Interpreting Models of Infectious Diseases in Terms of Integral Input-to-State Stability

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Abstract—The notions of integral input-to-state stability (iISS) and input-to-state stability (ISS) have been effective in addressing nonlinearities globally without domain restrictions in analysis and design of control systems. In particular, they provide useful tools of module-based methods integrating characteristics of components. This paper applies the framework of module-based analysis to ordinary differential equations which deterministically describe dynamics of prevalence and the duration of epidemics. The objective is to express fundamental properties of models of infectious diseases and vaccination through the language of iISS and ISS. The systematic treatment is expected to facilitate development of effective schemes of controlling the spread of diseases via non-conventional Lyapunov functions.

Index Terms—Epidemic models, integral input-to-state stability, Lyapunov functions, positive nonlinear network, small gain theorem.

I. INTRODUCTION

For many decades, mathematical models of infectious diseases have been recognized as useful tools for public health decision-making during epidemics [1]–[4]. Detailed models help predict the future course of outbreak, while simple models allow one to understand mechanisms whose interpretations can lead to ideas of control strategies, such as vaccination, isolation, digital contact tracing and culling, which slow or ultimately eradicate the infection from the population. The objective of this paper is to facilitate the development of the latter. This paper does not report any novel behavior of disease transmission. Instead, this paper is devoted to formulating a systematic understanding behavior of classical and simple models of infectious diseases in the language of integral input-to-state stability (iISS) and input-to-state stability (ISS). It aims to take a first step toward development of an iISS/ISS-theoretic foundation for systematic control design to combat infectious diseases. This paper reports that popular models share essentially the same qualitative behavior which can be analyzed and explained systematically via the same tools of iISS/ISS.

The notion of iISS and ISS have been accepted widely as mathematical tools to deal with and utilize nonlinearities effectively in the area of control [5], [6]. The notions offer a systematic framework of module-based design of control systems. Once a system or a network is divided into “stable” components, aggregating characteristics of components gives answers to control design problems systematically. The answers are global, and they are not restricted to small domains of variables. Without relying linearity, ISS allows one to handle systems based on boundedness of states with respect to bounded inputs. Importantly, the boundedness does not require finite operator gain, so that replacing linearity with ISS, we can handle a large class of nonlinear systems. However, nonlinearity such as bilinearity and saturation often prevent systems from being ISS. They are cases where nonlinearities retain convergence of state variables in the absence of inputs, but prevent state variables from being bounded in the presence of inputs. Such nonlinear systems are covered by iISS. Systems whose state is bounded for small inputs are grouped into the class of Strong iISS systems [7]. ISS and (Strong) iISS characterize both internal and external stability properties. The weak “stability” of (Strong) iISS components can be compensated by ISS components. This fact is one of useful and powerful tools of the iISS/ISS framework. Some of main ideas of iISS/ISS module-based arguments are packed in the iISS small-gain theorem [8]–[11] which is an extension of the ISS small-gain theorem [12]–[16]. One of the important features of the small-gain methodology is that for interconnected systems and networks, it gives formula to explicitly construct non-conventional Lyapunov functions which not only establish stability properties of equilibria, but also properties with respect to external variables and parameters. For understanding behavior of diseases transmission, construction of Lyapunov functions has been one of major directions in mathematical epidemiology, and Lyapunov functions are known to be useful for analyzing global properties of stability of each given equilibrium (see [17]–[24] and references therein). However, the Lyapunov functions are classical, so that they do not unite characterizations of stability properties which vary with parameters and external elements. In other words, bifurcation analysis need to be performed separately to divide the Lyapunov function analysis into cases.

This paper gives interpretations to behavior of typical models of infectious diseases in terms of basic characterizations of iISS and ISS [6], [23], [24] with the help of two tools provided by iISS and ISS. One tool is a criterion of the small-gain type. The other is a fusion of global and local nonlinear gain of components. The two tools formulated in this paper are not completely novel ideas, but they extend standard concepts in the iISS/ISS methodology by specializing in the setup of diseases models. In addition to their usefulness, this paper illustrates how the same set of the basic characterizations and tools of iISS/ISS can be applied to popular models of infectious diseases uniformly to help explain and capture their fundamental behavior globally without dividing the analysis into cases a priori.
II. Preliminaries

Let the set of real numbers be denoted by \( \mathbb{R} := (-\infty, \infty) \). This paper uses the symbols \( \mathbb{R}_+ := [0, \infty) \) and \( \mathbb{R}_+^n := [0, \infty)^n \). Used. A function \( f : \mathbb{R}^n \to \mathbb{R}^m \) is said to be of class \( \mathcal{C} \) and written as \( f \in \mathcal{C} \) if \( f \) is continuous and satisfies \( f(0) = 0 \) and \( f(s) > 0 \) for all \( s \in \mathbb{R}_+ \setminus \{0\} \). A class \( \mathcal{P} \) function is said to be of class \( \mathcal{K} \) if it is strictly increasing. A class \( \mathcal{K} \) function is said to be of class \( \mathcal{K}_\infty \) if it is unbounded. A continuous function \( \beta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+ \) is said to be of class \( \mathcal{K}_\infty \) if, for each fixed \( t \geq 0 \), \( \beta(t, \cdot) \) is of class \( \mathcal{K} \) and, for each fixed \( s > 0 \), \( \beta(s, \cdot) \) is decreasing and \( \lim_{t \to \infty} \beta(s, t) = 0 \).

The zero function of appropriate dimension is denoted by \( 0 \).

Composition of \( \eta_1, \eta_2 : \mathbb{R}_+ \to \mathbb{R}_+ \) is expressed as \( \eta_1 \circ \eta_2 \).

A function \( \eta : \mathbb{R}_+ \to \mathbb{R}_+ \), the function \( \eta^2 : \mathbb{R}_+ \to \mathbb{R}_+ := [0, \infty) \) is defined as \( \eta^2(s) = \sup \{ \tau \in \mathbb{R}_+ : s \geq \eta(\tau) \} \). By definition, for \( \eta \in \mathcal{K} \), \( \eta^2(s) = \infty \) holds for all \( s \geq \lim_{t \to \infty} \eta(t) \), and \( \eta^2(s) = \eta^{-1}(s) \) elsewhere. The set \( \{1, 2, 3, \ldots, n\} \) is denoted by \( \mathcal{N} \). For a set \( U \), its cardinality is denoted by \( |U| \). For \( U \subset \mathcal{N} \) and \( x \in \mathbb{R}^n \), the vector \( x_U \in \mathbb{R}^{|U|} \) is the collection of \( |U| \) components \( x_i, i \in U \).

A system of the form

\[
\dot{x}(t) = f(x(t), u(t))
\]  

is said to be integral input-to-state stable (iISS) with respect to the input \( u \) if there exist \( \beta \in \mathcal{K}_\infty, \chi, \eta \in \mathcal{K}_\cup \{0\} \) such that, for all measurable locally essentially bounded functions \( u : \mathbb{R}_+ \to \mathbb{R}^p \), all \( x(0) \in \mathbb{R}^n \) and all \( t \geq 0 \), its solution \( x(t) \) exists and satisfies

\[
|x(t)| \leq \beta(|x(0)|, t) + \chi \left( \int_0^t \mu(|u(\tau)|) d\tau \right),
\]

where the symbol \( | \cdot | \) denotes the Euclidean norm. System (1) is said to be strongly integral input-to-state stable (Strongly iISS) with respect to the input \( u \) if there exist \( R > 0 \) and \( \gamma \in \mathcal{K} \cup \{0\} \) such that\( \gamma \)

\[
\text{ess sup}_{t \in \mathbb{R}_+} |u(t)| < R \Rightarrow
|x(t)| \leq \beta(|x(0)|, t) + \gamma \left( \text{ess sup}_{t \in \mathbb{R}_+} |u(t)| \right)
\]

holds in addition to the above requirement of (2). The constant \( R \) is called an input threshold. If the requirement of (3) is met with \( R = \infty \), system (1) is said to be input-to-state stable (ISS). The function \( \gamma \) is called an ISS-gain function. An ISS system is Strongly iISS. A Strongly iISS system is iISS. Their converses do not hold true. iISS of (1) implies globally asymptotic stability of the equilibrium \( x = 0 \) for \( u = 0 \). If a radially unbounded and continuously differentiable function \( V : \mathbb{R}^n \to \mathbb{R}_+ \) satisfies

\[
\forall x \in \mathbb{R}^n \quad \forall u \in \mathbb{R}^p \quad \frac{\partial V}{\partial x}(x, u) f(x, u) \leq -\alpha(V(x)) + \sigma(|u|)
\]

for some \( \sigma \in \mathcal{K} \) and \( \alpha \in \mathcal{P} \) (resp., \( \alpha \in \mathcal{K} \) and \( \lim_{s \to \infty} \alpha(s) \geq \lim_{s \to \infty} \sigma(s) \)), the function \( V(x) \) is said to be an iISS (resp., ISS) Lyapunov function. The existence of an iISS (resp., ISS) Lyapunov function guarantees iISS (resp., ISS) of system (1) [25, 26]. If an iISS Lyapunov function admits \( \alpha \in \mathcal{K} \), the system is guaranteed to be Strong iISS [7]. iISS and ISS Lyapunov functions are conventional Lyapunov functions when the input \( u \) is zero in system (1). The Lyapunov-type characterization [4] yields

\[
\lim_{t \to \infty} \sup_{u \in \mathbb{R}_+} V(x(t)) \leq \gamma (\text{ess sup}_{t \in \mathbb{R}_+} |u(t)|),
\]

where \( \gamma := \alpha^{\circ} \circ \eta \). If \( u(t) \equiv u_0 \) is a constant and (4) holds with an equality sign, we have \( \lim_{t \to \infty} V(x(t)) = \gamma |u_0| \).

The inequality (5) is called the asymptotic gain property [25].

If system (1) is not ISS, there exists no \( \gamma \) in \( \mathcal{K} \) satisfying the asymptotic gain property (5). This is because (6) never holds with \( R = \infty \). As in (2), an iISS system which is not ISS accumulates its input, and the solution \( x(t) \) exists for all \( t \in \mathbb{R}_+ \), but unbounded if the input is persistent. All the above are standard definitions given for sign-indefinite system (1).

When the vector field \( f \) generates only non-negative \( x(t) \) in (1) defined with \( x(0) \in \mathbb{R}_+^n \) and \( u(t) \in \mathbb{R}_+^p \), all the above definitions and facts are valid by replacing \( \mathbb{R} \) with \( \mathbb{R}_+ \).

III. A SMALL-GAIN THEOREM FOR GENERALIZED BALANCING KINETICS

This section shows a small-gain type method for establishing stability of dynamical networks in the framework of iISS. To propose a generalized formulation which includes a previously-developed criterion as a special case, consider

\[
\dot{x}_i = -\eta_{i-1,i}(x_i) + \sigma_{i-1,i}(x_i) - \eta_{i+1,i}(x_i) + \sigma_{i+1,i}(x_i) \quad \text{for } i \in \mathcal{N} \quad (6)
\]

for any \( x(0) \in \mathbb{R}_+^n \) and any measurable and locally essentially bounded function \( w(t) = [w_1(t), w_2(t), \ldots, w_n(t)]^T \in \mathbb{R}_+^n \). In (6), the subscripts of \( \eta \) and \( \sigma \) are integers which are circular of length \( n \). If a subscript \( k \) by itself does not belong to \( \mathcal{N} \), it stands for \( ((k - 1) \mod n) + 1 \), where \( \mod n \) denotes the non-negative reminder of the division of an integer \( i \) by \( n \). All subscripts in this section are circular. Assume that the functions \( \eta_{i-1,i}, \eta_{i+1,i}, \sigma_{i-1,i}, \sigma_{i+1,i} : \mathbb{R}_+^n \to \mathbb{R}_+ \) and \( \beta_i \in \mathcal{P} \) are locally Lipschitz and satisfy

\[
\forall i \in \mathcal{N} \quad \eta_{i-1,i}(0) = \eta_{i+1,i}(0) = 0 \quad (7)
\]

for all \( i \in \mathcal{N} \). For all \( i \in \mathcal{N}, \kappa_i \in \mathcal{K} \cup \{0\} \) is assumed. Network (6) is made of balancing mechanisms between state variables. The component \( x_i \) is consumed at the rate \( -\eta_{i+1,i}(x) \) and the consumption leads to the production of the downstream component \( x_{i+1} \) at the rate \( +\sigma_{i+1,i}(x) \). In the same way, the consumption \( -\eta_{i-1,i}(x) \) of \( x_i \) produces the downstream component \( x_{i-1} \) at the rate \( +\sigma_{i-1,i}(x) \). The rates are allowed to be functions of \( x \) instead of the local variable \( x_i \). The extra rate \( \beta_i \) of consumption in either the upstream or the downstream direction is a function of the local variable \( x_i \). It is also important that the balancing between neighbors forms not only cycles of length 1, but also cycles of length \( n \). Assume that the rate functions in (6) satisfy

\[
\forall i \in \mathcal{N} \quad \forall j \in \{i - 1, i + 1\} \quad \exists \epsilon_{i,j} \geq 0 \quad \forall x \in \mathbb{R}_+^n \quad \sigma_{i,j}(x) \leq \epsilon_{i,j} \eta_{i,j}(x). \quad (8)
\]

1 Under the assumption (6), the implication (4) is necessary and sufficient for guaranteeing \( x(t) \in \mathbb{R}_+^n \).
The following theorem can be proved.

**Theorem 1:** Assume that

\[ \forall i \in \pi \quad \ell_{i,i+1} \ell_{i+1,i} \leq 1 \quad \text{(9)} \]

\[ \exists k \in \pi \quad \ell_{k,k+1} \ell_{k+1,k} \leq \prod_{i=1}^{n} \frac{\ell_{i,i+1}}{\ell_{i,i+1}} \leq \frac{1}{\ell_{k,k+1} \ell_{k+1,k}} \quad \text{(10)} \]

are satisfied. Then network (6) is iISS with respect the input \( w \).

### Proof:

Due to (9), from (8) and (12) it follows that

\[ \lambda_{i+1} \sigma_{i+1,i}(x) = \sqrt{\frac{\ell_{i,i+1} + \ell_{i+1,i}}{\ell_{i,i+1}}} \lambda_i \sigma_{i+1,i}(x) \]

\[ \leq \sqrt{\frac{\ell_{i+1,i} + \ell_{i,i+1}}{\ell_{i,i+1}}} \lambda_i \eta_{i+1,i}(x) \]

\[ \leq \lambda_i \eta_{i+1,i}(x) \]

\[ \lambda_i \sigma_{i,i+1}(x) = \sqrt{\frac{\ell_{i,i+1}}{\ell_{i+1,i}}} \lambda_{i+1} \sigma_{i,i+1}(x) \]

\[ \leq \lambda_{i+1} \eta_{i,i+1}(x) \]

for all \( x \in \mathbb{R}^n_+ \) at each \( i \in \{k+1, k+2, \ldots, k+n\} \). By virtue of the second inequality in (10), properties (6) and (12) yield

\[ \lambda_{k+1} \sigma_{k+1,k}(x) = \prod_{i=k+1}^{k+n-1} \sqrt{\frac{\ell_{i,i+1} + \ell_{i+1,i}}{\ell_{i,i+1}}} \lambda_{k+1} \sigma_{k,k+1}(x) \]

\[ \leq \sqrt{\frac{\ell_{k+1,k} + \ell_{k,k+1}}{\ell_{k,k+1}}} \lambda_{k+1} \sigma_{k,k+1}(x) \]

\[ \leq \lambda_{k+1} \eta_{k,k+1}(x) \]

In the same way, the first inequality in (10) gives

\[ \lambda_{k+1} \sigma_{k+1,k}(x) \leq \lambda_{k} \eta_{k+1,k}(x) \]

Therefore, the function \( V(x) \) given in (11) satisfies

\[ \dot{V} \leq \sum_{i \in \pi} \lambda_i (-\beta_i(x_i) + k_i(w_i)) \]

along the trajectory \( x(t) \) of network (6).

**Proof:**

Recall that circulating subscripts of length \( n \) are used for \( \ell_{i,j} \) and \( \lambda_i \). The above theorem extends a development of [27] in which \( \eta_{i,i} \) and \( \sigma_{i,i} \) were restricted to be functions of \( x_i \). The restriction disallows bilinearities and multiplicative nonlinearities to appear in \( \eta_{i,i} \) and \( \sigma_{i,i} \). Removal of the restrictions by Theorem 1 is the theoretical key in this paper.

**Remark 1:** If there exists \( k \in \pi \) such that \( \ell_{k,k+1} = 0 \) achieving (8), the first inequality in (10) is satisfied automatically with a sufficiently small \( \ell_{k,k+1} > 0 \). The same applies to the case of \( \ell_{k,k+1} = 0 \) with the second inequality in (10).

**Remark 2:** Theorem 1 reduces to a special case of the iISS small-gain theorem for networks proposed in [10]. When the functions in (6) are restricted to

\[ \exists \lambda_{i-i,i}, b_{i,i,i,i} > 0 \quad \forall x \in \mathbb{R}^n_+ \]

\[ b_{i-i,i} \eta_{i-i,i}(x) = b_{i,i,i,i}(x) = \beta_i(x_i) \]

\[ \forall x \in \mathbb{R}^n_+ \quad \forall w \in \mathbb{R}^m_+ \quad \sigma_{i-i,i}(x_i) = \sigma_{i,i,i,i}(\hat{x}) \]

\[ \sigma_{i,i,i}(x_i) = \sigma_{i,i,i,i}(\hat{x}) \]

for all \( i \in \pi \), network (6) fit in the setup of [10], and the conditions (9) and (10) coincide with the cyclic small-gain condition presented in [10]. If all the functions in (6) are non-zero, the network consists of \( n \) simple directed cycles of length 1, and 2 simple directed cycles of length \( n \). The inequality (9) is the small-gain requirement for the cycles of length 1, while the two inequalities in (10) are for length \( n \).

**IV. CONVERGENCE VIA ZERO LOCAL ISS-GAIN**

This section focuses on an extra property which iISS systems often possess due to bilinear or multiplicative nonlinearities. To formulate it, consider \( x(t) \in \mathbb{R}^n_+ \) governed by

\[ \dot{x} = f(x, w) := \begin{bmatrix} f_1(x, w) \\ f_2(x, w) \\ \vdots \\ f_n(x, w) \end{bmatrix} \]

for any \( x(0) \in \mathbb{R}^n_+ \) and any measurable and locally essentially bounded function \( w(t) = [w_1(t), w_2(t), \ldots, w_p(t)]^T \in \mathbb{R}^p_+ \).

It is assumed that \( f : \mathbb{R}^n_+ \times \mathbb{R}^m_+ \rightarrow \mathbb{R} \) is locally Lipschitz functions satisfying \( f(0,0) = 0 \) and

\[ x_i = 0 \Rightarrow \forall x \in \mathbb{R}^n_+ \quad \forall w \in \mathbb{R}^m_+ \quad f_i(x, w) \geq 0. \]

**Property (17)** is necessary and sufficient for guaranteeing \( x(t) \in \mathbb{R}^n_+ \) with respect to all \( x(0) \) and \( w \). The following proposition describes a property of iISS systems which completely reject the effect of small inputs on some state variables.

**Proposition 1:** Suppose that system (16) is iISS with respect the input \( w \), and admits a non-empty set \( U \subset \pi \), a radially unbounded and continuously differentiable function \( V_U : \mathbb{R}^n_+ \rightarrow \mathbb{R}_+ \), and class \( K \) functions \( \alpha_U, \sigma_U \) such that

\[ \forall x \in \mathbb{R}^n_+ \quad \forall w \in \mathbb{R}^m_+ \quad \frac{\partial V_U}{\partial x_U}(x_U f_U(x, w)) - \alpha_U(V_U(x_U)) + \sigma_U(w). \]
If there exist a non-empty set $L \subset \pi$, a real number $H > 0$, and a radially unbounded and continuously differentiable function $V_L : \mathbb{R}^{|L|} \rightarrow \mathbb{R}^+$ such that for each $k \in (0, 1)$,

$$\forall x \in \mathbb{R}_+^n \cap \{ V_U(x_U) \leq kH \} \quad \forall w \in \mathbb{R}_+^p \quad \frac{\partial V}{\partial x_L}(x, w) \leq -\alpha_L(V_L(x_L)) \quad (19)$$

holds for some $\alpha_L \in \mathcal{P}$, then the solution $x(t)$ of (16) satisfies

$$\sup_{t \in \mathbb{R}_+} w(t) < Q \Rightarrow \forall x(0) \in \mathbb{R}_+^n \lim_{t \rightarrow \infty} x_L(t) = 0 \quad (20)$$

for $Q = \lim_{s \rightarrow H^-} \sigma_U(s)^{\alpha_L(s)}$.

**Proof:** Since system (16) is iISS, a solution $x(t) < \infty$ exists and unique for all $t \in \mathbb{R}_+$. Assume that a real number $H \in (0, \infty)$ satisfies (19). Suppose that $\sup_{t \in \mathbb{R}_+} w(t) < Q$ for $Q = \lim_{s \rightarrow H^-} \sigma_U(s)^{\alpha_L(s)}$. In the case of $Q = \infty$, for each $x$, assumption (18) implies the existence of $T \in \mathbb{R}_+$ and $\epsilon \in (0, H)$ such that

$$\forall t \in [T, \infty) \quad V_U(x_U(t)) < H - \epsilon. \quad (21)$$

In the case of $Q < \infty$, since for each $w$, there exists $\delta > 0$ satisfying $\sup_{t \in \mathbb{R}_+} w(t) \leq Q - \delta$, evaluating (18) allows one to verify the existence of $T \in \mathbb{R}_+$ and $\epsilon \in (0, H)$ fulfilling (21) again. Therefore, the existence of $x_L \in \mathcal{P}$ satisfying (19) for each $k \in (0, 1)$ ensures (20). \qed

The above proposition makes use of property (19) which ensures the existence of a partial system completely rejecting the effect of its interconnecting inputs whose magnitude is smaller than a threshold. Let $L^C = \pi \setminus L$. For $x_L$-system defined by $\dot{x}_L = f_L(x, w)$, $x_L(t)$ and $w(t)$ are exogenous. Property (19) implies that the ISS-gain of the input $[x_L^T, w^T]^T$ to the state $x_L$ is zero as long as $V_U(x_U) < H$. Hence, in Proposition 1, $x_L$-system is required to admit zero ISS-gain locally, although it is not required to be ISS globally. In the case of $L = \pi$, property (19) implies Strong iISS of $x_L$-system, since iISS is assumed in Proposition 1. This property (19) is very common, although it may not have been focused very often in the literature of systematic control methodology. For example, any of scalar non-negative systems

$$\xi = -\xi + \xi w$$

$$\dot{\xi} = -\frac{\xi}{1+\xi} + \frac{\xi w}{1+\xi}$$

$$\dot{\xi} = -\frac{\xi}{1+\xi} + \frac{\xi w}{1+\xi^2}$$

has the threshold at $H = 1$ for $x_L = \xi$ and $V(x_L) = x_L$. The state $\xi$ converges to zero for $w < 1$, while $\xi$ increases as long as $w > 1$, although the increase is within the property of iISS. The above three systems are Strong iISS. The zero local ISS-gain they actually have is “stronger” than Strong iISS. In this way, the threshold is a bifurcation point bringing in a superior stability property. Bilinearity and multiplicative nonlinearity give rise to the bifurcation, and Proposition 1 aims at highlighting such systems.

**Remark 3:** Since Proposition 1 assumes the entire system (16) to be only iISS, the variable $x_L(t)$ can increase until $V_U(x_U(t)) < H$ is achieved. Then an outbreak of $x_L$ occurs, and $x_L(t)$ exhibits a peak. Property (18) allows one to estimate that the smaller $w$ is, the shorter the time when $x_L$ starts decreasing (the duration of the growth phase) is. The larger $Q$ or $H$ is, the shorter the growth phase is. The increasing rate of $x_L(t)$ until $V_U(x_U(t)) < H$ can be estimated by the iISS property of the entire system, or $x_L$-system, which is more specific than the entire system. For example, an upper bound of $(\partial V_U/\partial x_L)f_L$ for $V_U(x_U) > H$ gives such information, which is not stated explicitly in Proposition 1.

V. SIR MODEL

Consider the solution $x(t) := [S(t), I(t), R(t)]^T \in \mathbb{R}_+^3$ of the ordinary differential equation

$$\dot{S} = B - \mu S - \beta IS \quad (22a)$$

$$\dot{I} = \beta IS - \gamma I - \mu I \quad (22b)$$

$$\dot{R} = \gamma I - \mu R \quad (22c)$$

defined for any $[S(0), I(0), R(0)]^T \in \mathbb{R}_+^3$ and any measurable and locally essentially bounded function $B : \mathbb{R}_+ \rightarrow \mathbb{R}_+$. The variable $S(t)$ determines the (continuum) number of susceptible, $I(t)$ is the number of infectious, while $R(t)$ is of people recovered with immunity. $B(t)$ is the newborn rate. The positive number $\beta, \gamma$ and $\mu$ are parameters describing the contact rate, the recovery rate and the death late, respectively. The equation (22) is referred to as the (classic) SIR epidemic model. S-system (22a) and R-system (22c) are ISS with respect to the input $[B, I]^T$ and the input $I$, respectively. In fact, the positive variables $S$ and $R$ by themselves are ISS Lyapunov functions, due to the definition (4). The ISS property is also clear since R-system (22c) is linear, and S-system (22a) is bounded from above by the solution of the linear system $\dot{S} = B - \mu S$. The two linear systems are asymptotically stable. By contrast, due to the bilinear term $\beta IS$, I-system (22b) is not ISS with respect to the input $S$ since (22b) generates unbounded $I(t)$ for any constant input $S > (\gamma + \mu)/\beta$. I-system (22b) is Strong iISS since $V_I(I) = \log(1 + I)$ yields

$$\dot{V_I} \leq -\frac{(\gamma + \mu)I}{1 + I} + \beta S.$$ 

Hence, the SIR model (22) is a cascade consisting of an ISS system, an Strong iISS system and an ISS system. The argument of iISS cascade analysis [8, 28–31] can show that the SIR model (22) is Strong iISS with respect to the input $B$. This stability assessment is not yet very informative, although it holds true. The rest this section demonstrates that the developments in Sections III and IV improve the stability assessment for capturing discriminative behavior of the spread of infectious diseases.

Theorem 1 establishes that the SIR model (22) is ISS, which is “stronger” than Strong iISS, although the SIR model involves I-system which is not ISS. In fact, the model (22) satisfies (6) and (8) with

$$\ell_{i+1} = \ell_i + 1, \quad \beta_i(s) = \mu s, \quad i = 1, 2, 3. \quad (23)$$

These parameters satisfy (9) and (10), and yield $\lambda_1 = \lambda_2 = \lambda_3 = 1$. Theorem 1 gives the total number $N(t) := S(t) + I(t) + R(t)$.
For any constant $B$, the convergence of $x(t)$ to $S$ is satisfied along the solution $x(t)$ of (22). The above inequality implies
\[ \lim_{t \to \infty} N(t) = \frac{B}{\mu} \tag{25} \]
for any constant $B \in \mathbb{R}_+$. If $B$ is not constant, we have the asymptotic gain property
\[ \limsup_{t \to \infty} N(t) \leq \frac{1}{\mu} \text{ess sup}_{t \in \mathbb{R}_+} B(t). \tag{26} \]

SI-system consisting of (22a) and (22b) is ISS with respect to the input $B$ since defining the sum $V_U(x_U(t)) = S(t) + I(t)$ yields
\[ \dot{V}_U = -\mu V_U - \gamma I + B \]
for $x_U = [S, I]^T$. This confirms (15) with $\sigma_U(s) = \mu s$ and $\sigma_U(s) = s$. I-system defined by (22b) fulfills (19) with $x_L = I$ and
\[ H := \frac{\gamma + \mu}{\beta} \tag{27} \]
since $S \leq V_U(x_U)$. Recall that ISS of the entire model (22) implies iISS of (22). Hence, Proposition 1 with $Q = \mu H$ guarantees
\[ \text{ess sup}_{t \in \mathbb{R}_+} B(t) < \mu H \Rightarrow \lim_{t \to \infty} I(t) = 0. \tag{28} \]
The convergence of $I$ to zero implies $\lim_{t \to \infty} R(t) = 0$ since (22b) is ISS. Indeed, it is a stable linear system. Thus
\[ \text{ess sup}_{t \in \mathbb{R}_+} B(t) < \mu H \Rightarrow \lim_{t \to \infty} I(t) = \lim_{t \to \infty} R(t) = 0. \tag{29} \]
For any constant $B \in \mathbb{R}_+$, by virtue of (25) or (22a), we arrive at
\[ B < \mu H \Rightarrow \lim_{t \to \infty} x(t) = \left[ \frac{B}{\mu}, 0, 0 \right]^T \tag{30} \]
As Proposition 1 is applied in the above analysis, regarding $S$ as a parameter, I-system has a bifurcation point at $S = H$. The origin $I = 0$ is an unstable equilibrium if $S > H$. As explained in Remark 4, $I(t)$ increases until $S(t) \leq H$. It is not a possibility any more since it is confirmed that I-system is not ISS. The growth phase occurs. In the case of $B < \mu H$ and $S(0) > H$, if $I(0) > 0$, the infectious $I(t)$ peaks before converging to zero. The smaller $B$ and the larger $(\gamma + \mu)/\beta$ are, the shorter the time to the peak is. The larger $\mu$ and the smaller $\beta$ are, the smaller the increase rate of $I$ in the growth phase is.

Typical responses of the SIR model (22) are shown in Fig. 1 and Fig. 2 for $\beta = 0.0002$, $\mu = 0.015$ and $\gamma = 0.032$ with $S(0) = 700$, $I(0) = 200$ and $R(0) = 70$. For a general newborn rate $B$, the SIR model (22) is ISS. It means that the disease can remain as endemic. That is, the infectious population $I(t)$ is bounded, but it can become very large, and $\lim_{t \to \infty} I(t) > 0$ can hold. Since I-system is Strong iISS and it is not ISS, the infectious $I(t)$ starts with an growth phase unless the initial susceptible population is below the threshold $H = 235$. The infectious population $I(t)$ never decreases to zero if the newborn rate $B$ is above the threshold $\mu H = 3.525$ (Fig. 1). If the newborn rate $B$ does not exceed the threshold, the convergence of $I(t)$ to zero is guaranteed, and the disease is eradicated (Fig. 2). This bifurcation is the central feature of the SIR model (22).

In mathematical epidemiology, for constant $B \in \mathbb{R}_+$, the value
\[ R_0 := \frac{\beta B}{\mu(\gamma + \mu)} = \frac{B}{\mu H} \tag{31} \]
is called the basic reproduction number. Solving the simultaneous equation of $S = 0$, $I = 0$ and $R = 0$ in (22) with constant $B \in \mathbb{R}_+$ gives the steady-state value in (30) and
\[ R_0 \geq 1 \Rightarrow x_e = \left[ H, \frac{\mu (R_0 - 1)}{\beta}, \frac{\gamma (R_0 - 1)}{\beta} \right]^T. \tag{32} \]
The steady-state value in (30) is called the disease-free equilibrium, while $x_e$ in (32) is called the endemic equilibrium. Since $x(t) \in \mathbb{R}_+$, the endemic equilibrium exists only if $R_0 \geq 1$. For $R_0 = 1$, the endemic equilibrium is identical with the disease-free equilibrium. The endemic equilibrium is consistent with (25) since the definition of $R_0$ yields
\[ H + \frac{\mu (R_0 - 1)}{\beta} + \frac{\gamma (R_0 - 1)}{\beta} = \frac{(\gamma + \mu) R_0}{\beta} = \frac{B}{\mu}. \tag{33} \]
Recall that the entire SIR model (22) and SI-systems are ISS. Since iISS of I-system which is not ISS accumulates the amount $S(t) - H$, there exists an unbounded increasing sequence $\{t_i\}_{i \in \{0, 1, 2, \ldots\}}$ in $\mathbb{R}_+$ such that
\[ \forall x(0) \in \mathbb{R}_+ \setminus \{I(0) > 0\} \lim_{t \to \infty} x_2(t_i) = x_{e, 2} \tag{34} \]
if $R_0 > 1$ for constant $B \in \mathbb{R}_+$, where $x_e = [x_{e, 1}, x_{e, 2}, x_{e, 3}]^T$.

VI. SEIS MODEL

Consider $x(t) := [S(t), E(t), I(t)]^T \in \mathbb{R}_+^3$ governed by
\begin{align*}
\dot{S} & = B - \mu S - \beta IS + \gamma I \tag{35a} \\
\dot{E} & = \beta IS - \epsilon E - \mu E \tag{35b} \\
\dot{I} & = \epsilon E - \gamma I - \mu I \tag{35c}
\end{align*}
with $[S(0), E(0), I(0)]^T \in \mathbb{R}^3_+$ and $B : \mathbb{R}_+ \rightarrow \mathbb{R}_+$. The equation (35) is referred to as the SEIS model [18]. The SEIS model is known to be useful for describing diseases which have non-negligible incubation periods. The variable $E$ represents the (continuum) number of infected individuals who are not yet infectious. The SEIS model also considers infections which do not give long lasting immunity, and recovered individuals become susceptible again. As seen in (35), the short immunity forms a circle of length 3, which the SIR model does not have.

The SEIS model (35) satisfies (6) and (8) with (23). Conditions (9) and (10) are satisfied. Thus Theorem 1 establishes ISS of the SEIS model (35) with respect to the input $B$, and an ISS Lyapunov function is obtained as (11) with $\lambda_1 = \lambda_2 = \lambda_3 = 1$, i.e., $V(x) = S + E + I =: N$. In fact, properties (24), (25) and (26) are verified.

For $x_U := x = [S, E, I]^T$ and $V_U = V$, property (24) achieves (13) with $\alpha_U(s) = \mu S$ and $\sigma_U(s) = s$. EI-system consisting of (35b) and (35c) is iISS with respect to the input $S$ since the choice $V_{EI} = \log(1 + E + I)$ satisfies

$$V_{EI} \leq -\mu(E + I) \frac{1}{1 + E + I} + \beta S$$

along the solution $[E(t), I(t)]^T$ of EI-system. EI-system is, however, not ISS. EI-system is a Strongly iISS system admitting a zero local ISS-gain. To see this, one can make use of the Lyapunov function proposed in Theorem 1 by regarding a zero local ISS-gain. To see this, one can make use of the Lyapunov function proposed in Theorem 1 by regarding an arbitrarily given $a$ for an arbitrarily given (8) with the Lyapunov function proposed in Theorem 1 by regarding a zero local ISS-gain. To see this, one can make use of the Lyapunov function proposed in Theorem 1 by regarding an arbitrarily given $a$ for an arbitrarily given (8) with the Lyapunov function proposed in Theorem 1 by regarding a zero local ISS-gain.

$$\ell_{1,2} = \frac{\beta S^2}{a(\gamma + \mu)}, \quad \ell_{2,1} = \frac{\epsilon}{a(\epsilon + \mu)}$$

$$\beta_1(s) = (1-a)(\epsilon + \mu)s, \quad \beta_2(s) = (1-a)(\gamma + \mu)s$$

for an arbitrarily given $a \in (0, 1)$. Defining $V_L(x_L)$ for $x_L = [E, I]^T$ as in (11) and (12) gives

$$V_L(x_L) = E + \lambda_2 I, \quad \lambda_2 = \sqrt{\frac{\beta S^2(\epsilon + \mu)}{(\gamma + \mu)\epsilon}}.$$
I-system is zero for the input sup systems satisfy (19). Thus, Proposition 1 establishes

\[ \beta \text{ISS with respect to the input } \alpha \text{ the ultimate bounds (25) and (26) via (24). Property (18) holds } \]

which is called the MSIR model \([3], [32]\). The variable \(M\) represents delay in becoming susceptible due to the maternally derived immunity. The analysis of the MSIR model is almost the same as that of the SIR model. With

\[ \ell_{i+1} = \ell_{i, i+1} = 1, \beta_i(s) = \mu s, i = 1, 2, 3, 4, \quad (44) \]

Theorem 1 assures that the function \(N(t) := M(t) + S(t) + I(t) + R(t)\) proves ISS of (43), and the ultimate bounds (25) and (26) via (24). Thus, the choices \(V_U(x) = N\) and \(x = x_U\) give (18) with \(\alpha_U(s) = \mu s\) and \(\sigma_U(s) = s\). Because of the bilinear term \(\beta IS\), I-system in (43) is not ISS, but Strongly iISS. Thus, the variable \(I(t)\) increases until \(S(t) < H\), where the bifurcation point \(H\) is defined as (27). The ISS gain of I-system is zero for the input sup \(S(t) < H\). In fact, I-system satisfies (19). Thus, Proposition 1 establishes

\[ B < \mu H \Rightarrow \lim_{t \to \infty} x(t) = \left[ \frac{B}{\mu}, 0, 0, 0 \right]^T \quad (45) \]

for the MSIR model (43) in the case of constant \(B \in \mathbb{R}_+\).

Finally, the SEIR model consists of

\[
\begin{align*}
\dot{S} &= B - \mu S - \beta IS \quad (46a) \\
\dot{E} &= \beta IS - \gamma E - \mu E \quad (46b) \\
\dot{I} &= \gamma E - \gamma I - \mu I \quad (46c) \\
\dot{R} &= \gamma I - \mu R. \quad (46d)
\end{align*}
\]

Its state vector is \(x(t) := [S(t), E(t), I(t), R(t)]^T \in \mathbb{R}_+^4\). The SEIR model can be analyzed as done for the SIES model. Theorem 1 qualifies \(N(t) := S(t) + E(t) + I(t) + R(t)\) as an ISS Lyapunov function proving ISS of (46), and provides the ultimate bounds (25) and (26) via (24). Property (18) holds with \(\alpha_U(s) = \mu s\) and \(\sigma_U(s) = s\) for \(V_U(x) = N\) and \(x = x_U\). EIR-system consisting of (46a), (46c), and (46d) is Strongly iISS with respect to the input \(S\), although the bilinear term \(\beta IS\) prevents it from being ISS. Using \(V_L(x_L) = \lambda_E E + \lambda_I I + \lambda_R R\) for appropriate \(\lambda_E, \lambda_I, \lambda_R > 0\) given by Theorem 1 one can show that EIR-system is not ISS. The function \(V_L(x_L)\) also shows that EIR-system admits the zero ISS gain for the input sup \(S(t) < H\), where the bifurcation point \(H\) is defined as (27). EIR-system satisfies (19). Therefore, Proposition 1 concludes that the SEIR model (46) satisfies (45) for constant \(B \in \mathbb{R}_+\).

VIII. VACCINATION MODELS

One way of eradicating infectious diseases is to vaccinate newborns. Let the constant \(P \in (0, 1)\) denote the vaccination fraction. Considering a vaccine giving lifelong immunity \([3]\), the SIR model can be modified as

\[
\begin{align*}
\dot{S} &= B(1 - P) - \mu S - \beta IS \quad (47a) \\
\dot{I} &= \beta IS - \gamma I - \mu I \quad (47b) \\
\dot{R} &= \gamma I - \mu R \quad (47c) \\
A &= BP - \mu A. \quad (47d)
\end{align*}
\]

where \(A\) is the number of vaccinated individuals. Since (8) is satisfied with (44). Theorem 1 assures that \(N(t) := S(t) + I(t) + R(t) + A(t)\) is an ISS Lyapunov function for the model (47), and establishes the ultimate bounds (25) and (26) via (24). S-system is ISS with respect to the input \(B\). In fact, property (18) is met with \(V_U(x_U) = S, x_U = S, \alpha_U(s) = \mu s\) and \(\sigma_U(s) = (1 - P)s\). IR system is the same as that of the SIR model. Hence, a bifurcation point \(H\) is obtained as (27). A-system is ISS. The convergence of \(I(t)\) to zero does not imply \(\lim_{t \to \infty} R(t) = 0\). The variable \(R\) reaches its steady state since \(R\)-system is ISS. Indeed, it is a stable linear system. Hence, Proposition 1 guarantees

\[ B(1 - P) < \mu H \Rightarrow \lim_{t \to \infty} x(t) = \left[ \frac{B(1 - P)}{\mu}, 0, 0, \frac{BP}{\mu} \right]^T \quad (48) \]

for any constant \(B \in \mathbb{R}_+\) and \(P \in (0, 1)\). Hence, a vaccination fraction \(P\) which is sufficiently close to 1 can eradicate the disease.

Another way to model the newborn vaccination within the SIR model is

\[
\begin{align*}
\dot{S} &= B(1 - P) - \mu S - \beta IS \quad (49a) \\
\dot{I} &= \beta IS - \gamma I - \mu I \quad (49b) \\
\dot{R} &= \gamma I - \mu R + BP. \quad (49c)
\end{align*}
\]

Assumption (8) is satisfied with (24). Theorem 1 proves ISS of (49) with \(N(t) := S(t) + I(t) + R(t)\), which establishes (25) and (26) via (24). The reminder of the analysis is the same as that of the model (47), except that the convergence of \(I\) to zero does not imply \(\lim_{t \to \infty} R(t) = 0\). Since the scalar \(R\)-system is ISS, it is clear that

\[ B(1 - P) < \mu H \Rightarrow \lim_{t \to \infty} x(t) = \left[ \frac{B(1 - P)}{\mu}, 0, 0, \frac{BP}{\mu} \right]^T \quad (50) \]

for any constant \(B \in \mathbb{R}_+\) and \(P \in (0, 1)\). The same modifications to other disease models in the previous sections can be possible for modeling the newborn vaccination under different assumptions.
vaccination. Their analysis goes in essentially the same as to the one described above for the SIR model.

If non-newborns are vaccinated instead of the newborns, a way to modify the SIR model is

\[ \dot{S} = B - \rho S - \mu S - \beta IS \]
\[ \dot{I} = BIS - \gamma I - \mu I \]
\[ \dot{R} = \gamma I - \mu R \]
\[ \dot{A} = \rho S - \mu A, \]

where the constant \( \rho \in \mathbb{R}_+ \) is the vaccination rate. The analysis is the same as that of except that ISS of S-system with respect to the input \( B \) yields property \( \text{with } V_U(x_U) = S, x_U = S \) for \( \alpha_U(s) = (\rho + \mu)s \) and \( \sigma_U(s) = s \). Hence,

\[ B < (\rho + \mu)H \]
\[ \Rightarrow \lim_{t \to \infty} x(t) = \begin{bmatrix} (B(1-P)) \mu \end{bmatrix}^{\text{T}} \]

for any constant \( B \in \mathbb{R}_+ \) and \( \rho \in \mathbb{R}_+ \). Thus, the disease can be eradicated by a sufficiently high vaccination rate \( \rho \).

Irrespective of \( B < (\rho + \mu)H \), the ultimate bounds and hold, and the model also has the bifurcation point at \( S = H \) given in (27).

IX. CONCLUDING REMARKS

This paper has investigated popular models of infectious diseases from the viewpoint of iISS and ISS. It has been shown that behavior of all the models can be analyzed uniformly in terms of a Lyapunov function of ISS, and a Strongly iISS component which is not globally ISS, but admits a zero local ISS-gain function. The outbreak is caused by the Strongly iISS component which is not ISS. However, the disease is eradicable since the Strongly iISS component possesses zero local ISS-gain which takes effect if a characteristic value is below a threshold. The notions of (i)ISS absorb changes of equilibria, and provide a module-based framework. The analysis of global properties does not require direct and heuristic construction of different Lyapunov functions of the entire network depending on equilibria. This demonstration is the main contribution of this paper. The same procedure and explanation are valid even in the presence of an outer-loop caused by sort-time immunity. The source of the particular iISS component is bilinearity. Indeed, scalar linear systems can never exhibit peaks, the outbreak. Although the bilinearity is the only nonlinearity in the popular simplest models, the theoretical tools presented in this paper approximate a broad class of nonlinearities, such as saturation, non-monotone nonlinearities and others, as long as component models retain appropriate iISS and ISS properties. In fact, the arguments in this paper rely on neither linearity nor particular nonlinearities. Only ISS, iISS and ISS-gain characterizations are utilized.

This paper has not reported any new epidemiologic discoveries. Nevertheless, the systematic treatment is expected to be superior to heuristic approaches in finding control strategies for eradicating or containing the spread of diseases. The new option provided by this paper aims to facilitate the research on control design with global guarantees. It is worth noticing that Lyapunov functions constructed in this paper are weighted sum of populations, which are simpler than logarithmic functions that have been popular in the field of mathematical epidemiology. More importantly, (i)ISS Lyapunov functions constructed in this paper are different from Lyapunov functions in the conventional concept, and the construction of Lyapunov functions does not need preprocessing of equilibria. The vaccination discussed in this paper is open-loop. Interesting future research includes introduction of the (i)ISS framework to closed-loop control design (see, e.g., and references therein).

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