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Global stability for an epidemic model with applications to feline infectious peritonitis and tuberculosis

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A general compartmental model of disease transmission is studied. The generality comes from the fact that new infections may enter any of the infectious classes and that there is an ordering of the infectious classes so that individuals can be permitted (or not) to pass from one class to the next. The model includes staged progression, differential infectivity, and combinations of the two as special cases.

The exact etiology of feline infectious peritonitis and its connection to coronavirus is unclear, with two competing theories – mutation process vs multiple virus strains. We apply the model to each of these theories, showing that in either case, one should expect traditional threshold dynamics. A further application to tuberculosis with multiple progression routes through latency is also presented.

1. Introduction

In this paper, we study a model of infectious disease transmission that is flexible enough to allow for staged progression [3], differential infectivity [6] or some combination of the two. The system also allows for fast and slow progression to infectivity, as is sometimes included in models of tuberculosis [1,8].

An important benefit in being able to study such a general model is that it allows analysis to be performed in the presence of uncertainty in the underlying etiology of a disease, as is the case with feline infectious peritonitis.

Feline coronavirus (FCoV) infection is ubiquitous amongst domestic and feral cats [9]. Cats that are infected with FCoV are usually asymptomatic; for those that are symptomatic, the clinical signs are mild [2].

Feline infectious peritonitis (FIP) is a fatal disease that affects cats and is associated with FCoV infection [9]. Although FCoV infection is common, not all FCoV infected cats develop FIP [9]. Although the exact etiology is not completely understood, there are two theories that are currently being debated amongst biologists [9].

One theory is that once FCoV infection occurs, it has the potential to mutate within the host. After mutation, the result is feline infectious peritonitis virus (FIPV) which then causes FIP [10].

The alternative theory is that there are virulent and avirulent strains of the coronavirus circulating in the feline population [2]. The virulent strain manifests itself as FIPV giving rise to the fatal condition, FIP. The avirulent strain causes mild enteritis and is relatively harmless.

In either case, FIPV itself is not transmitted from cat to cat. Although FIPV can be isolated in feces, it is shed at very low levels [9]. Hence, the main focus of research rests upon investigating the primary FCoV infection, which is readily and commonly transmitted with the potential for FIP.

The mathematical system studied here is presented in Section 2, with preliminary analysis given in Section 3. Mathematical theorems related to global dynamics are stated in Section 4, with the proofs appearing in the appendices. Special cases of global stability for an epidemic model with applications to feline infectious peritonitis and tuberculosis

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The mathematical system studied here is presented in Section 2, with preliminary analysis given in Section 3. Mathematical theorems related to global dynamics are stated in Section 4, with the proofs appearing in the appendices. Special cases of
2. The model

A population is divided into susceptibles $S$ and infectives. The infective population is further divided into $n$ subgroups $I_1, \ldots, I_n$ based on the disease status of the individuals.

All recruitment of new individuals is assumed to be into the susceptible class. Thus, there is no vertical transmission and no immigration of infectives. This recruitment occurs at the constant rate $\Lambda > 0$.

Mass action incidence is assumed, but it is allowed that the different infective classes may have different levels of infectivity. Thus, individuals leave the susceptible class due to infections at rate $\sum_{m=1}^{n} \beta_m S I_m$. We assume that $\beta_m > 0$, for $m = 1, \ldots, n$, and that $\beta_1 + \cdots + \beta_n > 0$. For $j = 1, \ldots, n$, a fraction $q_j$ of the new infections appear in class $I_j$, where $q_j \in [0, 1]$, and $q_1 + \cdots + q_n \leq 1$. (Normally, we would have equality here, but we allow that a fraction of the new infections may result in rapid death, and therefore the sum may be less than one.)

For $j = 1, \ldots, n - 1$, individuals in class $I_j$ may progress to class $I_{j+1}$ with per capita rate coefficient $k_j > 0$. Thus, for those that leave $I_j$ by progressing rather than by dying, the average time spent in $I_j$ before progression occurs is $\frac{1}{k_j} \leq \infty$.

We assume that $q_1 > 0$ and that $q_j + k_{j-1} > 0$ for $j = 2, \ldots, n$. This ensures that there is a mechanism by which individuals can enter each of the infective classes.

The per capita death rate coefficient for susceptibles is $\mu > 0$ and for infective class $I_j$ is $d_j > \mu$, for $j = 1, \ldots, n$. We obtain the following system of ordinary differential equations:

$$\begin{align*}
\frac{dS}{dt} & = \Lambda - \mu S - \sum_{m=1}^{n} \beta_m S I_m, \\
\frac{dI_j}{dt} & = q_j \sum_{m=1}^{n} \beta_m S I_m + k_{j-1}I_{j-1} - (k_j + d_j)I_j, \quad \text{for } j = 1, \ldots, n,
\end{align*}$$

where $k_0 = l_0 = 0$, so that the identically zero term $k_0 l_0$ in the equation for $\frac{dI_1}{dt}$ is permitted for notational convenience.

It is useful, at times, to rewrite Eq. (2.1) in a more concise form. To do this, we define $I = [I_1, \ldots, I_n]^T$, $\Gamma(I) = \sum_{m=1}^{n} \beta_m I_m$, $Q = [q_1, \ldots, q_n]^T$ and

$$M = \begin{bmatrix}
k_1 + d_1 & -k_1 & & \\
-k_1 & k_2 + d_2 & -k_2 & \\
& -k_2 & k_3 + d_3 & \\
& & \ddots & \ddots \\
& & & -k_{n-1} & k_n + d_n
\end{bmatrix}_{n \times n},$$

where each of the omitted entries is zero. We note that $M$ is invertible and that $M^{-1}$ is a non-negative lower triangular matrix [5, Theorem 2.5.3].

Then Eq. (2.1) takes the form

$$\begin{align*}
\frac{dS}{dt} & = \Lambda - \mu S - \Gamma(I), \\
\frac{dI_j}{dt} & = \Gamma(I)Q - MI.
\end{align*}$$

The following transfer diagram describes the flow of individuals between the compartments.

![Transfer Diagram](image-url)

Standard theory implies that solutions exist for all time and are unique. Let $D \subseteq \mathbb{R}_{>0}^{n+1}$ be defined by $D = \{(S, I_1, \ldots, I_n) \in \mathbb{R}_{>0}^{n+1} : S + I_1 + \cdots + I_n \leq \frac{\Lambda}{\mu} \}$. 

**Proposition 2.1.** The set \( D \) is attracting and positively invariant.

**Proof.** First, we note that the vector field defined by Eq. (2.1) is smooth and so solutions are unique. Furthermore, since \( \gamma_2 \mid_{S=0} > 0 \) and \( \gamma_1 \mid_{U=0} \geq 0 \) within \( \mathbb{R}^{n+1} \). **Proposition 2.1** of [4] implies the non-negative orthant is positively invariant.

Now, consider the total population \( T = S + \sum_{i=1}^{n} I_i \). Then \( \frac{d}{dt} T = \Lambda - \mu S - \sum_{i=1}^{n} d_i I_i \leq \Lambda - \mu T \). This has two implications. First, \( \limsup_{t \to +\infty} T(t) \leq \frac{\Lambda}{\mu} \) and so \( D \) is attracting. Second, if \( T(t_0) \leq \frac{\Lambda}{\mu} \) for some \( t_0 \in \mathbb{R} \), then \( T(t) \leq \frac{\Lambda}{\mu} \) for all \( t \geq t_0 \) and so \( D \) is positively invariant. \( \square \)

Henceforth, we assume that semi-trajectories lie in the set \( D \).

### 3. Equilibria and the basic reproduction number

We begin by finding disease-free equilibria; that is, equilibria for which \( \Gamma(\bar{I}) \) is zero. Eq. (2.2) dictates that the disease-free equilibrium \( X^0 \) is unique and is given by

\[
X^0 = \left( \bar{S}, \bar{I} \right) = \left( \frac{\Lambda}{\mu} \bar{0} \right),
\]

where \( \bar{0} \in \mathbb{R}^n \) is the zero vector.

We now calculate the basic reproduction number \( R_0 \) using the next generation method of [11] and the FV-notation found there. In that notation, we have

\[
\mathcal{F} = \mathcal{S} \mathcal{I} \mathcal{Q} \quad \text{and} \quad \mathcal{V} = M L.
\]

Then, by defining the row vector \( \bar{\beta} = [\beta_1, \ldots, \beta_n] \), we have

\[
F = \frac{d\mathcal{F}}{dt} (X^0) = \frac{\Lambda}{\mu} \bar{Q} \bar{\beta} \quad \text{and} \quad V = \frac{d\mathcal{V}}{dt} (X^0) = M.
\]

We note that \( Q \bar{\beta} \) is an \( n \times n \) matrix. Following [11], and using \( \rho \) to denote the spectral radius, we have

\[
R_0 = \rho \left( \mathcal{F} \mathcal{V}^{-1} \right) = \rho \left( \frac{\Lambda}{\mu} \bar{Q} \bar{\beta} M^{-1} \right).
\]

Note that \( F \) has rank one and therefore \( \mathcal{F} \mathcal{V}^{-1} \) also has rank one. Thus, all but one of the eigenvalues of \( \mathcal{F} \mathcal{V}^{-1} \) are zero, and the remaining eigenvalue is equal to the trace. Denote the \( (i,j) \) entry of \( M^{-1} \) by \( m_{ij} \). Then,

\[
R_0 = \text{trace} \left( \frac{\Lambda}{\mu} \bar{Q} \bar{\beta} M^{-1} \right) = \frac{\Lambda}{\mu} \sum_{j=1}^{n} q_j \beta_j m_{ij} = \frac{\Lambda}{\mu} \sum_{i=1}^{n} \beta_i (M^{-1} \bar{Q})_i = \frac{\Lambda}{\mu} \bar{\beta} M^{-1} \bar{Q}
\]

and therefore

\[
R_0 = \bar{S} \Gamma \left( M^{-1} \bar{Q} \right).
\]

We note again that \( M^{-1} \) is a non-negative lower triangular matrix. In fact, for \( i, j \in 1, \ldots, n \), the \( (i,j) \) entry of \( M^{-1} \) satisfies

\[
M_{ij}^{-1} = \begin{cases} 0 & \text{if } i < j, \\ \frac{1}{k_i + dq_i} & \text{if } i = j, \\ \frac{k_i k_j}{(k_i - dq_i)} & \text{if } i > j. \end{cases}
\]

Thus, we may write \( R_0 \) as

\[
R_0 = \frac{\Lambda}{\mu} \sum_{i=1}^{n} \beta_i \frac{k_i \cdots k_{i-1}}{(k_i + dq_i) \cdots (k_i - dq_i)} q_i + \cdots + \frac{k_{i-1}}{k_{i-1} + dq_{i-1}} q_{i-1} + q_i.
\]  

(3.1)

Next, we determine equilibria for which \( \Gamma(\bar{I}) \) is non-zero, called endemic equilibria. Denote such an equilibrium by \( X^* = (S^*, I^*) \), where \( I^* = [I_1^*, \ldots, I_n^*]^T \), and let \( \Gamma^* = \Gamma(I^*) \).

Solving \( \frac{d}{dt} X^* = 0 \), we find

\[
\Lambda - \mu S = S^* \Gamma^*.
\]  

(3.2)

Then, solving \( \frac{d}{dt} \bar{I}^* = 0 \), we find

\[
\bar{I}^* = S^* \Gamma^* M^{-1} \bar{Q} = (\Lambda - \mu S^*) M^{-1} \bar{Q}.
\]  

(3.3)

Substituting this into \( \Gamma^* \) in (3.2), we obtain

\[
\Lambda - \mu S^* = S^* \Gamma^* = S^* \Gamma(I^*) = S^* \Gamma \left( (\Lambda - \mu S^*) M^{-1} \bar{Q} \right).
\]  

(3.4)
One may check that $S^*$ cannot equal $S_0$ (as this would give the disease-free equilibrium), and so $\Lambda - \mu S^*$ is non-zero. Also, $\Gamma$ depends linearly on its vector argument. Thus, (3.4) implies

$$1 = S^* \Gamma \left( M^{-1} Q \right),$$

which uniquely determines $S^*$ as $S^* = \frac{1}{\Gamma (M^{-1} Q)} = S_0$. Then, $\tilde{I}$ is determined by (3.3). Thus, the endemic equilibrium is unique and is given by

$$X^* = (S^*, \tilde{I}) = \left( \frac{S_0}{R_0} \Lambda \left( 1 - \frac{1}{R_0} \right) M^{-1} Q \right).$$

Using [11, Theorem 2], to obtain the local stability of $X^0$ as a function of $R_0$, we now have the following result.

**Theorem 3.1.** If $R_0 < 1$, then the $X^0$ is the only equilibrium and is locally asymptotically stable. If $R_0 > 1$, then the disease-free equilibrium $X^0$ is unstable, and there exists a unique endemic equilibrium $X^*$.

### 4. Global stability

In this section, we state the main mathematical results of the paper. Essentially, these results state that solutions of the system approach the disease-free equilibrium if $R_0 \leq 1$, and approach the endemic equilibrium if $R_0 > 1$. The proofs appear in Appendix A and Appendix B.

**Theorem 4.1.** If $R_0 \leq 1$, then the disease-free equilibrium $X^0$ is globally asymptotically stable in $\mathbb{R}^{n+1}$.

**Theorem 4.2.** If $R_0 > 1$, then the endemic equilibrium $X^*$ is globally asymptotically stable amongst solutions for which the disease is initially present (i.e. $I(0) \neq 0$).

### 5. Special cases

In this section we present several special cases of Eq. (2.1).

#### 5.1. Staged progression

The results described in earlier sections of the paper apply to the case where $q_1 = 1, q_2 = \cdots = q_n = 0$ and $k_1, \ldots, k_{n-1} > 0$. This reduces Eq. (2.1) to the following staged progression system:

$$\begin{align*}
\frac{dS}{dt} &= \Lambda - \mu S - \sum_{m=1}^{n} \beta_m S I_m, \\
\frac{dI_1}{dt} &= \sum_{m=1}^{n} \beta_m S I_m - (k_1 + d_1) I_1, \\
\frac{dI_j}{dt} &= k_{j-1} I_{j-1} - (k_j + d_j) I_j, \quad \text{for } j = 2, \ldots, n,
\end{align*}$$

which was thoroughly studied in [3,6]. The transfer diagram is:

\[ \begin{array}{cccccccc}
\Lambda & \rightarrow & S & \rightarrow & I_1 & \rightarrow & I_2 & \rightarrow & \cdots & \rightarrow & I_n \\
\downarrow & & \mu S & \downarrow & d_1 I_1 & \downarrow & d_2 I_2 & \downarrow & \cdots & \downarrow & d_n I_n \\
& & k_1 I_1 & & k_2 I_2 & & \cdots & & k_{n-1} I_{n-1} & & k_n I_n
\end{array} \]

In this case, an infected individual has the potential to pass through a sequence of infectious classes. Each progression corresponds to a change in infectivity or in mortality. Theorem 4.1 and Theorem 4.2 imply that the global dynamics are completely determined by the basic reproduction number.

$$R_0 = \frac{\Lambda}{\mu} \left[ \frac{\beta_1}{k_1 + d_1} + \frac{k_1}{k_1 + d_1} + \frac{\beta_2}{k_2 + d_2} + \cdots + \frac{k_1 \cdots k_{n-1}}{(k_1 + d_1)(k_2 + d_2) \cdots (k_{n-1} + d_{n-1})} \frac{\beta_n}{k_n + d_n} \right].$$

If $R_0 < 1$, then the disease dies out of the population. If $R_0 > 1$, then the system tends to the endemic equilibrium.
5.2. Differential infectivity

Next, we consider the case where \( k_1 = \cdots = k_n = 0 \) and \( q_1, \ldots, q_n > 0 \). Then Eq. (2.1) reduces to the following differential infectivity system:

\[
\frac{dS}{dt} = \Lambda - \mu S - \sum_{m=1}^{n} \beta_m S I_m
\]
\[
\frac{dI_j}{dt} = q_j \sum_{m=1}^{n} \beta_m S I_m - d_j I_j, \quad \text{for } j = 1, \ldots, n,
\]

which was considered in [6]. The transfer diagram is:

In this case, upon infection, an individual randomly enters one of the infectious classes. The interpretation here, is that different people have different reactions to the same infection. Theorem 4.1 and Theorem 4.2 imply that the global dynamics are completely determined by the basic reproduction number

\[
R_0 = \frac{\Lambda}{\mu} \sum_{m=1}^{n} \beta_m q_m.
\]

If \( R_0 < 1 \), then the disease dies out of the population. If \( R_0 > 1 \), then the system tends to the endemic equilibrium.

5.3. Differential infectivity and staged progression

Next, we simultaneously include differential infectivity and staged progression, as was considered in [6]. Here, upon infection, an individual randomly enters one of \( l \) infectious classes \( I_{i_1}, \ldots, I_{i_l} \), based on the individuals reaction to the pathogen. Then, the individual progresses through a sequence \( I_{j_1}, \ldots, I_{j_{p_j}} \) of infectious classes where each progression marks a change in infectiousness or mortality.

The transfer diagram for this case follows, however the arrows related to mortality have been omitted in order to present a clearer picture:
After relabelling, the system of differential equations associated with this transfer diagram can be written in the form of

\[ Eq. (2.1). \]

(The key to the relabelling is to order the infectious classes by concatenating the rows in the transfer diagram.) Theorem 4.1 and Theorem 4.2 imply that the global dynamics are completely determined by the basic reproduction number, which can be calculated by using Eq. (3.1). If \( R_0 < 1 \), then the disease dies out of the population. If \( R_0 > 1 \), then the system tends to the endemic equilibrium.

6. Applications

In this section we apply our main model to feline infectious peritonitis and to tuberculosis.

6.1. Feline infectious peritonitis – first theory: mutation

We now apply the original model to each of the two theories of the etiology of feline infectious peritonitis. According to the first theory, all transmission is of the harmless coronavirus FCoV. Then, there is the potential that the virus will mutate into FIPV within the host, causing FIP. FIPV is not directly transmitted between cats.

Upon infection with the coronavirus, cats enter the first infectious class \( I_1 \). The progression rate from \( I_1 \) to \( I_2 \) is \( k_1 \), occurring when the coronavirus mutates into FIPV. Some time later, these cats may develop FIP, thereby progressing into \( I_3 \). This progression from \( I_2 \) to \( I_3 \) happens at rate \( k_2 \).

The mass action coefficient for \( I_1 \) and \( I_2 \) is \( b \). Potentially, cats suffering from FIP shed the coronavirus at a different rate from other infected cats; thus, the mass action coefficient for \( I_3 \) is \( rb \), for some \( r \geq 0 \). Thus, the incidence is

\[ bSI_1 + I_2 + riI_3. \]

For all cats, the non-disease related mortality rate is \( l \); for cats in \( I_3 \), there is an additional death rate \( k_3 \). There is a constant flux \( K \) of new cats into \( S \). The system is described by the following differential equation:

\[
\frac{dS}{dt} = \Lambda - \mu S - bSI_1 + I_2 + \sigma I_3, \\
\frac{dI_1}{dt} = bSI_1 + I_2 + \sigma I_3 - (\mu + k_1)I_1, \\
\frac{dI_2}{dt} = k_1I_1 - (\mu + k_2)I_2, \\
\frac{dI_3}{dt} = k_2I_2 - (\mu + k_3)I_3, 
\]

which is a special case of the staged progression model (5.1). The transfer diagram for this case is:

\[
\begin{align*}
\Lambda & \rightarrow S & \rightarrow \beta S(I_1 + I_2 + \sigma I_3) & \rightarrow k_1I_1 & \rightarrow k_2I_2 & \rightarrow k_3I_3 \\
\mu S & \rightarrow \mu I_1 & \rightarrow \mu I_2 & \rightarrow \mu I_3 
\end{align*}
\]

The basic reproduction number is

\[ R_0 = \beta \frac{\Lambda}{\mu} \left[ \frac{1}{\mu + k_1} + \frac{k_1}{\mu + k_1} \frac{1}{\mu + k_2} + \frac{k_1}{\mu + k_1} \frac{k_2}{\mu + k_2} \frac{\sigma}{\mu + k_3} \right]. \]

According to Theorem 4.1 and Theorem 4.2, if \( R_0 < 1 \), then the disease dies out of the population, whereas, if \( R_0 > 1 \), then the system tends to the endemic equilibrium.

6.2. Feline infectious peritonitis – second theory: virulent and avirulent strains

According to this theory, there are virulent and avirulent strains of the coronavirus circulating within the population. We assume that there is no cross-immunity between the avirulent strain and the virulent strain. Thus, the avirulent strain is not explicitly included in the model. Instead, we focus only on infections with the virulent strain, which we will refer to as FIPV.

We allow that not all infections with FIPV necessarily lead to FIP. Rather, a fraction \( q \) of individuals that are newly infected with FIPV enter infectious class \( I_1 \) and FIP does not occur. The remaining fraction \( (1 - q) \) enter infectious class \( I_2 \) and FIP does occur. The mass action incidence coefficients for groups \( I_1 \) and \( I_2 \) are \( \beta_1 \) and \( \beta_2 \), respectively, so that the total incidence rate is \( \beta_1S + \beta_2S + I_2 \).

For all cats, the non-disease related mortality rate is \( \mu \); for cats in \( I_3 \), there is an additional death rate \( k \). There is a constant flux \( \Lambda \) of new cats into \( S \). The system is described by the following differential equation:
\[
\begin{align*}
\frac{dS}{dt} &= \Lambda - \mu S - (\beta_1 S I_1 + \beta_2 S I_2), \\
\frac{dI_1}{dt} &= q(\beta_1 S I_1 + \beta_2 S I_2) - \mu I_1, \\
\frac{dI_2}{dt} &= (1-q)(\beta_1 S I_1 + \beta_2 S I_2) - (\mu + k)I_2,
\end{align*}
\]

which is a special case of the differential infectivity model (5.2). The transfer diagram for this case is:

![Transfer Diagram](image)

The basic reproduction number is
\[
R_0 = \frac{\Lambda}{\mu} \left( \frac{q \beta_1}{\mu} + (1-q) \frac{\beta_2}{\mu+k} \right).
\]

According to Theorem 4.1 and Theorem 4.2, if \( R_0 < 1 \), then the disease dies out of the population, whereas, if \( R_0 > 1 \), then the system tends to the endemic equilibrium.

### 6.3. Tuberculosis with different progression routes

It is well-known [1] that tuberculosis can remain latent within an individual for years before becoming active. Upon activation two things happen; individuals become capable of transmitting the infection to susceptibles and they begin to suffer the deleterious effects of the disease, including a disease-induced mortality rate. The activation rate changes over time [1] and so models that allow different progression routes and rates to active tuberculosis are of interest.

This can be done by having slow progressors pass through latent or exposed classes before becoming infectious, while allowing others to bypass some or all of the exposed classes. Thus, we consider \( \beta_1 = \cdots = \beta_{n-1} = 0 \), \( \beta_n = \beta > 0 \) and \( k_1, \ldots, k_{n-1} > 0 \). We also relabel the compartments with \( (S, E_1, \ldots, E_{n-1}, I) = (S_1, I_1, \ldots, I_{n-1}, I_n) \). Then Eq. (2.1) becomes

\[
\begin{align*}
\frac{dS}{dt} &= \Lambda - \mu S - \beta SI, \\
\frac{dE_j}{dt} &= q_j \beta SI + k_{j-1} E_{j-1} - (k_j + d_j)E_j, \quad \text{for } j = 1, \ldots, n-1, \\
\frac{dI}{dt} &= q_n \beta SI + k_{n-1} E_{n-1} - (k_n + d_n)I,
\end{align*}
\]

where \( k_0 = E_0 = 0 \), so that the identically zero term \( k_0 E_0 \) in the equation for \( \frac{dE}{dt} \) is permitted for notational convenience. The transfer diagram is:

![Transfer Diagram](image)

The special case where there is only one exposed class, that is, an SEI-model with fast and slow progression was presented and studied in [1] with the global analysis completed in [7]. As presented here, the system is a special case of the one studied
in [8], Theorem 4.1 and Theorem 4.2 imply that the global dynamics are completely determined by the basic reproduction number

\[ R_0 = \frac{\Lambda}{\mu} \frac{\beta}{k_n + d_n} \left[ \frac{k_1 \cdots k_{n-1}}{(k_1 + d_1) \cdots (k_{n-1} + d_{n-1})} q_1 + \cdots + \frac{k_{n-1}}{k_{n-1} + d_{n-1}} q_{n-1} + q_n \right]. \]

If \( R_0 < 1 \), then the disease dies out of the population. If \( R_0 > 1 \), then the system tends to the endemic equilibrium.

7. Discussion

In Section 5, several special cases of Eq. (2.1) were presented, including the three classic progression structures: staged progression, differential infectivity, and the combination of the two. Our flexible model and the accompanying analysis show that the traditional threshold dynamics apply. In order to control the spread of an infectious disease for which one of these paradigms applies, one can study the effect that varying certain parameters has on \( R_0 \). If \( R_0 \) can be reduced below one, then an endemic disease can be eradicated. Disease eradication, of course, is a lofty goal and may not always be feasible. Fortunately, the model also provides a platform for performing analysis of how the level of endemicity depends on the various parameters.

In Section 6, the main model is applied to two transmission theories of feline infectious peritonitis (FIP) and to tuberculosis. The first application to FIP relates to the in-host mutation theory, where coronavirus infections have the potential to cause disease progression, differential infectivity, and the combination of the two. Our flexible model and the accompanying analysis show that the accurate representation of the distribution of waiting times is important.

Appendix A. Proof of Theorem 4.1

**Proof.** Suppose \( R_0 \leq 1 \). Consider the Lyapunov function

\[ W = \beta M^{-1} I \]

on the set \( D \). Then

\[ \frac{dW}{dt} = \beta M^{-1} \frac{dI}{dt} = \beta M^{-1} (\Gamma(I)Q - MI) = \Gamma(I)\beta M^{-1}Q - \beta I. \]

Recalling that \( \Gamma(I) = \beta I \), we have

\[ \frac{dW}{dt} = (S\beta M^{-1}Q - 1)\beta I = (S\frac{\mu}{\Lambda} R_0 - 1)\beta I \leq (R_0 - 1)\beta I \leq 0, \]

with equality only if \( I = 0 \). (Equality is also obtained if \( S = \frac{\Lambda}{\mu} \) but in the set \( D \), this also implies \( I = 0 \).) By LaSalle’s Extension, solutions converge to the largest invariant subset of the set on which \( \frac{dW}{dt} = 0 \). The only such invariant subset that is contained in \( D \) is the set consisting of only the disease-free equilibrium, and so \( \{X^0\} \) is the attractor, and is globally asymptotically stable. \( \square \)

Appendix B. Proof of Theorem 4.2

**Proof.** Suppose \( R_0 > 1 \). For any initial condition in \( D \), the solution satisfies \( S(t) > 0 \) for all \( t > 0 \). Then, since \( I(0) \neq 0 \), we have \( \Gamma(I) > 0 \) for \( t > 0 \). Then, since \( q_i + k_{i-1} > 0 \), it follows that \( I_i(t) > 0 \) for \( t > 0 \). Therefore, the Lyapunov function \( V \), defined below, can be evaluated along solutions, for \( t > 0 \), even if the initial condition has some variables equal to zero.

Define \( g : \mathbb{R}_{>0} \rightarrow \mathbb{R}_{>0} \) by
\[ g(u) = u - 1 - \ln u. \]

Note that \( g(u) \geq 0 \) for all \( u > 0 \), with a strict global minimum of \( g(1) = 0 \). Let

\[ V_S = g \left( \frac{S}{S} \right) \quad \text{and} \quad V_j = g \left( \frac{I_j}{I_j} \right). \]

for \( j = 1, \ldots, n \). Consider the Lyapunov function

\[ V = V_S + \sum_{j=1}^{n} \alpha_j V_j, \]

where \( \alpha_1, \ldots, \alpha_n \) are chosen so that

\[ \frac{\alpha_1}{\alpha_1} S \quad \text{and} \quad \frac{\alpha_n}{\alpha_n} S \]

is non-positive. To do this, we first find \( \alpha_1, \ldots, \alpha_n \). Using (B.2), we find

\[ \frac{dV}{dt} = \frac{\alpha_1}{\alpha_1} \left( \frac{S}{S} \right) \left( 1 - \frac{S}{S} \right) \left( A - \mu S - \sum_{m=1}^{n} \beta_m S l_m \right) = \frac{1}{S} \left( 1 - \frac{S}{S} \right) \left( \frac{\mu S - S}{S} + \sum_{m=1}^{n} \beta_m \left( S l_m - S l_m \right) \right) \]

\[ = -\mu \left( \frac{S - S}{S^2} \right) - \sum_{m=1}^{n} \beta_m l_m \left( 1 - \frac{S l_m}{S l_m} + \frac{S l_m}{S l_m} \right). \]

We now introduce the notation

\[ x = \frac{S}{S} \quad \text{and} \quad y_j = \frac{l_j}{l_j} \quad \text{for} \quad j = 1, \ldots, n. \]

Thus, we have

\[ \frac{dV}{dt} = -\mu \left( \frac{S - S}{S^2} \right) + \sum_{m=1}^{n} \beta_m l_m \left( 1 - x y_m - \frac{1}{x} + y_m \right). \]

Next, using (B.4), we find

\[ \frac{dV}{dt} = \frac{1}{l_j} \left( 1 - \frac{l_j}{l_j} \right) \left( q_j \sum_{m=1}^{n} \beta_m S l_m + k_j l_j - (k_j + d_j) l_j \right) \]

\[ = \frac{1}{l_j} \left( 1 - \frac{l_j}{l_j} \right) \left( q_j \sum_{m=1}^{n} \beta_m S l_m + k_j l_j - \left( q_j \sum_{m=1}^{n} \beta_m S l_m + k_j l_j \right) \right) \]

\[ = \frac{1}{l_j} \left( 1 - \frac{l_j}{l_j} \right) \left( q_j \sum_{m=1}^{n} \beta_m S l_m \left( \frac{S l_m}{S l_m} - l_j \right) + k_j l_j \left( l_j - \frac{l_j}{l_j} \right) \right) \]

\[ = \frac{1}{l_j} \left( q_j \sum_{m=1}^{n} \beta_m S l_m \left( x y_m - y_j - \frac{x y_m}{y_j} + 1 \right) + k_j l_j \left( y_j - y_j \frac{y_j}{y_j} + 1 \right) \right). \]

Combining (B.5) and (B.6), and then regrouping, we obtain
\[
\frac{dV}{dt} = -\mu \frac{(S - S^2)^2}{SS} + \sum_{m=1}^{n} \beta_m I_m^r (1 - xy_m - \frac{1}{x} + y_m) \\
+ \sum_{j=1}^{n} g_j \left( q_j \sum_{m=1}^{n} \beta_m S I_m^r \left( xy_m - y_j - \frac{xy_m}{y_j} + 1 \right) + k_{j-1} I_{j-1} \left( y_{j-1} - y_j - \frac{y_{j-1}}{y_j} + 1 \right) \right) \\
= -\mu \frac{(S - S^2)^2}{SS} + \sum_{m=1}^{n} \beta_m I_m^r \left( 1 - \frac{1}{x} \right) + \sum_{j=1}^{n} g_j \sum_{m=1}^{n} q_j k_{j-1} I_{j-1} \left( 1 - \frac{y_{j-1}}{y_j} \right) \\
+ A \sum_{m=1}^{n} \beta_m I_m^r y_m + \sum_{j=1}^{n} B_j y_j,
\]
(B.7)

where

\[
A = -1 + \sum_{j=1}^{n} g_j q_j S
\]

and

\[
B_j = \beta_j I_j^r + \frac{\gamma_{j+1} k_{j+1}}{I_j^r} - \frac{\gamma_j}{I_j^r} k_{j-1} I_{j-1}^r - \frac{\gamma_j}{I_j^r} q_j \sum_{m=1}^{n} \beta_m S I_m^r,
\]
(B.8)

where \(\gamma_{j+1} k_{j+1}\) and \(\gamma_j k_{j-1}\) are both zero.

Using (B.3) to introduce \(k_j + d_j\) into (B.8), factoring out \(I_j^r\), and then using the \(j\)th column of (B.1), we find

\[
B_j = \beta_j I_j^r + \frac{\gamma_{j+1} k_{j+1}}{I_j^r} - \frac{\gamma_j}{I_j^r} (k_j + d_j) I_j^r = \left( \beta_j + \frac{\gamma_{j+1}}{I_j^r} k_{j+1} - \frac{\gamma_j}{I_j^r} (k_j + d_j) \right) I_j^r = 0,
\]

for \(j = 1, \ldots, n\). First, this tells us that the final sum \(\sum B_j y_j\) in (B.7) consists of terms that are all zero. Additionally, summing the equations given by (B.8) yields

\[
0 = \sum_{j=1}^{n} B_j = \sum_{j=1}^{n} \beta_j I_j^r - \sum_{j=1}^{n} g_j q_j \sum_{m=1}^{n} \beta_m S I_m^r = \sum_{m=1}^{n} \beta_m I_m^r \left( 1 - \sum_{j=1}^{n} g_j q_j S \right) = -A \sum_{m=1}^{n} \beta_m I_m^r,
\]

and therefore

\[
A = 0.
\]

Thus, Eq. (B.7) becomes

\[
\frac{dV}{dt} = -\mu \frac{(S - S^2)^2}{SS} + \sum_{m=1}^{n} \beta_m I_m^r \left( 1 - \frac{1}{x} + \ln \frac{1}{x} - \ln \frac{1}{x} \right) + \sum_{j=1}^{n} g_j q_j k_{j-1} I_{j-1} \left( 1 - \frac{y_{j-1}}{y_j} - \ln \frac{y_{j-1}}{y_j} \right) \\
+ \sum_{j=1}^{n} g_j \sum_{m=1}^{n} q_j k_{j-1} I_{j-1} \left( 1 - \frac{y_{j-1}}{y_j} \right) \\
= L - \mu \frac{(S - S^2)^2}{SS} + \sum_{m=1}^{n} \beta_m I_m^r \left( \frac{1}{x} - \sum_{j=1}^{n} g_j q_j S \beta_m I_m^r \left( \frac{xy_m}{y_j} - \ln \frac{xy_m}{y_j} - \frac{y_{j-1}}{y_j} \right) \right) \\
+ \sum_{j=1}^{n} g_j k_{j-1} I_{j-1} \left( \frac{y_{j-1}}{y_j} \right),
\]
(B.9)

where

\[
L = \sum_{m=1}^{n} \beta_m I_m^r \ln \frac{1}{x} - \sum_{j=1}^{n} g_j q_j S \beta_m I_m^r \ln \frac{xy_m}{y_j} - \sum_{j=1}^{n} g_j k_{j-1} I_{j-1} \ln \frac{y_{j-1}}{y_j} \\
= \left( 1 - \sum_{j=1}^{n} g_j q_j S \right) \sum_{m=1}^{n} \beta_m I_m^r \ln x + \sum_{j=1}^{n} g_j q_j S \beta_m I_m^r \left( \ln y_j - \ln y_m \right) + \sum_{j=1}^{n} g_j k_{j-1} I_{j-1} \left( \ln y_j - \ln y_{j-1} \right).
\]

The coefficient of \(\ln x\) is a multiple of \(A\) and is therefore zero. Thus,
\[ L = \sum_{j=1}^{n} \left( q_j \sum_{m=1}^{n} \beta_m y_m \ln y_j - \frac{q_j S}{y_j} \beta_m y_m \ln y_m + \sum_{j=1}^{n} q_j^2 k_{j-1} l_{j-1} \ln y_j - \frac{q_j}{y_j} k_{j-1} l_{j-1} \ln y_j \right) \]

Using \( B_j = 0 \), we have
\[ L = \sum_{j=1}^{n} \beta_j l_j \ln y_j - \sum_{j=1}^{n} q_j S \sum_{m=1}^{n} \beta_m y_m \ln y_m = \left( 1 - \sum_{j=1}^{n} q_j S \right) \sum_{m=1}^{n} \beta_m y_m \ln y_m = -A \sum_{m=1}^{n} \beta_m y_m \ln y_m = 0. \]

Thus, (B.9) becomes
\[ \frac{dV}{dt} = -\mu (S - S)^2 + \sum_{m=1}^{n} \beta_m y_m \left( \frac{1}{x} - \sum_{j=1}^{n} q_j S \beta_m y_m g \left( \frac{X_y}{y_j} \right) - \sum_{j=2}^{n} q_j k_{j-1} l_{j-1} \ln y_j \right) \leq 0, \]

with equality only if \( x = 1 \). That is, the set on which \( \frac{dV}{dt} = 0 \) is a subset of \( \mathcal{M}_1 = \{ (S, I) : S = S' \} \). By LaSalle’s Extension, solutions tend to an invariant set \( \mathcal{M} \subseteq \mathcal{M}_1 \). In \( \mathcal{M} \), we have \( S(t) \equiv S' \) and so we must also have \( 0 = \frac{dS}{dt} = A - \mu S' - S' \Gamma(I) \). This can only happen if \( \Gamma(I) = \Gamma(I') \). Thus, within the set \( \mathcal{M} \), Eq. (2.2) yields
\[ \frac{dI}{dt} = S' \Gamma(I') Q - M I. \]

This is a linear system for which all solutions tend to \( I' \). Therefore, the only invariant subset of \( \mathcal{M}_1 \) is the set consisting of solely \( I' \). Thus, all solutions tend to \( I' \). \( \Box \)

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