A NON-AUTONOMOUS MULTI-STRAIN SIS EPIDEMIC MODEL

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This Paper is Dedicated to Jim Cushing's 65th Birthday

Abstract. In this paper we consider a non-autonomous multi-strain SIS epidemic model with periodic coefficients. Reproduction numbers and invasion reproduction numbers are derived which agree well with their counterparts usually derived from autonomous epidemic models. With conditions on these reproduction numbers typical results are obtained, such as the local and global stability of the disease-free equilibrium. Existence and uniqueness of a single-strain periodic solution is established. Based on conditions on the invasion reproduction numbers, local stability of the single-strain periodic solution is shown. In a two-strain version of the model, conditions for uniform strong persistence are derived, and coexistence of the two strains is established. Coexistence, however, does not occur if the transmission rates of the different strains are linearly dependent.

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1. Introduction

The incidence of many infectious diseases fluctuates over time and often exhibits periodic behavior. One of the well known examples are data on weekly measles notification in England and Wales for the period 1948-1968 (see [5], Fig. 6.3). The number of measles cases per week oscillates with a period between two peaks of two years. Other childhood diseases such as mumps, chicken-pox, rubella, and pertussis have also been found to exhibit seasonal behavior. The periodicity of one year in many childhood diseases is attributed to the periodic contact rate the children have during academic school years. Although not restricted to children, influenza also exhibits distinct seasonality, with a season in the US spanning the time between October and May. During the first two-three years after the first case, the number of human cases of avian influenza also seemed to follow seasonal pattern [34].

Numerous articles have been devoted to explaining the periodicity in the disease incidence rates (see [18] for a review). Various scenarios how periodicity may arise in epidemic models have been set forward. Those include

(1) the possibility that the presence of certain classes can destabilize the equilibrium of models with constant coefficients and lead to sustain oscillations,
(2) the possibility that the incidence is not bilinear but has more complex form,

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(3) the possibility that the transmission rates are periodic,
(4) the presence of delay(s) in the model,
(5) the presence of host age-structure,
(6) from the interaction of two strains, one of which mutates into the other [20].

The possibility that the contact rate is periodic has lead to the consideration of epidemic models with time-dependent coefficients. An epidemic SIS model with periodic contact rate was first considered by Hethcote [17]. Epidemic SIR and SEIR models with periodic contact rate were considered by Dietz [15]. The non-autonomous SIR and SEIR models were further investigated both analytically and numerically by Smith [38] and Schwartz (see [36] for a review). More recently Zhang and Teng [44] established persistence and extinction in the disease for a non-autonomous SEIR model with vital dynamics.

One of the key difficulties in working with non-autonomous models is defining the reproduction number $\mathcal{R}_0$. Many of the articles in the literature do not define a reproductive number but work with threshold conditions that fit best the analysis. Junling Ma and Zhien Ma [27] consider the problem of defining adequate reproduction numbers for various non-autonomous SIR and SEIR models. The authors argue that the reproduction number should be defined as the reproduction number of a constant coefficient system obtained from the non-autonomous system by averaging the time-dependent coefficients. In all cases they are able to establish local stability of the disease-free equilibrium with the usual condition on the reproduction number $\mathcal{R}_0 angle 1$. However, Junling Ma and Zhien Ma show through simulation that the SEIR model can have a solution where the number of infected individuals goes to zero despite that the reproduction number is larger than one (see Figure 1 in [27]). Thus, the condition $\mathcal{R}_0 > 1$ does not necessarily lead to persistence.

The causative agents of many diseases are represented by multiple genetically distinct variants. Early autonomous multi-strain models suggested that competitive exclusion is the only possible outcome of the competition of many strains. Bremermann and Thieme [7] show that even if all reproduction numbers are larger than one, only the strain with the largest reproduction number persists while the remaining strains are eliminated. These results opened a question regarding the mechanisms that are responsible for the genetic diversity of pathogens in nature. Mechanisms such as super-infection [30, 33], coinfection [31], mutation [20], vertical transmission [23], and host age heterogeneity [29] were proposed as possible mechanisms that support diversity of pathogens. There is a significant literature devoted to the problem of competition of strains in autonomous multi-strain epidemic models which is reviewed in [42], [28], and [24].

Diseases that exhibit seasonality may also be represented by pathogens that experience mutation and exist as multiple strains. The most notable example of this scenario is influenza. Several intrinsic mechanisms such as quarantine [35] or host age structure [8], leading to periodicity in autonomous epidemic models, have been suggested as possible mechanisms for the influenza seasonality. Other possible mechanisms such as crowding during cooler months (increased contact rate), weakening of the host immune system (increased susceptibility), and ability of the viral particles to persist in cooler temperatures [21] could be modeled with periodic transmission rates. This would require the development and analysis of multi-strain non-autonomous models. Multi-strain non-autonomous epidemic models do not seem to have been discussed so far.

In this paper we consider a multi-strain SIS model with periodic coefficients. Since we assume the total population size constant and equal to one, we eliminate the variable for the susceptible individuals. The resulting system is a variant of the classical Lotka-Volterra n-species competition system. In contrast to multi-strain non-autonomous epidemic models, Lotka-Volterra competition systems have been studied extensively not only in the constant coefficient case but also in the case of time dependent (periodic) coefficients. The pioneering work on non-autonomous Lotka-Volterra competition systems is due to Jim Cushing, whose contribution to science in general, and to mathematical biology in particular, we are celebrating today on occasion of his 65th birthday. In the late 1970's and early 1980's Cushing authored a number of articles devoted to the non-autonomous versions of many classical ecological models: Lotka-Volterra predator-prey models [9, 14], Lotka-Volterra 2-species competition models [10, 11], n-species predator-prey/competition models [12], and the more-general Kolmogorov systems with periodic coefficients [13]. In [10] Cushing showed that competing species may coexist in a competitive systems with periodic coefficients even if they will competitively exclude each other in a system with constant coefficients equal to the time averages of the periodic coefficients. Cushing's early results were extended [32]. Cushing's work motivated a number of articles on competitive non-autonomous Lotka-Volterra systems (e.g. [1, 3, 6, 16, 39, 25]). Even today the questions on global persistence and extinction of the species in such systems is still being investigated [2, 26, 4].

This paper is structured as follows. Section 2 introduces the model, its re-formulations, the reproduction numbers and results on extinction of the disease. Section 3 establishes the existence of a single-strain periodic solution corresponding to each strain. Section 4 derives conditions for the local stability of the single-strain periodic solutions. Section 5 considers a two-strain version of the model and establishes the existence and convergence to a periodic coexistence solution. Section 6 discusses the special case when the transmission rate is a product of a periodic contact rate and a constant probability of transmission, and establishes competitive exclusion in that case. Section 7 summarizes the results and draws conclusions.

2. A non-autonomous SIS model

In this section we introduce a non-autonomous SIS epidemic model with multiple strains. We study a model with recruitment and deaths. We assume all newly recruited individuals are susceptible. The recruitment and mortality rate are assumed equal and denoted by $\mu(t)$. The function $\mu(t)$ is assumed nonnegative and periodic. In nature the recruitment rate needs to be periodic if it models seasonality in births. Many species breed in strictly defined breeding seasons and the birth/recruitment rates may be periodic. The transmission rate of strain i is denoted by $\beta_i(t)$ for $i = 1 \dots n$. All transmission rates are also assumed nonnegative and periodic. The transmission rate may be periodic because of migratory patterns of host species. In human epidemic models the contact rate can vary with the time in the year as is the case with students academic years. Finally, we denote by $\gamma_i(t)$ the recovery rate from strain i. All recovery rates are also assumed nonnegative and periodic. All periodic functions have period ω. The SIS model

with multiple strains takes the form:

$$\begin{aligned} \frac{dS}{dt} &= \mu(t) - \textstyle\sum_{j=1}^{n} \beta_j(t) S I_j - \mu(t) S + \sum_{j=1}^{n} \gamma_j(t) I_j \\ \frac{dI_j}{dt} &= \beta_j(t) S I_j - (\mu(t) + \gamma_j(t)) I_j, \qquad j = 1, \dots, n \end{aligned} \tag{2.1}$$

The number of susceptibles in the population is denoted by $S(t)$. The number of individuals infected by strain j is denoted by $I_j(t)$. The total population is given by

$$N(t) = S(t) + \sum_{j=1}^{n} I_j(t).$$

The differential equation satisfied by the total population size is obtained by adding all equations in the system (2.1):

$$N'(t) = \mu(t) - \mu(t) N(t).$$

Integrating the equation for the total population size, we get

$$N(t) = e^{-\int_0^t \mu(\sigma) d\sigma} (N_0 - 1) + 1$$

where N_0 is the value of the total population size at time zero. Since

$$\int_0^{\infty} \mu(\sigma) d\sigma = \infty$$

we have $\lim_t N(t) = 1$. In the remainder of this article we will assume that the total population size is constant and rescaled to one. Thus, we will assume that system (2.1) is subject to the initial conditions $S(0) = S_0$, $I_j(0) = I_j^0$ for $j = 1, \dots, n$ that satisfy

$$S^0 + \sum_{j=1}^{n} I_j^0 = 1.$$

This assumption implies that $N(t) = 1$ for all t. We use this equation to eliminate the number of susceptible individuals $S(t)$. We have

$$S(t) = 1 - \sum_{j=1}^{n} I_j.$$

Using this expression the system (2.1) can be rewritten in the form

$$\frac{dI_j}{dt} = \beta_j(t)(1 - \sum_{k=1}^{n} I_k) I_j - (\mu(t) + \gamma_j(t)) I_j, \qquad j = 1, \dots, n \tag{2.2}$$

The slightly more general case where the initial conditions do not add to one will lead to a system similar to (2.2) in which the number 1 is replaced with the *given* function $N(t)$. Such a system can be handled similarly to system (2.2) but will not be discussed in this article. We consider the system (2.2) on the set:

$$\Omega = \{(I_1, \dots, I_n) \in R_+^n : \sum_{k=1}^{n} I_k \leq 1\}.$$

It is easy to see that the set Ω is positively invariant. Our aim is to define basic reproduction numbers of the strains such that if the parameter-functions $\mu(t)$, $\beta_j(t)$, $\gamma_j(t)$ are assumed constant, the reproduction numbers of the strains for the system with

constant coefficients are recovered. To define the basic reproduction numbers of the strains, we first introduce the average of a periodic function over its period. If $f(t)$ is a periodic function of period ω, then the average of f is given by

$$< f >= \frac{1}{\omega}\int_0^\omega f(t)\,dt.$$

It is not hard to see (a proof is given in [43], section 3.1.2) that

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t f(s)\,ds =< f > .$$

We define the reproduction numbers of the strains as

$$\mathcal{R}_j = \frac{<\beta_j>}{<\mu>+<\gamma_j>}, \qquad j=1,\dots,n.$$

This definition is basically the same definition as in [27] and a special case of the definition preceding Theorem 3.1 in [41]. The disease-free equilibrium of the system (2.1) is given by $\mathcal{E}_0 = (1,0,\dots,0)$. To establish the local stability or instability of the disease-free equilibrium we linearize around the disease-free equilibrium. Let $S(t) = s(t)+1$, $I_j(t) = i_j(t)$, for $j = 1,\dots n$, where $s(t)$ and $i_j(t)$ are the perturbations. Clearly $i_j(t)$ are nonnegative, but $s(t)$ does not necessarily have a definite sign. The systems for the perturbations becomes:

$$\begin{aligned} &\frac{ds}{dt} = -\textstyle\sum_{j=1}^n \beta_j(t) i_j + \sum_{j=1}^n \gamma_j(t) i_j \\ &\frac{di_j}{dt} = \beta_j(t) i_j - (\mu(t)+\gamma_j(t)) i_j, \qquad j=1,\dots,n \end{aligned} \tag{2.3}$$

Solving the equation for $i_j(t)$ we get

$$i_j(t) = i_j(0) e^{\int_0^t [\beta_j(s)-(\mu(s)+\gamma_j(s))]\,ds}$$

If $\mathcal{R}_j < 1$ then $\lim_{t\to\infty} i_j(t) = 0$ for $j = 1,\dots,n$. If, however, $\mathcal{R}_j > 1$ for some j, then $i_j(t) \to \infty$. We have established the following result:

Proposition 2.1. *The disease-free equilibrium $\mathcal{E}_0 = (1,0,\dots,0)$ of the system (2.1) is locally asymptotically stable if $\mathcal{R}_j < 1$ for all $j = 1,\dots,n$. If there exists $\mathcal{R}_k > 1$, then the disease-free equilibrium $\mathcal{E}_0$ is unstable.*

In fact a stronger result is possible. The following proposition gives a sufficient condition for the eradication of strain j. We will see in the next section that if that condition fails to hold, then the corresponding strain can survive in the absence of competition.

Proposition 2.2. *If $\mathcal{R}_j < 1$ for some j, then*

$$I_j(t) \to 0 \qquad as \qquad t\to\infty.$$

To see this result, notice that since $S(t) \le 1$ we have

$$I_j'(t) \le \beta_j(t) I_j(t) - (\mu(t)+\gamma_j(t)) I_j(t).$$

Solving this inequality we have

$$I_j(t) = I_j(0) e^{\int_0^t [\beta_j(s)-(\mu(s)+\gamma_j(s))]\,ds}$$

Thus, $I_j(t) \to 0$ as $t\to\infty$.

Proposition 2.2 implies that if $\mathcal{R}_j < 1$ for all $j = 1,\dots,n$, then the disease-free equilibrium $\mathcal{E}_0$ is globally asymptotically stable.

3. Existence of single-strain periodic solution

In this section we show that if $\mathcal{R}_j > 1$ for some j and $\mathcal{R}_k < 1$ for all $k = 1, \dots, n$ and $k \neq j$, then strain j may survive, while the rest will be eliminated. Without loss of generality we may assume $\mathcal{R}_1 > 1$, and the remaining basic reproduction numbers are smaller than one. As a first step we assume $I_k(0) = 0$ for $k = 2, \dots, n$. This implies that $I_k(t) = 0$ for all t. We will show that if $\mathcal{R}_1 > 1$, then the equation

$$\frac{dI}{dt} = \beta(t)(1 - I)I - (\mu(t) + \gamma(t))I \tag{3.1}$$

has a unique positive periodic solution $\xi(t)$. In the above equation we have omitted the subscript one. Equation 3.1 is known as the periodic Bernoulli equation and has received much attention in the literature. As a result the fact that it has a unique periodic solution is well-known. For alternative approach to it see [43].

We are considering equation (3.1) on the domain

$$\Omega_1 = \{I : I \in [0, 1]\}.$$

To see the existence of a periodic solution, we define the operator $\mathcal{P}$ which maps the interval $[0, 1]$ into itself:

$$\mathcal{P} : [0, 1] \longrightarrow [0, 1].$$

The operator $\mathcal{P}$ is the Poincaré map whose action is defined as follows. If $I(0) = I_0$, then

$$\mathcal{P}(I_0) = I(\omega, I_0)$$

where, $I(t, I_0)$ is the solution of the equation (3.1) which starts at I_0. The Poincaré map is continuously differentiable, one-to-one. It satisfies: $\mathcal{P}(0) = 0$, and $\mathcal{P}(1) < 1$. The number $I_p \in [0, 1]$ is an initial value of a periodic solution if and only if

$$\mathcal{P}(I_p) = I_p$$

that is, if I_p is a fixed point of the Poincaré map. Therefore, in order to show existence of a positive, periodic solution of (3.1), we have to show that the Poincaré map has a fixed point. Denote by

$$v(t) = \frac{\partial I}{\partial I_0}(t, I_0).$$

Then the derivative of the Poincaré map is given as follows:

$$\mathcal{P}'(I_0) = \frac{\partial I}{\partial I_0}(\omega, I_0) = v(\omega).$$

One can obtain the derivative of the Poincaré map by differentiating the equation (3.1) by the initial condition I_0:

$$v'(t) = v(t)[\beta(t)(1 - I(t, I_0)) - (\mu(t) + \gamma(t)) - \beta(t)I(t, I_0)]$$

Differentiating the initial condition of $I(0) = I_0$ by I_0 we obtain the following initial condition for v: $v(0) = 1$. The differential equation for v can be solved. That gives the following expression for the derivative of the Poincaré map:

$$\mathcal{P}'(I_0) = e^{\int_0^\omega [\beta(t)(1 - I(t, I_0)) - (\mu(t) + \gamma(t)) - \beta(t)I(t, I_0)]\, dt}.$$

Clearly $\mathcal{P}'(I_0) > 0$. This implies that Poincaré map is increasing. Thus, if I_1 and I_2 are two initial conditions satisfying $I_1 < I_2$ then $\mathcal{P}(I_1) < \mathcal{P}(I_2)$. Furthermore,

$$\mathcal{P}'(0) = e^{\int_0^\omega [\beta(t)-(\mu(t)+\gamma(t))]\,dt} = e^{\omega[<\beta>-(<\mu>+<\gamma>)]}.$$

This implies that $\mathcal{P}'(0) > 1$ because $\mathcal{R}_1 > 1$. Hence, for I_0 small enough we have

$$\frac{\mathcal{P}(I_0) - P(0)}{I_0} \approx \mathcal{P}'(0) > 1.$$

Therefore,

$$\mathcal{P}(I_0) > I_0$$

for I_0 small enough. Since $\mathcal{P}(1) < 1$ then $\mathcal{P}(I_0) - I_0$ changes sign in the interval (0,1). Therefore, there exists I_p, such that

$$\mathcal{P}(I_p) = I_p.$$

This establishes the existence of a positive periodic solution of (3.1).

To show uniqueness, assume there exist two fixed points I_{p1} and I_{p2} which are distinct. Without loss of generality we may assume $I_{p1} < I_{p2}$. We have

$$|I_{p1} - I_{p2}| = |P(I_{p1}) - \mathcal{P}(I_{p2})| = |\mathcal{P}'(I_m)||I_{p1} - I_{p2}| \tag{3.2}$$

where I_m satisfies $I_{p1} < I_m < I_{p2}$. These last inequalities imply

$$I(t, I_{p1}) < I(t, I_m) < I(t, I_{p2}).$$

First, we note that if $I(t, I_p)$ is a periodic solution that satisfies equation (3.1), then

$$\int_0^\omega [\beta(t)(1 - I(t, I_p)) - (\mu(t) + \gamma(t))]\,dt = 0.$$

Hence,

$$\begin{aligned} \mathcal{P}'(I_m) &= e^{\int_0^\omega [\beta(t)(1-I(t,I_m))-(\mu(t)+\gamma(t))-\beta(t)I(t,I_m)]\,dt} \\ &< e^{\int_0^\omega [\beta(t)(1-I(t,I_{p1}))-(\mu(t)+\gamma(t))-\beta(t)I(t,I_m)]\,dt} \\ &= e^{-\int_0^\omega \beta(t)I(t,I_m)\,dt} < 1 \end{aligned} \tag{3.3}$$

Thus, we obtain a contradiction with (3.2). The contradiction is a result of the assumption that we have two distinct positive periodic solutions.

Summarizing the results in this section we have the following Theorem.

Theorem 3.1. *For each i for which $\mathcal{R}_i > 1$, there exist a unique, positive periodic function $\xi_i(t)$ such that $(0, 0, \ldots, 0, \xi_i(t), 0 \ldots, 0)$ is a solution to the system (2.2). Furthermore, if $(0, \ldots, 0, I_i(t), 0 \ldots, 0)$ is a solution of the system (2.2) starting from $I_i(0) > 0$, we have*

$$\lim_{t\to\infty} |I_i(t) - \xi_i(t)| = 0. \tag{3.4}$$

To complete the proof of the Theorem we have to establish the convergence to the periodic solution. We again assume that $\mathcal{R}_1 > 1$, and we consider the solutions of equation (3.1). Let $I(t)$ is an arbitrary solution, starting from the initial condition I_0. We recall that I_p is the initial condition for the periodic solution. We assume that $I_0 \neq I_p$. We have two choices $\mathcal{P}(I_0) > I_0$ or $\mathcal{P}(I_0) < I_0$. Assume $\mathcal{P}(I_0) < I_0$. The other case can be addressed in a similar way. Since the Poicarè map is increasing, we have

$\mathcal{P}^n(I_0) < \mathcal{P}^{n-1}(I_0)$. Consequently, the sequence $\{\mathcal{P}^n(I_0)\}_{n=0}^{\infty}$ is decreasing, and since it is bounded, it must have a limit:

$$\lim_{n\to\infty} \mathcal{P}^n(I_0) = I_\infty.$$

The number I_∞ is necessarily a fixed point of the Pincarè map $\mathcal{P}(I_\infty) = I_\infty$. Thus, $I_\infty = 0$ or $I_\infty = I_p$. Assume that $I_\infty = 0$. Then for some N the number $\mathcal{P}^N(I_0)$ is small enough so that from the properties of the Poincarè map we have $\mathcal{P}^{N+1}(I_0) > \mathcal{P}^N(I_0)$ which contradicts the fact that the sequence is decreasing. Therefore, $I_\infty = I_p$. Consequently, the limit (3.4) holds. This completes the proof of the Theorem.

4. Local stability of the single-strain periodic solutions

The single-strain periodic solutions $\mathcal{E}_i(t) = (0, 0, \ldots, 0, \xi_i(t), 0 \ldots, 0)$ play the role of the dominance equilibria in models with constant coefficients. Just as in the constant coefficient case, the stability properties of these single-strain periodic solutions determine the outcome of the competition of the strains. Determining the global stability of the single-strain periodic solutions is only possible in some cases but it is difficult in the general case. We, however, can consider the local stability. To determine the local stability of each single strain periodic solution, one linearizes the system (2.2) around the single-strain periodic solution. Without loss of generality we may consider the single-strain solution corresponding to periodic solution for strain one $\mathcal{E}_1(t) = (\xi_1(t), 0 \ldots, 0)$. The other cases are symmetrical. Let $I_1(t) = x_1(t) + \xi_1(t)$ and $I_j(t) = x_j(t)$, where $x_j(t)$ with $j = 1, \ldots, n$ are the perturbations. Then the linearized system takes the form:

$$\begin{aligned} \frac{dx_1}{dt} &= \beta_1(t)(1-\xi_1(t))x_1 - \beta_1(t)\xi_1(t)\textstyle\sum_{k=1}^n x_k - (\mu(t)+\gamma_1(t))x_1, \\ \frac{dx_j}{dt} &= \beta_j(t)(1-\xi_1(t))x_j - (\mu(t)+\gamma_j(t))x_j, \qquad j = 2 \ldots n \end{aligned} \tag{4.1}$$

The linear system (4.1) can be written in vector form as $\mathbf{x}'(t) = A(t)\mathbf{x}(t)$ where $A(t)$ is the time-dependent matrix of the coefficients. The linearized systems gives the dynamics of the solutions near a periodic solution. To investigate the the stability of the zeroth solution of the linearized system, one has to use Floquet Theory. To use these theory, one needs a fundamental matrix. To find a fundamental matrix, we have to find a system of linearly independent solution of the system, that is we have to solve the system. Clearly, setting $x_k(t) = 0$ for $k = 2, \ldots, n$, and then solving the first equation, will give us one solution. The first equation becomes:

$$\frac{dx_1}{dt} = \beta_1(t)(1-\xi_1(t))x_1(t) - \beta_1(t)\xi_1(t)x_1(t) - (\mu(t)+\gamma_1(t))x_1(t) = a_{11}(t)x_1(t), \tag{4.2}$$

one solution of which is $x_1(t) = e^{\int_0^t a_{11}(s)ds}$, where $a_{11}(t)$ denotes the coefficient of x_1 in the right hand side. Hence, $(x_1(t), 0, \ldots, 0)$ is the first column of the fundamental matrix. To obtain the remaining solutions, we set $x_j(t) = 0$ for $j = 2, \ldots, n$ and $j \neq k$, where $k \neq 1$. Then we solve the kth equation:

$$x_k = e^{\int_0^t a_{kk}(s)ds}$$

where $a_{kk}(t)$ is the coefficient in front of x_k in the right hand side of the kth equation in the system (4.1). This value of $x_k(t)$ is substituted in the first equation, and the

first equation is then solved. The solution of the first equation in this case is a complex expression, which will be denoted by $x_{1k}(t)$. The following fundamental matrix is obtained:

$$\Phi(t) = \begin{pmatrix} e^{\int_0^t a_{11}(s)ds} & x_{12}(t) & \dots & x_{1n}(t) \\ 0 & e^{\int_0^t a_{22}(s)ds} & \dots & 0 \\ \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & e^{\int_0^t a_{nn}(s)ds} \end{pmatrix}$$

The Floquet multipliers are the eigenvalues of the matrix $\Phi(\omega)$. It is straightforward to see that they are

$$e^{\int_0^\omega a_{11}(s)ds}, \dots, e^{\int_0^\omega a_{nn}(s)ds}.$$

From here one can read off the Floquet exponents. The first Floquet exponent is different from the remaining exponents, and is given by the expression

$$\lambda_{11} = \frac{1}{\omega}\int_0^\omega \left[\beta_1(s)(1-\xi_1(s)) - \beta_1(s)\xi_1(s) - (\mu(s)+\gamma_1(s))\right] ds. \tag{4.3}$$

We recall that $\xi_1(t)$ is the periodic solution of the first equation. Therefore, this periodic solution satisfies the equation (3.1). We integrate equation (3.1) from zero to ω. Since we have

$$\int_0^\omega \xi_1'(t)dt = 0$$

we also have that

$$\int_0^\omega \left[\beta_1(s)(1-\xi_1(s)) - (\mu(s)+\gamma_1(s))\right] ds = 0.$$

Hence, the Floquet exponents are:

$$\begin{aligned} \lambda_{11} &= -\frac{1}{\omega}\int_0^\omega \beta_1(s)\xi_1(s)\, ds \\ \lambda_{12} &= \frac{1}{\omega}\int_0^\omega \left[\beta_2(s)(1-\xi_1(s)) - (\mu(s)+\gamma_2(s))\right] ds \\ &\dots \\ \lambda_{1n} &= \frac{1}{\omega}\int_0^\omega \left[\beta_n(s)(1-\xi_1(s)) - (\mu(s)+\gamma_n(s))\right] ds \end{aligned} \tag{4.4}$$

Clearly, the Floquet exponent $\lambda_{11} < 0$. Thus, the stability of the zero solution of the linearized system, and therefore the linear stability of the single-strain oscillatory solution $\mathcal{E}_1(t)$ of the system (2.2), depends on the remaining Floquet exponents. If $\lambda_{1j} < 0$ for all $j = 2, \dots, n$, then the single-strain oscillatory solution $\mathcal{E}_1(t)$ is locally asymptotically stable. If there exists $\lambda_{1k} > 0$ for some $2 \le k \le n$, then the single-strain oscillatory solution $\mathcal{E}_1(t)$ is unstable.

From the Floquet exponents we can define the invasion reproduction numbers of strain j at the equilibrium of strain one:

$$\hat{\mathcal{R}}_j^1 = \frac{< \beta_j(1-\xi_1) >}{< \mu > + < \gamma_j >} \qquad \text{for} \qquad j = 2, \dots, n.$$

The invasion reproduction numbers and the Floquet exponents are related: $\hat{\mathcal{R}}_j^1 < 1$ if and only if $\lambda_{1j} < 0$. The results of this section can be summarized in the following theorem.

Theorem 4.1. *The single-strain periodic solution* $\mathcal{E}_i(t) = (0, \dots, 0, \xi_i(t), 0, \dots, 0)$ *is locally asymptotically stable if*

$$\hat{\mathcal{R}}_j^i < 1 \qquad \text{for all} \qquad j = 1, \dots, n; j \neq i.$$

If $\hat{\mathcal{R}}_j^i > 1$ *for some* $j \neq i$*, then the single-strain periodic solution* $\mathcal{E}_i(t)$ *is unstable.*

In the remainder of this section we establish global stability of the single-strain periodic solution $\mathcal{E}_i(t)$ under given conditions. These conditions are sufficient but not necessary. We again derive the result for the single-strain periodic solution of strain one. Analogous results hold for the other single-strain periodic solutions.

Theorem 4.2. *If* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_j < 1$ *for* $j = 2, \dots, n$*, then the single-strain periodic solution* $\mathcal{E}_1(t) = (\xi_1(t), 0, \dots, 0)$ *is globally stable.*

To see this result we use Proposition 2.2. Let $\epsilon > 0$ be small so that $(1 - n\epsilon)\mathcal{R}_1 > 1$. Since Proposition 2.2 implies that $I_j(t) \to 0$ for $j = 2, \dots, n$ as $t \to \infty$. Then there exists T such that

$$I_j(t) \leq \epsilon \qquad \text{for} \quad t \geq T, j = 2, \dots, n.$$

By shifting the dynamical system (2.2) we may assume that

$$I_i(t) \leq \epsilon \qquad \text{for all} \quad t.$$

Thus, the solution of the first equation in system (2.2) satisfies the following inequalities:

$$\beta_1(t)(1 - n\epsilon - I_1)I_1 - (\mu(t) + \gamma_1(t))I_1 \leq \frac{dI_1}{dt} \leq \beta_1(t)(1 - I_1)I_1 - (\mu(t) + \gamma_1(t))I_1 \tag{4.5}$$

Together with the above inequalities, consider the following equations:

$$\begin{aligned} \frac{dX_1}{dt} &= \beta_1(t)(1 - X_1)X_1 - (\mu(t) + \gamma_1(t))X_1 \\ \frac{dY_1}{dt} &= \beta_1(t)(1 - n\epsilon - Y_1)Y_1 - (\mu(t) + \gamma_1(t))Y_1 \end{aligned} \tag{4.6}$$

The solution of the first equation of system (2.2) $I_1(t)$ satisfies

$$Y_1^\epsilon(t) \leq I_1(t) \leq X_1(t), \tag{4.7}$$

where $X_1(t)$ and $Y_1^\epsilon(t)$ are the solutions of the above two equations with the same initial conditions. The smaller the ϵ, the closer is the solution $Y_1^\epsilon(t)$ to $X_1(t)$. We saw in Section 3 that the first equation in (4.6) has a unique periodic solution $\xi_1(t)$. Similar deliberations as in Section 3 can show that the same is true for the second equation in (4.6), particularly because $(1 - n\epsilon)\mathcal{R}_1 > 1$. Denote by $\xi_1^\epsilon(t)$ the unique periodic solution of the second equation of (4.6). It can similarly be shown that that periodic solution is globally stable. Taking the limit as $t \to \infty$ in inequalities (4.7) by Theorem 3.1 we get

$$\xi_1^\epsilon(t) \leq I_1(t) \leq \xi_1(t).$$

Since the above inequalities are valid for any ϵ no matter how small, we obtain that $I_1(t) \to \xi_1(t)$ as $t \to \infty$. This completes the proof.

5. Coexistence

In this section we show that coexistence in a oscillatory regime is possible. Although we believe that the result below can be extended to n strains we consider a two-strain version of the model (2.2).

$$\begin{aligned} \frac{dI_1}{dt} &= \beta_1(t)(1-I_1-I_2)I_1 - (\mu(t)+\gamma_1(t))I_1, \\ \frac{dI_2}{dt} &= \beta_2(t)(1-I_1-I_2)I_2 - (\mu(t)+\gamma_2(t))I_2. \end{aligned} \tag{5.1}$$

The system (5.1) is competitive ([37], p. 33). If we denote by $f_i(t, I_1, I_2)$ the right hand side of equation i, for $i = 1, 2$, then

$$\begin{aligned} \frac{\partial f_1}{\partial I_2} &= -\beta_1(t)I_1 \leq 0 \\ \frac{\partial f_2}{\partial I_1} &= -\beta_2(t)I_2 \leq 0 \end{aligned} \tag{5.2}$$

Let $\mathcal{P}$ be the Poincarè map for the system (5.1). Therefore, if $\mathbf{I}_0 = (I_1(0), I_2(0))$, then $\mathcal{P}(\mathbf{I}_0) = (I_1(\omega, I_1(0)), I_2(\omega, I_2(0)))$. The following Theorem can be found in [40], p.170.

Theorem 5.1. *Let the sequence $\{\mathcal{P}^n(\mathbf{I}_0)\}_{n=1}^{\infty}$ be bounded. Then the sequence is converging, that is there exists $\mathbf{I}_p$ such that*

$$\lim_{n\to\infty} \mathcal{P}^n(\mathbf{I}_0) = \mathbf{I}_p.$$

Moreover, $\mathbf{I}_p$ is a fixed point of the Poincarè map $\mathcal{P}(\mathbf{I}_p) = \mathbf{I}_p$.

This theorem says that if $(I_1(t), I_2(t))$ is an arbitrary solution of system (5.1) starting from an arbitrary initial condition $(I_1(0), I_2(0))$, then there exists a periodic solution of the system (5.1), denoted by $(\eta_1(t), \eta_2(t))$ such that the solution $(I_1(t), I_2(t))$ converges to that periodic solution. The theorem does not say whether $\eta_1(t) \neq 0$ and $\eta_2(t) \neq 0$. Thus, in theory the limit periodic solution could be one of the single-strain periodic solutions $\mathcal{E}_1(t)$ or $\mathcal{E}_2(t)$ whose existence was established in the previous sections.

In what follows we show that under certain conditions the solution of the system (5.1) is persistent. We say that strain i is weakly uniformly persistent, if there exists $\delta > 0$, independent of the initial conditions, such that

$$\limsup_{t\to\infty} I_i(t) \geq \delta \qquad \text{for} \quad i = 1, 2.$$

We say that strain i is uniformly strongly persistent if there exists a number $\delta > 0$, independent of the initial conditions, such that

$$\liminf_{t\to\infty} I_i(t) \geq \delta \qquad \text{for} \quad i = 1, 2.$$

Clearly, if a strain is uniformly strongly persistent, it is also uniformly weakly persistent. The opposite statement is not true. We establish the uniform strong persistence for both strains in the following theorem.

Theorem 5.2. *Assume $\mathcal{R}_j > 1$ and that the invasion reproduction number of strain i is larger than one, $\hat{\mathcal{R}}_i^j > 1$. Then, strain i is uniformly strongly persistent.*

To see this result assume without loss of generality $\mathcal{R}_1 > 1$ and $\hat{\mathcal{R}}_2^1 > 1$. The first condition guarantees that strain one in the absence of strain two has a nontrivial periodic solution. The second condition says that strain two can invade the periodic solution of strain one. A consequence of the second condition is that $\mathcal{R}_2 > 1$. We will establish

uniformly strong persistence of strain two. The other case is established in the same way. First we establish the uniformly weak persistence. Assume the contrary, that is assume that for every ϵ we have $\limsup_{t\to\infty} I_2(t) \le \epsilon/2$. Then for a fixed $\epsilon > 0$ there exists T such that for all $t > T$, we have $I_2(t) \le \epsilon$.

From the first equation in (5.1) we obtain the following inequality:

$$I_1' \le \beta_1(t)(1 - I_1)I_1 - (\mu(t) + \gamma_1(t))I_1(t).$$

Let $X(t)$ be the solution of the equation corresponding to the above inequality and starting from the same initial condition as I_1 in the system (5.1). Thus, $X(t)$ solves:

$$X'(t) = \beta_1(t)(1 - X(t))X(t) - (\mu(t) + \gamma_1(t))X(t). \tag{5.3}$$

Then we have $I_1(t) \le X(t)$ for all t. Since $\mathcal{R}_1 > 1$, we know that equation (5.3) has a unique periodic solution $\xi_1(t)$, and every solution to equation (5.3) approaches that periodic solution. Thus, $X(t) \to \xi_1(t)$ as $t \to \infty$. We note that $\xi_1(t)$ is also the periodic function in the single-strain periodic solution $\mathcal{E}_1(t)$. Furthermore, there exists T_1 such that for all $t > T_1$ we have

$$I_1(t) \le \xi_1(t) + \epsilon.$$

Shifting the dynamical system we may assume that $I_2(t) \le \epsilon$ and $I_1(t) \le \xi_1(t) + \epsilon$ for all $t > 0$. Using these inequalities in the second equation of system (5.1) we have

$$I_2'(t) \ge \beta_2(t)(1 - \xi_1(t) - 2\epsilon)I_2(t) - (\mu(t) + \gamma_2(t))I_2(t)$$

Solving this inequality we have

$$I_2(t) \ge I_2(0)e^{\int_0^t [\beta_2(s)(1-\xi_1(s)) - (\mu(s)+\gamma_2(s))]\,ds - 2\epsilon\int_0^t \beta_2(s)\,ds}.$$

Assuming ϵ is small enough so that

$$\begin{aligned} \frac{1}{t}\left\{\int_0^t [\beta_2(s)(1 - \xi_1(s)) - (\mu(s) + \gamma_2(s))]\,ds - 2\epsilon\int_0^t \beta_2(s)\,ds\right\} \\ \to < \mu + \gamma_2 > (\hat{\mathcal{R}}_2^1 - 1) - 2\epsilon < \beta_2 >> 0 \end{aligned} \tag{5.4}$$

we get that $I_2(t) \to \infty$ as $t \to \infty$. That is a contradiction with our assumption that $I_2(t)$ is not uniformly weakly persistent. To show uniform strong persistence we use Theorem 2.3 in [41]. The existence of a compact attractive set follows from the fact that solutions are bounded $I_j(t) \le 1$ for all $t > 0$. The first condition in the theorem follows from the fact that $I_2(t) \ge I_2(s)e^{-\int_s^t \mu(\sigma)+\gamma_2(\sigma)\,d\sigma} > 0$ for all $s > 0$ such that $I_2(s) > 0$. Property (PS) can be established as in the case of the SIRS model in [41]. Then Theorem 2.3 in [41] implies the uniform strong persistence.

The above result leads to the following Corollary.

Corollary 5.1. *Assume $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$ and that both invasion reproduction numbers are larger than one, that is $\hat{\mathcal{R}}_1^2 > 1$ and $\hat{\mathcal{R}}_2^1 > 1$. Then, every solution converges to a coexistence periodic solution $\mathcal{E}^*(t) = (\eta_1(t), \eta_2(t))$, where $\eta_1(t) \ne 0$ and $\eta_2(t) \ne 0$.*

To see this corollary, we notice that under the above conditions Theorem 5.2 implies that both $I_1(t)$ and $I_2(t)$ are uniformly strongly persistent, that is there exists $\delta > 0$ such that

$$\liminf_{t\to\infty} I_1(t) \ge \delta \qquad \liminf_{t\to\infty} I_2(t) \ge \delta$$

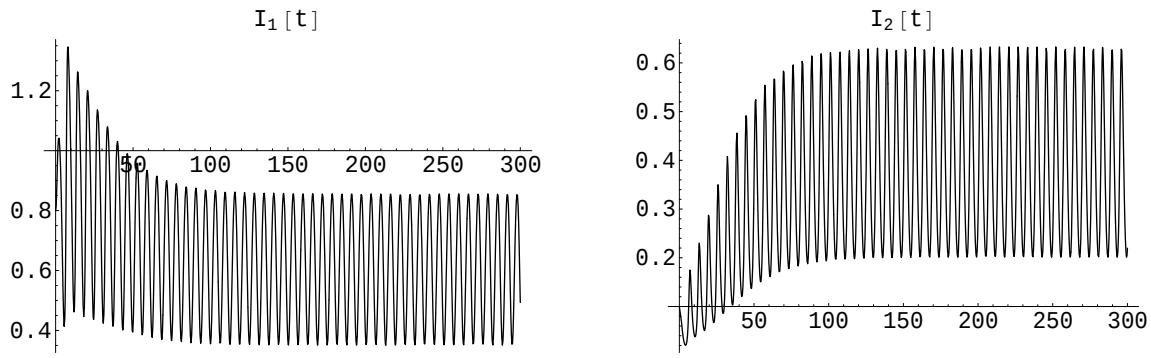

FIGURE 1. This figure gives an example of coexistence of the two strains in the population. The left figure illustrates that the number infected individuals with strain one $I_1(t)$ persists and tends to an oscillatory solution. The right figure illustrates that the number infected individuals with strain two $I_2(t)$ persists and tends to an oscillatory solution. The parameter values for both figures are: $\beta_1(t) = 1.1(1 + 0.9\sin(t))$, $\beta_2(t) = 1.5(1 + 0.1\cos(t))$, $\gamma_1 = 0.1$, $\gamma_2 = 0.5$, $\mu = 0.5$. The reproduction numbers of the two strains are $\mathcal{R}_1 = 1.83333$, $\mathcal{R}_2 = 1.5$.

for all initial conditions $(I_1(0), I_2(0))$ with both components being nonzero. Theorem 5.1 implies, however, that those solutions converge to a periodic solution $(\eta_1(t), \eta_2(t))$. Since,

$$\liminf_{t\to\infty} I_i(t) = \liminf_{t\to\infty} \eta_i(t) > \delta$$

we have that the two components of the periodic solution $\eta_1(t)$ and $\eta_2(t)$ are both nonzero. Therefore, the convergence is to a coexistence periodic solution.

We illustrate the periodic coexistence in Figure 1. The results in Theorem 5.2 and Corollary 5.1 presumably can be obtained from [32] but the rescaling there makes the mathematical conditions imposed difficult to interpret biologically.

6. Is periodicity in the contact rate sufficient for coexistence?

We motivated the consideration of multi-strain epidemic models with periodic coefficients by the observed periodicity in childhood diseases and influenza. In the case of the childhood diseases it has been suggested that periodicity stems from the school-year system which makes the contact rate among children periodic. Is periodic contact rate sufficient to sustain pathogen diversity? We address this question in this section. We recall that in the constant coefficient case the transmission rate of strain i is a product of the contact rate of the population c (assuming that all classes have the same contact rate) and the probability of transmission of strain i – p_i:

$$\beta_i = cp_i.$$

We consider the model (2.1) under the assumption that the strain-specific periodic transmission rate $\beta_i(t)$ is represented as follows:

$$\beta_i(t) = c(t)p_i$$

where the contact rate $c(t)$ is a nonnegative periodic function of period ω and the probability of transmission of strain i remains constant. The reproduction number of strain i is then given by:

$$\mathcal{R}_i = \frac{p_i < c >}{< \mu > + < \gamma_i >}.$$

Surprisingly, coexistence does not occur, and competitive exclusion is the only outcome of the multi-strain competition in periodic environments, even if the remaining parameters $\mu(t)$ and $\gamma_i(t)$ are still assumed periodic (see [42]). As before, the strain with the largest reproductive number eliminates the rest. This result is established in the following theorem, where we have assumed without loss of generality that strain one has the largest reproduction number.

Theorem 6.1. *Assume $\mathcal{R}_i > 1$ for $i = 1, \ldots, n$. Assume, in addition, that $\mathcal{R}_1 > \mathcal{R}_j$ for $j = 2, \ldots, n$. Then,*

$$I_j(t) \to 0 \qquad j = 2, \ldots, n, \qquad as \qquad t \to \infty$$

and

$$I_1(t) \to \xi_1(t) \qquad as \qquad t \to \infty.$$

To see the claim in this theorem, for a fixed $j > 1$ consider the quantity

$$\eta(t) = \frac{I_1^{p_j}(t)}{I_j^{p_1}(t)}.$$

Differentiating η with respect to time we get:

$$\eta'(t) = \eta(t)[p_1 p_j c(t) S(t) - p_j(\mu(t) + \gamma_1(t))] - \eta(t)[p_1 p_j c(t) S(t) - p_1(\mu(t) + \gamma_j(t))]$$

Simplifying the expression on the right hand side we obtain:

$$\eta'(t) = \eta(t)[p_1(\mu(t) + \gamma_j(t)) - p_j(\mu(t) + \gamma_1(t))].$$

Dividing by $\eta(t)$, integrating from zero to t, and dividing by t to get the averages, we are lead to:

$$\frac{1}{t} \ln \frac{\eta(t)}{\eta(0)} = p_1 p_j \left[\frac{1}{t} \int_0^t \frac{\mu(\sigma) + \gamma_j(\sigma)}{p_j} d\sigma - \frac{1}{t} \int_0^t \frac{\mu(\sigma) + \gamma_1(\sigma)}{p_1} d\sigma \right].$$

Taking the limit as $t \to \infty$, the right hand side above converges to the positive number

$$p_1 p_j < c > \left(\frac{1}{\mathcal{R}_j} - \frac{1}{\mathcal{R}_1} \right).$$

Since $\lim_{t\to\infty} \ln \frac{\eta(t)}{\eta(0)} > 0$ and $\eta(0) > 0$, then clearly $\eta(t) \to \infty$ as $t \to \infty$. Since $I_1(t)$ is bounded, the fact that $\eta(t) \to \infty$ as $t \to \infty$ implies that

$$I_j(t) \to 0 \qquad \text{as} \qquad t \to \infty.$$

Then, similarly to 4.2 one can show that strain one persists, and in fact the solutions of the system (2.2) converge to $\mathcal{E}_1(t)$.

7. Summary of results

In this paper we introduce an n-strain SIS model with periodic coefficients. The birth and death rates are assumed to be the same so that the total population is constant and equal to one. That is, the number of individuals in each class is in fact the proportion of individuals in the various classes. For this model we succeed in defining reproduction numbers for each strain $\mathcal{R}_i$ which agree with the corresponding reproduction numbers of the autonomous system obtained from system (2.1) by assuming all coefficients constant and equal to the averages of time dependent coefficients. We establish the following results:

(1) There is a unique disease-free equilibrium which is locally and globally stable if all reproduction numbers are smaller than one. The disease-free equilibrium is unstable if one of the reproduction number is greater than one. These observations agree with similar observations made for multi-strain autonomous models.
(2) Moreover, we establish that if $\mathcal{R}_i < 1$ for any strain i, then the number of individuals infected with this strain will go to zero, independently of the behavior of the other infective classes.
(3) We establish that to each strain there corresponds a unique single-strain periodic solution, if its reproduction number is greater than one. This periodic solution is globally stable in the hyper-plane where all other strains are extinct.
(4) The single-strain periodic solution is locally stable if the invasion numbers of all other strains at the equilibrium of the resident strain are less than one. The single-strain periodic solution is unstable if there is an invasion number grater than one.
(5) For the model with two strains we establish the existence of at least one periodic coexistence solution. As a part of this result, we derive conditions on the reproduction numbers and invasion reproduction numbers that guarantee uniform strong persistence of a strain.
(6) Finally, for the n-strain model we establish that if the transmission rate is periodic because the contact rate is periodic, but the probability of transmission given a contact is constant, $\beta_i(t) = c(t)p_i$, then coexistence does not occur, and competitive exclusion is the only outcome. In agreement with the autonomous system the strain with the largest reproduction number eliminates the rest.

The techniques used to establish competitive exclusion for the multi-strain SIR model in [7] could be used to establish that competitive exclusion is the only outcome in the autonomous version of model (2.1) with constant coefficients equal to the averages of the periodic coefficients. In contrast, our results show that the non-autonomous model (2.1) allows for coexistence. This result, however, is not entirely surprising. Coexistence between two competing bacteria as a result of periodicity in the dilution rate has been obtained in [40]. What causes the coexistence in our case? Our results shaw that coexistence occurs as a result of distinct, periodic transmission rates for the strains $\beta_i(t)$ which are not linearly dependent. As Figure 1 shows in this case periodicity in the death and recovery rates is not necessary. If the transmission rates are periodic only because of the contact rate, that is, they have the form:

$$\beta_i(t) = p_i c(t) \qquad i = 1, \dots, n$$

competitive exclusion is the only outcome. This observation has an interesting implication for influenza. The periodicity in influenza prevalence has facinated researchers for quite some time. Influenza seasonality is still not very well understood. Multiple hypotheses have been set forth [21]. Our results here suggest that from the hypotheses seth forth in [21], the mechanism(s) that have the potential to lead to influenza's seasonality, given influnza's genetic diversity, are those that could lead to periodic probability of transmission/susceptibility.

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