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Algorithmic Approach for a Unique Definition of the Next-Generation Matrix

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Abstract: The basic reproduction number R_0 is a concept which originated in population dynamics, mathematical epidemiology, and ecology and is closely related to the mean number of children in branching processes (reflecting the fact that the phenomena of interest are well approximated via branching processes, at their inception). Despite the very extensive literature around R_0 for deterministic epidemic models, we believe there are still aspects which are not fully understood. Foremost is the fact that R_0 is not a function of the original ODE model, unless we also include in it a certain (F, V) gradient decomposition, which is not unique. This is related to the specification of the "infected compartments", which is also not unique. A second interesting question is whether the extinction probabilities of the natural continuous time Markovian chain approximation of an ODE model around boundary points (disease-free equilibrium and invasion points) are also related to the (F, V) gradient decomposition. We offer below several new contributions to the literature: (1) A universal algorithmic definition of a (F, V) gradient decomposition (and hence of the resulting R_0). (2) A fixed point equation for the extinction probabilities of a stochastic model associated to a deterministic ODE model, which may be expressed in terms of the (F, V) decomposition. Last but not least, we offer Mathematica scripts and implement them for a large variety of examples, which illustrate that our recipe offers always reasonable results, but that sometimes other reasonable (F, V) decompositions are available as well.

Keywords: deterministic epidemic model; disease-free equilibrium; stability threshold; basic reproduction number; (F, V) gradient decomposition; next-generation matrix; Jacobian approach; CTMC stochastic model associated to a deterministic epidemic model; probability of extinction; rational univariate representation

MSC: 34D20; 65L07; 37N30

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1. Introduction

Motivation. Mathematical epidemiology had started by proposing simple models for specific epidemics and computing explicitly certain important characteristics like the basic reproduction number and the final size; for example, the SIR model was introduced, among other concepts, in the celebrated "A contribution to the mathematical theory of epidemics" [1]. The most fundamental, and actually the only general result of the field due to Diekmann, Heesterbeek, Van den Driesche and Watmough, expresses the disease-free equilibrium stability domain in terms of R_0, which is defined as the Perron–Frobenius eigenvalue of a certain (F, V) gradient decomposition (this is presented in detail in Section 2.2).

But, since the (F, V) decomposition is not unique, it seems to us that the question of what R_0 is still deserves further discussion.

On the other hand, one may note that nowadays, mathematical epidemiologists typically either restrict themselves to low-dimensional models, resolved symbolically, even by hand, or consider very complicated models which are resolved only numerically, for particular values gleaned from the medical literature. Missing from here are moderately complex models, which may be solved partly symbolically for any values of the parameters, but in a way where the use of computer algebra systems (CAS) is either indispensable or greatly facilitating. Even in the case of papers belonging to this level—see, for example [2], that the role of the CAS is deemphasized. Our paper is also an attempt to cast the CAS as one of the main heroes of our story.

Our main result . We provide below, for the first time, a universal recipe for choosing a natural (F, V) gradient decomposition, which only requires specifying the disease compartments (a subset of those which are zero for the boundary point under consideration) (informally, these are not far conceptually from the so-called fast components of singular perturbation theory). This decomposition is useful both for determining R_0 and for computing the extinction probabilities of an associated stochastic model. We identify also examples in which the (F, V) decomposition is not unique and in which choosing another decomposition with F of a lower rank may be beneficial for simplifying the R_0 formula.

First restriction (among others to follow). In this paper, we will restrict to mathematical epidemiology models for which there exist at least two possible special fixed states. The first, the disease-free equilibrium (DFE), corresponds to the elimination of all possible compartments involving sickness and will be assumed to be unique. Typically, this point is locally stable only for certain values of the parameters. Outside of this domain, it is typically replaced by another fixed point, which will be called "endemic" if all its components are positive, and "resident boundary point" otherwise.

Importantly, the stability of the DFE may be related to the historically famous **basic reproduction number** and **net reproduction rate**—see (1). These pillar concepts in population dynamics, mathematical epidemiology, virology, ecology, etc., were already introduced by the father of mathematical demography Lotka—see [3,4]—and also the introduction of the book [5], and in [6], the authors described the stability of the solution of differential systems.

A bit of history of the net reproduction rate $\mathcal{R}$, and its evolution into the mathematical concept of basic reproduction number/stability threshold R_0. Loosely speaking, in the case of only one infectious class, the net reproduction rate $\mathcal{R}$ describes the expected number of secondary cases which **one infected case** would produce in a homogeneous, completely susceptible population during the lifetime of the infection. This description is especially relevant at the start of an epidemic, when the dynamics is well approximated by that of a branching process (a fact which goes back to Bartlett and Kendall—see for example [7,8]). The main characteristic of a branching process is the "fertility", i.e., the expected number of descendants one individual produces in the next generation. As a consequence, in epidemiology, the branching result insuring extinction when the fertility is less than one translates into local stability results of the disease-free equilibrium involving $\mathcal{R}$.

The reproduction number $\mathcal{R}$ intervened already, in a particular case, in the foundational paper "A contribution to the mathematical theory of epidemics" [1], which showed that:

1. The condition
$$R_0 < 1, \quad \text{where } R_0 = \mathsf{s}_{dfe}\mathcal{R}, \tag{1}$$
implies local stability of the DFE. Here $\mathcal{R}$ is the net reproduction rate (number of secondary infections produced by one infectious individual), and s_{dfe} is the fraction of susceptibles at the DFE.
2. The condition
$$R_0 > 1$$
implies instability of the DFE.

With more infectious classes, one deals, at the inception of an epidemic, with approximate multi-class branching processes, whose stability is determined via a "**next-generation matrix** " (NGM)—see Section 2.2.

The "Jacobian approach" for computing R_0. For big size problems, this approach is doomed to fail symbolically, since it is equivalent to the Routh–Hurwitz conditions (RH), which rarely succeed symbolically beyond dimension 4 (also, RH is irrelevant numerically, since the eigenvalues themselves are just as easy to compute). Therefore, we studied below a variant, the "Jacobian factorization approach", which focuses on an approximation, which we show to yield always upper or lower bounds of the NGM R_0, depending on whether $R_0 \leq 1$ or not—see Theorem 1. Several questions around this bound are scattered below in Sections 6.3, 8.1, and 8.2.

Note, as mentioned in [9], that an example where the Jacobian method does not yield R_0 is offered in [10] (Exe 5.43) and that of [11] suggesting that when threshold parameters determined from the Jacobian do not have the biological interpretation of the dominant eigenvalue of the next-generation matrix, then they should not be called basic reproductive ratios nor denoted as R_0 (we follow their suggestion and use the notation R_J in this case).

The dilemma of the several different methods for computing R_0 has been discussed in many papers, see for example [9,12]. But, this is a direct consequence of the non-uniqueness of the (F, V) decomposition.

Deterministic or stochastic models? Most of the mathematical epidemiology papers belong exclusively to one of these two paradigms. However, any deterministic model may also be viewed as a stochastic continuous time Markov field (CTMC) evolving on the integers. One interesting CTMC, which seems not to have been discussed before, is presented in Section 2.4.

Contents. Our paper is structured as follows. Section 2 recalls the definition of the DFE and provides our algorithmic definition of the (F,V) decomposition, in the form of a Mathematica script, as well as a discussion—see Remark 6—of why other decompositions might turn out useful. This section also provides a new Equation (8) for computing extinction probabilities for associated continuous time Markov chain models in terms of the (F, V) decomposition, showing that the Jacobian factorization approach yields upper bounds and lower bounds for NGM R_0's in Appendix A.

We turn then to a series of examples, chosen to help investigate what may be the major open problem in the field nowadays, which, in our opinion, relates on one hand to R_0, and on the other hand, to the extinction probabilities—see below—and duration of minor epidemics [13–17], which is not further touched on here.

Let us now briefly explain why so many examples were included in the paper.

Section 4 is dedicated to a host-only model, with a single susceptible class and an F matrix of rank one, where the formula of R_0 may be "guessed by inspection" of the flow chart. These kinds of examples have kept alive the hope of "interpretable R_0 formulas", as illustrated in other recent papers—see for example [18,19]. But in fact, as far as we know, no interpretable R_0 formula has emerged outside the rank one case, which is already fully studied in [20]. The papers [18,19] start by presenting simple rank one cases, then proposing algorithms for more complex cases based on the graph structure of the flow chart, which, in our opinion, are not sufficiently detailed or documented. While it may well be that tools like Petri nets, as proposed in the second paper, will one day succeed for resolving flow charts with certain structures, this does not seem to have happened yet. Also, for models with a next-generation matrix of high rank, the lack of simple formulas for R_0 and of "simple biological interpretations" is naturally to be expected; simple formulas for the spectral radius can only be a consequence of a simple graph structure which has not been pinpointed yet.

Sections 5.1 and 7.1 offer two examples in which several R_0 formulas were offered in the literature, but we are at a loss of how to choose among them. In the first case (a virus–tumor model), the recipe R_0 is simpler than its competitor, but in the second case (a vector–host model), it is more complicated.

Section 6.2 shows that the boundary equilibria and the (invasion) reproduction numbers may be easily computed with our scripts; to illustrate this, we use a two-strain host-only model from [21] (Ch.8), where our recipe NGM yields the same answer as that given by the Jacobian factorization.

Section 6.3 offers another two-strain host-only example, this time including also vaccination, in which our recipe NGM yields again the same answer as that given by the Jacobian factorization.

Section 7.2 offers an example from the textbook of [21] in which the square relation stops holding.

Sections 8.1 and 8.2 offer yet more examples, this time in the two-strain vector–host context, in which our recipe NGM yields an R_0 formula which is precisely the square root of that given by the Jacobian approach. Note that here, the first of the three elegant relations concerning the invasion numbers from Section 6.3—see Remark 22—holds, but the other two seem to break down.

The last subsection provides, for the invasion numbers, a second example where another choice of R_0 may be more reasonable, on the grounds of leading to a simpler answer (but the admissibility requirement forces then extra assumptions on the parameters).

2. A Bird's Eye View of Mathematical Epidemiology: The Disease-Free Equilibrium, the Next-Generation Matrix, and an Algorithmic Definition of a Stability Threshold Associated to the Basic Reproduction Number R_0

2.1. The Disease-Free Equilibrium (DFE)

The DFE may be defined as a "maximal boundary state" and may be found by identifying a maximal sub-system of the ODE epidemic model which factors

$$\boldsymbol{i}' = M\boldsymbol{i}, \tag{2}$$

where the prime denotes the derivative with respect to time, and M is a matrix that may depend on $\boldsymbol{i}$, but also may not explode in the domain of interest, which we will take for the sake of simplicity to be $\mathbb{R}^n_+$.

Remark 1. *One fixed point of this system is $\boldsymbol{i} = 0$. This motivates us to call the components $\boldsymbol{i}$ disease or infectious states. The set of all its indices will be denoted by $\mathcal{I}$. Note that specifying '$\mathcal{I}$ induces a partition of both the coordinates and the equations of our original system into infection (eliminable) and "non-infection" (the others) components.*

The eventual other fixed points may be found by solving $M = 0$ together with the other non-infection equations under the condition $\boldsymbol{i} = 0$.

In this paper, we will assume the uniqueness of the DFE, at least after excluding biologically irrelevant fixed points, like an unreachable origin.

We end this section with the very elementary script that implements this. Note that any ODE model "mod" (like SIR, etc...) is a pair mod = (dyn,X) consisting of a vector field "dyn" and a list of variables "X", and that to find any boundary fixed point, it suffices to know the set of indices "inf" where it is 0, so that we solve the system "dyn==0" under the condition "X[[inf]]->0". But, since sometimes only numeric solutions are possible, our DFE Mathematica script below also has an optional numerical condition parameter "cn", which is taken by default as the empty set.

```
DFE[mod_,inf_,cn_:{}]:=Module[{dyn,X},
 dyn=mod[[1]]/.cn;X=mod[[2]];
 Solve[Thread[dyn==0]/.Thread[X[[inf]]->0],X]];
```

For the non-Mathematica users, only the Solve command is relevant, with the others being just Mathematica implementation details.

2.2. (F, V) Gradient Decompositions, the Next-Generation Matrix, R_0, and a Simple Recipe for Computing Them

From now on, the infection Equation (2) will be rewritten as

$$\boldsymbol{i}' = \mathcal{F} - \mathcal{V} = (F - V)\boldsymbol{i}. \tag{3}$$

Of course, such a decomposition is not unique, but we will also ask, following [7,22,23], that F, the gradient of $\mathcal{F}$, is a matrix with non-negative elements, and $-V$, the gradient of $-\mathcal{V}$, is a Markovian generating matrix (i.e., a matrix with non-negative off-diagonal elements and non-positive row sums). Conceptually, F models input to the disease compartments from outside ("new infections"), and $-V$ models transfer between the disease compartments. Still, a priori, the decomposition (3) is not unique.

Example 1. *Let us illustrate this via an SIR example with superinfection parameter ξ, in which the classes S and R play symmetric roles inspired by the works of [24–26]*

$$\begin{cases} \mathsf{s}'(t) & = \Lambda_s - \mathsf{s}(t)[\beta_s \mathsf{i}(t)(1 + \xi \mathsf{i}(t)) + d_s] + i_s \mathsf{i}(t) + \gamma_r \mathsf{r}(t) \\ \mathsf{i}'(t) & = \mathsf{i}(t)\Big[[\beta_s \mathsf{s}(t) + \beta_r \mathsf{r}(t)](1 + \xi \mathsf{i}(t))\Big] - d_i \mathsf{i}(t), d_i = i_r + i_s + \Lambda_s + \Lambda_r + \delta. \\ \mathsf{r}'(t) & = \Lambda_r - \mathsf{r}(t)[\beta_r \mathsf{i}(t)(1 + \xi \mathsf{i}(t)) + d_r] + i_r \mathsf{i}(t) + \gamma_s \mathsf{s}(t) \end{cases}$$

When $\xi = 0$, this reduces to the symmetric SIR model introduced for mathematical purposes by [25,26], in which births may also directly enter the R class, with parameter Λ_r, and may also infect, with parameter β_r. Furthermore, there are linear flows from i to both s and r, where the former does not make epidemiologic sense.

Here, the only infection equation, the second, is already written in a decomposed form $\mathcal{F} - \mathcal{V}, \mathcal{V} = d_i \mathsf{i}(t)$, and $F = \Big[[\beta_s \mathsf{s}(t) + \beta_r \mathsf{r}(t)](1 + \xi \mathsf{i}(t))\Big] + \xi \mathsf{i}(t)[\beta_s \mathsf{s}(t) + \beta_r \mathsf{r}(t)]$.

Note that for the application of the next-generation matrix method, we must finally plug $\mathsf{i} = 0$; therefore, the second term in F, due to "superinfection", is irrelevant for this purpose.

Remark 2. *The possible non-uniqueness of the decomposition brings us to a delicate point in mathematical epidemiology. Anticipating a bit, since R_0 is the Perron–Frobenius eigenvalue of FV^{-1}, strictly speaking, R_0 is not determined just by an ODE epidemical model, but also by the (F, V) gradient decomposition. If we want an ODE epidemical model to uniquely determine an R_0, we must include, in the definition of the ODE epidemical model, the (F, V) gradient decomposition we also adopt.*

Remark 3. *For us, an ODE epidemic model is an ODE dynamical model in which a certain subset of equations, usually called "disease/infection" equations, referred from now on as a* **zeroable set**, *admits at least one admissible decomposition (3), with $(\mathcal{F}, \mathcal{V})$ satisfying the conditions (A1–A5) of [23].*

Remark 4. *Note that (3) is the most common model used in population dynamics. This makes it natural to informally define ODE epidemic models as population dynamics models (3), with extra equations modeling interactions with the non-disease compartments, which admits at least one admissible decomposition.*

Remark 5. *The definition of ODE epidemic models above is imprecise, since it does not list all the requirements we must put on an ODE model. Some reasonable restrictions are*

1. *Essentially non-negative processes have a non-empty set of disease classes, so we deal with an epidemic (note, however, that we define disease classes in the sense of classes which satisfy (2), which excludes, for example, importation models).*
2. *Processes with a unique DFE, at least after excluding biologically irrelevant fixed points, like an unreachable origin.*
3. *The local stability domain of the DFE is non-empty and not the full set.*

4. *The dynamical system has polynomial coefficients to be able to take advantage of the remarkable symbolic computation tools available for this class.*

We make these assumptions because they are satisfied by most mathematical models which have already been used for modeling real-life biological phenomena. However, these assumptions might not be enough and further ones might be necessary for obtaining the currently missing precise definition of "real life ODE mathematical epidemiology models".

Remark 6. *Admissible decompositions need not be unique. A priori, one may "move terms from F to V", to lower its rank and simplify the formula for R_0, and also "move off-diagonal terms from V to F", which enlarges the domain of parameters which ensure that V^{-1} has positive terms. There is a tradeoff between these two possible moves, since the simplicity of R_0 comes at the cost of extra assumptions on the parameters. Our universal decomposition seems to strike a balance between the two directions.*

Remark 7. *It was emphasized from the outstart—see for example [12,27–29]—that an ODE mathematical epidemiology model might have several "admissible decompositions", which might yield distinct next-generation matrices and distinct R_0's.*

For any admissible decomposition, Diekmann, Heesterbeek, Van den Driesche, and Watmough established the following celebrated DFE stability theorem:

Proposition 1. *For any admissible decomposition (F, V), let*

$$R_0 = \rho(FV^{-1})$$

denote the Perron–Frobenius eigenvalue of the **next-generation matrix.** *Then, the DFE is unstable on $R_0 > 1$, and locally stable on $R_0 < 1$ [7,10,22,23].*

For a recent historical overview of R_0, next-generation matrices, and their calculation in many examples, we refer the reader to the delightful paper [30].

Unfortunately, the standard definition of a next-generation matrix (and hence of R_0) involves concepts like "new infections", which were defined in the original papers based on epidemiological considerations and therefore require the intervention of a human expert. This had created the impression that this method cannot be encapsulated into a computer program. However, we offer and implement below a simple algorithmic definition, based only on the structure of the system and of the "infectious/disease equations".

Our proposal is to use a special F-V decomposition, with F constructed as the positive part of all the interactions in the disease equations which involve both disease compartments and input/susceptible ones. The latter are defined as the complement of the disease compartments, after the possible removal of output compartments, which may be specified as deterministic functions of the other compartments (i.e., may be computed, once the other compartments are known). Note now that the concept of the "positive part of the interactions" may be hard to pinpoint mathematically, but useful enough to have been implemented in CAS's (Mathematica, Maple, Sage, etc.); this made us adopt the following definition:

Remark 8. *For a given zeroable set, an admissible (F, V) gradient decomposition (3) is one where F, the gradient of $\mathcal{F}$, does not contain, in its expanded form, syntactic minuses in its CAS representation, and also where V, the gradient of $\mathcal{V}$, is such that $-V$ is a "sub-generating matrix" under the assumption of non-negativity of all the model parameters.*

The problem of whether the R_0 of the decomposition provided satisfies, under certain conditions, the stability theorem of Van den Driessche and Watmough is still open; therefore, it should be viewed for now just as a recipe that works well in simple cases.

After lots of experimenting, we have found only few cases—see for example Section 8.2, where the recipe NGM has a serious competitor; it is for computing the invasion reproduction number for a two-strain vector–host model, with altered infectivity for co-infected vectors, and with ADE (antibody-dependent enhancement).

2.3. An Algorithmic $F - V$ Decomposition

We complement now the famous $\mathcal{F} - \mathcal{V}$ "equations decomposition" and the next-generation matrix method of [7,22,23] using a algorithmic $F - V$ decomposition.

1. The user supplies the model "mod" (a pair containing the RHS of the dynamical system and its variables) and the indices "inf" of the disease (or infectious) variables; the indices of the other compartments are denoted by "infc".
2. Subsequently, the Jacobian of the infectious equations M with respect to the corresponding variables is computed.
3. Define the interaction terms as terms in M which contain variables $s \in$ infc, and which, if positive, must end up in F. Their complement, denoted by $V1$, will form part of V.
4. As a first guess for F, $F1$ is constructed as the complement of $V1$. It contains all the interaction terms (which involve both disease and susceptible compartments).
5. F is obtained by retaining only the positive part of the matrix $F1$, i.e., the terms which do not contain syntactic minuses (we use the simplest algebraic representation of the equations and do not study the effect which algebraic manipulations introducing minuses might have). Finally, $V1$ is increased to V, which is the complement of F.
6. The script outputs $\{M, V1, F1, F, V, K\}$.

```
NGM[mod_,inf_]:=Module[{dyn,X,infc,M,V,F,F1,V1,K},
   dyn=mod[[1]];X=mod[[2]];
   infc=Complement[Range[Length[X]],inf];
   M=Grad[dyn[[inf]],X[[inf]]]
   (*The jacobian of the infectious equations*);
   V1=-M/.Thread[X[[infc]]->0]
   (*V1 is a first guess for V, retains all gradient terms which
   disappear when the non infectious components are null*);
   F1=M+V1
   (*F1 is a first guess for F, containing all other gradient terms*);
   F=Replace[F1, _. _?Negative -> 0, {2}];
   (*all terms in F1 containing minuses are set to 0*);
   V=F-M;
   K=(F . Inverse[V])/.Thread[X[[inf]]->0]//FullSimplify;
{M,V1,F1,F,V,K}]
```

Note that our NGM script requires a minimal input from the user, which is just the specification of the disease compartments; there is no need to specify "new infections".

The results of this decomposition seem to yield correct results in all the examples from the literature we checked. We would like to add that for dynamical systems satisfying the four conditions in Remark 5, this decomposition yields "admissible gradient decompositions" in the sense that V^{-1} will contain only non-negative terms, and that it is furthermore obtainable from an equations' decomposition, which is admissible in the sense of [23] and therefore yields the correct stability domain.

Remark 9. *Note that the "Replace" command in the script uses the powerful Mathematica capability of applying a "rule" to parts of an "expression", specified by "levelspec", and that it was furnished to us by the user Michael E2 in*

```
https://mathematica.stackexchange.com/questions/286500/
how-to-set-to-0-all-terms-in-a-matrix-which-contain-a-minus
/287406?noredirect=1#comment715559_287406
```

Finally, let us discuss an alternative possible implementation. We could just provide NGM with the right-hand side of the differential equations, compute the steady states, specify one of them, and then define the infected classes as the components with zeros.

However, this would be impractical, since for the majority of the models with explicit DFE, the other fixed points are either not explicit or require very long execution times. It is therefore much simpler to have the user help the AI by providing it with $\mathcal{I}$, which leads immediately to the matrix M. Essentially, we jump directly to the factorization (2) of the infected equations, postponing the solving of the non-infection variables to later.

2.4. A Multi-Dimensional Birth-and-Death CTMC Process Associated to a (F, V) Decomposition, Its Branching Process Approximation, and the Bacaer Equation for the Probability of Extinction

The works of Kendall and Bartlett suggest that ODE epidemic models may be associated to corresponding birth-and-death CTMC processes and then approximated further via branching process.

Citing [31] :"It has been noted by Bartlett (1955), p. 129, that for an epidemic in a large population, the number of susceptibles may, at least in the early stages of an outbreak, be regarded as approximately constant at its initial value and that this approximation will continue to hold throughout the course of an epidemic, provided that the final epidemic size is small relative to the total susceptible population. Thus the general epidemic process may be approximated by a simple birth-and-death process".

To make this more precise, a (F, V) decomposition (3) determines a naturally associated multi-dimensional birth-and-death CTMC process by fixing the values of the non-disease variables, so that the matrices (F, V) depend only on $\boldsymbol{i}$, and interpreting the transition rates between compartments as rates of BD transitions.If the CTMC has rates which are linear in the disease variables, one may associate it to a branching process and take advantage of the well-known equation for extinction probabilities. This procedure has been detailed in previous works like [13–17] and used to approximate extinction and invasion probabilities, as well as the duration of minor epidemics. If the CTMC has rates which are super linear in the disease variables, a further approximation of ignoring the higher power terms in $\boldsymbol{i}$ is necessary. At the end, this results in assuming that the matrices (F, V) are constant (they do not depend on $\boldsymbol{i}$).

Let us illustrate this philosophy on the famous SIR example. However, in line with our interest in this paper and also getting a bit ahead of ourselves, we will only look at a "disease process" of the infected, with the other components fixed. The state space of the process will thus be $\mathbb{N}$. We note this is similar in spirit with the "slow-fast/singular perturbation" technique of considering only variables whose lifetime is short and fixing the other variables whose lifetime is longer, which in fact is the idea behind the famous next-generation matrix approach.

Example 2. *The "SIR" disease process (i.e., defined on the disease compartments) is $i' = (\underline{s} - \gamma)i$. The natural* **SIR/linear CT birth-and-death** *disease stochastic process (DSP) is a Markov process $X_t \in \mathbb{N}$ with a generating operator on the set of functions $f : \mathbb{N} -> \mathbb{N}$ defined by*

$$\mathcal{G}f(i) = \underline{s}i(f(i+1) - f(i)) + \gamma i(f(i-1) - f(i)) = Af(i), \tag{4}$$

and corresponding to a semi-infinite generator matrix

$$A = \begin{pmatrix} -\beta & \beta & 0 & \cdots & 0 \\ \gamma & -\beta-\gamma & \beta & \cdots & 0 \\ 0 & \gamma & -\beta-\gamma & \beta & \ddots \\ \vdots & \ddots & \ddots & \ddots & \beta \\ 0 & 0 & \cdots & \gamma & -\beta-\gamma \end{pmatrix}. \tag{5}$$

Remark 10. *We recall, for the benefit of readers who have not been exposed to the (immense) literature on Markov processes, that the behavior of expectations of this class of stochastic processes always involves one deterministic operator A, the generator of the Markovian semigroup, which acts on a space of "appropriate functions" on the state space (4) and where "appropriate" may be skipped in simple cases like ours (5). The essential thing to note here is that our Markov generator operator A is completely defined by the rates, just like its "mean-field" deterministic ODE. Thus, from the practical point of view of estimating rates, we have added nothing to the parameters of the ODE model (as would be the case with other stochastic processes involving Brownian motion, etc.). We have only modified the state space and the operator; however, this way, phenomena which are invisible in the continuous mean-field limit become relevant.*

Finally, for readers puzzled by the question of where the randomness hidden in the deterministic operator (4) is , we mention that this arrives via two Poisson processes describing the times when the process jumps up and down, respectively, and we refer to the literature for more details.

This process converges to ∞ (i.e., is non-recurrent) or to a stationary distribution if $R_0 := \frac{S}{\frac{\gamma}{\gamma}}$ is strictly bigger than 1, or strictly smaller than 1, respectively. The probability of "extinction/absorbtion into 0", when starting the process with j infected, are

$$p(j) = q^j, \quad q = \begin{cases} 1 & R_0 < 1 \\ \frac{\gamma}{S} = \frac{1}{R_0} & R_0 \geq 1 \end{cases}. \tag{6}$$

This result may be found for example in the textbook [32] (it is, up to technical difficulties caused by the non-compact state space, the simplest illustration of the fact that solutions of "Dirichlet problems" of the form $p(j) = E_{X_0=j}[g(X_\tau)]$, where τ is the exit time from a domain S, must solve $\mathcal{G}p = 0$ and $p = g$ on the boundary of S).

The expected time to extinction when starting the process, with j infected and when $R_0 < 1$ may be found using the fact that solutions of "Poisson problems" of the form $T(j) = E_{X_0=j}[\int_0^\tau h(X(s)ds]$, must solve

$$\begin{cases} \mathcal{G}T + h = 0 \\ T = 0 \text{ on the boundary of } S \end{cases}.$$

Another interesting quantity is the expected time to extinction when $R_0 > 1$, in the case that extinction occurs. This "Dirichlet-Poisson problem" may be written as

$$T(j) = E_{X_0=j}[g(X_\tau) \int_0^\tau h(X(s)ds],$$

where $h = 1$, and g is the indicator of extinction occurring. Such expectations must solve

$$\begin{cases} \mathcal{G}T + hp = 0 \\ T = 0 \text{ on the boundary of } S \end{cases},$$

where p is the solution of the Dirichlet problem with boundary value g.

For SIR, we must solve, respectively,

$$\begin{cases} \beta sx(T(x+1) - T(x)) + \gamma x(T(x-1) - T(x)) + 1 = 0, T(0) = 0, T(K) = 0, K- > \infty, & \text{when } R_0 < 1 \\ \beta sx(T(x+1) - T(x)) + \gamma x(T(x-1) - T(x)) + q^x = 0, T(0) = 0, T(K) = 0, K- > \infty, & \text{when } R_0 \geq 1 \end{cases}. \tag{7}$$

These two equations may be solved explicitly. The limits are quite challenging even with Mathematica, as shown in Appendix A.1. We are able to recover and generalize the results of [33] (see also ([16] eq(10))) when $j \geq 1$ for the first problem, but not for the second one).

The Bacaer equation. One missing aspect in the previous works, however, characterizes the extinction probabilities via one final equation, without going through the discretization procedure employed in [13–17], solving each example individually. Interest-

ingly, such an equation in terms of (F, V) decompositions was provided by Griffiths in [31], except that this paper considers only BD's with no transfers.

We review now the work of [34] (who were motivated by analyzing the case of periodic steady solutions), but on the way also spelled out the simple Equation (8) below. To each fixed value for the disease variables, one may associate to a (F, V) decomposition $\boldsymbol{i}' = (F - V)\boldsymbol{i}$ a "multi-dimensional birth and death process" (BD), with birth rates given by F, and with transfer and death rates given by $-V$. ($\boldsymbol{i}' = (F - V)\boldsymbol{i}$ are precisely the mean-field equation for the multi-dimensional birth-and-death process; this is precisely ([31] eq(6)), under the extra condition that we assume that the immigration vector into the disease compartments is 0. In fact, the $-V$ matrix by itself generates an absorbing CTMC (and the F matrix models' rough inputs to be fed into this absorbing CTMC). This observation explains that an ODE mathematical epidemiology model has associated it to both a birth-and-death process, as well as a "death and transfer only" absorption CTMC—see Remark 24 for an example. Furthermore, if (F, V) are independent of $\boldsymbol{i}$, we are dealing with a branching process (approximation).

A useful fact to recall is that the probabilities of extinction of a multi-variate discrete time-branching process are of the form

$$\mathbb{P}_0 = q_1^{j_1} q_2^{j_2} ...,$$

where $q = (q_j, j = 1, ..., J)$, J is the number of disease compartments, andq_j satisfies the "Bacaer equation"

$$(q^t \circ F) * q + (1 - q) \circ V - q * f = 0 \Leftrightarrow q_j = \frac{\sum_{k=1}^{J}(1 - q_k)V_{kj}}{f_j - \sum_{k=1}^{J} q_k F_{kj}}, \tag{8}$$

where $*$ denotes the coordinate-wise product, the dot product is denoted by $\circ$, and $f_j = \sum_k F_{k,j}$. This equation is new, but it may be inferred from ([31] eq(9)) and refs. ([34] eq(11)) and ([35] eq(5.3)) (after some changes in the variables).

For the SIR process for example, (8) becomes

$$(q - 1)\underline{s}q + (1 - q)\gamma = (q - 1)(\underline{s}q - \gamma) = 0,$$

with the two roots $q = 1$ and $q = \frac{\gamma}{\underline{s}} = \frac{1}{R_0}$, recovering Whittle's result (the two roots yield the correct result when R_0 is strictly smaller than 1 and strictly bigger than 1, respectively).

We will check below that (8) also recovers other explicit particular cases offered in the literature, like SEIR [13], ([14] (Section 4)), SIV [36], etc.

2.5. The Jacobian Factorization Bound

Note first the following elementary fact:

Lemma 1. *A sufficient (but not necessary) condition for a polynomial with real coefficients and a* **positive leading term** *to admit a positive root is that $c_0 < 0$, where c_0 is the constant term of the polynomial.*

For polynomials of degree 1, this condition is also necessary. This converse result may be strengthened to "Descartes type polynomials".

Definition 1. *We will say that a parametric polynomial with real coefficients, whose constant coefficient may change signs, but whose all other coefficients are "sign definite" and of the same sign (which w.l.o.g. could be supposed as $+$), is of Descartes type.*

As an immediate consequence of Descartes's rule of signs, it follows that

Lemma 2. *A sufficient and necessary condition for a Descartes polynomial with a* **positive leading term** *to admit a positive root is that $c_0 < 0$, where c_0 is the constant term of the polynomial.*

Remark 11. *Note the immense simplification with respect to the Routh–Hurwitz conditions, when we need to establish the existence of a positive root for a Descartes type polynomial .*

We believe that "the mystery of the success of the Jacobian factorization approach" comes from the fact that "simple epidemic models" often feature Descartes type polynomials. However, this leaves us with many further questions, like when does this happen and what to do when it does not.

The Jacobian factorization approach consists in:

1. Putting all the rational factors of the characteristic polynomial of the Jacobian in a form normalized to have positive leading term, assuming they are sign definite (if this is not the case, this approach does not work but may be generalized).
2. Removing all linear factors with eigenvalues which are negative.
3. For all remaining factors F_i for which $c_0^{(i)} < 0$ may hold for certain parameter values, rewrite this inequality into the form

$$c_0^{(i)} = c_+ - c_- = c_+(1 - R_J^{(i)}) < 0 \Leftrightarrow R_J^{(i)} := \frac{c_-}{c_+} > 1,$$

   where c_+, c_- are the positive and negative parts of the expanded form of $c_0^{(i)}$.
4. Define the "Jacobian factorization R_0"

$$R_J = \max_i [R_J^{(i)}]. \tag{9}$$

Theorem 1. *(A) In the instability domain, R_J is a lower bound for* $\inf_{F \text{ admissible}} R_F$.
(B) In the stability domain, R_J is an upper bound for $\sup_{F \text{ admissible}} R_F$.

Proof. (A) Fix any admissible F and let R_F be its associated NGM R_0. Then

$$R_J > 1 \Leftrightarrow \exists i : R_J^{(i)} > 1 \Leftrightarrow \exists i : c_0^{(i)} < 0 \Longrightarrow \text{ DFE instability } \Leftrightarrow R_F > 1.$$

Thus

$$R_J > 1 \Longrightarrow R_F > 1 \Leftrightarrow R_J \leq R_F, \tag{10}$$

and the result follows.

(B) Similar proof.

Conjecture: We conjecture that if all the factors F_i are Descartes polynomials, then $R_J = R_F$ for any admissible decomposition (F, V) will denote the resulting object by R_0.

Open question 1: Under what conditions do our NGM R_0 and our Jacobian R_J coincide?

The implementation of the Jacobian factorization approach is provided in Appendix A. □

2.6. The "Rational Univariate Representation" (RUR) and the Reduced Order Quasi-Stationary Approximation

Hundreds of mathematical epidemiology papers have already employed the idea of reducing the fixed point system to one scalar equation in one of the disease variables via rational substitutions for the other variables. We note that this is a particular case of the so-called "rational univariate representation" (RUR), but for Mathematica users, this is irrelevant, since RUR is not implemented currently and we had to write our own script, included below, in which the user chooses a variable in a system that they want to restrict to.

The current code for this reduction to one equation algorithm is

```
RUR[mod_, ind_, cn_ : {}] := Module[{dyn, X, par, eq, elim},
      dyn = mod[[1]]; X = mod[[2]]; par = mod[[3]];
      elim = Complement[Range[Length[X]],ind];
```

```
  eq = Thread[dyn == 0];
  ratsub = Solve[Drop[eq, ind], X[[elim]]][[1]];
  pol =
   Collect[GroebnerBasis[Numerator[Together[dyn /. cn]],
     Join[par, X[[ind]]], X[[elim]]], X[[ind]]];
    {ratsub, pol}
]
```

Remark 12. *The command which does the essential work is "GroebnerBasis". When "ind" is a set with just one component, this reduces the system to a polynomial in this variable. Alternatively, this could be achieved by plugging the results of "ratsub" into the system.*

The script above works directly for models with demographics but must be modified for "conservation systems", where the fixed points are only determined by adding the total mass conservation equation to the fixed point equations.

This script may also be used for order reduction, both in the spirit of the (quasi-steady-state assumption) QSSA method in biochemistry and of the recent epidemiology paper [37]. We illustrate this for the simplest SIR example.

Example 3. *For the SIR process* $(S(t), I(t), R(t), t \geq 0)$ *with linear birth rates* b_s, b_r *for the susceptible and the recovered, the system for the fractions* $\mathsf{s}(t) = \frac{S(t)}{N}, \mathsf{i}(t) = \frac{I(t)}{N}, \mathsf{r}(t) = \frac{R(t)}{N}$, $N = S + I + R$ *is:*

$$\begin{cases} \mathsf{s}'(t) = b_s - \beta \mathsf{s}(t)\mathsf{i}(t) + \gamma_r \mathsf{r}(t) - d_s \mathsf{s}(t), & d_s = \gamma_s + \mu \\ \mathsf{i}'(t) = \beta \mathsf{s}(t)\mathsf{i}(t) - d_i \mathsf{i}(t), & d_i = \gamma_i + \mu + \delta\,. \\ \mathsf{r}'(t) = b_r + \gamma_i \mathsf{i}(t) + \gamma_s \mathsf{s}(t) - d_r \mathsf{r}(t), & d_r = \gamma_r + \mu \end{cases} \tag{11}$$

The DFE is: $(\frac{b_r\gamma_r + b_s(\mu+\gamma_r)}{\mu(\mu+\gamma_r+\gamma_s)}, 0, \frac{b_r(\mu+\gamma_s)+b_s\gamma_s}{\mu(\mu+\gamma_r+\gamma_s)})$.

The rational substitution with respect to i obtained via RUR is:

$$\left(s \to \frac{\gamma_r(b_r + b_s + i\gamma_i) + \mu b_s}{\beta i(\mu + \gamma_r) + \mu(\mu + \gamma_r + \gamma_s)}, r \to \frac{b_r(\beta i + \mu + \gamma_s) + b_s\gamma_s + i\gamma_i(\beta i + \mu + \gamma_s)}{\beta i(\mu + \gamma_r) + \mu(\mu + \gamma_r + \gamma_s)}\right).$$

Note that this reduces to the DFE when $i = 0$.

The reduced approximate model obtained via RUR is:

$$i' = i[a_0 - a_1 i], a_1 = \beta(\mu\gamma_i + (\delta + \mu)(\mu + \gamma_r)), \tag{12}$$

$$a_0 = \beta(b_r\gamma_r + b_s(\mu + \gamma_r)) - \mu(\mu + \gamma_r + \gamma_s)(\delta + \gamma_i + \mu) \tag{13}$$

$$= \mu(\mu + \gamma_r + \gamma_s)(\delta + \gamma_i + \mu)\left(\mathsf{s}_{dfe}\mathcal{R} - 1\right) = \mu(\mu + \gamma_r + \gamma_s)(\delta + \gamma_i + \mu)(R_0 - 1).$$

This has an explicit (rather formidable) analytic solution, provided in the Mathematica file.

One may notice that for the chosen numerical illustration, the plots of i and its approximation converge towards the same value but differ sharply for the chosen numeric values as far as shape is concerned; see Figure 1.

We mention finally the possibility to develop yet another possible algorithm for computing a "bifurcation R_0", suggested by the example above, which is based on the known fact that this parameter is expected to produce bifurcations at $R_0 = 1$.

The steps are:

1. Factor out the variable in the scalar polynomial of the reduced model (always possible if this is a disease variable).
2. Write the free coefficient of the divided polynomial as $F(R_0) = G(R_0)(R_0 - 1)$, where $F(R)$ is rational (always possible due to the known bifurcation at $R_0 = 1$).

3. Identify a factor which is linear in susceptible variables like s_{dfe}, etc., and write it as a difference of positive and negative terms. Upon normalizing one of them to one, the other will be R_0, or $1/R_0$.

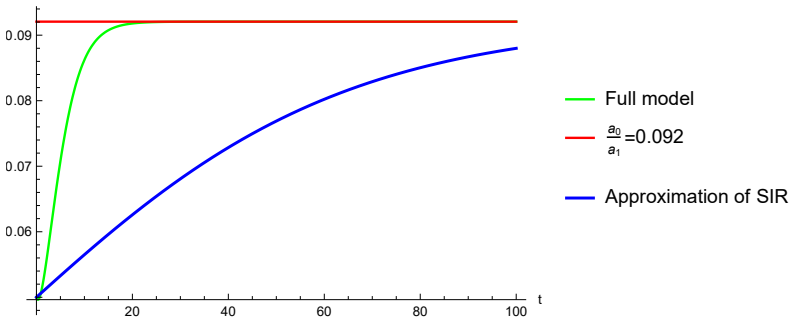


Figure 1. Illustration of the asymptotic convergence of $i(t)$ towards the endemic value $\frac{a_0}{a_1} = 0.092$, both for the full SIR model and its approximation.

3. R_0 and Extinction Probabilities for the SEIR Epidemic Model

The SEIR process $(S(t), E(t), I(t), R(t), t \geq 0)$ adds to the SIR model the class E(exposed). The model for the fractions $\mathsf{s}(t) = \frac{S(t)}{N}$, $\mathsf{e}(t) = \frac{E(t)}{N}$, $\mathsf{i}(t) = \frac{I(t)}{N}$, $\mathsf{r}(t) = \frac{R(t)}{N}$, $N = S + E + I + R$ is:

$$\begin{cases} \mathsf{s}'(t) = b_s - \beta \mathsf{s}(t)\mathsf{i}(t) + \gamma_r \mathsf{r}(t) - d_s \mathsf{s}(t), & d_s = \gamma_s + \mu \\ \mathsf{e}'(t) = \beta \mathsf{s}(t)\mathsf{i}(t) - \gamma_e \mathsf{e}(t) - d_e \mathsf{e}(t), & d_e = \gamma_e + \mu \\ \mathsf{i}'(t) = \gamma_e \mathsf{e}(t) - d_i \mathsf{i}(t), & d_i = \gamma_i + \mu + \delta \\ \mathsf{r}'(t) = b_r + \gamma_i \mathsf{i}(t) + \gamma_s \mathsf{s}(t) - d_r \mathsf{r}(t), & d_r = \gamma_r + \mu \end{cases}.$$

This is both a textbook model and one for which answers to many open questions (concerning, for example, the emergence of chaos under stochastic and periodic perturbations) are still awaited—see for example [38–40].

The DFE of (14) is $(\frac{b_r\gamma_r + b_s(\mu+\gamma_r)}{\mu(\mu+\gamma_r+\gamma_s)}, 0, 0, \frac{b_r(\mu+\gamma_s)+b_s\gamma_s}{\mu(\mu+\gamma_r+\gamma_s)})$. The decomposition matrices and basic reproduction number are:

$$F = \begin{pmatrix} 0 & \beta s \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \gamma_e + \mu & 0 \\ -\gamma_e & \delta + \gamma_i + \mu \end{pmatrix}, R_0 = \frac{\beta s \gamma_e}{(\gamma_e + \mu)(\delta + \gamma_i + \mu)}.$$

The associated disease stochastic process $X = (e, i) \in \mathbb{N}^2$ has a generating operator

$$\mathcal{G} = \underline{s}i(f(x + e_1) - f(x)) + \gamma_e e(f(x + tr) - f(x)) + d_e e(f(x + e_3) - f(x)) + d_i i(f(x + e_2) - f(x)),$$

where $x = (e, i), e_1 = (1, 0) = -e_3, tr = (-1, 1), e_2 = (0, -1)$.

The extinction probabilities obtained by solving (8) are

$$\begin{cases} q_i = 1, q_e = 1 & \text{when } R_0 < 1 \\ q_i = \frac{1}{R_0}, q_e = \frac{\mu}{d_e} + \frac{\gamma_e}{d_e}\frac{1}{R_0} & \text{when } R_0 \geq 1 \end{cases}.$$

This checks with the particular case in [13], where $\mathsf{s}_{dfe} = 1$.

Remark 13. *It is not clear intuitively why separating the transition rates into those of F (which increase the norm of x) and those of V (which do not increase the norm of x) should matter for determining the extinction probabilities, as happens in* (8)*. This seems to be an interesting question.*

4. Rank One Host-Only Models with Pathogen and R_0 Readable from the Flow-Chart

The SEIARW Model with "Catalyzing Pathogen" of [18] Has Rank One Next-Generation Matrix and $R_0 = R_J$

Ref. [18] attempted to offer a "**definition-based method**" for "computing R_0 of dynamic models of single host species, which is mutually coherent with the next-generation method (NGM)" (and somewhat unclear for "computing R_0 for a population with multi-group models"). Unfortunately, these authors do not seem aware of the fact that all the single host species they examined have a next-generation matrix of rank one, and that in this case, there exists a simple general formula [20,41,42], which is also related to the definition-based method of [43].

We review now the SEIAR model (susceptibles, exposed, infected, asymptomatic, and recovered), to which [18] add also a pathogen compartment W, resulting in the SEIARW model. See also Figure 2.

$$\begin{cases} \begin{cases} e' = s(a\beta_a + i\beta_i + w\beta_w) - ed_e, & d_e = e_i + e_a + \mu \\ i' = ee_i - id_i, & d_i = \gamma_i + \mu + \delta, \\ a' = ee_a - ad_a, & d_a = \gamma_a + \mu, \\ w' = a\epsilon_a + i\epsilon_i - wd_w \\ r' = a\gamma_a + \gamma_i i - \mu r \end{cases} \\ s' = \Lambda - s(a\beta_a + i\beta_i + w\beta_w + \mu). \end{cases} \tag{14}$$

In matrix form, the disease equations are:

$$\begin{pmatrix} e' \\ i' \\ a' \\ w' \\ r' \end{pmatrix} = \begin{pmatrix} -d_e & s\beta_i & s\beta_a & s\beta_w & 0 \\ e_i & -d_i & 0 & 0 & 0 \\ e_a & 0 & -d_a & 0 & 0 \\ 0 & \epsilon_i & \epsilon_a & -d_w & 0 \\ 0 & \gamma_i & \gamma_a & 0 & -\mu \end{pmatrix} \begin{pmatrix} e \\ i \\ a \\ w \\ r \end{pmatrix}.$$

In the absence of a pathogen, SEIAR is a rank one "generalized stage-structured infectious disease model" as revealed by its $F = \begin{pmatrix} 0 & s\beta_i & s\beta_a \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$ and by its $V = \begin{pmatrix} d_e & 0 & 0 \\ -e_i & d_i & 0 \\ -e_a & 0 & d_a \end{pmatrix}$ matrix, which is triangular (compare to ([14] (Section 3))).

The R_0 has a very intuitive and easily explainable form:

$$R_0 = \frac{\mathsf{s}_{dfe}}{d_e}\left[\beta_i \frac{e_i}{d_i} + \beta_a \frac{d_a}{e_a}\right] \tag{15}$$

(compare to ([14] (Section 3)) to see the general pattern for more stages).

Remark 14. *Note that this result may be obtained with $\mathcal{I} = \{e, i, a, r\}$ and also with $\mathcal{I} = \{e, i, a\}$, which raises the question of defining the concept of a minimal or "sufficient disease" set in such a way that it allows for deriving both R_0 and the extinction probabilities.*

After the addition of the catalyzing pathogen, the SEIARW is still a rank one "generalized stage-structured infectious disease model", but the R_0 is less intuitive

$$R_0 = \frac{\mathsf{s}_{dfe}}{d_e}\left[\beta_i \frac{e_i}{d_i} + \beta_a \frac{d_a}{e_a} + \frac{\beta_w}{d_w}\left(\epsilon_i \frac{e_i}{d_i} + \epsilon_a \frac{e_a}{d_a}\right)\right]; \tag{16}$$

still, it may be read out of the flow chart "almost by inspection" (see also [18] for an algorithm computing this).

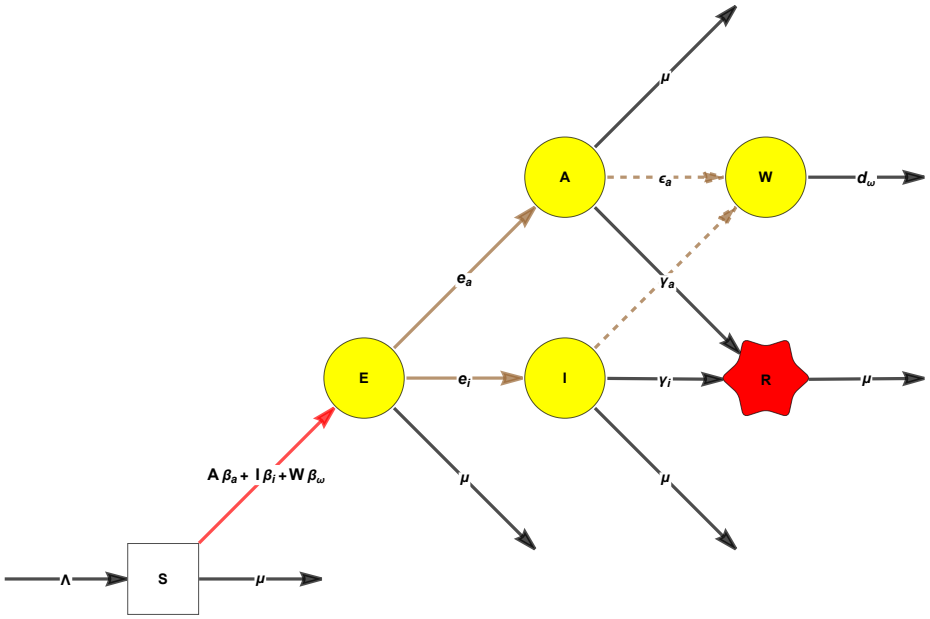


Figure 2. Flow chart corresponding to the SEIARW model (14).

Despite the fact that the characteristic polynomial is not of the Descartes type, all our three R_0 recipes yield the above result. We provide now details for the NGM method. After removing the compartment r (since it does not appear in the other equations), the calls "inf=Range[4];DFE[SEIARW,inf]; NGM[SEIARW,inf]" of our scripts yield that the DFE is

$$\left\{s \to \frac{\Lambda}{\mu}, e \to 0, i \to 0, a \to 0, w \to 0\right\}$$

and

$$F = s\begin{pmatrix} 0 & \beta_i & \beta_a & \beta_w \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} = s\begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}\begin{pmatrix} 0 & \beta_i & \beta_a & \beta_w \end{pmatrix}, V = \begin{pmatrix} d_e & 0 & 0 & 0 \\ -e_i & d_i & 0 & 0 \\ -e_a & 0 & d_a & 0 \\ 0 & -\epsilon_i & -\epsilon_a & d_w \end{pmatrix}. \tag{17}$$

Here the dominant eigenvalue of $K = FV^{-1}$, that of the transpose

$$K^t = s\begin{pmatrix} \frac{\beta_i d_w e_i d_a + \beta_a e_a d_w d_i + \beta_w (e_i \epsilon_i d_a + e_a \epsilon_a d_i)}{d_e d_i d_a d_w} & \frac{\beta_i d_w + \epsilon_i \beta_w}{d_w d_i} & \frac{\beta_a d_w + \epsilon_a \beta_w}{d_w d_a} & \frac{\beta_w}{d_w} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

the rank 1 formula of [20,41,42]

$$(1,0,0,0).(V^t)^{-1}.(0,\beta_i,\beta_a,\beta_w)^t,$$

as well as the Jacobian factorization confirm all the results (16) of [18].

5. Target-Infection-Virus Models

5.1. Two Admissible (F, V) Decompositions and R_0's for the Three Dimensional Model of [44]

The three dimensional model of ([44] eq(1)) is:

$$\begin{cases} x' = \Lambda(x) - \beta x v - \beta_{xy} x y, \quad \Lambda(x) = \mu_x(x_{dfe} - x) \\ \begin{pmatrix} y' \\ v' \end{pmatrix} = \begin{pmatrix} \beta x v + \beta_{xy} x y \\ 0 \end{pmatrix} - \begin{pmatrix} \mu_y y \\ \mu_v v + \beta_{xv} x v + \beta_{yv} y v - b\mu_y y \end{pmatrix}, \end{cases} \tag{18}$$

where we represented already the infectious equations as a difference of "new (positive) infection" terms and "transfers". The DFE is $x = x_{dfe}, y = 0, v = 0$.

This reduces to the case with zero delays in ([45] eq(5.1)), when the rate of viruses moving into a healthy cell β_{xv} and the rate of viruses moving into an infected cell β_{yv} are both 0, and to the case in [46], when $\beta_{yv} = 0 = \beta_{xy}$ (the latter is the cell-to-cell infection rate) and $\beta_{xv} = \beta$.

The gradient of the infectious equations is

$$M = \begin{pmatrix} x\beta_{xy} - \mu_y & \beta x \\ b\mu_y - v\beta_{yv} & -\mu_v - x\beta_{xv} - y\beta_{yv} \end{pmatrix}. \tag{19}$$

Calling our NGM script with "inf = {2,3}" yields [44]'s result: namely,

$$F = x_{dfe}\begin{pmatrix} \beta_{xy} & \beta \\ 0 & 0 \end{pmatrix}, -V = \begin{pmatrix} -\mu_y & 0 \\ b\mu_y & -\mu_v - x_{dfe}\beta_{xv} \end{pmatrix},$$

the next-generation matrix (NGM) of the infectious coordinates at the DFE

$$K = \begin{pmatrix} \frac{\beta b x}{\mu_v + x\beta_{xv}} + \frac{x\beta_{xy}}{\mu_y} & \frac{\beta x}{\mu_v + x\beta_{xv}} \\ 0 & 0 \end{pmatrix},$$

and that the DFE is Lyapunov–Malkin stable when R_0 defined in

$$R_0 = \frac{x_{dfe}}{x_c} + \beta b \frac{x_{dfe}}{\mu_v + x_{dfe}\beta_{xv}}, \quad x_c := \frac{\mu_y}{\beta_{xy}}, \tag{20}$$

is smaller than 1 and unstable when $R_0 > 1$.

The Jacobian factorization provides the same formula, despite the fact that the characteristic polynomial is of the Descartes type only conditionally, when $\beta_{xv} \geq \beta_{xy}$.

Remark 15. *Interestingly, another admissible decomposition* $\mathcal{F} = \begin{pmatrix} \beta x v + \beta_{xy} x y \\ beta\mu_y y \end{pmatrix}$, *appears in an earlier version of [44] at https://people.clas.ufl.edu/pilyugin/files/cosner60-dcdsB.pdf (accessed on 1 November 2023):*

$$F = \begin{pmatrix} x\beta_{xy} & \beta x \\ b\mu_y & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu_y & 0 \\ 0 & \mu_v + \beta_{xv} x_{dfe} \end{pmatrix}, K = \begin{pmatrix} \frac{x_{dfe}}{x_c} & \frac{\beta x_{dfe}}{\mu_v + \beta_{xv} x_{dfe}} \\ b & 0 \end{pmatrix} \tag{21}$$

This second decomposition yields a different R_0*:*

$$R_0 = \frac{x_{dfe}}{2x_c}\left(1 + \sqrt{1 + \frac{4\beta b x_c^2}{x_{dfe}(x_{dfe}\beta_{xv} + \mu_v)}}\right). \tag{22}$$

Furthermore, this early version also shows that the two decompositions have the same stability domain for the DFE, which may be reexpressed as

$$R_0 = K_{1,1} + K_{1,2}K_{2,1} = \frac{x_{dfe}}{x_c} + b\beta\frac{x_{dfe}}{\mu_v + \beta_{xv} x_{dfe}} < 1. \tag{23}$$

We note that this equivalence also follows by applying the first criterion in [47] (when the characteristic polynomial, given here by $\lambda^n - a_1\lambda^{n-1} - a_2\lambda^{n-1} - ...$ *has all coefficients as non-negative, then* $\sum_i a_i$ *may be used as the threshold parameter instead of* R_0*), with* $n = 3, a_1 = K_{1,1}, a_2 = K_{1,2}K_{2,1}$, $a_3 = 0$.

Remark 16. *Note the second decomposition has one more non-zero term in F, which does not appear in ours, since we view it as a transfer and not as an interaction. We see here an excellent*

example of non-uniqueness, where one must choose between an answer with F of a lower rank and a simpler R_0 formula, but which is valid only under certain conditions (that the non-diagonal term $b\mu_y$ in V is small enough), and an answer with a simpler V, which requires less assumptions on the parameters but yields a more complicated R_0.

Remark 17. The domain of stability, in terms of the parameters. *As an aside, it is easy to show that* (23) *is equivalent to*

$$x_{dfe} < x_c, b < b_0 := \frac{\mu_v + \beta_{xv} x_{dfe}}{\beta x_{dfe}} \left(1 - \frac{x_{dfe}}{x_c}\right), \tag{24}$$

where b_0 is the solution of equation $R_0(b) = 1$. Thus, the stability of the DFE is equivalent to both x_{dfe} and the "burst parameter" b being small enough.

We offer now a third gradient decomposition, which turns out to be inadmissible sometimes, but it again yields our recipe's R_0. Taking $F = \begin{pmatrix} x_{dfe}\beta_{xy} & 0 \\ b\mu_y & 0 \end{pmatrix}$ yields

$$V = F - M = \begin{pmatrix} \mu_y & -\beta x_{dfe} \\ 0 & \mu_v + x_{dfe}\beta_{xv} \end{pmatrix}, V^{-1} = \begin{pmatrix} \frac{1}{\mu_y} & \frac{\beta x_{dfe}}{\mu_y(\mu_v + x_{dfe}\beta_{xv})} \\ 0 & \frac{1}{\mu_v + x_{dfe}\beta_{xv}} \end{pmatrix}.$$

Note that V is a sub-generating matrix only if $x_{dfe} \leq \frac{\mu_y}{\beta}$.

However $K = \begin{pmatrix} \frac{x_{dfe}\beta_{xy}}{\mu_y} & \frac{\beta x_{dfe}^2 \beta_{xy}}{\mu_v \mu_y + x_{dfe}\beta_{xv}\mu_y} \\ b & \frac{\beta b x_{dfe}}{\mu_v + x_{dfe}\beta_{xv}} \end{pmatrix}$ yields the correct

$$R_0 = \max\left(0, \frac{\beta b x_{dfe}}{\mu_v + x_{dfe}\beta_{xv}} + \frac{x_{dfe}\beta_{xy}}{\mu_y}\right).$$

In the current example, the RUR algorithm works as well. The difference of the two positive terms is

$$\beta b x_{dfe}\mu_y + x_{dfe}\beta_{xy}(\mu_v + x_{dfe}\beta_{xv}) - \mu_y(\mu_v + x_{dfe}\beta_{xv}) = \mu_y(\mu_v + x_{dfe}\beta_{xv})(R_0 - 1),$$

for both choices y and v as scalar variables, and the appropriate cosmetics recover the recipe NGM R_0.

This example illustrates the fact that sometimes several admissible and even conditionally non-admissible decompositions, as well as other approaches, may lead to the same R_0.

5.2. Two Distinct Approximate Extinction Probabilities, One for Each Admissible (F, V) Decomposition for the Model of [44]

The extinction probabilities of the stochastic model are of course unique. We may use the result of Bacaer's formula as approximations. In this interesting example, we find out that both (F, V) decompositions yield reasonable results. This suggests that we have not one, but two deterministic epidemiologic approximations for a single stochastic model. This strengthens our point of view that a deterministic epidemiologic model must include a specification of the (F, V) decomposition.

The respective results we obtained are:

1. For the first decomposition, the extinction probabilities obtained by solving (8) are

$$\begin{cases} q_y = 1, q_z = 1, \text{when } R_0 \leq 1, \\ q_y = \frac{\pm\sqrt{x^2\left(\left(\beta_{xy}(\mu_v + x(\beta+\beta_{xv})) + \beta\mu_y\right)^2 - 4\beta\beta_{xy}\mu_y(x(\beta - b\beta + \beta_{xv}) + \mu_v)\right)} + x\left(\mu_v\beta_{xy} + \beta\mu_y\right) + x^2(\beta+\beta_{xv})\beta_{xy}}{2\beta x^2\beta_{xy}}, \text{when } R_0 > 1 \\ q_z = \frac{(\mu_v + x\beta_{xv})\left(\pm\sqrt{x^2\left(\left(\beta_{xy}(\mu_v + x(\beta+\beta_{xv})) + \beta\mu_y\right)^2 - 4\beta\beta_{xy}\mu_y(x(\beta - b\beta + \beta_{xv}) + \mu_v)\right)} - x\mu_v\beta_{xy} + x^2(\beta+\beta_{xv})(-\beta_{xy}) + \beta x\mu_y\right)}{2\beta^2 b x^2 \mu_y}. \end{cases}$$

2. For the second decomposition, the extinction probabilities obtained by solving (8) are:

$$\begin{cases} q_y = 1, q_z = 1, \text{when } R_0 \le 1, \\ q_y = \frac{\pm\sqrt{x^2\left(\left(\beta(b+1)\mu_y+\beta_{xy}(\mu_v+x(\beta+\beta_{xv}))\right)^2-4\beta\beta_{xy}\mu_y(\mu_v+x(\beta+\beta_{xv}))\right)}+\beta(b+1)x\mu_y+x\mu_v\beta_{xy}+x^2(\beta+\beta_{xv})\beta_{xy}}{2\beta x^2\beta_{xy}}, \text{when } R_0 > 1, \\ q_z = \frac{(\mu_v+x\beta_{xv})\left(\pm\sqrt{x^2\left(\left(\beta(b+1)\mu_y+\beta_{xy}(\mu_v+x(\beta+\beta_{xv}))\right)^2-4\beta\beta_{xy}\mu_y(\mu_v+x(\beta+\beta_{xv}))\right)}+\beta(b+1)x\mu_y-x\mu_v\beta_{xy}+x^2(\beta+\beta_{xv})\left(-\beta_{xy}\right)\right)}{2\beta bx\mu_y(\mu_v+x(\beta+\beta_{xv}))}. \end{cases}$$

In a numeric instance, we found the two results reasonably close to each other.

6. Multi-Strain Host-Only Models

Multi-strain diseases are diseases that consist of several strains, or serotypes. One interesting thing about multi-strain models is that, besides the DFE, we have new boundary points which are relevant epidemiologically, in which one subset of strains A is present ("resident"). We have then a natural coexistence of several "$\mathcal{R}$ thresholds":

1. R_A is the bifurcation threshold at which the DFE stops being stable, when the only compartments present are those of A.
2. $\mathcal{R}_A$ is the bifurcation threshold at which the boundary point E_A starts existing (in the presence of the A^c compartments).
3. $R_{A^c,A}$ is the bifurcation threshold at which the boundary point E_A stops being stable, i.e., when the A^c compartments invade the A compartments.

Note that for two strains already, we have at least two new thresholds, R_{21}, R_{12}, which, together with R_0 and the thresholds R_1, R_2 of the individual strains, divide the line into six regions with different stability properties. Studying the relations between the various thresholds in the parameter space is quite a challenging topic. However, their calculation is a priori of the same level of difficulty as for the DFE.

6.1. The Two-Strain SIS Tuberculosis Model of ([22] (Section 4.4))

The model presented here is a limiting case of that presented in the next section, obtained when the transition rates γ_1, γ_2 converge to ∞. It also generalizes the two-strain SIS tuberculosis model of ([22] (Section 4.4)) by allowing for cross infections in both directions

$$\begin{cases} i_1' = i_1(i_2(\nu_2-\nu_1)+\beta_1 s-\sigma_1-b) = i_1(i_2(\nu_2-\nu_1)+\beta_1 s-d_1), \\ i_2' = i_2(i_1(\nu_1-\nu_2)+\beta_2 s-\sigma_2-b) = i_2(i_1(\nu_1-\nu_2)+\beta_2 s-d_2), \\ s' = b-s(\beta_1 i_1+\beta_2 i_2+b)+i_1\sigma_1+i_2\sigma_2, \end{cases}$$

where we put $d_1 = \sigma_1 - b, d_2 = \sigma_2 - b$ in the first two equations to simplify their notation (the last equation may be removed, since $s = 1 - i_1 - i_2$).

Noting that the first two equations' factor yields the following three boundary steady states, where $\mathbf{x} = (i_1, i_2, s)$:

$$\mathbf{x}_0 = (0,0,1), \tag{25}$$

$$\mathbf{x}_1 = \left(1-\mathcal{R}_1^{-1}, 0, \mathcal{R}_1^{-1}\right), \tag{26}$$

$$\mathbf{x}_2 = \left(0, 1-\mathcal{R}_2^{-1}, \mathcal{R}_2^{-1}\right),$$

where we put

$$\mathcal{R}_1 = \frac{\beta_1}{b+\sigma_1}, \mathcal{R}_2 = \frac{\beta_2}{b+\sigma_2}.$$

The *disease-free steady state* $\mathbf{x}_0$ exists for all parameter values, while the *original strain-only steady state* $\mathbf{x}_1$ is physically relevant if and only if $\mathcal{R}_1 > 1$, and the *emerging strain-only steady state* $\mathbf{x}_2$ is physically relevant if and only if $\mathcal{R}_2 > 1$.

There may also be a fourth non-negative coexistence equilibrium (COE), given by

$$\begin{cases} i_1 = \frac{\beta_1 d_2 - \beta_2 d_1 - (\nu_1 - \nu_2)(\beta_2 - d_2)}{(\nu_1 - \nu_2)(\beta_1 - \beta_2 + \nu_1 - \nu_2)} \\ i_2 = \frac{d_1(\beta_2 - \nu_1 + \nu_2) - \beta_1(d_2 - \nu_1 + \nu_2)}{(\nu_1 - \nu_2)(\beta_1 - \beta_2 + \nu_1 - \nu_2)} \\ s = 1 - i_1 - i_2 \end{cases}. \tag{27}$$

Note that this depends only on $\nu_1 - \nu_2$, which shows that the case $\nu_1 = 0$ considered in ([22] (Section 4.4)) is not that restrictive (However, the appearance of $\nu_1 - \nu_2$ in the denominator suggests limiting the diffusion phenomena, which may be worth studying in their own right.) In this case, the COE point simplifies to:

$$\begin{cases} i_1 = \frac{d_2(d_1(\mathcal{R}_1 - \mathcal{R}_2) + \nu(\mathcal{R}_2 - 1))}{\nu(-d_1\mathcal{R}_1 + d_2\mathcal{R}_2 + \nu)} \\ i_2 = \frac{d_1(d_2(\mathcal{R}_2 - \mathcal{R}_1) + \nu(1 - \mathcal{R}_1))}{\nu(-d_1\mathcal{R}_1 + d_2\mathcal{R}_2 + \nu)} \\ s = 1 - i_1 - i_2 \end{cases}, \tag{28}$$

which is positive if $\mathcal{R}_2 > 1$ and the following conditions hold

$$\begin{cases} \mathcal{R}_1 > \frac{\nu + \mathcal{R}_2 d_2}{\nu + d_2},\ 0 < \nu < \frac{d_1(\mathcal{R}_2 - \mathcal{R}_1)}{\mathcal{R}_2 - 1},\ \text{or,} \\ \mathcal{R}_1 < \frac{\nu + \mathcal{R}_2 d_2}{\nu + d_2}, \left(0 < d_1 < \nu(1 - \frac{1}{\mathcal{R}_2}) \text{ or } d_1 > \nu(1 - \frac{1}{\mathcal{R}_2}), \nu < \frac{d_1(\mathcal{R}_2 - \mathcal{R}_1)}{1 - \mathcal{R}_2}\right). \end{cases} \tag{29}$$

We give now some details of the NGM implementation for the three boundary points. Recall that the idea is to project the ODE at each boundary point on the 0 coordinates (or some subset), while fixing the other coordinates. We must therefore compute new (F, V) pairs at each boundary point, since the respective zero coordinates are different.

1. At the DFE, the zero coordinates are $\{i_1, i_2\}$, and so $\mathcal{I} = \{1, 2\}$.
   Our script yields the expected result

$$R_0 = Max\left[\frac{\beta_2 s_{dfe}}{\sigma_2 + b}, \frac{\beta_1 s_{dfe}}{\sigma_1 + b}\right] = Max[R_1, R_2], R_i = \mathsf{s}_{dfe}\mathcal{R}_i = \mathcal{R}_i, i = 1, 2.$$

2. At $\mathbf{x}_2$, $\mathcal{I} = \{1\}$, and

$$R_{12} = \frac{\mathcal{R}_1}{\mathcal{R}_2} + \frac{(\nu_2 - \nu_1)\left(1 - \mathcal{R}_2^{-1}\right)}{b + \sigma_1}.$$

   When $\nu_1 = 0, \nu_2 = \nu$, we recover the result ([22] (18)) $R_{12} = \frac{\mathcal{R}_1}{\mathcal{R}_2} + \frac{\nu}{b+\sigma_1}\left(1 - \mathcal{R}_2^{-1}\right)$.
   This implies that the stability holds if $\mathcal{R}_2 > 1$ and $\mathcal{R}_1$ are not too big, more precisely:

$$R_{12} < 1 \Leftrightarrow \mathcal{R}_1 < \mathcal{R}_2 + \frac{\nu(1 - \mathcal{R}_2)}{b + \sigma_1}. \tag{30}$$

   For a sanity check, we will derive the stability condition of the point $\mathbf{x}_2$ also by the direct Jacobian approach. The Jacobian at $\mathbf{x}_2$ is

$$\begin{pmatrix} \frac{-\beta_2(b + \nu_1 - \nu_2 + \sigma_1) + \beta_1(b + \sigma_2) + (\nu_1 - \nu_2)(b + \sigma_2)}{\beta_2} & 0 & 0 \\ -\frac{(\nu_1 - \nu_2)(b - \beta_2 + \sigma_2)}{\beta_2} & 0 & -b + \beta_2 - \sigma_2 \\ \sigma_1 - \frac{\beta_1(b + \sigma_2)}{\beta_2} & -b & \sigma_2 - \beta_2 \end{pmatrix}.$$

   In the case of [22], the eigenvalues are

$$\left\{-b, -((\mathcal{R}_2 - 1)(b + \sigma_2)), \frac{(b + \sigma_1)(\mathcal{R}_1 - \mathcal{R}_2) + \nu(\mathcal{R}_2 - 1)}{\mathcal{R}_1}\right\}.$$

The second eigenvalue is negative if $\mathcal{R}_2 > 1$, and the third eigenvalue is negative when

$$(\mathcal{R}_1 - \mathcal{R}_2) + \frac{\nu}{b+\sigma_1}(\mathcal{R}_2 - 1) < 0 \Leftrightarrow R_{12} < 1 \text{ see (30)}.$$

3. An analog result holds via symmetry at $\mathbf{x}_1$, where $\mathcal{I} = \{2\}$, and

$$\mathcal{R}_{21} = \frac{(\nu_1 - \nu_2)(\mathcal{R}_1 - 1)}{d_2 \mathcal{R}_1} + \frac{\mathcal{R}_2}{\mathcal{R}_1}.$$

We illustrate now in Figure 3 via an i_1 bifurcation diagram that, as natural, when β_1 is small enough, the x_2 fixed point is stable enough to be replaced as an attractor, first by the COE, and finally by the x_1 fixed point, when β_1 increases. Figure 4 illustrate time and phase plots at the critical point $\beta_{1c} = 2$.

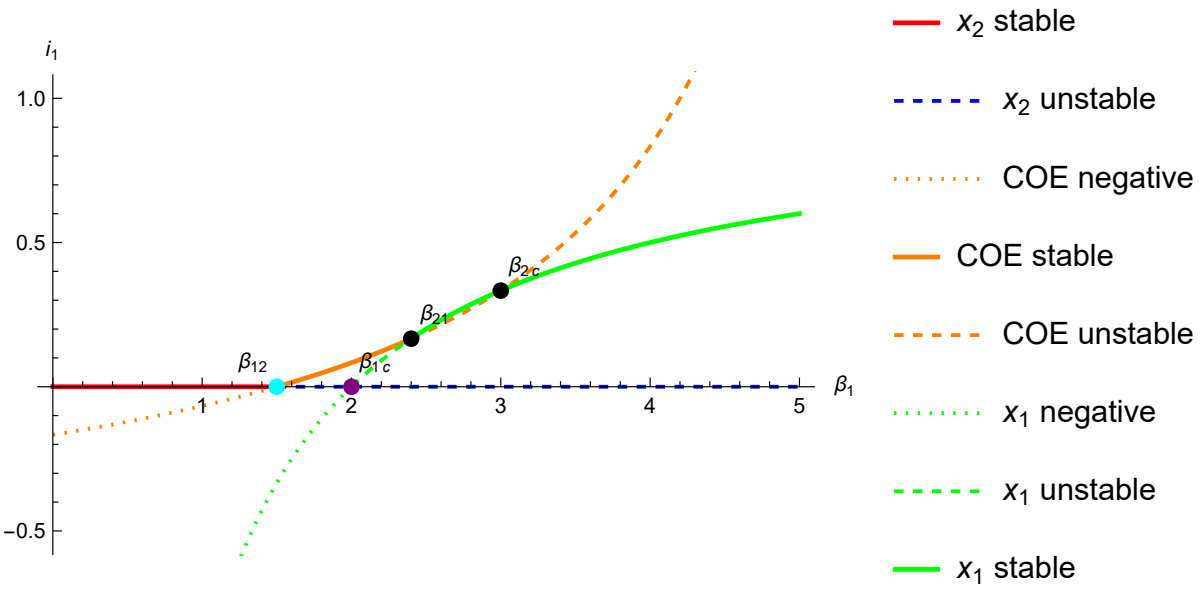
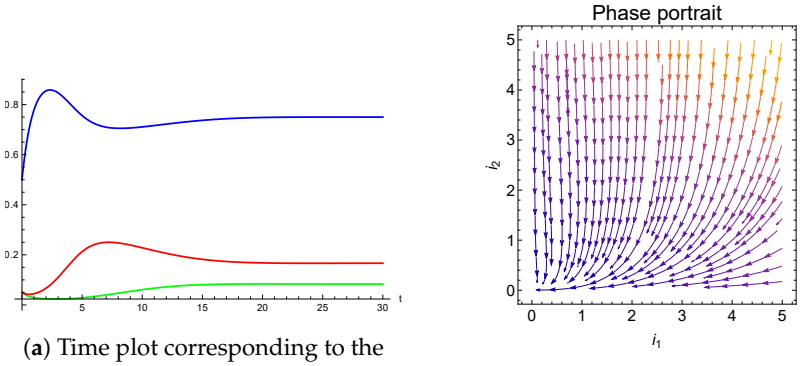


Figure 3. i_1 bifurcation diagram when β_1 varies and $\nu_1 = 0, \nu_2 = \nu = 3 = \beta_2 = 3, b = \sigma_1 = \sigma_2 = 1$, $R_1 = \frac{\beta_1}{2}, R_2 = \frac{3}{2}$, so that x_2 is always positive. Since $R_0 \geq R_2 > 1$, the DFE is never stable. Observe the following three regimes: (a) until $\beta_{12} = 1.5$ is defined by equality in $R_{12} := \frac{\nu(\mathcal{R}_2 - 1)}{d_1 \mathcal{R}_2} + \frac{\mathcal{R}_1}{\mathcal{R}_2} \leq 1 \Leftrightarrow \beta_{12} \leq \frac{\beta_2(b - \nu + \sigma_1)}{b+\sigma_2} + \nu$, where the only stable solution is x_2. (b) At $\beta_{12} = 1.5$, x_2 becomes unstable and the coexistence solution becomes non-negative and stable, until β_{21} is defined by $\mathcal{R}_{21} = \frac{\mathcal{R}_2}{\mathcal{R}_1} - \frac{\nu(\mathcal{R}_1 - 1)}{d_2 \mathcal{R}_1} = 1 \Leftrightarrow \beta_{21} = \frac{(b+\sigma_1)(\beta_2 + \nu)}{b+\nu+\sigma_2} = 2.4$. This is also the first intersection point of the COE and x_1. For a numerical check, at $\beta_{1c} = 2$, defined by $\mathcal{R}_1 = 1 \Leftrightarrow \beta_{1c} = b + \sigma_1$, where the x_1 solution emerges and is initially unstable, the eigenvalues for the COE are $(-1, -0.333333 \pm 0.235702\,\text{Im})$. (c) After $\beta_1 = \beta_{21} \Leftrightarrow \mathcal{R}_{21} < 1$, the x_1 solution becomes stable and the COE loses its stability (the latter was checked numerically). Note that at $\beta_{2c} = 3 \Leftrightarrow \mathcal{R}_1 = R_{12} \Leftrightarrow \beta_1 = \nu$, there is no stability change: the COE and x_1 continue to be unstable and stable, respectively.



(**a**) Time plot corresponding to the dynamics

(**b**) Phase plot at $\beta_{1c} = 2$

Figure 4. Time and phase plot at the point $\beta_{1c} = 2$ illustrating convergence towards COE = $(i_1 \to 0.0833333, i_2 \to 0.166667, s \to 0.75)$. (**a**) (i_1, i_2, s)-time plot at the point $\beta_{1c} = 2$ reveals convergence towards the COE. (**b**) $(i_1, i_2)-$stream plot.

6.2. The Minimal Disease Set of the Multi-Strain Host-Only Dengue Model with Antibody-Dependent Enhancement (ADE) [48]

The ADE (antibody-dependent enhancement) effect, believed to occur for dengue and Zika, means that infection with a single serotype is asymptomatic, but infection with a second serotype may lead to serious illness accompanied by greater infectivity. It was first studied mathematically by [49,50], who showed that for sufficiently small ADE, the numbers of infectives of each serotype synchronize, with outbreaks occurring in phase, but when the ADE increases past a threshold, the system becomes chaotic, and infectives of each serotype desynchronize (however, certain groupings of the primary and secondary infectives remain synchronized even in the chaotic regime). Subsequently, Ref. [51] examined the effects of single-strain vaccine campaigns on the dynamics of an epidemic multi-strain dengue model. We cite now the eloquent dengue description given by these authors:

"What makes modeling the dengue virus so interesting is that it has developed a sophisticated spreading process. Dengue is known to exhibit as many as four coexisting serotypes (strains) in a region. Once a person is infected and recovered from one serotype, they confer life-long immunity from that serotype. However, the antibodies that the body develops for the first serotype will not counteract a second infection by a different serotype. In fact, due to the nature of the disease, the antibodies developed from the first infection form complexes with the second serotype so that the virus can enter more cells, increasing viral production. The increased transmission rate in subsequent infections is known as antibody-dependent enhancement (ADE). ADE is an alarming evolutionary development in multistrain viruses with respect to vaccines. An optimal vaccination would need to cover all strains of the disease at once, or the vaccinations could increase transmission of the strains not covered. This is particularly dangerous for people who have dengue because the infections are more severe in individuals who already have dengue antibodies".

A multi-strain model which adds further compartments allowing for temporary cross-immunity has been developed in the works of Aguiar, Stollenwerk, and Kooi [48,52–55].

In this section, we consider a ten-compartmentasymmetric version of the model of [48], whose variables, denoted by capital letters, represent

1. S as individuals susceptible to both strains;
2. I_i, for $i, j = 1, 2$, as individuals infected with strain i and with temporary cross-immunity to strain $j \neq i$;
3. R_i as individuals who have recovered from strain i, but are not yet susceptible to the other strain j;
4. S_i as individuals who have recovered from strain i, and have become susceptible to the other strain j;
5. $Y_j = I_{ij}$ as individuals previously infected with strain i and are now immune to it, but became reinfected with strain $j, i, j = 1, 2, i \neq j$;

6. R, omitted in (31) since they do not feed back to the other components, as the recovered individuals immune to all the strains.

After denoting by small letters the corresponding proportions, we arrive at:

$$\begin{cases} s' = \mu - s(\beta_1 i_1 + \beta_2 i_2 + \mu + \beta_1 y_1 \phi_1 + \beta_2 y_2 \phi_2), \\ i_1' = \beta_1 s(i_1 + y_1 \phi_1) - i_1(\gamma_1 + \mu), \\ r_1' = \gamma_1 i_1 - r_1(\theta_1 + \mu), \\ s_1' = \theta_1 r_1 - s_1(\beta_2 \alpha_2 (i_2 + y_2 \phi_2) + \mu), \\ y_2' = \beta_2 \alpha_2 s_1 (i_2 + y_2 \phi_2) - y_2(\gamma_2 + \mu), \\ i_2' = \beta_2 s(i_2 + y_2 \phi_2) - i_2(\gamma_2 + \mu), \\ r_2' = \gamma_2 i_2 - r_2(\theta_2 + \mu), \\ s_2' = \theta_2 r_2 - s_2(\beta_1 \alpha_1 (i_1 + y_1 \phi_1) + \mu), \\ y_1' = \beta_1 \alpha_1 s_2 (i_1 + y_1 \phi_1) - y_1(\gamma_1 + \mu). \end{cases} \tag{31}$$

In addition to the DFE where $s = 1$ and all the other compartments are 0, this system also has two other boundary points. With $\mathcal{R}_i = \frac{\beta_i}{\gamma_i + \mu}$, these are:

1. one with $i_2 = r_2 = s_2 = y_1 = y_2 = 0$, given by

$$E_1 = \left(\frac{\mu}{\beta_1}(\mathcal{R}_1 - 1), \frac{\mu \gamma_1}{\beta_1(\alpha_1 + \mu)}(\mathcal{R}_1 - 1), \frac{\alpha_1 \gamma_1}{\beta_1(\alpha_1 + \mu)}(\mathcal{R}_1 - 1), 0, 0, 0, 0, 0, \frac{1}{\mathcal{R}_1} \right),$$

2. and one with $i_1 = r_1 = s_1 = y_1 = y_2 = 0$, given by

$$E_2 = \left(0, 0, 0, 0, \frac{\mu}{\beta_2}(\mathcal{R}_2 - 1), \frac{\mu \gamma_2}{\beta_2(\alpha_2 + \mu)}(\mathcal{R}_2 - 1), \frac{\alpha_2 \gamma_2}{\beta_2(\alpha_2 + \mu)}(\mathcal{R}_2 - 1), 0, \frac{1}{\mathcal{R}_2} \right). \tag{32}$$

Thus, $\mathcal{R}_i, i = 1, 2$ are the bifurcation values at which these two boundary points appear.

The maximal disease set contains $I_i, R_i, S_i, Y_i, i = 1, 2$. The DFE may be determined already using the disease set $I_i, Y_i, i = 1, 2$, which has the advantage of possessing a simple characteristic polynomial with two factors $R_1(X), R_2(X)$, which yields:

$$R_J = \max[R_1(X), R_2(X)], R_1(X) = \frac{\beta_2(\alpha_2 s_1 \phi_2 + s)}{\gamma_2 + \mu}, R_2(X) = \frac{\beta_1(\alpha_1 s_2 \phi_1 + s)}{\gamma_1 + \mu}.$$

Also, our scripts find that

$$R_{ji} = \mathsf{s}_{dfe}\, \mathcal{R}_j, j \neq i, i = 1, 2. \tag{33}$$

Finally, applying the NGM script to $E_i, i = 1, 2$ yields the elegant relation

$$R_0 = \mathsf{s}_{dfe} \max[\mathcal{R}_1, \mathcal{R}_2] = \max[R_{21}, R_{12}]. \tag{34}$$

Remark 18. *Note the notations $R_1(X), R_2(X)$, suggesting that we want to view these as polynomials in the variables of the model, rather than as values evaluated at one of the fixed points.*

We end this section by drawing the attention to the object which allowed for computing the key polynomials $R_1(X), R_2(X)$.

Definition 2. *(A) A minimal disease set $\mathcal{I}$ is a minimal set which still allows the computation of the DFE, after being set to* 0*.*

(B) The model factors are the factors which may admit positive roots in the characteristic polynomial of the Jacobian with all variables in $\mathcal{I}$ set to 0*.*

Remark 19. *Assume w.l.o.g.* $\mathcal{R}_1 < \mathcal{R}_2$. *Two situations may arise:*

$$\begin{cases} \mathsf{s}_{dfe}\mathcal{R}_1 < \mathcal{R}_1 < \mathsf{s}_{dfe}\mathcal{R}_2 < \mathcal{R}_2 \\ \mathsf{s}_{dfe}\mathcal{R}_1 < \mathsf{s}_{dfe}\mathcal{R}_2 < \mathcal{R}_1 < \mathcal{R}_2, \end{cases}$$

and in each of them, 1 *may lie in any of the partition intervals. This gives raise to six disjoint cases:*

$$\begin{cases} \mathcal{R}_1 < \mathcal{R}_2 \leq 1 & \text{the DFE is the only boundary equilibrium} \\ \mathsf{s}_{dfe}\mathcal{R}_1 < \mathsf{s}_{dfe}\mathcal{R}_2 < 1 < \mathcal{R}_1 < \mathcal{R}_2 & \text{both } E_1, E_2 \text{ exist and are unstable} \\ \mathsf{s}_{dfe}\mathcal{R}_1 < 1 < \min[\mathcal{R}_1, \mathsf{s}_{dfe}\mathcal{R}_2] < \mathcal{R}_2 & E_1 \text{ unstable, } E_2 \text{ stable} \\ \mathsf{s}_{dfe}\mathcal{R}_1 < \mathcal{R}_1 < 1 < \mathsf{s}_{dfe}\mathcal{R}_2 < \mathcal{R}_2 & \text{only } E_2 \text{ exists and is stable} \\ \mathsf{s}_{dfe}\max[\mathcal{R}_1, \mathsf{s}_{dfe}\mathcal{R}_2] < 1 < \mathcal{R}_2 & \text{only } E_2 \text{ exists and is unstable} \\ 1 < \mathsf{s}_{dfe}\mathcal{R}_1 < \mathsf{s}_{dfe}\mathcal{R}_2 & \text{competition between the two stable dominants} \\ & \text{strains } E_1, E_2. \end{cases} \tag{35}$$

All these cases have been investigated in detail; for a more general model, see [56], which reviewed in the next section. Thus, it turns out that the results are fully determined by the model factors.

Before proceeding, let us give a name to the very interesting structure we have started to investigate.

Definition 3. *A Descartes multi-strain model of order M is an epidemic model for which the characteristic polynomial of the Jacobian factors are completely over the rationals as a product of terms, where precisely M of which are "Descartes polynomials". For such models, the Jacobian factorization threshold is defined as*

$$R_J(X) := \max_{1 \leq m \leq M} R_m(X).$$

One may check that

Lemma 3. *For Descartes multi-strain models of order K, the local stability set is a subset of*

$$R_J(X) \leq 1.$$

Remark 20. *The example of this section is a Descartes two-strain model (since the characteristic polynomial has only linear factors, precisely two of which have constant coefficients which may change signs).*

6.3. Effects of Single-Strain Vaccination on the Dynamics of a Multi-Strain Host-Only Dengue Model with ADE

In this section, we will show that the mysterious Formula (34) continues to hold under the considerably more complicated two-strains model of [56], with vaccination applied to one strain only. The model studied in [56] is depicted in Figure 5.

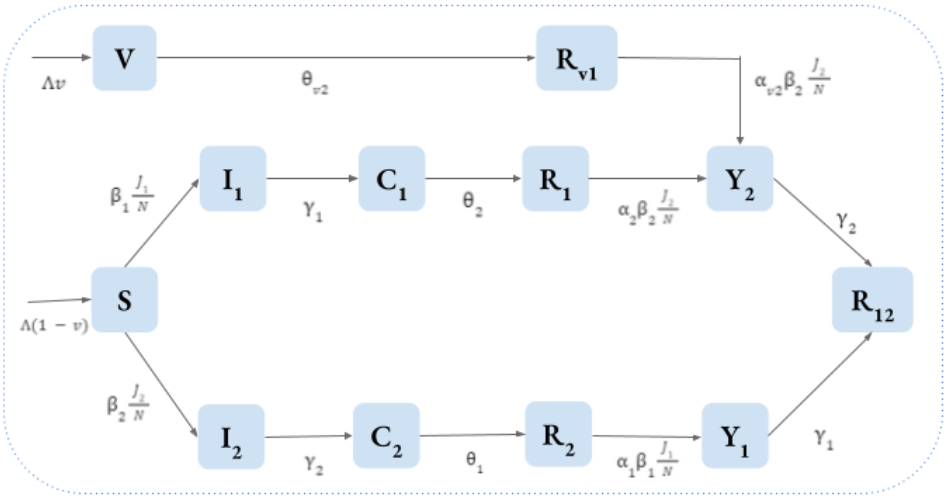


Figure 5. Schematic representation of the infection status due to the concomitant transmission of viruses 1 and 2, considering that the population is vaccinated against virus 1.

This model involves twelve compartments, two of which capture the vaccination against strain 1.

1. $S = S_0$ are individuals susceptible to both strains;
2. I_i, for $i, j = 1, 2$ are individuals infected with strain i, with temporary cross-immunity to strain $j \neq i$;
3. C_i (R_i in the original model of [52]) are individuals recovered from strain i, and hence, are permanently immune to it, with temporary cross-immunity to strain $j \neq i$;
4. R_i (S_i in the original model of [52]) are unvaccinated individuals who have recovered from strain i, but have now become susceptible to the other strain j;
5. Y_j (I_{ij} in the original model of [52]) are individuals previously infected with strain i and are immune to it, but have become reinfected with strain $j, i, j = 1, 2, i \neq j$;
6. $R = R_{12}$ are individuals immune to all the strains;
7. Finally, there are individuals V who are vaccinated against strain 1 and are still susceptible to strain 2, and individuals $R_{v1} = S_v = Z$ who have been vaccinated against strain 1 and have subsequently become infected by strain 2.

Denote by $N(t) = S(t) + V(t) + I_1(t) + I_2(t) + C_1(t) + C_2(t) + R_1(t) + R_2(t) + Y_1(t) + Y_2(t) + S_v(t) + R_{12}(t)$ the total population, put $J_i = I_i + Y_i, \quad i = 1, 2$, and assume that the two forces of infection acting on S are:

$$F_i = \beta_i \frac{J_i}{N},$$

and that the forces of infection acting on $Y_i = S_i, i = 1, 2$ are:

$$\alpha_1\beta_1 \frac{J_1}{N}, \alpha_2\beta_2 \frac{J_2}{N}, \alpha_v\beta_2 \frac{J_2}{N},$$

where $\alpha_1, \alpha_2, \alpha_v$ denote the decreases or increases in the susceptibility to secondary infections ($\alpha_i > 1$ implying an ADE effect).

The following equations, with appropriate initial conditions, represent the disease dynamics model:

$$
\begin{aligned}
\frac{dS}{dt} &= (1-\xi)\mu - \beta_1 J_1 \frac{S}{N} - \beta_2 J_2 \frac{S}{N} - \mu S \\
\frac{dI_1}{dt} &= \beta_1 J_1 \frac{S}{N} - (\gamma_1 + \mu) I_1 \\
\frac{dC_1}{dt} &= \gamma_1 I_1 - (\theta_1 + \mu) C_1 \\
\frac{dR_1}{dt} &= \theta_2 C_1 - \alpha_2 \beta_2 J_2 \frac{R_1}{N} - \mu R_1 \\
\frac{dY_2}{dt} &= \alpha_2 \beta_2 J_2 \frac{R_1}{N} + \alpha_v \beta_2 J_2 \frac{S_v}{N} - (\gamma_2 + \mu) Y_2 \\
\frac{dI_2}{dt} &= \beta_2 J_2 \frac{S}{N} - (\gamma_2 + \mu) I_2 \\
\frac{dC_2}{dt} &= \gamma_2 I_2 - (\theta_2 + \mu) C_2 \\
\frac{dR_2}{dt} &= \theta_1 C_2 - \alpha_1 \beta_1 J_1 \frac{R_2}{N} - \mu R_2 \\
\frac{dY_1}{dt} &= \alpha_1 \beta_1 J_1 \frac{R_2}{N} - (\gamma_1 + \mu) Y_1 \\
\frac{dV}{dt} &= \xi\mu - (\theta_v + \mu) V \\
\frac{dS_v}{dt} &= \theta_v V - \alpha_v \beta_2 J_2 \frac{S_v}{N} - \mu S_v \\
\frac{dR_{12}}{dt} &= \gamma_1 Y_1 + \gamma_2 Y_2 - \mu R_{12}
\end{aligned}
\tag{36}
$$

Table 1 summarizes the parameters and compartments of the model.

Table 1. Parameters and compartments of the model.

Parameter	Description (for $i, j = 1, 2$)
μ	Birth rate
μ	Per capita death rate
β_i	Transmission rate of virus i
γ_i	Per capita recovery rate of infected people with virus i
θ_i	Per capita loss rate of cross-immunity to virus i after previous infection with virus j
θ_v	Per capita loss rate of cross-immunity to virus 2 obtained via vaccination
α_i	ADE factor that can alter the susceptibility of unvaccinated individuals to the virus i
α_v	ADE factor that can alter the susceptibility of vaccinated individuals to virus 2
ξ	Per capita vaccination rate
Compartments	**Description**
S	Susceptible individuals to both viruses
V	Vaccinated individuals against the virus 1
I_i	Individuals with primary infection by the virus i
C_i	Individuals recovered from infection with virus i and have cross-immunity to virus j
R_i	Unvaccinated individuals immune to virus i and susceptible to virus j
$Z = S_v$	Individuals vaccinated for virus 1, and susceptible to virus 2
Y_1	Individuals infected by virus 1 and recovered and hence, immune to virus 2
Y_2	Individuals infected by virus 2 and immune to virus 1 either due to recovery or vaccination
R_{12}	Individuals immune to both virus

This system does not have negative cross effects; therefore, it leaves the non-negative quadrant invariant [57]. It follows from the equations that

$$\frac{dN(t)}{dt} = \mu(1 - N(t)).$$

Therefore,

$$\lim_{t \to +\infty} N(t) = 1.$$

Assuming $N(0) = 1$ implies that $N(t) = 1$, for $t \geq 0$. Using this, we may assume w.l.o.g. that $N = 1$, working with the proportions, is to be denoted by the corresponding lowercase letters.

The only non-zero compartments in the DFE, to be denoted by E_0, are easily found to be

$$s_0 = 1 - \xi, z_0 = \xi \frac{\theta_v}{\mu + \theta_v}, v_0 = \xi \frac{\mu}{\mu + \theta_v};$$

in fact, the last value holds at any fixed point. As known from [56], there are also two endemic points on the boundary, whose rather complicated formulas will be given later.

Remark 21. *From a modeling point of view, this system has crucial parameters like α_v (note that $\alpha_v = 0$ means perfect vaccination, and $\alpha_v = 1$, which means that infection by the second strain is equally likely for vaccinated people).*

Due to conservation, the system evolves in a compact domain, and so we may eliminate one compartment, for example, V, from the analysis. Finally, the last compartment does not send input to the others and therefore may also be disregarded in the analysis.

6.3.1. The Jacobian $R_J(X)$ is the Max of Two Polynomials, Obtained Using a Minimal Disease Set

We may tackle this example via the Jacobian factorization approach, choosing the **minimal disease set** $\mathcal{I} = (i_1, i_2, y_1, y_2)$, just like in the previous section. Again, the characteristic polynomial of the Jacobian with the variables in $\mathcal{I}$ are set to 0 factors completely as a product of the linear terms

$$(\mu + u)^5(\gamma_1 + \mu + u)(\gamma_2 + \mu + u)(\theta_1 + \mu + u)(\theta_2 + \mu + u)(\mu + u + \theta_v)\times$$

$$(\gamma_1 + \mu - \alpha_1\beta_1 r_2 - \beta_1 s + u)(\gamma_2 + \mu - \alpha_2\beta_2 r_1 - \beta_2 s - \beta_2 z\alpha_v + u),$$

only two of which (the seventh and eighth factors) may yield positive eigenvalues. Both are of the Descartes type, and instability may occur if

$$R_J(X) := \max[R_1(X), R_2(X)] = \max[\frac{\beta_1(\alpha_1 r_2 + s)}{\gamma_1 + \mu}, \frac{\beta_2(\alpha_2 r_1 + z\alpha_v + s)}{\gamma_2 + \mu}] > 1. \quad (37)$$

At the DFE, $r_1 = r_2 = 0$, and this yields

$$R_J := R_J(E_0) = R_N = \max[s_0\frac{\beta_1}{d_1}, s_0\frac{\beta_2}{d_2} + z_0\frac{\beta_2\alpha_v}{d_2}], \quad d_1 = \gamma_1 + \mu, d_2 = \gamma_2 + \mu. \quad (38)$$

This expression reveals a pattern similar to (16), with the difference that the existence of two strains are reflected in the max and that the second strain is alimented by two classes of susceptibles, one of which is the people vaccinated against the first strain.

In addition to the disease-free equilibrium, there might exist two more equilibriums on the boundary: the endemic equilibrium where there are only infections by strain 1, E_1, and the endemic equilibrium where there are only infections by strain 2, E_2; this will be reviewed in the next section.

6.3.2. The Endemic Boundary Equilibrium E_i Exist If $R_i(E_0) > 1$

At the equilibrium E_1, the values of I_2, C_2, R_2, Y_1, Y_2 and R_{12} are zero. The coordinates are easily found using the "Solve" command. Those of V, Z are the same as at the DFE, and the others are:

$$s_1 = \frac{\gamma_1 + \mu}{\beta_1},\ i_1 = \frac{\mu}{\beta_1}\left[\frac{1 - \xi}{s_1} - 1\right] := \frac{\mu}{\beta_1}(\mathcal{R}_1 - 1),\ c_1 = \frac{\gamma_1}{\theta_1 + \mu}i_1,\ r_1 = \frac{\theta_1}{\mu}c_1 \quad (39)$$

where

$$\mathcal{R}_1 = (1-\xi)\frac{\beta_1}{\gamma_1+\mu} = R_1(E_0) \tag{40}$$

(the endemic equilibrium E_1 exists if and only if $\mathcal{R}_1 > 1$).

At the equilibrium E_2, the values of I_1, C_1, R_1 and Y_1 are zero, and that of V is the same as at the DFE.

The solutions of the E_2 system involve all complicated square roots. In such a case, it is more convenient to replace the "Solve" command by our RUR algorithm, which requires the user to input a variable to reduce 2. The normal choice is i_2 (which transitions to positive at the bifurcation value), but here we will use s, to check the results of [56], who find, using as a reduction scalar $x = \beta_2 j_2$, that

$$\begin{aligned}
s_2 &= \frac{(1-\xi)\mu}{x+\mu}, \quad i_2 = \frac{(1-\xi)x\mu}{(x+\mu)(\gamma_2+\mu)}, \quad c_2 = \frac{(1-\xi)x\gamma_2\mu}{(x+\mu)(\gamma_2+\mu)(\theta_1+\mu)},\\
r_2 &= \frac{(1-\xi)x\gamma_2\theta_1}{(x+\mu)(\gamma_2+\mu)(\theta_1+\mu)}, \quad z_2 = \frac{v\theta_v\mu}{(\theta_v+\mu)(\alpha_v x+\mu)},\\
y_2 &= \frac{v\alpha_v x\theta_v\mu}{(\alpha_v x+\mu)(\theta_v+\mu)(\gamma_2+\mu)},
\end{aligned} \tag{41}$$

and that x is the solution of the quadratic equation

$$ax^2+bx+c=0, \quad \begin{cases} a &= \alpha_v \\ b &= \mu\alpha_v\left[1-\frac{\beta_2(1-\xi)}{\gamma_2+\mu}\right]+\mu\left[1-\frac{\beta_2\alpha_v\theta_v v}{(\gamma_2+\mu)(\theta_v+\mu)}\right]. \\ c &= \mu^2(1-\mathcal{R}_2) \end{cases}$$

The equilibrium E_2 exists if $\mathcal{R}_2 > 1$, where

$$\mathcal{R}_2 = \frac{\beta_2}{\gamma_2+\mu}\left[1-\xi+\xi\frac{\alpha_v\theta_v}{\theta_v+\mu}\right] = \frac{\beta_2}{\gamma_2+\mu}[s_0+\alpha_v z_0] = R_2(E_0). \tag{42}$$

If $\mathcal{R}_2 \leq 1$, the fractions in the expression of b must be smaller than one or equal to one, and it is not possible for both to be one. Therefore, $b > 0$. We also have $c \geq 0$. Since that $a > 0$, Equation (42) does not have roots with positive real parts. This implies that there is no endemic equilibrium like E_2. Thus, in this case, $c < 0$. Since the coefficient a is positive, Equation (42) has two real roots and only one of them is positive. To resume, if $\mathcal{R}_2 > 1$, there is a unique endemic equilibrium where there are infections only by strain 2.

6.3.3. The Recipe next-generation matrix R_0 and the Jacobian Factorization One Coincide

This section shows that the polynomials $R_1(X), R_2(X)$ in this example may also be obtained via the next-generation matrix approach as eigenvalues of the K matrix via a judicious choice of infectious classes.

One may choose, as the infectious subset, the nine compartments that are 0 in the limit, but a luckier choice here is the smaller subset $\mathcal{I} = \{I_1, I_2, Y_2, Y_1\}$, which precisely has, as eigenvalues, the expressions $R_1(X), R_2(X)$ in (37).

The decomposition matrices are

$$V = \begin{pmatrix} \gamma_1+\mu & 0 & 0 & 0 \\ 0 & \gamma_2+\mu & 0 & 0 \\ 0 & 0 & \gamma_1+\mu & 0 \\ 0 & 0 & 0 & \gamma_2+\mu \end{pmatrix}, F = \begin{pmatrix} \beta_1 s & 0 & 0 & \beta_1 s \\ 0 & \beta_2 s & \beta_2 s & 0 \\ 0 & \beta_2 z\alpha_v & \beta_2\zeta\alpha_v & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} = sB_0 + zB_v,$$

where B_0, B_v are:

$$B_0 = \begin{pmatrix} \beta_1 & 0 & 0 & \beta_1 \\ 0 & \beta_2 & \beta_2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \; B_v = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \beta_2\alpha_v & \beta_2\alpha_v & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The explicit non-zero eigenvalues of the next-generation matrix $(\mathsf{s}B_0 + zB_v)V^{-1}$ are

$$\left(\frac{\beta_1 \mathsf{s}}{\gamma_1 + \mu}, \frac{\beta_2(z\alpha_v + \mathsf{s})}{\gamma_2 + \mu}\right), \tag{43}$$

confirming the result of the Jacobian method.

Let us note finally that (37), as well as the result of this section, imply the relation

$$R_0 = \max[\mathcal{R}_1, \mathcal{R}_2], \tag{44}$$

where $\mathcal{R}_i, i = 1, 2$ denote the bifurcation parameters at which the boundary points E_i start to exist.

Remark 22. *Interestingly, $R_0 = \max[\mathcal{R}_1, \mathcal{R}_2]$ is the max of two quantities which satisfy that $\mathcal{R}_i > 1, i = 1, 2$ are precisely the domains where endemic points E_i containing exactly one of the strains appear—see* (44)*. This formula, natural in cases where the next-generation matrix has a block structure, seems to be a general feature of multi-strain models, even when the block structure is not apparent.*

In the case of this section, there seems to be a more specific structure: the Jacobian factorization approach allows for introducing two "Descartes type" (see Definition 1) factors $R_i(X), i = 1, 2$ of the characteristic polynomial, which are that

1. *The existence conditions for E_i may be expressed as $\mathcal{R}_i := R_i(DFE) > 1$—see* (40), (42), *and* (46).
2. *The invasion reproduction numbers may be obtained simply by substituting the coordinates of the dominance boundary equilibria into the corresponding factor. More precisely, the invasion number of the fixed point E_i for strain i is given by $R_{ji} = R_j(E_i)$.*

Open question 2: Does the relation $R_0 = \max_1^K \mathcal{R}_k$ hold for all Descartes multi-strain models of order K? (recall Definition 3 and Lemma 3).

6.3.4. The Invasion Reproduction Number of E_i is Given by $R_j(E_i)$

The invasion reproduction numbers (see for example [58]) may, just as the basic reproduction number, be calculated using the next-generation matrix.

Our script yields quickly that

$$\mathcal{R}_{ji} = R_j(E_i), i = 1, 2, j \neq i. \tag{45}$$

Open question 3: Do the formulas connecting (44) and (45) to the Jacobian factorization

$$\begin{cases} \mathcal{R}_i = R_i(E_0), R_0 = \max[\mathcal{R}_1, \mathcal{R}_2], \\ \mathcal{R}_{ji} = R_j(E_i), \text{ where } R_i \text{ denote polynomials obtained via} \\ \text{the Jacobian factorization approach,} \end{cases} \tag{46}$$

hold for some general class of epidemic models?

(C) For "two strain epidemic models", what conditions must be satisfied to ensure the inequalities $\mathcal{R}_{ji} < \mathcal{R}_j, i = 1, 2, j \neq i$?

To resolve these questions, it might be useful to study the three and four strain generalizations of this problem and to investigate "non-simple" multi-strain models (in which the characteristic polynomial contains non-Descartes type polynomials).

7. Vector–Host Models

7.1. The Jacobian R_0 is the Square of the Recipe NGM R_0 for the Dengue Vector–Host Model without Demography of [30]

Ref. ([30] eq(28)) considers a "no demography/conservation" model with six compartments, three of which represent hosts, while the rest represent the vector. Note that such models with no demography do not have a finite set of fixed points. The DFE is not unique, it coincides with the initial conditions. However, our algorithm works just fine. The model, after removing two "R" classes which do not affect the rest, is:

$$\begin{cases} S_1' = -\frac{\beta_{21} I_2 S_1}{N_1} \\ S_2' = -\frac{\beta_{12} I_1 S_2}{N_2} \\ \begin{pmatrix} I_1' \\ I_2' \end{pmatrix} = \begin{pmatrix} -\gamma_1 & \frac{\beta_{21} S_1}{N_1} \\ \frac{\beta_{12} S_2}{N_2} & -\gamma_2 \end{pmatrix} \begin{pmatrix} I_1 \\ I_2 \end{pmatrix} \end{cases} . \tag{47}$$

The call "inf $= \{1,2\}; NGM[Brouwer22, \text{inf}]$" of our script yields that the decomposition matrices are

$$F = \begin{pmatrix} 0 & \frac{\beta_{21} S_1}{N_1} \\ \frac{\beta_{12} S_2}{N_2} & 0 \end{pmatrix}, \; V = \begin{pmatrix} \gamma_1 & 0 \\ 0 & \gamma_2 \end{pmatrix},$$

$$K = \begin{pmatrix} 0 & \frac{\beta_{21} S_1}{\gamma_2 N_1} \\ \frac{\beta_{12} S_2}{\gamma_1 N_2} & 0 \end{pmatrix},$$

and

$$R_F = \sqrt{\frac{S_1 S_2 \beta_{12} \beta_{21}}{N_1 N_2 \gamma_1 \gamma_2}}. \tag{48}$$

After using the fact that the DFE is determined by the initial conditions $S_1 = N_1$, and $S_2 = N_2$, we obtain the basic reproduction number

$$R_F = \sqrt{\frac{\beta_{12} \beta_{21}}{\gamma_1 \gamma_2}} \tag{49}$$

of ([30] eq(40)).

Here the characteristic polynomial is of the Descartes type and the Jacobian method, as well as the RUR method, yielding for both the square of the (modified) formula (48) $R_J = \frac{\beta_{12} \beta_{21}}{\gamma_1 \gamma_2}$.

Remark 23. *Note that ([30] eq(35)) offers yet another admissible decomposition, based on a different biological interpretation, with $R_F = R_J$, and raises the question of which of the answers is more relevant for a given epidemic. Deciding this from the ODE model only seems impossible.*

7.2. The Two Groups Model in ([21] eq(5.8)) Does not Obey a Square Relation

The two groups model in ([21] eq(5.8)) defined by

$$\begin{cases} S_1' = -\frac{\beta_{11} I_1 S_1}{N_1} - \frac{\beta_{21} I_2 S_1}{N_1} + \lambda_1 - \mu_1 S_1 \\ S_2' = -\frac{\beta_{12} I_1 S_2}{N_2} - \frac{\beta_{22} I_2 S_2}{N_2} + \lambda_2 - \mu_2 S_2 \\ \begin{pmatrix} I_1' \\ I_2' \end{pmatrix} = \begin{pmatrix} -\gamma_1 - \mu_1 - \delta_1 + \frac{\beta_{11} S_1}{N_1} & \frac{\beta_{21} S_1}{N_1} \\ \frac{\beta_{12} S_2}{N_2} & \frac{\beta_{22} S_2}{N_2} - \gamma_2 - \mu_2 - \delta_2 \end{pmatrix} \begin{pmatrix} I_1 \\ I_2 \end{pmatrix} \end{cases}$$

is not a vector–host model anymore, due to the addition of the "intra-group contact infection rates" β_{11}, β_{22}.

The DFE is $\left\{0, 0, \frac{\lambda_1}{\mu_1}, \frac{\lambda_2}{\mu_2}\right\}$, and the R_N is quite complicated:

$$\begin{aligned}&\frac{\sqrt{(\beta_{22}N_1S_2(\gamma_1+\delta_1+\mu_1)+\beta_{11}N_2S_1(\gamma_2+\delta_2+\mu_2))^2+4(\beta_{12}\beta_{21}-\beta_{11}\beta_{22})N_1N_2S_1S_2(\gamma_1+\delta_1+\mu_1)(\gamma_2+\delta_2+\mu_2)}}{2N_1N_2(\gamma_1+\delta_1+\mu_1)(\gamma_2+\delta_2+\mu_2)}\\&+\frac{\beta_{22}\gamma_1N_1S_2+\beta_{11}\gamma_2N_2S_1+\beta_{22}\delta_1N_1S_2+\beta_{11}\delta_2N_2S_1+\beta_{22}\mu_1N_1S_2+\beta_{11}\mu_2N_2S_1}{2N_1N_2(\gamma_1+\delta_1+\mu_1)(\gamma_2+\delta_2+\mu_2)}.\end{aligned} \tag{50}$$

The Jacobian factorization method yields a different answer for a characteristic polynomial which is not of the Descartes type, precisely because of the addition of β_{11}, β_{22}.

$$R_J = \frac{\beta_{22}N_1S_2(\gamma_1+\delta_1+\mu_1)+\beta_{11}\gamma_2N_2S_1+\beta_{11}\delta_2N_2S_1+\beta_{11}\mu_2N_2S_1+\beta_{12}\beta_{21}S_1S_2}{N_1N_2(\gamma_1+\delta_1+\mu_1)(\gamma_2+\delta_2+\mu_2)+\beta_{11}\beta_{22}S_1S_2}.$$

8. Multi-Strain Vector–Host Models

8.1. A Two-Strain Vector–Host Model of Feng and Velasco-Hernández [59], Where the Square Relation Holds for the Basic Reproduction Number

Ref. [59] considered a human population settled in a region where a mosquito population of the genus Aedes is present and is a carrier of two strains of the dengue virus. Let $V_i, I_i, Y_i, i = 1, 2$ denote the infected mosquitoes, individuals infected by one strain, and individuals having suffered a secondary infection, respectively, let $N = S + R + \sum_{i=1}^{2} I_i + Y_i$ denote the total human population, and let $B_1 = \frac{\beta_1 V_1(t)}{c+w_h N}, B_2 = \frac{\beta_2 V_2(t)}{c+w_h N}$ denote the rates of infections in human hosts produced by the two strains. The model is defined as follows:

$$\begin{cases}S'(t) = h - S(t)(B_1 + B_2) - \mu S(t),\\ I_1'(t) = B_1 S(t) - \sigma_2 B_2 I_1(t) - \mu I_1(t),\\ I_2'(t) = B_2 S(t) - \sigma_1 B_1 I_2(t) - \mu I_2(t),\\ Y_1'(t) = \sigma_1 B_1 I_2(t) - (e_1 + \mu + r) Y_1(t),\\ Y_2'(t) = \sigma_2 B_2 I_1(t) - (e_2 + \mu + r) Y_2(t),\\ R'(t) = r(Y_1(t) + Y_2(t)) - \mu R(t),\\ \\ V_1'(t) = \alpha_1 \frac{I_1(t)+Y_1(t)}{c+w_v N} M(t) - \delta V_1(t),\\ V_2'(t) = \alpha_2 \frac{I_2(t)+Y_2(t)}{c+w_v N} M(t) - \delta V_2(t)\\ M'(t) = q - M(t)\left(\alpha_1 \frac{I_1(t)+Y_1(t)}{c+w_v N} + \alpha_2 \frac{I_2(t)+Y_2(t)}{c+w_v N}\right) - \delta M(t).\end{cases}$$

The DFE is given by $E_0 = (h/\mu, 0, 0, 0, 0, 0, 0, q/\delta)$. For the infectious set $I_1, I_2, Y_1, Y_2, V_1, V_2$, the F and V matrices used in the next-generation approach are given by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & \beta_1 s_{dfe} & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_2 s_{dfe} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha_1 M_{dfe} & 0 & \alpha_1 M_{dfe} & 0 & 0 & 0 \\ 0 & \alpha_2 M_{dfe} & 0 & \alpha_2 M_{dfe} & 0 & 0 \end{pmatrix}, \tag{51}$$

$$V = \begin{pmatrix} \mu & 0 & 0 & 0 & 0 & 0 \\ 0 & \mu & 0 & 0 & 0 & 0 \\ 0 & 0 & e_1 + r + \mu & 0 & 0 & 0 \\ 0 & 0 & 0 & e_2 + r + \mu & 0 & 0 \\ 0 & 0 & 0 & 0 & \delta & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta \end{pmatrix} \tag{52}$$

with $M_{dfe} = q/\delta$. Then,

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{\beta_1 s_{dfe}}{\delta} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_2 s_{dfe}}{\delta} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\alpha_1 M_{dfe}}{\mu} & 0 & \frac{\alpha_1 M_{dfe}}{e_1+\mu+\tilde{\xi}} & 0 & 0 & 0 \\ 0 & \frac{\alpha_2 M_{dfe}}{\mu} & 0 & \frac{\alpha_2 M_{dfe}}{e_2+\mu+\tilde{\xi}} & 0 & 0 \end{pmatrix}$$

We obtain a basic reproduction number, which is a max

$$\mathcal{R} = max\left(\sqrt{\mathcal{R}_1}, \sqrt{\mathcal{R}_2}\right), \mathcal{R}_i := s_0 m_0 \frac{\alpha_i \beta_i}{\delta \mu}, \tag{53}$$

just like (44), but also contains the extra square roots typical of vector–host models.

Furthermore, it may be checked that this is precisely the square root of the answer given by the Jacobian factorization method, which decomposes the characteristic polynomial of the Jacobian as the product of five linear factors with negative roots and two quadratic Descartes type polynomials.

There also two boundary (dominance) equilibria where only one strain survives. The non-zero coordinates at the first one, E_1, are given by

$$\alpha_1 i_1 = \delta \frac{\mathcal{R}_1 - 1}{m_0 \beta_1 / (\mu) + 1}, \beta_1 v_1 = \mu \frac{\mathcal{R}_1 - 1}{s_0 \alpha_1 (\delta) + 1}, s = \mu \frac{\alpha_1 s_0 + \delta}{\alpha_1 \beta_1 m_0 + \alpha_1 \mu},$$

with similar formulas holding for the other boundary point E_2, using symmetry. Thus, these points become positive precisely when the corresponding factor of the DFE becomes bigger than 1, causing instability.

Since we had trouble with computing the invasion reproduction numbers, we switched to the "simplified model" of [59], in which M is eliminated by noting that the equation for the total vector population $T = M + V_1 + V_2$ is $T' = q - \delta T$, and also by assuming that $T_0 = \lim_{t\to\infty} T(t) = q/\delta$, M can be removed from the system by substituting

$$M = q/\delta - V_1 - V_2. \tag{54}$$

As a first consequence of using (54), the R_N becomes equal to R_J.

However, the recipe R_0 at E_1 for the natural choice of "inf" is very complicated, and [59] provides here a laborious local stability analysis, with a complicated result, via the third-order Routh–Hurwitz conditions.

We note finally that the characteristic polynomial for $jac(E_1)$ has two factors of degree 3, one of which is the Descartes type, and one which is not. The Descartes type factor yields a polynomial $R_1(X)$. Putting this together with its symmetric $R_2(X)$ allows us to finally define

$$R_J(X) = max_j[R_1(X), R_2(X)] = max_j[\frac{\alpha_j \beta_j q s/\delta}{(\beta_j v_j + \mu)(\alpha_j i_j + \delta) + \beta_j v_j \alpha_j s}].$$

Invasion Numbers of [59]

The two-strain vector–host model in [59] admits two boundary equilibria beside the DFE in which

$S_1^*, S_2^*, I_1^*, I_2^*, V_1^*, V_2^*$ are the invasion infection classes. In this case, we consider the subset $\text{in}_1 = (I_2, Y_1, Y_2, V_2)$ corresponding to the invasion infection class of E_1, then

$$F = \begin{pmatrix} 0 & 0 & 0 & b_2 S \\ b_1\sigma_1 v_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_2 i_1 \sigma_2 \\ a_2\left(\frac{q}{\delta} - v_1\right) & 0 & a_2\left(\frac{q}{\delta} - V_1\right) & 0 \end{pmatrix}, \tag{55}$$

$$V = \begin{pmatrix} b_1\sigma_1 V_1 + \mu & 0 & 0 & 0 \\ 0 & e_1 + \mu + \xi & 0 & 0 \\ 0 & 0 & e_2 + \mu + \xi & 0 \\ a_2\left(\frac{q}{\delta} - V_1\right) - a_2\left(\frac{q}{\delta} - V_1 - V_2\right) & 0 & a_2\left(\frac{q}{\delta} - V_1\right) - a_2\left(\frac{q}{\delta} - V_1 - V_2\right) & a_2(I_2 + Y_2) + \delta \end{pmatrix}, \tag{56}$$

$$K = \begin{pmatrix} 0 & 0 & 0 & \frac{b_2 S}{\delta} \\ \frac{b_1\sigma_1 V_1}{b_1\sigma_1 V_1 + \mu} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{b_2 I_1 \sigma_2}{\delta} \\ \frac{a_2\left(\frac{q}{\delta} - V_1\right)}{b_1\sigma_1 V_1 + \mu} & 0 & \frac{a_2\left(\frac{q}{\delta} - V_1\right)}{e_2 + \mu + \xi} & 0 \end{pmatrix}$$

then the IRN of strain 1 at E_1 is

$$R_1 = \frac{\sqrt{a_2}\sqrt{b_2}\sqrt{q}\sqrt{S(e_2 + \mu + \xi)}}{\delta\sqrt{\mu}\sqrt{e_2 + \mu + \xi}}.$$

Similarly, we chose the other subset $\text{in}_1 = (I_1, Y_1, Y_2, V_1)$ corresponding to the invasion infection class at E_2, where we obtain

$$F = \begin{pmatrix} 0 & 0 & 0 & b_1 S \\ 0 & 0 & 0 & b_1 I_2 \sigma_1 \\ b_2\sigma_2 V_2 & 0 & 0 & 0 \\ a_1\left(\frac{q}{\delta} - V_2\right) & a_1\left(\frac{q}{\delta} - V_2\right) & 0 & 0 \end{pmatrix}, \tag{57}$$

$$V = \begin{pmatrix} b_2\sigma_2 V_2 + \mu & 0 & 0 & 0 \\ 0 & e_1 + \mu + \xi & 0 & 0 \\ 0 & 0 & e_2 + \mu + \xi & 0 \\ a_1\left(\frac{q}{\delta} - V_2\right) - a_1\left(\frac{q}{\delta} - V_1 - V_2\right) & a_1\left(\frac{q}{\delta} - V_2\right) - a_1\left(\frac{q}{\delta} - V_1 - V_2\right) & 0 & a_1(I_1 + Y_1) + \delta \end{pmatrix}, \tag{58}$$

$$K = \begin{pmatrix} 0 & 0 & 0 & \frac{b_1 S}{\delta} \\ 0 & 0 & 0 & \frac{b_1 I_2 \sigma_1}{\delta} \\ \frac{b_2\sigma_2 V_2}{b_2\sigma_2 V_2 + \mu} & 0 & 0 & 0 \\ \frac{a_1\left(\frac{q}{\delta} - V_2\right)}{b_2\sigma_2 V_2 + \mu} & \frac{a_1\left(\frac{q}{\delta} - V_2\right)}{e_1 + \mu + \xi} & 0 & 0 \end{pmatrix}$$

then the maximum eigenvalue of K yields the IRN at E_2 which is

$$R_2 = \frac{\sqrt{a_1}\sqrt{b_1}\sqrt{q - \delta v_2}\sqrt{I_2\sigma_1(b_2\sigma_2 V_2 + \mu) + e_1 S + S(\mu + \xi)}}{\delta\sqrt{e_1 + \mu + \xi}\sqrt{b_2\sigma_2 V_2 + \mu}}.$$

8.2. The dengue–Zika Model with Coinfection and ADE [2]

The model studied in this paper continues previous papers like Isea and Lonngren 2016 [60] and Okuneye et al. 2017 [61], most notably by taking into account the possibility of coinfection and of direct transmission of Zika via sex (which entails two forces of infection for Zika transmissions in their flowchart, hence leading to an asymmetry in the results).

Introduce the following forces of infection:

$$\begin{cases} F_{vd} = \beta_{hd} T_{vd}, T_{vd} = I_{vd} + I_{vc}\nu_d, & \text{dengue vector force} \\ F_{vz} = \beta_{hz} T_{vz}, T_{vz} = I_{vz} + I_{vc}\nu_z, & \text{zika vector force} \\ F_{hz} = \beta_{vz} T_{hz}, T_{hz} = I_z + I_c + J_z k_z, & \text{zika human force} \\ F_{hd} = \beta_{vd} T_{hd}, T_{hd} = I_d + I_c + J_d k_d, & \text{dengue human force} \\ F_s = \beta_s T_{hz} & \text{zika human-to-human force.} \end{cases} \tag{59}$$

Note that ν_d, ν_z and k_d, k_z are, respectively, the parameters of altered infectivity for co-infected vectors and of ADE, and note that even when $\nu_d = \nu_z = 1$, the co-infection model is more accurate than previous works like [59], since it takes into account the existence of doubly infected vectors I_{vc} which influence both chains of infection.

We will consider the model :

$$\begin{cases} S_h' = (N_h - S_h)\mu - S_h(F_{vd} + F_{vz} + F_s), \\ I_d' = S_h F_{vd} - \rho I_d(F_{vz} + F_s) - I_d(\gamma_d + \mu), \\ I_z' = S_h(F_{vz} + F_s) - \rho I_z F_{vd} - I_z(\gamma_d + \mu), \\ I_c' = \rho[I_d(F_{vz} + F_s) + I_z F_{vd} - I_c(\gamma_d + \gamma_c)] - \mu I_c, \\ R_d' = I_d\gamma_d - R_d(F_{vz} + F_s + \mu), \\ R_z' = I_z\gamma_d - R_z(F_{vd} + \mu), \\ J_d' = \rho\gamma_z I_c + R_z(F_{vd} - \gamma_d - \mu), \\ J_z' = \rho\gamma_d I_c + R_d(F_{vz} + F_s - \gamma_z - \mu), \\ R' = J_d\gamma_d + J_z\gamma_z - \mu R, \\ S_v' = (N_v - S_v)\mu_v - S_v(F_{hd} + T_{hz}), \\ I_{vd}' = F_{hd} S_v - \rho F_{hz} I_{vd} - I_{vd}\mu_v, \\ I_{vz}' = F_{hz} S_v - \rho F_{hd} I_{vz} - I_{vz}\mu_v, \\ I_{vc}' = \rho(F_{hz} I_{vd} + F_{hd} I_{vz}) - I_{vc}\mu_v, \end{cases} \tag{60}$$

which generalizes a bit [2] by introducing the parameter ρ, whose purpose is to allow for simplifying the model to remove the I_c, I_{vc} classes, by setting $\rho = 0$.

Note that humans are born fully susceptible to dengue and Zika at a rate of μN_h, where μ is the natural birth/death rate for humans and N_h is the total human population. Susceptible individuals can become infected with dengue from either a dengue-infected (I_{vd}) or coinfected female mosquito (I_{vc}). The mosquito-to-human dengue infection rate is given by β_{hd}. This rate is modified by a factor of ν_d to indicate the altered infectivity of coinfected mosquitoes. Once infected with dengue, humans can recover or become co-infected with Zika (by a Zika-infected (I_{vz}) or a coinfected female mosquito (I_{vc}), or via sexual transmission from a Zika-infected (I_z) or coinfected (I_c) human) and transition into the Rd or Ic class, respectively. In a similar manner, fully susceptible humans become infected with Zika from a mosquito in the I_{vz} or I_{vc} compartment.

The DFE has only non-zero components $S_v = N_v, S_h = N_h$. Choosing, as the infectious set, all the compartments except S_v, S_h yields

$$R_0 = \max[\sqrt{\frac{\beta_{hd} N_v \beta_{vd}}{N_h \mu_v(\gamma_d + \mu)}}, \frac{\beta_s + \sqrt{\beta_s^2 + \frac{4N_v\beta_{hz}\beta_{vz}(\mu+\gamma_z)}{N_h\mu_v}}}{2(\mu + \gamma_z)}] := \max[\mathcal{R}_d, \mathcal{R}_z], \tag{61}$$

confirming ([2] (Section 4)) and also the multi-strain structure we already met in (44) and (53). Furthermore, one may show that $\mathcal{R}_d > 1, \mathcal{R}_z > 1$ are necessary and sufficient conditions for the existence of the dengue-only and Zika-only fixed points—see subsequent sections.

We end this section by reporting on the Jacobian factorizations at E_0, when choosing as the infectious set

$$\mathcal{I} = \{I_d, I_z, I_c, J_d, J_z, I_{vd}, I_{vz}, I_{vc}\}.$$

Now the characteristic polynomial has two second-order factors:

1. One of the Descartes type which yields the polynomial $R_1(X) = \frac{\beta_{hd}S_v\beta_{vd}(k_dR_z+S_h)}{N_h^2\mu_v(\gamma_d+\mu)}$, which generalizes $\mathcal{R}_d$, in the sense that $R_1(E_0) = \mathcal{R}_d^2$; this raises the question of whether this is related to the Zika IRN.
2. One not of the Descartes type, which raises the question of how to exploit non-Descartes type second-order factors.

8.2.1. The Dengue-Only Resident Fixed Point E_d

Even though the coordinates of the dengue-only resident fixed point E_d are pretty simple, obtaining them is not. We have an a priori choice of zeroable set $in_{1'} = \{I_z, R_z, J_z, I_{zv}\}$ which turns out to lead to about 2.5 h for "Solve" (due to the existence of four extra fixed points which are non-positive for the numeric values of [2]. After performing the computation, it turns out that the full zeroable set is $in_1 = \{I_z, I_c, R_z, J_d, J_z, R, I_{vz}, I_{vc}\}$. The remaining set of equations:

$$\begin{pmatrix} -\gamma_d I_d - \mu I_d + \frac{I_{vd}S_h\beta_{hd}}{N_h} & = 0 \\ \gamma_d I_d - \mu R_d & = 0 \\ \frac{I_d S_v\beta_{vd}}{N_h} - I_{vd}\mu_v & = 0 \\ \mu(N_h - S_h) - \frac{I_{vd}S_h\beta_{hd}}{N_h} & = 0 \\ -\frac{I_d S_v\beta_{vd}}{N_h} + N_v\mu_v - S_v\mu_v & = 0 \end{pmatrix}$$

may be easily solved. In addition to the DFE, it has one extra fixed point:

$$R_d = \frac{\gamma_d I_d}{\mu}, S_v = \frac{\mu_v N_h N_v}{\mu_v N_h + \beta_{vd} I_d} = \frac{\mu_v(\gamma_d+\mu)(\mu N_h + \beta_{hd}N_v)}{\beta_{hd}[\mu_v(\gamma_d+\mu)+\mu\beta_{vd}]}, \tag{62}$$

$$S_h = \frac{N_h^2(\mu_v(\gamma_d+\mu)+\mu\beta_{vd})}{\beta_{vd}(\mu N_h + \beta_{hd}N_v)}, I_d = \frac{\mu N_h^2\mu_v}{\beta_{vd}(\mu N_h + \beta_{hd}N_v)}\left(\frac{N_v\beta_{hd}\beta_{vd}}{N_h\mu_v(\gamma_d+\mu)} - 1\right), \tag{63}$$

$$I_{dv} = \beta_{vd} I_d \frac{S_v}{\mu_v N_h} = \frac{I_d N_v \beta_{vd}}{I_d\beta_{vd} + N_h\mu_v}, I_{vz} = 0, I_{vc} = 0.$$

The bifurcation value for E_d is thus

$$\frac{N_v\beta_{hd}\beta_{vd}}{N_h\mu_v(\gamma_d+\mu)} := \mathcal{R}_d^2,$$

confirming ([2] Lemma 1).

The Jacobian factorizations when choosing, as the infectious set, the complement of $I_d, R_d, I_{vd}, S_v, S_h$, has a characteristic polynomial with one non-Descartes type, third-order factor.

8.2.2. The Zika Only Resident Fixed Point E_z

Using the full zeroable set given in [2] $in_2 = \{I_d, I_c, R_d, J_d, J_z, R, I_{dv}, I_{vc}\}$, yields the set of equations:

$$\begin{pmatrix} S_h\left(\frac{\beta_{hz}I_{vz}}{N_h} + \frac{I_z\beta_s}{N_h}\right) - I_z\gamma_z - \mu I_z & = 0 \\ I_z\gamma_z - \mu R_z & = 0 \\ \frac{I_z S_v\beta_{vz}}{N_h} - I_{vz}\mu_v & = 0 \\ \mu(N_h - S_h) - S_h\left(\frac{\beta_{hz}I_{vz}}{N_h} + \frac{I_z\beta_s}{N_h}\right) & = 0 \\ -\frac{I_z S_v\beta_{vz}}{N_h} + N_v\mu_v - S_v\mu_v & = 0 \end{pmatrix}.$$

The Zika-only resident fixed point E_z satisfies

$$R_z = \frac{\gamma_z I_z}{\mu}, S_v = \frac{\mu_v N_h N_v}{\mu_v N_h + \beta_{vz} I_z}, I_{dv} = \beta_{vz} I_z \frac{S_v}{\mu_v N_h} = \frac{I_z \beta_{vz} N_v}{\mu_v N_h + \beta_{vz} I_z}, I_{vz} = 0, I_{vc} = 0, \tag{64}$$
$$S_h = \frac{\mu N_h^2 (N_h \mu_v + I_z \beta_{vz})}{I_z \beta_{vz} (\mu N_h + \beta_{hz} N_v + I_z \beta_s) + N_h \mu_v (\mu N_h + I_z \beta_s)} = \frac{N_h^2 (\mu_v (\gamma_d + \mu) + \mu \beta_{vd})}{\beta_{vd} (\mu N_h + \beta_{hd} N_v)},$$

where I_z is a positive root of the quadratic equation $aI_z^2 + bI_z + c = 0$, with coefficients:

$$\begin{cases} c = \mu N_h (N_h \mu_v (\mu - \beta_s + \gamma_z) - \beta_{hz} N_v \beta_{vz}), \\ b = N_h \beta_s \mu_v (\mu + \gamma_z) + \mu N_h \beta_{vz} (\mu - \beta_s + \gamma_z) + \beta_{hz} N_v \beta_{vz} (\mu + \gamma_z), \\ a = \beta_s \beta_{vz} (\mu + \gamma_z) \end{cases}$$

Assume first that β_s is small enough so that $b > 0$; then, this equation has a unique positive root if $c < 0$, which may be written also as

$$\frac{N_h \beta_s \mu_v + \beta_{hz} N_v \beta_{vz}}{N_h \mu_v (\mu + \gamma_z)} > 1. \tag{65}$$

It is shown in ([2] Theorem 1) that this is equivalent to $R_z > 1$ (both conditions determine the correct stability domain and both reduce when $\beta_s = 0$ to the same answer $\frac{\beta_{hz} N_v \beta_{vz}}{N_h \mu_v (\mu + \gamma_z)}$).

The model of [2] contains several interesting particular cases, to which we turn next.

8.2.3. The Dengue Invasion Reproduction Number (IRN) and Two Possible (F, V) Decompositions

The dengue fixed point has non-zero values $S_h, S_v, I_d, R_d, I_{dv}$. Computing the IRN's requires specifying the "invasion infection classes". Ref. [2] works with a subset of

$$in_{2'} = \{I_d, I_c, R_d, J_d, J_z, I_{dv}, I_{cv}, R_c\},$$

given by $in_2 = \{I_d, I_c, J_d, I_{dv}, I_{cv}\}$.

The resulting recipe V matrix is diagonal, and the recipe F matrix, after denoting proportions by minuscule letters, is:

$$F = \begin{pmatrix} 0 & 0 & 0 & s_h \beta_{hd} & \nu_d s_h \beta_{hd} \\ \rho(\beta_{hz} i_{zv} + i_z \beta_s) & 0 & 0 & \rho \beta_{hd} i_z & \rho \nu_d \beta_{hd} i_z \\ 0 & 0 & 0 & \beta_{hd} r_z & \nu_d \beta_{hd} r_z \\ s_v \beta_{vd} & s_v \beta_{vd} & k_d s_v \beta_{vd} & 0 & 0 \\ i_{zv} \beta_{vd} & i_{zv} \beta_{vd} & k_d i_{zv} \beta_{vd} & i_z \beta_{vz} & 0 \end{pmatrix} \tag{66}$$

and the spectral radius of the resulting recipe K matrix satisfies a polynomial equation of degree 4.

Now ([2] Section 5.1) move two of the F terms in the V matrix, yielding

$$F = \begin{pmatrix} 0 & 0 & 0 & s_h \beta_{hd} & \nu_d s_h \beta_{hd} \\ 0 & 0 & 0 & \rho \beta_{hd} i_z & \rho \nu_d \beta_{hd} i_z \\ 0 & 0 & 0 & \beta_{hd} r_z & \nu_d \beta_{hd} r_z \\ s_v \beta_{vd} & s_v \beta_{vd} & k_d s_v \beta_{vd} & 0 & 0 \\ i_{zv} \beta_{vd} & i_{zv} \beta_{vd} & k_d i_{zv} \beta_{vd} & 0 & 0 \end{pmatrix}, \tag{67}$$

with the $-V$ matrix being:

$$\begin{pmatrix} -\gamma_d-\mu-\rho(\beta_{hz}i_{zv}+i_z\beta_s) & \rho(\beta_{hz}i_{zv}+i_z\beta_s) & 0 & 0 & 0 \\ 0 & -\rho(\gamma_d+\gamma_z)-\mu & \rho\gamma_z & 0 & 0 \\ 0 & 0 & -\gamma_d-\mu & 0 & 0 \\ 0 & 0 & 0 & -i_z\beta_{vz}-\mu_v & i_z\beta_{vz} \\ 0 & 0 & 0 & 0 & -\mu_v \end{pmatrix}. \tag{68}$$

They thus reduce the rank of K to 2 and obtain a simpler R_0. On the other hand, their decomposition is admissible only under extra conditions of the parameters which ensure the non-positivity of the row sums of $-V$, which they omit to mention.

Remark 24. *The associated CTMC is the union of two disjoint generalized Erlangs, on the host and vector, respectively. These are employed in the probabilistic/epidemic interpretations in [2].*

The probabilistic/epidemic significance of F is better understood after decomposing this matrix as a sum of matrices of rank 1 *as follows:*

$$F=\begin{pmatrix} \beta_{hd}s_h \\ \rho\beta_{hd}i_z \\ \beta_{hd}k_dr_z \\ 0 \\ 0 \end{pmatrix}\begin{pmatrix} 0 & 0 & 0 & 1 & \nu_d \end{pmatrix}+\begin{pmatrix} 0 \\ 0 \\ 0 \\ \beta_{vd}s_v \\ \beta_{vd}i_{zv} \end{pmatrix}\begin{pmatrix} 1 & 1 & 1 & 0 & 0 \end{pmatrix}. \tag{69}$$

The column vector are total infectivity rates for the resident compartments, the row vectors are distribution vectors, and this decomposition yields immediately both the Diekmann kernel and R_0—see [41,42].

9. Conclusions

The possible non-uniqueness of the NGM matrix has not been sufficiently studied in the literature. Sometimes, like in the example of the last section, one simplifying choice is justified a posteriori on the grounds of some interpretability of the results, ignoring the fact that other choices might lead to even simpler answers, and there is the fact that a priori, there is no reason to expect simple answers.

To this classic dilemma, we answer by showing, via numerous examples, that the first "recipe NGM" to come to mind leads quickly to most of the results found in the literature. The question of whether our recipe may always be associated to admissible equation decompositions remains open.

We have also examined a variant of the Jacobian approach, a "factorization Jacobian approach", which draws the attention to certain polynomials with interesting properties (46) and raises interesting questions—see especially Open Question 3. Notably, the relation (44) holds in all the three "multi-strain" examples we examined and raises the additional question of how to define multi-strain models in terms of the dynamical system, to ensure that this always holds for this class.

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Appendix A. The Implementation of the Jacobian Factorization Approach

First, we use a utility which, for a given model, infectious set, and dummy variable (taken always as u, to avoid confusions) outputs the Jacobian at the DFE, the trace and determinant (for other purposes), the characteristic polynomial in u, the NGM matrix, and R_F.

```
JR0[mod_,inf_,u_,cn_:{}]:=
  Module[{dyn,X,par,cinf,cp,cX,jac,tr,det,chp,ngm,K,R0},
    dyn=mod[[1]];X=mod[[2]];par=mod[[3]];
    Print[‘‘ dyn=’’,dyn//FullSimplify//MatrixForm,X,par];
    cinf=Thread[X[[inf]]->0];
    cp=Thread[par>0];cX=Thread[X>0];
    cdfe=Join[DFE[mod,inf],cinf];
    jac=Grad[dyn,X]/.cinf/.cn;
    tr=Tr[jac];
    det=Det[jac];
    chp=CharacteristicPolynomial[jac,u];
    ngm=NGM[mod,inf];
    K=ngm[[6]];
   Print[‘‘K=’’,K//MatrixForm];
   R0=Assuming[Join[cp,cX],Max[Eigenvalues[K]]];
  {chp,R0,K,jac,tr,det}];
```

Most of the work is performed after calling this utility by another one, JR02. This splitting of JR0 in two parts is necessary since the detection of the non-sign definite factors, which must be analyzed, is easier to perform by eye than by using a program. The JR02 script is:

```
JR02[pol_,u_]:=Module[{co,co1,cop,con,R_J},co=CoefficientList[pol,u];
  Print[‘‘the  factor ’’,pol,’’ has degree ’’,Length[co]-1];
  co1=Expand[co[[1]]* co[[Length[co]]]];
  Print[‘‘its leading * constant coefficient product is ’’,co1];
  cop=Replace[co1, _. _?Negative -> 0, {1}](*level 1 here ?*);
  con=cop-co1;
  Print[‘‘R_J is’’];
  R_J=con/cop//FullSimplify;
{R_J,co}
]
```

For a specific “mod”, both R_0’s may be obtained by typing:

```
jr = JR0[mod, inf, u];
chp = jr[[1]] // Factor
Print[‘‘factor is ’’, pol = chp[[5]]]
pc = JR02[pol,
   u];(*the script JR02 determines R_J, using the index,
   for example 5, determined by \eye inspection in the previous command*)
Print[‘‘R_J is ’’, R_J = pc[[1]] // FullSimplify]
Print[‘‘R_N is ’’, R_N = jr[[2]] // FullSimplify]
```

Appendix A.1. Proof of [33]’s Result via Mathematica

1. The solution of the first recurrence equation in (7) for the expected time to extinction of a linear birth-and-death process with arrival rate A and death rate qA (relevant when $R_0 < 1$) via Mathematica is:

$$\frac{q\left(H_K\left(1-q^j\right)+H_j\left(q^K-1\right)+\log\left(\frac{q-1}{q}\right)\left(q^K-q^j\right)\right)-\left(\left(q^j-1\right)\Phi\left(\frac{1}{q},1,K+1\right)\right)+\left(q^K-1\right)\Phi\left(\frac{1}{q},1,j+1\right)}{A(q-1)q\left(q^K-1\right)},$$

where H denotes the Harmonic function.
Since Mathematica cannot compute the limit when K converges to infinity directly, we break the limit into its three parts and end up with the following generalization:
Making now $j = 1$ yields [33]'s result, which is

$$\frac{\log(q) - \log(q-1)}{A}.$$

2. When $R_0 > 1$, we cannot obtain the limit for general j. When $j = 1$, similarly with the previous case, the limit is divided into four parts:

$$\begin{cases} a_1 = \text{Limit}\left[\frac{q\left(q^K\left(q\left(-\left(-\frac{\log(1-q)}{q}-1\right)\right)\right)\right)}{q} - q^K(H_K+\log(1-q))}{A(q-1)\left(q^K-1\right)}, K \to \infty, \text{Assumptions} \to \{A > 0, 0 < q < 1\}\right], \\ a_2 = \text{Limit}\left[\frac{q\left((H_K-1)q^K+\log(1-q)-\frac{\log(1-q)}{q}\right)}{A(q-1)\left(q^K-1\right)}, K \to \infty, \text{Assumptions} \to \{A > 0, 0 < q < 1\}\right], \\ a_3 = \text{Limit}\left[-\frac{qq^K\Phi(q,1,K+1)}{A(q-1)\left(q^K-1\right)}, K \to \infty, \text{Assumptions} \to \{A > 0, 0 < q < 1\}\right], \\ a_4 = \text{Limit}\left[\frac{q\left(q^K(q\Phi(q,1,K+1))\right)}{A(q-1)\left(q^K-1\right)}, K \to \infty, \text{Assumptions} \to \{A > 0, 0 < q < 1\}\right] \end{cases}$$

Here Mathematica yields that $a_1 = 0$, $a_2 = -\frac{\log(1-q)}{A}$, the second being precisely Whittle's result, but we were unable to confirm with Mathematica that $a_3 = a_4 = 0$.

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