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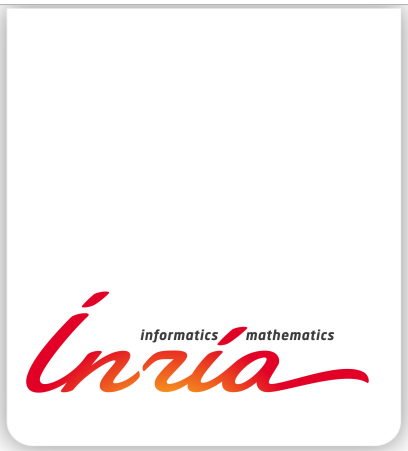

Onset of a vector borne disease due to human circulation - uniform, local and network reproduction ratios

Moacyr Alvim*, Abderrahman Iggidr†, Jair Koiller*, Maria Lucia F. Penna‡, Gauthier Sallet†, Max O. Souza§

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Abstract: We study the effect of human circulation on the onset of an epidemics for a arboviral (mosquito-borne) illness such as dengue. The underlying dynamics on a metapopulation is given by a classical SIR (human)/SI (vector) model. We consider three concepts of reproduction numbers: *local* (for each isolated subsystem), *uniform* or *mixing* (disregarding movement and non-uniformity in the whole region), and *network* (coupling the patches via human circulation). Interrelations between the three concepts are obtained. Depending on the biological contact assumptions, two types of network models result. In *destination* type models, the force of infection depends on mosquito density, relative to human population or to area. In *origin* based models, it is assumed that the transmission is determined by the behaviour of susceptible humans. Archetypal examples can be found where each node has local reproduction ratio less than one, and the uniform reproduction number is also less than one, but the network reproduction number is greater than one. This shows that the disease can propagate among the patches solely as a consequence of human circulation. An estimate about the effect of vector control on a given patch is given. The conceptual framework presented here may help decision makers to plan vector control policies and medical care in case of an outbreak.

Key-words: vector borne disease, network models, reproduction rates, matrix analysis

Apparition d'une maladie à transmission vectorielle en raison des mouvements humains
Nombre de reproduction de base local, uniforme et pour un réseau

Résumé : Cet article étudie les effets des mouvements humains sur l'apparition d'une épidémie pour une arbovirose comme la dengue. On considère un modèle de métapopulation où la dynamique dans chaque patch est décrite par un modèle SIR/SI. Nous considérons 3 concepts de nombre de reproduction de base : un concept local (quand chaque patch est isolé), un concept d'uniforme distribution (la dynamique est identique dans les patchs) et enfin le concept de réseau (couplant les mouvements et une dynamique locale non uniforme). Nous obtenons des relations entre ces trois concepts. En fonction des hypothèses sur le contact biologique deux types de réseaux sont obtenus. Dans les modèles dits par «destination», la force d'infection dépend de la densité vectorielle, qu'elle soit relative à la population humaine ou relative à la zone considérée. Dans les modèles dits par «origine», on suppose que la transmission est déterminée par le comportements des humains susceptibles. Nous donnons un exemple où le taux de reproduction de base local, ainsi que le taux de reproduction uniforme sont tous inférieurs à 1, mais où cependant le taux de reproduction du réseau est supérieur à 1. Cela signifie que la maladie peut se propager le long des patchs seulement par l'effet des mouvements humains. Une estimation de l'effet du contrôle vectoriel sur un match est donné. Le cadre conceptuel présenté peut servir d'outil pour les décideurs de santé publique dans le cas d'une épidémie.

Mots-clés : arboviroses, transmission vectorielles, mouvement humains, modèles de métapopulations, taux de reproduction de base, analyse matricielle.

Contents

1 Introduction

In metapopulation or multigroup epidemiological models the population is divided, say, into geographic zones, each one of them with uniform characteristics. The same underlying mathematical model is used for all sub-populations. Heterogeneity among patches is usually characterized by differences in the local infectivity parameters, that can be large. Therefore, different *prevalences* at the nodes are in general attributed to differences in the *force of infection*, see e.g., Clancy and Pearce 2012; Xue and Scoglio 2013.

In contradistinction, in this work we study a metapopulation model for the onset of a vector borne disease (such as dengue, yellow fever, or other arboviruses, see e.g., Gubler 2004, Gubler 2009) under the two main assumptions: (i) that there are no differences in the transmission

functions (for both host and vectors), and hence that the only distinction between patches are in the carrying capacities; (ii) that the visits between the patches are short. Such a modelling choice allows to focus in the *effect of human circulation* on the stability of the disease free equilibrium.

In particular, the ensuing analysis will show that there are network configurations and circulation patterns where one can see the persistence of the disease, even though all the patches have, isolated, reproduction ratios less than unity. These results are consistent with a number of findings by several authors (using various models and methods) that sources of heterogeneity may increase the chance of a disease to invade a population. Some congenial work, from a vast literature, are briefly commented in §2. We single out the article by Adams and Kapan (2009), for which our paper can offer some complementary views.

Hopefully, understanding how circulation and biological contact affect the overall dynamics could help planning preventive vector control measures, and medical care facilities deployment, in case of an outbreak.

1.1 A patchy environment

For the building block we consider the simplest possible model, consisting of five equations, SIR for humans and SI for vectors (Bailey, 1975), which in the case of dengue takes into consideration just one serotype. Let S_h, I_h, R_h denote, as usual, the number of, respectively, susceptible, infectious and removed host individuals and S_v, I_v the number of susceptible, infectious vectors.

$$\begin{cases} \dot{S}_h = & \Lambda_h - T_h(S_h, I_v, N_h) - \mu_h S_h \\ \dot{I}_h = & T_h(S_h, I_v, N_h) - \gamma_h I_h - \mu_h I_h \\ \dot{R}_h = & \gamma_h I_h - \mu_h R_h \\ \dot{S}_v = & \Lambda_v - T_v(S_v, I_h, N_h) - \mu_v S_v \\ \dot{I}_v = & T_v(S_v, I_h, N_h) - \mu_v I_v, \end{cases} \tag{1}$$

where the *transmission rates* are given by the frequency dependent bilinear functions (McCallum et al., 2001):

$$T_h(S_h, I_v, N_h) = \beta_1 S_h \frac{I_v}{N_h}, \ , \ T_v(S_v, I_h, N_h) = \beta_2 S_v \frac{I_h}{N_h} \tag{2}$$

relative to the total current population

$$N_h = S_h + I_h + R_h \ . \tag{3}$$

Thus the *force of infection* on humans and vectors are assumed to be proportional to the densities relative to the total human population:

Definition 1. *(Force of Infection)*

$$g_h = \beta_1 \frac{I_v}{N_h} \ , \ g_v = \beta_2 \frac{I_h}{N_h} \tag{4}$$

The constant β_1 is a composite object that embodies all the biological processes relating to transmission from mosquito to man, from the biting rate of the mosquitoes through the probability to develop and infection after a bite, see the next §3. Analogously β_2 captures the effect of transmission from man to mosquito. Λ_h is the constant recruitment of humans, and μ_h is the per capita human mortality; γ_h denotes the per capita rates at which infectious individuals recover and become permanently immune. The parameter Λ_v is the constant recruitment of mosquitoes and μ_v is the per capita vector mortality.

We denote

$$\bar{N} = \frac{\Lambda_h}{\mu_h} \ , \ \bar{V} = \frac{\Lambda_v}{\mu_v} \ , \ m = \frac{\bar{V}}{\bar{N}} \ . \tag{5}$$

$\bar{N}$ and $\bar{V}$ are the carrying capacities at the disease free equilibrium. m is a classical concept, the *Ross vector/humans density*. See Smith et al. (2012) for a comprehensive review about the contributions of Ross and Macdonald to vector borne diseases and recent developments.
The reproduction number of (1, 2) is

Definition 2.

$$\mathcal{R}_0^2 = \frac{\beta_1 \, \beta_2 \, \bar{V}}{\mu_v \, (\mu_h + \gamma_h) \, \bar{N}} = \frac{\beta_1 \, \beta_2 \, m}{\mu_v \, (\mu_h + \gamma_h)} \tag{6}$$

It is the same as in the classical Ross' model (Smith et al. 2012; Anderson and May 1991; Auger et al. 2008; Bailey 1975; Ross 1911) and for completeness we give the derivation in appendix A.

Remark 1. *i) We could make explicit the biting rate parameter making $\beta_1 \to b\beta_1 \ \ \beta_2 \to b\beta_2$. Since $\mathcal{R}_0$ depends linearly on b, the biting rate is a natural candidate for bifurcation parameter. ii) To allow flexibility for both two types of models (origin or destination based) we will introduce scaling parameters, see (24).*

The patchy model is then given at each node i by

$$\begin{cases} \dot{S}_{h,i} = & \Lambda_{h,i} - T_{h,i}(S_{h,i}, I_v) - \mu_{h,i} \, S_{h,i} \\ \dot{I}_{h,i} = & T_{h,i}(S_{h,i}, I_v) - \gamma_{h,i} \, I_{h,i} - \mu_{h,i} \, I_{h,i} \\ \dot{R}_{h,i} = & \gamma_{h,i} \, I_{h,i} - \mu_{h,i} \, R_{h,i} \\ \dot{S}_{v,i} = & \Lambda_{v,i} - T_{v,i}(I_h, S_{v,i}) - \mu_{v,i} \, S_{v,i} \\ \dot{I}_{v,i} = & T_{v,i}(I_h, S_{v,i}) - \mu_{v,i} \, I_{v,i}, \end{cases} \tag{7}$$

The functions $T_{h,i}$ and $T_{v,i}$ describe how the epidemiological connection between the patches is accomplished. For more details about these functions see §3, and a more precise description of the model in §4. The description of the various parameters is given in Table 1.

We assume that the infections occur at the destination patch in the network. When the travelling susceptible humans carry their original characteristics or habits to the destination patch, we call the model *origin based*. On the other hand, two *destination based* models are considered, where the contact rate depends on mosquito density, related either to area or to effective human population at the node. If the infections are modelled by mass action, those distinctions are irrelevant. The contact assumptions are discussed in §3 and implemented for metapopulations in §4.

1.2 Main results and outline

The results are formulated in a form that can be used for the origin based or destination based models. We are primarily interested in obtaining relationships between three concepts of reproduction numbers:

- Uniform (for the region as a whole), $\widetilde{R_0}$
- Local (for each isolated patch), $R_0^{i,\mathrm{loc}}$

Table 1: Notations and formulas

Notation	meaning
b, $\Lambda_{h,i}$, μ_h, γ_h, $\Lambda_{v,i}$, μ_v, $C=(C_{ij})$	parameters for the models, circulation matrix
$S_{h,i}(t)$	susceptible human population in patch i at time t
$I_{h,i}(t)$	infected human population in patch i at time t
$N_{h,i}(t)$	total human population in patch i at time t
$\hat{N}_{h,i}(t)=\sum_\ell C_{\ell i}\, N_{h,\ell}(t)$	effective human population in patch i at time t
$I_{v,i}(t)$	infected vector population in patch i at time t
$N_{v,i}(t)$	total vector population in patch i at time t
S_h, I_h, N_h, $\hat{N}_h$, I_v, N_v	vectors of $\mathbb{R}^n_+$
$\bar{N}_{v,i}=\dfrac{\Lambda_{v,i}}{\mu_v}$	vectors carrying capacity at patch i
$\bar{N}_{h,i}=\dfrac{\Lambda_{v,i}}{\mu_v}$	humans carrying capacity at patch i
$\bar{N}=\sum \bar{N}_{h,i}$, $\bar{V}=\sum \bar{N}_{v,i}$	total human and vector populations at the DFE
$\bar{m}=\dfrac{\bar{V}}{\bar{N}}$	uniformity mosquito density
$\bar{F}_{h,i}=\dfrac{\bar{N}_{h,i}}{\bar{N}}$, $D_h=\mathrm{diag}(\bar{F}_h)$	density distribution of hosts
$\bar{F}_{v,i}=\dfrac{\bar{N}_{v,i}}{\bar{V}}$, $D_v=\mathrm{diag}(\bar{F}_v)$	density distribution of vectors
$(1/n)\,\mathbb{1}=(1/n,\cdots,1/n)$	homogeneous distribution
$K=(K_1,\cdots,K_n)$, $D_K=(1/\bar{N})\mathrm{diag}(K)$	scaling parameters for infectivities
$\delta=b\,\beta_h\bar{m}$, $\sigma=b\,\beta_v$	shorthand symbols
$A_O=D_K^{-1}C$ or $A_V=CD_K^{-1}$	interaction matrices A (origin or destination models)
$L_O=D_h^{1/2}D_K^{-1}CD_v^{1/2}$ or $L_V=D_h^{1/2}CD_K^{-1}D_v^{1/2}$	balanced interaction matrices (origin or destination models)
Relations between the reproduction numbers	
$\mathcal{R}_0^2=\dfrac{b^2\beta_h\,\beta_v m}{\mu_v(\mu_h+\gamma_h)}$	reproduction number, 1 patch
$\widetilde{R_0}^2=\dfrac{b^2\,\beta_h\beta_v\bar{m}}{\mu_v(\mu_h+\gamma_h)}$	uniform reproduction number
$R_0^{i,\mathrm{loc}}=\widetilde{R_0}\left(\dfrac{F_{v,i}}{F_{h,i}}\right)^{1/2}$	local reproduction number
$R_0^{\mathrm{network}}=\widetilde{R_0}\,\hat{\theta}$, $\hat{\theta}=\sigma_1(L)$	network reproduction number

- Network (global reproduction number due to human circulation), R_0^{network}.

The uniform and local reproduction ratios in §5 are defined following (6). The network reproduction number is associated to the Jacobian of the full system at the disease free equilibrium, where the equations are written in terms of prevalences.

The main results can then be briefly described as follows:

1. The local reproduction rates are obtained from the uniform reproduction number multiplying by the square root of the local mosquito to human density,

$$R_0^{i,\text{loc}} = \widetilde{R_0}\sqrt{\frac{F_{v,i}}{F_{h,i}}} \tag{8}$$

2. The network reproduction number is obtained from the uniform reproduction number multiplying it by the *correction factor* $\hat{\theta}$,

$$R_0^{\text{network}} = \widetilde{R_0}\,\hat{\theta} \quad , \quad \hat{\theta} = \sigma_1(L)\,. \tag{9}$$

   This factor $\hat{\theta}$, that can amplify or reduce the spread of the disease, is the largest singular value of the *balanced interaction matrix* L, appearing in Table 1, where notations and main formulas are summarized.

3. A quantitative result is obtained about the effect on the network reproduction number of mosquito control on a chosen patch.

The matrix L can be of two types, origin (L_O) or destination based (L_v) and involves: the circulation matrix C, the relative densities steady state populations $F_h = (F_{h,1}, \cdots, F_{h,n})$, $F_v = (F_{v,1}, \cdots, F_{v,n})$ of humans and vectors, and a vector K of scaling parameters, that reflect the contact rates assumptions at the patches.

A numerical exploration is presented in §6, for the origin based model. It is intended as a "proof of concept": the network reproduction rate can be bigger than 1 while the uniform and local ones both are less than 1.

The statements for the Main Theorem and some Corollaries are given on §5 and the proofs are presented in the appendices. In fact, once the definitions and notations are organized, the proofs become straightforward. They rely on finding the spectrum of Metzler matrices of the form

$$\begin{pmatrix} -2pI & qL \\ rL^t & -2sI \end{pmatrix}\,. \tag{10}$$

2 A glimpse on the literature

To put our work in context, we now comment a few articles from the vast literature of multi-group models, that we perceived to be congenial to ours, in that *heterogeneities may increase the chances of a disease to invade a population.*

Specifically for mosquito borne diseases, Hasibeder and Dye (1988) considered a malaria model where mosquitoes and hosts live in "patches". A mosquito from any one of vector patches take blood meals in any one of host patches. Nonhomogeneous host selection by mosquitoes leads to basic reproductive rates never smaller than those obtained under uniform host selection. Strong associations between particular groups of mosquitoes and hosts lead to still higher basic reproductive rates.

The intensification effect due to heterogeneity also appears in direct contact diseases. A general analysis is given by Diekmann, Heesterbeek, and Metz (1990) formulated in terms of continuous variables. In Andreasen and Christiansen (1989) the classic Kermack/McKendrick's SIR is taken as the underlying model in each patch. They assume that the force of infection in the i-th group is the weighted sum of prevalences, where the weights σ_{ij} represent the average number of contacts per time unit that an individual in group i makes with individuals in group j. The main question they are interested is if the disease persistence is due to intragroup activity or due to intergroup transmission. They generalize a result of Hethcote (1978) on the bifurcation at the disease free equilibrium leading to a unique global endemic equilibrium, relaxing the usual assumption on the irreducibility of a contact matrix.

To define the σ_{ij} they consider either *proportionate mixing* or *homing (preferred mixing)*, where a fraction $1-\phi_i$, of the contacts that a person in group i makes are made with individuals in the same group. Their point is that the disease can be maintained by either mechanism: local disease persistence in centres with high internal transmission or global persistence due to exchange in a larger pool.

Even simpler models were considered, a few years later, by Adler (1992) and by Dushoff and Levin (1995). The underlying model (without recruiting) is taken as $\dot{I} = \beta\lambda I(N-I)$ where β is the rate of contacts, and λ is the probability that a contact results in infection. The multi-group version is given by

$$\dot{I}_i = \beta \left(\sum_j \lambda_{ij} I_j \right) (N_i - I_i) \ . \tag{11}$$

Adding a constant recovery rate allows one to define a R_o (proportional to the leading eigenvalue of the mixing matrix Λ) such that the disease dies out globally if $R_o < 1$ and that a stable endemic equilibrium exists for $R_o > 1$.

Assuming proportionate or preferred mixing, Adler (1992) showed that the leading eigenvalue of the Jacobian matrix associated with the homogenized system is less than or equal to that associated with the full system.

Dushoff and Levin (1995) considered basically the same system as Adler (1992), written in the form

$$\dot{I}_i = S_i \left(\sum_j \gamma_{ij} I_j \right) - \delta_i I_i \ , \tag{12}$$

where the γ_{ij} may depend on the dynamic variables. They consider either random or preferred mixing. Rather than defining a threshold R_o, they focus on various conditions so that a disease can invade the heterogeneous population. They assume that at the disease free equilibrium $\gamma^*_{ij} = \dfrac{\mu_i \nu_i}{N_j} P_{ij}$, where μ_i is the mixing rate of members of group i, or the number of potentially

infectious contacts per unit time; ν_i is the probability that a member of group i will get the disease from an infectious contact – a measure of susceptibility. N_i is the total population of group i (all susceptible), and P_{ij} is the proportion of group i's contacts that are with members of group j.

Dushoff and Levin (1995) assume the symmetry condition $\mu_i \nu_i P_{ij} = \mu_j \nu_j P_{ji}$ which is natural for direct contact diseases, but may be not the case for vector borne diseases.

3 Contact rates in vector-host models

The main characteristic of our model is to add the vector SI dynamics to the underlying host (humans) SIR dynamics, coupling the nodes via host circulation.

The most common transmission functions used in the literature are collected in McCallum et al. (2001) and Hoch et al. (2008). We call the attention to recent works by Novozhilov (2008, 2009, 2012) where power law transmission functions are derived from first principles. Empirical studies to formulate and validate models for transmission rates are just starting. They can also be function of time and of adaptive human behaviour. For vector borne diseases, different transmission functions may produce conflicting predictions (Wonham et al., 2006).

In this work we confine ourselves with the simplest bilinear transmission functions. In (1) the standard (frequency dependent) functional form for the *force of infection* (McCallum et al., 2001) is used, namely the force of infection on humans g_h directly proportional to the infected mosquito/human density I_v/N_h, and likewise the force of infection on mosquitoes g_v proportional to infected human density I_h/N_h in the patch, see (4), leading to (49).

Differences on biological assumptions about the contact behaviour, that do not matter mathematically in the 1-patch case, will have a deep impact on multi-patch models, as we will see in §4. In fact, Begon et al. (2002) call the attention on the importance of making clear the assumptions being made about the *contact rates* of hosts and vectors, and in fact, this is fundamental for our network modelling. We now present a short review.

The master formula is

$$\dot{I}_h = S_h \, s \, p \, \nu, \tag{13}$$

where S_h is the number of susceptible humans available, s is the contact rate of humans and mosquitoes, p is a probability that such a contact is with an infected mosquito, and ν the probability that infection on humans upon the contact is successful. For each specific disease ν is a constant, and

$$p = \frac{I_v}{N_v} \tag{14}$$

We are left with the contact rate s. According to Ross and Macdonald, s should be assumed proportional to the mosquito/human density,

$$s = \kappa \, m \;\; , \;\; m = \frac{N_v}{N_h} \tag{15}$$

(where κ has dimension 1/time) and this will give the frequency dependent model

$$\dot{I}_h = \beta \, S_h \, \frac{I_v}{N_h} \;\; , \;\; \beta = \kappa \, \nu. \tag{16}$$

It could be argued, however, that after a certain level of human crowding, the the factor κ could be better modelled not as a constant value, but grow proportionally to N_h. Then the forces of infection (for humans and vectors) will be given directly by mass action, without the denominator N_h. The mathematical expression for $\mathcal{R}_0$ can be adapted without difficulty.

On a single patch this is merely a matter of conventional notation (with due respect to the change in dimensions of the β's).

For a metapopulation, the mass action law will furnish simple bilinear products $\beta_h S_{h,i} I_{v,k}$ or $\beta_v S_{v,i} I_{h,k}$. If the biological and ecological characteristics (e.g., availability of breeding sites) are the same, the same β will be used on all patches, leading to (29). Some conditions upon which mass-actions model is adequate are discussed in Rhodes and Anderson (2008).

It is important to notice that, for metapopulations, the contact assumptions lead to two distinct types models, namely *origin node vs. destination node based models.*

If one assumes that the contact rate is proportional to the area density of mosquitoes in a patch,

$$s = \kappa \frac{N_v}{A} \tag{17}$$

(where κ has the strange dimension area/time) one gets

$$\dot{I}_h = (\nu\, \kappa) \frac{I_v}{A} S_h \tag{18}$$

leading to a destination based model.

A contact rate assumption being explored in current research, is *adaptive human behaviour* (Fenichel et al., 2011). For the origin based model, we assume that susceptible humans from a given patch carry, when visiting other patches, their protective habits (say, proper clothing, repellents, etc.). We may assume, for instance, that these habits are directly correlated to the total population of the node they live in. This leads to the origin dependent network model.

4 Multi-patch models: equations for prevalences

In the case of a large city, or a large country with a good transportation system the movements from one location to another are fast, and it may be assumed that the propagation of the disease takes place at the destination locations. In such situations, it is natural to consider discrete spatial models, i.e, metapopulation models. The population is distributed among discrete locations named *patches.* The metapopulation model involves movement of the individuals between discrete locations, but there is no exchange of individuals between the subpopulations. It is supposed that the individuals make short visits to other patches. For example, in the case of dengue, an individual can infect and be infected either at home or at its work location, during daylight, but when becoming infectious it might transmit the virus to the mosquitoes at its location of residence.

It is a growing wisdom that epidemics are strongly determined by the movement of the human hosts (Teurlai et al. 2012; Stoddard et al. 2009). Although the vectors essentially do not move between patches, they behave, roughly speaking, as "capacitors", as if being bitten by infected humans (Adams and Kapan, 2009).

We consider a region divided in n patches, each patch i has a human population of $N_{h,i}$ and a vector population of $N_{v,i}$. Let $N = \sum N_{h,i}$ and $V = \sum N_{v,i}$ be respectively the total host and vector populations. We adjoin the domicile index i to S_h, I_h, R_h so that at any given time instant

$$N_{h,i}(t) = S_{h,i}(t) + I_{h,i}(t) + R_{h,i}(t)$$

and likewise

$$N_{v,i}(t) = S_{v,i}(t) + I_{v,i}(t)\ .$$

We emphasize that the vectors do not move between nodes, it is the human population that moves fast between patches, but it does not migrate, as modelled for instance in Arino (2009). The type of movement we consider is described by a *circulation matrix* with non-negative entries $C = (C_{ij})$, $i, j = 1, \ldots, n$. The main assumptions on C are that it is column stochastic, irreducible and that $C_{ii} > 0$. The convention is the usual one, C_{ij} represents movement from patch i to patch j. It can be interpreted as the fraction of time that, in average, an individual whose *registered domicile* is patch i stays in patch j.

The former two assumptions mean that all movements are confined within the region, and that the region is connected in the sense that given any pair of nodes there exists a path, with some length, that connect these nodes. The latter condition can be interpreted as a non-ghost region assumption, i.e., for any given region there are always some inhabitants that stay on it.

There is more than one possible extension of the one-patch model, depending on the biological assumptions about the contact rates between man and mosquito (including "sociological" characteristics of human habits at a given patch) that were discussed in §3. Our results will be stated in a form that will be valid for a large class of extensions, but the results should be interpreted accordingly. We will attempt to make the model as simple as possible to call the attention to the effects of human circulation. Thus we have all the other aspects to be uniform. In particular, we have not considered, for instance, the distinction between day and night that might be important for commuter neighbourhoods.

4.1 General form of the models

At each node i we have

$$\begin{cases} \dot{S}_{h,i} = & \Lambda_{h,i} - T_{h,i}(S_{h,i}, I_v) - \mu_{h,i}\, S_{h,i} \\ \dot{I}_{h,i} = & T_{h,i}(S_{h,i}, I_v) - \gamma_{h,i}\, I_{h,i} - \mu_{h,i}\, I_{h,i} \\ \dot{R}_{h,i} = & \gamma_{h,i}\, I_{h,i} - \mu_{h,i}\, R_{h,i} \\ \dot{S}_{v,i} = & \Lambda_{v,i} - T_{v,i}(I_h, S_{v,i}) - \mu_{v,i}\, S_{v,i} \\ \dot{I}_{v,i} = & T_{v,i}(I_h, S_{v,i}) - \mu_{v,i}\, I_{v,i}, \end{cases} \tag{19}$$

Since humans circulate, but mosquitoes do not, we can write the transmission rates, respectively, as follows:
For humans,

$$T_{h,i}(S_{h,i}, I_v) = \sum_k T_h^k(c_{ik}\, S_{h,i},\, I_{v,k}) \tag{20}$$

Note that the functional forms T_h^k may in principle vary among patches, reflecting for example economic and social factors (residential or work neighbourhoods, factories/schools), local preventive measures (window mosquito nets) rather than direct vector control measures. The rate of infections of the fraction of time $c_{ik}\, S_{h,i}$ that residents from node i spend on node k depend on the infected mosquito population on node k. That is why we used the notation $I_v = (I_{v,1}, \cdots, I_{v,n})$. For vectors, with analogous conventions,

$$T_{v,i}(I_h, S_{v,i}) = T_v^i(\, S_{v,i}, \sum_k c_{k,i}\, I_{h,k}) \tag{21}$$

Mosquitoes at patch i have at their disposal a pool of blood proportional to $\sum_k c_{k,i}\, I_{h,k}$. In principle, the functional forms on the patches could be also different, reflecting for instance environmental heterogeneities.

4.2 Four distinct bilinear transmission models

In order to concentrate on the effect of human mobility, we will assume that the following biological parameters

$$\beta_{h,k},\ \beta_{v,k},\ \gamma_{h,k},\ \mu_{h,k},\ \mu_{v,k}$$

do not depend on k and we will drop the patch index on them. In particular, there is no differences among patches in their transmission functions (for humans and vectors).

The only possible source of heterogeneities will be on the constant recruiting rates $\Lambda_{h,k}$, $\Lambda_{v,k}$ for which we allow to depend on patch k.

As in the 1-patch case, the total human and total vector populations at every patch will tend to *steady state populations*

$$\bar{N}_{h,i} = \frac{\Lambda_{h,i}}{\mu_h}\ ,\ \bar{N}_{v,i} = \frac{\Lambda_{v,i}}{\mu_v}\ . \tag{22}$$

It is clear that the set defined by

$$\Omega = \{(S_h, I_h, N_h, S_v, I_v) \in \mathbb{R}^{5n}_+ |\ \ 0 \le S_{h,i} + I_{h,i} \le \bar{N}_{h,i}\ \ 0 \le S_{v,i} + I_{v,i} \le \bar{N}_{v,i}\}$$

is a compact positively invariant absorbing set. Hence using Theorem 2, discussed in Appendix A, the stability study of our general system (19) is reduced to the study of

$$\begin{cases} \dot{S}_{h,i} = & \Lambda_{h,i} - T_{h,i}(S_{h,i}, I_v) - \mu_{h,i}\, S_{h,i} \\ \dot{I}_{h,i} = & T_{h,i}(S_{h,i}, I_v) - \gamma_{h,i}\, I_{h,i} - \mu_{h,i}\, I_{h,i} \\ \dot{I}_{v,i} = & T_{v,i}(I_h, S_{v,i}) - \mu_{v,i}\, I_{v,i} = T_{v,i}(I_h, \bar{N}_{v,i} - I_{v,i}) - \mu_{v,i}\, I_{v,i}, \end{cases} \tag{23}$$

The biological assumptions on contact rates, considered in §3 lead to important differences in the network models. Let

$$K = (K_1, \cdots, K_n) \tag{24}$$

be a vector of parameters.

Definition 3 (Origin/Destination based transmissions)**.** *In destination node based models, the transmission functions are given by*

$$T_{h,i} = b \sum_\ell \beta_h\, C_{i\ell}\, S_{h,i}\, I_{v,\ell}/K_\ell\ \ ,\ \ T_{v,i} = b \sum_\ell \beta_v\, I_{v,i}\, C_{\ell i}\, S_{h,\ell}/K_i \tag{25}$$

In origin node based models, the transmission functions are given by

$$T_{h,i} = b \sum_\ell \beta_h\, C_{i\ell}\, S_{h,i}\, I_{v,\ell}/K_i\ \ ,\ \ T_{v,i} = b \sum_\ell \beta_v\, I_{v,i}\, C_{\ell i}\, S_{h,\ell}/K_\ell \tag{26}$$

The concrete models considered here are:

1. Effective population model (destination based), for which

$$K_\ell = \hat{N}_{h,\ell} \tag{27}$$

where

$$\hat{N}_{h,k} = \sum_\ell c_{\ell k}\, N_{h,\ell} \tag{28}$$

is the *effective epidemiological population* at a node k. Recall that N_ℓ is the population with (registered) domicile at node ℓ (see the final comments about the non-trivial interplay between administrative vs. truly biological issues).

2. Mass action model,
$$K_\ell = 1 \tag{29}$$
for which there is no distinction between origin or destination.

3. Area model (destination based) with
$$K_j = N_j \tag{30}$$

4. Human behaviour model based (origin based) with
$$K_i = N_i \tag{31}$$

Remark 2. *Clearly, if $C = I$ (no circulation) each of the four models reduce to n uncoupled systems, having the basic form (1), with the same parameters, except for the recruiting rates.*

4.3 Equations for the prevalences

We can now write a system of $3n$ ODEs in terms of the prevalences
$$X_i = \frac{S_{h,i}}{\bar{N}} \ , \ Y_i = \frac{I_{h,i}}{\bar{N}} \ , \ Z_i = \frac{I_{v,i}}{\bar{V}}. \tag{32}$$
relative to the total steady state populations, which will hold for all the four models. In compact form, we have
$$\left\{ \begin{array}{ll} \dot{X} = & \mu_h \ (F_h - X) - \delta \, \mathrm{diag}(X) \, A \, Z \\ \dot{Y} = & \delta \, \mathrm{diag}(X) \, A \, Z - (\mu_h + \gamma_h) \, Y \\ \dot{Z} = & \sigma \, \mathrm{diag}(F_v - Z) A^T \, Y - \mu_v \, Z. \end{array} \right. \tag{33}$$
or, more explicitly,
$$\left\{ \begin{array}{ll} \dot{X}_i = & \mu_h \, \bar{F}_{h,i} - \delta \, X_i \left(\sum_{j=1}^{n} a_{ij} \, Z_j \right) - \mu_h \, X_i \\ \\ \dot{Y}_i = & \delta \, X_i \left(\sum_{j=1}^{n} a_{ij} \, Z_j \right) - (\gamma_h \ + \mu_h) \, Y_i \\ \\ \dot{Z}_i = & \sigma \ \left(\bar{F}_{v,i} - Z_i \right) \left(\sum_{j=1}^{n} a_{ji} \, Y_j \right) - \mu_v \, Z_i, \end{array} \right. \tag{34}$$

5 Relationships among the reproduction numbers

Definition 4.

- *Uniform reproduction number:*

$$\widetilde{R_0}^2 = \frac{b^2\beta_h\beta_v\bar{m}}{\mu_v(\mu_h+\gamma_h)} (= \frac{\sigma\delta}{\mu_v(\mu_h+\gamma_h)}) \,, \tag{35}$$

  where δ and σ are defined in Table 1.

  It is the basic reproduction disregarding the movement and non-uniformity in the region, and therefore using a single patch model for the whole region.

- *Local basic reproduction numbers $R_0^{i,\mathrm{loc}}$. It is the reproduction number that we will get, for the uncoupled systems when $C = I$. It is sufficient to assume that patch i is isolated: there are no visits from other patches and the hosts of this peculiar patch do not visit the other patches.*

- *Network reproduction number R_0^{network}: it is defined by the formula*

$$R_0^{\mathrm{network}} = \widetilde{R_0}\,\sigma_1(L)\,. \tag{36}$$

  where $\sigma_1(L)$ is largest singular value of the balanced circulation matrix L.

As we shall see below, host movement, and differences on demographics (density distributions of both hosts and vectors) combine to either amplify, or reduce, the uniform reproduction number - to yield the network reproduction number. If the density distributions $\bar{F}_h$ of hosts and $\bar{F}_v$ of vectors are uniform, and if the circulation matrix is bi-stochastic, i.e., if host movements does not break such uniformity, then we will show (Corollary 1) that $\widetilde{R_0}$ is the correct basic reproduction number for the whole region as if it were a *single* patch.

5.1 Results

Let J be the Jacobin of (34) at the DFE. We introduce the notation

$$c = \frac{\mu_v+\mu_h+\gamma_h}{2} \quad , \quad d = \mu_v\,(\mu_h+\gamma_h) \tag{37}$$

Theorem 1.

1. *The local reproduction numbers satisfy*

$$R_0^{i,\mathrm{loc}} = \widetilde{R_0}\sqrt{\frac{F_{v,i}}{F_{h,i}}}\,. \tag{38}$$

2. *All the eigenvalues of J are real. The largest one is given by*

$$-\,c + \sqrt{c^2 + d(R_0^2-1)} \tag{39}$$

   where R_o is the network reproduction number given by (36).

3. *If $R_0 < 1$ then J is negative definite; if $R_0 > 1$ then J has at least one positive eigenvalue. In particular, if $R_0 < 1$ then the DFE is locally stable, and if $R_0 > 1$ the DFE is locally unstable.*

The proof is given in appendix B. Equation (36) states that $\hat{\theta}$ is actually a *correction factor* on the uniform reproduction number $\widetilde{R_0}$ yielding the *network reproduction number*. The balanced circulation matrix L is given in §1.1. Its expression varies according to the model considered for the contact rates.

We also present a corollary, which shows that is not every heterogeneity that yields a change in the reproductive number. If the circulation is balanced then the uniform R_0 is the appropriate threshold parameter.

Corollary 1. *If $F_h = F_v = 1/n\,\mathbb{1}$, and C is doubly stochastic, then*

$$R_0^{\text{network}} = \widetilde{R_0}\,.$$

5.2 Additional results

We now present a number of additional results that might help to illuminate the behaviour of the circulation modified dynamics.

For the case of the origin dependent model we have the following result. We denote by

$$R_0^{i,j,\text{loc}}$$

the local reproduction number at node j, taking the vector density there as $\bar{F}_{v,j}$ and *as if* the host density there was $\bar{F}_{h,i}$. We define the *movement averaged reproduction number at region j* as:

$$\hat{R}_0^j = \sum_{i=1}^{n} C_{i,j} R_0^{i,j,\text{loc}}. \tag{40}$$

and we define the *the averaged global reproduction number* as

$$\hat{R}_0 = \frac{1}{n} \sum_{j=1}^{n} \hat{R}_0^j. \tag{41}$$

Proposition 1.

$$R_0 \geq \hat{R}_0\ . \tag{42}$$

The proof is given in Appendix C.

Finally, motivated by some of the examples in the next section, we have obtained a mathematical result about the effect of control on a given patch:

Proposition 2. *Assume that a fraction α of mosquitoes was slayed in region k. Denote the modified network reproduction number by $\bar{R}_0(\alpha)$. Then, $\bar{R}_0$ is a non-increasing function of α, and we have the bound*

$$(1-\alpha)^{1/2} R_0^{\text{network}} \leq \bar{R}_0(\alpha). \tag{43}$$

The proof is given in Appendix D.

6 An exploratory numerical study

The purpose of these examples is to show that the epidemiological outcomes are very sensitive to human circulation. Here we consider only the origin to destination model. Imagine a hypothetical city divided into three regions:

- the city centre (Region 0)
- a better infra structured area (Region 1), and
- a poorer infra structured area (Region 2).

The city centre (Region 0) is where a large a number of inhabitants holds their jobs, and receive a large flow from both Region 1 and 2; the outflow of the city centre is very small. Region 1 has a significant outflow to the city centre, but the majority of the inhabitants stay within the region. Also, there is some small outflow to Region 2. Finally, Region 2 has a large outflow to the city centre, and a significant outflow to Region 1, while only a small fraction of inhabitants stay within the region. The connectivity graph of such a city, not including loops, is given in Figure 1.

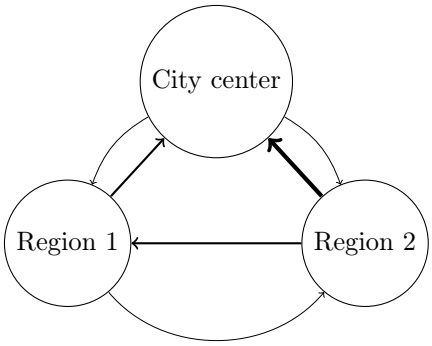


Figure 1: Connectivity graph for a hypothetical city. Notice that the thickness of the edges is proportional to the population flow along them.

We consider the following circulation matrix:

$$C = \begin{pmatrix} 0.9 & 0.3 & 0.6 \\ 0.05 & 0.6 & 0.3 \\ 0.05 & 0.1 & 0.1 \end{pmatrix} \tag{44}$$

which is consistent with the description above. Moreover, we took the total host population as $N = 300,000$, and the total vector population as $V = 30,000$. The host densities at each region were chosen to be 0.1, 0.35, and 0.55 respectively. Following Nishiura (2006), we take $\beta_v = \beta_h = 0.4$, $b = 1.0$, $\mu_h = 0.00004$, $\mu_v = 0.25$ and $\gamma = 0.167$. For these parameter values, the uniform basic reproduction number, as defined by (35), can be computed to be:

$$\widetilde{R_0} = 0.61906.$$

Therefore, if we disregard the internal movement of the city, and if we make the assumption that both hosts and vectors are homogeneously distributed, so as to use a single patch model, we would conclude that we should be in a non-epidemic situation.

Nevertheless, we shall now investigate the influence of both non-uniformity and circulation. In order to do this, we first study various possible combinations of *vector densities* distribution, and compute the local R_0^i and R_0^{network}. More specifically, we allow the vector incidence in the City Centre, $F_{v,1}$, to vary from 0.05 to 0.9 in the city centre. Meanwhile the vector incidence in Region 1, $F_{v,2}$, varies from 0.0 to $0.9 - F_{v,1}$, leaving the corresponding incidence for Region 2 as $F_{v,3} = 1 - F_{v,1} - F_{v,2}$. The results of such calculations are given in Figure 2.

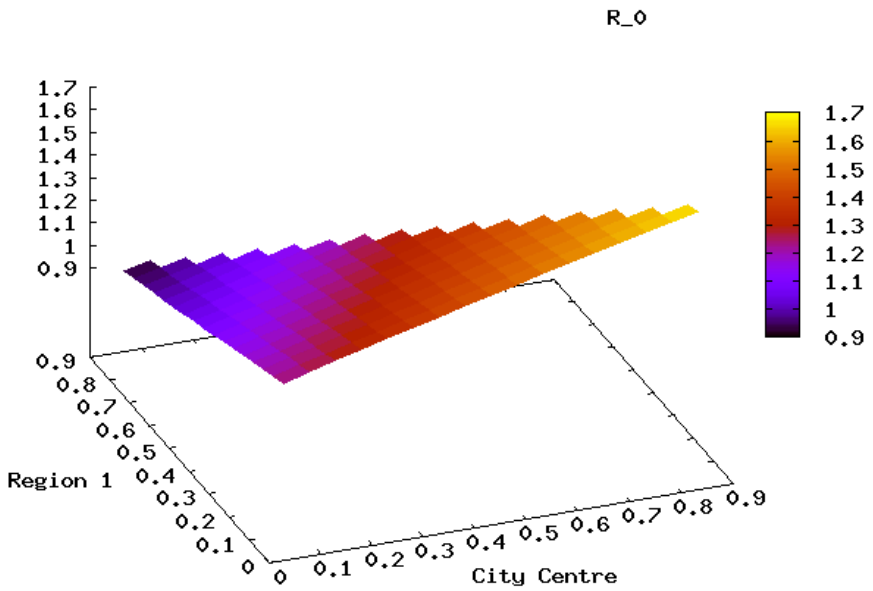


Figure 2: R_0^{network} *for various distributions of vector densities in the three regions. It can vary from 0.9 to 1.7. It is more sensible to variations in the city centre region than on the others.*

In order to bring attention and to make more precise the effects of circulation, in contradistinction to the effects of non-uniformity in densities, we focus on two specific distribution of hosts and vectors distributions taken from batch displayed in Figure 2. These are given, with some further information, in Tables 2 and 3.

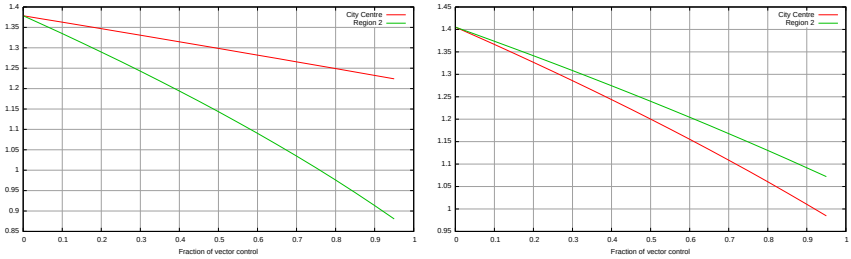
Regions	Host Density	Vector Density	R_0^{loc}	R_0^{newtork}
center	0.1	0.15	0.76	
1	0.35	0.05	0.23	1.29
2	0.55	0.8	0.75	

Table 2: *In this example, taken from the batch computed previously and displayed in figure 2, we see that it is possible that one has* $\widetilde{R_0} < 1$*, and also each* $R_0^{\text{loc}} < 1$*, but with the global* $R_0^{\text{network}} > 1$*. In particular, this shows an example where both an aggregated analysis (with uniformity and no movement assumptions) and an area by area analysis would both predict disease extinction. Our analysis, however, clearly indicates disease outbreak. Notice that the outbreak will affect Region 1, although its local reproduction number* $R_0^{\text{loc}} = 0.23$*, which is very low.*

Regions	Host Density	Vector Density	R_0^{loc}	R_0^{network}
center	0.1	0.35	1.16	
1	0.35	0.05	0.23	1.41
2	0.55	0.6	0.65	

Table 3: *In this example, taken from the batch computed previously and displayed in figure 2, we see that it is possible that one has* $\widetilde{R_0} < 1$*, and also* $R_0^{\text{loc}} < 1$ *for Regions 1 and 2. However, in this case, we have* $R_0^{\text{loc}} > 1$ *for the city centre, and also the global* $R_0^{\text{network}} > 1$*. In this example, an aggregated analysis (with uniformity and no movement) would predict disease extinction, whereas an area by area analysis would predict a localized outbreak only in the city centre. Once again, the analysis of the patchy model clearly predicts the disease outbreak in the whole city.*

To conclude the section we present a result with a bias to further studies on outbreak control measures. It has been recognized that the network topology is often important in epidemiological models, and the concept of a *super hub* (SH) is a recurrent one (Stein 2011; Lloyd-Smith et al. 2005; Galvani and May 2005; Paull et al. 2011; Callaway et al. 2000). A SH can be described as a node that enhances diffusion of its state in the network. When a node that is a SH gets infected, it spreads the infection everywhere in the network, while if it is not infected, the disease cannot be endemic. In the current model, it is tempting to assert that the center region described above would be a SH. Thus, we investigate what happens to R_0^{network} when we apply vector control either to the center or to Region 2. The results are depicted in Figure 3.



(a) Example from Table 2 (b) Example from Table 3

Figure 3: *In 3a we see that a decrease in mosquitoes in the city centre reduces* R_0^{network}*, however not enough to prevent an outbreak even when the control reaches 95% of mosquito population in the region. When vector control is done in Region 2, we then see a much larger decreasing of* R_0^{network}*, leading to outbreak prevention when the control reaches about 80% of the mosquito population in the region. Nevertheless, for a given fraction of the total population to be slayed, the reduction in* R_0^{network} *is larger for interventions on the city centre. On the other hand, in 3b, we see exactly the opposite behaviour. In particular, controlling one third of the total mosquito population is sufficient, provided that such control is done in the centre.*

The above results show that the ultimate outbreak behaviour seems to be a complex combination of vectors and host densities distributions, together with particular features of a given circulation matrix. In particular, for the examples above the following conclusions seem to emerge:

1. For a given level of mosquito control, it always more efficient to perform the control on the centre, than on any other region—although for some densities distributions, it might not prevent outbreak.

2. When the mosquitoes eliminated are in the center, we observe that both $\widetilde{R_0}$ and $\hat{\theta}$ decrease. On the other hand, when we eliminate mosquitoes from the other regions, we see that $\widetilde{R_0}$ decreases, but $\hat{\theta}$ increases. In all examples investigated the net behaviour of vector control was to promote a decreasing in R_0^{newtork}.

This case study motivated Proposition 2, stated for the origin based model with $K_i = N_i$. Analogous results should hold for the other model types.

7 Discussion

In this paper we focused on defining three reproduction ratios (uniform, local and network), and finding their relationships. We apply the concept to a metapopulation model of a vector borne disease, where the patches are coupled by human circulation.

We chose to present a simple vector-host model at the nodes, so that the formulas became transparent. The modelling can be refined to consider other factors for which data are available. In Lunelli et al. (2009), the geographic regions are further subdivided according to age structure and social characteristics. The latter can be associated to activity (e.g. schools, factories) or to behaviour (e.g. drug use, sexual habits). Sometimes the effect of human (and animal) movements on disease spread must be traced to individual level, see Keeling et al. (2010).

7.1 The three R_0's

The numerical experiments go in line with some of the caveats about the "failure" of R_0, see Roberts (2007), Li et al. (2011), Heffernan and Smith (2005), Massad and Coutinho (2012), but we hope to have found more "pros" than "cons".

The basic reproduction ratio (6) is the classical Ross-Macdonald one for mosquito-borne diseases (Smith et al., 2012) and as usual in epidemiology it gives the average number of new humans infected when a single infected human enters a completely susceptible (vector and host) population. This interpretation holds true for the uniform and for the local reproduction numbers.

We are confident that the same interpretation also holds for the network reproduction number, since it is the uniform reproduction number corrected by the factor $\sigma_1(L)$. Proposition 1 is a strong indicator in this direction.

The general ideas about the " three R_0's " considered here also appear in other areas where distributed dynamical systems over networks are used for modelling. We mention just two examples. In Gatto et al. (2012) a model for a waterborne disease (such as cholera) is presented, taking into account the influence of human mobility together with hydrological data. In ecology there is an honourable tradition in studies about competition in patchy environments, and circulation of agents can also be a determining factor, see Schreiber and Lloyd-Smith (2009).

7.2 Superspreaders

In the examples we have just touched the possible special role of certain areas of a town: the city center, market zones, the beach, etc. The following quote is intriguing: "In contrast to previous common wisdom that epidemic activity in heterogeneous networks is dominated by the hubs with the largest number of connections, recent research has pointed out the role that the innermost, dense core of the network plays in sustaining epidemic processes (Castellano and Pastor-Satorras, 2012)."

7.3 More general transmission functions

We assumed that the transmission functions are bilinear on the susceptible and infected populations. Nonetheless, we presented the general model in a way that general functional forms could be used. *Power laws* $r(S, I) = \beta S^p I^q$ are mathematically convenient since the ODES can be rewritten in terms of *prevalences*. Moreover, it has been asserted that power laws not only provide a wide range of possible dynamic behaviour (Liu et al., 1987) but also improve accuracy of mean-field SIR models (Novozhilov, 2008).

7.4 An inverse problem

A disease notification from a given patch does not tell, offhand, where the infection actually took place. Estimating $I_{h,i}(t)$, the number of infected humans with domicile at patch i could be be helpful to plan medical assistance, but for the sake of control measures it would be more important to identify the most important nodes where the infections are occurring.

7.5 Final size of the epidemics

In our paper, we do not address the question of the *final size* of the epidemics. In the sequel paper we show the existence and uniqueness of the endemic equilibrium. However, our preliminary numerical simulations indicate that the convergence may be very slow.

We mention two recent studies in this direction in the case of direct contact diseases. Andreasen (2011) showed that if the heterogeneities arise only from variation in contact rates and proportionate mixing, the final size of the epidemic in a heterogeneously mixing population is always smaller than that in a homogeneously mixing population with the same basic reproduction number. Interestingly, the relation may be reversed for other mixing patterns. Katriel (2012) considers a general epidemic model with a continuous distribution of susceptibility in the population. It is possible then to estimate the effect of vaccination of a fraction of the population, with a partially effective vaccine and the effect of an epidemic of a pathogen inducing partial immunity on the size of a future epidemic (issues that are of relevance for dengue).

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Appendix A Basic model: vector density and $\mathcal{R}_0$

The compact K defined by

$$K = \{(S_h, I_h, R_h, S_v, I_v) \in \mathbb{R}^5_+ \mid S_h + I_h + R_h \leq \bar{N} \quad , \quad S_v + I_v \leq \bar{V}\},$$

is a positively invariant absorbing compact set for system (1). We can replace the two last equations of (1) by

$$\begin{cases} \dot{I}_v = & \beta_2 \frac{S_v I_h}{N_h} - \mu_v I_v \\ \dot{N}_v = & \Lambda_v - \mu_v N_v, \end{cases}$$

with $S_v = N_v - I_V$ to obtain an equivalent system. The following result allow us to reduce the stability analysis to a smaller system:

Theorem 2 (Vidyasagar (1980), Theorem 3.1)**.** *Consider the $\mathcal{C}^1$ system*

$$\begin{cases} \dot{x} = f(x) \\ \dot{y} = g(x, y) \end{cases} \tag{45}$$

for $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$ with an equilibrium point,(x^*, y^*). If x^* is globally asymptotically stable (GAS) in $\mathbb{R}^n$for the system $\dot{x} = f(x)$, and if y^* is GAS in $\mathbb{R}^m$ for the system $\dot{y} = g(x^*, y)$, then (x^*, y^*) is (locally) asymptotically stable for (45). Moreover, if all trajectories of (45) are forward bounded, then (x^*, y^*) is GAS for (45).

Again replacing the equation for $\dot{R}_h$ by $\dot{N}_h = \Lambda_h - \mu_h N_h$, remarking that K is absorbing, using the same argument of triangularity we see that the stability analysis of system (1) is equivalent to the stability analysis of the following system

$$\begin{cases} \dot{S}_h = & \mu_h \bar{N} - \frac{\beta_1}{\bar{N}} S_h I_v - \mu_h S_h \\ \dot{I}_h = & \frac{\beta_1}{\bar{N}} S_h I_v - (\mu_h + \gamma_h) I_h \\ \dot{I}_v = & \frac{\beta_2}{\bar{N}} (\bar{V} - I_v) I_h - \mu_v I_v, \end{cases} \tag{46}$$

defined on

$$\bar{K} = \{(S_h, I_h, I_v) \in \mathbb{R}^3_+ \mid S_h + I_h \leq \bar{N} \ , \ I_v \leq \bar{V}\}.$$

Following Ross' viewpoint, we write the equations in terms of *prevalences*.

Definition 5. *(the 1-patch system in terms of prevalences)*

$$\begin{cases} \dot{x}_1 = & \mu_h \ - \beta_1 \, m \, x_1 \, y - \mu_h \, x_1 \\ \dot{x}_2 = & \beta_1 \, m \, x_1 \, y - (\mu_h + \gamma_h) \, x_2 \\ \dot{y} = & \beta_2 \, (1 - y) \, x_2 - \mu_v \, y \end{cases} \tag{47}$$

where

$$x_1 = \frac{S_h}{\bar{N}} \ , \ x_2 = \frac{I_h}{\bar{N}} \ , \ y = \frac{I_v}{\bar{V}} \ . \tag{48}$$

Now this system is defined on the compact absorbing set

$$\Omega = \{(x_1, x_2, z) \in \mathbb{R}^3 \ \mid \ x_1 + x_2 \leq 1 \quad y \leq 1\} \ .$$

Two equilibria can exist : the disease free equilibrium $(\mathbf{1}, 0, \mathbf{0})$ and, when $\mathcal{R}_0 > 1$, an endemic equilibrium $(\bar{x}_1, \bar{x}_2, \bar{y}) \in \Omega$ given by

$$\bar{x}_1 = \frac{1 + \frac{1}{\mathcal{R}_0} \frac{\beta_1 \, m}{\mu_h}}{1 + \frac{\beta_1 \, m}{\mu_h}} \qquad \bar{x}_2 = \frac{\mu_h}{\mu_h + \gamma_h} \frac{1 - \frac{1}{\mathcal{R}_0}}{1 + \frac{\mu_h}{\beta_1 \, m}} \qquad \bar{y} = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0 + \frac{\beta_1 \, m}{\mu_h}}.$$

We now show have the following result:

Proposition 3. *Let*

$$\mathcal{R}_0^2 = \frac{\beta_1 \, \beta_2 \, m}{\mu_v \, (\mu_h + \gamma_h)}. \tag{49}$$

If $\mathcal{R}_0 \leq 1$ then the disease free equilibrium of system (1) is globally asymptotically stable on its domain. If $\mathcal{R}_0 > 1$ then there exists an unique endemic equilibrium which is globally asymptotically stable.

Proof. (We use the proof given in Souza (2013).)
The global stability of the DFE, when $\mathcal{R}_0 \leq 1$ is obtained by using the Lyapunov function on $\mathbb{R}_{+,*} \times R \times R_*$ defined by

$$V(x_1, x_2, y) = x_1 - \ln x_1 + x_2 + \frac{\beta_1 \, m}{\mu_h} \ln y.$$

When $\mathcal{R}_0 > 1$, the following Volterra-Lyapunov function (see Fall et al. (2007); Korobeinikov (2004); Thieme (2009),...) , defined on the interior of Ω, is used

$$V(x_1, x_2, y) = \left((x_1 - \bar{x}_1 \ \ln \frac{x_1}{\bar{x}_1} \right) + \left((x_2 - \bar{x}_2 \ \ln \frac{x_2}{\bar{x}_2} \right) + \frac{\beta_1 \, m \, \bar{x}_1}{\mu_v} \ \left(y - \bar{y} \ \ln \frac{y}{\bar{y}} \right).$$

The computations are done in Souza (2013), the two functions are strict Lyapunov functions. □ □

Appendix B Proof of Main Theorem and Corollaries

Our system (34) has $(F_h, 0, 0)$ as an equilibrium—termed the *disease free equilibrium* (DFE). Since we are interested in defining a threshold parameter for the model, we must study the stability of the the DFE. The Jacobian of System 33 at the DFE is given by

$$J = \begin{pmatrix} -\mu_h I & 0 & -\delta D_h A \\ 0 & -(\mu_h + \gamma_h) I & \delta D_h A \\ 0 & \sigma D_v A^t & -\mu_v I \end{pmatrix} \tag{50}$$

Thus we have that the spectrum of J is

$$\sigma(J) = \{-\mu_h\} \cup \sigma(\hat{J}), \qquad \hat{J} = \begin{pmatrix} -(\mu_h + \gamma_h) I & \delta D_h A \\ \sigma D_v A^t & -\mu_v I \end{pmatrix}. \tag{51}$$

The eigenvectors of the $2n \times 2n$ matrix $\hat{J}$ have a very special structure that can used to characterize local stability in terms of the uniform replication rate and the correction factor. As we anticipated, instrumental for the proof will be the *balanced interaction matrix* L.

B.1 Proof of the Main Theorem

The core of proof is an elementary observation that $\hat{J}$ is similar to a Metzler matrix of the form

$$\begin{pmatrix} -2pI & qL \\ rL^t & -2sI \end{pmatrix} , \tag{52}$$

see (B.2) below.

Let W a right singular vector of L associated to a nonzero singular value θ,

$$L^t L W = \theta^2 W \ . \tag{53}$$

It is clear that $Z = LW$ is a left singular vector, also nonzero,

$$L L^t Z = \theta^2 Z \ . \tag{54}$$

Let us try the following ansatz in the spectral equation

$$\begin{pmatrix} -2pI & qL \\ rL^t & -2sI \end{pmatrix} \begin{pmatrix} \rho LW \\ W \end{pmatrix} = \lambda \begin{pmatrix} \rho LW \\ W \end{pmatrix} \tag{55}$$

which gives

$$-2p\rho LW + qLW = \lambda \rho LW \ , \ \ r\rho L^t LW - 2sW = \lambda W$$

and hence two scalar equations

$$-p\rho + q = \lambda\rho \ , \ \ \theta^2 r\rho - s = \lambda \ . \tag{56}$$

Eliminating λ we get a quadratic equation for ρ,

$$\theta^2 r\rho^2 - 2(s-p)\rho - q = 0$$

hence

$$\theta^2 r\rho_\pm = s - p \pm \sqrt{(s-p)^2 + \theta^2 rq} \ .$$

and

$$\lambda_{\pm} = -(p+s) \pm \sqrt{(s-p)^2 + \theta^2 rq}\ . \tag{57}$$

Clearly the eigenvalues are real. The ones that correspond to the plus sign increase with θ. The biggest eigenvalue is

$$\lambda_{\max} = -(p+s) \pm \sqrt{(s-p)^2 + \hat{\theta}^2 rq} \tag{58}$$

where

$$\hat{\theta} = \sigma_1(L) \tag{59}$$

is the biggest singular value of L. We rewrite the expression inside the square root as

$$(s-p)^2 + \hat{\theta}^2 rq = (p+s)^2 + \hat{\theta}^2 rq - 4ps$$

$\lambda_{\max}$ turns from negative to positive when the expression $\hat{\theta}^2 rq - 4ps$ changes sign. Again, as customary in epidemiology, we rewrite it as follows,

$$\hat{\theta}^2 rq - 4ps = 4ps(R_o^2 - 1) \quad , \quad R_o^2 = \hat{\theta}\frac{rq}{4ps} \tag{60}$$

Finally, substituting into $rp/4ps$ the values

$$r = \sigma\ ,\ q = \delta\ ,\ 2p = \mu_h + \gamma_h\ ,\ 2s = \mu_v\ .$$

a true "miracle" happens:

$$\frac{rq}{4ps} = \frac{\sigma\delta}{\mu_v(\mu_h + \gamma_h)} = \widetilde{R_0}^2\ . \tag{61}$$

The expression (39) for the biggest eigenvalue of J follows from inserting (37) in (58). □

B.2 Balancing trick: origin and destination cases

How do we balance $\hat{J}$ into a Metzler matrix like (52) ? For the origin based model $K_i = N_i$ in definition 3 we get we get

$$L = D_h^{-1/2} C D_v^{1/2} \tag{62}$$

via

$$\begin{pmatrix} D_h^{-1/2} & 0 \\ 0 & D_v^{-1/2} \end{pmatrix} \hat{J} \begin{pmatrix} D_h^{1/2} & 0 \\ 0 & D_v^{1/2} \end{pmatrix} = \begin{pmatrix} -(\mu_h + \gamma_h) I & \delta L \\ \sigma L^t & -\mu_v I \end{pmatrix} \tag{63}$$

More generally, for origin $A = A_O$ or destination $A = A_V$ models, the balanced matrix L is given by

$$L_O = D_h^{1/2} D_K^{-1} C D_v^{1/2} \tag{64}$$

$$L_V = D_h^{1/2} C D_K^{-1} D_v^{1/2}. \tag{65}$$

In fact, for the origin dependent model (i.e., $L = L_0$) with $K_i = N_i$ in definition 3 we make $D_K = D_h$. The other choices of models presented in §4.2 are

- Area based model

  $$A = A_V,\ D_K = D_h.$$

  This amounts to take $K_j = N_j$.

- Effective population model

  $$A = A_V,\ D_K = F_h^t C.$$

  This amounts to take $K_j = \sum_{i=1}^{n} F_{h,i} C_{ij}$.

B.3 Proof of Corollary 1

Proof.

$$D_h^{-1/2} = \sqrt{n}\, I \text{ and } D_v^{1/2} = \frac{1}{\sqrt{n}}\, I$$

Hence, $L = C$. But since C is doubly stochastic, we have $\hat{\theta} = 1$. □

□

Appendix C Proof of Proposition 1

Proof.

From the bounds in Nikiforov (2007), we have

$$\hat{\theta} \geq \frac{1}{n} \sum_{i,j=1}^{n} L_{i,j}.$$

On using the definitions of L and R_0, we find that

$$\begin{aligned} R_0 &= \widetilde{R_0}\hat{\theta} \\ &\geq \widetilde{R_0} \frac{1}{n} \sum_{i,j=1}^{n} L_{i,j} \\ &= \frac{1}{n} \sum_{j=1}^{n} \sum_{i=1}^{n} C_{i,j} \widetilde{R_0} \left(\frac{F_{v,j}}{F_{h,i}} \right)^{1/2} \\ &= \frac{1}{n} \sum_{j=1}^{n} \sum_{i=1}^{n} C_{i,j} R_0^{i,j,\mathrm{loc}} \\ &= \frac{1}{n} \sum_{j=1}^{n} \hat{R}_0^j = \hat{R}_0. \end{aligned}$$

□ □

Appendix D Proof of Proposition 2

Proof. First notice that, after changing the vector density in region k, we have that the new uniform reproduction number is

$$\widetilde{\bar{R}_0} = \widetilde{R_0} \left(1 - \alpha \bar{F}_{v,k}\right)^{1/2}.$$

On the other hand, we have also a new matrix L given by

$$\bar{L} = L\hat{D}, \qquad \hat{D} = \left(\frac{1}{\mathrm{tr}(D_\alpha D_v)} \right)^{1/2}, \; D_\alpha = \mathrm{diag}(1, 1, \ldots, 1-\alpha, 1, \ldots, 1),$$

where $1-\alpha$ is in the kth position.

Also, we have

$$\mathrm{tr}(D_\alpha D_v) = \sum_{i=1 i\neq k}^{n} \bar{F}_{v,i} + (1-\alpha)\bar{F}_{v,k} = 1 - \alpha\bar{F}_{v,k}.$$

On one hand, a standard majorization argument, see Horn and Johnson (1990) for instance, this yields

$$\sigma_1(L\hat{D}) \leq \sigma_1(L)\sigma_1(\hat{D}) = \frac{1}{\left(1-\alpha\bar{F}_{v,k}\right)^{1/2}}.$$

Hence, multiplication by $\widetilde{\bar{R}_0}$ yields

$$\bar{R}_0(\alpha) \leq R_0.$$

This argument can be repeated replacing R_0 with $R_0(\alpha)$, and this shows that $\bar{R}_0(\alpha)$ is non-increasing.

Finally, again by a majorization result in singular values of products (cf. Horn and Johnson (1991) for instance), we have

$$\sigma_1(L\hat{D}) \geq \sigma_1(L)\sigma_n(\hat{D}) = \left(\frac{1-\alpha}{1-\alpha\bar{F}_{v,k}}\right)^{1/2}.$$

and the lower bound follows analogously. □ □

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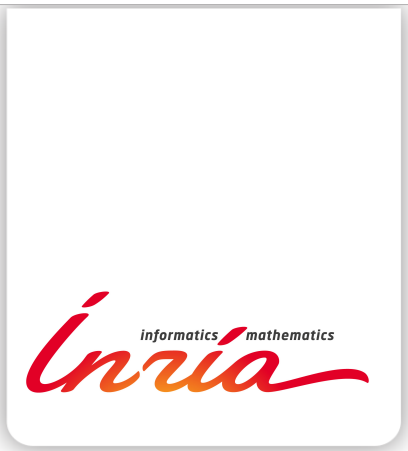

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