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Stability and oscillations of multistage SIS models depend on the number of stages

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ABSTRACT

In this paper we consider multistage SIS models of infectious diseases, where infected individuals are passing through infectious stages $I_1, I_2, \ldots I_n$ and then return to the susceptible compartment. First we calculate the basic reproduction number $\mathcal{R}_0$, and prove that the disease dies out for $\mathcal{R}_0 \leq 1$, while a unique endemic equilibrium exists for $\mathcal{R}_0 > 1$. Our main result is that the stability of the endemic equilibrium depends on the number of stages: the endemic equilibrium is always stable when $n \leq 3$, while for any $n > 3$ it can be either stable or unstable, depending on the particular choice of the parameters. We generalize previous stability results for SIRS models as well and point out a mistake in the literature for multistage SEIRS models. Our results have important implications on the discretization of infectious periods with varying infectivity.

1. Introduction

Compartmental models of infectious diseases are based on a partition of the population according to their disease status [1]. One of the simplest approaches is the SIS model, which considers the proportion of the population that are susceptible to (S), or infected with (I) the particular disease. This model is suitable to describe the transmission dynamics of diseases that confer no immunity, such as many bacterial and sexually transmitted diseases. The simplest SIS model is

$$S'(t) = -\beta S(t)I(t) + \gamma I(t),$$
$$I'(t) = \beta S(t)I(t) - \gamma I(t),$$

where β is the transmission rate and γ is the recovery rate. A reasonable extension to make this simplistic model more realistic is to divide the infectious period into stages, following the progression of the disease within the host, given that the infectiousness of an individual may change during the course of infection. Epidemic models with stage structure (see for example [4,6,7,9]) and more general SIS models [2,8,12] have been widely analyzed in the literature. In this paper we investigate the stage progression SIS model

$$S'(t) = b(N(t)) + p_n I_n(t) - \sum_{k=1}^{n} \beta_k I_k(t) S(t) - \mu S(t),$$

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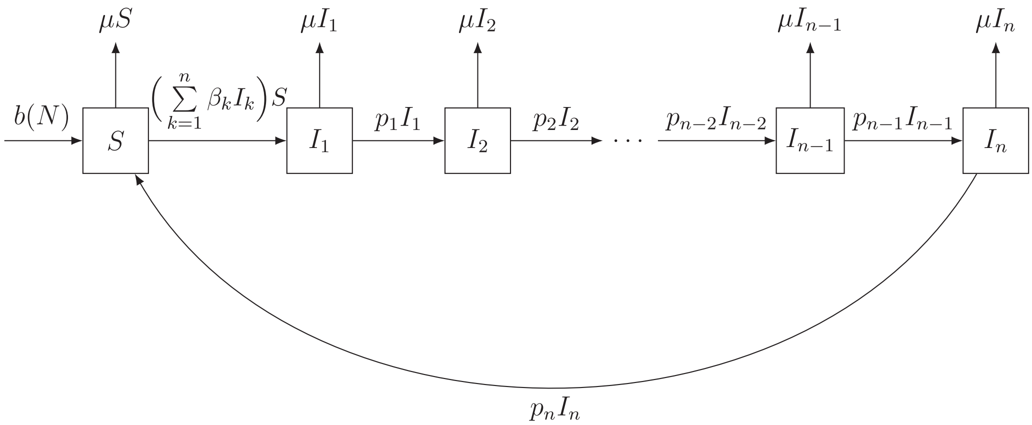

Fig. 1. The transfer diagram of model (1).

$$
\begin{aligned}
I_1'(t) &= \sum_{k=1}^{n} \beta_k I_k(t) S(t) - p_1 I_1(t) - \mu I_1(t),\\
I_2'(t) &= p_1 I_1(t) - p_2 I_2(t) - \mu I_2(t),\\
&\vdots\\
I_n'(t) &= p_{n-1} I_{n-1}(t) - p_n I_n(t) - \mu I_n(t),
\end{aligned}
\tag{1}
$$

which describes the spread of a non-fatal infectious disease in a population with recruitment rate $b(N)$ and natural death rate μ. For simplicity, we will assume $b(N) = \mu N$, hence the total population $N(t) = S(t) + \sum_{j=1}^{n} I_j(t)$ will remain constant. Here, $S = S(t)$ represents the susceptible compartment, $I_1 = I_1(t), I_2 = I_2(t), \ldots, I_n = I_n(t)$ represent the infected compartments corresponding to stages $1, 2, \ldots, n$. We denote by β_i $(i = 1, 2, \ldots, n)$ the disease transmission rates in compartment I_i, and by p_i $(i = 1, 2, \ldots, n)$ the progression rates from disease stage i to $i + 1$, i.e. from compartment I_i to I_{i+1}. We schematically depict the transfer diagram in Fig. 1.

We normalize the constant population to unity ($N = 1$), hence the variables $S, I_1, \ldots, I_n$ represent the proportion of susceptible and infected individuals in the population, therefore we can write

$$
S = 1 - \sum_{k=1}^{n} I_k. \tag{2}
$$

Using (2) and decoupling the S equation, we obtain the n-dimensional system

$$
\begin{aligned}
I_1' &= \sum_{k=1}^{n} \beta_k I_k \left(1 - \sum_{k=1}^{n} I_k\right) - p_1 I_1 - \mu I_1,\\
I_2' &= p_1 I_1 - p_2 I_2 - \mu I_2,\\
&\vdots\\
I_n' &= p_{n-1} I_{n-1} - p_n I_n - \mu I_n.
\end{aligned}
\tag{3}
$$

In the sequel, we analyse system (3) in details.

2. The basic reproduction number and the endemic equilibrium

First we calculate the basic reproduction number $\mathcal{R}_0$ for system (3). This is an important threshold parameter connected to the stability of the disease free equilibrium (DFE) and the existence of the endemic equilibrium (EE) for a large class of epidemic models, see [1] or [3]. Here we use the next generation matrix method for calculating the basic reproduction number, following the notion of [13,15]. We write the system (3) in the form of

$$
\boldsymbol{I}' = \mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I}),
$$

where $\boldsymbol{I} = (I_1, I_2, \ldots I_n)^T$ and

$$
\mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2, \ldots \mathcal{F}_n)
$$

represents the new infections, while

$$\mathcal{V} = (\mathcal{V}_1, \mathcal{V}_2, \dots \mathcal{V}_n)$$

contains the transitions between infected compartments. We linearize (3) at the DFE $(0, 0, \dots, 0)$ to obtain the equation

$$\boldsymbol{I}' = A\boldsymbol{I},$$

where A is the Jacobian matrix. Next, we take the decomposition $A = F - V$, where

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial I_j}(DFE)\right],\ V = \left[\frac{\partial \mathcal{V}_i}{\partial I_j}(DFE)\right].$$

The obtained linearized system is

$$\begin{aligned} I_1' &= \sum_{k=1}^{n} \beta_k I_k - p_1 I_1 - \mu I_1, \\ I_2' &= p_1 I_1 - p_2 I_2 - \mu I_2, \\ &\ \vdots \\ I_n' &= p_{n-1} I_{n-1} - p_n I_n - \mu I_n, \end{aligned}$$

with

$$F = \begin{pmatrix} \beta_1 & \beta_2 & \dots & \beta_n \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{pmatrix}, \quad V = \begin{pmatrix} p_1+\mu & 0 & \dots & 0 & 0 \\ -p_1 & p_2+\mu & \dots & 0 & 0 \\ 0 & -p_2 & \ddots & \vdots & \vdots \\ \vdots & \vdots & \ddots & p_{n-1}+\mu & 0 \\ 0 & 0 & \dots & -p_{n-1} & p_n+\mu \end{pmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is the spectral radius $\rho(FV^{-1})$ of the next generation matrix FV^{-1}. It's easy to see that V^{-1} is a lower-triangular matrix, and all the elements of FV^{-1} are zero, except in its first row. Therefore its spectral radius is the only nonzero eigenvalue, that is

$$\mathcal{R}_0 = \sum_{k=1}^{n} \frac{\beta_k}{p_k+\mu} \left(\prod_{j=1}^{k-1} \frac{p_j}{p_j+\mu} \right). \tag{4}$$

Note that this expression for $\mathcal{R}_0$ matches the biological interpretation: taking a single infected individual, if we multiply the infection rate in stage k, the average time spent in stage k and the probability that the individual survives up to stage k, and sum up for all stages, we obtain (4).

Theorem 2.1. *For system (3), a unique endemic equilibrium* $(I_1^*, I_2^*, \dots I_n^*)$ *(with* $I_k^* > 0$ *for all* $1 \le k \le n$*) exists if and only if* $\mathcal{R}_0 > 1$. *It is given by*

$$I_k^* = \frac{p_{k+1}+\mu}{p_k} \dots \frac{p_n+\mu}{p_{n-1}} \cdot \frac{1-\frac{1}{\mathcal{R}_0}}{Q}, \text{where } Q = 1 + \frac{p_n+\mu}{p_{n-1}} + \dots + \prod_{i=1}^{n-1} \frac{p_{i+1}+\mu}{p_i}. \tag{5}$$

Proof. See Appendix A1. □

3. Threshold dynamics: disease extinction and persistence

We introduce the notation $D = \{\boldsymbol{I} \in \mathbb{R}_+^n \,|\, \sum_{j=1}^n I_j \le 1\}$ for the feasible phase space of model (3).

Theorem 3.1. *If* $\mathcal{R}_0 \le 1$ *then the disease free equilibrium is globally asymptotically stable in the domain D, that is, the disease will be eradicated. If* $\mathcal{R}_0 > 1$ *then the disease persists uniformly in the population.*

Proof. We prove this result by following the methods of Theorem 2.1 and Theorem 2.2 from [13]. First we show that for system (3), the inequality

$$(F - V)\boldsymbol{I} \ge \mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I})$$

holds for any $\boldsymbol{I} \in D$. Note that $V\boldsymbol{I} = \mathcal{V}(\boldsymbol{I})$. It's easy to see that in the first component of $\mathcal{F}$, the elements are multiplied by $1 - \sum_{k=1}^n I_k$, which is obviously less or equal than 1 in D. The first row of the matrix F does not contain this factor, so the linearized form $(F - V)\boldsymbol{I}$ is greater or equal than $\mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I})$ for any $\boldsymbol{I} \in D$, with equality holding only at the DFE.

Let ω^T be the left eigenvector of the nonnegative matrix $V^{-1}F$ corresponding to the eigenvalue $\mathcal{R}_0 = \rho(V^{-1}F) = \rho(FV^{-1})$. The matrix V^{-1} is lower-triangular and its nonzero elements are positive. The elements in the first row of F are all positive, and applying the rule of matrix multiplication, all elements of $V^{-1}F$ will be positive, and therefore, its adjacency matrix is strongly connected. Since FV^{-1} is irreducible and nonnegative, $\omega > 0$.

Consider $U := \omega^T V^{-1}\boldsymbol{I}$. Differentiation along solutions gives

$$\frac{dU}{dt} = \omega^T V^{-1}(\mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I})) \le \omega^T V^{-1}(F - V)\boldsymbol{I} = \omega^T V^{-1}F \cdot \boldsymbol{I} - \omega^T \cdot \boldsymbol{I} = (\mathcal{R}_0 - 1)\omega^T \cdot \boldsymbol{I}.$$

For $\mathcal{R}_0 < 1$, U is a Lyapunov function and the global asymptotic stability of the DFE in D follows. For $\mathcal{R}_0 = 1$, the same conclusion follows from LaSalle's invariance principle, noticing that in this case $\frac{dU}{dt} = 0$ implies $\mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I}) = 0$, which holds if and only if $\boldsymbol{I}$ is an equilibrium. For $\mathcal{R}_0 = 1$, this can only be the DFE $(0, 0, \ldots, 0)$.

Now assume $\mathcal{R}_0 > 1$. For any $\epsilon > 0$, in the ϵ-neighborhood of the DFE we have $\mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I}) \ge (F(1-\epsilon) - V)\boldsymbol{I}$. Let $\epsilon > 0$ be so small that $\mathcal{R}_0(1-\epsilon) > 1$ holds. Then, in this neighborhood,

$$\frac{dU}{dt} = \omega^T V^{-1}(\mathcal{F}(\boldsymbol{I}) - \mathcal{V}(\boldsymbol{I})) \ge \omega^T V^{-1}(F(1-\epsilon) - V)\boldsymbol{I} = (\mathcal{R}_0(1-\epsilon) - 1)\omega^T \cdot \boldsymbol{I} \ge 0.$$

We conclude that positive solutions can not converge to the DFE, and using standard arguments, the persistence result follows, thus there is an $\eta > 0$ such that for all positive solutions $\liminf_{t\to\infty} ||\boldsymbol{I}(t)|| > \eta$. □

4. The endemic equilibrium is always stable for $n = 1, 2, 3$

The stability results are based on the Routh–Hurwitz-theorem, which we state below.

Theorem A. *For a given polynomial $P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots + a_{n-1}\lambda + a_n$ we define the Hurwitz-matrices*

$$H_1 = \begin{pmatrix} a_1 \end{pmatrix},\ H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},\ H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \ldots,$$

and

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \ldots & 0 \\ a_3 & a_2 & a_1 & 1 & \ldots & 0 \\ a_5 & a_4 & a_3 & a_2 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \ldots & a_n \end{pmatrix},$$

where $a_j = 0$ if $j > n$. All of the roots of $P(\lambda)$ are negative or have negative real part if and only if the determinants of all Hurwitz-matrices are positive:

$$\det(H_j) > 0 \; forall \; j = 1, 2, \ldots, n.$$

Theorem 4.1. *If $\mathcal{R}_0 > 1$ and $n = 1, 2, 3$, then the endemic equilibrium is locally asymptotically stable.*

Proof. See Appendix A2. □

5. Dynamics in higher dimensions: the endemic equilibrium can be either stable or unstable for any $n \ge 4$

5.1. Stable case

We prove first that the endemic equilibrium can be stable in (3) for any $n \ge 4$, with suitable parameters β_i, p_i and μ. Let us set in (3) $\beta := \beta_1 = \beta_2 = \cdots = \beta_n$, and $p := p_1 = \ldots p_n$, and $\mu = 0$. Then we have

$$\begin{aligned} I_1' &= \beta \sum_{k=1}^{n} I_k \left(1 - \sum_{k=1}^{n} I_k\right) - pI_1, \\ I_2' &= pI_1 - pI_2, \\ &\vdots \\ I_n' &= pI_{n-1} - pI_n. \end{aligned} \tag{6}$$

From (4) and (5), we obtain the basic reproduction number and the EE as

$$\mathcal{R}_0 = \frac{\beta \cdot n}{p}, \quad I_1^* = I_2^* = \cdots = I_n^* = \frac{1 - \frac{p}{\beta n}}{n}. \tag{7}$$

Theorem 5.1. *The characteristic polynomial of (6) at the EE is*

$$\chi_n(\lambda) = (-1)^n \left((p+\lambda)^n + \left(\beta - \frac{2p}{n}\right) \cdot \sum_{i=0}^{n-1} (p+\lambda)^i \cdot p^{n-1-i} \right). \tag{8}$$

Proof. We use the notation $[(p+\lambda)^i][X]$ for the coefficient of $(p+\lambda)^i$ in some expression X. With such a notation, we will prove by induction that

$$[(p+\lambda)^i][\chi_n(\lambda)] = \begin{cases} (-1)^n, & i = n \\ (-1)^n \cdot \left(\beta - \frac{2p}{n}\right) \cdot p^{n-1-i}, & i = 0, 1, \dots, n-1. \end{cases}$$

From (6) and (7) we obtain the $n \times n$-size characteristic matrix

$$D_n(\lambda) = \begin{pmatrix} \frac{2p}{n} - \beta - p - \lambda & \frac{2p}{n} - \beta & \frac{2p}{n} - \beta & \dots & \frac{2p}{n} - \beta \\ p & -p-\lambda & 0 & \dots & 0 \\ 0 & p & -p-\lambda & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -p-\lambda \end{pmatrix},$$

and we look for it's determinant. One can easily check the $n = 1$ case. If we expand $|D_n(\lambda)|$ by the last column, we find

$$\chi_n(\lambda) = |D_n(\lambda)| = (-1) \cdot (p+\lambda) \cdot |C_{n-1}(\lambda)| + (-1)^{n+1} \left(\frac{2p}{n} - \beta\right) \cdot p^{n-1}, \tag{9}$$

where

$$C_{n-1}(\lambda) = \begin{pmatrix} \frac{2p}{n} - \beta - p - \lambda & \frac{2p}{n} - \beta & \frac{2p}{n} - \beta & \dots & \frac{2p}{n} - \beta \\ p & -p-\lambda & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \dots & p & -p-\lambda \end{pmatrix} \in \mathbb{R}^{(n-1)\times(n-1)}.$$

From the Leibniz formula of computing determinants, we deduce

$$[(p+\lambda)^i][|C_{n-1}(\lambda)|] = \begin{cases} (-1)^{n-1}, & i = n-1 \\ [(p+\lambda)^i][|D_{n-1}(\lambda)|] \cdot \frac{\beta - \frac{2p}{n}}{\beta - \frac{2p}{n-1}}, & i = 0, 1, \dots, n-2. \end{cases}$$

Combining this with (9) and using the induction hypothesis for $n-1$, we arrive at

$$[(p+\lambda)^i][\chi_n(\lambda)] = \begin{cases} (-1)^n, & i = n \\ (-1)^n p^{n-1-i} \cdot \left(\beta - \frac{2p}{n}\right), & i = 0, 1, \dots, n-1. \end{cases}$$

□

Theorem 5.2. *The endemic equilibrium of (6) is stable.*

Proof. We prove first that for $1 < \mathcal{R}_0 \le 2$ the characteristic equation does not have a root with positive real part. Substituting $\alpha + i\omega$ with $\alpha > 0$ to the characteristic equation $\chi_n(\lambda) = 0$ and dividing by the non-zero $(p + \alpha + i\omega)^n$ yield

$$1 = \left(\frac{2p}{n} - \beta\right) \cdot \left(\frac{1}{p+\alpha+i\omega} + \frac{p}{(p+\alpha+i\omega)^2} + \dots + \frac{p^{n-1}}{(p+\alpha+i\omega)^n} \right). \tag{10}$$

Taking the absolute value of both sides, we get

$$1 = \left(\frac{2p}{n} - \beta\right) \cdot \left| \frac{1}{p+\alpha+i\omega} + \frac{p}{(p+\alpha+i\omega)^2} + \dots + \frac{p^{n-1}}{(p+\alpha+i\omega)^n} \right|, \tag{11}$$

because $1 < \mathcal{R}_0 \le 2$ implies the nonnegativity of $\frac{2p}{n} - \beta$. The right-hand side is clearly smaller than

$$n \cdot \left| \frac{1}{p+\alpha+i\omega} \right|,$$

so

$$1 < n\left(\frac{2p}{n} - \beta\right) \left| \frac{1}{p+\alpha+i\omega} \right| = (2p - \beta n) \left| \frac{1}{p+\alpha+i\omega} \right|. \tag{12}$$

Since $\mathcal{R}_0 > 1$ implies $\beta n > p$, we have $(2p - \beta n) < p$ and thus

$$1 < (2p - \beta n) \left| \frac{1}{p+\alpha+i\omega} \right| < p \left| \frac{1}{p+\alpha+i\omega} \right| < 1 \tag{13}$$

whenever $\alpha > 0$, which is a contradiction.

The next step is to prove that (8) does not have a root $i\omega$ with $\omega > 0$ for any $\mathcal{R}_0 > 1$. Substituting $i\omega$ to $\chi_n(\lambda) = 0$ and dividing by $(p + i\omega)^n$ we derive

$$1 = \left(\frac{2p}{n} - \beta\right) \cdot \left(\frac{1}{p+i\omega} + \frac{p}{(p+i\omega)^2} + \cdots + \frac{p^{n-1}}{(p+i\omega)^n}\right) = \left(\frac{2p}{n} - \beta\right) \cdot \frac{1 - \left(\frac{p}{p+i\omega}\right)^n}{i\omega}. \tag{14}$$

This implies

$$i\omega - \left(\frac{2p}{n} - \beta\right) = (-1) \cdot \left(\frac{2p}{n} - \beta\right) \cdot \left(\frac{p^n}{(p+i\omega)^n}\right). \tag{15}$$

Taking the absolute value of both sides yields

$$\left|i\omega - \left(\frac{2p}{n} - \beta\right)\right| = \left|\left(\frac{2p}{n} - \beta\right)\right| \cdot \left|\frac{p^n}{(p+i\omega)^n}\right|, \tag{16}$$

and there is a contradiction, because of $\omega > 0$, the left-hand side is greater than $|\frac{2p}{n} - \beta|$ and the right-hand side is less than $|\frac{2p}{n} - \beta|$. This implies the stability of the equilibrium because the eigenvalues are depending continuously on the characteristic equation (see [10]). Since the endemic equilibrium is stable for $\mathcal{R}_0 \leq 2$, if it would be unstable for some (β, n, p) configuration, there must be a configuration with purely imaginary root $i\omega$ as well, which is not possible. □

5.2. Unstable case

We have seen that the endemic equilibrium in system (3) can be stable. Now we would like to show that one can choose the parameters such that the endemic equilibrium will be unstable, therefore we can discover oscillation in the dynamics. We will set now in (3) $\beta_1 = \beta > 0,\ \beta_2 = \beta_3 = \cdots = \beta_n = 0,\ p_1 = p > 0,\ p_2 = p_3 = \cdots = p_n = q > 0$ and $\mu = 0$, this means we reduced (3) to

$$\begin{aligned} I_1' &= \beta I_1\left(1 - \textstyle\sum_{k=1}^n I_k\right) - pI_1, \\ I_2' &= pI_1 - qI_2, \\ I_3' &= qI_2 - qI_3, \\ &\vdots \\ I_n' &= qI_{n-1} - qI_n. \end{aligned} \tag{17}$$

It is easy to calculate the basic reproduction number as $\mathcal{R}_0 = \dfrac{\beta}{p}$. The endemic equilibrium satisfies $I_2^* = \cdots = I_n^* = \frac{p}{q} I_1^*$, and substituting to the first equation yields

$$I_1^* = \frac{1 - \frac{p}{\beta}}{(n-1)\frac{p}{q} + 1}, \quad I_2^* = \cdots = I_n^* = \frac{p}{q}\,\frac{1 - \frac{p}{\beta}}{(n-1)\frac{p}{q} + 1}. \tag{18}$$

Theorem 5.3. *The characteristic polynomial of (17) is*

$$\chi_n(\lambda) = (-1)^n\left((q+\lambda)^{n-1}(\beta \cdot I_1^* + \lambda) + \frac{p \cdot \beta \cdot I_1^*}{\lambda}\left((q+\lambda)^{n-1} - q^{n-1}\right)\right). \tag{19}$$

Proof. See Appendix A3. □

We will prove that $\chi_n(\lambda)$ has pure imaginary roots $\lambda = i\omega$. With the notation $\dfrac{p}{q} = \alpha$, $\dfrac{\lambda}{q} = z$ and using $\dfrac{\beta}{p} = \mathcal{R}_0$, after some manipulation we can write $\chi_n(\lambda) = 0$ in the form

$$z + \frac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1} + \frac{\alpha}{z} \cdot \frac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1}\left(1 - \frac{1}{(z+1)^{n-1}}\right) = 0. \tag{20}$$

Substituting $z = i\omega$ yields

$$i\omega + \frac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1} - i\frac{\alpha}{\omega} \cdot \frac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1}\left(1 - \frac{1}{(i\omega+1)^{n-1}}\right) = 0. \tag{21}$$

The real and imaginary parts of this equation are

(i) $\dfrac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1} - \dfrac{\alpha}{\omega} \cdot \dfrac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1} \cdot \operatorname{Im}\left(\dfrac{1}{(i\omega+1)^{n-1}}\right) = 0,$

(ii) $\omega^2 = \alpha \cdot \dfrac{\alpha \cdot (\mathcal{R}_0 - 1)}{(n-1)\cdot\alpha + 1}\left(1 - \operatorname{Re}\left(\dfrac{1}{(i\omega+1)^{n-1}}\right)\right).$

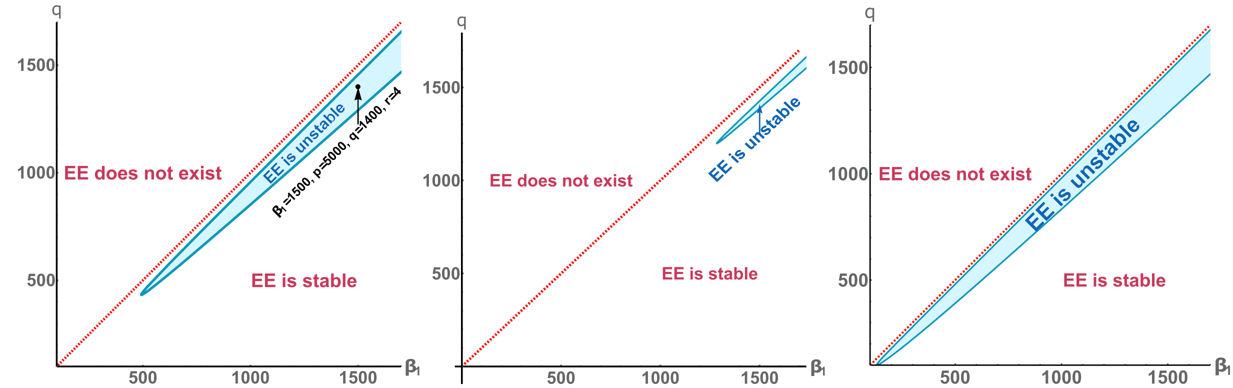

Fig. 2. Two-parameter stability charts for the endemic equilibrium of some variants of (23): system (46) and parameter configuration (48) (on the left); three I-compartments and parameter configuration $\beta_2 = 4 \cdot 10^{-5}, \beta_3 = 0, p = 5000, r = 4, \mu_S = \mu_E = \mu_1 = \mu_2 = \mu_3 = \mu_R = 10^{-1}$ (in the middle); and four I-compartments and parameter configuration $\beta_2 = 0, \beta_3 = 0, \beta_4 = 0, p = 5000, r = 4, \mu_S = \mu_E = \mu_1 = \mu_2 = \mu_3 = \mu_R = 0$ (on the right).

Solving these equations for α and $\sigma := \mathcal{R}_0 - 1$, we find

$$\alpha = \frac{\omega}{\mathrm{Im}\left(\frac{1}{(i\omega+1)^{n-1}}\right)}, \qquad (22)$$

$$\sigma = \frac{\mathrm{Im}\left(\frac{1}{(i\omega+1)^{n-1}}\right)\left((n-1)\cdot\omega + \mathrm{Im}\left(\frac{1}{(i\omega+1)^{n-1}}\right)\right)}{1 - \mathrm{Re}\left(\frac{1}{(i\omega+1)^{n-1}}\right)}.$$

Theorem 5.4. *For every $n \geq 4$ there is a suitable $\omega > 0$, $\alpha > 1$ and $\sigma > 0$ that solves (22) and the transversality condition Re $z'(\sigma) \neq 0$ is satisfied for (20). Therefore a Hopf bifurcation occurs, and the endemic equilibrium can be unstable.*

Proof. See Appendix A4. □

6. Instability in an SEIRS model

In [11], the transmission dynamics of an SEIRS model was investigated for an infectious disease with m infectious stages, given by the system

$$\begin{aligned}
S' &= \pi + \theta R - \textstyle\sum_{j=1}^{m} \frac{\beta_j I_j}{N} S - \mu_S S,\\
E' &= \textstyle\sum_{j=1}^{m} \frac{\beta_j I_j}{N} S - \sigma_E E - \mu_E E,\\
I_1' &= \sigma_E E - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1,\\
I_j' &= \sigma_{j-1} I_{j-1} - \sigma_j I_j - \mu_j I_j - \delta_j I_j, ; \qquad j = 2, 3, \ldots, m\\
R' &= \sigma_m I_m - \theta R - \mu_R R,
\end{aligned} \qquad (23)$$

where π is the recruitment rate of susceptible individuals into the population, θ is the rate of the loss of immunity among recovered individuals, β_j are the effective contact rates and σ_E, σ_j, μ_S, μ_E, μ_j, μ_R, δ_j $(j = 1, 2, \ldots, m)$ describe per capita rates of disease progression, natural death and disease-induced death, respectively. We assume that all these parameters are nonnegative. We denote by N the total population $(N = S + E + \sum_{j=1}^{m} I_j + R)$, by E the compartment of exposed individuals, by I_j the compartment of infected individuals in disease stage j, and by R the compartment of recovered and immune individuals. By applying a similar method as in Theorem 5.4, we can show that the endemic equilibrium can be unstable.

Proposition 6.1. *There exist a parameter set for (23) such that the endemic equilibrium exists and it is unstable.*

Proof. See Appendix A5. □

Remark 6.1. This proposition contradicts Theorem 3 of [11], which stated that the endemic equilibrium of system (23) is always locally asymptotically stable, therefore that theorem seems to be false. In [11], the authors formulated Conjecture 1 about the global asymptotic stability of the endemic equilibrium. Consequently, in light of Proposition 6.1, this conjecture is also disproved. This can also be illustrated by the stability charts in Fig. 2 and the depicted periodic solution in Fig. 3. The error in the proof of Theorem 3 in [11] is that the authors assumed $|1 + F_1(\omega)| > 1$ (defined in (30) in [11]) while it is not necessarily true. As a matter of fact we calculated numerically that expression for our counterexample with the parameters used in Appendix A5, and the eigenvalue calculated in Appendix A5. We obtained that in that case $|F_1(\omega) + 1| = 0.999928 < 1$. This shows that the proof of Theorem 3 in [11] is not correct. Note that in general, in SIRS or SEIRS models with many stages, we can expect the appearance of sustained oscillations, see for example the related models in [5] or [16].

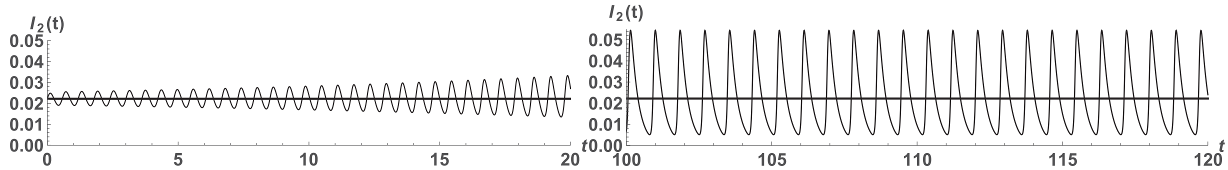

Fig. 3. Snapshots of an oscillatory solution of system (46) with parameter configuration (48), with $t \in [0, 20]$ (in the left) and $t \in [100, 120]$ (in the right), see Appendix A5.

7. Discussion

We studied a multistage SIS model, also known as $SI_1I_2 \dots I_nS$ model, where infectious individuals progress through a number of disease stages. The model was rigorously analyzed to gather information about its dynamical features. We have calculated the basic reproduction number $\mathcal{R}_0$ and shown its threshold property, namely that when $\mathcal{R}_0$ is less than or equal to 1, the disease-free equilibrium is globally asymptotically stable, and when $\mathcal{R}_0 > 1,$ the disease persists uniformly in the population. So far this is a standard result for many epidemiological models. The main result of this paper is that the stability properties of the endemic equilibrium depend on the number of infectious stages. For $n = 1, 2, 3,$ the endemic equilibrium is always stable whenever exists, regardless of the particular choice of parameters β_j, p_j. However, for $n \geq 4$, instability of the endemic equilibrium is possible, and for any $n \geq 4$ there exist stable and unstable configurations of the parameters. In the unstable case, we expect oscillatory disease dynamics. This has an important implication for the modelling of infectious diseases with varying infectivity. During the course of infection, the infectivity of a host naturally changes continuously alongside disease progression, and this may cause oscillations, as it has been pointed out is some models in the context of HIV [14]. Multistage compartmental models represent a discretization of this variation of infectivity in time. For some cases it may very well be a possibility, that the real life disease dynamics is oscillatory, which we can capture by a model with sufficiently many stages, but an oversimplification to three or less disease stages causes that the model prediction of global stability will be false.

A somewhat similar phenomenon has been observed for waning immunity models of $SIR_1 \dots R_nS$-type, where the immune period was divided into stages, and the stability could be lost if there were at least three R-stages, see Section 4 in [5]. Since from an epidemiological point of view it does not make a difference if a host is in an R-compartment, or in an I-compartment with zero infectivity, the SIRS model in Section 4 of [5] can be considered as a very special case of our system (1) with $\beta_j = 0$ for $j > 1$ and $p_2 = \dots = p_n$. Similarly, multistage SEIRS models can also be considered as special cases of SIS model (1) with setting the transmission parameter $\beta_k = 0$ for some appropriate compartments. In this regard, we found a mistake in the literature where local asymptotic stability of the endemic equilibrium in a multistage SEIRS model was claimed while in fact the endemic equilibrium can be unstable. A numerical illustration of the resulting oscillatory behaviour is depicted in Fig. 3.

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Appendix A

A1. Proof of Theorem 2.1

Setting the time derivatives zero in (3) yields

$$0 = \sum_{k=1}^{n} \beta_k I_k^* \left(1 - \sum_{k=1}^{n} I_k^*\right) - p_1 I_1^* - \mu I_1^*,$$

$$I_k^* = \frac{p_{k+1} + \mu}{p_k} \cdot I_{k+1}^*, \quad k = 1, \dots, n-1.$$

By iteration we find

$$I_k^* = \frac{p_{k+1} + \mu}{p_k} \dots \frac{p_n + \mu}{p_{n-1}} I_n^*. \tag{24}$$

If $I_n^* = 0$, then every $I_k^* = 0,\ k = 1, 2, \dots, n$. Now we assume that I_n^* is positive. Now we can see that

$$Q = \frac{I_n^*}{I_n^*} + \frac{I_{n-1}^*}{I_n^*} + \dots + \frac{I_1^*}{I_n^*} = \frac{\sum_{k=1}^{n} I_k^*}{I_n^*}. \tag{25}$$

We claim that

$$\sum_{k=1}^{n} \beta_k I_k^* = (p_1+\mu)\prod_{j=1}^{n-1}\frac{p_{j+1}+\mu}{p_j}\cdot I_n^*\cdot \mathcal{R}_0. \tag{26}$$

First we substitute (4) in $\mathcal{R}_0$, and then the coefficient of β_k in the right hand side is

$$(p_1+\mu)\prod_{j=1}^{n-1}\frac{p_{j+1}+\mu}{p_j}\cdot I_n^*\cdot\frac{1}{p_k+\mu}\prod_{l=1}^{k-1}\frac{p_l}{p_l+\mu}.$$

By (24), we find that it is indeed I_k^* and thus Eq. (26) holds. Substituting (26) into (24) and using (25), we find

$$(p_1+\mu)\prod_{k=1}^{n-1}\frac{p_{k+1}+\mu}{p_k}I_n^*\cdot(1-I_n^*Q)\cdot\mathcal{R}_0=(p_1+\mu)I_1^*.$$

From (24) with $k=1$ and dividing by I_n^* we obtain

$$\frac{(p_1+\mu)(p_2+\mu)\dots(p_n+\mu)}{p_1p_2\dots p_{n-1}}(1-I_n^*Q)\cdot\mathcal{R}_0=\frac{(p_1+\mu)(p_2+\mu)\dots(p_n+\mu)}{p_1p_2\dots p_{n-1}}.$$

Therefore,

$$(1-I_n^*Q)\cdot\mathcal{R}_0=1,$$

that is,

$$I_n^*=\frac{1-\frac{1}{\mathcal{R}_0}}{Q},$$

and substituting this into (24), the proof is completed.

A2. Proof of Theorem 4.2

To apply the Routh–Hurwitz-theorem, we determine the Jacobian matrix and the characteristic polynomial $\chi(\lambda)$ of our system.

(a) $n=1$: In this case our system is

$$I_1' = \beta_1 I_1(1-I_1)-p_1I_1-\mu I_1 = I_1(\beta_1-p_1-\mu-\beta_1 I_1). \tag{27}$$

Since $\mathcal{R}_0>1$ means $\beta_1-p_1-\mu>0$, the stability of the positive equilibrium of this logistic equation is obvious.

(b) $n=2$: In this case our system is

$$\begin{aligned} I_1' &= (\beta_1 I_1+\beta_2 I_2)(1-I_1-I_2)-p_1I_1-\mu I_1,\\ I_2' &= p_1I_1-p_2I_2-\mu I_2, \end{aligned} \tag{28}$$

and the basic reproduction number is

$$\mathcal{R}_0=\frac{\beta_1}{p_1+\mu}+\frac{\beta_2 p_1}{(p_1+\mu)(p_2+\mu)}=\frac{\beta_1(p_2+\mu)+\beta_2p_1}{(p_1+\mu)(p_2+\mu)}. \tag{29}$$

The Jacobian of the system at the EE is the 2×2 matrix

$$\begin{pmatrix} \frac{\beta_1}{\mathcal{R}_0}-f-p_1-\mu & \frac{\beta_2}{\mathcal{R}_0}-f \\ p_1 & -p_2-\mu \end{pmatrix},$$

where

$$f=\sum_{k=1}^{2}\beta_k I_k^*. \tag{30}$$

The characteristic polynomial is

$$\begin{aligned}\chi(\lambda) =&\lambda^2+\lambda\cdot\left(2\mu+p_1+p_2+f-\frac{\beta_1}{\mathcal{R}_0}\right)\\ &+\left(f\mu+fp_1+fp_2+\mu p_1+\mu p_2+p_1p_2+\mu^2-\mu\frac{\beta_1}{\mathcal{R}_0}-p_1\frac{\beta_2}{\mathcal{R}_0}-p_2\frac{\beta_1}{\mathcal{R}_0}\right).\end{aligned}$$

It's enough to prove that $\det(H_1)=a_1$ and $\det(H_2)=a_1a_2$ are positive, which is equivalent to

(i) $a_1>0$,

(ii) $a_2 > 0$.

(i) We show that

$$f + 2\mu + p_1 + p_2 > \frac{\beta_1}{\mathcal{R}_0}.$$

Indeed, using (4) for $n = 2$, this is equivalent to

$$f + (p_2 + \mu) + (p_1 + \mu) > \frac{\beta_1(p_1 + \mu)(p_2 + \mu)}{\beta_1(p_2 + \mu) + \beta_2 p_1}.$$

If we multiply by the denominator of the right-hand side, we can clearly see that the left hand side is greater.

(ii) We have to prove that

$$f\mu + fp_1 + fp_2 + \mu p_1 + \mu p_2 + p_1p_2 + \mu^2 - \mu\frac{\beta_1}{\mathcal{R}_0} - p_1\frac{\beta_2}{\mathcal{R}_0} - p_2\frac{\beta_1}{\mathcal{R}_0} > 0,$$

that is,

$$f\mu + fp_1 + fp_2 + (p_1 + \mu)(p_2 + \mu) > \mu\frac{\beta_1}{\mathcal{R}_0} + p_1\frac{\beta_2}{\mathcal{R}_0} + p_2\frac{\beta_1}{\mathcal{R}_0}. \tag{31}$$

Because of (29), it is true that

$$(p_1 + \mu)(p_2 + \mu) = (p_2 + \mu)\frac{\beta_1}{\mathcal{R}_0} + p_1\frac{\beta_2}{\mathcal{R}_0}.$$

If we subtract this from (31), we have $f\mu + fp_1 + fp_2 > 0$, and we conclude $a_2 > 0$.

(c) $n = 3$: In this case our system is

$$\begin{aligned} I_1' &= \textstyle\sum_{k=1}^{3}\beta_k I_k\left(1 - \sum_{k=1}^{n} I_k\right) - p_1 I_1 - \mu I_1, \\ I_2' &= p_1 I_1 - p_2 I_2 - \mu I_2, \\ I_3' &= p_2 I_2 - p_3 I_3 - \mu I_3. \end{aligned} \tag{32}$$

The basic reproduction number is

$$\mathcal{R}_0 = \frac{\beta_1}{p_1 + \mu} + \frac{\beta_2 p_1}{(p_1 + \mu)(p_2 + \mu)} + \frac{\beta_3 p_1 p_2}{(p_1 + \mu)(p_2 + \mu)(p_3 + \mu)}. \tag{33}$$

We can easily deduce the Jacobian matrix

$$\begin{pmatrix} \frac{\beta_1}{\mathcal{R}_0} - f - p_1 - \mu & \frac{\beta_2}{\mathcal{R}_0} - f & \frac{\beta_3}{\mathcal{R}_0} - f \\ p_1 & -p_2 - \mu & 0 \\ 0 & p_2 & -p_3 - \mu \end{pmatrix},$$

where

$$f = \sum_{k=1}^{3}\beta_k I_k^*, \tag{34}$$

and

$$\begin{aligned} \chi(\lambda) = &-\lambda^3 - \lambda^2\left(f + p_1 + p_2 + p_3 + 3\mu - \frac{\beta_1}{\mathcal{R}_0}\right) \\ &- \lambda\Big(fp_1 + fp_2 + fp_3 + p_1p_2 + p_1p_3 + p_2p_3 + 2p_1\mu + 2p_2\mu + 2p_3\mu + 2f\mu \\ &+ 3\mu^2 - p_1\frac{\beta_2}{\mathcal{R}_0} - p_2\frac{\beta_1}{\mathcal{R}_0} - p_3\frac{\beta_1}{\mathcal{R}_0} - 2\mu\frac{\beta_1}{\mathcal{R}_0}\Big) \\ &- \Big(fp_1p_2 + fp_1p_3 + fp_2p_3 + p_1p_2p_3 + p_1p_2\mu + p_1p_3\mu + p_2p_3\mu \\ &+ fp_1\mu + fp_2\mu + fp_3\mu + f\mu^2 + p_1\mu^2 + p_2\mu^2 + p_3\mu^2 + \mu^3 \\ &- p_1p_2\frac{\beta_3}{\mathcal{R}_0} - p_1p_3\frac{\beta_2}{\mathcal{R}_0} - p_2p_3\frac{\beta_1}{\mathcal{R}_0} - p_1\frac{\beta_2}{\mathcal{R}_0}\mu - p_2\frac{\beta_1}{\mathcal{R}_0}\mu - p_3\frac{\beta_1}{\mathcal{R}_0}\mu - \frac{\beta_1}{\mathcal{R}_0}\mu^2\Big). \end{aligned}$$

We apply the Routh–Hurwitz criterion to -$\chi(\lambda)$, which has the same roots as $\chi(\lambda)$. It's enough to prove that

$$\det(H_1) = a_1,\ \det(H_2) = a_1a_2 - a_3 and \det(H_3) = a_3\cdot(a_1a_2 - a_3)$$

are positive, which is equivalent to

(i) $a_1 > 0$,
(ii) $a_3 > 0$, and
(iii) $a_2 \cdot a_1 > a_3$.

(i) We show that

$$f + 3\mu + p_1 + p_2 + p_3 > \frac{\beta_1}{\mathcal{R}_0}. \tag{35}$$

Consider an equivalent form of (33):

$$(p_1+\mu)(p_2+\mu)(p_3+\mu) = (p_2+\mu)(p_3+\mu)\frac{\beta_1}{\mathcal{R}_0} + p_1(p_3+\mu)\frac{\beta_2}{\mathcal{R}_0} + p_1p_2\frac{\beta_3}{\mathcal{R}_0}. \tag{36}$$

Multiplying (35) with $\mathcal{R}_0$ and using (36), we obtain

$$\frac{\beta_3p_1p_2 + \beta_2p_1(p_3+\mu) + \beta_1(p_2+\mu)(p_3+\mu)}{(p_1+\mu)(p_2+\mu)(p_3+\mu)}(f + 3\mu + p_1 + p_2 + p_3) > \beta_1. \tag{37}$$

Multiplying both sides with $(p_1+\mu)(p_2+\mu)(p_3+\mu)$, it is easy to see that the left hand side is greater.

(ii) From (36):

$$a_3 = f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3,$$

which is obviously positive.

(iii) It's enough to prove that the expression

$$\Big(-\frac{\beta_1}{\mathcal{R}_0} + f + 3\mu + p_1 + p_2 + p_3\Big)\Big(-2\frac{\beta_1}{\mathcal{R}_0}\mu + 2f\mu + fp_1 + fp_2 + fp_3 + 3\mu^2 - \frac{\beta_2}{\mathcal{R}_0}p_1 + 2\mu p_1 + p_1p_2 + p_1p_3 - \frac{\beta_1}{\mathcal{R}_0}p_2 + 2\mu p_2 + p_2p_3 - \frac{\beta_1}{\mathcal{R}_0}p_3 + 2\mu p_3\Big) - \Big(f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3\Big)$$

is positive (we used (36) for a_3). This is equivalent to the inequality

$$\Big(-\frac{\beta_1}{\mathcal{R}_0} + f + 3\mu + p_1 + p_2 + p_3\Big)\Big(-2\frac{\beta_1}{\mathcal{R}_0}\mu + 2f\mu + fp_1 + fp_2 + fp_3 + 3\mu^2 - \frac{\beta_2}{\mathcal{R}_0}p_1 + 2\mu p_1 + p_1p_2 + p_1p_3 - \frac{\beta_1}{\mathcal{R}_0}p_2 + 2\mu p_2 + p_2p_3 - \frac{\beta_1}{\mathcal{R}_0}p_3 + 2\mu p_3\Big) > f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3.$$

Because of (36), obviously

$$(p_1+\mu)(p_2+\mu)(p_3+\mu) > (p_2+\mu)(p_3+\mu)\frac{\beta_1}{\mathcal{R}_0} + p_1(p_3+\mu)\frac{\beta_2}{\mathcal{R}_0},$$

and the even weaker inequality

$$(p_1+\mu)(p_2+\mu)(p_3+\mu) > (p_2+\mu)(p_3+\mu)\frac{\beta_1}{\mathcal{R}_0}$$

holds. Dividing these by $(p_3+\mu)$ and $(p_2+\mu)$, respectively, we find

$$(p_1+\mu)(p_2+\mu) > \frac{\beta_1}{\mathcal{R}_0}(p_2+\mu) + \frac{\beta_2}{\mathcal{R}_0}p_1, \tag{38}$$

and

$$(p_1+\mu)(p_3+\mu) > \frac{\beta_1}{\mathcal{R}_0}(p_3+\mu). \tag{39}$$

Considering (38) and (39), we can write

$$\Big(f + p_1 + p_2 + p_3 + 3\mu - \frac{\beta_1}{\mathcal{R}_0}\Big)\Big(2f\mu + fp_1 + fp_2 + fp_3 + 3\mu^2 + 2\mu p_1 + p_1p_2 + p_1p_3 + 2\mu p_2 + p_2p_3 + 2\mu p_3 - \Big(\frac{\beta_1}{\mathcal{R}_0}(p_2+\mu) + \frac{\beta_2}{\mathcal{R}_0}p_1 + \frac{\beta_1}{\mathcal{R}_0}(p_3+\mu)\Big)\Big)$$
$$> \Big(f + p_1 + p_2 + p_3 + 3\mu - \frac{\beta_1}{\mathcal{R}_0}\Big)\Big(2f\mu + fp_1 + fp_2 + fp_3 + 3\mu^2 + 2\mu p_1 + p_1p_2$$

$$+ p_1p_3 + 2\mu p_2 + p_2p_3 + 2\mu p_3\Big) - \big(p_1p_2 + p_1\mu + p_2\mu + \mu^2 + p_1p_3 + \mu p_3 + \mu p_1 + \mu^2\big)$$
$$= \left(f + p_1 + p_2 + p_3 + 3\mu - \frac{\beta_1}{\mathcal{R}_0}\right)\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu + \mu^2\right).$$

We will prove that

$$\left(f + p_1 + p_2 + p_3 + 3\mu - \frac{\beta_1}{\mathcal{R}_0}\right)\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu + \mu^2\right)$$
$$> f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3.$$

This is true if and only if

$$\left(f + p_1 + p_2 + p_3 + 3\mu\right)\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu + \mu^2\right)$$
$$> f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3$$
$$+ \frac{\beta_1}{\mathcal{R}_0}\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu\right).$$

From $p_1 + \mu > \frac{\beta_1}{\mathcal{R}_0}$ which is an immediate implication of (33), it remained to prove that

$$\left(f + p_1 + p_2 + p_3 + 3\mu\right)\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu + \mu^2\right)$$
$$> f\mu^2 + f\mu p_1 + fp_1p_2 + fp_1p_3 + f\mu p_2 + fp_2p_3 + f\mu p_3$$
$$+ (p_1 + \mu)\left(fp_1 + fp_2 + fp_3 + p_2p_3 + 2f\mu + p_2\mu + p_3\mu + \mu^2\right).$$

Expanding both sides, one can easily see that the left-hand side is greater indeed.

A3. Proof of Theorem 5.3

We prove this by induction. One can easily check the base case $n = 1$. For the induction step, assume that (19) holds for some n, and our goal is to show

$$\chi_{n+1}(\lambda) = (-1)^{n+1}\left((q+\lambda)^n(\beta\cdot I_1^* + \lambda) + \frac{p\cdot\beta\cdot I_1^*}{\lambda}\left((q+\lambda)^n - q^n\right)\right).$$

We have to compute the following determinant:

$$\chi_{n+1}(\lambda) = \begin{vmatrix} -\beta\cdot I_1^* - \lambda & -\beta\cdot I_1^* & -\beta\cdot I_1^* & -\beta\cdot I_1^* & \cdots & -\beta\cdot I_1^* & -\beta\cdot I_1^* \\ p & -q-\lambda & 0 & 0 & \cdots & 0 & 0 \\ 0 & q & -q-\lambda & 0 & \cdots & 0 & 0 \\ 0 & 0 & q & -q-\lambda & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & q & -q-\lambda & 0 \\ 0 & 0 & 0 & \cdots & 0 & q & -q-\lambda \end{vmatrix}.$$

We start to expand it by the last column:

$$\chi_{n+1}(\lambda) = (-1)(q+\lambda)\chi_n(\lambda) + (-1)^{n+1}(\beta\cdot I_1^*)\cdot p\cdot q^{n-1}.$$

Using (19) yields

$$\chi_{n+1}(\lambda) = (-1)^{n+1}\left((q+\lambda)^n(\beta\cdot I_1^* + \lambda)\right) + (-1)^{n+1}(q+\lambda)\frac{p\cdot\beta\cdot I_1^*}{\lambda}\left((q+\lambda)^{n-1} - q^{n-1}\right)$$
$$+ (-1)^{n+1}\beta\cdot I_1^*\cdot p\cdot q^{n-1}.$$

Notice that

$$(q+\lambda)\frac{p\cdot\beta\cdot I_1^*}{\lambda}\left((q+\lambda)^{n-1} - q^{n-1}\right) = \frac{p\cdot\beta\cdot I_1^*}{\lambda}(q+\lambda)^n - \frac{p\cdot\beta\cdot I_1^*}{\lambda}q^n - p\cdot\beta\cdot I_1^*\cdot q^{n-1},$$

Removing the parentheses,

$$\chi_{n+1}(\lambda) = (-1)^{n+1}(q+\lambda)^n(\beta\cdot I_1^* + \lambda) + \frac{p\cdot\beta\cdot I_1^*}{\lambda}(-1)^{n+1}\cdot(q+\lambda)^n$$
$$+ \frac{p\cdot\beta\cdot I_1^*}{\lambda}(-1)^n q^{n-1}(q+\lambda) + (-1)^{n+1}\beta\cdot I_1^*\cdot p\cdot q^{n-1},$$

and

$$\chi_{n+1}(\lambda) = (-1)^{n+1}(q+\lambda)^n(\beta \cdot I_1^* + \lambda) + \frac{p \cdot \beta \cdot I_1^*}{\lambda}(-1)^{n+1}(q+\lambda)^n + \frac{p \cdot \beta \cdot I_1^*}{\lambda}(-1)^n q^n + \Theta,$$

where

$$\Theta = (-1)^n \cdot p \cdot \beta \cdot I_1^* \cdot q^{n-1} + (-1)^{n+1} \cdot p \cdot \beta \cdot I_1^* \cdot q^{n-1} = 0.$$

Now we have

$$\chi_{n+1}(\lambda) = (-1)^{n+1}\Big((q+\lambda)^n(\beta \cdot I_1^* + \lambda) + \frac{p \cdot \beta \cdot I_1^*}{\lambda}\Big((q+\lambda)^n - q^n\Big)\Big),$$

and the induction step is completed.

A4. Proof of Theorem 5.4.

Using

$$\mathrm{Re}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) = \frac{\cos((n-1)\cdot \arctan\omega)}{(1+\omega^2)^{\frac{n-1}{2}}}, \tag{40}$$

and

$$\mathrm{Im}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) = -\frac{\sin((n-1)\cdot \arctan\omega)}{(1+\omega^2)^{\frac{n-1}{2}}}, \tag{41}$$

it is clear that $-1 < \mathrm{Re}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) < 1$, so whenever

$$0 < \mathrm{Im}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) < \omega \tag{42}$$

holds, from (22) we can see that $\alpha > 1$ and $\sigma > 0$.

We confirm that

$$\omega = \tan\left(\frac{5\pi}{12}\right)\text{is suitable for } n = 4, \qquad \omega = \tan\left(\frac{\pi}{n-2}\right)\text{is suitable for every } n > 4. \tag{43}$$

In the case $n = 4$, using (41),

$$\mathrm{Im}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) = -\sin\left(\frac{15\pi}{12}\right)\cdot\cos^3\left(\frac{5\pi}{12}\right) = \frac{(\sqrt{3}-1)^3}{32},$$

which is positive, but smaller than $\tan\left(\frac{5\pi}{12}\right) = 2+\sqrt{3}$. Similarly, for $n > 4$,

$$\mathrm{Im}\Big(\frac{1}{(i\omega+1)^{n-1}}\Big) = -\sin\left(\frac{(n-1)\pi}{n-2}\right)\cdot\cos^{n-1}\left(\frac{\pi}{n-2}\right).$$

Since $-\sin\left(\frac{(n-1)\pi}{n-2}\right) = \sin\left(\frac{\pi}{n-2}\right) < \tan\left(\frac{\pi}{n-2}\right)$, (42) holds.

We found that for $n \geq 4$, purely imaginary roots may exist. Implicit differentiation of

$$G(z(\sigma),\sigma) := z + \frac{\alpha\cdot\sigma}{(n-1)\cdot\alpha+1} + \frac{\alpha}{z}\cdot\frac{\alpha\cdot\sigma}{(n-1)\cdot\alpha+1}\Big(1 - \frac{1}{(z+1)^{n-1}}\Big) = 0$$

shows that $\mathrm{Re}\, z'(\sigma) \neq 0$ if and only if

$$\mathrm{Re}\Big(-\frac{\partial G}{\partial\sigma}\Big/\frac{\partial G}{\partial z}\Big) \neq 0.$$

Noting that

$$\frac{\partial G}{\partial\sigma} = \frac{G-z}{\sigma} = -\frac{z}{\sigma},$$

and

$$\frac{\partial G}{\partial z} = 1 - \frac{1}{z}\cdot\left(-z - \frac{\alpha\sigma}{(n-1)\cdot\alpha+1}\right) + \frac{\alpha}{z}\cdot\frac{\alpha\sigma}{(n-1)\cdot\alpha+1}(n-1)\cdot\frac{1}{(1+z)^n},$$

at $z = i\omega$ it is enough to show that

$$\text{Im}\frac{\partial G}{\partial z} = -\frac{\alpha\sigma}{(n-1)\cdot\alpha+1}\cdot\frac{1}{\omega} - \frac{\alpha}{\omega}\frac{\alpha\sigma}{(n-1)\cdot\alpha+1}(n-1)\frac{\cos(n\arctan\omega)}{(1+\omega^2)^{\frac{n}{2}}} \neq 0.$$

We can divide by the nonzero $\frac{\alpha\sigma}{(n-1)\cdot\alpha+1}\cdot\frac{1}{\omega}$ to obtain

$$-1-\alpha\cdot(n-1)\cdot\frac{\cos(n\arctan\omega)}{(1+\omega^2)^{\frac{n}{2}}} \neq 0. \tag{44}$$

In the case of $n = 4$, the left hand side is

$$-1+\frac{3\sin\left(\frac{5\pi}{12}\right)}{\sin\left(\frac{15\pi}{12}\right)\cos^3\left(\frac{5\pi}{12}\right)}\cdot\cos\left(\frac{20\pi}{12}\right)\cdot\cos^4\left(\frac{5\pi}{12}\right) = -1-\frac{3}{4\sqrt{2}}.$$

If $n > 4$, we get from (22) and (43) that $\alpha = \frac{1}{\cos^n\left(\frac{\pi}{n-2}\right)}$, so we can write (44) as

$$-1-(n-1)\cdot\cos\left(\frac{n}{n-2}\pi\right) \neq 0.$$

This is equivalent to

$$\cos\left(\frac{2\pi}{n-2}\right) \neq \frac{1}{n-1},$$

and one can check by elementary calculus that this holds for any integer $n \geq 5$.

A5. Proof of Proposition 6.1

Let $m = 3$ and set

$$\begin{aligned} \pi &= 0, N = 1, \mu_S = \mu_E = \mu_1 = \mu_2 = \mu_3 = \mu_R = 0, \sigma_E = p,\\ \sigma_1 &= q, \sigma_2 = \sigma_3 = \theta = r, \beta_2 = \beta_3 = 0. \end{aligned} \tag{45}$$

Normalizing the constant population size to unity, we can omit S from the system to get

$$\begin{aligned} E' &= \beta_1 I_1\left(1-E-\textstyle\sum_{k=1}^3 I_k - R\right) - pE,\\ I_1' &= pE - qI_1,\\ I_2' &= qI_1 - rI_2,\\ I_3' &= rI_2 - rI_3,\\ R' &= rI_3 - rR. \end{aligned} \tag{46}$$

Using (4) and (5) to calculate the positive equilibrium and $\mathcal{R}_0$, we find

$$E^* = \frac{qr\beta_1 - q^2 r}{(3pq+pr+qr)\beta_1},\ I_1^* = \frac{pr\beta_1 - pqr}{(3pq+pr+qr)\beta_1},\ I_2^* = I_3^* = R^* = \frac{pq\beta_1 - pq^2}{(3pq+pr+qr)\beta_1} \text{ and } \mathcal{R}_0 = \frac{\beta_1}{q}.$$

One can easily compute the characteristic matrix

$$C = \begin{pmatrix} \frac{pqr-pr\beta_1}{3pq+pr+qr} - p - \lambda & q + \frac{pqr-pr\beta_1}{3pq+pr+qr} & \frac{pqr-pr\beta_1}{3pq+pr+qr} & \frac{pqr-pr\beta_1}{3pq+pr+qr} & \frac{pqr-pr\beta_1}{3pq+pr+qr}\\ p & -q-\lambda & 0 & 0 & 0\\ 0 & q & -r-\lambda & 0 & 0\\ 0 & 0 & r & -r-\lambda & 0\\ 0 & 0 & 0 & r & -r-\lambda \end{pmatrix}.$$

If we denote $\frac{pqr-pr\beta_1}{3pq+pr+qr}$ by s, the characteristic polynomial can be written as

$$|C| = A_1\cdot\lambda^5 + A_2\cdot\lambda^4 + A_3\cdot\lambda^3 + A_4\cdot\lambda^2 + A_5\cdot\lambda + A_6, \tag{47}$$

where

$$\begin{aligned} A_1 &= -1,\\ A_2 &= -p-q-3r+s,\\ A_3 &= -3pr-3qr-3r^2+ps+qs+3rs,\\ A_4 &= -3pr^2-3qr^2-r^3+pqs+3prs+3qrs+3r^2\ s,\\ A_5 &= -pr^3-qr^3+3pqrs+3pr^2\ s+3qr^2\ s+r^3\ s, \end{aligned}$$

and $A_6 = 3pqr^2\ s + pr^3\ s + qr^3\ s.$

Setting

$$\beta_1 = 1500,\ q = 1400,\ p = 5000 \ \text{ and } r = 4, \tag{48}$$

we have eigenvalues

$$\begin{aligned} \lambda_1 &\approx 0.061614 - 10.4084i, \\ \lambda_2 &\approx 0.061614 + 10.4084i, \end{aligned}$$

hence, the endemic equilibrium is unstable and there is oscillation in the dynamics (see Fig. (3)). From the continuous dependence of the eigenvalues on parameters (see [10]), we find that instability is possible when all parameters are positive as well.

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