

# Global stability of epidemic models with uniform susceptibility

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Transmission dynamics of infectious diseases are often studied using compartmental mathematical models, which are commonly represented as systems of autonomous ordinary differential equations. A key step in the analysis of such models is to identify equilibria and find conditions for their stability. Local stability analysis reduces to a problem in linear algebra, but there is no general algorithm for establishing global stability properties. Substantial progress on global stability of epidemic models has been made in the last 20 years, primarily by successfully applying Lyapunov's method to specific systems. Here, we show that any compartmental epidemic model in which susceptible individuals cannot be distinguished and can be infected only once, has a globally asymptotically stable (GAS) equilibrium. If the basic reproduction number  $\mathcal{R}_0$  satisfies  $\mathcal{R}_0 > 1$ , then the GAS fixed point is an endemic equilibrium (i.e., constant, positive disease prevalence). Alternatively, if  $\mathcal{R}_0 \leq 1$ , then the GAS equilibrium is disease-free. This theorem subsumes a large number of results published over the last century, strengthens most of them by establishing global rather than local stability, avoids the need for any stability analyses of these systems in the future, and settles the question of whether co-existing stable solutions or non-equilibrium attractors are possible in such models: they are not.

epidemics | compartmental models | ordinary differential equations | global stability

Mathematical modelling of infectious disease transmission dates back to Daniel Bernoulli in the 18<sup>th</sup> century (1). Compartmental epidemic models were first published in the early 20<sup>th</sup> century (2, 3), which led to the landmark paper of Kermack and McKendrick (4) (KM) in 1927. In its simplest form, the KM model reduces to a system of three ordinary differential equations (ODEs),

$$\frac{dS}{dt} = -\beta SI, \quad \frac{dI}{dt} = \beta SI - \gamma I, \quad \frac{dR}{dt} = \gamma I, \quad [1]$$

where  $S$ ,  $I$ , and  $R$  are the numbers of susceptible, infected, and recovered hosts, and the total population size is  $N = S + I + R$ . In this *SIR model*, the parameters,  $\beta$  and  $\gamma$ , are the rates of transmission and recovery; the mean infectious period is  $1/\gamma$  and the basic reproduction number is  $\mathcal{R}_0 = N\beta/\gamma$ . The *incidence function*,  $i(S, I) = \beta SI$ , is linear in  $S$  and  $I$ , representing homogeneous mixing of susceptible and infected individuals, as if they were elements of an ideal gas. There is no flow from  $I$  or  $R$  back to  $S$ , so infected individuals become permanently immune upon recovery.

Because there is no source of new susceptibles in Eq. 1, any initial state yields at most one outbreak, and ultimately converges on a *disease-free equilibrium* (DFE) at which  $I = 0$ . However, Eq. 1 ignores *vital dynamics* (births and deaths). In the more realistic situation that includes vital dynamics,  $\mathcal{R}_0$  depends on the vital rates and, if  $\mathcal{R}_0 > 1$ , there is an *endemic equilibrium* (EE) at which  $I > 0$ . It has been known for at least 50 years that the SIR model with vital dynamics always has a *globally asymptotically stable* (GAS) equilibrium: if  $\mathcal{R}_0 \leq 1$  then all solutions converge to the DFE, and if  $\mathcal{R}_0 > 1$  then all initial states (except those with  $I = 0$ ) yield solutions that converge to the EE (5).

The vast majority of compartmental epidemic models that have been studied over the last century are generalizations of the simplified KM model

## Significance Statement

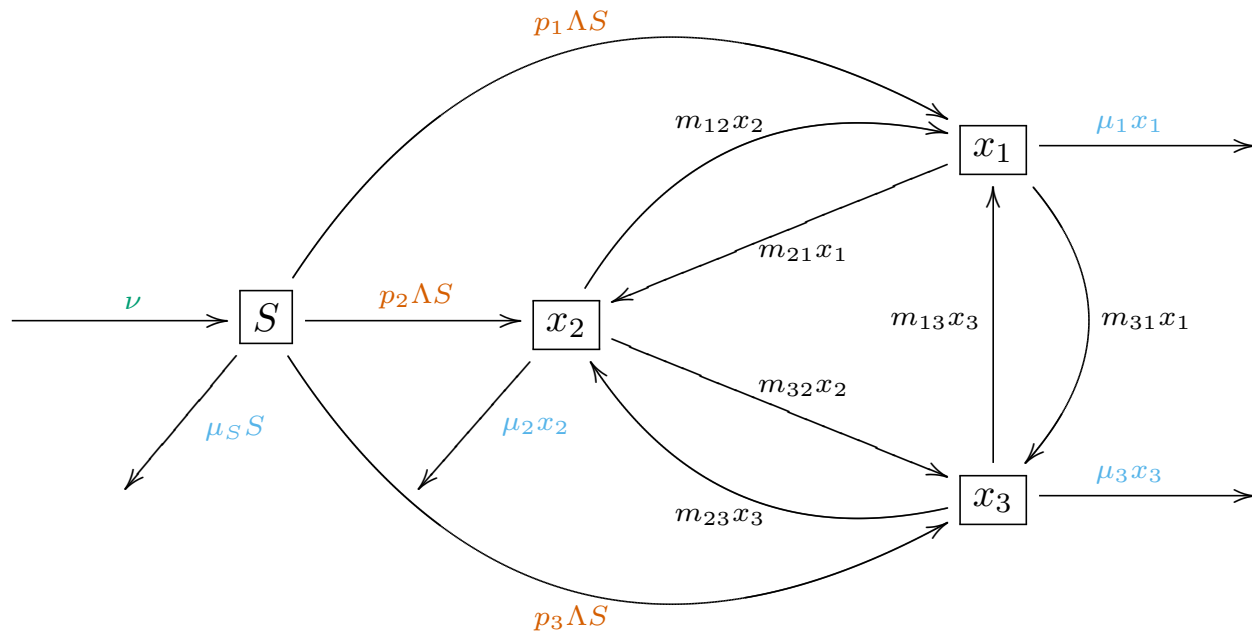
Mathematical models are widely used to study the spread of infectious diseases. A central question is whether these models predict that disease incidence will: oscillate indefinitely, settle down to a constant level, or behave unpredictably over time. While dynamics near a steady state can often be determined straightforwardly, it is usually more challenging to establish behaviour from arbitrary starting conditions. We prove—for a broad class of models, including thousands studied previously—that there is a *unique*, stable equilibrium prevalence that is approached whenever the disease is present. This result eliminates the need for further case-by-case analysis, and clarifies that such models cannot exhibit more complicated long-term behaviour, such as sustained oscillations or multiple stable outcomes.

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**Fig. 1.** Transfer diagram for the most general  $Sx_1 \cdots x_n$  model with  $n = 3$  non-susceptible compartments ( $x_i$ ). The subgraph excluding  $S$  is a complete directed graph on  $n$  nodes. There is no flow from any  $x_i$  back to  $S$ . The general class of  $Sx_1 \cdots x_n$  models is defined formally by Eqs. (3) to (6) and 2.

(Eq. 1) and can be represented by a *transfer diagram* like that shown in Fig. 1 with a single susceptible compartment ( $S$ ) and  $n$  other compartments ( $x_1, \dots, x_n$ ) from which there are no flows to  $S$ . We say these  $Sx_1 \cdots x_n$  models have the property of *uniform susceptibility* because there is no distinction (biological, epidemiological or sociological) between susceptibles; in particular, no current susceptible has ever been infected. The standard SIR model with vital dynamics corresponds to  $n = 2$ , with  $x_1 = I$  and  $x_2 = R$ . Including a latent period, which requires an exposed compartment ( $E$ ), yields the *SEIR model* with  $n = 3$ ,  $x_1 = E$ ,  $x_2 = I$ , and  $x_3 = R$ . More generally, any number of infected and immune compartments are possible—for example including compartments in which individuals are hospitalized, treated, isolated, or temporarily not infectious—and flows among any or all of these compartments are possible. Moreover, the distributions of durations in any of the compartments can be essentially arbitrarily distributed (6, 7).

In the thousands of papers written about models in the general class indicated in Fig. 1—many of which have been used to support infectious disease management and policy development (8–10)—the typical first steps of analysis are to find equilibria and determine their local stability or instability. The more challenging question of global stability has been resolved much less frequently. Indeed, even for the simple SEIR model, GAS of the EE was not established until 1995 (11). Yet only global analysis can fully characterize the long-term dynamics that can be displayed by epidemic models.

Substantial advances in global stability analysis have been made in the last 20 years, including a variety of special cases in the class of epidemic models depicted in Fig. 1; in particular, GAS has been proved for a large class of staged progression models (12), SIR/SEIR models with both serial and parallel infectious stages (13, 14), and a class of models similar to those depicted in Fig. 1 but with the restriction that all new infections arrive in class  $x_1$  (15). It has remained unclear, however, how much of the class of  $Sx_1 \cdots x_n$  models has the GAS property. We definitively answer this question here, and discuss what scope there is to broaden our result to include more general classes of epidemiological models.

## Results

We formalize the class of  $Sx_1 \cdots x_n$  models (Fig. 1) by writing

$$\frac{dS}{dt} = \nu - \mu_S S - \Lambda S, \quad [2a]$$

$$\frac{d\vec{x}}{dt} = \Lambda S \vec{P} - M \vec{x}, \quad [2b]$$

with non-negative initial conditions\*

$$S(t_i) = S_i, \quad \bar{x}(t_i) = \bar{x}_i. \quad [3]$$

In Eq. 2,  $\nu$  represents natality, all of which is into the susceptible compartment. The *per capita* mortality rate from class  $S$  is  $\mu_S$  and from each  $x_j$  is  $\mu_j$ . The *force of infection* is

$$\Lambda = \bar{\beta}^\top \bar{x}, \quad \text{where } \bar{\beta} = [\beta_1, \dots, \beta_n]^\top \quad \text{and} \quad \bar{x} = [x_1, \dots, x_n]^\top. \quad [4]$$

The transmission rates  $\beta_j$  must be non-negative, and to ensure that transmission is *possible*, it is essential that  $\beta_j > 0$  for at least one  $j$ , but there are no other restrictions on the  $\beta_j$ ; thus, transmission from the various  $x_j$  classes can be arbitrarily heterogeneous. In Eq. 2b,

$$\bar{P} = [p_1, \dots, p_n]^\top \quad [5]$$

is the vector of probabilities with which newly infected individuals move from class  $S$  to each  $x_j$  (so each  $p_j \geq 0$  and  $\sum_{j=1}^n p_j = 1$ ). The non-susceptible flow rates are specified by what we call the *post-infection transfer (PIT) matrix*,

$$M = [M_{ij}]_{n \times n} \quad \text{with} \quad \begin{cases} M_{ij} = -m_{ij} & \text{for } i \neq j, \\ M_{jj} = \mu_j + \sum_{i=1}^n m_{ij}. \end{cases} \quad [6]$$

Here, the transfer coefficients  $m_{ij}$  must be non-negative. Flows from  $x_j$  directly back into  $x_j$  have no impact, so we assume without loss of generality that  $m_{jj} = 0$ . The vital rate parameters  $\mu_j$  must be strictly positive. Consequently, the off-diagonal entries of the PIT matrix are non-positive, the diagonal entries are strictly positive, and the  $j^{\text{th}}$  column sum is equal to  $\mu_j > 0$ . The column sum positivity and sign pattern imply that the PIT matrix is a non-singular **M-matrix** (17, 18), which necessarily has a non-negative inverse and eigenvalues that all have positive real parts.<sup>†</sup>

Finally, to prevent the occurrence of formal equilibria that are biologically meaningless, we assume that no compartments are isolated from the  $S$  compartment, *i.e.*, for each  $j$ , it must be *possible* for initially susceptible individuals to reach  $x_j$  eventually. To formalize this property, we note that any  $n \times n$  matrix  $A = [a_{ij}]$ , with non-negative off-diagonal entries, induces a directed graph (or *digraph*) based on those off-diagonal entries, namely the graph with a directed edge from node  $j$  to node  $i$  if and only if  $a_{ij} > 0$  for  $i \neq j$ ; we consider the digraph induced in this way by the negative of the PIT matrix,  $-M$ . In the example of Fig. 1,  $-M$  induces the subgraph made up of the edges with black labels. Thus, we assume that each node in the transfer diagram (*e.g.*, Fig. 1) can be reached by following a path beginning at  $S$ . Using the terminology of graph theory,  $S$  would be called a *source node*. We stress that we do *not* assume the PIT matrix (Eq. 6) to be irreducible, which would be much more restrictive.

With these assumptions, in Methods we show that the basic reproduction number for the general  $Sx_1 \dots x_n$  model (Eq. 2) is

$$\mathcal{R}_0 = \frac{\nu}{\mu_S} \bar{\beta}^\top M^{-1} \bar{P}, \quad [7]$$

and using the fact that  $S$  is a source node, we show that  $\mathcal{R}_0$  is necessarily positive. Eq. 7 is a generalization<sup>‡</sup> of the simple expression  $\mathcal{R}_0 = N\beta/\gamma$  for Eq. 1, since  $\nu/\mu_S$  is the equilibrium population size, and  $\bar{\beta}^\top$  and  $M^{-1}\bar{P}$  are analogous to  $\beta$  and  $\gamma^{-1}$ .

We find that if  $\mathcal{R}_0 \leq 1$  then there is a unique (disease-free) equilibrium,

$$(S^{\text{DFE}}, \bar{x}^{\text{DFE}}) = \left( \frac{\nu}{\mu_S}, \bar{0} \right), \quad [8]$$

whereas if  $\mathcal{R}_0 > 1$  then there is a second (endemic) equilibrium,

$$(S^{\text{EE}}, \bar{x}^{\text{EE}}) = \left( \frac{\nu/\mu_S}{\mathcal{R}_0}, \nu \left( 1 - \frac{1}{\mathcal{R}_0} \right) M^{-1} \bar{P} \right). \quad [9]$$

The system exhibits a standard transcritical bifurcation (20); the two equilibria coincide at  $\mathcal{R}_0 = 1$  and exchange stabilities as  $\mathcal{R}_0$  passes through 1. We prove, moreover, that if  $\mathcal{R}_0 \leq 1$  then the DFE (Eq. 8) is GAS, whereas if  $\mathcal{R}_0 > 1$  then the EE (Eq. 9) is GAS.

**Thus, any  $Sx_1 \dots x_n$  model—any epidemic model with a transfer diagram in the class illustrated by Fig. 1—is globally stable.**

\* Standard existence and uniqueness theory (16, Chapter I) ensures that solutions of Eq. 2 exist and are unique for each initial condition. In Methods, we show that solutions approach a bounded set, a consequence of which is that solutions exist for all  $t \geq t_i$ .

† An *M-matrix* is a square matrix with non-positive off-diagonal elements and eigenvalues with non-negative real parts (see (17, Chapter 6) or (18, Chapter 5)). If an *M-matrix* is non-singular, then its inverse is non-negative and its eigenvalues all have positive real part; see (17, Theorem 6.2.3, statements (G<sub>20</sub>) and (N<sub>38</sub>)).

‡ In addition to being essential for our asymptotic stability analysis in this paper, the explicit formula for  $\mathcal{R}_0$  (Eq. 7) has practical value on its own, whenever an expression for  $\mathcal{R}_0$  is needed, since it avoids having to apply the standard algorithm (19) in any specific case.

## Discussion

Our approach to proving global stability is to construct a Lyapunov function (21) that works for this very general class of models (Eq. 2). Compared to previous work, which has depended on identifying details of specific models, our key innovation is to recognize that construction of a Lyapunov function for a generic  $Sx_1 \cdots x_n$  model can be reduced to a system of linear equations that can always be solved, together with a set of algebraic inequalities that we show are always satisfied.

Having settled this question, it is natural to ask whether the class of models can be expanded further without losing the guarantee of a GAS equilibrium.

**Maternally-acquired immunity.** Thus far, we have implicitly assumed that individuals are susceptible when they are born, which is not always true: a period of maternally acquired immunity is common for many infectious diseases (8, 22). It follows from Corollary 4.3 of Ref. (23) that any “pre-susceptible” transfer diagram can be pasted onto the left of Fig. 1 without affecting global stability. In particular, including maternally acquired immunity still yields a GAS equilibrium, regardless of how the duration of maternally-acquired immunity is distributed (6, 7).

**Vaccination.** If a vaccine that provides permanent immunity is given to a proportion  $p$  of newborns, the susceptible recruitment rate is reduced from  $\nu$  to  $\nu(1-p)$ , and the perfectly vaccinated individuals can be thought of as residing in a vaccinated compartment  $V$  (separated from the potentially infectious classes  $x_1, \dots, x_n$ ). Our GAS result still holds in this situation. Moreover, GAS follows even if vaccine-induced immunity decays, *i.e.*, if there is a flow from  $V$  to  $S$  at rate  $\delta V$  for some  $\delta > 0$  (permanent vaccine-induced immunity corresponds to  $\delta = 0$ ).

Alternatively, or in addition, if susceptibles are vaccinated at a constant *per capita* rate *i.e.*, if there is a flow from  $S$  to  $V$  at rate  $\alpha S$  for some  $\alpha > 0$ , GAS still follows (again, even if vaccine-induced immunity decays).

Note that for some models involving a “leaky vaccine”—one that provides only a temporary *reduction* in susceptibility, rather than full immunity—it is *possible* to have *two* stable equilibria (24). However, this bistability is possible only if there is flow from a vaccinated class to the infected classes, contradicting our assumption of [uniform susceptibility](#).

**Decay of infection-induced immunity.**  $Sx_1 \cdots x_n$  models assume that infection-induced immunity is permanent, *i.e.*, there is no flow back to  $S$  after becoming infected. This assumption of permanent immunity after infection cannot be dropped. Some models with decay of immunity do have a GAS equilibrium (5, 25), however there are simple models with decay of infection-induced immunity that have an unstable EE accompanied by a stable periodic orbit (26). (Ref. (26) ignores births and deaths, but the result holds with vital dynamics as well because stable periodic orbits persist under small perturbations; see Theorem 2 in §4.1 of Ref. (27).)

**Permanent infections.** The class of  $Sx_1 \cdots x_n$  models includes diseases from which individuals never recover to an immune state (*e.g.*, tuberculosis, HIV). Our global stability result still applies in the absence of immunity, since the only requirement is that individuals never return to the susceptible class after being infected.

**Non-exponential lifetime distributions.** As drawn, Fig. 1 suggests that host lifetimes are exponentially distributed. In fact, since essentially arbitrary stage duration distributions can be represented using collections of serial and parallel compartments (6, 7), there is really no such restriction: an arbitrary sub-graph can be pasted onto the end of any of the mortality paths (which point out of the diagram in Fig. 1) without disrupting our global stability analysis, as the resulting PIT matrix would still be a non-singular M-matrix (which can be established using statement (L<sub>32</sub>) of Theorem 6.2.3 in Ref. (17)).

**Infection age and class age.** In their most general model, KM allowed for continuous changes in infectiousness during an individual’s infectious period (4), *i.e.*, the transmission rate  $\beta$  can depend on how long individuals have been infectious (their *infection age*). KM expressed this general model as an integro-differential equation, but there are ODEs in the class of  $Sx_1 \cdots x_n$  models that approximate it to any desired degree of accuracy. The reason is that any compartment (say, represented by  $x_k$ ) can be subdivided into a sequence of subcompartments (say,  $x_{k,1}, \dots, x_{k,K}$ ), each with a different transmission rate. All such subcompartmentalized models in which transmission rate depends on infection-age (or more generally *class-age*) can be represented by Eq. 2, implying they each have an equilibrium that is GAS. In the limit that the number of subcompartments  $K \rightarrow \infty$ , we obtain an integro-differential equation like KM’s. While the limiting equation itself is not an ODE, the fact that it can be approximated arbitrarily closely by GAS systems formalized by Eq. 2, strongly suggests (though does not prove) that the limiting equation also has a GAS equilibrium.

**Delay.** Many models (see refs. (28–30), for example) include delays, whereby individuals that leave one group arrive in another group  $\tau > 0$  time units later. The resulting delay differential equation (DDE) corresponds to individuals spending a period of time ( $\tau$ ) in a *hidden* class that is not explicitly represented in the model, such as a latent class in which individuals are infected but not infectious. The delay ( $\tau$ ) could be the same for all individuals (*i.e.*, discrete

delay), could take values from a continuous distribution (*i.e.*, distributed delay), or could be a combination of the two (31).

As an example, suppose that upon infection, all individuals experience a latent period of the same duration ( $\tau$ ), before proceeding to classes  $x_1, \dots, x_n$ . Then Eq. 2 would become

$$\frac{dS}{dt}(t) = \nu - \mu_S S(t) - \Lambda(t)S(t), \quad [10a]$$

$$\frac{d\vec{x}}{dt}(t) = e^{-\mu_L \tau} \Lambda(t - \tau) S(t - \tau) \vec{P} - M \vec{x}(t), \quad [10b]$$

where  $\mu_L$  is the *per capita* mortality rate while in the latent class. Thus, a fraction  $e^{-\mu_L \tau}$  of those that are infected at time  $t - \tau$  survive to progress to the remaining classes at time  $t$ .

In Methods, we perform global analysis for the ODE version (Eq. 2), using one Lyapunov function for the case  $\mathcal{R}_0 > 1$  and another for the case  $\mathcal{R}_0 \leq 1$ . Theorem 7.1 of Ref. (31) allows our result for  $\mathcal{R}_0 > 1$  to be extended to include the type of delay represented in Eq. 10, and much more general delays that are represented as mixtures of discrete and continuous distributions. A similar approach can be used to extend our result for  $\mathcal{R}_0 \leq 1$ .

**Disease-induced mortality.** Because the death rate  $\mu_j$  in each compartment can be different, disease-induced mortality is implicitly included in our general structure. Indeed, mortality resulting from any characteristic of a given compartment is covered (*e.g.*, post-infection mortality from a secondary infection, such as fatal pneumonia following influenza infection).

**Proportional scaling.** In our formulation of the class of  $Sx_1 \cdots x_n$  models (Eq. 2), we assumed a constant rate of susceptible recruitment (32), rather than a rate that increases in proportion to the population size  $N$ . If we replace  $\nu$  with  $\nu N$  in Eq. 2 and  $\vec{\beta}$  by  $\vec{\beta}/N$  in Eq. 4 then our global stability results are unaffected. This follows because a model that has recruitment  $\nu N$  and transmission  $\vec{\beta}/N$ —but is otherwise identical to Eq. 2—is formally equivalent to Eq. 2 after changing variables to proportions rather than numbers of individuals in each compartment. See, *e.g.*, (33, Section 2) for a similar calculation.

**Heterogeneity.** In the simple KM model (Eq. 1), the transmission rate  $\beta$  represents the product of the contact rate and the probability of infection upon contact. In general  $Sx_1 \cdots x_n$  models (Eq. 2), there can be a distinct transmission rate  $\beta_j$  associated with each  $x_j$ . Thus, it is straightforward to represent heterogeneity in the rates at which individuals in each of the  $x_j$  classes contact susceptibles, or in the probabilities of infection upon contact, or both.

**Environmental reservoirs.** The transmission dynamics of some infections (*e.g.*, cholera) are driven, at least in part, by hosts shedding pathogen into the environment, which becomes an additional source of infection. Many models that include an environmental reservoir (34, 35) fall into the class of  $Sx_1 \cdots x_n$  models (Eq. 2).

**Nonlinear incidence.** The models defined by Eq. 2 assume bilinear incidence,  $S\Lambda$ . Incidence functions  $i(S, \Lambda)$  that are nonlinear in  $S$  or  $\Lambda$  (or both) are commonly considered, often as a means to approximate density-dependent mixing heterogeneities (36–38). In this more general setting,  $\Lambda$  is still defined by Eq. 4 but does not correspond to the force of infection in the usual sense.

Many models with nonlinear incidence have been shown to have a GAS equilibrium (39, 40), but others exhibit periodic orbits and bistability (37, 41). Consequently, our results cannot be generalized to models with *arbitrary* incidence functions  $i(S, \Lambda)$ . However, our results do generalize to any incidence function that satisfies some biologically sensible constraints; in particular, to establish GAS it is sufficient that (i)  $i(S, \Lambda)$  is zero if either argument is zero, (ii)  $i$  is a non-negative increasing function of both  $S$  and  $\Lambda$ , (iii)  $\frac{\partial i}{\partial \Lambda}$  is a non-increasing function of  $\Lambda$  ( $\frac{\partial^2 i}{\partial \Lambda^2} \leq 0$ ) and (iv)  $\frac{\partial i}{\partial \Lambda}$  is a non-decreasing function of  $S$  ( $\frac{\partial^2 i}{\partial S \partial \Lambda} \geq 0$ ). (Note that  $\frac{\partial i}{\partial \Lambda}$  is a measure of the sensitivity of incidence to changes in the infectious level of the population.) The proof of this more general result is substantially longer than the bilinear case on which we focus here, but the structure of the proof is similar.

**Structured populations.** The generic  $Sx_1 \cdots x_n$  model places no restrictions on stratification of *infected* individuals by age, spatial location, or other physiological or social factors, but we have assumed that individuals are indistinguishable when they are susceptible. It remains to be seen whether the general result we have presented here can be extended—or to what extent it can be extended—to include heterogeneous mixing patterns that depend on stratification of susceptibles into distinct classes.

**Non-equilibrium attractors.** Our focus here has been on the existence of a GAS equilibrium. Of course, other types of attractors are possible and can be globally stable. Some of the counter-examples we have cited have a stable periodic orbit, while others exhibit bistability. Our approach—based on considering generic digraphs rather than specific properties of epidemic models—may facilitate additional fruitful developments that help characterize model

structures that necessarily give rise to one globally stable attractor or several co-existing attractors, further enhancing our understanding of the ecology and evolution of infectious diseases.

## Materials and Methods

The intuitive idea that motivates Eq. 2 is that after initial infection, individuals may experience a variety of disease states or situations that can be modelled as passing through compartments that are connected by a digraph structure. Such graphs can always be represented by an M-matrix that we call the PIT matrix [Eq. 6]. This framework includes systems as simple as the common SEIR model (42) and as complex as those involving multiple infectious groups, quarantine, treatment, quiescence, and essentially arbitrarily distributed durations in each compartment. At one extreme,  $M$  could be a diagonal matrix (though this would require that  $\bar{P}$  be strictly positive), while at the other extreme all of the off-diagonals of  $M$  could be negative.

We restrict attention to models in which there is no return from post-infection classes to susceptibility because it is known (26) that models allowing a return to  $S$  can exhibit non-constant periodic solutions, precluding a GAS equilibrium.

We use differential inequalities to establish that solutions that are initially non-negative remain so (a biological necessity), and also to show that there is a bounded set that attracts all solutions.

For  $\mathcal{R}_0 > 1$ , we perform a global stability analysis by constructing a Lyapunov function based on the Volterra function  $g(\theta) = \theta - 1 - \ln(\theta)$ , which has been used extensively for specific subclasses of  $Sx_1 \cdots x_n$  models. This leads to a calculation where a set of Lyapunov coefficients must be found so that certain non-linearities cancel out. We use the digraph structure of the post-infection compartments, *i.e.*, the M-matrix structure of the PIT matrix, to show that a suitable choice of coefficients exists.

**Biological well-posedness.** We write the full state of the system as  $\vec{X} = (S, \vec{x})$ . (Note that we use a double-headed arrow to distinguish  $(n+1)$ -dimensional vectors such as  $\vec{X}$  from  $n$ -dimensional vectors such as  $\vec{x}$ .) If  $\vec{X}$  is non-negative ( $\vec{X} \in \mathbb{R}_{\geq 0}^{n+1}$ ) and one of its components is zero, then the time-derivative of that variable, as given in Eq. 2, is non-negative. Consequently, by (43, Proposition 2.1), the non-negative orthant ( $\mathbb{R}_{\geq 0}^{n+1}$ ) is positively invariant, *i.e.*, biologically sensible initial conditions yield biologically sensible solutions for all time.

**Bounds on solutions.** We denote the column vector in  $\mathbb{R}^n$  with a 1 in each component by  $\bar{1}$ , which allows us to write the total population size conveniently as

$$N(t) = S(t) + \bar{1}^T \vec{x}(t). \quad [11]$$

Then

$$\frac{dN}{dt} = \frac{dS}{dt} + \bar{1}^T \frac{d\vec{x}}{dt} = (\nu - \mu_S S - \Lambda S) + \bar{1}^T (\Lambda S \bar{P} - M \vec{x}). \quad [12]$$

Noting that  $\bar{1}^T \bar{P} = \sum p_j = 1$  and that  $\bar{1}^T M$  gives a row vector containing the column sums of  $M$ , we have

$$\frac{dN}{dt} = \nu - \mu_S S - \mu_1 x_1 - \cdots - \mu_n x_n \leq \nu - \mu N, \quad [13]$$

where  $\mu = \min \{\mu_S, \mu_1, \dots, \mu_n\} > 0$ . Consequently, it follows from standard theory for differential inequalities (16, Theorem I.6.1) that  $N(t) \leq \frac{\nu}{\mu} + e^{-\mu t} (N(t_1) - \frac{\nu}{\mu})$ , and hence

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{\nu}{\mu}. \quad [14]$$

Since  $N$  is asymptotically bounded (Eq. 14), and the state variables that sum to  $N$  are all non-negative, any linear combination of the state variables is also asymptotically bounded. In particular, it follows that there exists  $K > 0$  such that  $\Lambda(t) \leq K$  for sufficiently large  $t$ , say  $t \geq t_K$ . Hence, Eq. 2a implies that for  $t \geq t_K$ ,

$$\frac{dS}{dt} \geq \nu - (\mu_S + K) S, \quad [15]$$

and therefore all solutions to Eq. 2 must satisfy

$$\liminf_{t \rightarrow \infty} S(t) \geq \frac{\nu}{\mu_S + K} > 0. \quad [16]$$

Similarly,  $\frac{dS}{dt} \leq \nu - \mu_S S$ , and so

$$\limsup_{t \rightarrow \infty} S(t) \leq \frac{\nu}{\mu_S}. \quad [17]$$

Inequalities (Eq. 14), (Eq. 16), and (Eq. 17), together imply that solutions of Eq. 2 asymptotically approach the set

$$\mathcal{D} = \left\{ (S, \vec{x}) \in \mathbb{R}_{\geq 0}^{n+1} : \frac{\nu}{\mu_S + K} \leq S \leq \frac{\nu}{\mu_S} \quad \text{and} \quad S + x_1 + \cdots + x_n \leq \frac{\nu}{\mu} \right\}. \quad [18]$$

More precisely, under the dynamics of Eq. 2 with initial conditions given by (3), the following statements are true.

- 1  $0 \leq S(t) \leq N(t) \leq \max \left\{ \frac{\nu}{\mu}, N(t_1) \right\}$  for all  $t \geq t_1$ .
- 2 The set  $\mathcal{D}$  is positively invariant and attracts all solutions.
- 3 The attractor (omega limit set) of each solution is bounded and is contained in  $\mathcal{D}$ .
- 4 All equilibria are contained in  $\mathcal{D}$ .



**The disease-free equilibrium (DFE).** For all parameter values, there is a unique disease-free equilibrium

$$\vec{X}^{\text{DFE}} = (S^{\text{DFE}}, \vec{0}) = \left( \frac{\nu}{\mu_S}, 0, \dots, 0 \right). \quad [19]$$

**The basic reproduction number  $\mathcal{R}_0$ .** We use the next generation matrix method as detailed in Ref. (44) to calculate the basic reproduction number. Let

$$\mathcal{F} = \Lambda S \vec{P} \quad \text{and} \quad \mathcal{V} = M \vec{x}. \quad [20]$$

Then

$$F = \frac{\partial \mathcal{F}}{\partial \vec{x}} \left( \vec{X}^{\text{DFE}} \right) = \frac{\nu}{\mu_S} \vec{P} \vec{\beta}^T \quad \text{and} \quad V = \frac{\partial \mathcal{V}}{\partial \vec{x}} \left( \vec{X}^{\text{DFE}} \right) = M. \quad [21]$$

The next generation matrix  $\mathbf{N}$  is

$$\mathbf{N} = FV^{-1} = \frac{\nu}{\mu_S} \vec{P} \vec{\beta}^T M^{-1}, \quad [22]$$

and  $\mathcal{R}_0$  is the spectral radius of this matrix (44, 45). Noting that  $\vec{\beta}^T M^{-1}$  is a row vector, it follows from Eq. 22 that each column of  $\mathbf{N}$  is a scalar multiple of  $\vec{P}$ , and so  $\mathbf{N}$  has rank one. Consequently, at most one eigenvalue of the next generation matrix is non-zero. Eq. 22 also implies that  $\mathbf{N}\vec{P} = \frac{\nu}{\mu_S} \vec{P} (\vec{\beta}^T M^{-1} \vec{P}) = \frac{\nu}{\mu_S} (\vec{\beta}^T M^{-1} \vec{P}) \vec{P}$ , and therefore  $\vec{P}$  is an eigenvector of  $\mathbf{N}$  corresponding to the eigenvalue  $\lambda_0 = \frac{\nu}{\mu_S} \vec{\beta}^T M^{-1} \vec{P}$ . In **Proof that the eigenvalue  $\lambda_0$  of  $\mathbf{N}$  is positive** we show that  $\lambda_0 > 0$ , from which it follows that it is the spectral radius of  $\mathbf{N}$ , and hence  $\mathcal{R}_0 = \lambda_0$ , as stated in Eq. 7.

**The endemic equilibrium (EE).** We now look for an equilibrium  $\vec{X}^{\text{EE}} = (S^{\text{EE}}, \vec{x}^{\text{EE}})$  with  $S^{\text{EE}}, \vec{x}^{\text{EE}} > 0$ , where  $\Lambda^{\text{EE}} = \vec{\beta}^T \vec{x}^{\text{EE}}$ . We will see that such an equilibrium exists (and is unique) if and only if  $\mathcal{R}_0 > 1$ .

If such an  $\vec{X}^{\text{EE}}$  exists, then  $\frac{dS}{dt}(\vec{X}^{\text{EE}}) = 0$ , and so it follows from Equations (Eq. 2a) and (Eq. 19) that

$$S^{\text{EE}} = \frac{\nu}{\mu_S + \Lambda^{\text{EE}}} < S^{\text{DFE}}. \quad [23]$$

In addition, Eq. 2b becomes  $\frac{d\vec{x}}{dt}(\vec{X}^{\text{EE}}) = \vec{0}$ , which implies  $\vec{x}^{\text{EE}} = \Lambda^{\text{EE}} S^{\text{EE}} M^{-1} \vec{P}$ . Left multiplying by  $\vec{\beta}^T$  yields

$$\Lambda^{\text{EE}} = \Lambda^{\text{EE}} S^{\text{EE}} \vec{\beta}^T M^{-1} \vec{P}. \quad [24]$$

Cancelling  $\Lambda^{\text{EE}}$  and recalling the definition of  $\mathcal{R}_0$  [Eq. 7], we find

$$S^{\text{EE}} = \frac{S^{\text{DFE}}}{\mathcal{R}_0}. \quad [25]$$

Since  $S^{\text{EE}} < S^{\text{DFE}}$  (Eq. 23), Eq. 25 implies that  $\mathcal{R}_0 > 1$ , precluding the possibility of sub-threshold endemic equilibria (see Ref. (44)). Using  $\frac{dS}{dt}(\vec{X}^{\text{EE}}) = 0$  again, we find  $\Lambda^{\text{EE}} S^{\text{EE}} = \nu - \mu_S S^{\text{EE}}$ , allowing the expression for  $\vec{x}^{\text{EE}}$  to be rewritten as

$$\vec{x}^{\text{EE}} = (\nu - \mu_S S^{\text{EE}}) M^{-1} \vec{P} = \nu \left( 1 - \frac{1}{\mathcal{R}_0} \right) M^{-1} \vec{P}. \quad [26]$$

Since  $M^{-1}$  and  $\vec{P}$  are non-negative, it follows that  $\vec{x}^{\text{EE}}$  is also a non-negative vector; moreover, since Eq. 26 implies that the non-zero vector  $\vec{P}$  is a scalar multiple of  $M\vec{x}^{\text{EE}}$ , it follows further that  $\vec{x}^{\text{EE}}$  is not the zero vector. In fact, our assumption that each node in the transfer diagram can be reached by a path beginning at  $S$  implies that *none* of the components of  $\vec{x}^{\text{EE}}$  can be zero, so  $\vec{x}^{\text{EE}} \in \mathbb{R}_{>0}^n$ ; see **Proof that  $\vec{x}^{\text{EE}}$  is strictly positive**. Summarizing, we have:

**Lemma.** For any  $\mathcal{R}_0 > 0$ , Eq. 2 has a unique disease-free equilibrium,  $\vec{X}^{\text{DFE}} = (S^{\text{DFE}}, \vec{x}^{\text{DFE}}) = (\nu/\mu_S, \vec{0})$ . If  $\mathcal{R}_0 \leq 1$ , then  $\vec{X}^{\text{DFE}}$  is the only non-negative equilibrium for Eq. 2. If  $\mathcal{R}_0 > 1$ , then there is also a (unique) endemic equilibrium  $\vec{X}^{\text{EE}} = (S^{\text{EE}}, \vec{x}^{\text{EE}}) \in \mathbb{R}_{>0}^{n+1}$ .

**The Volterra function  $g$ .** In our definition and analysis of Lyapunov functions below, we make judicious use of the Volterra function<sup>§</sup>

$$g(\theta) = \theta - 1 - \ln \theta, \quad [27]$$

and several of its properties, which we list here:

**P1**  $g(\theta)$  has a unique minimum at  $\theta = 1$ , with  $g(1) = 0$ .

**P2** If  $A_1, A_2, B_1, B_2 > 0$  then

$$(A_1 - A_2)(B_1 - B_2) = g(A_1 B_1) - g(A_1 B_2) - g(A_2 B_1) + g(A_2 B_2). \quad [28]$$

**P3** Suppose  $A, B > 0$ ,  $T_i \neq 0$  for  $i = 1, \dots, i_{\max}$ ,  $\text{sign}(T_i) = \text{sign}(T_i^*)$ , and  $\sum_i T_i^* = 0$ . If  $t_i = \frac{T_i}{T_i^*}$  for each  $i$  then

$$(A - B) \sum_i T_i = \sum_i T_i^* [g(A t_i) - g(B t_i)]. \quad [29]$$

A proof of **Property P1** is elementary. **Property P2** appears as Lemma 2.3 in Ref. (31). A proof of **Property P3** is given in **Proof that the Volterra function  $g$  satisfies Property P3**.

<sup>§</sup>We adopt this name in honour of Vito Volterra's work (46, 47) on predator-prey models, in which he calculated first integrals that can be written in terms of  $g$ .

**Lyapunov analysis for  $\mathcal{R}_0 \leq 1$ .** We define

$$L_S^{\text{DFE}} = \mathcal{R}_0 S^{\text{DFE}} g\left(\frac{S}{S^{\text{DFE}}}\right) \quad \text{and} \quad L_{\vec{x}}^{\text{DFE}} = S^{\text{DFE}} \vec{\beta}^\top M^{-1} \vec{x}, \quad [30]$$

and let

$$L^{\text{DFE}} = L_S^{\text{DFE}} + L_{\vec{x}}^{\text{DFE}}. \quad [31]$$

As noted after Eq. 6,  $M^{-1}$  is non-negative, and therefore  $L_{\vec{x}}^{\text{DFE}} \geq 0$ . The function  $L^{\text{DFE}}$  is defined for  $S > 0$ ,  $x_1, \dots, x_n \geq 0$ . We will show that  $L^{\text{DFE}}$  is a Lyapunov function for Eq. 2 if  $\mathcal{R}_0 \leq 1$ , and hence that all solutions in  $\mathbb{R}_{\geq 0}^{n+1}$  tend to  $\vec{X}^{\text{DFE}}$ .

We begin by differentiating  $L_S^{\text{DFE}}$  with respect to time as points  $(S, \vec{x})$  move along solutions to Eq. 2, obtaining

$$\frac{dL_S^{\text{DFE}}}{dt} = \frac{\partial L_S^{\text{DFE}}}{\partial S} \frac{dS}{dt} = \mathcal{R}_0 \left(1 - \frac{S^{\text{DFE}}}{S}\right) [\nu - \mu_S S - \Lambda S]. \quad [32]$$

Inserting  $\nu = \mu_S S^{\text{DFE}}$ , we write

$$\frac{dL_S^{\text{DFE}}}{dt} = -\frac{\mu_S \mathcal{R}_0}{S} (S - S^{\text{DFE}})^2 - \mathcal{R}_0 \Lambda S + \mathcal{R}_0 \Lambda S^{\text{DFE}}. \quad [33]$$

Differentiating  $L_{\vec{x}}^{\text{DFE}}$  with respect to time gives

$$\begin{aligned} \frac{dL_{\vec{x}}^{\text{DFE}}}{dt} &= S^{\text{DFE}} \vec{\beta}^\top M^{-1} \frac{d\vec{x}}{dt} \\ &= S^{\text{DFE}} \vec{\beta}^\top M^{-1} \vec{P} \Lambda S - S^{\text{DFE}} \vec{\beta}^\top M^{-1} M \vec{x} \\ &= \mathcal{R}_0 \Lambda S - S^{\text{DFE}} \Lambda. \end{aligned} \quad [34]$$

Adding  $\frac{dL_S^{\text{DFE}}}{dt}$  and  $\frac{dL_{\vec{x}}^{\text{DFE}}}{dt}$  together to get  $\frac{dL^{\text{DFE}}}{dt}$ , and then recalling  $\mathcal{R}_0 \leq 1$ , we obtain

$$\frac{dL^{\text{DFE}}}{dt} = -\frac{\mu_S \mathcal{R}_0}{S} (S - S^{\text{DFE}})^2 + (\mathcal{R}_0 - 1) \Lambda S^{\text{DFE}} \leq 0, \quad [35]$$

where necessary conditions for equality include  $S = S^{\text{DFE}}$ .

Let  $\mathcal{B}$  be the set on which  $\frac{dL^{\text{DFE}}}{dt}$  is zero and let  $\mathcal{A}$  be the largest invariant subset of  $\mathcal{B} \cap \mathcal{D}$ . Note that  $\mathcal{A}$  is bounded since  $\mathcal{D}$  as defined in Eq. 18 is bounded. Since  $S = S^{\text{DFE}}$  throughout  $\mathcal{B}$  (and hence  $\mathcal{A}$ ), and  $\mathcal{A}$  is invariant, it follows that  $\frac{dS}{dt} \equiv 0$  in  $\mathcal{A}$ . Thus, in  $\mathcal{A}$ ,

$$0 = \frac{dS}{dt} = \nu - \mu_S S^{\text{DFE}} - \Lambda S^{\text{DFE}} = -\Lambda S^{\text{DFE}}. \quad [36]$$

The only possibility is that  $\Lambda \equiv 0$ . Consequently, within  $\mathcal{A}$ , Eq. 2b becomes

$$\frac{d\vec{x}}{dt} = -M \vec{x}. \quad [37]$$

Since all of the eigenvalues of  $M$  have positive real part, the only solution  $\vec{x}(t)$  of Eq. 37 that is bounded for all  $t \in \mathbb{R}$  (and hence for which the corresponding  $\vec{X}(t) = (S^{\text{DFE}}, \vec{x}(t))$  lies in  $\mathcal{A}$  for all  $t \in \mathbb{R}$ ) is the zero solution,  $\vec{x}(t) \equiv \vec{0}$ . Therefore,

$$\mathcal{A} = \{(S^{\text{DFE}}, \vec{0})\} = \{\vec{X}^{\text{DFE}}\}. \quad [38]$$

Thus, by LaSalle's Invariance Principle (21), any solution to Eq. 2 starting in the domain of  $L^{\text{DFE}}$  will tend to  $\vec{X}^{\text{DFE}}$ . Since any solution that starts with  $S = 0$  immediately moves to a state with  $S > 0$ , we see that any solution starting in  $\mathbb{R}_{\geq 0}^{n+1}$  tends to  $\vec{X}^{\text{DFE}}$ , giving:

**Theorem 1.** *If  $\mathcal{R}_0 \leq 1$ , then Eq. 2 has a globally asymptotically stable disease-free equilibrium,  $\vec{X}^{\text{DFE}}$ .*

**Lyapunov analysis for  $\mathcal{R}_0 > 1$ .** We define

$$L_S^{\text{EE}} = S^{\text{EE}} g\left(\frac{S}{S^{\text{EE}}}\right) \quad \text{and} \quad L_k^{\text{EE}} = x_k^{\text{EE}} g\left(\frac{x_k}{x_k^{\text{EE}}}\right) \quad \text{for } k = 1, \dots, n, \quad [39]$$

and let

$$L^{\text{EE}} = L_S^{\text{EE}} + \sum_{k=1}^n a_k L_k^{\text{EE}}, \quad [40]$$

where the *Lyapunov coefficients*  $a_1, \dots, a_n \geq 0$ , so  $L^{\text{EE}}: \mathbb{R}_{>0}^{n+1} \rightarrow \mathbb{R}_{\geq 0}$ . Specific values of the  $a_k$  will be determined below. If each  $a_k$  is positive, then  $L^{\text{EE}}$  achieves its minimum value of zero only at the endemic equilibrium  $\vec{X}^{\text{EE}}$ . However, if some of the  $a_k$  are zero, then there is a larger set on which  $L^{\text{EE}}$  is zero; additional calculations that are required for this situation are presented in [Analysis details if some Lyapunov coefficients are zero when  \$\mathcal{R}\_0 > 1\$](#) .

To establish that  $L^{\text{EE}}$  is a Lyapunov function (thereby showing that  $\vec{X}^{\text{EE}}$  is GAS), we must show that  $\frac{dL^{\text{EE}}}{dt}$  is non-positive. To that end, it is convenient to define

$$s = \frac{S}{S^{\text{EE}}} \quad \text{and} \quad y_k = \frac{x_k}{x_k^{\text{EE}}} \quad \text{for } k = 1, \dots, n. \quad [41]$$



Differentiating  $L_S^{\text{EE}}$  with respect to time gives

$$\frac{dL_S^{\text{EE}}}{dt} = \frac{\partial L_S^{\text{EE}}}{\partial S} \frac{dS}{dt} = \left(1 - \frac{S^{\text{EE}}}{S}\right) \left[\nu - \mu_S S - \sum_{j=1}^n \beta_j x_j S\right]. \quad [42]$$

Using the above definitions of  $s$  and  $y_k$ , the fact that  $g(1) = 0$  [Property P1], and Property P3 with  $A = 1$ ,  $B = \frac{S^{\text{EE}}}{S}$ ,  $\{T_i\}$  given by  $\{\nu, -\mu_S S, -\beta_1 x_1 S, \dots, -\beta_n x_n S\}$ , and  $T_i^*$  given by the equilibrium value of the corresponding  $T_i$ , we obtain

$$\frac{dL_S^{\text{EE}}}{dt} = -\nu g\left(\frac{1}{s}\right) - \mu_S S^{\text{EE}} g(s) + \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} [g(y_j) - g(y_j s)]. \quad [43]$$

Next, for  $k = 1, \dots, n$ , we differentiate  $L_k^{\text{EE}}$  with respect to time, obtaining

$$\frac{dL_k^{\text{EE}}}{dt} = \frac{\partial L_k^{\text{EE}}}{\partial x_k} \frac{dx_k}{dt} = \left(1 - \frac{x_k^{\text{EE}}}{x_k}\right) \left[p_k \sum_{j=1}^n \beta_j x_j S + \sum_{j=1}^n m_{kj} x_j - \left(\mu_k + \sum_{l=1}^n m_{lk}\right) x_k\right]. \quad [44]$$

Noting that  $\frac{dx_k}{dt}$  is zero at  $\vec{X}^{\text{EE}}$ , leads to  $(\mu_k + \sum_{l=1}^n m_{lk}) x_k^{\text{EE}} = p_k \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} + \sum_{j=1}^n m_{kj} x_j^{\text{EE}}$ , and hence

$$\begin{aligned} \frac{dL_k^{\text{EE}}}{dt} &= \left(1 - \frac{x_k^{\text{EE}}}{x_k}\right) \left[p_k \sum_{j=1}^n \beta_j x_j S + \sum_{j=1}^n m_{kj} x_j - \left(p_k \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} + \sum_{j=1}^n m_{kj} x_j^{\text{EE}}\right) \frac{x_k}{x_k^{\text{EE}}}\right] \\ &= \left(1 - \frac{1}{y_k}\right) \left[p_k \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} (y_j s - y_k) + \sum_{j=1}^n m_{kj} x_j^{\text{EE}} (y_j - y_k)\right] \\ &= p_k \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} \left(1 - \frac{1}{y_k}\right) (y_j s - y_k) + \sum_{j=1}^n m_{kj} x_j^{\text{EE}} \left(1 - \frac{1}{y_k}\right) (y_j - y_k). \end{aligned} \quad [45]$$

Again using the fact that  $g(1) = 0$ , but now exploiting Property P2, we have

$$\frac{dL_k^{\text{EE}}}{dt} = p_k \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} \left[g(y_j s) - g(y_k) - g\left(\frac{y_j s}{y_k}\right)\right] + \sum_{j=1}^n m_{kj} x_j^{\text{EE}} \left[g(y_j) - g(y_k) - g\left(\frac{y_j}{y_k}\right)\right]. \quad [46]$$

From the definition of  $L^{\text{EE}}$  in Eq. 40, we have

$$\frac{dL^{\text{EE}}}{dt} = \frac{dL_S^{\text{EE}}}{dt} + \sum_{k=1}^n a_k \frac{dL_k^{\text{EE}}}{dt}. \quad [47]$$

We now use Eq. 43 and 46 to expand the right-hand side of Eq. 47. We then collect all terms in which the argument of  $g$  is simply  $y_j$  or  $y_k$ , and rewrite those terms such that the separate sums over  $j$  and  $k$  are combined to form a single sum over  $\ell$ ; thus, all terms involving  $g(y_j)$  or  $g(y_k)$  are replaced with terms involving  $g(y_\ell)$ , yielding

$$\begin{aligned} \frac{dL^{\text{EE}}}{dt} &= -\nu g\left(\frac{1}{s}\right) - \mu_S S^{\text{EE}} g(s) - \sum_{k=1}^n \sum_{j=1}^n \left[a_k p_k \beta_j x_j^{\text{EE}} S^{\text{EE}} g\left(\frac{y_j s}{y_k}\right) + a_k m_{kj} x_j^{\text{EE}} g\left(\frac{y_j}{y_k}\right)\right] \\ &\quad + \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} g(y_j s) \left[-1 + \sum_{k=1}^n a_k p_k\right] \\ &\quad + \sum_{\ell=1}^n g(y_\ell) \left[\beta_\ell x_\ell^{\text{EE}} S^{\text{EE}} - a_\ell p_\ell \sum_{j=1}^n \beta_j x_j^{\text{EE}} S^{\text{EE}} + \sum_{k=1}^n a_k m_{k\ell} x_\ell^{\text{EE}} - \sum_{j=1}^n a_\ell m_{\ell j} x_j^{\text{EE}}\right]. \end{aligned} \quad [48]$$

We now work to show that the coefficients  $a_k \geq 0$  can be chosen so that the final two lines of Eq. 48 vanish. Let

$$A_{kj} = m_{kj} x_j^{\text{EE}} \quad \text{and} \quad B_\ell = \beta_\ell x_\ell^{\text{EE}} S^{\text{EE}}, \quad [49]$$

and note that  $\sum_{\ell=1}^n B_\ell = \Lambda^{\text{EE}} S^{\text{EE}} \neq 0$ . Suppose now that it is possible to choose the  $a_k$  such that, for each  $\ell$ , the coefficient of  $g(y_\ell)$  on the final line of Eq. 48 (appearing in square brackets) vanishes, *i.e.*, such that

$$0 = B_\ell - a_\ell p_\ell \Lambda^{\text{EE}} S^{\text{EE}} + \sum_{k=1}^n a_k A_{k\ell} - a_\ell \sum_{j=1}^n A_{\ell j}, \quad \ell \in \{1, \dots, n\}. \quad [50]$$

Summing over  $\ell$ , the terms involving the  $A$ 's cancel, giving

$$0 = \sum_{\ell=1}^n B_\ell - \sum_{\ell=1}^n a_\ell p_\ell \Lambda^{\text{EE}} S^{\text{EE}} = \left(1 - \sum_{\ell=1}^n a_\ell p_\ell\right) \Lambda^{\text{EE}} S^{\text{EE}}. \quad [51]$$

Since  $\Lambda^{\text{EE}} S^{\text{EE}}$  is non-zero, we see that any choice of the  $a_k$  that solves Eq. 50 for each  $\ell$ , will give  $(1 - \sum_{\ell=1}^n a_\ell p_\ell) = 0$ , thereby eliminating the second line of Eq. 48. Thus, eliminating the third line of Eq. 48 automatically eliminates the second as well<sup>¶</sup>,

<sup>¶</sup>This cancellation is consistent with a phenomenon that arises in the global analysis of many models, where there are fewer Lyapunov coefficients to choose than there are restrictions to satisfy, and yet a valid choice exists; see (48, 49) for example.

leaving only the first line, which is non-positive (as desired) since  $g \geq 0$  (Property P1). It remains to show that the  $a_k$  can be chosen such that Eq. 50 is satisfied.

We write

$$\bar{a} = [a_1, a_2, \dots, a_n]^T \quad \text{and} \quad \bar{B} = [B_1, B_2, \dots, B_n]^T, \quad [52]$$

so that Eq. 50 can be expressed in matrix form as

$$Q\bar{a} = \bar{B}, \quad [53]$$

where

$$Q = \begin{bmatrix} p_1 \Lambda^{\text{EE}} S^{\text{EE}} + \sum_{j \neq 1} A_{1j} & -A_{21} & \cdots & -A_{n1} \\ -A_{12} & p_2 \Lambda^{\text{EE}} S^{\text{EE}} + \sum_{j \neq 2} A_{2j} & \cdots & -A_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ -A_{1n} & -A_{2n} & \cdots & p_n \Lambda^{\text{EE}} S^{\text{EE}} + \sum_{j \neq n} A_{nj} \end{bmatrix}. \quad [54]$$

The column sums of  $Q$  can be written as a column vector,

$$Q^T \bar{1} = \Lambda^{\text{EE}} S^{\text{EE}} \bar{P}, \quad [55]$$

the components of which are non-negative and not all zero (since  $\Lambda^{\text{EE}} > 0$ ,  $S^{\text{EE}} > 0$ ,  $\bar{P} \geq 0$ , and  $\sum_k p_k = 1$ ). Combining this fact with the sign pattern of  $Q$  and our assumption that each node in the transfer diagram can be reached by a path beginning at  $S$ , it follows from statement (L<sub>32</sub>) of (17, Theorem 6.2.3) that  $Q^T$ , and hence  $Q$ , is a non-singular M-matrix. Consequently,  $Q$  satisfies all fifty enumerated statements of (17, Theorem 6.2.3), including statement (N<sub>38</sub>), which implies that each of the entries of  $Q^{-1}$  is non-negative. Rewriting Eq. 53 as  $\bar{a} = Q^{-1} \bar{B}$ , and recalling that the components of  $\bar{B}$  as defined in Eq. 49 are non-negative, it follows that  $\bar{a}$  is non-negative. Moreover, since at least one  $B_l$  is non-zero (as  $\Lambda^{\text{EE}} \neq 0$ ) Eq. 53 implies that  $\bar{a}$  cannot be the zero vector.

Since Eq. 53 is equivalent to Eq. 50, the choice  $\bar{a} = Q^{-1} \bar{B}$  successfully eliminates the second and third lines of Eq. 48, and therefore

$$\frac{dL^{\text{EE}}}{dt} = -\nu g\left(\frac{1}{s}\right) - \mu_S S^{\text{EE}} g(s) - \sum_{k=1}^n \sum_{j=1}^n \left[ a_k p_k \beta_j x_j^{\text{EE}} S^{\text{EE}} g\left(\frac{y_j s}{y_k}\right) + a_k m_{kj} x_j^{\text{EE}} g\left(\frac{y_j}{y_k}\right) \right] \leq 0. \quad [56]$$

Here, non-positivity follows from the fact that the Volterra function ( $g$ ), the state variables ( $S, x_k$ ), and the parameters ( $\nu, \mu_S, a_k, p_k, \beta_k, m_{kj}$ ), are all non-negative. In addition, given that  $g(\theta) = 0$  if and only if  $\theta = 1$  [Property P1], and  $\nu > 0$ , a necessary condition for equality in Eq. 56 is that  $s = 1$  or, equivalently,  $S = S^{\text{EE}}$ .

Similar to the argument in the previous section, we complete the proof that  $\vec{X}^{\text{EE}}$  is GAS using LaSalle's Invariance Principle (21). Let  $\mathcal{B} \subset \mathbb{R}_{>0}^{n+1}$  be the set on which  $\frac{dL^{\text{EE}}}{dt}$  is zero. Let  $\mathcal{A}$  be the largest invariant subset of  $\mathcal{B} \cap \mathcal{D}$ , and note that  $\mathcal{A} \subset \mathcal{D}$  is bounded. Then in the set  $\mathcal{A}$ , we have  $S = S^{\text{EE}}$ . Hence, by the invariance of  $\mathcal{A}$ , we also have  $\frac{dS}{dt} \equiv 0$ . Thus,

$$0 = \frac{dS}{dt} = \nu - \mu_S S^{\text{EE}} - \Lambda S^{\text{EE}}. \quad [57]$$

The only solution is  $\Lambda \equiv \Lambda^{\text{EE}}$ . Thus, the equation for  $\frac{d\vec{x}}{dt}$  becomes

$$\frac{d\vec{x}}{dt} = \Lambda^{\text{EE}} S^{\text{EE}} \bar{P} - M\vec{x}. \quad [58]$$

Since all of the eigenvalues of  $M$  have positive real part, the only solution of Eq. 58 that is bounded for all  $t \in \mathbb{R}$  is the constant solution  $\vec{x} \equiv \Lambda^{\text{EE}} S^{\text{EE}} M^{-1} \bar{P} = \vec{x}^{\text{EE}}$ . It follows that  $\vec{x}(t) \equiv \vec{x}^{\text{EE}}$  for any solution  $(S^{\text{EE}}, \vec{x}(t))$  in  $\mathcal{A}$ , and so

$$\mathcal{A} = \{(S^{\text{EE}}, \vec{x}^{\text{EE}})\} = \{\vec{X}^{\text{EE}}\}. \quad [59]$$

By LaSalle's Invariance Principle, any solution to Eq. 2 with strictly positive initial conditions tends to  $\vec{X}^{\text{EE}}$ , giving:

**Theorem 2.** *If  $\mathcal{R}_0 > 1$ , then Eq. 2 has a globally asymptotically stable endemic equilibrium,  $\vec{X}^{\text{EE}}$ .*

#### Further technical details.

**Proof that  $\vec{x}^{\text{EE}}$  is strictly positive.** When determining the equilibria (see The endemic equilibrium (EE)), we showed that  $\vec{x}^{\text{EE}} \in \mathbb{R}_{>0}^n$  is a non-zero vector and, therefore, at least one component of  $\vec{x}^{\text{EE}}$  is positive. Suppose some of the components of  $\vec{x}^{\text{EE}}$  are zero. Without loss of generality, we may assume that

$$\vec{x}^{\text{EE}} = \begin{bmatrix} \bar{q}_\ell \\ \vec{0}_{n-\ell} \end{bmatrix}, \quad [60]$$

where  $\bar{q}_\ell \in \mathbb{R}_{>0}^\ell$  for some  $\ell \in \{1, \dots, n-1\}$  and  $\vec{0}_{n-\ell}$  is the zero vector in  $\mathbb{R}^{n-\ell}$ . The PIT matrix can be written as

$$M = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}, \quad [61]$$

where  $B_{11}$  is  $\ell \times \ell$ ,  $B_{22}$  is  $(n-\ell) \times (n-\ell)$  and the blocks  $B_{12}$  and  $B_{21}$  are non-positive. Additionally,  $\bar{P}$  can be written as

$$P = \begin{bmatrix} \bar{P}_1 \\ \bar{P}_2 \end{bmatrix}, \quad [62]$$

where  $\bar{P}_1 \in \mathbb{R}_{\geq 0}^\ell$  and  $\bar{P}_2 \in \mathbb{R}_{\geq 0}^{n-\ell}$ . Then, at the endemic equilibrium, Eq. 2b can be written as

$$\begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix} \begin{bmatrix} \bar{q}_\ell \\ \bar{0}_{n-\ell} \end{bmatrix} = \Lambda^{\text{ee}} S^{\text{ee}} \begin{bmatrix} \bar{P}_1 \\ \bar{P}_2 \end{bmatrix}, \quad [63]$$

and therefore

$$B_{21} \bar{q}_\ell = \Lambda^{\text{ee}} S^{\text{ee}} \bar{P}_2. \quad [64]$$

Noting that  $\bar{q}_\ell$  is a strictly positive vector and that  $\Lambda^{\text{ee}} S^{\text{ee}} > 0$ , while  $B_{21}$  is non-positive and  $\bar{P}_2$  is non-negative, it follows that the only way Eq. 64 can be satisfied is for  $B_{21}$  and  $\bar{P}_2$  to both be zero.

Since  $\bar{P}_2$  is zero, the transfer diagram does not include flow from  $S$  directly to any of the nodes  $x_{\ell+1}, \dots, x_n$ . Since  $B_{21}$  is zero, there is no flow from nodes  $x_1, \dots, x_\ell$  into nodes  $x_{\ell+1}, \dots, x_n$ . This contradicts our assumption that each node in the transfer diagram can be reached by a directed path beginning at  $S$ . Thus, it must be the case that  $\bar{x}^{\text{ee}}$  is strictly positive.  $\square$

**Proof that the Volterra function  $g$  satisfies Property P3.**

$$\sum_i T_i^* [g(At_i) - g(Bt_i)] = \sum_i T_i^* \left[ (At_i - 1 - \ln A - \ln t_i) - (Bt_i - 1 - \ln B - \ln t_i) \right] \quad [65a]$$

$$= \sum_i T_i^* \left[ (At_i - \ln A) - (Bt_i - \ln B) \right] \quad [65b]$$

$$= (A - B) \sum_i T_i^* t_i + (\ln B - \ln A) \sum_i T_i^* \quad [65c]$$

$$= (A - B) \sum_i T_i, \quad [65d]$$

as desired, where the final step to conclude (Eq. 65d) follows from the definition of  $t_i$  and the fact that the  $T_i^*$  sum to zero.  $\square$

**Analysis details if some Lyapunov coefficients are zero when  $\mathcal{R}_0 > 1$ .** In **Lyapunov analysis for  $\mathcal{R}_0 > 1$** , we introduced the Lyapunov coefficients  $a_k \geq 0$ , but assumed for convenience that  $a_k > 0$  for all  $k$  in Eq. 40. We now show—via reduction to a representative submodel—that it is sufficient for one of the  $a_k$  to be positive.

Suppose some of the  $a_k$  are zero. For instance, suppose  $a_1, \dots, a_\ell > 0$  and  $a_{\ell+1}, \dots, a_n = 0$  with  $1 \leq \ell < n$ . (If  $\ell = n$ , then all of the Lyapunov coefficients are positive, which is the “main” case.)

Write  $Q$ ,  $\bar{a}$  and  $\bar{B}$  in block form as

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix}, \quad \begin{bmatrix} \bar{a}_\ell \\ \bar{0}_{n-\ell} \end{bmatrix} \quad \text{and} \quad \begin{bmatrix} \bar{B}_1 \\ \bar{B}_2 \end{bmatrix}, \quad [66]$$

where  $Q_{11}$  is  $\ell \times \ell$ ,  $Q_{22}$  is  $(n-\ell) \times (n-\ell)$ ,  $\bar{a}_\ell \in \mathbb{R}_{\geq 0}^\ell$ ,  $\bar{B}_1 \in \mathbb{R}_{\geq 0}^\ell$ ,  $\bar{B}_2 \in \mathbb{R}_{\geq 0}^{n-\ell}$ , and  $\bar{0}_{n-\ell}$  is the zero vector in  $\mathbb{R}^{n-\ell}$ . Note that the entries of  $Q_{12}$  and  $Q_{21}$  are all non-positive. Eq. 53 can be written as

$$Q_{11} \bar{a}_\ell = \bar{B}_1 \quad \text{and} \quad Q_{21} \bar{a}_\ell = \bar{B}_2. \quad [67]$$

Based on the signs of the entries in  $Q_{21}$ ,  $\bar{a}_\ell$  and  $\bar{B}_2$ , Eq. 67 implies  $Q_{21}$  is a zero matrix and  $\bar{B}_2$  is a zero vector.

The fact that  $Q_{21}$  and  $\bar{B}_2$  are zero is consequential when we consider the original differential equation Eq. 2. The  $(i, j)$  off-diagonal entry of  $Q$  is  $-A_{ji} = -m_{ji} x_i^{\text{ee}}$ . Since  $\bar{x}^{\text{ee}} \in \mathbb{R}_{> 0}^n$ , the fact that  $Q_{21} = 0$  implies the matrix  $M$  has a block of zeros in the transpose position (corresponding to the location of  $Q_{12}$ ). The fact that  $\bar{B}_2 = \bar{0}_{n-\ell}$  implies  $\Lambda = \sum_{j=1}^\ell \beta_j x_j$ .

Combining these facts, it follows that the differential equations for  $\frac{dS}{dt}$ ,  $\frac{dx_1}{dt}$ ,  $\dots$ ,  $\frac{dx_\ell}{dt}$  do not depend on  $x_{\ell+1}, \dots, x_n$ . Thus, it is understandable that the Lyapunov function would be a function of  $S, x_1, \dots, x_\ell$ , and not depend on  $x_{\ell+1}, \dots, x_n$ , as is the case if  $a_{\ell+1} = \dots = a_n = 0$ . In such a case, the Lyapunov function could be used to show that the subsystem of  $(S, x_1, \dots, x_\ell)$  tends to an equilibrium. Then, the subsystem of  $(x_{\ell+1}, \dots, x_n)$  can be studied as a non-autonomous linear system, driven by  $\Lambda S \bar{P}$ , and would also tend to an equilibrium.

Thus, no generality is actually lost by our assumption in the main text that each  $a_k > 0$ .

**Proof that the eigenvalue  $\lambda_0$  of  $N$  is positive.** When calculating  $\mathcal{R}_0$  (see **The basic reproduction number  $\mathcal{R}_0$** ) we showed that the next generation matrix  $N$  [Eq. 22] has at most one non-zero eigenvalue. We show here that the eigenvalue  $\lambda_0$  (equal to  $\frac{\nu}{\mu_S} \bar{\beta}^T M^{-1} \bar{P}$ ) is, in fact, positive. Consequently, as stated earlier, this positive eigenvalue is the spectral radius of  $N$ , i.e.,  $\lambda_0$  is equal to  $\mathcal{R}_0$  (44, 45).

Recalling that the vital rates  $\nu$  and  $\mu_S$  are positive, and that  $\bar{\beta}$ ,  $\bar{P}$  and  $M^{-1}$  are non-negative [see the paragraph containing Eqs. 4–6], it follows that  $\lambda_0$  is also non-negative. It remains to show that  $\lambda_0$  is non-zero.

Observe that

$$\int_0^\infty e^{-M\tau} d\tau = -M^{-1} e^{-M\tau} \Big|_{\tau=0}^\infty = -M^{-1} \left( \lim_{\tau \rightarrow \infty} e^{-M\tau} \right) + M^{-1} e^{-M\tau} \Big|_{\tau=0}. \quad [68]$$

Since the real parts of the eigenvalues of  $M$  are all positive [see Footnote †], the limit above gives the zero matrix. For the evaluation at  $\tau = 0$ , we note that the exponential of the zero matrix is the identity, and so

$$M^{-1} = \int_0^\infty e^{-M\tau} d\tau. \quad [69]$$

Now, since the off-diagonal entries of  $M$  are non-positive (as discussed after Eq. 6), we can choose  $r > 0$  such that  $H = rI - M$  is non-negative. Then  $H^\ell$  is non-negative for any integer  $\ell \geq 0$ . Note that  $H$  has the same off-diagonal entries as  $-M$ , and so the digraph induced by  $H$  is the same as the one induced by  $-M$ .

In the digraph induced by  $H$  (or by  $-M$ ), a directed edge from node  $j$  to node  $i$  would imply  $m_{ij} > 0$ . This can also be called a path of length one. A path of length  $\ell = 2$  from node  $j$  through node  $i'$  to node  $i$  would imply  $m_{i'i}, m_{i'j} > 0$ . The  $(i, j)$  entry of  $H^2$  is the sum  $\sum_k m_{ik} m_{kj}$ , which, due to the non-negativity of  $H$  would be at least as large as the product  $m_{ii'} m_{i'j} > 0$ . Thus, we see that a path of length  $\ell = 2$  implies the corresponding entry of  $H^2$  is positive.

More generally, if the digraph induced by  $H$  contains a path of length  $\ell \geq 2$  from node  $j$  to node  $i$ , then  $H$  contains  $\ell$  positive off-diagonal entries  $m_{i_k i_{k-1}}$  (for  $k = 1, \dots, \ell$ ) with  $i_0 = j$  and  $i_\ell = i$ . The  $(i, j)$  entry of  $H^\ell$  is a sum of non-negative terms that includes the positive product  $m_{i_\ell i_{\ell-1}} \dots m_{i_1 i_0}$ . Thus, the existence of a path of length  $\ell \geq 1$  implies the  $(i, j)$ -entry of  $H^\ell$  is positive.

If an index  $j$  is in the support both of  $\bar{P}$  and  $\bar{\beta}$ , then we say there is a path of length  $\ell = 0$  from node  $j$  to node  $i$  (with  $i = j$ ). The matrix  $H^0$  is the identity matrix, and so we can now assert that the existence of a path of length  $\ell \geq 0$  implies that the  $(i, j)$ -entry of  $H^\ell$  is positive.

Using the definition of the matrix exponential as a power series (50) (i.e.,  $e^{H\tau} = \sum_{\ell=0}^{\infty} \frac{1}{\ell!} H^\ell \tau^\ell$ ), it follows that the existence of a directed path of any length from node  $j$  to node  $i$  implies that the  $(i, j)$ -entry of  $e^{H\tau}$  is also positive for all  $\tau > 0$ .

Choose integers  $j$  and  $i$  such that  $p_j, \beta_i > 0$  and such that there exists a path from  $x_j$  to  $x_i$ . (Our assumption that each node in the original transfer diagram can be reached by a path starting at  $S$  implies that such a choice exists.) Let  $h(\tau) > 0$  be the  $(i, j)$ -entry of  $e^{H\tau}$ . Then

$$\bar{\beta}^T e^{H\tau} \bar{P} \geq \beta_i h(\tau) p_j > 0. \quad [70]$$

Since  $-M = -rI + H$ , we have  $e^{-M\tau} = e^{-r\tau I + H\tau} = e^{-r\tau} e^{H\tau}$ . Combining this with Eq. 69, we obtain

$$\bar{\beta}^T M^{-1} \bar{P} = \int_0^\infty e^{-r\tau} \bar{\beta}^T e^{H\tau} \bar{P} d\tau \geq \int_0^\infty e^{-r\tau} \beta_i h(\tau) p_j d\tau > 0, \quad [71]$$

from which it follows that  $\lambda_0$  is positive, and therefore  $\mathcal{R}_0 = \lambda_0$ , proving the validity of Eq. 7.  $\square$

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