# On the Similarity between Epidemiologic Strains, Minimal Self-Replicable Siphons, and autocatalytic cores in (Chemical) Reaction Networks: Towards a Unifying Framework

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## Abstract

**Motivation**: We aim to study boundary stability and persistence of positive odes in mathematical epidemiology models by importing structural tools from chemical reaction networks.

This is largely a review work, which attempts to bring closer together the fields of mathematical epidemiology (ME), and chemical reaction networks (CRNs), based on several observations. We started by observing that *epidemiologic strains*, defined as disjoint blocks in either the Jacobian on the infected variables, or as blocks in the next generating matrix (NGM), coincide, in most of the examples we studied, with either the set of *critical minimal siphons* or with the set of *minimal autocatalytic sets (cores)* in an underlying CRN (an exception, not fully understood yet, is offered in Section 5). We leveraged this to provide a definition of the disease free equilibrium (DFE) face/infected set as the union of either all minimal siphons, or of all cores (they coincide always in our examples). Next, we provide a proposed definition of ME models, as models which have a unique boundary fixed point on the DFE face, and for which the Jacobian of the infected subnetwork admits a regular splitting, which allows defining the famous next generating matrix. We then define the *interaction graph on minimal siphons* (IGMS), whose vertices are minimal siphons, and whose edges indicate the existence of reactions producing species in one siphon from species in another. When this graph is acyclic, we say the model exhibits a *Acyclic Minimal Siphon Decomposition* (AMSD). For AMSD models whose minimal siphons partition the infection species, we show that the NGM is block triangular after permutation, which implies the classical max structure of the reproduction number $R_0$ for multi-strain models. In conclusion, using irreversible reaction networks, minimal siphons and acyclic siphon decompositions we provide a natural bridge from CRN to ME.

We implement algorithms to compute IGMS and detect AMSD in the `Epid-CRN` Mathematica package (`https://github.com/florinav/EpidCRNmodels`) (which contains already modules to identify minimal siphons, criticality, drainability, self-replicability, etc). Finally, we illustrate on several multi-strain ME examples how the block structure induced by AMSD, and the ME reproduction functions (as introduced in [Avram et al., 2024c, Avram et al., 2025], these are the eigenvalues of the NGM which are always positive, for any values of the non-infection variables), allow expressing boundary stability and persistence conditions by comparing growth numbers to 1, as customary in ME. Note that while not addressing the general Persistence Conjecture mentioned in the title, our work provides a systematic method for deriving boundary instability conditions for a significant class of structured models.

**Keywords:** biochemical interaction networks; essentially nonnegative/positive systems; chemical reaction networks; mathematical epidemiology; multi-strain models; reproduction functions; invasion numbers; regular splitting; chemical reaction networks; stoichiometric matrix; siphons/semi-locking sets; critical self-replicable siphons; autocatalytic cores; disease free equilibrium; admissible communities; Routh-Hurwitz stability conditions; polynomial factorization; Descartes-type polynomials.

# Contents

# 1 Introduction

Population dynamics, ecology, mathematical epidemiology (ME), virology, the theory of chemical reaction networks (CRN), to name just some biological interaction networks (BIN) subfields, study all positive dynamical systems, and have similar preoccupations: the existence and multiplicity of equilibria, their local and global stability, the occurrence of bifurcations, persistence, permanence, extinction, etc.

CRN offers a versatile mathematical framework for modelling positive systems in a variety of disciplines; examples include biochemical, pharmacokinetic, epidemiological, ecological, social, neural, and multi-agent networks [Goutsias and Jenkinson, 2013]. Of special relevance to us is that CRN theory (CRNT) investigates mass–action systems, which include ME models, and revealed the roles of Petri graphs and siphons in determining boundary behavior. For some recent papers combining both new CRNT results (including for the SIR mathematical epidemiology (ME) model) and interesting historical references, see [Plesa, 2025, Gagrani et al., 2024, Xu, 2024a, Xu, 2024b, Blokhuis et al., 2025].Let us mention also that

CRNT is unavoidable in the study of ODEs with many variables (tens, hundreds). Note however that a considerable part of CRNT focuses on systems which enjoy various degrees of "reversibility", which is absent in ME.

Ecology studies often Lotka–Volterra–Kolmogorov/generalized Lotka–Volterra (LVK/GLV) systems, whose behaviour might seem simpler than those in ME, due to the linear complementarity principle (LCP); however, as shown by Smale, generalized Lotka–Volterra systems may have already very complicated dynamical behaviors, and display chaos [Smale, 1976]. For some recent developments, including some which tie Smale's work to CRNs and to ecology, see [Vano et al., 2006, Sprott, 2010, Wang et al., 2023, Susits and Tóth, 2024, Banaji et al., 2024, Chen et al., 2024, Jafari et al., 2025, Plesa, 2025].

One subfield in which CRNT and ecology come together is that of Chemical organisation theory [Dittrich and Di Fenizio, 2007, Heylighen et al., 2015, Veloz and Razeto-Barry, 2017, Veloz, 2020, Heylighen et al., 2024]. These authors study both ODE and PDE models, and touched also briefly the topic of ME models [Peter et al., 2020].

Epidemiology is especially relevant to our unification quest due to the intricate boundary behaviors encountered in the study of its multi-strain models, whose stability and persistence may sometimes be expressed via remarkably simple threshold conditions involving basic and reproduction numbers and invasion numbers (these are essentially the particular case of the invasion rates used in ecology, obtained when the resident invariant set of boundary faces reduce to single fixed points).

Ecology, ME and CRNT share also common open problems, like the notorious persistence and permanence conjectures, which they formulate however differently. Thus, CRNT considers only the case of weakly-reversible systems (see Section 7 for a short review and further references). In ecology, the accent is on general, non-polynomial rates, but possibly generating strongly monotone semi-flows [Butler and McGehee, 1979, Hutson, 1984a, Schreiber, 2000, Thieme, 2003b, Hirsch and Smith, 2005, Smith and Thieme, 2011a]. Finally, in ME, which is the focus of this paper, the accent is on using the often simpler reproduction and invasion numbers obtained via regular splitting (see Section 8.2) and on restricting to ME models, which need still to be defined (note that both ME and ecology models lack a precise definition, in the literature preceding our papers).

The fact that the persistence and permanence conjectures are only studied by each of the three fields for restricted structural classes suggests the interest of integrating their different perspectives; let us also note that CRNs have started been applied in ecology and related fields in a few recent papers [Veloz and Flores, 2021, Heylighen et al., 2022, Vassena et al., 2024, Avram et al., 2025, Reyes and Dunkel, 2025].

Our paper focuses brings together several key concepts from different fields:

1. Siphons and reaction networks from CRNT.

2. The next generation matrix (NGM) method from ME, which is also related to the regular splitting method in numerical analysis.

3. The use of the ME reproduction functions – see Definition 16– for expressing stability in terms or reproduction and invasion numbers/rates, where the second concept originated in ecology (see [Schreiber, 2000, Hofbauer and Schreiber, 2022, Feng et al., 2025, Seno, 2025] for some references), but is different from the one used in ME, due to the application here of regular-splitting, for models where resident invariant sets (see Definition 21) of boundary faces reduce to single fixed points.

To argue our thesis that not sufficient effort has been invested in cross-pollination (interdisciplinary integration) of CRNT, ecology and ME, we add now some more information on the three points enumerated above.

1. The reaction network (RN) representation of ODEs, and the concept of siphons are essential in CRNT, and absent in ME, even though they seem intuitively important. In support of this, our main result below started from the observation that there is a correspondence between minimal siphons and strains

in multi-strain epidemic models. This lead to the notion of interaction graph on the minimal siphons (IGMS), and to Theorem 2: if IGMS is acyclic, and the minimal siphons do not intersect, then the NGM can be block-triangularized (recovering well-known results obtained previously only in examples).

2. The "next generation matrix" (NGM) method (which expresses the stability of the "disease free equilibrium" (DFE) in terms of one inequality $R_0 < 1$, where $R_0$ is the spectral radius of a certain matrix, obtained by "regular splitting" of the Jacobian of the "invading variables"), is omnipresent in ME, and almost absent outside the field. But, we have shown in [Avram et al., 2024b, Johnston and Avram, 2025], that it is equally efficient for CRN models.
3. Our final piece of evidence are multi-strain ME models. Note that while $R_0$ and NGM are typically presented as closed chapters in ME, for the analog stability problem of non-DFE boundary fixed points of multi-strain ME models, a general theory is definitely lacking. Our first observation here is that in simple multi-strain models, boundary fixed points are into a one to one correspondence with the minimal siphon facets $S_i, i = 1, ..., n$ on which they are situated, and we incorporate this observation in our definition of multi-strain models 15. Furthermore, it was observed in various multi-strain ME models that certain "invasion numbers" $R^{S_i} = R^{S_i}_{\widetilde{S}_i{}^c}$, with definitions similar to $R_0$, play a central role in stability criteria, and we provide a definition for them in 16. Now minimal siphons are a well-known concept in chemical reaction networks (CRN), but never used in ME and ecology (note also that invasion numbers are compared to 1 in ME, and to 0 in ecology). We believe that for a general theory of multi-strain models, in particular for progressing on problems like whether k-strain models satisfy linear complementarity problem/competitive exclusion principle (Open Problem 1), a better integration of CRN, ME and ecology might be useful. As a first step in this direction, we offer a general purpose Mathematica package Epid-CRN, available at `https://github.com/florinav/EpidCRNmodels`, and illustrate its use throughout the paper.

**Contributions.**

- We prove block-triangularity of the NGM when minimal siphons form an acyclic partition (Theorem 2).
- We implement detection of cycles of IGMS in `Epid-CRN`, and illustrate the theory on multi-strain examples.
- Our paper may be viewed also as a users manual for EpidCRN, and also as an essay around several not enough known themes:
  1. We outline first an "x–y framework" extending the NGM method, and connect it to the older theory of regular splitting of matrices.
  2. We suggest one possible rigorous definition of ME models, see Definition 12, by imposing the existence of a DFE, and the existence of a regular splitting of the Jacobian matrix of the invasion vector field with respect to the invasion variables at the DFE.
  3. We review the role played by reproduction functions [Avram et al., 2024c, Avram et al., 2025] for the stability analysis of multi-strain ME models (these are basically the reproduction numbers, in which the resident variables $\boldsymbol{y}$ are left free).

**Organization.** We start with some mathematical underpinnings in Section 2, which include the regular splitting of Metzler matrices, a fundamental result in ME.

Section 4 introduces a new type of interaction graphs on minimal siphons (IGMS) and provides a structural result for the NGM (Theorem 2), which assumes the acyclicity of IGMS.

The first ME example in Section 3 revisits a ME model of [Ashrafur Rahman and Zou, 2011], which illustrates both the important complementarity principle of Lotka-Volterra-Kolmogorov models, and revisits the reproduction functions introduced in [Avram et al., 2024c, Avram et al., 2025].

Section 4 introduces the directed interaction graphs on minimal siphons (IGMS), and establishes in Theorem 2 that next–generation matrix $K = FV^{-1}$ inherits a block–triangular structure from $V$ whenever the minimal siphons form a partition of the DFE support– see Theorem 2.

Section 5, following [Aguiar and Stollenwerk, 2007, Gavish and Rabiu, 2023, Gavish, 2024b, Gavish, 2024a], revisits a quite complex multi-strain example, with temporary cross-immunity, with ADE and immunity waning, but without co-infection. Some stability results are easy, due to the block-diagonal structure of the NGM, but the domain of Hopf bifurcations remains an open problem.

Section 6 presents a co-infection ME model where the minimal siphons intersect; nevertheless, the NGM has a triangular structure. Furthermore, there are more reproduction functions than minimal siphons. This poses challenges from the point of view of interpreting the stability/invasion results via reproduction functions, which we leave for further work.

Sections 7 offers a brief review of persistence theory. We argue here that its open problems might be easier under the restriction to ME models (in particular when the resident invariant sets of all proper siphon faces reduce to single fixed points). Also, we include a sketch of the theory of invasion graphs [Hofbauer and Schreiber, 2022], which we believe might throw a light on the open problems of persistence and permanence of the model in the preceding section.

Section 8 offers further comments on the NGM method.

Finally, sections 9.1, 9.2, 9.3 review further topics from CRNT which we conjecture might become relevant for ME in the future. These might look at a first reading like vague similarities between disparate fields. But, as as it happened to two of the authors [Vassena et al., 2024], we discovered that certain CRN results throw a whole new light on mathematical epidemiology. For example, it turns out that the presence of certain submatrices in the stoichiometric matrix (which is independent of the choice of admissible rates) render automatic the presence of various types of instabilities [Vassena, 2023, Vas, 2024, Blokhuis et al., 2025], under "parameter-rich kinetics" (which do not include mass-action, but do include "Michaelis Menten saturated" kinetics).

# 2 Mathematical underpinnings

## 2.1 Positive dynamical systems

**Definition 1** (Positive / non-negative dynamical system). *A dynamical system is called* positive *[Rantzer, 2015] or* non-negative *[Haddad and Chellaboina, 2011] if the non-negative orthant*

$$\mathbb{R}^n_{\geq 0} := \{x \in \mathbb{R}^n : x_i \geq 0,\ i = 1, \dots, n\}$$

*is forward invariant under the flow.*

The BIN disciplines are all concerned with positive dynamical systems, but neglect sometimes important results in their "sister sciences".

In this essay, we are making the case that more sharing of information between the positive dynamical systems fields could be beneficial.

**Remark 1.** *As a first argument, we ask the reader to compare the ODE description of our first example* (10) *to its "reaction networks" (RN) representation* (9)*. The superiority of the latter, encapsulated in lines with biological meaning like $i_1 + s \to 2\, i_1$, seems clear to us:*

1. *Firstly, reactions represent a clear phenomenological description: in the case above, "one susceptible meets one infected, and two infected depart", is a precise description of the infection process.*
2. *Note that after inputting the corresponding rates (rts), numerous packages will produce the ODE description (simply by "adding up" the reactions), as well as various graphs illustrating the interactions in this network, numerical simulations, and, possibly in the future, also symbolic-numeric information on the fixed points and their stability (EpidCRN does that for simple examples).*
3. *Using the RN representation, exploring the model by changing the rates, or by adding/removing reactions can be achieved with minimal effort.*

*For a second argument, we recall the well-known CRNT result that assuming all free parameters are non-negative, a positive polynomial ODE system may be recognized by the absence of "syntactically negative cross-terms" [Hárs and Tóth, 1981]. This result seems practically unknown outside CRNT, and has been reproved numerous times.*

It seemed to us that one step towards advancing unification of the BIN sciences could be via creating a common general purpose package (symbolic, numeric, simulation and estimation of parameters). Below, we present the Mathematica package Epid-CRN, available at `https://github.com/florinav/EpidCRNmodels`, which is used in solving all the examples of this paper.

## 2.2 Notations

We denote by $\mathbb{R}^n$, $\mathbb{R}^n_+$ and $\mathbb{R}^n_{\geq 0}$ the set of order $n$ column vectors of reals, positive reals and non-negative reals, respectively. The usual euclidean norm is denoted by $\|z\|_2^2$. The family $\{e_1, \dots, e_n\}$ denotes the canonical basis of the vector space $\mathbb{R}^n$. If $z \in \mathbb{R}^n$, we denote by $z_i$ the $i$th component of $z$. The notation $x \gg 0$ means that $x \in \mathbb{R}^n_+$.

The set of $n \times m$ matrices with real entries is denoted by $\mathbb{R}^{n \times m}$. For a matrix $A \in \mathbb{R}^{n\times m}$ we denote by $A(i,j)$ the entry at the row $i$, column $j$. $A^t$ denotes the transpose of $A$, and $A^{-t}$ will denote the transpose of the inverse of $A$. For matrices $A, B$ we write $A \leq B$ if $A(i,j) \leq B(i,j)$ for all $i$ and $j$, $A < B$ if $A \leq B$ and $A \neq B$, and $A \ll B$ if $A(i,j) < B(i,j)$ for all $i$ and $j$. Let $U \subset \mathbb{R}^{n\times m}$, then $\bar{U}$ denotes its closure with respect to the standard Euclidean topology. Let $A \in \mathbb{R}^{n\times m}$ be a matrix, then $\ker(A)$ is its kernel or null space, while $\Im A$ is its image space. Let $V : \mathcal{X} \to \mathbb{R}$ be a function, then $\ker V := \{x \in \mathcal{X} | V(x) = 0\}$. Let $\mathcal{Y} \subset \mathcal{X}$, then $\ker V|_{\mathcal{Y}} := \{x \in \mathcal{Y} | V(x) = 0\}$. Let $x = (x_1, .., x_n)^t \in \mathbb{R}^n$, then $\|x\|_\infty := \max_i |x_i|$. Let $A \in \mathbb{R}^{n\times n}$, then $\sigma_i(A) := a_{ii} + \sum_{j\neq i} |a_{ij}|$, $i = 1, .., n$, and $\mu_\infty(A) := \max_i \sigma_i(A)$.

Let $S$ be a set, then $|S|$ denotes its cardinality.

**Definition 2** (spectral radius, spectral abscissa, and Hurwitz matrix)**.** *[Horn and Johnson, 2012] A) The spectral radius of a matrix A is defined by*

$$\rho(A) = \max\{|\lambda|, \lambda \in Sp(A)\},$$

*where $Sp(A)$ denotes the spectrum of A.*

*B) The spectral abscissa, i.e. the largest real part among the eigenvalues of A, is denoted by*

$$s(A) = \max\{\mathrm{Re}(\lambda) \ : \ \lambda \in Sp(A)\}.$$

*C) A matrix $A$ is said to be Hurwitz if $s(A) < 0$.*

**Definition 3** (Metzler matrix)**.** *[Berman and Plemmons, 1994, Farina and Rinaldi, 2011] A Metzler matrix* $A$ *is a matrix such that* $i \neq j \implies A(i,j) \geq 0$. *These matrices are also called quasi-positive matrices.*

**Lemma 1. The "half eigenvector" inequalities** . *Let* $A$ *be an irreducible Metzler matrix. Then,* $s(A)$ *is a simple eigenvalue of* $A$ *and there exists a unique (up to scalar multiple) vector* $x > \vec{0}_n$ *such that* $Ax = s(A)x$. *Let* $z \geq \vec{0}_n$ *be a given non-zero vector.*

1. *If* $Az \leq \lambda z$ *for some scalar* $\lambda$, *then* $s(A) \leq \lambda$, *with equality if and only if* $Az = \lambda z$.
2. *If* $Az \geq \lambda z$ *and* $Az \neq \lambda z$, *for some scalar* $\lambda$, *then* $s(A) > \lambda$.

The first half of the lemma is a direct consequence of the Perron–Frobenius Theorem for nonnegative matrices [Berman and Plemmons, 1994]. The second part can be obtained from a straightforward application of [Berman and Plemmons, 1994, Theorem 2.1.11].

Scalar functions like the logarithm and quotients will be applied to vectors componentwise:

$$\ln y = (\ln y_1, \ln y_2, ...), \frac{1}{y} = \left(\frac{1}{y_1}, \frac{1}{y_2}, ...\right), \frac{y^*}{y} = \left(\frac{y_1^*}{y_1}, \frac{y_2^*}{y_2}, ...\right)$$

## 2.3 Invasion criteria for extinct coordinates via sub–Jacobians

Let $\dot{x} = f(x)$ on $\mathbb{R}^n_{\geq 0}$ and let $F_W = \{x_i = 0 : \ i \in W\}$ be a boundary face (the variables with indices $W$ are "extinct" on $F_W$). If $E \in F_W$ is a boundary equilibrium, write the Jacobian in block form $Df(E) = \begin{bmatrix} J_{WW}(E) & * \\ * & * \end{bmatrix}$. Define the *invasion spectral abscissa*

$$\alpha_W(E) := \max\{\, \Re\lambda : \ \lambda \in \sigma(J_{WW}(E))\,\}.$$

Then:

$\alpha_W(E) < 0 \Rightarrow$ attracting in the $W$–directions (no invasion), $\qquad \alpha_W(E) > 0 \Rightarrow$ repelling in the $W$–directions (invasion).

For **LVK/GLV** systems (see Definition 11) $\dot{x}_i = x_i\big(c_i + (Ax)_i\big)$ one has, on $F_W$,

$$J_{WW}(E) = \operatorname{diag}\big(g_i(E)\big)_{i \in W}, \quad g_i(E) := c_i + (AE)_i,$$

hence

$$\alpha_W(E) = \max_{i \in W} g_i(E).$$

**Persistence criterion in a GLV.** Because $\dot{x}_i$ has the factor $x_i$, each singleton $\{i\}$ is a minimal semilocking set. Persistence holds if every siphon face either has no boundary equilibrium or, when it does, satisfies $\alpha_W(E) > 0$ (i.e. at least one extinct coordinate has positive per-capita growth at $E$).

## 2.4 How to represent CRN and ME ODE models in a symbolic package?

For parameterizing ME and CRN ODE models, there are three natural choices:

1. The parametrization used traditionally for ODE models is $X' = RHS(X)$. A model is thus a pair $(X, RHS)$ where $X$ is the vector of the variables whose evolution we study and $RHS$ (right hand side) denotes the function that gives the derivatives. This parametrization is sufficient for studying small size symbolic bifurcation problems, but becomes awkward beyond that.

2. In chemical reaction networks theory, $RHS$ is decomposed as

   $$X' = RHS(X) = \Gamma \, rts(X) \tag{1}$$

   where

   - $\Gamma$ is the "stoichiometric matrix" (SM), whose columns represent directions in which several species/compartments change simultaneously, it is viewed as an embodiment of the "structure" of the model.
   - $rts(X)$ is the vector of rates of change associated to each direction (assumed all to be non-negative), also known as kinetics. They are separated from the structure $\Gamma$, since they are less certain; this fact, well accepted in CRNT, is equally true in ME.

   A model hence is defined as a triple $(X, \Gamma, rts)$.

   **Example 1** (SIRS ODE without inflows and outflows (that is, without demography))**.** *This is defined by the triple* $(X, \Gamma, rts)$*:*

   $$X' = \begin{pmatrix} s' \\ i' \\ r' \end{pmatrix} = \begin{pmatrix} -1 & 0 & 1 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 1 \end{pmatrix} \begin{pmatrix} \beta s i \\ \gamma_i i \\ \gamma_r r \\ \gamma_s s \end{pmatrix} := \Gamma \, rts(X). \tag{2}$$

   Note that this representation is also a natural first step towards defining an associated CTMC model (continuous-time Markov chain) on the integers.

   This parametrization has had remarkable successes, including recently for studying *robust questions* like the existence of *robust Lyapunov functions* which depend only on the reaction rates $rts(X)$ [Al-Radhawi and Angeli, 20 Blanchini and Giordano, 2014, Blanchini and Giordano, 2017, Blanchini, 1995, Ali Al-Radhawi et al., 2020].

   All these papers assume admissibility conditions for the rates $rts(X)$ (see [Angeli et al., 2007a, Duvall et al., 2024]), which make them behave essentially like polynomial mass-action systems.

3. **The reaction network (RN) representation**. The third parametrization, via reactions, the traditional one used in CRNT, replaces each column of $\Gamma$ by a *reaction/interaction*. For SIR, the reactions and rates are respectively:

   $$\text{RN} = \left\{ \begin{array}{rcl} S + I & \longrightarrow & 2I, \\ I & \longrightarrow & R, \\ R & \longrightarrow & S, \\ S & \longrightarrow & R \end{array} \right\}. \qquad \text{rts} = \left\{ \begin{array}{l} \beta S I, \\ \gamma_i I, \\ \gamma_r R, \\ \gamma_s S \end{array} \right\}.$$

   Note that the first column in (2) is replaced by $s + i \to 2i$ (not by $s \to i$), which constitutes a precise phenomenological representation of infections at the individual level: the meeting of a susceptible and an infectious results in two infectious. This is called mass-action representation.

   **Definition 4** (mass-action reaction)**.** *[Horn and Jackson, 1972a]. A reaction is said to be mass-action if the coefficients multiplying the reactant species* $(s + i)$ *in this case appear also as exponents in the rate of the reaction.*

   The other columns in (2), represented like $i \to r$, etc, which correspond to transfers which do not occur after meeting individuals from other compartments, do not require explanation.

**Remark 2.**

- *Essentially, the RN representation replaces* $\Gamma$ *by the difference of two non-negative matrices (found on the LHS and RHS of each reaction), such that*

  $$\Gamma = \beta - \alpha \tag{3}$$

  *(which are called input/reactants and output/products matrices, respectively).*

  *In fact, the RN representation may be viewed as an elegant way of visualizing corresponding columns of* $\alpha$ *and* $\beta$*, in parallel.*

- *Note that the RN representation* (3) *is the first step towards defining an associated discrete time Markov chain (DTMC) model on the integers, where we distinguish between inflows and outflows in a state, which is only possible in discrete time.*

  *It is surprising that even though the ODE only depends on* $\Gamma$*, useful information about the ODE, like for example the siphons (see below) requires* $\alpha$ *and* $\beta$*.*

  *This gets even more surprising once we note that to one stoichiometric matrix* $\Gamma$ *one may associate an infinite family of* $(\alpha, \beta)$ *pairs which satisfy* $\beta - \alpha = \Gamma$*, with different mass-action rates, but the same ODE.*

- *The computation of siphons –see Definition 6– may be achieved either algorithmically, using the matrices* $(\alpha, \beta)$*, or, for small examples, by eye inspection.*

- *The RN representation is the one that best avoids human errors, when entering large systems with tens of reactions.*

In the RN representation, each column of $\Gamma$, that is, each *reaction* is associated to a directed pair consisting of a *source complex*, and a *product complex*, which we proceed now to define.

**Definition 5** (CRN)**.** *[Feinberg, 2019] A CRN is defined by a triple* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$*, where* $\mathcal{S}, \mathcal{C}, \mathcal{R}$ *are the set of species, complexes and reactions, respectively.*

$$\begin{aligned}
\mathcal{S} &= \{s_1, ..., s_i, ..., s_{|\mathcal{S}|}\} \\
\mathcal{C} &= \{y_1, ..., y_\alpha, ..., y_{|\mathcal{C}|} : y_\alpha \in \mathbb{N}^{|\mathcal{S}|}\} \\
\mathcal{R} &= \{y_\alpha \xrightarrow{k_{y_\alpha \to y_\beta} \cdot x^{y_\alpha}} y_\beta : k_{y_\alpha \to y_\beta} \geq 0\},
\end{aligned}$$

*where Roman letters* $(i, j)$ *and Greek letters* $(\alpha, \beta)$ *are used to denote species and complex indices, respectively. A complex is a multi-set of species, and is described by a column vector* $y_\alpha$ *representing the stoichiometry/direction of the multi-set. The actual state of the system is described by the vector* $x = (s_1, ..., s_i, ..., s_{|\mathcal{S}|})$ *(that is, a species and its quantity is denoted the same way). The term* $x^{y_\alpha}$ *is defined as*

$$x^{y_\alpha} = \prod_{i=1}^{|\mathcal{S}|} x_i^{y_{\alpha,i}}.$$

**Example 2** (reactions representation of SIRS without demography)**.**

$$\begin{cases}
s + i \xrightarrow{\beta s i} 2i \\
i \xrightarrow{\gamma_i\, i} r \\
r \xrightarrow{\gamma_r\, r} s \\
s \xrightarrow{\gamma_s\, s} r
\end{cases} \tag{4}$$

*Here,*

$$\mathcal{S} = \{s, i, r\}, x = (s, i, r),$$
$$\mathcal{C} = \{y_1 = (1,1,0)^t, y_2 = (0,2,0)^t, y_3 = (1,0,0)^t, y_4 = (0,1,0)^t, y_5 = (0,0,1)^t\}$$
$$\mathcal{R} = \{y_1 \xrightarrow{k_{y_1 \to y_2} x^{y_1} = \beta x^{y_1} = \beta s i} y_2, y_4 \xrightarrow{k_{y_4 \to y_5} x^{y_4} = \gamma_i x^{y_4} = \gamma_i i} y_5, ...\},$$

## 2.5 Locking sets and semilocking sets/siphons

Recall first that the zero coordinate set $Z(s)$ of any fixed boundary point in a mass action reaction network is a siphon/semilocking set [Angeli et al., 2007a, Prop. 4.5], [Shiu and Sturmfels, 2010], [Marcondes de Freitas et al., 2017a, Lem. 63], a concept introduced in the CRN literature by Anderson [Anderson, 2008] and Angeli et al. [Angeli et al., 2007a], where the last authors made also the connection with the parallel concept of siphons in the Petri networks literature (see also [Koch et al., 2010] for a survey of the Petri net approach in systems biology). Siphons provide essential information for non-negative ODEs about whether trajectories can escape from or remain trapped on boundaries.

**Definition 6** (siphon/semilocking set, locking set)**.** *[Feinberg, 1987, Angeli et al., 2007b].*

- *A* ***siphon/semilocking set*** *$W \subseteq \mathcal{S}$ is a nonempty subset of species such that whenever a species in $W$ appears in a product complex, at least one species in $W$ must appear in the corresponding reactant complex.*
- *A* ***locking set*** *$W \subseteq \mathcal{S}$ is a nonempty subset where every reaction has at least one species from $W$ in its reactant complex.*
- *A siphon/semilocking set is* ***minimal*** *when it contains no other siphon included within.*

**Remark 3.** *Note that the RN representation is not unique, and that the search for "good representations" is a very active field – see for example [Buxton et al., 2025, Hong et al., 2023] (whether the "good representations" in chemistry, which enjoy weak-reversibility and low-deficiency, for example, will also be useful in ME is a topic for further research). However, the only theoretical CRN concept used in this paper, the set of minimal siphons, depends only on the ODE and not on the RN representation – see Remark 4.*

**Remark 4.** *Angeli, De Lenheer, Sontag [Angeli et al., 2007a, Prop 2] (see also Shiu and Sturmfels [Shiu and Sturmfels, 2010, Prop 2.1]) proved that a nonempty set $I$ is semilocking/siphon iff the boundary face $F_I$ is forward-invariant for the dynamics. This implies that siphons are determined by the ODE, and are the same for any RN representation (while the proof of [Angeli et al., 2007a, Prop 2] does use a specific representation, any other representation would have lead to the same result).*

The semi-locking property is fundamental for understanding persistence.

**Definition 7** (persistence)**.** *For a mass–action system on $\mathbb{R}^n_{\geq 0}$,* persistence *means trajectories starting in the positive orthant remain bounded away from the boundary: if $x_i(0) > 0$ for all $i$, then $\liminf_{t \to \infty} x_i(t) > 0$ for all $i$ [Angeli et al., 2007a].*

[Angeli et al., 2007a] showed that if the $\omega$-limit set does not intersect semi-locking boundaries except at equilibria, and if all trajectories starting on non-semilocking boundaries eventually leave those boundaries, then the system exhibits persistence.

## 2.6 Constructing minimal siphons for ME models, by eye inspection

ME models are characterized by the presence of infection-type reactions, like S+I→ 2 I, which are called in CRN “autocatalytic”.

**Definition 8** (autocatalytic reactions)**.** *[Horn and Jackson, 1972b] A reaction is called autocatalytic if there exist a species which appears both as reactant and as product, with net production (coefficient as product exceeds that as reactant).*

**Remark 5.**
- *An input species (which has external arrivals) cannot be included in any siphon.*
- *A species which is product of an autocatalytic reaction is always included in a (minimal) siphon.*
- *The total set of species, excluding the input species, is always a locking set (and siphon).*

The example below introduces the reader to the CRNT idea that crucial algebraic information like siphons may be obtained directly by examining the RN (first) column of the reaction description.

**Example 3** (detecting the siphons of an example with two “infections”, one “combination” and two “ mutations”)**.** *The model defined by the reactions and rates representation below has two intersecting minimal siphons.*

```
RN = {0 -> "S",            rts = {Lambda,        (* birth *)
 "S" -> 0,                  muS*S,               (* S death *)
 "I1" -> 0,                 mu*I1,              (* I1 death *)
 "I2" -> 0,                 mu*I2,              (* I2 death *)
 "I3" -> 0,                 mu*I3,              (* I3 death *)
 "S" + "I1" -> 2*"I1",      ba1*S*I1,            (* infection I1 *)
 "S" + "I2" -> 2*"I2",      be2*S*I2,            (* infection I2 *)
 "I1" + "I2" -> "I3"        de*I1*I2}            (* combination *)
 "I3" -> "I1",              m1*I3,              (* mutation I3→I1*)
 "I3" -> "I2",              m2*I3,              (* mutation I3→I2*)
 };                         ;
```

*with ODE*

$$X' = \begin{pmatrix} -\beta_1 i_1 S - \beta_2 i_2 S - \beta_3 i_3 S + \lambda - S\mu_s \\ -\delta i_1 i_2 - i_1\mu_1 + i_3 m_1 + \beta_1 i_1 S \\ -\delta i_1 i_2 - i_2\mu_2 + i_3 m_2 + \beta_2 i_2 S \\ \delta i_1 i_2 - i_3\mu_3 - i_3 m_1 - i_3 m_2 + \beta_3 i_3 S \end{pmatrix}$$

**Remark 6.** *“Combination” reactions like* ”$I1$” +”$I2$” $\to$ ”$I3$” *are absent from classical epidemic models, but may occur in viral models (for example, a healthy cell and a virus combine into one unhealthy cell).*

Here, after excluding S, which may not be involved in any siphon due to its external arrivals, we find that the species $\{I_1\}$ and $\{I_2\}$ which intervene in autocatalytic reactions may be completed to the minimal siphons $\{I_1, I_3\}$, and $\{I_2, I_3\}$. It may be checked that the NGM matrices have the following triangular structure:

$$F = \begin{pmatrix} \beta_1 S & 0 & 0 \\ 0 & \beta_2 S & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \mu_1 & 0 & -m_1 \\ 0 & \mu_2 & -m_2 \\ 0 & 0 & \mu_3 + m_1 + m_2 \end{pmatrix}, K = \begin{pmatrix} \frac{\beta_1 S}{\mu_1} & 0 & \frac{\beta_1 m_1 S}{\mu_1(\mu_3+m_1+m_2)} \\ 0 & \frac{\beta_2 S}{\mu_2} & \frac{\beta_2 m_2 S}{\mu_2(\mu_3+m_1+m_2)} \\ 0 & 0 & 0 \end{pmatrix}$$

We note here the usual upper triangular structure, which implies that $R_0 = \max[\frac{\beta_1 S}{\mu_1}, \frac{\beta_2 S}{\mu_2}]$, in a model which does not have a straightforward ME interpretation.

## 2.7 From critical minimal siphons to the disease free equilibrium (DFE), and locally monotone x-y models

The only minimal siphons encountered in actual ME models have the property that their supporting boundary faces can be either attracting or repelling (depending on the parameters, or on reproduction and invasion numbers/rates). Cf. [Angeli et al., 2007a], such siphons must be "critical" in the sense of satisfying the following:

**Definition 9** (critical siphon)**.** *[Angeli et al., 2007a]. A siphon $T$ in a CRN with stoichiometric matrix $\Gamma$ is* critical *if it contains no support of a positive conservation relation, that is, if there exists no nonzero vector $c \geq 0$ with $c^\top \Gamma = 0$ and $\operatorname{supp}(c) \subseteq T$.*

**Remark 7.** *A) The concept of critical siphon is also dependent only on the ODE, and not on a particular RN representation.*

*B) Boundary faces associated with uncritical siphons may not be reached by the ODE, when starting in their exterior [Angeli et al., 2007a].*

Since minimal siphons are considerably easier to compute than fixed boundary points (and the chemical reaction networks literature provides several algorithms for that), they are the first thing we compute for any autocatalytic model. For small models, this may be achieved by eye inspection, as in the example below.

**Example 4** (Example with both critical and non–critical minimal siphons)**.**

```
RN = {
  0 -> "S",
  "S" -> 0,

  "S" + "I1" -> 2*"I1",
  "S" + "I2" -> 2*"I2",

  "D" -> "E",
  "E" -> "D"
};
```

*There are three minimal siphons: $T_1 = \{I_1\}$ (critical), $T_2 = \{I_2\}$ (critical), $T_3 = \{D, E\}$ (non–critical). $T_1$ and $T_2$, induced by the autocatalytic reactions, include no positive conservation, hence they are* critical*. The siphon with reversible complex graph $\{D, E\}$ supports the positive linear conservation $D+E = const$, hence it is* non–critical.

The minimal critical siphons (whose associated invariant faces may be reached by the ODE, and have maximal dimension), provide a rigorous definition of the disease free equilibrium (DFE).

**Definition 10** (DFE)**.** *The union $TS = \cup_E I_E$ of the indices of all* **minimal critical siphons** *$E$ will be called the total siphon, and the face $W_{TS} = \{X : X_i = 0, \forall i \in TS\}$ will be called the DFE face.*

*If a boundary fixed point $E_0 \in W_{TS}$ exists, it will be called DFE.*

**Remark 8.** *The total siphon is itself an invariant face, by Remark 4.*

**Remark 9.**

- *We might restrict the definition 10 to all minimal critical siphons which are both self-replicable and drainable (see [Deshpande and Gopalkrishnan, 2014] for definitions), since minimal siphons are always both self-replicable and drainable in ME examples. However, we do not do this now, for simplicity.*

- *Minimal self-replicable siphons are connected conceptually to the concept of cores/minimal self-amplifying subhypergraphs [Blanco et al., 2024], which originate in the exciting theory of autocatalytic systems – see [Blokhuis et al., 2020, Peng et al., 2020, Vas, 2024, Gagrani et al., 2024], and see section 9.1 for some further definitions. An alternative definition for the DFE zero set could be as the union of all the cores (in our examples this coincides with the union of the minimal siphons).*

  *Note that precise relations between the two concepts do not seem to have published yet; however, they suggest relations between multi-strain ME models and the multi-tier Seed-Dependent Autocatalytic Systems (SDAS) [Peng et al., 2021, Peng et al., 2022, Peng et al., 2023, Blokhuis et al., 2023] –see section 9.2. Relating the two fields seems a promising research direction.*

- *If there exist several boundary fixed points whose set of zero values is $TS$, they might be all called DFEs, but for now we are excluding this possibility in our definition 12 of ME models.*

**Definition 11** (x-y models, Lotka-Volterra-Kolmogorov/generalized Lotka-Volterra models)**.**
*Here, at each boundary fixed point, the "invading variables" $\boldsymbol{x}$ are those that take the value $0$, and the "resident variables" $\boldsymbol{y}$ are their complement.*

*A) A positive ODE which admits a DFE $E_0$, will be called an x-y model. In this case, after removing eventual conservations, the ODE may be written as:*

$$\begin{cases} \frac{d\boldsymbol{x}}{dt} = \mathbf{f}(\boldsymbol{x}, \boldsymbol{y}) = M(\boldsymbol{x}, \boldsymbol{y})\boldsymbol{x}, \\ \frac{d\boldsymbol{y}}{dt} = \mathbf{g}(\boldsymbol{x}, \boldsymbol{y}). \end{cases} \tag{5}$$

*where $\boldsymbol{x}, \boldsymbol{y}$ denote the zero and positive coordinates of the DFE.*

*B) x-y models with equations of the form*

$$x_i' = x_i f_i(\boldsymbol{x}, \boldsymbol{y}), \forall i \in \boldsymbol{x}_{E_0}, \tag{6}$$

*i.e. with $M$ diagonal, will be called below Lotka-Volterra-Kolmogorov-type (LVK) x-y models.*

*When $\boldsymbol{y}$ further varies in a compact space, these were studied by [Patel and Schreiber, 2018, Hofbauer and Schreiber, 2022].*

*C) An $\boldsymbol{x} - \boldsymbol{y}$ model with $\boldsymbol{y} = \emptyset$ will be called $\boldsymbol{x}$ model.*

*D) An $\boldsymbol{x}$ model with Kolmogorov-type equations for each $\boldsymbol{x}$ variable*

$$x_i' = x_i f_i(\boldsymbol{x}), \forall i \in \boldsymbol{x}_{E_0}, \tag{7}$$

*will be called generalized Lotka-Volterra model (GLV) following Goh and subsequent literature, or Lotka-Volterra-Kolmogorov (LVK).*

**Remark 10.** *The matrix $M(\boldsymbol{x}, \boldsymbol{y})$ satisfies, by (5), that the non-zero steady states must all satisfy*

$$det(M(\boldsymbol{x}, \boldsymbol{y})) = 0, \tag{8}$$

*but is not uniquely defined.*

*For typical ME models, it is possible to choose a matrix $M(\boldsymbol{x}, \boldsymbol{y})$ appearing in the equations for $\boldsymbol{x}'$ at the DFE which is Metzler, for any $\boldsymbol{y} \in \mathbb{R}^m_{\geq 0}$ which is equivalent to saying that the flow of the $\boldsymbol{x}$ variables, when the other variables are fixed, is monotone.*

One foundational result of ME, the NGM method [Diekmann et al., 1990, Van den Driessche and Watmough, 2002, Van den Driessche and Watmough, 2008] reviewed in Section 8.3, consists in expressing the stability domain of the disease free equilibrium in the form $R_0 \leq 1$. This result is related to the regular splitting theorem reviewed in next section.

### 2.8 Defining ME models by assuming the existence of a regular splitting for the Jacobian $J_x$ and stability of the Jacobian $J_y$ at the DFE

Currently, there is no accepted definition of ME models. It is accepted that ME models are a subset of mass-action representable non-negative models, but this is a very general class. We believe that "relevant" ME models are a subset of CRN models, a class which in itself rules out certain "physically unrealistic behaviors like hidden inflow reactions (HIR)/cornucopias [Müller et al., 2022] like $D + Y \to 2D + Y$ (which result into a non-negative stoichiometric vector, but are not pure inflow reactions).

Furthermore, we conjecture that the existence of a regular splitting for the $x - y$ partition induced by the DFE could be taken as definition of ME models, and we offer two possible definitions in this direction.

**Definition 12** (ME model, classic and algorithmic)**.**

- *We will call classic ME model a CRN with no hidden inflow reactions, and such that:*

  1. *The DFE index set (the union all minimal critical siphons) is nonvoid, and contains a compact invariant set, which is composed of precisely one point; furthermore, this point may be, depending on the parameters, either stable or unstable.*
  2. *The Jacobian $J_y$ at the DFE, where $\mathbf{y}$ are the non-DFE (resident) variables, is stable.*
  3. *The Jacobian $J_x$ at the DFE is Metzler (equivalently, the ODE is locally increasing in $\mathbf{y}$ at the DFE)*
  4. *$J_x$ admits some regular splitting $J_x = F - V$ (and as a consequence, the instability domain of the DFE may be expressed as $R_0 = \rho(FV^{-1}) > 1$).*

- *We will call algorithmic ME model an x-y model satisfying 1. - 4. above, and such that 5. is satisfied with F obtained from the totality of reactions involving x and y reactants, by removal of all terms preceded by a minus, as proposed in [Avram et al., 2023].*

## 3 A two strain SI$^2$V Lotka-Volterra-Kolmogorov model with permanent cross-immunity and vaccination, where the persistence conjecture holds [Ashrafur Rahman and Zou, 2011]; SI2V.nb

This section presents an example which satisfies both the persistence conjecture and the competitive exclusion principle.

**Definition 13** (Competitive Exclusion/Linear Complementarity Principle)**.** *We will say that a k-strain ODE satisfies the competitive exclusion principle (CEP) or Linear Complementarity Principle if its parameter space may be partitioned the into $2^k$ stability regions, each of which contains precisely one LAS equilibrium.*

The SI$^2$V two-strain model of [Ashrafur Rahman and Zou, 2011] is defined by the following reactions + rates representation:

$$\begin{pmatrix} 0 \to s & \Lambda(s) \\ i_1 + s \to 2i_1 & \beta_1 i_1 s \\ i_2 + s \to 2i_2 & \beta_2 i_2 s \\ s \to v & \rho s \\ i_2 + v \to 2i_2 & i_2 v \beta_v \\ v \to 0 & \mu_v v \\ i_1 \to 0 & i_1 \mu_1 \\ i_2 \to 0 & i_2 \mu_2 \end{pmatrix} \tag{9}$$

(this is the simplified version, where the recovered class, which does not affect the others, is omitted).

For a discussion of the advantages of using this representation for ME models, see [Vassena et al., 2024, Avram et al., 2024c, Avram et al., 2025].

The two minimal siphons are $i_1$,$i_2$. The induced ODE is:

$$X' = \begin{cases} -\beta_1 i_1 s - \beta_2 i_2 s + \Lambda(s) - \rho s \\ \begin{pmatrix} \mathcal{R}_1 s - 1 & 0 \\ 0 & \mathcal{R}_2 s + \mathcal{R}_v v - 1 \end{pmatrix} \begin{pmatrix} \mu_1 i_1 \\ \mu_2 i_2 \end{pmatrix} \\ -i_2 v \beta_v + \rho s - \mu_v v \end{cases} := \begin{cases} -\beta_1 i_1 s - \beta_2 i_2 s + \Lambda(s) - \rho s \\ M(s,v) \begin{pmatrix} \mu_1 i_1 \\ \mu_2 i_2 \end{pmatrix} \\ -i_2 v \beta_v + \rho s - \mu_v v \end{cases} \tag{10}$$

with

$$\mathcal{R}_j = \frac{\beta_j}{\mu_j}, j = 1, 2, \quad \mathcal{R}_v = \frac{\beta_v}{\mu_2}.$$

**Assumption 1.** *From now on, we will assume that* $\Lambda(s) = \Lambda - \mu s := \Lambda(1 - s/s_0)$.

**Remark 11.** *The fact that in* (10) *the* $M = Diag[f_j(\boldsymbol{y})] = Diag[R_j(\boldsymbol{y}) - 1], \boldsymbol{y} = (s, v)$ *is diagonal makes the infection problem (with fixed s) a Lotka-Volterra-Kolmogorov ODE (see definition 11), with*

$$f_1 = \mathcal{R}_1 s - 1, f_2 = \mathcal{R}_2 s + \mathcal{R}_v v - 1.$$

*We expect therefore to find four possible fixed points (see also [Rahman and Zou, 2012, Avram et al., 2025] for a similar problem); furthermore, the diagonal structure of* $M$ *suggests combining the local stability problems for all the fixed points into the single linear complementarity problem type optimization problem defined in* (11).

**Definition 14** (The linear complementarity problem associated to a Lotka-Volterra-Kolmogorov ODE)**.** *The linear complementarity problem associated to a Lotka-Volterra-Kolmogorov ODE is:*

$$\begin{cases} max \sum_j \mu_j i_j f_j, \\ i_j \geq 0, f_j \leq 0, \forall j \end{cases}. \tag{11}$$

Clearly, (11) obtains the maximum value 0, and the solutions are into a one to one correspondence with cases of the type $i_S = 0, f_{S^c} \leq 0$, (where S runs over all subsets of the infection set), which may be seen to correspond exactly to the stability conditions for individual fixed points.

We conjecture that a unified proof for CEP/LCP, which has only been established in particular cases, may be provided by rigorously defining k-strain models, and using their reproduction functions, defined below:

**Definition 15** (simple k-strain model)**.** *A simple k-strain model is an ME model for which the NGM matrix has, after permutation, a triangular block structure with* **precisely** $k$ **blocks***, each of which has a unique unconditionally positive eigenvalue, and for which in all siphon faces which contain a compact invariant set in their interior, this is composed of precisely one point.*

**Corollary 1.** *For a simple k-strain model* $\rho(K) = \max_{j=1}^{k} \rho(K_{jj})$*, where* $k$ *is the number of blocks in the decomposition of the NGM.*

**Definition 16** (reproduction functions, invasion numbers and reproduction numbers for simple k-strain models)**.**

*For a simple k-strain model:*

1. *the unique strictly positive eigenvalues of the NGM blocks, $R_i(\boldsymbol{y}), i = 1, ...k$, with the $\boldsymbol{y}$ variables left free, will be called* **R-reproduction functions** *(associated to the strain $i$).*

2. $$R_i(s_0) = \mathcal{R}_i s_0 := R_i^{\widetilde{0}} := R_i, i = 1, ..., k \tag{12}$$

   *will be called the* **basic reproduction number of strain** $i$.

3. *Finally, in the case $k = 2$ with two strains which correspond to two minimal siphons with resident values $s_j$,*

   $$R_i^{\widetilde{j}} := R_i(s_j) \tag{13}$$

   *will be called the* **invasion number of invading strain** $i$ **on resident strain** $j$ *(see Definition 23 for the general case).*

**Remark 12.** *Note that here we have given a precise mathematical definition for the ME concept of invasion number, as the reproduction function of one (invading) strain, evaluated at the resident boundary fixed point of the other strain (this is formalized to more than two strains below). Note also that in ecology, the invasion rates turn out to be proportional to $R_i(s_j)-1$, in the simple case when resident invariant sets are singletons.*

**Example 5** (reproduction functions and invasion numbers of SI2V)**.** *For the [Ashrafur Rahman and Zou, 2011] model, the NGM*

$$K = \begin{pmatrix} \frac{\beta_1 s}{\mu_1} & 0 \\ 0 & \frac{\beta_2 s + \beta_v v}{\mu_2} \end{pmatrix} := \begin{pmatrix} \mathcal{R}_1 s & 0 \\ 0 & \mathcal{R}_2 s + \mathcal{R}_v v \end{pmatrix}$$

*reveals that the reproduction functions –see Definition 16– are*

$$R_1(s, v) := \mathcal{R}_1 s, R_2(s, v) := \mathcal{R}_2 s + \mathcal{R}_v v. \tag{14}$$

*The partition or the parameter space in terms of $R_1, R_2, R_2^{\widetilde{1}}, R_1^{\widetilde{2}}$ turns out to be:*

1. **DFE stable***:* $\max[R_1, R_2] \le 1$.
2. $E_1$ **stable***:* $R_1 > 1, R_2^{\widetilde{1}} \le 1$*, i.e. strain 2 cannot invade.*
3. $E_2$ **stable***:* $R_2 > 1, R_1^{\widetilde{2}} \le 1$*, i.e. strain 1 cannot invade.*
4. $E^*$ **stable***:* $\min[R_1, R_2, R_2^{\widetilde{1}}, R_1^{\widetilde{2}}] > 1$*, i.e. both strains 1,2 can exist and can invade.*

**Remark 13.** *DFE is stable iff it is the only boundary equilibrium. The coexistence equilibrium is stable iff both single-strain equilibria exist and are unstable.*

### 3.1 The Fixed Points, and the Solution of the Linear Complementarity Problem

The DFE, E1, and the coexistence point EE turn out to be explicit, and the solution of E2 reduces to resolving a quadratic. Finally, the LCP is equivalent to the following four cases, obtained by letting $S$ run over the two minimal siphons, their union, and the empty set:

(1) $S = \{i_1, i_2\} \Leftrightarrow i_1 = i_2 = 0$ (with $f_1, f_2 \le 0$ for stability) yields the **Disease-Free Equilibrium (DFE)** $E_0$:

$$E_0 = \left(s_0 = \frac{\Lambda}{\mu + \rho}, 0, 0, v_0 = \frac{\rho}{\mu_v} s_0\right),$$

and direct or NGM analysis confirm the expected result that stability holds iff $R_0 = \max[R_1, R_2] \le 1$, where $R_1, R_2$ are the reproduction numbers of each strain –see definition 16.3.

(2) $S = \{i_2\} \Leftrightarrow i_1 > 0, i_2 = 0 \Rightarrow f_1 = 0, f_2 \le 0$ yield the **strain 1 only** equilibrium:

$$E_1 = \left( s_1 = \frac{\mu_1}{\beta_1},\, i_{1,1} = \frac{\beta_1 \Lambda - \mu_1 \rho - \mu \mu_1}{\beta_1 \mu_1} = \frac{\rho + \mu}{\beta_1}(R_1(s_0) - 1) = \frac{\rho + \mu}{\beta_1 s_1}(s_0 - s_1),\, 0,\, v_1 = \frac{\rho}{\mu_v} s_1 \right),$$

with existence condition:

$$R_1 := R_1(s_0) > 1 \Leftrightarrow s_0 > s_1, \tag{15}$$

where we recall that the R-reproduction function $R_1(s)$ is defined in definition 16.1, as the unique strictly positive eigenvalue of the NGM, with the y variables left free, associated to the block corresponding to strain 1.

The analysis of the Jacobian at $E_1$ (see Mathematica file) confirms the predicted stability condition

$$R_2^{\tilde{1}} := R_2(s_1, v) = \mathcal{R}_2 s_1 + \mathcal{R}_v v \le 1.$$

(3) $S = \{i_1\} \Leftrightarrow i_2 > 0, i_1 = 0$, the **strain 2 only equilibrium** has $i_2$ satisfying a quadratic equation $A i_2^2 + B i_2 + C = 0$, with coefficients:

$$C = \mu_2(\mu + \rho)\mu_v - \Lambda((\beta_2 \mu_v + \rho \beta_v)), B = \mu_2(\mu + \rho)\beta_v + \beta_2\left(\mu_2 \mu_v - \Lambda \beta_v\right), A = \beta_2 \beta_v \mu_2$$

As proved in [Ashrafur Rahman and Zou, 2011], A positive free coefficient $C$ occurs iff

$$R_2 := R_2(s_0, v_0) > 1, \tag{16}$$

and in this case the quadratic has precisely one positive root. Furthermore, $s, v$ are also positive if $i_2$ is.

The direct LAS approach involves analyzing the stability of a third order polynomial, and reveals that the result is as expected, stability holds iff $R_1^{\tilde{2}} < 1$.

(4) $S = \emptyset$ yields the **endemic equilibrium** $E^*$, which, surprisingly, is rational

$$s = s_1 = \frac{\mu_1}{\beta_1}, v = \frac{\mu_1 \mu_2(\mathcal{R}_1 - \mathcal{R}_2)}{\beta_1 \beta_v}, i_2 = \frac{\rho}{\mu_2(\mathcal{R}_1 - \mathcal{R}_2)} - \frac{\mu_v}{\beta_v}, i_1 = \frac{\Lambda}{\mu_1} + \frac{\frac{\beta_2 \mu_v}{\beta_v} - \mu}{\beta_1} - \frac{\rho}{\mu_1(\mathcal{R}_1 - \mathcal{R}_2)}.$$

It turns out that the (positivity) existence conditions may be written in the form

$$\mathcal{R}_1 > \mathcal{R}_2 > 1, R_2^{\tilde{1}} > 1, R_1^{\tilde{2}} > 1; \tag{17}$$

the first three are obvious, and the last two may be checked easily to be the positivity conditions for $i_1, i_2$ (or, see file SI2V.nb).

(17) are precisely the expected LAS conditions. That this is indeed the case, namely that existence implies LAS could be proved by the direct LAS approach, but this is rather challenging, since it requires solving 4'th order Routh-Hurwitz conditions. Fortunately, LAS has been already established in [Ashrafur Rahman and Zou, 2011], by offering a Lyapunov function which shows that GAS holds whenever EE exists.

**Theorem 1** (persistence of the SI2V model)**.** *The SI2V model of [Ashrafur Rahman and Zou, 2011] satisfies both the persistence conjecture and the competitive exclusion principle.*

We conclude this section with an open problem.

**Problem 1** (LCP/CEP for k-strain models)**.** *Which k-strain models satisfy LCP/CEP, and under what conditions the stability regions for the fixed points may be expressed in terms of the* $2^k$ *reproduction functions* $R^S_{\tilde{S^c}}$*, where* $S$ *runs over the k minimal siphons?*

# 4 A directed graphs on minimal siphons (IGMS)

This section establishes that next–generation matrices $K = FV^{-1}$ have a block–triangular structure from $V$ whenever the minimal siphon partition the infected, and the graph defined below is acyclic.

**Definition 17** (The Interaction Directed Graph on Minimal Siphons (IGMS))**.** *The Interaction Directed Graph on Minimal Siphons (IGMS) is the graph on the minimal siphons $T_j, j = 1, ..., m$, with a directed edge $T_i \to T_j$ whenever there exists a reaction net-producing at least one species in $T_j$ from reactants in $T_i$.*

**Example 6** (a tree IGMS for a three-tier Seed-Dependent Autocatalytic Systems (SDAS) -type ME model)**.** *The RN*

$$\begin{pmatrix} 0 \to S & \lambda \\ S \to 0 & S\mu_s \\ I1 + S \to 2 * I1 & \beta_1 i_1 S \\ I1 + I2 \to 2 * I2 & \beta_2 i_1 i_2 \\ I2 + I3 \to 2 * I3 & \beta_3 i_2 i_3 \\ I1 \to 0 & i_1 \mu_1 \\ I2 \to 0 & i_2 \mu_2 \\ I3 \to 0 & i_3 \mu_3 \end{pmatrix}$$

*has three disjoint minimal siphons, and a tree IGMS, as shown in Figure 1. The NGM matrix is triangular (in fact diagonal), in line with theorem 2.*

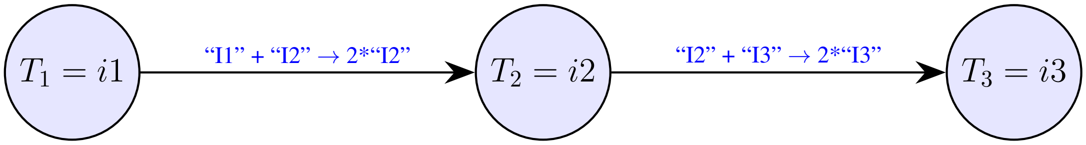


**Figure 1:** Three-tier sequential SDAS-type ME model. Siphons $T_i$ are represented by circles. The reactions are of autocatalytic infection type, where contact between strains leads to conversion.

*This RN can not be interpreted as an existing ME model, but it has been used in the quite similar Seed-Dependent Autocatalytic System (SDAS) theory. Originally proposed to model stepwise prebiotic chemical evolution, this is now used to identify hierarchically nested autocatalytic motifs in large reaction networks [Peng et al., 2022, Peng et al., 2023, Blokhuis et al., 2020, Blokhuis et al., 2023]. This theory provides general results for ecological and potential multi-strain epidemic systems, where new functional tiers emerge only after the appearance of specific seed species.*

## 4.1 Block structure of the Next–Generation Matrix under Acyclic Minimal Siphon Decompositions (AMSD)

We show in this section that in epidemic models where the minimal siphons partition the DFE support and IGMS is acyclic, we have: (i) *block–triangular* NGMs $K = FV^{-1}$, after reordering, and (ii) *decomposition of the threshold* $\rho(K) = \max_i \rho(K_{ii})$ by blocks.

**Theorem 2** (acyclic minimal siphon decomposition implies triangularity of NGM)**.** *Let $\mathcal{I}$ be the set of infected variables and suppose $\{T_1, \ldots, T_m\}$ is a decomposition of $\mathcal{I}$ into siphons, and let $G_{\text{out}}$ denote the IGMS (on vertices $\{T_1, \ldots, T_m\}$, with a directed edge $T_i \to T_j$, $i \neq j$, whenever there exists a reaction whose reactant set intersects $T_i$ and whose product set intersects $T_j$). Assume $G_{\text{out}}$ is acyclic. Let $\pi$ be any topological ordering of $G_{\text{out}}$, and reorder the infected variables by listing first all species in $T_{\pi(1)}$, then* *those in $T_{\pi(2)}$, and so on, with arbitrary order within each block. Under this ordering, $F$ is block diagonal and $V$ is block lower triangular; hence $K = FV^{-1}$ is block lower triangular with $m$ diagonal blocks. If $G_{\text{out}}$ has no edges, then $K$ is block diagonal.*

*Proof.* Let $\mathcal{I} = T_1 \sqcup \cdots \sqcup T_m$ be the decomposition of infected variables into minimal siphons, and let $\pi$ be a topological ordering of $G_{\text{out}}$. Write the linearized infection subsystem as $\dot{x} = (F - V)x$, where $F$ represents new infection terms and $V$ the transition and removal terms.

The acyclicity of the IGMS implies that both $F$ and $V$ are block lower triangular, and hence the product $K = FV^{-1}$ is also block lower triangular.

$\square$

**Corollary 2.** *If $\mathcal{I}$ admits an acyclic siphon decomposition, then $\rho(K) = \max_i \rho(K_{ii})$ after a compatible ordering of variables; hence threshold behavior decomposes by blocks.*

**Remark 14.** *AMSD is a sufficient, but not necessary condition for block triangular NGM structure, as the next example shows.*

### 4.2 Example of cyclic IGMS, with block diagonal NGM structure: 5cycles.nb

```
RN = {                              rts = {
  0 -> "S",                           la,              (* birth *)
  "S" -> 0,                           mu*S,            (* S death *)
  "S" + "I1" -> 2*"I1",               be1*S*I1,        (* inf. I1 *)
  "S" + "I2" -> 2*"I2",               be2*S*I2,        (* inf. I2 *)
  "I1" + "I2" -> "I12",               de*I1*I2,        (* I1+I2->I12 *)
  "I1" + "I12" -> "I2",               et1*I1*I12,      (* I1+I12->I2 *)
  "I2" + "I12" -> "I1",               et2*I2*I12,      (* I2+I12->I1 *)
  "I1" -> 0,                          mu1*I1,          (* I1 death *)
  "I2" -> 0,                          mu2*I2,          (* I2 death *)
  "I12" -> 0                          mu12*I12         (* I12 death *)
};                                  };
```

The minimal siphons: $T_1 = \{I_1, I_2\}, T_2 = \{I_2, I_{12}\}, T_3 = \{I_1, I_{12}\}$ yield an IGMS with two three–cycles $T_1 \rightleftarrows T_2 \rightleftarrows T_3$, and $T_1 \rightleftarrows T_3 \rightleftarrows T_2$, and three pair cycles. Despite this, the NGM has block-diagonal structure:

$$K = \begin{pmatrix} \frac{\beta_1 s}{\mu_1} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_2 s}{\mu_2} \end{pmatrix}$$

# 5 A two strain model with temporary cross-immunity, with ADE and immunity waning, that may exhibit Hopf bifurcations: [Ferguson et al., 1999, Schwartz et al., 2005, Nuno et al., 2005, Aguiar and Stollenwerk, 2007, Chung and Lui, 2 Gavish and Rabiu, 2023, Gavish, 2024b, Gavish, 2024a];GavScan.nb

### 5.1 Background

The two strain model may be traced back to [Ferguson et al., 1999, Schwartz et al., 2005], and is appropriate for modelling simultaneous epidemics with different pathogens, like for example Dengue and Zika. Subsequently, two-strain models which add further compartments allowing for temporary cross-immunity have been developed in the works of Aguiar, Stollenwerk and Kooi [Aguiar and Stollenwerk, 2007, Aguiar et al., 2008, Aguiar et al., 2009, Stollenwerk et al., 2017, Aguiar et al., 2022], and [Billings et al., 2008, Bulhosa and Oliveira, 2023] examined the effects of single-strain vaccination on the dynamics of an epidemic multi-strain Dengue model (see also [Avram et al., 2023] for a first public notebook). This model has also been used for several strains of pathogens (without immunity-effectors compartments), and in ecology [Minayev and Ferguson, 2009, Lazebnik, 2023].

## 5.2 The reaction network representation

The goal of this section is both to present an interesting variant model, and also to provide some comments on its analysis using EpidCRN.

Figure 2 shows a model with eight compartments: susceptibles (s), those infected first by strain $j$ ($i_j$, primary infection), those recovered from strain $j$ ($r_j$, as a result of primary infection), those infected with strain $j$ after they had recovered from strain $i$ ($y_i$) and those recovered from both strains ($r_{12}$). There is one inflow into $S$, 8 outflows out of all compartments, and 15 inner reactions for the “closed model”, with RN:

| Reactions | Type | Parameters |
|---|---|---|
| `RNc={ "S"+"i1"->2"i1", "S"+"i2"->2"i2",` | primary infection | $\beta_1, \beta_2$ |
| `"R2"+"i1"->"i1"+"i21","R1"+"i2"->"i2"+"i12",` | cross infection | $\beta_1\sigma_1, \beta_2\sigma_2$ |
| `"S"+"i21"->"i21"+"i1","S"+"i12"->"i12"+"i2"` | catalytic infection | $\beta_1\eta_1, \beta_2\eta_2$ |
| `"R2"+"i21"->2"i21", "R1"+"i12"->2"i12"` | amplification | $\beta_1\sigma_1\eta_1, \beta_2\sigma_2\eta_2$ |
| `"i1"->"R1","i2"->"R2","i21"->"R12","i12"->"R12",` | recovery | $\gamma_1, \gamma_2, \gamma_1, \gamma_2$ |
| `"R1"->"S", "R2"->"S", "R12"->"S" }` | waning immunity | $\theta_1, \theta_2, \theta_{12}$ |

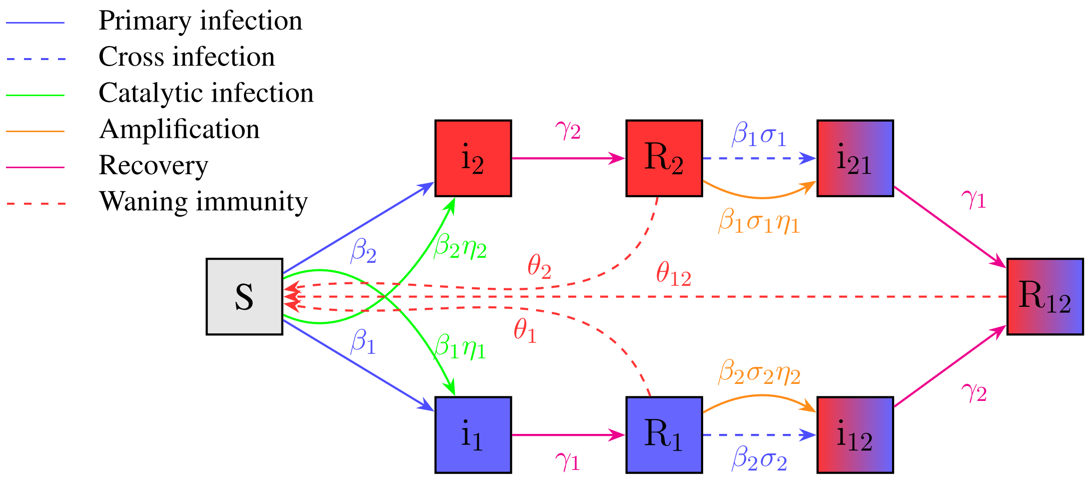


**Figure 2:** Schematic diagram of disease dynamics for two co-circulating strains. The diagram includes all reactions: primary infections ($\beta_i$), cross-infections ($\beta_j\sigma_j$), catalytic secondary infections ($\beta_i\eta_i$), amplification reactions ($\beta_j\sigma_j\eta_j$), recoveries ($\gamma_i$), and waning immunity ($\theta_i$). Green arrows represent catalytic infections where secondary cases catalyze new primary infections. Orange arrows represent amplification where recovered individuals become secondary cases through contact with existing secondary cases.

## 5.3 The ODE formulation of the model

We present first an extension of the mass-action model allowing for saturation, which we plan to study in the future. Putting

$$J_k = i_k + \eta_k i_{\widetilde{k},k}, k = 1, 2, \widetilde{k} := 3 - k. \tag{18}$$

and $X = (s, i_1, i_2, i_{21}, i_{12}, r_1, r_2, r_{12})$, the model with saturation is given by

$$X' = \begin{cases} \varphi(s) - \sum_{k=1}^{2} \beta_k J_k S + \sum_{k=1}^{3} \theta_k r_k, \quad \varphi(s) = \Lambda - \mu s \\ \beta_1 J_1 s - (\mu + \gamma_1) i_1, \\ \beta_2 J_2 s - (\mu + \gamma_2) i_2, \\ \beta_1 \sigma_1 J_1 r_2 - (\mu + \gamma_1) i_{21}, \\ \beta_2 \sigma_2 J_2 r_1 - (\mu + \gamma_2) i_{12}, \\ \gamma_1 i_1 - \beta_2 \sigma_2 J_2 r_1 - (\mu + \theta_1) r_1, \\ \gamma_2 i_2 - \beta_1 \sigma_1 J_1 r_2 - (\mu + \theta_2) r_2, \\ \sum_i \gamma_i y_i - (\mu + \theta_{12}) r_{12}, \end{cases} \tag{19}$$

were $\Lambda$ is the rate at which individuals are born, $\mu$ is the mortality rate, $\beta_i$ denotes the transmission coefficient for strain $i$, $\gamma_i$ denotes the recovery rate from strain $i$, $\theta_i$ is the rate at which immunity to re-infection by strain $i$ wanes and $\theta_{12} := \theta_3$ is the rate at which immunity to re-infection by both strains wanes. Finally, $\sigma_i$ is the relative susceptibility to strain $i$ for an individual previously infected with and recovered from strain $j$ ($i \neq j$), so that $\sigma_i = 0$ corresponds to total cross-immunity, $0 < \sigma_i < 1$ corresponds to reduced susceptibility (partial cross-immunity) and $\sigma_i > 1$ corresponds to enhanced susceptibility, called ADE.

**Definition 18** (ADE). *[Ferguson et al., 1999, Schwartz et al., 2005, Cummings et al., 2005]. For a multi-strain model, we say a secondary infection parameter $\sigma_1$ has Antibody-Dependent Enhancement (ADE) if it is bigger than* $1$.

**Assumption 2.** *In this paper, we consider only the mass action model obtained when $\alpha_i = 0$.*

Then:

1. The two forces of infection acting on $s$ are:

$$F_i = \beta_i J_i, \quad J_i = i_i + \eta_i y_i, i = 1, 2, \tag{20}$$

2. and the forces of infection acting on $r_i, i = 1, 2$, are:

$$\sigma_1 \beta_1 J_1 := \widetilde{\beta}_1 J_1, \sigma_2 \beta_2 J_2 := \widetilde{\beta}_2 J_2, \tag{21}$$

   where $\sigma_1, \sigma_2$ denote decrease or increase factors of the susceptibility to secondary infections.

**Assumptions on model parameters**: The feasible range of the problem parameters is

$$\beta_i > 0, \quad \gamma_i > 0, \quad \mu \geq 0, \quad \theta_k \geq 0, \quad \eta_i > 0, \quad \sigma_i \geq 0, \qquad i = 1, 2, \quad k = 1, 2, 3. \tag{22a}$$

Assume that the susceptible group is replenished by demographic turnover ($\mu > 0$) and/or by waning of the immune response generated following infections ($\theta_k > 0$),

$$\max\{\mu, \theta_1, \theta_2, \theta_{12}\} > 0 \tag{22b}$$

(this enables the system to converge to an endemic equilibrium, rather than gradually exhausting the susceptible pool and converging to a disease-free state).

**Remark 15.** *Some interesting features of the model, already revealed in [Nuno et al., 2005, Chung and Lui, 2016], are:*

1. *The expected form*

   $$R_1 > 1, R_2^{\tilde{1}} < 1,$$

   *of the interior of the local stability domain of the boundary fixed point $E_1$ (with an analog statement for $E_2$), may be proved by factoring the full Jacobian at $E_1$.*

2. *An interior fixed point is believed to exist, and may be proved under additional conditions – see [Gavish, 2024b, Thm 2.2]. The general case is a hard problem, even in the particular case of Chung & Lui.*

3. *It appears from simulations that when both fixed boundary points exist and are unstable, either a unique endemic point, or an attracting periodic cycle may exist. The separation between the two is not fully understood (note that the Jacobian at the endemic point does not factor, and thus the respective Hopf bifurcation occurs in dimension 7).*

4. *Existence of the endemic point implies LAS – see [Chung and Lui, 2016, Thm 1.1, 1.2].*

**Problem 2** (factoring the full Jacobian at boundary fixed points)**.** *Is factoring the full Jacobian at boundary fixed points always possible for some class of multi-strain models?*

### 5.4 Getting the minimal siphons, the DFE, the ngm, and the reproduction functions with `bdAn`

After inputting the model as a pair (RN,rts) we initiate the analysis by calling the simplest bdAn (boundary analysis) module:

```
{RHS, var, par, cp, mSi, Jx, Jy, E0, K, R0A, ngm, infV} =
  bdAn[RN, rts];
Print["RHS=", RHS // FullSimplify // MatrixForm, "mSi=", mSi, " K= ",
K // MatrixForm, infV];
```

The outputs of bdAn are:

1. **RHS**: Right-hand side vector of the ODE system
2. **var**: List of all variables
3. **par**: List of all parameters
4. **cp**: List of positivity constraints for all parameters
5. **mSi**: Minimal siphons as variables (obtained by `minSiph`)
6. **Jx**: Jacobian of infection/invasion variables (obtained by `NGM`)
7. **Jy**: Jacobian of non-infection variables (obtained by `NGM`)
8. **E0**: DFE condition
9. **K**: next generation matrix (obtained by `NGM`)
10. **R0A**: List of non-zero eigenvalues of K
11. **ngm**: complete output of `NGM`, including $F, V$, and the alternative $K_d$ next generation matrix

12. **infV**: the order of inf variables used in `NGM`.

This reveals that the minimal siphons correspond precisely to the two infectious strains: $i_1, i_{21}$ and $i_2, i_{12}$. The total siphon is the union of the two minimal siphons, $\boldsymbol{x} = (i_1, i_{21}, i_2, i_{12})$, $\boldsymbol{y} = (s, r_1, r_2, R = r_{12})$ .

At the DFE $E_0$, we find all species are 0, except $s_0 = \frac{\Lambda}{\mu}$.

The NGM $K$ is outputted in the order $i_1, i_2, i_{21}, i_{12}$, and after permutation to $i_1, i_{21}, i_2, i_{12}$, has a block structure $K = \begin{pmatrix} \frac{\beta_1 s}{\gamma_1+\mu} & \frac{\beta_1 \eta_1 s}{\gamma_1+\mu} & 0 & 0 \\ \frac{\beta_1 r_2 \sigma_1}{\gamma_1+\mu} & \frac{\beta_1 \eta_1 r_2 \sigma_1}{\gamma_1+\mu} & 0 & 0 \\ 0 & 0 & \frac{\beta_2 s}{\gamma_2+\mu} & \frac{\beta_2 \eta_2 s}{\gamma_2+\mu} \\ 0 & 0 & \frac{\beta_2 r_1 \sigma_2}{\gamma_2+\mu} & \frac{\beta_2 \eta_2 r_1 \sigma_2}{\gamma_2+\mu} \end{pmatrix}$.

**Remark 16.** *Note the diagonal structure of the NGM, which could be takes as definition of multi-strain models, and explains the typical "max" formulas that appear in multi-strain GLV or multi-strain SIR.*

The two diagonal blocks are the NGMs of the boundary fixed points defined by the two minimal siphons. They have one 0 eigenvalue, and the reproduction functions (the unique positive eigenvalues, in this case), are precisely the traces of the two blocks, given by

$$\begin{cases} R_1(\boldsymbol{y}) = \frac{\beta_1(\eta_1 r_2 \sigma_1 + s)}{\gamma_1+\mu}, \\ R_2(\boldsymbol{y}) = \frac{\beta_2(\eta_2 r_1 \sigma_2 + s)}{\gamma_2+\mu}. \end{cases}$$

It may be checked, both by direct stability analysis, and by the NGM method, that:

**Lemma 2.** *The DFE, with $s_0 = \frac{\Lambda}{\mu}$, and all other coordinates zero, is unstable if*

$$R_0 = \max[R_1(s_0), R_2(s_0)] = \max\left[\frac{s_0}{s_1}, \frac{s_0}{s_2}\right] > 1. \tag{23}$$

**Remark 17.** *The reproduction functions are increasing, and the DFE instability inequalities stated in Open Problem 5 hold. Hence, the invasion stability conditions divide the parameter space in 4 pieces.*

**Remark 18.** *There is a version of bdAn, bdCo, which assumes that the all boundary points are rational, and furnishes them, and we could have used it here. However, we have preferred to give the more gradual analysis, where the non-DFE points are analyzed in a second stage.*

### 5.5 Obtaining the single-strain endemic equilibrium points with `bdFp` and `inv2`

Put now

$$\mathcal{R}_i := \frac{\beta_i}{\gamma_i + \mu}, R_i := R_i(E_0) = \mathcal{R}_i s_0. \tag{24}$$

Assume from now on w.l.o.g. that $E_1$ is the more virulent strain, (excluding the non-generic equality case), i.e. $\mathcal{R}_2 < \mathcal{R}_1 \Leftrightarrow R_2 < R_1$.

The single-strain endemic equilibrium points of (19) are found by solving the fixed point system under the siphon conditions, using `bdFp`. For each boundary system, the output consists of a pair consisting of all rational solutions, and of a polynomial satisfied by the non-rational solutions. Here, the output of `bdFp`

```
bdfp = bdFp[RHS, var, mSi];
Print["rat sols on first siphon facet are"]
bd1 = bdfp[[1, 1]] // FullSimplify
bdfp[[1, 2]]
```

reveals that all solutions are rational, and that on each of the two siphon facets we have three fixed points, one of which is the DFE, and one of which is not non-negative. The indexes of the correct solution (2,2) are then passed on to `invN2`, which computes the invasion numbers and a numerical example under which the system is conjectured to be persistent:

```
{E1, E2, R12, R21, coP} =
  invN2[bdfp[[1, 1]], bdfp[[2, 1]], R0A, E0, par, cp, 2, 2];
Print["invasion numbers R12, R21 are ", R12 // Apart, R21 // Apart]
```

We may conclude that:

**Theorem 3** (stability of the boundary fixed points for the Gavish model)**.** *Assume the parameters* $\mu$, $\{\gamma_i\}_{i=1}^{2}$, $\{\theta_k\}_{k=1}^{3}$, $\{\eta_i\}_{i=1}^{2}$, $\sigma_2$ *and* $\sigma_1$ *satisfy* (22). *Then:*

*1) If* $R_1 > 1 \Leftrightarrow s_0 > s_1$, *then, the system* (19) *has a unique single-strain endemic equilibrium* $\phi^{E,1}$ *with* $i_2 = i_{12} = 0$ *and* $i_1 > 0$. *Putting*

$$\widetilde{\gamma}_1 = \frac{\gamma_1}{\gamma_1 + \theta_1 + \mu},$$

*this solution satisfies*

$$\begin{aligned} &s_1 = \tfrac{1}{\mathcal{R}_1}, \quad r_1^{E,1} = \widetilde{\gamma}_1\,(s_0 - s_1) = \widetilde{\gamma}_1 s_0 \left(1 - \tfrac{1}{R_1}\right), i_1^{E,1} = (1 - \widetilde{\gamma}_1)\,(s_0 - s_1) = (1 - \widetilde{\gamma}_1) s_0 \left(1 - \tfrac{1}{R_1}\right) \\ &\quad i_2^{E,1} = i_{12}^{E,1} = r_2^{E,1} = i_{21}^{E,1} = 0, \\ &s_1 + i_1^{E,1} + r_1^{E,1} = s_0, \end{aligned}$$

*and an analog statement holds for a unique single-strain endemic equilibrium* $\phi^{E,2}$ *with* $i_1 = i_{21} = 0$ *and* $i_2 > 0$.

*2) The invasion number* $R_2^{\tilde{1}}$ *is given by:*

$$R_2^{\tilde{1}} = \mathcal{R}_2 \left(\sigma_2 \eta_2 r_1^{E,1} + s_1\right) = \mathcal{R}_2 \left(\sigma_2 \eta_2 \widetilde{\gamma}_1 s_0 \left(1 - \frac{1}{\mathcal{R}_1}\right) + \frac{1}{\mathcal{R}_1}\right) \tag{25}$$

*see [Gavish, 2024b, 5].*

*3)* $\phi^{E,1}$ *is LAS if* $R_2^{\tilde{1}} < 1$ *and unstable if* $R_2^{\tilde{1}} > 1$.

**Proof:**For the last point, we exploit the key observation made by [Nuno et al., 2005, Chung and Lui, 2016] (for the simpler particular case of permanent immunity) that the full Jacobian at $E_1$ factors into one quadratic with negative roots when $r_1 > 1$, and linear terms, only one of which may have positive roots. The condition that this root [Chung and Lui, 2016, (2.2)] is positive may be finally be expressed as $R_2^{\tilde{1}} > 1$.

□

**Remark 19.** *The proof offered in [Gavish, 2024b, Thm (2.1)] is incomplete, since the conditions of [Van den Driessche and Watm are not checked, and this is not at all trivial at the non-DFE boundary fixed points; however, as implemented in our .nb file, the characteristic polynomial factorization proof of [Chung and Lui, 2016] is easily checked to extend to this case.*

## 5.6 The endemic point, in the particular case of [Chung and Lui, 2016]

The existence of the endemic point is a hard problem, still unresolved even in the particular case of Chung & Lui [Chung and Lui, 2016], when $\eta_1 = \eta_2 = 1, \theta_i = 0, i = 1, 2, 3, \Lambda = \mu$.

For this model studied already in [Chung and Lui, 2016], the fixed point system may be reduced to the scalar equation $a_0 + a_1 s + a_2 s^2 + a_{12} s^3$, where

$$\begin{cases} a_0 = \sigma_1\sigma_2(\gamma_1+\mu)^2(\gamma_2+\mu)^2 \\ a_1 = (\gamma_1+\mu)(\gamma_2+\mu)(\sigma_1(\gamma_1+\mu)(\gamma_2+\mu) - \sigma_2(\sigma_1(\gamma_2+\mu)(\beta_1+\gamma_1+\mu) \\ \qquad +\beta_2\sigma_1(\gamma_1+\mu) - ((\gamma_1+\mu)(\gamma_2+\mu)))) \\ a_2 = (-\beta_2)\sigma_1(\gamma_2+\mu)(\gamma_1+\mu)^2 + \beta_1(\gamma_2+\mu)(\gamma_1+\mu)((\sigma_1-1)\sigma_2(\gamma_2+\mu) - \mu\sigma_1) \\ \qquad +\beta_2\sigma_2(\sigma_1(\gamma_1\mu(\beta_1+2(\gamma_2+\mu)) + \mu(\beta_1+\mu)(\gamma_2+\mu) + \gamma_1^2(\gamma_2+\mu)) - \mu(\gamma_1+\mu)(\gamma_2+\mu)) \\ a_{12} = \beta_1\beta_2\mu(\sigma_1(\gamma_1+\mu) + \sigma_2(-\sigma_1(\gamma_1+\gamma_2+\mu) + \gamma_2+\mu)) \end{cases},$$

which confirms [Gavish, 2024a, (6b)]. A generalization including the immunity parameters may be found in the .nb file.

Here is the plot of an instance of the partition. Further experiments are necessary to determine if Hopf bifurcations are possible (in this instance there is none).

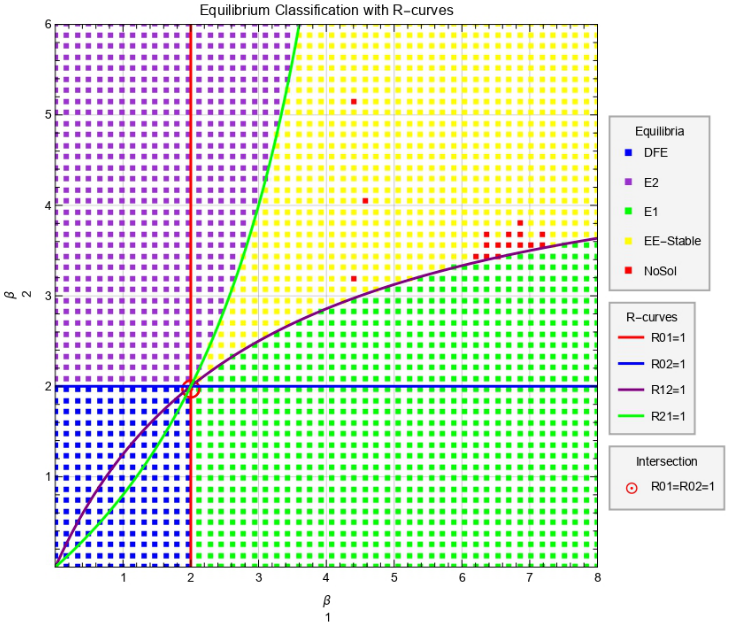


**Figure 3:** The stability partition scan obtained numerically in GavScan.nb almost coincides with the symbolic one obtained using the explicit reproduction and invasion numbers. The file GavScan.nb may be modified (simply change the reactions) to obtain partition scans in cases where the symbolic picture is incomplete (for example when Hopf bifurcations are possible)

**Problem 3** (coexistence of several locally stable fixed points)**.** *For general two-strain models, is it possible that both strains coexist and are locally stable? (recall this is impossible for LVK models)*

We end this section with a fundamental open problem.

**Problem 4** (The persistence conjecture)**.** *The examples studied here and others suggest that for a positive ODE, the instability of all fixed boundary points (or maybe even only the instability of the disease-free equilibrium and the boundary equilibria whose zero set is a maximal non-DFE siphon) ensures the persistence.*

For some positive results in particular cases, see [Angeli et al., 2011, Pantea, 2012, Craciun et al., 2013, Gopalkrishnan et al., 2014, Craciun, 2019].

For another particular case where the persistence conjecture holds, we recall the following:

**Proposition 1.** *([Bulhosa and Oliveira, 2023, Thm 4.19]) Two-strain models which live on a compact non-negative invariant subset and have* $R_j > 1, j = 1, 2$, *and* $R_{\tilde{2}}^1 > 1, R_{\tilde{1}}^2 > 1$, *so that both strains exist, but are unstable, are uniformly persistent.*

### 5.7 Can the persistence and global stability of this two strain model be resolved by removing intermediates?

This question is inspired by the CRN papers [Marcondes de Freitas et al., 2017b, de Freitas et al., 2017], which provide conditions under which the removal of intermediates does not affect persistence. This suggests that there might be a relation between the persistence or GAS property of this model when $r_0 > 1$, and those of the model where the intermediate states $r_i$ are removed.

However, the [Marcondes de Freitas et al., 2017b, de Freitas et al., 2017] theory does not apply: the cross-immunity assumption $\sigma_i > 0$ implies that $r_1, r_2$ are essential species, which do not satisfy the FFW reducibility assumption that intermediates may not appear in mixed complexes which mix "intermediates" and "non-intermediates" (r1+i2, r1+i12, r2+i1, r2+i21). Cross-immunity creates a "biological memory" that prevents mathematical reduction; the two-strain model with cross-immunity is "FFW-irreducible".

## 6 A SI$^2$R model with co-infections of [Ghersheen et al., 2019], which has more reproduction functions than minimal siphons;SI2Coinf.nb

Co-infection models [Regoes and Bonhoeffer, 2004, Vautrin et al., 2007, Althaus and De Boer, 2008, Lipsitch et al., 2009, Ganusov et al., 2011, Alizon, 2013, Lion, 2013, Gao et al., 2016, Mitchell and Kribs, 2019, Belluccini et al., 2024b] pose a mathematical dilemma in our construction. Consider for example the logistic growth SI$^2$R model of [Ghersheen et al., 2019], shown in figure 4 below; should it be viewed as two-strain, or three strain?

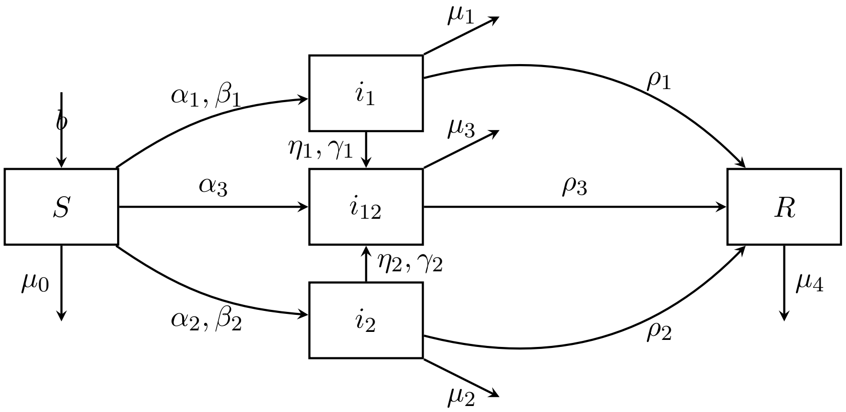


**Figure 4:** Flow diagram for [Ghersheen et al., 2019] two-strain coinfection model

where the following notation was used:

- $i_1$ and $i_2$ are infected classes from strain 1 and strain 2 respectively.
- $i_{12} = i_3$ is the compartment consisting of individuals infected by both diseases.
- $R$ represents the recovered class.

Due to the permanent immunity assumed, we may remove R from the analysis; the total removal rates of the infected will be denoted by $\mu_i = \mu_i' + \rho_i, i = 1, 2, 3$.

We open now a parenthesis about the similar Volpert/Petri/directed species reaction graph (DSR) bipartite graph, which plays a big role in CRNT. The graph below, for pairs of species connected by more than one reaction in Figure 4, includes an edge for each reaction, and it indicates the complete rate inside a circle, which represents the reaction. However, for pairs of species connected by one reaction only, it keeps the structure of 4, except that is indicates the complete rate, not just its constant. The DSR graph is obtained by trasforming all edges in an edge with a circle in the middle. Clearly, the DSR representation is more complete than the flow diagram in Figure 4.

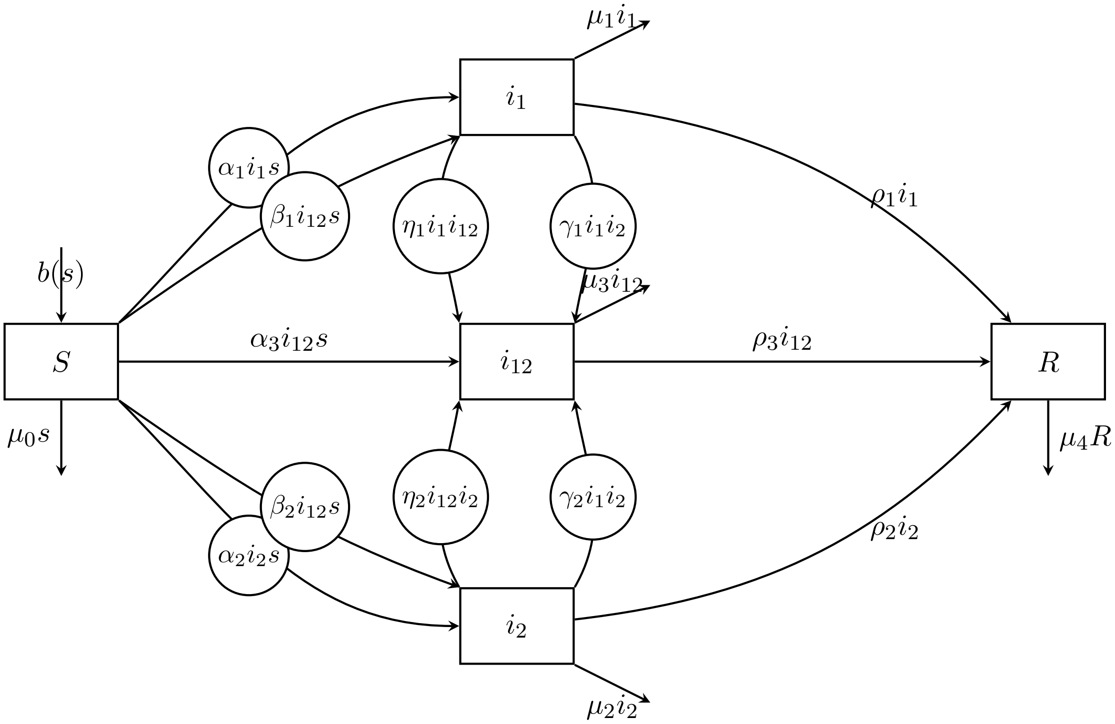


**Figure 5:** Flow diagram for [Ghersheen et al., 2019] two-strain coinfection model in DSR format

For a historical note on these Volpert/Petri/DSR graphs, see Table 1.

**Table 1:** Comparison of common graph representations of chemical reaction networks.

| Name | Origin | Nodes | Edge Direction | Typical Use |
|---|---|---|---|---|
| Volpert graph | Chemical kinetics (Volpert, 1960s) | Species and reactions | Directed | Reachability, persistence |
| Petri net | Computer science (Petri, 1962) | Places and transitions | Directed | Discrete simulation, invariants |
| SR graph | CRN theory (Craciun, Feinberg, 2000s) | Species and reactions | Undirected (signed) | Injectivity tests |
| DSR graph | Dynamical systems (Banaji & Craciun, 2010s) | Species and reactions | Directed (signed) | Stability, monotonicity |

The reaction network representation of the [Ghersheen et al., 2019] model is:

$$\begin{pmatrix}
0\to \mathrm{s} & b(s)\\
\mathrm{i1}+\mathrm{s}\to 2\mathrm{i1} & \alpha_1 i_1 s\\
\mathrm{i2}+\mathrm{s}\to 2\mathrm{i2} & \alpha_2 i_2 s\\
\mathrm{i12}+\mathrm{s}\to 2\mathrm{i12} & \alpha_3 i_3 s\\
\mathrm{i1}+\mathrm{i12}\to 2\mathrm{i12} & \eta_1 i_1 i_3\\
\mathrm{i12}+\mathrm{i2}\to 2\mathrm{i12} & \eta_2 i_3 i_2\\
\mathrm{i1}+\mathrm{i2}\to \mathrm{i12}+\mathrm{i2} & \gamma_1 i_1 i_2\\
\mathrm{i1}+\mathrm{i2}\to \mathrm{i12}+\mathrm{i1} & \gamma_2 i_1 i_2\\
\mathrm{i12}+\mathrm{s}\to \mathrm{i12}+\mathrm{i1} & \beta_1 i_3 s\\
\mathrm{i12}+\mathrm{s}\to \mathrm{i12}+\mathrm{i2} & \beta_2 i_3 s\\
\mathrm{s}\to 0 & \mu_0 s\\
\mathrm{i1}\to 0 & i_1\mu_1\\
\mathrm{i2}\to 0 & i_2\mu_2\\
\mathrm{i12}\to 0 & i_3\mu_3
\end{pmatrix}.$$

The EpidCRN script *b*dAn, furnishes many preliminary results for an epidemiologic analysis:

```
{RHS, var, par, cp, mSi, Jx, Jy, E0, K, R0A, infVars, gam, ng} =
  bdAn[RN, rts];
  {edg, cyc, graph} = IGMS[RN, mSi];
Print["siphons are", mSi, " edges are",
 edg, "  DFE is", E0, " repr. functions=  ", R0A]; F =
 ng[[2]]; V = ng[[3]];
Print["K=", K // MatrixForm, "F=", F // MatrixForm,
"V=",V // MatrixForm];
```

*b*dAn provides:

1. The RHS of the ODE.
2. The minimal siphons mSi, which, assuming $\beta > 0, \gamma > 0$, are {i1,i12},{i2,i12}; the total DFE siphon is therefore {i1,i2,i12}.
3. The subsequent command *I*GMS[RN,mSi] reveals that the IGMS is a cycle

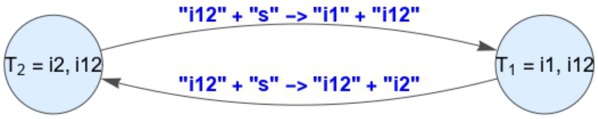


**Figure 6:** IGMS for [Ghersheen et al., 2019] two-strain model; edges denote coinfection reactions

4. The stability of the jacobian $J_y = -\left(i_3\left(\alpha_3+\beta_1+\beta_2\right)+\alpha_1 i_1+\alpha_2 i_2+\mu_0\right) < 0$ is one of the necessary conditions we ask from a ME model.

5. Another one is the existence of a regular splitting of $J_x$, or of a matrix $M$ appearing in the factorization of the fixed point equations may be written as:

$$\mathbf{0} = \begin{pmatrix} b - s\left(i_3\left(\alpha_3+\beta_1+\beta_2\right)+\alpha_1 i_1+\alpha_2 i_2+\mu_0\right) \\ \begin{pmatrix} \alpha_1 s-\gamma_1 i_2-\eta_1 i_3-\mu_1 & 0 & \beta_1 s \\ 0 & \alpha_2 s-\gamma_2 i_1-\eta_2 i_3-\mu_2 & \beta_2 s \\ \eta_1 i_3+\gamma_1 i_2 & \eta_2 i_3+\gamma_2 i_1 & \alpha_3 s-\mu_3 \end{pmatrix} \begin{pmatrix} i_1 \\ i_2 \\ i_3 \end{pmatrix} \end{pmatrix} \tag{26}$$

$$= \begin{pmatrix} b - s\left(i_3\left(\alpha_3+\beta_1+\beta_2\right)+\alpha_1 i_1+\alpha_2 i_2+\mu_0\right) \\ \begin{pmatrix} \alpha_1 s-\gamma_1 i_2-\eta_1 i_3-\mu_1 & 0 & \beta_1 s \\ 0 & \alpha_2 s-\gamma_2 i_1-\eta_2 i_3-\mu_2 & \beta_2 s \\ \gamma_1 i_2 & \gamma_2 i_1 & \eta_1 i_1+\eta_2 i_2+\alpha_3 s-\mu_3 \end{pmatrix} \begin{pmatrix} i_1 \\ i_2 \\ i_3 \end{pmatrix} \end{pmatrix}$$

   Denoting by $M$ the matrix multiplied by $\begin{pmatrix} i_1 \\ i_2 \\ i_3 \end{pmatrix}$ in the first representation in (26) above, and spitting $M = F - V$ as the difference of a non-negative matrix and of a matrix with positive inverse

$$M = s\begin{pmatrix} \alpha_1 & 0 & \beta_1 \\ 0 & \alpha_2 & \beta_2 \\ 0 & 0 & \alpha_3 \end{pmatrix} + \begin{pmatrix} -\gamma_1 i_2-\eta_1 i_3-\mu_1 & 0 & 0 \\ 0 & -\gamma_2 i_1-\eta_2 i_3-\mu_2 & 0 \\ \gamma_1 i_2+\eta_1 i_3 & \gamma_2 i_1+\eta_2 i_3 & -\mu_3 \end{pmatrix}$$

   we may conclude that our model satisfies our definition of ME models.

6. The second representation in (26) reveals that when $\beta = \gamma = 0$, this is a Lotka-Volterra-Kolmogorov model.

7. The next generation matrix may be made triangular

$$K = FV^{-1} = \begin{pmatrix} \frac{\alpha_1 s}{\mu_1} & 0 & \frac{\beta_1 s}{\mu_3} \\ 0 & \frac{\alpha_2 s}{\mu_2} & \frac{\beta_2 s}{\mu_3} \\ 0 & 0 & \frac{\alpha_3 s}{\mu_3} \end{pmatrix}$$

   by ordering the variables as $i_1, i_2, i_{12}$. This suggests that the most convenient ordering of the DFE support must start with elements which appear only in one siphon.

   Finally, triangularity reveals that $R_0 = s_0 \max_{i=1}^{3}[\mathcal{R}_i]$, where

$$\mathcal{R}_i = \frac{\alpha_i}{\mu_i}, \quad i = 1, 2, 3, \tag{27}$$

   and where $s_0 = \frac{b}{\mu_0}$ in the linear growth case (and equal to the carrying capacity in the logistic case). This concludes the stability analysis of the DFE.

8. ngm is the list of all the outputs of NGM, which includes the matrices F,V.

9. Using the notation (27), we may express some of the boundary fixed points which have precisely one positive infection variable in a revealing form:

$$E_1 = (s = \frac{1}{\mathcal{R}_1}, i_1 = \frac{\mu_0}{\alpha_1}\left(\mathcal{R}_1 s_0 - 1\right), i_2 = 0, i_3 = 0),$$

with similar formulas for $E_2, E_3$. These points exist iff

$$R_i := \mathcal{R}_i s_0 > 1, i = 1, 2, 3. \tag{28}$$

$$R_i(s) := \mathcal{R}_i s, \tag{29}$$

called reproduction functions and applied at the s-value of the other fixed points (besides (28)), will be seen to intervene in the stability analysis in Section 6.1.

### 6.1 Further analytical results

Recall the reaction network from Section 6:

$$\begin{pmatrix} 0 \to \mathrm{s} & b(s) \\ \mathrm{i1} + \mathrm{s} \to 2\mathrm{i1} & \alpha_1 i_1 s \\ \mathrm{i2} + \mathrm{s} \to 2\mathrm{i2} & \alpha_2 i_2 s \\ \mathrm{i12} + \mathrm{s} \to 2\mathrm{i12} & \alpha_3 i_3 s \\ \mathrm{i1} + \mathrm{i12} \to 2\mathrm{i12} & \eta_1 i_1 i_3 \\ \mathrm{i12} + \mathrm{i2} \to 2\mathrm{i12} & \eta_2 i_3 i_2 \\ \mathrm{i1} + \mathrm{i2} \to \mathrm{i12} + \mathrm{i2} & \gamma_1 i_1 i_2 \\ \mathrm{i1} + \mathrm{i2} \to \mathrm{i1} + \mathrm{i12} & \gamma_2 i_1 i_2 \\ \mathrm{i12} + \mathrm{s} \to \mathrm{i1} + \mathrm{i12} & \beta_1 i_3 s \\ \mathrm{i12} + \mathrm{s} \to \mathrm{i12} + \mathrm{i2} & \beta_2 i_3 s \\ \mathrm{s} \to 0 & \mu_0 s \\ \mathrm{i1} \to 0 & i_1 \mu_1 \\ \mathrm{i2} \to 0 & i_2 \mu_2 \\ \mathrm{i12} \to 0 & i_3 \mu_3 \end{pmatrix},$$

with ODE

$$X' = \begin{pmatrix} b - s\left(i_3\left(\alpha_3 + \beta_1 + \beta_2\right) + \alpha_1 i_1 + \alpha_2 i_2 + \mu_0\right) \\ i_1\left(-\gamma_1 i_2 - \eta_1 i_3 - \mu_1 + \alpha_1 s\right) + \beta_1 i_3 s \\ i_2\left(-\gamma_2 i_1 - \eta_2 i_3 - \mu_2 + \alpha_2 s\right) + \beta_2 i_3 s \\ \left(\gamma_1 + \gamma_2\right) i_1 i_2 + i_3\left(\eta_1 i_1 + \eta_2 i_2 - \mu_3 + \alpha_3 s\right) \end{pmatrix}$$

The parameters of the system are:

- $b$ is the intrinsic growth of $s$. [Ghersheen et al., 2019] study the logistic case with $b = r{*}s{*}(1-s/K)$, containing two further parameters, the per capita birth rate $r$, and the carrying capacity $K$, but we study the case when $b$ is constant.
- $\gamma_i$ is the rate at which individuals infected with one strain get infected with the other strain after a meeting with single infected individuals, and move to the coinfected class ($i = 1, 2$).
- $\mu_i', i = 1, 2, 3$ (not shown in figure) are the death rates of the infected compartments.
- $\alpha_1$, $\alpha_2$, $\alpha_3$ are the rates of transmission of strain 1, strain 2 and both strains (i.e. coinfection),
- $\beta_i$ is the rate at which susceptibles contract disease $i = 1, 2$ but not the other disease, from a coinfected individuals.
- $\eta_i, i = 1, 2$ is the rate at which individuals infected by one strain gets coinfected, after a meeting with a coinfected individual.

The following vector notations will be used:

$$\alpha = (\alpha_1, \alpha_2, \alpha_3), \quad \mu = (\mu_0, \mu_1, \mu_2, \mu_3), \quad \eta = (\eta_1, \eta_2), \quad \text{and}$$

The parameters are split into three groups:

$$\mathcal{B} = (b, \alpha, \mu, \eta),\ \text{(basic)}\ ,\ \beta = (\beta_1, \beta_2), \quad \gamma = (\gamma_1, \gamma_2), \quad \Omega = (\gamma_1, \gamma_2, \beta_1, \beta_2)\ \text{(coinfection)}. \tag{30}$$

It is reasonable to assume that the coinfection constants from $\Omega$, involved in terms describing double infection, are small with respect to basic constants.

Assume that $\mathcal{B}$ are positive, and $\beta, \gamma$ are non-negative.

**Remark 20.** *One interesting aspect of this model is the sensitivity of the IGMS structure to the parameters. When $\beta > 0, \gamma > 0$, the minimal siphons are $\{i1,i12\},\{i2,i12\}$. When $\beta = 0, \gamma > 0$, the unique minimal siphons is $\{i12\}$.*

*And when $\beta = 0 = \gamma$, there are three minimal siphons $\{\{i1\},\{i2\},\{i12\}\}$, and the IGMS is a union of two cycles:*

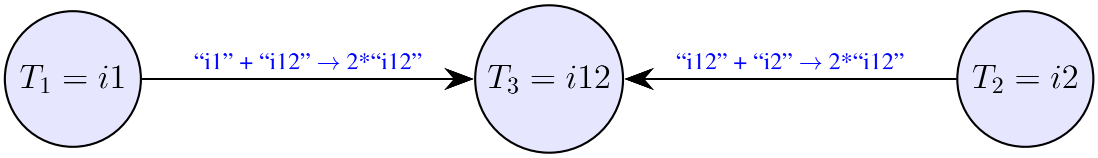


**Figure 7:** The IGMS of the $\beta = 0 = \gamma$ coinfection Kozlov model with coinfection strain i12 has two cycles. Strains i1 and i2 both lose to the coinfection strain i12 when they come into contact.

Furthermore, as noted already, when $\beta_1 = \beta_2 = \gamma_1 = \gamma_2 = 0$, the infection part is a Lotka-Volterra-Kolmogorov model with antisymmetric interaction matrix, to be studied in the next section.

## 6.2 The antisymmetric Lotka-Volterra-Kolmogorov case of the [Ghersheen et al., 2019] model, with 0 coinfection parameters

With 0 coinfection parameters, $\beta_j = \gamma_j = 0, j = 1, 2$, the [Ghersheen et al., 2019] ODE has its infection part of Lotka-Volterra-Kolmogorov type:

$$X' = \begin{pmatrix} \mu_0 s_0 - s\left(i_3\mu_3\mathcal{R}_3 + \mu_1\mathcal{R}_1 i_1 + \mu_2\mathcal{R}_2 i_2 + \mu_0\right) \\ i_1\left(-\eta_1 i_3 - \mu_1 + \mu_1\mathcal{R}_1 s\right) \\ i_2\left(-\eta_2 i_3 - \mu_2 + \mu_2\mathcal{R}_2 s\right) \\ i_3\left(\eta_1 i_1 + \eta_2 i_2 - \mu_3 + \mu_3\mathcal{R}_3 s\right) \end{pmatrix}$$

The infection equations may be written as:

$$x' = \begin{pmatrix} i_1 \\ i_2 \\ i_3 \end{pmatrix} \circ \left[ \begin{pmatrix} \mu_1(s\mathcal{R}_1 - 1) \\ \mu_2(s\mathcal{R}_2 - 1) \\ \mu_3(s\mathcal{R}_3 - 1) \end{pmatrix} + \begin{pmatrix} 0 & 0 & -\eta_1 \\ 0 & 0 & -\eta_2 \\ \eta_1 & \eta_2 & 0 \end{pmatrix} \cdot \begin{pmatrix} i_1 \\ i_2 \\ i_3 \end{pmatrix} \right] := x \circ (c + Ax)$$

with $A$ antisymmetric. The persistence - extinction dichotomy can thus be tackled via the theory of Lotka-Volterra-Kolmogorov ODEs with anti-symmetric $A$ [Xu et al., 2024].

This model has six fixed points, all rational, given respectively by:

$$\begin{cases} E_1 = \left\{ s = \frac{1}{\mathcal{R}_1} := s_1, i_1 = \frac{\mu_0}{\mu_1}(s_0 - s_1) = \frac{\mu_0 s_1}{\mu_1}(s_0\mathcal{R}_1 - 1) := \widetilde{i}_1, i_2 = 0, i_3 = 0 \right\}, \\ E_2 = \left\{ s = \frac{1}{\mathcal{R}_2} := s_2, i_1 = 0, i_2 = \frac{\mu_0}{\mu_2}(s_0 - s_2) = \frac{\mu_0 s_2}{\mu_1}(s_0\mathcal{R}_2 - 1) := \widetilde{i}_2, i_3 = 0 \right\}, \\ E3 = \left\{ s = \frac{1}{\mathcal{R}_3} := s_3, i_1 = 0, i_2 = 0, i_3 = \frac{\mu_0}{\mu_3}(s_0 - s_3) := \widetilde{i}_3 \right\}, DFE = \left\{ s = \frac{s_0\mu_0}{\mu_0}, i_1 = 0, i_2 = 0, i_3 = 0 \right\}, \\ E13 = \left\{ s_{13} = \frac{s_0\mu_0\eta_1}{\mu_1\mu_3(\mathcal{R}_1 - \mathcal{R}_3) + \eta_1\mu_0}, i_1 = \frac{\mu_3}{\eta_1}(1 - \mathcal{R}_3 s_{13}) = \frac{\alpha_3}{\eta_1}(s_3 - s_{13}), i_3 = \frac{\mu_1}{\eta_1}(\mathcal{R}_1 s_{13} - 1) = \frac{\alpha_1}{\eta_1}(s_{13} - s_1), i_2 = 0 \right\}, \\ E23 = \left\{ s_{23} = \frac{s_0\mu_0\eta_2}{\mu_2\mu_3(\mathcal{R}_2 - \mathcal{R}_3) + \eta_2\mu_0}, i_1 = 0, i_2 = \frac{\mu_3}{\eta_2}(1 - \mathcal{R}_3 s_{23}), i_3 = \frac{\mu_2}{\eta_2}(\mathcal{R}_2 s_{23} - 1) \right\} \end{cases}$$

This reveals that the minimal siphon i12=0 does not have any fixed point in its interior (however, it contains the two fixed points $E_1, E_2$ on the boundary).

Finally, the endemic point $EE$ has coordinates:

$$s = \frac{\eta_1\mu_2 - \eta_2\mu_1}{\mu_2\mathcal{R}_2\eta_1 - \mu_1\mathcal{R}_1\eta_2} := s_{ee}, i_3 = \frac{\mu_1\mu_2(\mathcal{R}_1 - \mathcal{R}_2)}{\mu_2\mathcal{R}_2\eta_1 - \mu_1\mathcal{R}_1\eta_2} = \frac{\mu_1\mu_2(\mathcal{R}_1 - \mathcal{R}_2)s_{ee}}{\eta_1\mu_2 - \eta_2\mu_1}$$

$$i_1 = \frac{\mu_2(\mu_3\mathcal{R}_3\eta_2\mu_1 + \mu_2\mathcal{R}_2\eta_1\mu_3 + \eta_1\eta_2\mu_0) + \mu_3\mathcal{R}_3\eta_1\left(-\mu_2^2\right) - \eta_2\mu_1(\mu_2\mathcal{R}_2\mu_3 + \eta_2\mu_0) + s_0\mu_0\eta_2(\mu_1\mathcal{R}_1\eta_2 - \mu_2\mathcal{R}_2\eta_1)}{(\mu_2\mathcal{R}_2\eta_1 - \mu_1\mathcal{R}_1\eta_2)(\eta_1\mu_2 - \eta_2\mu_1)},$$

$$i_2 = \frac{\mu_1(\mu_3\mathcal{R}_3\eta_1\mu_2 + \mu_1\mathcal{R}_1\eta_2\mu_3 + \eta_1\eta_2\mu_0) + \mu_3\mathcal{R}_3\eta_2\left(-\mu_1^2\right) - \eta_1\mu_2(\mu_1\mathcal{R}_1\mu_3 + \eta_1\mu_0) + s_0\mu_0\eta_1(\mu_2\mathcal{R}_2\eta_1 - \mu_1\mathcal{R}_1\eta_2)}{(\mu_2\mathcal{R}_2\eta_1 - \mu_1\mathcal{R}_1\eta_2)(\eta_1\mu_2 - \eta_2\mu_1)}.$$

Until a point, the stability analysis is easy. DFE is stable iff $R_i \leq 1, i = 1, 2, 3$.

**Remark 21.** *The formulas suggest introducing also*

$$R_{13} = R_1(s_{13}), R_{23} = R_2(s_{23}), R_{31} = R_3(s_{13}), R_{32} = R_3(s_{23}),$$

*where we recall that $s_{13}, s_{23}$ represent the boundary value of $s$ on $i_1 = 0$ and $i_2 = 0$, respectively.*

### 6.2.1 Stability analysis for E1, E2

Direct analysis implies that E1 is stable iff

$$\begin{cases} R_1 \geq \max[1, R_2], \\ R_{13} = R_1(s_{13}) > 1 \Leftrightarrow s_{13} > s_1, \end{cases} \tag{31}$$

with analog conditions holding for the stability of E2.

**Remark 22.** *Recall that E13 exists iff $R_{13} > 1$, and $R_{31} < 1$, thus stability of E1 does not prelude existence of E13.*

To check (31), note that the jacobian at $E1$ is $\begin{pmatrix} -\mu_0 R_1 & -\mu_1 & -\frac{\mu_2 R_2}{R_1} & -\frac{\mu_3 R_3}{R_1} \\ \mu_0(R_1 - 1) & 0 & 0 & -\frac{\eta_1\mu_0(R_1 - 1)s_0}{\mu_1 R_1} \\ 0 & 0 & \mu_2\left(\frac{R_2}{R_1} - 1\right) & 0 \\ 0 & 0 & 0 & \frac{\mu_1\mu_3(R_3 - R_1) + \eta_1\mu_0(R_1 - 1)s_0}{\mu_1 R_1} \end{pmatrix}$,

and the numerator of the characteristic polynomial at $E1$ is:

$$(\mu_2(R_1 - R_2) + R_1 u)\left(\mu_0\mu_1(R_1 - 1) + \mu_0 R_1 u + u^2\right)(\mu_1\mu_3(R_1 - R_3) + \eta_1\mu_0 s_0(1 - R_1) + \mu_1 R_1 u)$$

The linear terms are stable iff

$$R_1 - R_2 > 0, \mu_1\mu_3(R_1 - R_3) + \eta_1\mu_0 s_0(1 - R_1) > 0 \Leftrightarrow \mu_1\mu_3(R_1 - R_3) + \eta_1\mu_0 s_0 < \eta_1\mu_0 s_0 R_1 \Leftrightarrow \mathcal{R}_1 s_{13} > 1,$$

and the quadratic term is stable iff $R_1 - 1 > 0$.

**Remark 23.** *Besides the first stability conditions for E1 in* (31)*, we have obtained a second one, which we are tempted to describe as "E1 can invade E3", with the caveat that the invasions in situations with at least three siphons do not seem to be rigorously defined – see though [Mitchell and Kribs, 2019, Madec and Gjini, 2020, Kribs and Greenhalgh, 2023, Belluccini et al., 2024a] for some works in this direction.*

### 6.2.2 Stability analysis for E3

At E3, the numerator of characteristic polynomial is $\left(\mu_0\mu_3(R_3-1)+\mu_0R_3u+u^2\right)*$

$$(\mu_1\mu_3(R_3-R_1)+\eta_1\mu_0s_0(R_3-1)+\mu_3R_3u)\,(\mu_2\mu_3(R_3-R_2)+\eta_1\mu_0s_0(R_3-1)+\mu_3R_3u)\,.$$

Thus, stability holds iff

$$\begin{cases}\max[R_1,R_2,1]\le R_3\\ R_{31}=\mathcal{R}_3s_{13}>1, R_{32}=\mathcal{R}_3s_{13}>1\end{cases}$$

holds, whose invasion interpretation is that besides $i_{12}$ being the dominant strain, it must also be able to invade strains $i_1,i_2$.

### 6.2.3 Stability analysis for E23

At E13,E23 the direct Routh-Hurwitz analysis becomes more cumbersome, because one of the factors of the characteristic polynomial has degree 3, but the "stability via LCP" is not that hard. Recall $E23=\left\{s_{23}=\frac{s_0\mu_0\eta_2}{\mu_2\mu_3(\mathcal{R}_2-\mathcal{R}_3)+\eta_2\mu_0}, i_1=0, i_2=\frac{\mu_3}{\eta_2}(1-\mathcal{R}_3s_{23}), i_3=\frac{\mu_2}{\eta_2}(\mathcal{R}_2s_{23}-1)\right\}$. To the positivity conditions of the above, we must add the negative flow condition near $i_1=0$, which is $\mathcal{R}_1s<\frac{\eta_1}{\mu_1}i_3+1$. A common reduce of these equations yields

**Existence and Stability conditions for E23**

$$\begin{cases}\alpha_2\mu_3>\alpha_3\mu_2\Leftrightarrow\mathcal{R}_2>\mathcal{R}_3\Leftrightarrow R_2>R_3 \quad \text{and}\\ \frac{\mu_2}{\alpha_2}<s_{23}<\frac{\mu_3}{\alpha_3}\Leftrightarrow s_2<s_{23}<s_3\Leftrightarrow 1<\mathcal{R}_2s_{23}=R_{23}, \mathcal{R}_3s_{23}=R_{32}<1\\ s_{23}<\frac{\eta_2\mu_1-\eta_1\mu_2}{-\alpha_2\eta_1+\alpha_1\eta_2}=s_{ee}\end{cases} \tag{32}$$

The first three conditions ensure the existence. The fourth condition, ensuring stability, does not seem to be expressable in terms of reproduction functions. It is however elegantly expressed in terms of the $s$ values at E23 and EE.

The formulas above suggest:

**Problem 5** (partition via resident variable inequalities)**.** *The parameter space may be divided via inequalities of the form $s_S\le s_{S'}$ where $S\subset S'$ run over certain pairs of siphons (it may be possible to make this more precise using the theory of invasion graphs [Hofbauer and Schreiber, 2022, Almaraz et al., 2024, Schreiber, 2025a].*

Finally, we show that this model does not satisfy the CEP, i.e. the existence conditions of EE are not that all the other fixed points exist and are unstable. To simplify the existence conditions, assume first w.l.o.g. that

$$\eta_1/\mu_1>\eta_2/\mu_2\Longrightarrow\mathcal{R}_2<\mathcal{R}_1<\mathcal{R}_2\frac{\eta_1/\mu_1}{\eta_2/\mu_2}.$$

The existence conditions are still too long to reproduce here, so we further assume that all death rates equal $\mu$. Then we find a conjunction of four conditions

$$1<R_2<R_1<1+(R_2-1)\frac{\eta_1}{\eta_2}, R_3<\frac{\eta_1R_2-\eta_2R_1}{\eta_1-\eta_2}, \mu>\sqrt{\frac{\eta_2R_1}{\eta_1R_2}}$$
$$\frac{(\eta_1-\eta_2)\,\mu\,(R_1-R_3)}{\eta_1\,(\eta_2+\eta_1\,(R_2-1)-\eta_2R_1)}<s_0<\frac{(\eta_1-\eta_2)\,\mu\,(R_2-R_3)}{\eta_2\,(\eta_1(R_2-1)-\eta_2\,(R_1-1))},$$

which leave several regions not covered by any of the previous cases.

# 7 A Review of Persistence Theory for Positive Dynamical Systems

Let $\dot{x} = f(x)$ be a positive ODE defined on a compact, forward-invariant set $E \subset \mathbb{R}^n_+$, with semiflow $\Phi_t$.

**Definition 19** (Persistence)**.** *[Smith and Thieme, 2011b, Craciun et al., 2013]. The system is* ***persistent*** *if for every component $i$ and every trajectory starting in* $\operatorname{int}(E)$*,*

$$\liminf_{t \to \infty} x_i(t) > 0.$$

**Definition 20** (Uniform Persistence)**.** *[Smith and Thieme, 2011b, Craciun et al., 2013]. The system is* ***uniformly persistent*** *if there exists $\varepsilon > 0$ such that*

$$\liminf_{t \to \infty} x_i(t) \geq \varepsilon$$

*uniformly for all trajectories starting in* $\operatorname{int}(E)$.

The fundamental problems of persistence, permanence, and extinction have been studied extensively, in particular in the context of generalized Lotka–Volterra systems [Hutson, 1984b, Butler et al., 1986, Hofbauer and So, 1989, Hutson and Schmitt, 1992, Hofbauer and Sigmund, 1998], for mathematical ecology models [Thieme, 1992, Thieme, 2003a, Smith and Thieme, 2011c] and also for CRNs [Angeli et al., 2007a, Johnston and Siegel, 2011, Pantea, 2012, Craciun et al., 2013, Anderson et al., 2014, Gopalkrishnan et al., 2014].

## 7.1 General Persistence Theory

**Theorem 4** (Butler–Waltman [Butler et al., 1986]; Fonda [Fonda, 1988]; Hutson–Schmitt [Hutson and Schmitt, 1992]; Smith–Thieme [Smith and Thieme, 2011c])**.** *For a dissipative semiflow $\Phi_t$ on a compact invariant set $E$, the system is uniformly persistent if and only if the boundary $\partial E$ is a uniform repeller, i.e., there exists $\eta > 0$ such that*

$$\operatorname{dist}(\Phi_t(x), \partial E) \geq \eta$$

*for all $t$ sufficiently large and all $x \in \operatorname{int}(E)$.*

**Remark 24** (On the insufficiency of linear instability for boundary fixed points)**.** *The criterion above is not constructive. The simplest constructive condition—that all boundary equilibria are unstable—does* not *imply persistence – see the May-Leonard example, subsection 7.3. This observation motivated the repeller theorem 4 of Hutson–Schmitt [Hutson and Schmitt, 1992] and Smith–Thieme [Smith and Thieme, 2011c], which assumes that the boundary repelling property must hold for the* entire boundary set*, not just for fixed points.*

## 7.2 Mass-Action CRNT Persistence Results

In CRNT, the driving force behind persistence theory has been the global attractor conjecture for weakly-reversible systems, still unresolved; however, several partial results are available [Angeli et al., 2007a, Anderson, 2008, Craciun et al., 2013, Pantea, 2012, Craciun, 2015, Gopalkrishnan et al., 2014].

**Theorem 5** (Angeli–De Leenheer–Sontag [Angeli et al., 2007a], 2007)**.** *A mass-action chemical reaction network such that every siphon $Z$ of the network contains the support of at least one conservation law is persistent.*

**Theorem 6** (Anderson [Anderson, 2008], 2011)**.** *A weakly reversible, deficiency zero reaction network with mass-action kinetics satisfies:*

1. *within each positive stoichiometric compatibility class, there exists a unique equilibrium;*
2. *this equilibrium is globally asymptotically stable;*
3. *the system is persistent on* $\mathbb{R}^n_{++}$.

**Theorem 7** (Pantea [Pantea, 2012], 2012)**.** *Every weakly reversible mass-action system of dimension* $d \leq 3$ *(where* $d = \dim(S)$ *is the dimension of the stoichiometric subspace) is persistent and permanent.*

**Remark 25.** *Pantea's proof uses:*

1. *Brouwer degree theory for* $d = 2$
2. *Poincaré–Bendixson theory ruling out boundary attractors*
3. *For* $d = 3$*: Analysis of possible boundary limit sets using* $\omega$*-limit set structure*

*The result does* not *extend to* $d \geq 4$ *where more complex boundary attractors can exist.*

**Remark 26** (Why standard CRN persistence results fail for epidemics)**.** *Typical compartmental epidemic models satisfy:*

1. ***No weak reversibility****: Infection reactions* $S + I \to 2I$ *lack reverse* $2I \to S + I$.
2. ***Infection strains do not contain positive conservation laws****, due to possible deaths.*
3. ***Deficiency*** $\geq 1$.

### 7.3 Failure of Persistence due to Boundary Heteroclinic Cycles:May–Leonard system; MayLeonard.py, MayLeonard.nb

Persistence may fail even when all boundary equilibria are unstable. One mechanism illustrating this is an attracting *boundary heteroclinic cycle*: a sequence of boundary saddle equilibria connected cyclically, each unstable toward the next, collectively forming a closed boundary orbit that attracts all interior trajectories.

**Example 7** (Symmetric May–Leonard system)**.** *A classical three-species competitive Lotka–Volterra equations ([May and Leonard, 1975, Hofbauer, 1993])*

$$\begin{aligned} \dot{x}_1 &= x_1\big(1 - x_1 - \mathtt{al}\,x_2 - \mathtt{be}\,x_3\big), \\ \dot{x}_2 &= x_2\big(1 - \mathtt{be}\,x_1 - x_2 - \mathtt{al}\,x_3\big), \\ \dot{x}_3 &= x_3\big(1 - \mathtt{al}\,x_1 - \mathtt{be}\,x_2 - x_3\big). \end{aligned} \tag{33}$$

*satisfies that for* $\mathtt{al} < 1 < \mathtt{be}$*, the boundary equilibria* $E_1 = (1, 0, 0)$*,* $E_2 = (0, 1, 0)$*, and* $E_3 = (0, 0, 1)$ *are saddles connected in a heteroclinic cycle* $E_1 \to E_2 \to E_3 \to E_1$ *that attracts all interior trajectories, causing persistence failure.*

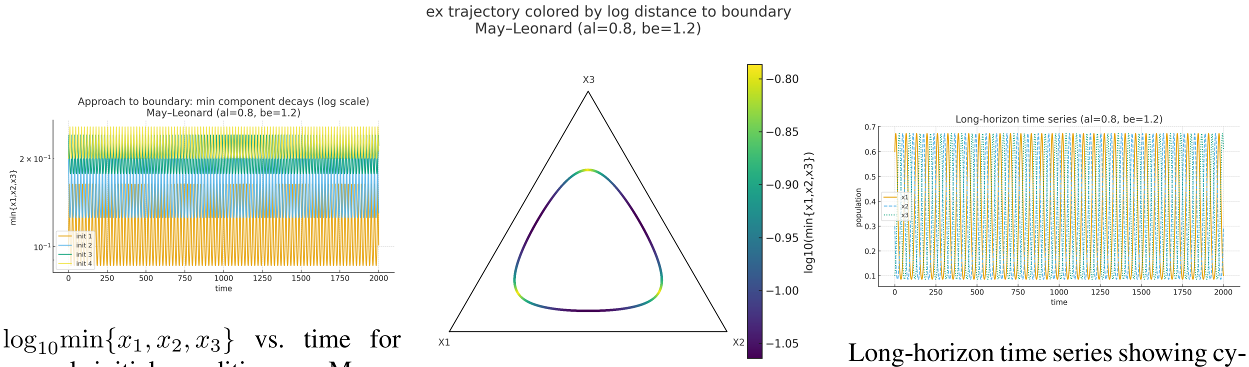
The Figure 8 below visualizes the May–Leonard heteroclinic cycle regime with parameters $al = 0.8$ and $be = 1.2$, demonstrating nonpersistence through three complementary perspectives:

1. The left panel plot tracks $\log_{10} \min x_1, x_2, x_3$ over time essentially monitoring the smallest population abundance. The y-axis uses a logarithmic scale to capture orders of magnitude declines. Starting from multiple initial conditions (shown as different colored trajectories), all paths exhibit monotone decay toward $-\infty$ on the log scale. This means the minimum population size continually decreases, approaching zero asymptotically. The smooth downward trend confirms that no trajectory stabilizes at a positive interior equilibrium; instead, populations drift inexorably toward boundary faces where at least one species becomes vanishingly rare.

2. For the middle plot, it shows a single representative trajectory projected onto the 2-simplex (the triangular constraint $x_1 + x_2 + x_3 = 1$), color-coded by distance to the nearest boundary face.
   (a) Yellow bright regions: trajectory far from boundaries (interior of simplex),
   (b) Blue dark regions: trajectory near boundaries (edges or vertices).

   Darker shading near the vertices indicates prolonged visits to states where one species dominates temporarily while the other two remain suppressed. The trajectory never settles but instead circulates endlessly around the boundary loop, never stabilizing in the interior.
3. For the right pannel, it plots the time evolution of all three species over the interval $[0, 2000]$ time units, capturing long-term oscillatory behavior. The vertical axis shows population densities $x_1, x_2, x_3$, and horizontal lines separate successive epochs where different species dominate.

This multi-faceted visualization clarifies why classical stability theory focused on interior equilibria and local linearizations fails to predict dynamics in systems with boundary attractors. The May-Leonard example remains a canonical warning that ecological coexistence requires more than merely unstable single species states; the connectivity and geometry of boundary equilibria matter profoundly.



$\log_{10}\min\{x_1, x_2, x_3\}$ vs. time for several initial conditions. Monotone decay evidences approach to the boundary.

Simplex trajectory colored by $\log_{10}\min\{x_1, x_2, x_3\}$. Darker colors indicate closer proximity to boundary faces.

Long-horizon time series showing cycling dominance and longer boundary visits.

**Figure 8:** May–Leonard heteroclinic-cycle regime with `al=` 0.8, `be=` 1.2. Left: $\log_{10}\min\{x_1, x_2, x_3\}$ clearly $\to -\infty$, hence nonpersistence. Middle: simplex projection with distance-to-boundary coloring. Right: time series on $[0, 2000]$ showing the characteristic increase of dwell times near the boundary saddles. These are obtained in MayLeonard.nb

For checking this with EpidCRN, we use the mass–action representation:

```
RN = {
  "X1" -> 2*"X1",
  "X1" + "X1" -> "X1",
  "X1" + "X2" -> "X2",
  "X1" + "X3" -> "X3",

  "X2" -> 2*"X2",
  "X2" + "X2" -> "X2",
```

```
  "X2" + "X3" -> "X3",
  "X2" + "X1" -> "X1",

  "X3" -> 2*"X3",
  "X3" + "X3" -> "X3",
  "X3" + "X1" -> "X1",
  "X3" + "X2" -> "X2"
};
rts = {
  x1, x1*x1, al*x1*x2, be*x1*x3,
  x2, x2*x2, al*x2*x3, be*x2*x1,
  x3, x3*x3, al*x3*x1, be*x3*x2
};
```

### 7.4 Invasion graphs

In this subsection we revisit the invasion graphs theory which arose from the works of [Schreiber, 2000, Schreiber, 2006, Patel and Schreiber, 2018, Mitchell and Kribs, 2019, Madec and Gjini, 2020, Hofbauer and Schreiber, 2022, Le et al., 2023, Schreiber, 2025b] using the notions of siphons and reproduction functions.

Throughout, $X \subset \mathbb{R}_+^{m+n}$ is the phase space of an ME system with infection set $TS = \{1, \ldots, n\}$.

**Definition 21** (Proper siphons and communities)**.** *Let $S \subset TS$ be a siphon and let*

$$F_S = \{x \in X : \; x_j = 0 \, \textit{for all } j \in S\}$$

*denote the associated positively invariant face.*

*A siphon $S$ is called* proper *if the restriction of the flow to $F_S$ admits a compact invariant set $M_S \subset F_S$ and $M_S$ contains a point with all coordinates in $S^c$ strictly positive.*

*The complement $S^c = TS \setminus S$ is called the* community.

**Definition 22** (Invasion rates)**.** *Let $S$ be a proper siphon and $M_S$ its compact invariant set. For $j \in S$ the $j$–equation linearizes along $\phi_t(x)$, $x \in M_S$, to*

$$z_j' = a_j(t)\, z_j, \qquad a_j(t) = \partial_{x_j} f_j(\phi_t(x)).$$

*The (upper) Lyapunov exponent*

$$\lambda_j(M_S) = \limsup_{t \to \infty} \frac{1}{t} \int_0^t a_j(\tau)\, d\tau$$

*is the* invasion rate *of coordinate $j$ into the community $S^c$. We say $j$* invades *$S^c$ whenever $\lambda_j(M_S) > 0$.*

**Remark 27** (Reduction for ME models with resident equilibria)**.** *In all ME models considered here, $M_S$ is a single equilibrium $E_{S^c}$ with susceptible level $s_S$. Then $a_j(t) \equiv a_j$, and*

$$\lambda_j(M_S) = \partial_{x_j} f_j(E_{S^c}),$$

*so invasion rate reduces to a single Jacobian evaluation.*

*Moreover, using the $F\!-\!V$ splitting of infection terms,*

$$\lambda_j(M_S) > 0 \Longleftrightarrow R_j(s_S) > 1$$

*where $R_j$ is the reproduction function of the $j$–th NGM block.*

**Definition 23** (Invasion numbers for ME models)**.** *Let $T_j$ be an NGM block, with reproduction function $R_j(\cdot)$. For a proper siphon $S$, let $E_{S^c} = (x_S = 0,\ y_{S^c})$ be the resident equilibrium on $F_S$, and let $s_S$ denote its susceptible coordinate.*

*The* invasion number *of block $T_j$ into the community $S^c$ is*

$$R_j^{S^c} = R_j(s_S).$$

*The* reproduction number *of $T_j$ is*

$$R_j^0 = R_j(s_0) = R_j(E_0).$$

**Remark 28.** *If the minimal siphons partition $TS$ and determine the NGM blocks, the preceding definition reduces to the previous definition 16.*

**Example 8** (Invasion graph of the GK coinfection model)**.** *We consider the GK model with blocks*

$$T_1 = \{i_1\}, \qquad T_2 = \{i_2\}, \qquad T_3 = \{i_{12}\},$$

*and reproduction functions*

$$R_j(s) = \mathcal{R}_j s, \qquad \mathcal{R}_j = \frac{\alpha_j}{\mu_j}.$$

*For $\beta > 0$ and $\gamma > 0$ the minimal siphons are*

$$\Sigma_1 = \{i_2, i_{12}\}, \qquad \Sigma_2 = \{i_1, i_{12}\}, \quad TS = \{i_1, i_2, i_{12}\},$$

*and the proper siphons are*

$$S_* = \emptyset, \qquad S_1 = \Sigma_1, \qquad S_2 = \Sigma_2, \qquad S_0 = TS.$$

*Each $S$ determines a unique resident equilibrium $E_{S^c}$ with susceptible value $s_S$. Table 2 lists all these values. Invasion inequalities are of the form*

$$R_j(s_S) > 1, \qquad j \in S.$$

**Table 2:** Resident susceptible values $s_S$ for proper siphons in the GK model.

| Proper siphon $S$ | Community $S^c$ | Resident susceptible value $s_S$ |
|---|---|---|
| $S_0 = \{1,2,3\}$ | $\emptyset$ | $s_0$ (DFE value) |
| $S_1 = \{2,3\}$ | $\{1\}$ | $s_1 = \frac{1}{\mathcal{R}_1}$ |
| $S_2 = \{1,3\}$ | $\{2\}$ | $s_2 = \frac{1}{\mathcal{R}_2}$ |
| $S_* = \emptyset$ | $\{1,2,3\}$ | $s_* = s_3 = \frac{1}{\mathcal{R}_3}$ |

*Note that the indices $(1,2,3)$ correspond to $(i_1, i_2, i_{12})$.*

*To handle mixed equilibria on $i_1 = 0$ or $i_2 = 0$ we also introduce*

$$s_{13} = \pi_s(E_{13}), \qquad s_{23} = \pi_s(E_{23}),$$

*given explicitly in the main text. All invasion inequalities $R_j(s_S) > 1$ are listed in Table 3.*

*The* invasion graph *is the directed graph whose vertices are the proper siphons*

$$S_*,\ S_1,\ S_2,\ S_0$$

*and whose edges are exactly those pairs $S \to S'$ for which the block removed in passing from $S$ to $S'$ satisfies $R_j(s_S) > 1$.*

**Table 3:** Invasion inequalities $R_j(s_S) > 1$ for GK. Each inequality corresponds to a directed edge $S \to S'$ in the invasion graph.

| Invaded siphon $S$ | Invading block $T_j$ | Inequality $R_j(s_S) > 1$ |
|---|---|---|
| $S_0$ | $T_1$ | $R_1(s_0) > 1$ |
| $S_0$ | $T_2$ | $R_2(s_0) > 1$ |
| $S_0$ | $T_3$ | $R_3(s_0) > 1$ |
| $S_1$ | $T_2$ | $R_2(s_1) > 1$ |
| $S_2$ | $T_1$ | $R_1(s_2) > 1$ |
| $S_1$ | $T_3$ | $R_3(s_{13}) > 1$ |
| $S_2$ | $T_3$ | $R_3(s_{23}) > 1$ |
| $S_*$ | $T_1$ | $R_1(s_*) > 1$ |
| $S_*$ | $T_2$ | $R_2(s_*) > 1$ |
| $S_*$ | $T_3$ | $R_3(s_*) > 1$ |

# 8 Appendix A

## 8.1 Glossary of the acronyms

| **Acronymes** | **Explanation** | **References** |
|---|---|---|
| MS/AMSD | Minimal Siphon/ Acyclic Minimal Siphon Decomposition | [Shiu and Sturmfels, 2010,<br>You et al., 2021] |
| IGMS | interaction graph on minimal siphons | [Shiu and Sturmfels, 2010,<br>Banaji and Craciun, 2009] |
| SDAS | Seed-Dependent Autocatalytic Systems | [Peng et al., 2021, Peng et al., 2022, Peng et al., 2023, Blokhuis et al., 2023] |
| LCP/CEP | linear complementarity principle/competitive exclusion principle | [Bremermann and Thieme, 1989,<br>Camlibel et al., 2007] |
| DSR | Directed Species-Reaction graph | [Banaji and Craciun, 2009] |
| NGM | Next-Generation Matrix | [Diekmann et al., 1990,<br>Van den Driessche and Watmough, 2002,<br>Van den Driessche and Watmough, 2008] |

## 8.2 A useful background result for positive ODEs : the Regular Splitting theorem for Metzler matrices

The NGM method consists of two steps:

1. the reduction of the Jacobian to the Jacobian matrix of the invasion vector field with respect to the invasion variables, and, assuming this is Metzler,
2. studying its stability by finding a *regular matrix splitting*.

**Definition 24** (regular splitting)**.** *[Varga, 1962, Berman and Plemmons, 1979]. Given a Metzler (quasi-positive) matrix $M$, a decomposition $M = F - V$ is a regular splitting if:*

- $F \geq 0$
- $V^{-1} \geq 0$

*Equivalently, $A = -V$ must be a Metzler-Hurwitz /Markovian semi-group generating matrix.*

**Remark 29.** *Note that a decomposition like in Definition 24 needs neither exist, nor be unique.*

*In quadratic ME examples, a regular splitting is sometimes obtained by separating the quadratic part $F$ of $J_x$ from the linear part $V$.*

Assuming a regular splitting exists, the spectral radius of the *next generation matrix*:

$$K := F(-A)^{-1}$$

provides a representation of the stability domain of $M$:

**Proposition 2.** *(Varga, [Varga, 1962, Thm 3.13], [Berman and Plemmons, 1994, Fall et al., 2007, Thieme, 2009])*

*Let $M$ be a real Metzler matrix admitting regular splitting(s). Then*

$$\begin{cases} \rho(FV^{-1}) < 1 \Longrightarrow M & \textit{is Metzler-Hurwitz} \\ \rho(FV^{-1}) > 1 \Longrightarrow M & \textit{is unstable} \end{cases},$$

*where $M = F - V$ is any regular splitting of $M$.*

This result originates in Varga's work on iterative methods.

**Definition 25** (next generation matrix)**.** *[Diekmann et al., 2010, Van den Driessche and Watmough, 2002]. For a real Metzler matrix $M$ admitting a regular splitting $M = F - V$, the matrices $FV^{-1}, V^{-1}F$ (which have equal spectrum) will both be called next generation matrices.*

Below, we will use the first form.

## 8.3 Informal description of the next generation matrix method

Once the DFE is identified, its stability threshold may be determined via the NGM method, which analyzes the DFE by projecting the Jacobian onto infection variables. Let $M = \partial f/\partial x$ at the DFE. If $M$ is Metzler and admits a regular splitting $M = F - V$, the DFE is locally stable iff:

$$R_0 = R_0(F) := \rho(K) := \rho(FV^{-1}) < 1$$

We give now an informal description of the NGM method (see [Diekmann et al., 1990, Van den Driessche and Watmough, 20
Van den Driessche and Watmough, 2008] for precise statements):

1. One restricts to the "disease equations", i.e. the equations involving the 0 coordinates of the DFE. This may be justified by
   (a) verifying the conditions of [Diekmann et al., 1990, Van den Driessche and Watmough, 2002, Van den Driessche and V
   or, in particular cases, by
   (b) factoring the characteristic polynomial of the Jacobian matrix, and by eliminating trivial factors (which correspond always to the non-disease variables).
2. Assuming the Jacobian matrix of the invasion vector field with respect to the invasion variables $J_x$ is a Metzler matrix, and that it admits a regular splitting

$$J_x = F + A := F - V, \tag{34}$$

   the study of $J_x$ may be replaced by that of one of the "next generation matrices"

$$K_d = V^{-1}F, K = FV^{-1} = VK_dV^{-1} \tag{35}$$

which have probabilistic interpretations, and may also be obtained by an algebraic trick:

$$J_x = F - V = V\left[V^{-1}F - I\right] = V\left[K_d - I\right] = \left[K - I\right]V. \tag{36}$$

The final result is the DFE stability threshold

$$R_0 = R_0(F) := \rho(K) = \rho(K_d) < 1 \tag{37}$$

(a corollary of Varga's regular splitting Lemma [Varga, 1962, Thm 3.13], [Berman and Plemmons, 1994, Fall et al., 2007, Thieme, 2009]).

We will call the inequality (37) the first law of mathematical epidemiology; it states that the (interior of the) stability domain of the DFE has a representation (37), for any admissible matrix $F$.

**Remark 30.** *Note that we introduced above two NGMs, $K_d$, and $K$, related by a similarity transformation, and having thus the same characteristic polynomial, $R_0$, and stability properties.*

*The comparison of the two matrices $K, K_d$ was addressed in [Diekmann et al., 2010], who claimed that $K_d$ leads to simpler computations than $K$, but we have encountered mainly the opposite situation, and prefer to use $K$. Let us add here an empirical observation, that the computation of $R_0$ from $K$ or $K_d$ is typically easier than via the reduced Jacobian $J_x$, in the sense that their characteristic polynomials factor more.*

*Further research into the respective advantages of the two NGMs seems necessary.*

**Definition 26** (minimal $R_0$ degree)**.** *When $R_0$ is algebraic, the degree of the smallest irreducible polynomial satisfied by $R_0(F)$ for some admissible decomposition will be called the degree of the decomposition, and the minimal degree over all admissible decompositions will be called the minimal $R_0$ degree.*

### 8.4 A heuristic NGM approach

We believe it may be useful to complement the rigorous NGM [Van den Driessche and Watmough, 2002] with the following "heuristic" NGM approach (which is actually what many papers seem to use in practice):

1. For a positive ODE, compute the union of minimal siphons $\boldsymbol{x}_E$, and verify algebraically the existence of a boundary fixed point $E$ on the facet determined by $\boldsymbol{x}_E$.
2. Compute the resident Jacobian block $J_y(0, \boldsymbol{y}_E) = \frac{\partial f}{\partial \boldsymbol{y}}(0, \boldsymbol{y}_E)$ and verify its stability.
3. If it is stable, compute also the invasion Jacobian block

   $$J_x(0, \boldsymbol{y}),$$

   without plugging the values of the resident variables (this is useful for symbolic manipulations, and has also theoretical implications which require further investigation), and verify whether it is Metzler.
4. If it is, find a decomposition $J_x = F - V$, where:
   - $F$: gain terms (nonlinear, positive)
   - $V$: loss/removal terms verifies that $V^{-1}$ has only positive elements.

If all the steps were successful, we are dealing with an ME model, and we may further compute the matrix $K = FV^{-1}$.

**Remark 31.** *Sometimes, eliminating trivial factors from the characteristic polynomial of $K$ further eases the symbolic analysis, effectively replacing the model by a simpler one.*

In the opposite case, we would have identified the reason why our positive ODE is not a ME model.

**Problem 6** (conditions for the $R_0$ dichotomy to hold, in terms of the partition Jacobians)**.** *Provide conditions for the $R_0$ dichotomy to hold for ME models, in terms of the partition of the Jacobian in $J_x, J_y, J_{xy}, J_{yx}$.*

# 9 Appendix B: Further pointers to the literature and ideas

## 9.1 Relation between minimal self-replicating siphons and autocatalytic cores

### 9.1.1 Background

In the framework of persistence theory, Deshpande and Gopalkrishnan [Deshpande and Gopalkrishnan, 2014] introduced the notion of *self-replicable siphons*. Let $S$ denote the stoichiometric matrix of a chemical reaction network (CRN), and let $A$ be the restriction of $S$ to a subset of species forming a minimal critical siphon. A siphon $T$ is said to be *self-replicable* if there exists a nonnegative flux vector $v > 0$ such that $Av > 0$. Theorem 5.3.3 of [Deshpande and Gopalkrishnan, 2014] shows that every minimal critical siphon is either *drainable* ($Av < 0$ for some $v > 0$) or *self-replicable*, and that CRNs without drainable siphons are persistent.

Several years later, Blokhuis *et al.* [Blokhuis et al., 2020] introduced the concept of *autocatalytic cores* as the minimal stoichiometric submatrices $A$ satisfying $Av > 0$ for some $v > 0$, subject to additional structural constraints: each reaction must consume and produce species within the same subnetwork and involve exactly one reactant per column. These authors proved that minimal autocatalytic matrices are necessarily *square, invertible, and Metzler*, thus linking stoichiometric minimality to algebraic irreducibility.

More recently, Vassena and Stadler [Vas, 2024] formalized this connection in dynamical terms: an *autocatalytic core* are precisely the subset of *child-selection matrices* that are both Metzler and Hurwitz-unstable, which is equivalent to the existence of a positive vector $v > 0$ for which $Av > 0$.

### 9.1.2 Definitions

Let $\mathcal{G} = (\mathcal{S}, \mathcal{R})$ be a chemical reaction network with stoichiometric matrix $S$.

**Definition 27** (Self-replicating siphon)**.** *[Deshpande and Gopalkrishnan, 2014]. A siphon $T \subseteq \mathcal{S}$ is* self-replicating *if there exists a flux $v \geq 0$, $v \neq 0$, such that $(Sv)_i > 0$ for all $i \in T$ and $(Sv)_i = 0$ for all $i \notin T$.*

The existence of such a flux ensures that, once $T$ is nonempty, the reactions of the network can increase all species in $T$ without aid from outside $T$.

**Definition 28** (Autocatalytic Siphon)**.** *[Deshpande and Gopalkrishnan, 2014, Unterberger and Nghe, 2022].*

*Let $G = (S, R)$ be a chemical reaction network with stoichiometric matrix $S$. A siphon $T \subseteq S$ is called* autocatalytic *if there exists a nonzero flux vector $v \geq 0$ such that:*

1. *All species in $T$ increase under the flux:*
$$(Sv)_i > 0 \quad \textit{for all } i \in T;$$
2. *Every species in $T$ participates as a reactant in at least one reaction contributing to $v$, meaning it helps catalyze its own production;*
3. *The flux is supported entirely within $T$:*
$$(Sv)_i = 0 \quad \textit{for all } i \notin T.$$

*In other words, once $T$ is nonempty, the species in $T$ can increase themselves through internal reactions, without relying on species outside $T$.*

**Remark 32.** *1. Every autocatalytic siphon is a self-replicating siphon, but not every self-replicating siphon is autocatalytic.*

*2. Autocatalytic siphons capture the idea of* internal catalytic feedback *within a siphon, which makes them key structures for persistence and potential growth in chemical reaction networks.*

**Theorem 8** (Deshpande–Gopalkrishnan)**.** *[Deshpande and Gopalkrishnan, 2014]:Every minimal critical siphon of a weakly reversible CRN is either* drainable *or* self-replicating.

**Theorem 9** (Blokhuis, Lacoste, Nghe)**.** *[Blokhuis et al., 2020]: For mass-action kinetics, every minimal self-replicating siphon contains a minimal* autocatalytic core*, i.e. a minimal square submatrix $A$ of $S$ admitting a positive flux vector $v > 0$ with $Av > 0$. Conversely, every autocatalytic core defines a self-replicating siphon equal to its species support.*

**Theorem 10** (Vassena–Stadler)**.** *[Vas, 2024]: Minimal autocatalytic cores are precisely the minimal Metzler–Hurwitz-unstable submatrices of the Jacobian at boundary equilibria. Hence each minimal self-replicating siphon corresponds to a boundary-unstable face of the positive orthant.*

**Remark 33.** *Theorems 8–9 establish a bijective correspondence between minimal self-replicating siphons and autocatalytic cores: the structural condition of self-replication (existence of a positive stoichiometric flux restricted to $T$) coincides with the dynamical condition of local instability (positive Perron–Frobenius eigenvalue of a Metzler block).*

### 9.1.3 Comparative Summary

Although the discussion above suggest a relation between *self-replicable siphons* and *autocatalytic cores*, **precise results** in this direction are more read between the lines, than stated explicitly in the literature. Conceptually, Deshpande's self-replicable siphons describe *combinatorial minimal positive supports* in the stoichiometric geometry, while Blokhuis cores represent *minimal autonomous subnetworks* that satisfy the same positivity condition together with stoichiometric closure and invertibility. In this sense, autocatalytic cores can be interpreted as *square, autonomous realizations* of minimal self-replicable siphons, but the equivalence remains heuristic.

| **Concept** | **Defining Condition** | **Structural Constraints** | **Source** |
|---|---|---|---|
| Self-replicable siphon | $\exists\, v > 0 :\ Av > 0$ | Minimal critical subset of species (not necessarily square) | Desh. & Gopal. (2014) |
| Autocatalytic core | $\exists\, v > 0 : Av > 0$ and $A$ square, invertible, Metzler | Each species unique reactant; autonomous subnetwork | Blokhuis *et al.* (2020) |
| Unstable core (child selection) | $A$ Metzler and Hurwitz-unstable $\Leftrightarrow \exists\, v > 0 : Av > 0$ | Dynamical realization of an autocatalytic core | Vassena & Stadler (2024) |

### 9.1.4 Discussion

The absence of a formal equivalence theorem can be attributed to methodological differences: self-replicable siphons are defined combinatorially in terms of reachable states and persistence, while cores are algebraic objects derived from the stoichiometric matrix structure. Nonetheless, both capture the same necessary positivity condition that guarantees self-maintenance and amplification within a subnetwork.

## 9.2 Tree IGMS vs. multi-tier Seed-Dependent Autocatalytic Systems (SDAS)

### 9.2.1 Definitions

Let $\mathcal{S}$ be the set of species, $R$ the set of reactions, and $S \in \mathbb{R}^{|\mathcal{S}|\times|R|}$ the stoichiometric matrix.

**Definition 29** (Stoichiometric autocatalysis and core)**.** *[Deshpande and Gopalkrishnan, 2014]. For* $U \subseteq \mathcal{S}$ *and* $R_U \subseteq R$*, the restricted matrix* $A = S_{U,R_U}$ *is* stoichiometrically autocatalytic *if there exists* $v \geq 0$*,* $v \neq 0$*, such that* $Av > 0$*. A minimal square such submatrix is an* autocatalytic core.

**Definition 30** (Strict catalysis)**.** *[Deshpande and Gopalkrishnan, 2014]. A motif (flux vector* $v \geq 0$*) is* catalytic *if* $Av > 0$.

**Definition 31** (formal autocatalysis)**.** *[Andersen et al., 2021]. A subnetwork* $\mathcal{G}' = (\mathcal{S}', \mathcal{R}')$ *of CRN* $\mathcal{G} = (\mathcal{S}, \mathcal{R})$ *is defined to be formally autocatalytic in the subset* $\mathcal{M}$ *of* $\mathcal{S}'$ *if (see [Andersen et al., 2021]):*

1. *There exists a positive real flow (*$\gg 0$*) on* $\mathcal{G}'$ *such that the resulting composite reaction is of the form*

$$(F) + \boldsymbol{m}\mathcal{M} \to \boldsymbol{n}\mathcal{M} + (W),$$

*where* $\boldsymbol{0} \ll \boldsymbol{m} \ll \boldsymbol{n}$*. Here* $\boldsymbol{m}$ *and* $\boldsymbol{n}$ *are the stoichiometries of the set* $\mathcal{M}$ *in the input and output of the composite reaction, respectively, and* $\boldsymbol{o}\mathcal{M} = \sum_i \boldsymbol{o}_i\mathcal{M}_i$*.*

**Definition 32** (exclusive autocatalysis)**.** *[Andersen et al., 2021]. A formally autocatalytic subnetwork* $\mathcal{G}' = (\mathcal{S}', \mathcal{R}')$ *of CRN* $\mathcal{G} = (\mathcal{S}, \mathcal{R})$ *is defined to be exclusively autocatalytic in the subset* $\mathcal{M}$ *(see [Deshpande and Gopalkrishnan, 2014 Andersen et al., 2021]) if:*

- *Every reaction in* $\mathcal{R}'$ *consumes at least one species from the set* $\mathcal{M}$*. This ensures that the flow is inadmissible, or there is no flow, if the population of any species in the set* $\mathcal{M}$ *is zero.*

**Definition 33** (Seed-dependent autocatalytic system (SDAS))**.** *[Peng et al., 2022]. Let* $\mathcal{F} \subseteq \mathcal{S}$ *denote the externally supplied species. A subnetwork* $(\mathcal{S}', R')$ *is an* SDAS *if there exists a nonempty seed set* $\Sigma \subseteq \mathcal{S}' \setminus \mathcal{F}$ *such that (i)* $\mathcal{F} \cup \Sigma$ *generates all reactants of* $R'$ *under* $R'$*, and (ii) there exists* $v \geq 0$*,* $v \neq 0$*, with* $S_{\mathcal{S}',R'}v > 0$*.*

**Proposition 3** (Tree IGMS is not sufficient for SDAS)**.** *Acyclicity of IGMS is necessary for hierarchical seeding but does not imply the existence of a positive flux* $v$ *with* $Av > 0$*. Hence a tree IGMS does not guarantee an SDAS.*

**Proposition 4** (Cyclic IGMS can admit SDAS)**.** *Mutual seeding between two siphons may yield a cycle in IGMS while a joint autocatalytic core on their union satisfies* $Av > 0$ *and constitutes an SDAS.*

### 9.2.2 Examples

The following examples illustrate the correspondence between the definition of *exclusive autocatalysis* in a subset $\mathcal{M} \subseteq \mathcal{S}$ (Definition 32) and *stoichiometric autocatalysis* defined by the existence of a nonnegative flux vector $v$ such that $S_{\mathcal{M},R'}v > 0$. Condition (i) of Definition 32 ensures that all reactions in the subnetwork consume at least one member of $\mathcal{M}$, so any feasible flux must vanish if any component of $\mathcal{M}$ is zero. Stoichiometric autocatalysis adds the quantitative requirement that a strictly positive flux $v$ exists, implying net production of all species in $\mathcal{M}$.

In the following examples, $\mathcal{M}$ is indicated for each subnetwork, and the feasibility of $Av > 0$ determines whether it is stoichiometrically autocatalytic.

**Example 9** (Tree IGMS without stoichiometric autocatalysis).
```
RN = {
  0 -> "S",
  "S" -> 0,
  "S" + "I1" -> "I1",
  "I1" + "I2" -> "I2",
  "I1" -> 0,
  "I2" -> 0
};
rts = {
  la*s,
  mu*s,
  be*s*i1,
  ro*i1*i2,
  mu1*i1,
  mu2*i2
};
```
*Here $\mathcal{M} = \{$”I1”, ”I2”$\}$ is exclusive: every reaction consumes at least one member of $\mathcal{M}$. However, the restricted stoichiometric matrix $A_{\mathcal{M}}$ has no nonzero $v \geq 0$ with $A_{\mathcal{M}}v > 0$. The network is therefore exclusively but not stoichiometrically autocatalytic, yielding a tree IGMS without an SDAS.*

**Example 10** (Cyclic IGMS with stoichiometric autocatalysis).
```
RN = {
  0 -> "S",
  "S" -> 0,
  "S" + "I1" -> 2*"I1",
  "I1" + "I2" -> 2*"I2",
  "I2" + "I1" -> 2*"I1",
  "I1" -> 0,
  "I2" -> 0
};
rts = {
  la*s,
  mu*s,
  be*s*i1,
  ro12*i1*i2,
  ro21*i2*i1,
  mu1*i1,
  mu2*i2
};
```
*Each reaction consumes either $I_1$ or $I_2$, hence the subsystem is exclusive in $\mathcal{M} = \{I_1, I_2\}$. The restricted matrix $A_{\mathcal{M}}$ admits a vector $v > 0$ with $A_{\mathcal{M}}v > 0$, so the network is both exclusive and stoichiometrically autocatalytic. The corresponding IGMS contains a two-cycle $T_1 \leftrightarrow T_2$, demonstrating that cyclic IGMS can still realize an SDAS.*

**Example 11** (Three-tier SDAS with strict catalysis).
```
RN = {
  0 -> "S",
  "S" -> 0,
  "S" + "I1" -> 2*"I1",
  "I1" -> 0,
  "I1" + "I2" -> 2*"I2",
```

```
  "I2" -> 0,
  "I2" + "I3" -> 2*"I3",
  "I3" -> 0
};
rts = {
  la*s,
  mu*s,
  be1*s*i1,
  mu1*i1,
  be2*i1*i2,
  mu2*i2,
  be3*i2*i3,
  mu3*i3
};
```

*Each tier $\mathcal{M}_j = \{I_j\}$ is exclusive, and the corresponding restricted submatrix $A_{\mathcal{M}_j}$ admits a positive flux $v_j$ with $A_{\mathcal{M}_j} v_j > 0$. The system therefore satisfies both exclusivity and stoichiometric autocatalysis on each tier, forming a hierarchical SDAS with a tree IGMS.*

**Example 12** (Cross-tier catalysis coupling tiers). `RN = {`

```
  0 -> "S",
  "S" -> 0,
  "S" + "I1" -> 2*"I1",
  "I1" -> 0,
  "S" + "I2" -> 2*"I2",
  "I2" -> 0,
  "I2" + "I1" -> "I2" + "I3",
  "I3" -> 0
};
rts = {
  la*s,
  mu*s,
  be1*s*i1,
  mu1*i1,
  be2*s*i2,
  mu2*i2,
  si*i2*i1,
  mu3*i3
};
```

*The subnetwork is exclusive in $\mathcal{M} = \{I_1, I_2, I_3\}$ since all reactions consume at least one member of $\mathcal{M}$. The cross-tier reaction $I_2 + I_1 \to I_2 + I_3$ introduces additional coupling so that $A_{\mathcal{M}}$ is no longer block-triangular. Nevertheless, a positive flux $v > 0$ with $A_{\mathcal{M}} v > 0$ can still exist, indicating stoichiometric autocatalysis despite the loss of tier separation.*

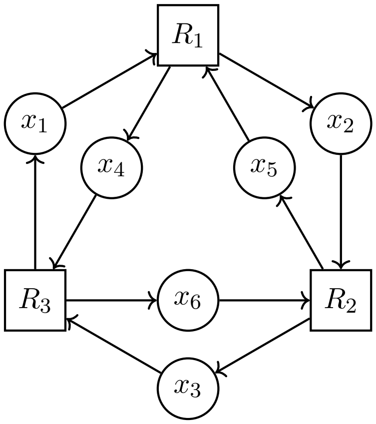
**Summary** In these examples, *exclusive autocatalysis* ensures that each subnetwork ceases to function when its internal species vanish, whereas *stoichiometric autocatalysis* verifies that a strictly positive internal flux exists. The distinction clarifies why tree IGMS can lack SDAS and why cyclic IGMS can still realize it.

Tree-structured IGMS ensures hierarchical dependency but not autocatalysis. SDAS requires a strictly positive stoichiometric flux. Cyclic IGMS may still sustain SDAS through joint autocatalytic cores.

### 9.3 The structural point of view on positive ODEs

In this last section, we make a digression on the so called "structural/robust" features of positive ODEs (like the Petri graph), which are fundamental in CRNT, and which we speculate might be useful in ME as well.

For an informal definition, a structural aspect is a feature which is common to all the ODEs in a subclass, and in particular, it may be obtained by asking an AI to produce it. For example, the figure 9 below (unrelated to the rest of the paper) was achieved by typing "Claude, draw the Volpert graph of the pasted RN example, arranging the reactions in a triangle, and the species in two nested triangles, such that the outer one forms a regular hexagon together with the reactions triangle":



$$R_1: \quad x_1 + x_5 \to x_2 + x_4$$

$$R_2: \quad x_2 + x_6 \to x_3 + x_5$$

$$R_3: \quad x_3 + x_4 \to x_1 + x_6$$

**Figure 9:** Petri net of a CRN. The three reactions/transitions $R_1, R_2, R_3$ appear as squares arranged in a triangle, and the six species/places $x_1, \ldots, x_6$ appear as circles.

Now, the ME literature has rarely paid attention to structural features, with the notable exception of the (F,V,K) NGMs, which we consider a structural feature of all ME models.

Historically, ME ODE research is divided in symbolic analyses of small examples for all possible parameters (of which we also bring a sample in this paper), and in numerical analyses of large examples, using "estimated realistic values" of the constants. CRNT brings two more points of view. One is identifying subclasses of ODEs for which stability/multistationarity/global attractivity results hold for any values of the positive parameters of the model. The second, more recent, is identifying results which hold for any "admissible rates" (differentiable, monotone, etc) – see [Al-Radhawi and Angeli, 2014, Al-Radhawi and Angeli, 2015b, Al-Radhawi and Angeli, 2015a, Angeli et al., 2021, Al-Radhawi, 2023]. Neither of these particular two directions has yet proven useful in ME, but in this paper, we offer a first structural contribution of CRNT to ME, the construction of the DFE as union of minimal siphons, answering a question we asked in [Avram et al., 2024a]. As an aside, note that once the DFE variables are provided, most AI's will have no difficulty producing the (F,V,K) matrices, for any ME model, specified either in ODE or in RN form. By defining the DFE, and using the algorithmic choice of F in [Avram et al., 2023], we have made this computation automatic, as a function of the ODE. We speculate that other CRNT structures, like the Petri graph, will also become useful in future research.

## 10 Conclusion

In this work, we aimed to address the fragmented landscape of three traditionally separate disciplines: mathematical epidemiology, chemical reaction network theory, and ecological modeling by proposing a unifying theoretical framework.

This work demonstrates that epidemic strains are fundamentally analogous to minimal siphons, that govern boundary behavior in positive dynamical systems. This correspondence, encoded in the stoichiometric matrices that define how species interact, influences the block structure of next-generation matrices.

What emerges from this synthesis is a rigorous pathway for analyzing multi-strain epidemic systems through the lens of reproduction functions. These functions, evaluated at various boundary equilibria, capture the invasion potential of competing strains and naturally extend the classical threshold theorem of [Van den Driessche and Watmough, 2002] to settings where multiple pathogens coexist or compete. The integration of reaction network formalism into epidemiology also brings algorithmic advantages, illustrated in the accompanying software package via symbolic and numerical tools.

In conclusion, this work suggests that the tools of CRNT are not incidental conveniences, but fundamental structures governing multi-strain epidemic behavior. By making these tools accessible to epidemiologists and ecologists, and by demonstrating their equivalence to reproduction number based reasoning, the framework presented here contributes to a unified mathematical theory of biological interaction networks.

Looking forward, several directions promise to extend this framework's scope. Extending beyond mass-action kinetics to frequency-dependent transmission, saturating incidence, or resource-mediated interactions will broaden applicability to contexts where density-dependent assumptions fail.

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