health authorities in the country. Dengue is a mandatory notifiable disease in Mexico but only diagnosed cases are reported (50% or more, [63]) so we can expect our data to be biased by unnotified asymptomatic cases, under-reporting and misreported (a certain amount of cases that are not related to Dengue but to some other diseases with similar symptoms). As mentioned before there is evidence [64,65], that movement is a key factor for understanding epidemic episodes and large outbreaks that occur along the years. The time series for Dengue cases is presented in Fig. 6.

To parametrize our model we need to estimate the force of infection through the estimation of the reproduction number for each location and in each of the years during the period 2004–2009. Once these estimates are obtained, we infer the infection rate for each site. From its definition \( R_0 \) is determined from early stages of the epidemic and its magnitude is a useful indicator of both the risk of an epidemic and the effort required to control an infection.
3.1.1. Exponential growth rate method for $R_0$

The rate of exponential growth $r$ is defined as the per capita change in number of new cases per unit of time (epidemic growth rate) [66]. One of the way of inferring $R_0$ from $r$ is through the use of a moment generating function for the reproductive number. According to [67], the reproductive number defined as expected secondary infections is given by $R_0 = \int_{0}^{\infty} n(a) da$, where $a$ is the time since infection, $n(a)$ expected rate of generation of secondary cases at time $a$ since infection. The rate $n(a)$ can be normalized to a distribution $g(a)$, i.e. $g(a) = n(a)/R_0$. The Lotka-Euler equation is given by

$$1 = \int_{a=0}^{\infty} e^{-ra}n(a) da$$

and substituting $g(a)$ (generation interval distribution) into it we obtain

$$\frac{1}{R_0} = \int_{a=0}^{\infty} e^{-ra}g(a) da.$$  

The term in the right-hand side, is the moment generating function $M(z)$ of the distribution $g(a)$, i.e. $M(z) = \int_{a=0}^{\infty} e^{za}g(a) da$ [68]. Evaluating at $z = -r$ we obtain the reproductive number $R_0 = \frac{1}{M(-r)}$. This method is called exponential growth (EG).

During the initial phase of an outbreak, we assumed that the reported cases and the real ones have a consistent relationship with exponential growth (defined by the per capita change in the number of new cases of infected people per unit time). To estimate $R_0$ from data we use the EG method of the R0-package of R language [69], we choose a period in the epidemic curve over which the incidence growth is approximately exponential and then a Poisson regression is applied (rather than linear regression of the logged incidence). As an example, in Fig. 7, an initial inspection of the incidence data shows that the exponential growth period occurs during the first 23 weeks of the outbreak for Oaxaca during the year 2005.

Important parameters in an epidemiological model are the per capita contact rate between susceptible and infected individuals and the infection recovery rate. No births or deaths are taken into account given that the rate of dengue mortality is low. The incidence data is given as number of new cases per epidemiological week and we use a time dependent maximum likelihood method with the distribution of generation times rescaled to weeks (as in e.g., [70]) to obtain the values reported in Table 1 that lists the estimated values of $R_0$ for Oaxaca State. The dengue virus evolution in Mexico is typified by frequent lineage replacement [40], such that only a single viral lineage dominates in a specific serotype at a specific time point while the others circulate at low densities at a specific time point, for this reason we can calculate $R_0$. Once the estimate of each reproduction number is obtained, we solve for the infection rate denoted by $\beta_i(t)$. For numerical simulations of the next section, we only consider the average value of $R_0$ for all locations (see Appendix).

For Dengue dynamics, a vector transmitted disease, the basic reproductive number is given by $R_0 = \frac{\alpha_m \beta_h}{\delta_m}$ [71], where $\beta_h$ is the infection rate from human to mosquito, $\alpha_m$ the infection rate from mosquito to human, $\delta_m$ the mortality rate
of the mosquito and \( \mu_h \) the recovery rate of the human. In the absence of dynamics for the mosquito population we set, \( \beta = \alpha_m \beta_h \), without regard to the mortality rate of the mosquito, as previously mentioned, the life cycle of the mosquito is associated with precipitation.

4. Numerical results

Dengue is mainly transmitted to humans through the bite of infected vectors. Mosquitoes are one of the main actors, which are implicitly in our model, however, their dynamics are simple but very difficult to quantify, therefore we represent vector capacity by function the \( f_i(t) \) that represents the habitat suitability for mosquitoes during their entire life cycles.

We start first with a simple case for \( \eta_i \). We do not explicitly include the migration rate (this factor will be introduced later), only temporal variability. Let

\[
\eta_i(t) = \sigma f_i(t) \beta_i(t), \quad i \in E.
\]

(5)

\( f_i(t) \beta_i(t) \) gives the time-dependent infection rate of location \( i \), and \( \sigma \) is an interaction factor to be determined numerically to find the best fit, in all simulations we consider the mean value of \( R_0 \) to determine \( \beta_i(t) \). In Fig. 8 we show the observed and predicted incidence (rate of new cases per week) from Eq. (4), we take the average cases of the four states of the observed incidence for the years 2004–2009, otherwise with \( \eta_i(t) \) given by Eq. (5), the network average probability of an outbreak (predicted incidence) is computed as

\[
\rho(t) = \frac{1}{4} \sum_{i=1}^{4} p_i(t)
\]

As we can see from the data, the seasonal peaks are not the same (see Fig. 6), we take the maximum of the precipitation for each year as a reference for \( f_i(t) \), which would serve to make the model look like the data, but it does not have to resemble reality.
Fig. 8. Comparative between average observed outbreaks and numerical simulations given by \( \rho(t) \) and \( \sigma = 0.000106 \) during the years 2004–2009 without mobility effect. The x-axis is epidemiological weeks.

Fig. 9. Comparative between average observed outbreaks and numerical simulations for the whole network for the years 2004–2009 with host mobility.

Notice that the model reproduces the frequency of outbreaks, but overestimates the last two outbreaks. Later, we will incorporate the mobility and contacts that are supporting the foundation of our model.

Now we proceed to include host mobility to adjust the fraction of individuals that moved from location \( j \) to \( i \) and subsequently compare our simulations with the real data. To incorporate the displacement of people we use the following explicit expression for (3):

\[
\eta(t) = 1 - \prod_{j=1}^{4} \left( 1 - f_i(t) \tilde{\beta}_i(t) a_{ij} r_{ji} p_j(t) \right)
\]

that describes the colonization-extinction of the disease by counting cases moving to location \( i \), cases that stay in location \( i \) and those that recover in location \( i \).

Mexico has no centralized data warehouse for transportation data. In order to investigate the influence of the migration component using data from Mexico, we perform simulations from our mathematical model Eq. (3) with the aim to approximate the values for the probability \( r_{ji} \) of movement between the locations.
Fig. 10. Comparison between observed outbreaks and numerical simulations for Oaxaca during 2004–2009 with host mobility.

Fig. 11. Comparison between observed outbreaks and numerical simulations for Veracruz during 2004–2009 with host mobility.

Fig. 9 shows a comparison between real and simulated aggregated outbreaks (average cases of all locations) for the whole network considering the mobility component. Observe that relative to the results shown in Fig. 8, the fit has significantly improved since we consider more parameters in the calibration.

Our data and simulations are scaled to proportions so our fit is qualitative in that sense. However, note that in our predictions, the phase of the outbreaks is slightly delayed by one or two weeks but both the amplitude and the inter-epidemic period (which in general is an event with very low numbers), are well approximated but the peaks, which it is the most difficult and most important to the public health management, they are collected much better.

In Figs. 10, 11, 12, 13 we compare the probabilities generated by the model with the proportion of reported cases for each location. This shows a qualitatively reasonable approximation for Oaxaca and Veracruz. In both cases the slight out of phase estimation is evident but once again both the amplitudes and inter-epidemic periods are well approximated. The best estimates are those for Oaxaca, because it is the most connected node in the network and thus the estimation uses the information of all its neighbors.

However in Chiapas and Guerrero, our model does not perform well. For Guerrero the phase of the outbreaks misses two of them and the amplitude of the epidemic curves is underestimated. For Chiapas we obtain spurious outbreaks. We should
mention however that Guerrero and Chiapas are states with very many weeks with no reported cases and that this scarcity of data is most likely the cause of the relatively bad fit.

For all numerical results, we determine the transmission rate using weekly data on with confirmed cases, however the unreported also influence the contagion, according to simulations, we can expect that if there was a report of asymptomatic cases for each location, we would obtain a better approximation.

5. Discussion

The network model presented in this work is a generalization of the simplest patch dynamic framework pioneered by Richard Levins [51,53] now adapted to describe epidemic outbreaks linked by migration and forced by environmental or climatic fluctuations. Our model is a Markov model (discrete time stochastic equation) where we have used weekly incidence data and network topology to estimate the migration or movement rates that describe.

The parameter $\eta(P(t))$ plays a central role. It incorporates the neighborhood topology of the network and the other non-linearities related to population movement and climatic variability into the dynamics of outbreaks in a given spatial region.
Fig. 14. Patch dynamics over the whole network at the beginning of 2004. The red circles are due to that outbreak probability is greater unlike green circles. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Fig. 14** represents the time evolution of our system for four time periods (weeks), we can see that there is no connection between Veracruz and Guerrero i.e. for these two nodes $r_{ij} = 0$.

Given the very complex interplay of the different dengue serotypes and the lack of data for their individual incidence or prevalence, we aggregated the incidence data into four large geographical locations to understand the spatial dynamics of Dengue. This framework, albeit simple in terms of the actual population dynamics of Dengue, is able to identify mobility patterns underlying the spread of this disease in a large region of South Eastern Mexico.

Our model is stochastic in nature and we have incorporated into it climate variability represented by an index based upon monthly precipitation data as approximation to more general indexes of climatic variability. Our parameter $\eta(P(t))$, is a general contact rate that represents a local measure of the population size of hosts that arrives at a given location as a function of population size, current incidence at neighboring locations and the connectivity of the patches.

Regarding our illustrative example, from our results one can see that the node with the lowest degree (Chiapas) is the one with the poorest incidence fit. Our data lacks locations that have common boundary with the Guerrero location and, therefore, the outbreak risk index for this location does not integrate all the input and output events acting of the site. The other nodes in the network present a better fit since incidence data from more first neighbors is available.

With this very simple framework we are able to reproduce the incidence dynamics in all four locations except for a number of outbreaks where incidence data is particularly scarce or null. We interpret this result simply as a verification that, regardless of the complexity of the population dynamics of Dengue, movement at a geographical scale is a relatively simple colonization extinction process taking place in a network (a spatially extended system) whose dynamics is dependent on its topological arrangement, and neighborhood interactions [51,72]. Our model considers, as in [11], a connectivity matrix in which population flow changes as a function of climatic variability (precipitation), total population size of connected sites and weekly incidence. Our results indicate that our assumption that the directional mobility of human populations in the four sites considered here, changes seasonally in a given year is plausible.

6. Conclusions

During the years covered by our data, the Dengue strains that have circulated have been mainly Dengue II and I with lower prevalence of Dengue III and IV. Immunity, therefore, must play a role in the observed reinfection dynamics. However, since we are aggregating all data at the level of the location, i.e., we are adding all cases in all the regional hospitals that
report them each week, we miss, at this very large spatial scale, the impact of immunity. However, there are other confounding effects that compensate this lack of information, like unknown but variable mosquito density, and the application of mosquito control measures. In our data, Dengue outbreaks at the town or municipality level are notoriously asynchronous and there are large gaps with no cases in the weekly records. To improve our colonization-extinction model, an ongoing effort is been made to generalize and adapt our results is the SIS model to the ideas of [52] where patch unsuitability is introduced into the patch classes of Levins’ model. In our case unsuitable patches for colonization would be locations with a large population of immune hosts. This approach should improve our estimates and shed light into the dynamics of movement in Dengue.

The main focus of this paper has been the examination of the role of the inoculum size and precipitation effects. The results presented constitute an approximation to the study of movement patterns and epidemic outbreaks of Dengue. We have only looked at a small network with a large spatial resolution (state level). We have shown that it is possible to reproduce the outbreak patterns using weekly data on confirmed cases. The highest resolution that our data provides is that of municipality. It is at this spatial scale where we think our approach can be more useful through the generation of scenarios of likely epidemic events.

In this work, we have only data at a small network that corresponds to four localities that are part of a region in southern Mexico, which are relevant by the number of cases in recent years. The model proposed in this paper can be extended to describe the dynamics in more locations by modifying the adjacency matrix that describes the connectivity of locations. Also, to describe how the infection progress, more compartments could be considered. However, due to the number of equations and parameters, in addition to that, and the high non-linear behavior, it is very complicated to estimate all parameters associated with the model, so it is necessary to use other mathematical tools that will be explored in a future work.

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Appendix

The basic reproduction number is defined as the number of secondary infections that a single infectious individual produces in a population where all hosts are susceptible.

During the early phase of an outbreak, the exponential growth rate is defined by the per capita change in number of new cases of infected per unit of time. For the calculation of $R_0$ from the real data is necessary to choose a period in the epidemic curve over which growth is exponential, the values are in the confidence interval as an estimated range of values for $R_0$ ($p$-value $\leq 0.05$) with EG method, for the purpose of calculating the infection rate $\beta_i(t)$ according to Eq. (1) of the text. The transmission rate is calculated from the reported data, although the non-reported also influence the contagion, these are not considered when calculating the force of infection.

Infection rate was calculated as $\beta = \frac{1}{\lambda} R \ast \mu$, where $\lambda_A = 3.17009$. According to Table A.1, small $\beta$ values are assumed for those years in which data are not available.

Finally, using a heuristic approach, we calculate the matrices $R$(year) whose elements are independent probabilities $T_{ij}$, the estimated elements of each of the matrices are those that minimize the error between real and simulated data.

From top to bottom, the rows represent Chiapas, Guerrero, Oaxaca and Veracruz. From left to right, the columns have the same order.

$$R(2004) = \begin{pmatrix} 0.31 & 0.00 & 0.13 & 0.93 \\ 0.00 & 0.99 & 0.99 & 0.00 \\ 0.60 & 0.99 & 0.20 & 0.90 \\ 0.38 & 0.00 & 0.20 & 0.92 \end{pmatrix}, \quad R(2005) = \begin{pmatrix} 0.26 & 0.00 & 0.42 & 0.45 \\ 0.00 & 0.99 & 0.99 & 0.00 \\ 0.76 & 0.99 & 0.35 & 0.36 \\ 0.39 & 0.00 & 0.20 & 0.32 \end{pmatrix}$$

Table A1

| Año | $R_0$ Chi | $R_0$ Gue | $R_0$ Oax | $R_0$ Ver | $\beta$ Chi | $\beta$ Gue | $\beta$ Oax | $\beta$ Ver |
|-----|----------|----------|----------|----------|------------|------------|------------|------------|
| 2004 | 3.018901 | 2.964451 | 2.883671 | 7.500000 | 0.231857   | 0.145923   | 0.221471   | 0.576013   |
| 2005 | 5.565420 | 5.157346 | 4.043462 | 7.761656 | 0.427434   | 0.396093   | 0.310545   | 0.596109   |
| 2006 | 6.417567 | 5.165929 | 5.473978 | 7.407847 | 0.010000   | 0.010000   | 0.420411   | 0.568935   |
| 2007 | 7.269714 | 5.174511 | 7.427206 | 4.810614 | 0.558327   | 0.397411   | 0.570422   | 0.010000   |
| 2008 | 2.877680 | 4.763556 | 3.081718 | 2.213381 | 0.220111   | 0.010000   | 0.236681   | 0.169991   |
| 2009 | 3.830250 | 4.352600 | 2.479011 | 4.644224 | 0.294170   | 0.334287   | 0.190461   | 0.356884   |
The $f_j$ values give us an interaction average between the state i and the state j that could yield the infection. According to our results, we can note that $f_j$ vary in each year, except for Guerrero y Oaxaca, where the lack of data is counterbalanced with large values of their respective $f_j$ values. On the other hand, it is important to mention that Guerrero and Oaxaca are well-known for its high tourist inflow and as results high mobility is to be expected.

Note that, the applicability of the result obtained in Eq. (6) has the drawback that, due to the high complexity of the model it is clear to think that many solutions could match our simulations with data, however combining our results with mobility data will allow estimate in the best way all model parameters which will allow to explore other models or even to explore the possibility of applying control strategies based on models that consider climate and mobility as part of the propagation dynamics.

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