Sustained Oscillations in an Evolutionary Epidemiological Model of Influenza A Drift

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Abstract

Understanding the seasonal/periodic reoccurrence of influenza will be very helpful in designing successful vaccine programs and introducing public health interventions. However, the reasons for seasonal/periodic influenza epidemics are still not clear even though various explanations have been proposed. In this paper, we study an age-structured type evolutionary epidemiological model of influenza A drift, in which the susceptible class is continually replenished because the pathogen changes genetically and immunologically from one epidemic to the next, causing previously immune hosts to become susceptible (Pease, *Theoret. Pop. Biol.* **31** (1987), 422-452). Applying our recent established center manifold theory for semilinear equations with non-dense domain, we show that Hopf bifurcation occurs in the model. This demonstrates that the age-structured type evolutionary epidemiological model of influenza A drift has an intrinsic tendency to oscillate due to the evolutionary and/or immunological changes of the influenza viruses.

Key words. Epidemic model, endemic equilibrium, stability, Hopf bifurcation, influenza A drift.

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Contents

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1 Introduction

Influenza viruses are negative-stranded RNA viruses which are divided into three types: A, B, and C, based on antigenic differences in nucleoprotein and matrix protein (Schweiger et al. [40], Earn et al. [12], WHO [53]). Influenza A and B are currently associated with human diseases, while influenza C has only subclinical importance (Schweiger et al. [40]). Influenza A viruses are further classified into subtypes based on two different spike-like protein components, *hemagglutinin* (HA) and *neuraminidase* (N), called antigens, on the surface of the virus (WHO [53]). There are 16 different HA subtypes and 9 different NA subtypes. H1N1 (the subtype responsible for the 1918 Spanish pandemic) and H3N2 (the strain caused the 1968 Hong Kong pandemic) are two influenza A subtypes that are important for human (WHO [53]), which, together with influenza B, are included in each year's influenza vaccine (CDC [8]).

Genes of influenza viruses mutate with high frequency (Buonagurio et al. [6], Fitch [15]) which plays an important role in causing reccurent influenza epidemics (Pease [38]). Influenza type A viruses undergo two kinds of changes. *Antigenic drift* is a major process that accumulates point mutations at the antibody sites in the HA protein, leading to the emergence of immunologically distinct strains and enabling the viruses to evade recognition by hosts' antibodies (Treanor [49], Shih et al. [41], Schweiger et al. [40]). The immunologically distinct influenza virus strains can reinfect hosts that are immune to the progenitor influenza strain and reinvade the communities that recently suffered an epidemic of the progenitor strain (Pease [38]). *Antigenic shift* is an abrupt major change resulting in new HA and/or new HA and N proteins in influenza viruses that infect humans. When shift happens, most people have little or no protection against the new influenza A subtype virus. While influenza viruses are changing by antigenic drift all the time, antigenic shift happens only occasionally and causes pandemics (CDC [8], WHO [53]).

During antigenic drift, point mutations include substitutions, deletions, and insertions produce genetic variation in influenza viruses. These genetic changes encode amino acid changes in the surface proteins that permit the virus to escape neutralization by antibody generated to previous strains (Cox and Subbarao [9]). It is reported that for sites involved in antigen determination, amino acid substitutions are more frequent than synonymous substitutions (Ina and Gojobori [20], Earn et al. [12]). Also, an approximately equal number of amino acid substitutions occur in the influenza each year between the immunizing and challenge virus strains (Pease [38], Smith et al. [42]), Koelle et al. [27].

To study the evolutionary epidemiological mechanism of influenza A drift, Pease [38] developed an age-structured type model in which the susceptible class is continually replenished because the pathogen changes genetically and immunologically from one epidemic to the next, causing previously immune hosts to become susceptible. Conditions were derived to show how the equilibrium number of infected hosts, the interepidemic period, and the probability that a host becomes reinfected depend on the rate of amino acid substitution in the pathogen, the effect on these substitutions on host immunity, the host size, and the recovery rate. However, applied to influenza A the model only predicted damped oscillations, while the observed oscillations in the incidence of influenza are undamped over the long term (Pease [38], Dushoff et al. [11], Viboud et al. [50]).

Pease's model has been modified and improved by several researchers. For example, Thieme and Yang [48] re-parameterized Pease's model by using recovery age, which is the duration of time that has passed since the moment of recovering from the disease, as a structural variable. They investigated uniform disease persistence and global stability of the endemic equilibrium in their model with variable re-infection rate. Andreasen et al. [2] improved Pease's model by including mutation as a diffusion process in a phenotype space of variants. The existence of traveling waves in this generalized SIR model of influenza A drift was established by Lin et al. [29]. Andreasen et al. [3] developed models that describe the dynamics of multiple influenza A strains conferring partial cross-immunity and showed that such models exhibit sustained oscillations. See also Castillo-Chavez et al. [7], Lin et al. [30], Andreasen [1], Nuño et al. [37] and the references cited therein for other multiple strain influenza models with cross-immunity or immune-selection. Note that Castillo-Chavez et al. [7] observed that sustained oscillations do not seem possible for a single-strain model even with age-specific mortalities.

Inaba [21, 22] modified Pease's model slightly by assuming that the effect of amino acid substitutions on host immunity (the transmission rate) is a monotone increasing function with a finite upper bound, proved the existence and uniqueness of solutions of the model, and studied the stability of the endemic steady state by using the semigroup approach. Inaba [22] further conjectured that for realistic parameter values, the steady state could be destabilized and lead to a periodic solution via Hopf bifurcation.

The existence of non-trivial periodic solutions in age structured models has been a very interesting and difficult problem. It is believed that such periodic solutions are induced by Hopf bifurcation, however there is no general Hopf bifurcation theorem available for age structured models (Inaba [22]). One of the difficulties is that, rewriting age structured models as a semilinear equation, the domain of the linear operator may be not dense. Recently, we (Magal and Ruan [33]) developed the center manifold theory for semilinear equations with non-dense domain.

In this paper, following the pioneer work of Kermack and McKendrick [24, 25, 26], we first modify the model of Pease [38] and Inaba [22] by using the age of infection (instead of the number of amino acid substitutions) as a variable. We then apply the center manifold theorem in Magal and Ruan [33] to study Hopf bifurcation in the age-structured type evolutionary epidemiological model of influenza A drift. The results indicate that sustained oscillations can occur in such models with a single strain (Castillo-Chavez et al. [7]) and without the seasonal force (Dushoff et al. [11]). Thus, the periodic recurrence of influenza may be a result of the evolutionary and/or immunological changes of the influenza viruses.

2 The Model

To model the evolutionary epidemiological mechanism of influenza A drift, Pease [38] made the following assumptions: (i) There is an approximately linear relation between the probability of reinfection and the number of amino acid substitutions between the immunizing and challenge virus strains. (ii) Only one virus strain circulates in the human population at any one time. (iii) Random drift causes amino acid substitutions to occur in the influenza virus.

Suppose that the total host population size N is a constant. Let $I(t)$ be the number of infected individuals at time t. Let $a \geq 0$ be the time since the last infection, that is, the duration of time since a individual has been susceptible. Assume that the average number of amino acid substitutions is a continuous variable. More precisely, let $k > 0$ be the average number of amino acid substitutions per unit of time (that is, the mutation rate). Then the number of substitutions after a period of time a in the susceptible class is given by ka. Let $s(t,a)$ be the density of uninfected hosts (structured with respect to a), so that

$$\int_{a_0}^{a_1} s(t,a)da = \int_{ka_0}^{ka_1} s(t,k^{-1}l)k^{-1}dl$$

is the number of uninfected hosts that were last infected by a virus which differed by more than ka_0 and less than ka_1 amino acid substitutions from the virus strain prevailing at time t. Here we consider a modified version of the model considered by Pease [38] and Inaba [21, 22]. The model to describe the evolutionary epidemiological model of influenza A drift takes the following form

$$\begin{cases} \dfrac{\partial s(t,a)}{\partial t} + \dfrac{\partial s(t,a)}{\partial a} = -\gamma(ka)s(t,a)I(t),\ t \geq 0,\ a \geq 0, \\ s(t,0) = \nu I(t), \\ \dfrac{dI(t)}{dt} = -\nu I(t) + I(t) \int_0^{+\infty} \gamma(kl)s(t,l)dl, \\ s(0,.) = s_0 \in L^1_+(0,+\infty) \text{ and } I(0) = I_0 \geq 0, \end{cases} \tag{2.1}$$

where $\nu > 0$ is the recovery rate of the infected hosts and $\gamma \in L^\infty_+(0,+\infty)$ describes how amino acid substitutions affect the probability of reinfection.

First, we make the following assumptions.

Assumption 2.1 Assume that $k > 0$, $\nu > 0$, $\gamma \in L^{\infty}_{+}(0, +\infty)$, and $\liminf_{a\to+\infty} \gamma(ka) > 0$.

From now on, we set

$$S(t) := \int_0^{+\infty} s(t,a)da.$$

In this model we do not have a disease free equilibrium. Indeed, we observe that if $I_0 = 0$, then

$$I(t) = 0,\ \forall t \geq 0,\ \ s(t,a) = \begin{cases} s_0(a-t), & \text{if } a \geq t, \\ 0, & \text{if } a < t \end{cases}$$

is a solution of equation (2.1). So we do not obtain an equilibrium solution in the usual sense. Nevertheless the total number of susceptible individuals remains constant with time, that is, $S(t) = S_0 := \int_0^{+\infty} s_0(a)da, \forall t \geq 0$. It is clear that

$$\frac{dS(t)}{dt} = \nu I(t) - I(t) \int_0^{+\infty} \gamma(kl)s(t,l)dl,$$

so $\frac{d[S(t)+I(t)]}{dt} = 0$. It follows that $I(t) = N - S(t),\ \ \forall t \geq 0$, where N is the total number of individuals in the population. With this, we can rewrite system (2.1) as follows:

$$\begin{cases} \dfrac{\partial s(t,a)}{\partial t} + \dfrac{\partial s(t,a)}{\partial a} = -\gamma(ka)s(t,a)\left(N - \int_0^{+\infty} s(t,l)dl\right),\ t \geq 0,\ a \geq 0, \\ s(t,0) = \nu\left(N - \int_0^{+\infty} s(t,l)dl\right), \\ s(0,.) = s_0 \in L^1_+(0,+\infty) \text{ with } \int_0^{+\infty} s_0(l)dl \leq N. \end{cases} \tag{2.2}$$

In Peace's original article [38] the function $\gamma(ka)$ is a linear function. To consider such unbounded functions, we must change the state space by introducing the weighted L^1 space in order to discuss the existence of solutions. Since this is not the goal of this work, we make a simplified assumption that $\gamma(ka)$ is bounded. More precisely, we consider the following step function. Define

$$\rho := \tau/k$$

as the threshold of sensitivity, where τ will be discussed late. We make following assumption.

Assumption 2.2 Assume that

$$\gamma(ka) := \begin{cases} \delta, & \text{if } a \geq \rho \\ 0, & \text{if } a \in (0,\rho), \end{cases}$$

where $\delta > 0$ and $\rho \geq 0$.

The function $\gamma(ka)$ describes the rate at which individuals become re-infected per average number of amino acid substitution ka. The above construction thus provides a threshold ρ which is the time necessary to be re-infected after one infection. This is also equivalent to assume that it is necessary to reach an threshold value τ for the average number of amino acid substitutions before re-infection. When the threshold value $\rho = 0$, the function $\gamma(ka)$ becomes a constant δ, and $S(t)$ satisfies the following ordinary differential equation

$$\frac{dS(t)}{dt} = (\nu - \delta S(t))\, I(t) = (\nu - \delta S(t))\,(N - S(t))\,.$$

The following is an easy consequence of the fact that $S(t)$ satisfies the above ordinary differential equation.

Lemma 2.3 *Let Assumptions 2.1 and 2.2 be satisfied and assume that $\tau = 0$. Then there are two cases:*

(a) If $\dfrac{\nu}{\delta} \geq N$ and $I(0) = N - S(0) > 0$, then $S(t) \to N$ and $I(t) \to 0$ as $t \to +\infty$.

(b) If $\dfrac{\nu}{\delta} < N$, then system (2.1) has a unique equilibrium solution $(\overline{s}(\cdot), \overline{I})$ such that $\overline{S} = \int_0^{+\infty} \overline{s}(a)da = \frac{\nu}{\delta}$, $\overline{s}(a) = \nu \overline{I} e^{-\delta \overline{I} a}$, and $\overline{I} = N - \frac{\nu}{\delta}$. Moreover, if $I(0) = N - S(0) > 0$, then $s(t,a) \to \overline{s}(a)$ as $t \to +\infty$ in $L^1(0,+\infty)$. Furthermore, $(\overline{s}(\cdot), \overline{I})$ is globally asymptotically stable for system (2.1) in

$$M_0 = \left\{ (\varphi, I) \in L^1_+(0,+\infty) \times (0,+\infty) : \int_0^{+\infty} s(l)dl + I = N \right\}.$$

The above lemma shows that when $\tau = 0$, if there exists an endemic equilibrium then it is locally asymptotically stable. Nevertheless, since the system does not depend smoothly on τ, we cannot conclude that for $\tau > 0$ small enough the endemic equilibrium $(\overline{s}(\cdot), \overline{I})$ is also asymptotically stable.

From now on we assume that $\tau > 0$ and make the following change of variable. By considering

$$u(t,a) = \frac{\rho s(\rho t, \rho a)}{N},$$

we obtain

$$\begin{cases} \dfrac{\partial u(t,a)}{\partial t} + \dfrac{\partial u(t,a)}{\partial a} = -\rho N \gamma(k\rho a) u(t,a) \left(1 - N^{-1} \int_0^{+\infty} s(\rho t, l)dl\right), \ t \geq 0, \ a \geq 0, \\ u(t,0) = \rho\nu \left(1 - N^{-1} \int_0^{+\infty} s(\rho t, l)dl\right) \end{cases}$$

and

$$N^{-1} \int_0^{+\infty} s(\rho t, l)dl = N^{-1} \int_0^{+\infty} s(\rho t, \rho r)\rho dr = \int_0^{+\infty} u(t,s)ds.$$

Thus, by the above changes of variables we obtain the following system

$$\begin{cases} \dfrac{\partial u(t,a)}{\partial t} + \dfrac{\partial u(t,a)}{\partial a} = -\rho\delta N \chi(a) u(t,a) \left(1 - \int_0^{+\infty} u(t,l)dl\right), \ t \geq 0, \ a \geq 0, \\ u(t,0) = \rho\nu \left(1 - \int_0^{+\infty} u(t,l)dl\right), \\ u(0,.) = u_0(\cdot) \in L^1_+(0,+\infty) \ \text{with} \ \int_0^{+\infty} u_0(l)dl \leq 1, \end{cases} \tag{2.3}$$

where

$$\chi(a) := \begin{cases} 1, \ \text{if } a \geq 1 \\ 0, \ \text{if } a \in [0,1). \end{cases}$$

Since the case $\tau = 0$ has been fully described in Lemma 2.3, in the sequel we will only consider the case $\tau > 0$. Moreover, by making the above changes of variables, and by replacing the parameters δ and ν respectively by $\hat{\delta} = \rho\delta N$ and $\hat{\nu} = \rho\nu$ in system (2.2), we can assume without loss of generality that

$$\rho = 1 \text{ and } N = 1.$$

3 Preliminary results

The global existence and positivity of solutions follow by considering the system

$$\begin{cases} \dfrac{\partial s(t,a)}{\partial t} + \dfrac{\partial s(t,a)}{\partial a} = -\delta \chi(a) s(t,a) \left(1 - \int_0^{+\infty} s(t,l)dl\right)^+, \ t \geq 0, \ a \geq 0, \\ s(t,0) = \nu \left(1 - \int_0^{+\infty} s(t,l)dl\right)^+, \\ s(0,.) = s_0 \in L^1_+(0,+\infty) \ \text{with} \ \int_0^{+\infty} s_0(l)dl \leq 1, \end{cases} \tag{3.1}$$

where $x^+ = \max(x,0)$.

3.1 Global existence

In order to give a sense to the solutions of problem (3.1) we will use integrated semigroup theory. We refer to Arendt [4], Neubrander [36], Kellermann and Hieber [23], Thieme [45, 47], Arendt *et al.* [5], and Magal and Ruan [32, 33, 34] for more detailed results on the subject.

Consider the Banach space $X = \mathbb{R} \times L^1(0,+\infty)$ endowed with the usual product norm $\|\begin{pmatrix} \alpha \\ \varphi \end{pmatrix}\| = |\alpha| + \|\varphi\|_{L^1}$. Consider a linear operator $A : D(A) \subset X \to X$ defined by

$$A\begin{pmatrix} 0 \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' \end{pmatrix} \quad \text{with} \quad D(A) = \{0\} \times W^{1,1}(0,+\infty).$$

Then $X_0 := \overline{D(A)} = \{0\} \times L^1(0,+\infty)$. Set $X_+ := \mathbb{R}_+ \times L^1_+(0,+\infty)$ and $X_{0+} := X_0 \cap X_+ = \{0\} \times L^1_+(0,+\infty)$. We also consider the nonlinear operator $F : (0,+\infty) \times (0,+\infty) \times \overline{D(A)} \to X$ defined by

$$F\left(\nu, \delta, \begin{pmatrix} 0 \\ \varphi \end{pmatrix}\right) = \begin{pmatrix} \nu\left(1 - \int_0^{+\infty} \varphi(l)dl\right)^+ \\ -\delta\chi\varphi\left(1 - \int_0^{+\infty} \phi(l)dl\right)^+ \end{pmatrix}.$$

By identifying $s(t,.)$ with $u(t) = \begin{pmatrix} 0 \\ s(t,.) \end{pmatrix}$, we can rewrite the system as the following abstract Cauchy problem

$$\frac{du(t)}{dt} = Au(t) + F(\nu, \delta, u(t)) \text{ for } t \geq 0 \text{ and } u(0) = \begin{pmatrix} 0 \\ s_0 \end{pmatrix} \in \overline{D(A)}. \tag{3.2}$$

The global existence and positivity of solutions of equation (3.2) now follow from the results in Thieme [44], Magal [31], Magal and Ruan [32, 34]. See also the results in Inaba [21, 22].

Lemma 3.1 *For each $\nu > 0$ and $\delta > 0$, there exists a unique continous semiflow $\{U(t)\}_{t\geq 0}$ on X_{0+} such that for each $x \in X_{0+}$, the map $t \to U(t)x$ is an integrated solution of the Cauchy problem (3.2), that is, $t \to U(t)x$ satisfies for each $t \geq 0$ that*

$$\int_0^t U(l)x dl \in D(A)$$

and

$$U(t)x = x + A\int_0^t U(l)x dl + \int_0^t F(\nu, \delta, U(t)x)dl.$$

3.2 Equilibrium solutions

We have

$$\frac{dS(t)}{dt} = \left(\nu - \delta \int_1^{+\infty} s(t,l)dl\right)(1 - S(t))^+,$$

so

$$\frac{dS(t)}{dt} \geq (\nu - \delta S(t))(1 - S(t))^+.$$

We obtain the following lemma.

Lemma 3.2 *If $S(0) < 1$, then $S(t) \in [0,1)$ for $t \geq 0$ and $\liminf_{t\to+\infty} S(t) \geq \min(1, \frac{\nu}{\delta})$. In particular, if $\frac{\nu}{\delta} \geq 1$, then $\lim_{t\to+\infty} S(t) = 1$.*

If $\begin{pmatrix} 0 \\ \overline{s}(a) \end{pmatrix} \in X_0$ is an equilibrium solution of the system, we must have

$$\begin{pmatrix} 0 \\ \overline{s} \end{pmatrix} \in D(A) \text{ and } A\begin{pmatrix} 0 \\ \overline{s} \end{pmatrix} + F(\nu, \delta, \begin{pmatrix} 0 \\ \overline{s} \end{pmatrix}) = 0.$$

This is equivalent to

$$\begin{array}{rcl} \overline{s}'(a) & = & -\delta\chi(a)\left(1-\overline{S}\right)^{+}\overline{s}(a) \text{ for } a \geq 0, \\ \overline{s}(0) & = & \nu\left(1-\overline{S}\right)^{+} \end{array}$$

with $\overline{S} = \int_0^{+\infty} \overline{s}(l)dl$. So we must have $\overline{S} < 1$ and obtain

$$\overline{s}(a) = \begin{cases} \nu\left(1-\overline{S}\right)e^{-\delta\left(1-\overline{S}\right)(a-1)}, & \text{if } a \geq 1, \\ \nu\left(1-\overline{S}\right), & \text{if } a \in [0,1]. \end{cases} \tag{3.3}$$

By integrating $\overline{s}(a)$ over $(0,+\infty)$, we obtain

$$\overline{S} = \nu\left(1-\overline{S}\right)\int_1^{+\infty} e^{-\delta\left(1-\overline{S}\right)(a-1)}da + \nu\left(1-\overline{S}\right),$$

which implies that $\overline{S} = \frac{\nu}{\delta} + \nu\left(1-\overline{S}\right)$. Thus

$$\overline{S} = \frac{1+\delta^{-1}}{1+\nu^{-1}}. \tag{3.4}$$

Moreover, $\overline{S} \in (0,1)$ if and only if $\delta > \nu$. Now we can state the following lemma.

Lemma 3.3 *System (3.1) has an equilibrium if and only if $\delta > \nu$. Moreover, when the equilibrium exists it is unique and given by (3.3).*

4 Linearized equation

Since $\overline{S} \in (0,1)$, the map $x \to F(\nu,\delta,x)$ is differentiable in a neigborhood of $\left(\begin{array}{c} 0 \\ \overline{s} \end{array}\right)$, and the linearized equation of (3.2) at $\left(\begin{array}{c} 0 \\ \overline{s} \end{array}\right)$ is given by

$$\frac{dw(t)}{dt} = Aw(t) + \partial_x F(\nu,\delta,\left(\begin{array}{c} 0 \\ \overline{s} \end{array}\right))(w(t)),\ t \geq 0, \text{ and } w(0) = x \in X_0. \tag{4.1}$$

We may rewrite this as the following PDE

$$\begin{cases} \dfrac{\partial w(t,a)}{\partial t} + \dfrac{\partial w(t,a)}{\partial a} = -\delta\left(1-\overline{S}\right)\chi(a)w(t,a) + \delta\chi(a)\overline{s}(a)\int_0^{+\infty} w(t,l)dl,\ t \geq 0,\ a \geq 0, \\ w(t,0) = -\nu\int_0^{+\infty} w(t,l)dl, \\ w(0,.) = \varphi \in L^1(0,+\infty). \end{cases} \tag{4.2}$$

4.1 Associated linear operator

We consider a linear operator $B : D(B) \subset X \to X$ defined by

$$B\left(\begin{array}{c} 0 \\ \varphi \end{array}\right) = \left(\begin{array}{c} -\varphi(0) \\ -\varphi' - \delta\left(1-\overline{S}\right)\chi\varphi \end{array}\right) \text{ with } D(B) = D(A)$$

and a bounded linear operator $C : X_0 \to X$ defined by

$$C\left(\begin{array}{c} 0 \\ \varphi \end{array}\right) = \left(\begin{array}{c} -\nu\int_0^{+\infty}\varphi(l)dl \\ \delta\chi\overline{s}\int_0^{+\infty}\varphi(l)dl \end{array}\right).$$

Then $A+\partial_x F(\nu,\delta,\begin{pmatrix} 0 \\ s \end{pmatrix})=B+C$ and the Cauchy problem (4.1) can be rewritten as

$$\frac{dw(t)}{dt}=(B+C)\,w(t) \text{ for } t\geq 0 \text{ with } w(0)=x\in X_0.$$

By applying the results in Thieme [44] or Magal [31] and Magal and Ruan [32], we obtain the following result.

Lemma 4.1 *The resolvent set of B contains $\left(-\delta\left(1-\overline{S}\right),+\infty\right)$. More precisely, for each $\lambda>-\delta\left(1-\overline{S}\right)$,*

$$\begin{array}{rcl}(\lambda-B)^{-1}\begin{pmatrix}\alpha\\ \varphi\end{pmatrix} & = & \begin{pmatrix}0\\ \psi\end{pmatrix}\\ \Leftrightarrow\ \psi(a) & = & e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\alpha+\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\varphi(s)\,ds.\end{array}$$

Moreover, B is a Hille-Yosida operator and

$$\left\|(\lambda-B)^{-n}\right\|_{\mathcal{L}(L^1(0,+\infty))}\leq\frac{M_B}{(\lambda-\omega_B)^{-n}} \text{ for each } \lambda>\omega_B \text{ and each } n\geq 1$$

with $\omega_B:=-\delta\left(1-\overline{S}\right)$ and $M_B:=\left(1+e^{\delta\left(1-\overline{S}\right)}\right)$.

Recall that B_0, the part of B in $\overline{D(B)}=X_0$, is defined by

$$B_0\begin{pmatrix}0\\ \varphi\end{pmatrix}=B\begin{pmatrix}0\\ \varphi\end{pmatrix} \text{ for each } \begin{pmatrix}0\\ \varphi\end{pmatrix}\in D(B_0)$$

and

$$D(B_0)=\left\{\begin{pmatrix}0\\ \varphi\end{pmatrix}\in D(B): B\begin{pmatrix}0\\ \varphi\end{pmatrix}\in X_0\right\}.$$

So we obtain

$$D(B_0)=\left\{\begin{pmatrix}0\\ \varphi\end{pmatrix}\in\{0\}\times W^{1,1}(0,+\infty):\varphi(0)=0\right\},\ B_0\begin{pmatrix}0\\ \varphi\end{pmatrix}=\begin{pmatrix}0\\ \widehat{B}_0\varphi\end{pmatrix},$$

where $\widehat{B}_0\varphi=-\varphi'-\delta\left(1-\overline{S}\right)\chi\varphi$ with $D\left(\widehat{B}_0\right)=\left\{\varphi\in W^{1,1}(0,+\infty):\varphi(0)=0\right\}$. Since B is a Hille-Yosida operator, it follows that B_0 is the infinitesimal generator of a strongly continuous semigroup of bounded linear operators $\{T_{B_0}(t)\}_{t\geq 0}$ on X_0. More precisely, we have the following result.

Lemma 4.2 *The linear operator B_0 is the infinitesimal generator of a strongly continuous semigroup of bounded linear operators $\{T_{B_0}(t)\}_{t\geq 0}$ on X_0, and for each $t\geq 0$ the linear operator $T_{B_0}(t)$ is defined by*

$$T_{B_0}(t)\begin{pmatrix}0\\ \varphi\end{pmatrix}=\begin{pmatrix}0\\ T_{\widehat{B}_0}(t)\varphi\end{pmatrix},$$

where $\left\{T_{\widehat{B}_0}(t)\right\}_{t\geq 0}$ is a strongly continuous semigroup of bounded linear operators on $L^1(0,+\infty)$ and

$$T_{\widehat{B}_0}(t)(\varphi)(a)=\begin{cases}e^{-\int_{a-t}^a\delta\left(1-\overline{S}\right)\chi(l)dl}\varphi(a-t) & \text{if } a>t\\ 0 & \text{if } a\leq t.\end{cases}$$

Moreover,

$$\|T_{B_0}(t)\|\leq M_B e^{\omega_B t},\ \forall t\geq 0.$$

Definition 4.3 Let $L : D(L) \subset X \to X$ be the infinitesimal generator of a linear C_0-semigroup $\{T_L(t)\}_{t\geq 0}$ on a Banach space X. Define the *growth bound* $\omega_0(L) \in [-\infty, +\infty)$ of L by

$$\omega_0(L) := \lim_{t\to+\infty} \frac{\ln\left(\|T_L(t)\|_{\mathcal{L}(X)}\right)}{t}.$$

The *essential growth bound* $\omega_{0,\text{ess}}(L) \in [-\infty, +\infty)$ of L is defined by

$$\omega_{0,\text{ess}}(L) := \lim_{t\to+\infty} \frac{\ln\left(\|T_L(t)\|_{\text{ess}}\right)}{t},$$

where $\|T_L(t)\|_{\text{ess}}$ is the essential norm of $T_L(t)$ defined by

$$\|T_L(t)\|_{\text{ess}} = \kappa\left(T_L(t)B_X(0,1)\right),$$

here $B_X(0,1) = \{x \in X : \|x\|_X \leq 1\}$, and for each bounded set $B \subset X$,

$$\kappa(B) = \inf\{\varepsilon > 0 : B \text{ can be covered by a finite number of balls of radius } \leq \varepsilon\}$$

is the Kuratovsky measure of non-compactness.

Since $\|T_B(t)\|_{\text{ess}} \leq \|T_B(t)\|$, we deduce that $\omega_{0,\text{ess}}(B) \leq \omega_0(B)$. By using Lemma 4.2 we have $\omega_{0,\text{ess}}(B_0) \leq \omega_0(B_0) \leq \omega_B = -\delta\left(1-\overline{S}\right)$. Since C is a bounded linear operator, it follows that $B + C : D(B) \subset X \to X$ is a Hille-Yosida operator. Thus, $(B+C)_0$, the part of $(B+C)$ on X_0, is the infinitesimal generator of a strongly continuous semigroup of bounded linear operators $\left\{T_{(B+C)_0}(t)\right\}_{t\geq 0}$ on X_0. Moreover, since C is compact, by using the perturbation results in [46, 10] it follows that

$$\omega_{0,\text{ess}}\left((B+C)_0\right) \leq \omega_{0,\text{ess}}(B_0) \leq \omega_0(B_0) \leq -\delta\left(1-\overline{S}\right) < 0. \tag{4.3}$$

Next we recall some results in spectral theory. In the following result, the existence of the projector was first proved by Webb [51, 52] and the fact that there is a finite number of points of the spectrum was proved by Engel and Nagel [13].

Theorem 4.4 *Let $L : D(L) \subset X \to X$ be the infinitesimal generator of a linear C_0-semigroup $\{T_L(t)\}$ on a Banach space X. Then*

$$\omega_0(L) = \max\left(\omega_{0,\text{ess}}(L), \max_{\lambda\in\sigma(L)\setminus\sigma_{\text{ess}}(L)} \operatorname{Re}(\lambda)\right).$$

Assume in addition that $\omega_{0,\text{ess}}(L) < \omega_0(L)$. Then for each $\gamma \in (\omega_{0,\text{ess}}(L), \omega_0(L)]$, $\{\lambda \in \sigma(L) : \operatorname{Re}(\lambda) \geq \gamma\} \subset \sigma_p(L)$ is nonempty, finite and contains only poles of the resolvent of L. Moreover, there exists a finite rank bounded linear projector $\Pi : X \to X$ satisfying the following properties:

(a) $\Pi(\lambda - L)^{-1} = (\lambda - L)^{-1}\Pi, \ \forall \lambda \in \rho(L)$;

(b) $\sigma\left(L_{\Pi(X)}\right) = \{\lambda \in \sigma(L) : \operatorname{Re}(\lambda) \geq \gamma\}$;

(c) $\sigma\left(L_{(I-\Pi)(X)}\right) = \sigma(L) \setminus \sigma\left(L_{\Pi(X)}\right)$.

In Theorem 4.4 the projector Π is the projection on the direct sum of the generalized eigenspaces of L associated to all points $\lambda \in \sigma(L)$ with $\operatorname{Re}(\lambda) \geq \gamma$. As a consequence of Theorem 4.4 we have the following corollary.

Corollary 4.5 *Let $L : D(L) \subset X \to X$ be the infinitesimal generator of a linear C_0-semigroup $\{T_L(t)\}$ on a Banach space X, and assume that $\omega_{0,\text{ess}}(L) < \omega_0(L)$. Then*

$$\{\lambda \in \sigma(L) : \operatorname{Re}(\lambda) > \omega_{0,\text{ess}}(L)\} \subset \sigma_P(L)$$

and each $\widehat{\lambda} \in \{\lambda \in \sigma(L) : \mathrm{Re}(\lambda) > \omega_{0,\mathrm{ess}}(L)\}$ *is a pole of the resolvent of* L. *That is,* $\widehat{\lambda}$ *is isolated in* $\sigma(L)$, *and there exists an integer* $k_0 \geq 1$ *(the order of the pole) such that the Laurent's expansion of the resolvent takes the following form*

$$(\lambda I - L)^{-1} = \sum_{n=-k_0}^{\infty} (\lambda - \lambda_0)^n B_n^{\lambda_0},$$

where $\{B_n^{\lambda_0}\}$ *are bounded linear operators on* X, *and the above series converges in the norm of operators whenever* $|\lambda - \lambda_0|$ *is small enough.*

4.2 Characteristic equation

By using Lemma 2.1 in Magal and Ruan [33], we know that $\sigma((B+C)_0) = \sigma((B+C))$. By using Theorem 4.4, Corollary 4.5, and (4.3) we deduce that for each $\varepsilon > 0$,

$$\left\{\lambda \in \sigma((B+C)_0) : \mathrm{Re}(\lambda) > -\delta\left(1-\overline{S}\right) + \varepsilon\right\}$$

is either empty or finite. Moreover, we have the following result.

Lemma 4.6 *For each* $\lambda \in \mathbb{C}$ *with* $\mathrm{Re}(\lambda) > -\delta\left(1-\overline{S}\right)$,

$$\lambda \in \sigma(B+C) \Leftrightarrow \Delta(\lambda) = 0,$$

where

$$\Delta(\lambda) = 1 + \nu \int_0^{+\infty} e^{-\int_0^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl} da - \int_0^{+\infty}\int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl} \delta\chi(s)\overline{s}(s) ds da.$$

Furthermore, if $\lambda \in \mathbb{C}$ *with* $\mathrm{Re}(\lambda) > -\delta\left(1-\overline{S}\right)$ *and* $\Delta(\lambda) \neq 0$, *then*

$$(\lambda I - (B+C))^{-1}\begin{pmatrix}\widehat{\alpha}\\ \widehat{\varphi}\end{pmatrix} = \begin{pmatrix}0\\ \varphi\end{pmatrix}$$

is equivalent to

$$\begin{aligned}\varphi(a) \;&=\; e^{-\int_0^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\left[\Delta(\lambda)^{-1}\left((1-C_1)\widehat{\alpha} - \nu\widehat{I}\right)\right] \\ &\quad + \Delta(\lambda)^{-1}\left(C_2\widehat{\alpha} + \widehat{I}\right)\int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(s)\overline{s}(s)ds + \int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\widehat{\varphi}(s)ds,\end{aligned}$$

where

$$\widehat{I} := \int_0^{+\infty}\int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\widehat{\varphi}(s)\, ds da. \tag{4.3}$$

Proof. For $\lambda \in \mathbb{C}$ with $\mathrm{Re}(\lambda) > -\delta\left(1-\overline{S}\right)$, since $\lambda I - B$ is invertible, it follows that $\lambda I - (B+C)$ is invertible if and only if $I - C(\lambda I - B)^{-1}$ is invertible and

$$(\lambda I - (B+C))^{-1} = (\lambda - B)^{-1}\left[I - C(\lambda - B)^{-1}\right]^{-1}.$$

Note that

$$\left(I - C(\lambda - B)^{-1}\right)\begin{pmatrix}\alpha\\ \varphi\end{pmatrix} = \begin{pmatrix}\widehat{\alpha}\\ \widehat{\varphi}\end{pmatrix} \quad\Leftrightarrow\quad \begin{cases}\alpha + \nu\int_0^{+\infty}\psi(l)dl = \widehat{\alpha},\\ \varphi(a) - \delta\chi(a)\overline{s}(a)\int_0^{+\infty}\psi(l)dl = \widehat{\varphi},\end{cases} \tag{4.4}$$

where

$$\psi(a) = e^{-\int_0^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\alpha + \int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\varphi(s)\, ds.$$

So we must have

$$\int_0^{+\infty}\psi(a)da=\int_0^{+\infty}e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}da\alpha+\int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\varphi\left(s\right)ds.$$

By using the second equation of system (4.4) we obtain

$$\begin{aligned}\int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\varphi\left(s\right)dsda &= \int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(s)\overline{s}(s)dsda\int_0^{+\infty}\psi(l)dl\\ &\quad+\int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\widehat{\varphi}\left(s\right)dsda.\end{aligned}$$

Thus, we have

$$I-C_1\int_0^{+\infty}\psi(l)dl=\widehat{I}, \tag{4.5}$$

where

$$I:=\int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\varphi\left(s\right)dsda,\ \ C_1:=\int_0^{+\infty}\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(a)\overline{s}(a)dsda,$$

and $\widehat{I}$ is given by (4.3). Moreover

$$\int_0^{+\infty}\psi(a)da=C_2\alpha+I, \tag{4.6}$$

where $C_2:=\int_0^{+\infty}e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}da$. Combining the first equation of system (4.4) with (4.5) and (4.6), we obtain

$$\left(1+\nu C_2\right)\alpha+\nu I=\widehat{\alpha},\quad -C_1C_2\alpha+\left(1-C_1\right)I=\widehat{I}.$$

So

$$\begin{aligned}\left[\left(1-C_1\right)\left(1+\nu C_2\right)+\nu C_1C_2\right]\alpha &= \left(1-C_1\right)\widehat{\alpha}-\nu\widehat{I},\\ \left[\nu C_1C_2+\left(1-C_1\right)\left(1+\nu C_2\right)\right]I &= C_1C_2\widehat{\alpha}+\left(1+\nu C_2\right)\widehat{I}.\end{aligned}$$

The characteristic function is given by

$$\Delta\left(\lambda\right)=\nu C_1C_2+\left(1-C_1\right)\left(1+\nu C_2\right)=\left(1+\nu C_2\right)-C_1.$$

It follows that

$$\alpha=\frac{1}{\Delta\left(\lambda\right)}\left[\left(1-C_1\right)\widehat{\alpha}-\nu\widehat{I}\right] \tag{4.7}$$

and

$$I=\frac{1}{\Delta\left(\lambda\right)}\left[C_1C_2\widehat{\alpha}+\left(1+\nu C_2\right)\widehat{I}\right]. \tag{4.8}$$

By using the second equation of (4.4), $\varphi(a)=\delta\chi(a)\overline{s}(a)\int_0^{+\infty}\psi(l)dl+\widehat{\varphi}$, together with (4.6), (4.7) and (4.8), we obtain

$$\int_0^{+\infty}\psi(a)da=C_2\alpha+I=\frac{1}{\Delta\left(\lambda\right)}\left[C_2\left(1-C_1\right)\widehat{\alpha}-\nu C_2\widehat{I}+C_1C_2\widehat{\alpha}+\left(1+\nu C_2\right)\widehat{I}\right]=\frac{1}{\Delta\left(\lambda\right)}\left(C_2\widehat{\alpha}+\widehat{I}\right).$$

Hence,

$$\varphi(a)=\frac{1}{\Delta\left(\lambda\right)}\delta\chi(a)\overline{s}(a)\left(C_2\widehat{\alpha}+\widehat{I}\right)+\widehat{\varphi}.$$

Finally, we deduce that

$$\left(I-C\left(\lambda-B\right)^{-1}\right)^{-1}\begin{pmatrix}\widehat{\alpha}\\ \widehat{\varphi}\end{pmatrix}=\begin{pmatrix}\Delta\left(\lambda\right)^{-1}\left[\left(1-C_1\right)\widehat{\alpha}-\nu\widehat{I}\right]\\ \Delta\left(\lambda\right)^{-1}\delta\chi(\cdot)\overline{s}(\cdot)\left(C_2\widehat{\alpha}+\widehat{I}\right)+\widehat{\varphi}(\cdot)\end{pmatrix}$$

and the explicit formula for the resolvent of $B+C$ follows by using the explicit formula for the resolvent of B.

Now assume that $\Delta(\lambda)=0$. It remains to show that $\lambda I-(C+B)$ is not invertible, so it is sufficient to find $\begin{pmatrix} 0 \\ \varphi \end{pmatrix} \in D(A)$ such that

$$(C+B)\begin{pmatrix} 0 \\ \varphi \end{pmatrix} = \lambda \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \quad \Leftrightarrow \begin{cases} \varphi' = -\left[\lambda+\delta\left(1-\overline{S}\right)\chi\right]\varphi + \delta\chi\overline{s}\int_0^{+\infty}\varphi(l)dl, \\ \varphi(0) = -\nu\int_0^{+\infty}\varphi(l)dl, \end{cases}$$

which is in turn equivalent to

$$\begin{aligned} \varphi(a) &= -\nu e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\int_0^{+\infty}\varphi(l)dl \\ &\quad + \int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(s)\overline{s}(s)ds\int_0^{+\infty}\varphi(l)dl. \end{aligned}$$

If we fix $\int_0^{+\infty}\varphi(l)dl=-C\neq 0$, then we obtain

$$\varphi(a) = \left(\nu e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl} - \int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(s)\overline{s}(s)ds\right)C.$$

Since $\Delta(\lambda)=0$, we deduce that $\int_0^{+\infty}\varphi(a)da=C$. The result follows. ∎

Lemma 4.7 *We have* $\Delta(0)=1+\nu>0$. *So we deduce that* $0\notin\sigma(B+C)$.

Proof. We have

$$\Delta(0) = 1+\nu J_1 - J_2$$

with

$$\begin{aligned} J_1 &:= \int_0^{+\infty} e^{-\int_0^a \delta\left(1-\overline{S}\right)\chi(l)dl}da = \int_1^{+\infty} e^{-\delta\left(1-\overline{S}\right)(a-1)}da + 1 = \frac{1}{\delta\left(1-\overline{S}\right)}+1, \\ J_2 &:= \int_0^{+\infty}\int_0^a e^{-\int_s^a \delta\left(1-\overline{S}\right)\chi(l)dl}\delta\chi(s)\overline{s}(s)dsda = \int_1^{+\infty}\int_1^a e^{-\delta\left(1-\overline{S}\right)(a-s)}\delta\overline{s}(s)dsda. \end{aligned}$$

But $\overline{s}(a)=\nu\left(1-\overline{S}\right)e^{-\delta\left(1-\overline{S}\right)(a-1)}$ for $a\geq 1$, so we have

$$\begin{aligned} J_2 &= \nu\delta\left(1-\overline{S}\right)\int_1^{+\infty}\int_1^a e^{-\delta\left(1-\overline{S}\right)(a-s)}e^{-\delta\left(1-\overline{S}\right)(s-1)}dsda \\ &= \nu\delta\left(1-\overline{S}\right)\int_1^{+\infty}(a-1)e^{-\delta\left(1-\overline{S}\right)(a-1)}da = \nu\delta\left(1-\overline{S}\right)\int_0^{+\infty} le^{-\delta\left(1-\overline{S}\right)l}dl \\ &= \nu\int_0^{+\infty}e^{-\delta\left(1-\overline{S}\right)l}dl = \frac{\nu}{\delta\left(1-\overline{S}\right)}, \end{aligned}$$

which implies that

$$\Delta(0) = 1+\frac{\nu}{\delta\left(1-\overline{S}\right)}+\nu-\frac{\nu}{\delta\left(1-\overline{S}\right)} = 1+\nu>0.$$

This completes the proof. ∎

Lemma 4.8 *For each* $\lambda\in\mathbb{C}$ *with* $\operatorname{Re}(\lambda)>\delta\left(1-\overline{S}\right)$ *and* $\lambda\neq 0$, *we have*

$$\Delta(\lambda) := 1+\nu\left[\frac{\delta\left(1-\overline{S}\right)}{\lambda\left[\lambda+\delta\left(1-\overline{S}\right)\right]}\right]\left(1-e^{-\lambda}\right).$$

Proof. We have

$$\Delta(\lambda) = 1 + \nu I_1 - I_2$$

with

$$\begin{aligned} I_1 : &= \int_0^{+\infty} e^{-\int_0^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl} da = e^{-\lambda} \int_1^{+\infty} e^{-\left[\lambda+\delta\left(1-\overline{S}\right)\right](a-1)} da + \int_0^1 e^{-a\lambda} da \\ &= e^{-\lambda} \int_0^{+\infty} e^{-\left[\lambda+\delta\left(1-\overline{S}\right)\right]a} da + \frac{1}{\lambda}\left(1-e^{-\lambda}\right) = \frac{e^{-\lambda}}{\left[\lambda+\delta\left(1-\overline{S}\right)\right]} + \frac{1-e^{-\lambda}}{\lambda} \end{aligned}$$

and

$$\begin{aligned} I_2 : &= \int_0^{+\infty} \int_0^a e^{-\int_s^a \left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl} \delta\chi(s)\overline{s}(s) ds da \\ &= \int_1^{+\infty} \int_1^a e^{-\left[\lambda+\delta\left(1-\overline{S}\right)\right](a-s)} \delta\nu\left(1-\overline{S}\right) e^{-\delta\left(1-\overline{S}\right)(s-1)} ds da \\ &= \delta\nu\left(1-\overline{S}\right) \int_1^{+\infty} e^{-\delta\left(1-\overline{S}\right)(a-1)} e^{-\lambda a} \int_1^a e^{\lambda s} ds da \\ &= \frac{1}{\lambda}\delta\nu\left(1-\overline{S}\right) \int_1^{+\infty} e^{-\delta\left(1-\overline{S}\right)(a-1)} e^{-\lambda a}\left(e^{\lambda a}-e^{\lambda}\right) da \\ &= \frac{1}{\lambda}\delta\nu\left(1-\overline{S}\right)\left[\int_1^{+\infty} e^{-\delta\left(1-\overline{S}\right)(a-1)} da - \int_1^{+\infty} e^{-\left[\delta\left(1-\overline{S}\right)+\lambda\right](a-1)} da\right] \\ &= \frac{1}{\lambda}\delta\nu\left(1-\overline{S}\right)\left[\frac{1}{\delta\left(1-\overline{S}\right)} - \frac{1}{\delta\left(1-\overline{S}\right)+\lambda}\right] \\ &= \frac{1}{\lambda}\delta\nu\left(1-\overline{S}\right)\left[\frac{\lambda}{\delta\left(1-\overline{S}\right)\left[\delta\left(1-\overline{S}\right)+\lambda\right]}\right] \\ &= \frac{\nu}{\delta\left(1-\overline{S}\right)+\lambda}. \end{aligned}$$

Therefore,

$$\begin{aligned} \Delta(\lambda) &= 1 + \nu\left[\frac{e^{-\lambda}}{\lambda+\delta\left(1-\overline{S}\right)} + \frac{1-e^{-\lambda}}{\lambda}\right] - \frac{\nu}{\delta\left(1-\overline{S}\right)+\lambda} \\ &= 1 + \nu\left[\frac{1}{\lambda} - \frac{1}{\lambda+\delta\left(1-\overline{S}\right)}\right]\left(1-e^{-\lambda}\right) \\ &= 1 + \nu\left[\frac{\delta\left(1-\overline{S}\right)}{\lambda\left(\lambda+\delta\left(1-\overline{S}\right)\right)}\right]\left(1-e^{-\lambda}\right). \end{aligned}$$

The result thus follows. ∎

The following lemma demonstrates that the purely imaginary eigenvalues of $B+C$ are simple.

Lemma 4.9 *Assume that $\Delta(\widehat{\lambda}) = 0$ for some $\widehat{\lambda} = i\omega$ with $\omega > 0$. Then $\widehat{\lambda}$ is a simple eigenvalue of $B+C$.*

Proof. Assume that $\widehat{\lambda} = i\omega$ with $\omega > 0$ is a solution of $\Delta(\widehat{\lambda}) = 0$. Assume first that

$$\frac{d\Delta(\widehat{\lambda})}{d\lambda} \neq 0. \tag{4.9}$$

Then by using the explicit formula for the resolvent of $B+C$ in Lemma 4.6, we deduce that the following limit exists

$$B_{-1}^{\widehat{\lambda}}\begin{pmatrix} \widehat{\alpha} \\ \widehat{\varphi} \end{pmatrix} = \lim_{\substack{\lambda\to\widehat{\lambda} \\ \lambda\neq\widehat{\lambda}}} \left(\lambda-\widehat{\lambda}\right)\left(\lambda I-(B+C)\right)^{-1}\begin{pmatrix} \widehat{\alpha} \\ \widehat{\varphi} \end{pmatrix}.$$

Moreover, we have

$$B_{-1}^{\widehat{\lambda}}\left(\begin{array}{c}\widehat{\alpha}\\ \widehat{\varphi}\end{array}\right)=\left(\begin{array}{c}0\\ \varphi\end{array}\right) \quad\Leftrightarrow\quad \varphi=e^{-\int_0^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\frac{d\Delta(\widehat{\lambda})}{d\lambda}^{-1}\left[\left(1-C_1\right)\widehat{\alpha}-\nu\widehat{I}\right]$$
$$+\frac{d\Delta(\widehat{\lambda})}{d\lambda}^{-1}\left(C_2\widehat{\alpha}+\widehat{I}\right)\int_0^a e^{-\int_s^a\left[\lambda+\delta\left(1-\overline{S}\right)\chi(l)\right]dl}\delta\chi(s)\overline{s}(s)ds.$$

So $\widehat{\lambda}$ is a pole of order 1 of the resolvent of $B+C$, and $B_{-1}^{\widehat{\lambda}}$, the projector on the generalized eigenspace of $B+C$ associated to $\widehat{\lambda}$, has rank 1. It follows that $\widehat{\lambda}$ is a simple eigenvalue of $B+C$.

It remains to show (4.9). We have that

$$\Delta\left(\widehat{\lambda}\right):=1+\nu\left[\frac{\delta\left(1-\overline{S}\right)}{\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)}\right]\left(1-e^{-\widehat{\lambda}}\right)=0$$

is equivalent to

$$e^{-\widehat{\lambda}}-1=\frac{1}{\nu\delta\left(1-\overline{S}\right)}\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]. \tag{4.10}$$

Notice that

$$\frac{d\Delta\left(\widehat{\lambda}\right)}{d\lambda}=\nu\delta\left(1-\overline{S}\right)\left\{e^{-\widehat{\lambda}}\left[\frac{1}{\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)}\right]-\frac{2\widehat{\lambda}+\delta\left(1-\overline{S}\right)}{\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]^2}\left(1-e^{-\widehat{\lambda}}\right)\right\}.$$

Therefore,

$$\frac{d\Delta\left(\widehat{\lambda}\right)}{d\lambda}=0 \quad\Leftrightarrow\quad e^{-\widehat{\lambda}}\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]+\left[2\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right]\left(e^{-\widehat{\lambda}}-1\right)=0$$

and by using (4.10) we obtain

$$\left\{\frac{1}{\nu\delta\left(1-\overline{S}\right)}\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]+1\right\}\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]$$
$$+\left[2\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right]\frac{1}{\nu\delta\left(1-\overline{S}\right)}\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]=0,$$

which is equivalent to

$$\left[\widehat{\lambda}\left(\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right)\right]+\nu\delta\left(1-\overline{S}\right)+\left[2\widehat{\lambda}+\delta\left(1-\overline{S}\right)\right]=0.$$

Since $\widehat{\lambda}=i\omega$ with $\omega>0$, we obtain

$$-\omega^2+i\omega\delta\left(1-\overline{S}\right)+\nu\delta\left(1-\overline{S}\right)+2i\omega+\delta\left(1-\overline{S}\right)=0,$$

which is impossible since the imaginary part is non-null. ∎

5 Stability

In the section we investigate the stability of the endemic equilibrium $\overline{s}$. We observe that the linear operator $A+\partial_x F(\nu,\delta,\left(\begin{array}{c}0\\ \overline{s}\end{array}\right))$ can be decomposed as the sum of the linear operator $\widetilde{B}:D(\widetilde{B})\subset X\to X$ defined by

$$\widetilde{B}\left(\begin{array}{c}0\\ \varphi\end{array}\right)=\left(\begin{array}{c}-\varphi\left(0\right)\\ -\varphi'-\delta\chi\varphi\end{array}\right) \text{ with } D(L)=D(A)$$

and the bounded linear operator $\widetilde{C} : X_0 \to X$ defined by

$$\widetilde{C}\begin{pmatrix} 0 \\ \varphi \end{pmatrix} = \begin{pmatrix} -\nu\int_0^{+\infty}\varphi(l)dl \\ -\delta\overline{S}\chi\varphi + \delta\chi\overline{s}\int_0^{+\infty}\varphi(l)dl \end{pmatrix}.$$

That is, we have $A + \partial_x F(\nu, \delta, \begin{pmatrix} 0 \\ \overline{s} \end{pmatrix}) = \widetilde{B} + \widetilde{C}$. Observe that $\|\widehat{C}\|_{\mathcal{L}(X_0)} \le 2\delta\overline{S} + \nu$. In order to have the existence of the endemic equilibrium (i.e. $\overline{I} > 0$ or $\overline{S} = 1 - \overline{I} < 1$) we must impose $\delta > \nu$. Fix $\delta > 0$. Then we have $\delta\overline{S} = \nu(\frac{\delta+1}{1+\nu}) \to 0$ as $\nu \to 0$. Hence, $\|\widetilde{C}\|_{\mathcal{L}(X_0)} \to 0$ as $\nu \to 0$. Moreover, $\widetilde{B}_0$, the part of $\widetilde{B}$ on X_0, is the infinitesimal generator of the strongly continuous semigroup of bounded linear operators $\left\{T_{\widetilde{B}_0}(t)\right\}_{t\ge 0}$ on X_0 defined by

$$T_{\widetilde{B}_0}(t)\begin{pmatrix} 0 \\ \varphi \end{pmatrix} = \begin{pmatrix} 0 \\ \widehat{T}_{\widetilde{B}_0}(t)\varphi \end{pmatrix},$$

where

$$\widehat{T}_{\widetilde{B}_0}(t)(\varphi)(a) = \begin{cases} \exp\left(-\int_{a-t}^{a}\delta\chi(l)dl\right)\varphi(a-t), & \text{if } a < t \\ 0, & \text{if } a \le t. \end{cases}$$

Since $\liminf_{a\to+\infty}\delta\chi(a) = \delta > 0$, it follows that $\omega_0\left(\widetilde{B}_0\right) \le -\delta$. By using the standard perturbation arguments (see Thieme [44] or Magal and Ruan [34]) we obtain the following stability result.

Lemma 5.1 *Let $\delta > 0$ be fixed. Then there exists $\nu_s^- \in (0, \delta)$ such that for each $\nu \in (0, \nu_s^-)$, the equilibrium $\overline{s}$ is locally asymptotically stable.*

By using a similar argument we also have the following lemma.

Lemma 5.2 *There exists $\varepsilon > 0$ such that if $\delta + \nu \le \varepsilon$, then the equilibrium $\overline{s}$ is locally asymptotically stable.*

Remark 5.3 Now we return to the original system (2.1) and assume that the parameters $\nu > 0$, $\delta > 0$, and $N > 0$ of system (2.1) are fixed such that $\frac{\nu}{\delta} < N$. Then we can regard $\tau > 0$, defined in Assumption 2.2, as a parameter of system (2.1). By the changes of variables described in section 2, it corresponds to some parameters $\widehat{\delta} > 0$ and $\widehat{\nu}$ of system (3.1) with $\widehat{\delta} = \tau c_1$ and $\widehat{\nu} = \tau c_2$ for some $c_1 > c_2 > 0$. By Lemma 5.2, we deduce that if $\tau > 0$ is small enough, then the endemic equilibrium of the original system (2.1) is stable (see the numerical simulations in section 7).

We have

$$1 - \overline{S} = 1 - \frac{1 + \delta^{-1}}{1 + \nu^{-1}} = \frac{\nu^{-1} - \delta^{-1}}{1 + \nu^{-1}}.$$

Let $h : [0, \delta] \to \mathbb{R}$ be defined by

$$h(\nu) := \delta\left(1 - \overline{S}\right) = \frac{\delta - \nu}{1 + \nu}. \tag{5.1}$$

Then the characteristic equation can be rewritten as

$$1 + \nu\left[\frac{h(\nu)}{\lambda(\lambda + h(\nu))}\right]\left(1 - e^{-\lambda}\right) = 0.$$

Since $\mathrm{Re}(\lambda) > -h(\nu)$, the characteristic equation is equivalent to

$$\lambda + h(\nu) = \nu h(\nu)\frac{e^{-\lambda} - 1}{\lambda}. \tag{5.2}$$

Lemma 5.4 *Assume that $\lambda \in \mathbb{C}$ with $\mathrm{Re}(\lambda) \ge 0$ satisfies the characteristic equation. Then we have the following estimation*

$$|\lambda| \le 2\nu + 2h(\nu).$$

Proof. From (5.2) we have

$$[\lambda + h(\nu)]^2 = h(\nu)\left\{\nu\left(e^{-\lambda} - 1\right) + [\lambda + h(\nu)]\right\}.$$

So

$$\left[\frac{\lambda}{h(\nu)} + 1\right]^2 = \frac{\nu}{h(\nu)}\left(e^{-\lambda} - 1\right) + \left[\frac{\lambda}{h(\nu)} + 1\right].$$

It follows that

$$\left|\frac{\lambda}{h(\nu)} + 1\right|^2 \leq \frac{\nu}{h(\nu)}\left(e^{-\mathrm{Re}\lambda} + 1\right) + \left|\frac{\lambda}{h(\nu)} + 1\right|.$$

Since $\mathrm{Re}(\lambda) \geq 0$, we obtain that

$$\left|\frac{\lambda}{h(\nu)} + 1\right| \leq \frac{\nu}{h(\nu)}\frac{2}{\left|\frac{\lambda}{h(\nu)} + 1\right|} + 1 \leq \frac{2\nu}{h(\nu)} + 1,$$

so $|\lambda + h(\nu)| \leq 2\nu + h(\nu)$ and $|\lambda| \leq |\lambda + h(\nu)| + |h(\nu)| \leq 2\nu + 2h(\nu)$ .This proves the lemma. ∎

Now, we are in the position to state and prove the main result in this section.

Theorem 5.5 (Stability) *Let $\delta > 0$ be fixed. Then there exists $0 < \nu_s^- < \nu_s^+ < \delta$ such that for each $\nu \in (0, \nu_s^-) \cup (\nu_s^+, \delta)$, the equilibrium $\overline{s}$ of system (3.1) is locally asymptotically stable.*

Proof. Assume that there exist two sequences $\{\nu_n\}$ with $\nu_n(< \delta) \to \delta$ and $\lambda_n \in \mathbb{C}\setminus\{0\}$ such that $\mathrm{Re}(\lambda_n) \geq 0$ and $\Delta(\lambda_n) = 0$. Then by Lemma 5.4, we have $|\lambda_n| \leq 2\nu_n + 2h(\nu_n)$, $\forall n \geq 0$. We can find a converging subsequence $\{\lambda_{n_p}\}$ with $\lambda_{n_p} \to \lambda^*$. By using the characteristic equation we obtain

$$\lambda_{n_p} + h\left(\nu_{n_p}\right) = \nu_{n_p} h\left(\nu_{n_p}\right)\frac{e^{-\lambda_{n_p}} - 1}{\lambda_{n_p}}$$

and $\lambda_{n_p} \to 0$. So $\lambda^* = 0$. Notice that

$$\frac{\lambda_{n_p}}{h\left(\nu_{n_p}\right)} + 1 = \nu_{n_p}\frac{e^{-\lambda_{n_p}} - 1}{\lambda_{n_p}},$$

so we obtain $\lim_{p\to+\infty}\frac{\lambda_{n_p}}{h\left(\nu_{n_p}\right)} = -(1+\delta)$. Thus, for $p \geq 0$ large enough, we have $\mathrm{Re}(\frac{\lambda_{n_p}}{h\left(\nu_{n_p}\right)}) < -\frac{1+\delta}{2}$, which implies for each $p \geq 0$ large enough that

$$\mathrm{Re}\left(\lambda_{n_p}\right) < -\frac{(1+\delta)\,h\left(\nu_{n_p}\right)}{2} < 0,$$

a contradiction. ∎

6 Hopf bifurcation

Recall that $h(\nu) = \frac{\delta-\nu}{1+\nu}$, we have $h'(\nu) < 0$. So h is strictly decreasing and $h(0) = \delta$ and $h(\delta) = 0$. Thus $h((0,\delta)) \subset (0,\delta)$. The characteristic equation becomes equivalent to find $\lambda \in \mathbb{C}$ with $\mathrm{Re}(\lambda) > -h(\nu)$ such that one of the following is satisfied

$$\begin{aligned}
e^{-\lambda} = \frac{\lambda^2}{\nu h(\nu)} + \frac{\lambda}{\nu} + 1 \quad &\Leftrightarrow \quad e^{-\lambda} = \frac{1}{\nu h(\nu)}\lambda\left[\lambda + h(\nu)\right] + 1 \\
&\Leftrightarrow \quad \nu h(\nu)\left[e^{-\lambda} - 1\right] = \lambda\left[\lambda + h(\nu)\right] \\
&\Leftrightarrow \quad \nu h(\nu)\left[e^{-\lambda} - 1\right] + h(\nu)\left[\lambda + h(\nu)\right] = \left[\lambda + h(\nu)\right]^2 \\
&\Leftrightarrow \quad \frac{\nu}{h(\nu)}\left[e^{-\lambda} - 1\right] + \left[\frac{\lambda}{h(\nu)} + 1\right] = \left[\frac{\lambda}{h(\nu)} + 1\right]^2.
\end{aligned}$$

6.1 Existence of purely imaginary solutions

Assume that $\lambda = i\omega$ with $\omega > 0$ is a solution of the characteristic equation. We must have

$$e^{-i\omega} = \frac{-\omega^2}{\nu h(\nu)} + i\frac{\omega}{\nu} + 1. \tag{6.1}$$

This implies that $1 = \left|e^{-i\omega}\right| = \left(1 - \frac{\omega^2}{\nu h(\nu)}\right)^2 + \frac{\omega^2}{\nu^2}$ and $1 = 1 - 2\frac{\omega^2}{\nu h(\nu)} + \frac{\omega^4}{(\nu h(\nu))^2} + \frac{\omega^2}{\nu^2}$. So we obtain

$$\omega^2 = 2\nu h(\nu) - h(\nu)^2 = \nu h(\nu)\left(2 - \frac{h(\nu)}{\nu}\right).$$

Since we look for $\omega > 0$, the above equality is possible only if $\frac{h(\nu)}{\nu} < 2$. Thus,

$$\omega(\nu) = \nu\sqrt{\frac{h(\nu)}{\nu}\left(2 - \frac{h(\nu)}{\nu}\right)}.$$

As a consequence we obtain the following lemma.

Lemma 6.1 *Assume that there exists $\lambda^* = i\omega^*$ for some $\omega^* > 0$ and $\Delta(\lambda^*) = 0$. Then*

$$\Delta\left(\overline{\lambda^*}\right) = 0 \quad \text{and} \quad \omega^* = \nu\sqrt{\frac{h(\nu)}{\nu}\left(2 - \frac{h(\nu)}{\nu}\right)}$$

with $\frac{h(\nu)}{\nu} < 2$. Moreover, $\Delta(i\omega) \neq 0,\ \forall \omega \neq \mathbb{R} \setminus \{-\omega^*, \omega^*\}$.

By considering the real and the imaginary parts of equation (6.1) with $\omega > 0$, we obtain

$$\frac{\omega}{\nu} = -\sin(\omega), \quad \frac{\omega^2}{\nu h(\nu)} = 1 - \cos(\omega).$$

Since $\omega > 0$ and $\nu > 0$, we must have $\omega \in \bigcup_{k=0}^{+\infty}((2k+1)\pi, (2k+2)\pi)$,

$$\nu = -\frac{\omega}{\sin(\omega)}, \quad \nu h(\nu) = \frac{\omega^2}{1 - \cos(\omega)}. \tag{6.2}$$

The definition (5.1) of $h(\nu)$ yields

$$\delta = \nu + \frac{1+\nu}{\nu}\frac{\omega^2}{1 - \cos(\omega)}. \tag{6.3}$$

By using (6.2) and (6.3), we obtain a family of curves in the (ν, δ)-plane parameterized by $\omega \in \bigcup_{k=0}^{+\infty}((2k+1)\pi, (2k+2)\pi)$ (see Figures 6.1).

Proposition 6.2 *Assume that $\delta = c\nu$ for some constant $c > 1$. Then we can find a sequence $\{\nu_n\}$ with $\nu_n \to +\infty$ as $n \to +\infty$, such that for each ν_n there exists $\omega_n > 0$ so that $\lambda_n = i\omega_n$ satisfies the characteristic equation*

$$e^{-i\omega_n} = \frac{-\omega_n^2}{\nu_n \frac{\delta_n - \nu_n}{1+\nu_n}} + i\frac{\omega_n}{\nu_n} + 1.$$

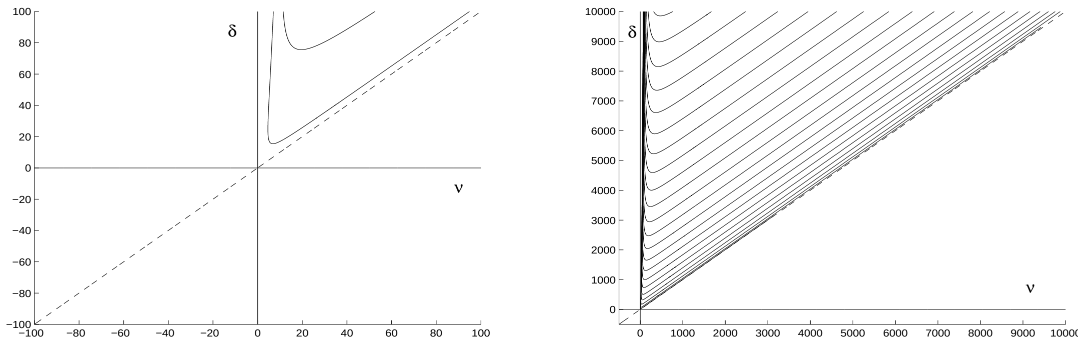

Figure 6.1: Bifurcation diagrams. *Left*: A couple of bifurcation curves given by (6.3) in the (ν, δ)-plane with small (ν, δ) values. *Right*: A family of bifurcation curves defined by (6.3) in the (ν, δ)-plane.

Proof. By using (6.2) and (6.3) for $\omega \in \bigcup_{k=0}^{+\infty} ((2k+1)\pi, (2k+2)\pi)$, we have

$$\nu = -\frac{\omega}{2\sin(\omega/2)\cos(\omega/2)}, \quad \delta = \nu + \frac{1+\nu}{\nu}\frac{\omega^2}{2\sin(\omega/2)^2}.$$

These are equivalent to

$$\nu = -\frac{\omega}{\sin(\omega)}, \quad \delta = \nu + 2(1+\nu)\,\nu\frac{\cos(\omega/2)^2}{\sin(\omega/2)^2}.$$

Since by the assumption we have $\delta = c\nu$ with $c > 1$, it follows that

$$\nu = -\frac{\omega}{\sin(\omega)} \quad \text{and} \quad \nu = \frac{(c-1)}{2}\tan\left(\frac{\omega}{2}\right)^2 - 1.$$

A simple analysis shows that both curves intersect infinitely many times in $\bigcup_{k=0}^{+\infty} ((2k+1)\pi, (2k+2)\pi)$. ∎

Remark 6.3 By Remark 5.3 and Proposition 6.2, we deduce that there is an infinite sequence $\{\tau_n\}$ with $\tau_n(>0) \to +\infty$, such that the linearized equation of system (3.1) around the endemic equilibrium $\overline{s}$ has some purely imaginary eigenvalues in its spectrum. As a consequence we deduce that the linearized equation of system (2.1) for the same values τ_n also has some purely imaginary eigenvalues. Therefore, when τ increases the original system (2.1) may exhibit an infinite number of Hopf bifurcations.

In order to find an infinite number of purely imaginary eigenvalues we consider the curves in the (ν, δ)-plane of parameters

$$\delta = \nu + \frac{1+\nu}{\nu}\frac{\left(\frac{\nu}{c}\right)^2}{1-\sqrt{1-\frac{1}{c^2}}} \tag{6.4}$$

for some $c \geq 1$. Taking $\nu = \dfrac{\omega}{c}$, equations (6.2) and (6.3) become

$$\sin(\omega) = -\frac{1}{c} \quad \text{and} \quad \cos(\omega) = \sqrt{1-\frac{1}{c^2}}$$

for $\omega \in \bigcup_{k=0}^{+\infty} ((2k+1)\pi, (2k+2)\pi)$. We have the following lemma.

Lemma 6.4 *There is an infinite sequence* $\{\omega_n\}$ *defined by*

$$\omega_n = \arcsin\left(-\frac{1}{c}\right) + 2(n+1)\pi,$$

such that for $n \geq 0$ *if*

$$\nu_n = \frac{\omega_n}{c} \quad \textit{and} \quad \delta_n = \nu_n + \frac{1+\nu_n}{\nu_n} \frac{\left(\frac{\nu_n}{c}\right)^2}{1 - \sqrt{1 - \frac{1}{c^2}}},$$

then $\Delta(i\omega_n) = 0$.

Similarly, for the case

$$\delta = \nu + \frac{1+\nu}{\nu} \frac{\left(\frac{\nu}{c}\right)^2}{1 + \sqrt{1 - \frac{1}{c^2}}}, \tag{6.5}$$

we have $\sin(\omega) = -\frac{1}{c}$, $\cos(\omega) = -\sqrt{1 - \frac{1}{c^2}}$ and the following lemma.

Lemma 6.5 *There is a second sequence* $\{\widehat{\omega}_n\}$ *given by*

$$\widehat{\omega}_n = \arcsin\left(\frac{1}{c}\right) + \pi + 2n\pi,$$

such that for $n \geq 0$ *if*

$$\widehat{\nu}_n = \frac{\widehat{\omega}_n}{c} \quad \textit{and} \quad \widehat{\delta}_n = \widehat{\nu}_n + \frac{1+\widehat{\nu}_n}{\widehat{\nu}_n} \frac{\left(\frac{\widehat{\nu}_n}{c}\right)^2}{1 + \sqrt{1 - \frac{1}{c^2}}},$$

then $\Delta(i\widehat{\omega}_n) = 0$.

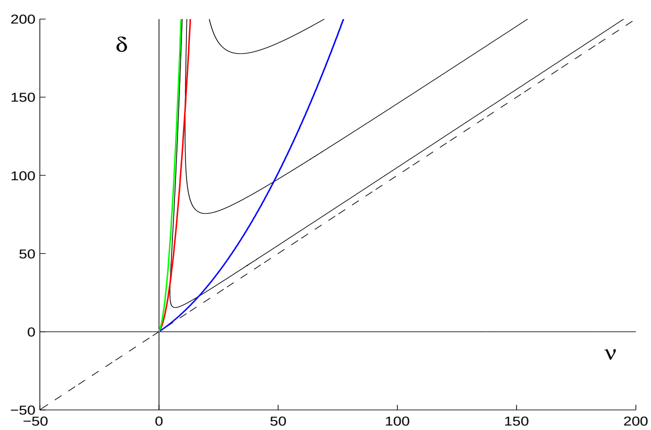

Figure 6.2: In this figure we plot the curve $\delta = \nu + \frac{1+\nu}{\nu} \frac{\left(\frac{\nu}{c}\right)^2}{1+\sqrt{1-\frac{1}{c^2}}}$ for $c = 1$ in red, for $c = 5$ in blue, and the curve $\delta = \nu + \frac{1+\nu}{\nu} \frac{\left(\frac{\nu}{c}\right)^2}{1-\sqrt{1-\frac{1}{c^2}}}$ for $c = 5$ in green.

6.2 Transversality condition

For $\lambda \in \mathbb{C} \setminus \{0\}$ with $\mathrm{Re}(\lambda) > -h(\nu)$, the characteristic equation $\Delta(\lambda) = 0$ is equivalent to

$$\Delta_1(\nu, \lambda) = 0$$

with $\Delta_1(\nu, \lambda) := \lambda [\lambda + h(\nu)] + \nu h(\nu) \left(1 - e^{-\lambda}\right)$. Recall the form of $h(\nu)$, by (6.4) we have $h(\nu) = \nu\kappa(c)$, where

$$\kappa(c) := \frac{\left(\frac{1}{c}\right)^2}{1 - \sqrt{1 - \frac{1}{c^2}}} > 0.$$

Hence, $\Delta_1(\nu, \lambda) := \lambda [\lambda + \nu\kappa(c)] + \nu^2\kappa(c) \left(1 - e^{-\lambda}\right)$. Moreover, we knew that if $\lambda_n = \omega_n i$ and $\nu_n = c\omega_n$, then $\Delta_1(\nu_n, \lambda_n) = 0$, and

$$\sin(\omega_n) = -\frac{1}{c}, \quad \cos(\omega_n) = \sqrt{1 - \frac{1}{c^2}} > 0.$$

So $e^{-\omega_n i} = \sqrt{1 - \frac{1}{c^2}} + i\frac{1}{c}$. Since $\frac{\partial\Delta_1(\nu,\lambda)}{\partial\lambda} = 2\lambda + \nu\kappa(c) + \nu^2\kappa(c)\, e^{-\lambda}$, it follows that

$$\begin{aligned}
\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda} = 0 \quad &\Leftrightarrow \quad 2\omega_n i + \nu_n\kappa(c) + \nu_n^2\kappa(c) \left[\sqrt{1 - \frac{1}{c^2}} + i\frac{1}{c}\right] = 0 \\
&\Leftrightarrow \quad \left[\nu_n\kappa(c) + \nu_n^2\kappa(c)\sqrt{1 - \frac{1}{c^2}}\right] + \left[2\omega_n + \nu_n^2\kappa(c)\frac{1}{c}\right] i = 0,
\end{aligned}$$

which is impossible since both the real and the imaginary parts are strictly positive.

Next we have $\frac{\partial\Delta_1(\nu,\lambda)}{\partial\nu} = \lambda\kappa(c) + 2\nu\kappa(c)\left[1 - e^{-\lambda}\right]$. Hence,

$$\begin{aligned}
\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\nu} &= \omega_n i\kappa(c) + 2\nu_n\kappa(c)\left[1 - \sqrt{1 - \frac{1}{c^2}} - i\frac{1}{c}\right] \\
&= 2\nu_n\kappa(c)\left[1 - \sqrt{1 - \frac{1}{c^2}}\right] + i\left[\omega_n\kappa(c) - \frac{2\nu\kappa(c)}{c}\right].
\end{aligned}$$

Now since $\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda} \neq 0$, applying the implicit function theorem, we deduce that there exists a C^1 map $\widetilde{\lambda}_n : [\nu_n - \varepsilon_n, \nu_n + \varepsilon_n] \to \mathbb{C}$ such that

$$\widetilde{\lambda}_n(\nu_n) = \lambda_n \quad \text{and} \quad \Delta_1(\nu, \widetilde{\lambda}_n(\nu)) = 0,\ \forall \nu \in [\nu_n - \varepsilon_n, \nu_n + \varepsilon_n].$$

Thus, we have

$$\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu} = -\frac{\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\nu}}{\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}} = -\frac{\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\nu}\overline{\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}}}{\left|\dfrac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}\right|^2}.$$

Notice that

$$\begin{aligned}
\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\nu}\overline{\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}} &= \left\{2\nu_n\kappa(c)\left(1 - \sqrt{1 - \frac{1}{c^2}}\right) + i\left[\omega_n\kappa(c) - \frac{2\nu_n\kappa(c)}{c}\right]\right\} \\
&\quad \times \left\{\left[\nu_n\kappa(c) + \nu_n^2\kappa(c)\sqrt{1 - \frac{1}{c^2}}\right] - \left[2\omega_n + \nu_n^2\kappa(c)\frac{1}{c}\right] i\right\},
\end{aligned}$$

it follows that

$$\left|\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}\right|^2 \mathrm{Re}\left(\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu}\right) = -\mathrm{Re}\left(\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\nu}\overline{\frac{\partial\Delta_1(\nu_n, \lambda_n)}{\partial\lambda}}\right)$$

$$
\begin{aligned}
&= -2\nu_n\kappa(c)\left(1-\sqrt{1-\frac{1}{c^2}}\right)\left[\nu_n\kappa(c)+\nu_n^2\kappa(c)\sqrt{1-\frac{1}{c^2}}\right] \\
&\quad -\left[\omega_n\kappa(c)-\frac{2\nu_n\kappa(c)}{c}\right]\left[2\omega_n+\nu_n^2\kappa(c)\frac{1}{c}\right].
\end{aligned}
$$

Since $\nu_n = c\omega_n$, we obtain

$$
\begin{aligned}
\left|\frac{\partial\Delta_1(\nu_n,\lambda_n)}{\partial\lambda}\right|^2 \operatorname{Re}\left(\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu}\right) &= -2c\omega_n\kappa(c)\left(1-\sqrt{1-\frac{1}{c^2}}\right)\left[c\omega_n\kappa(c)+c^2\omega_n^2\kappa(c)\sqrt{1-\frac{1}{c^2}}\right] \\
&\quad -\left[\omega_n\kappa(c)-2\omega_n\kappa(c)\right]\left[2\omega_n+c\omega_n^2\kappa(c)\right] \\
&= -2c^2\omega_n^2\kappa(c)\left(1-\sqrt{1-\frac{1}{c^2}}\right)\left[\kappa(c)+c\omega_n\kappa(c)\sqrt{1-\frac{1}{c^2}}\right] \\
&\quad +\omega_n^2\kappa(c)\left[2+c\omega_n\kappa(c)\right],
\end{aligned}
$$

but $c^2(1-\sqrt{1-\frac{1}{c^2}})\kappa(c) := 1$ and $\kappa(c) > 0$, so we have

$$
\begin{aligned}
\left|\frac{\partial\Delta_1(\nu_n,\lambda_n)}{\partial\lambda}\right|^2 \operatorname{Re}\left(\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu}\right) &= -2\omega_n^2\kappa(c)\left[1+c\omega_n\sqrt{1-\frac{1}{c^2}}\right]+\omega_n^2\kappa(c)\left[2+c\omega_n\kappa(c)\right] \\
&= c\omega_n^3\kappa(c)\left[\kappa(c)-2\sqrt{1-\frac{1}{c^2}}\right] \\
&= c\kappa(c)^2\omega_n^3\left[1-2c^2\left(1-\sqrt{1-\frac{1}{c^2}}\right)\sqrt{1-\frac{1}{c^2}}\right].
\end{aligned}
$$

Set $y = \sqrt{1-\frac{1}{c^2}} \in [0,1)$. Then

$$
1-2c^2\left(1-\sqrt{1-\frac{1}{c^2}}\right)^2\sqrt{1-\frac{1}{c^2}} = 1-2\frac{(1-y)\,y}{(1-y^2)} = 1-2\frac{y}{1+y}.
$$

Since the map $y \to 2\frac{y}{1+y}$ is strictly increasing on $[0,1]$ and is equal to 1 for $y=1$, it implies that $\operatorname{Re}(\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu}) > 0$.

The above analysis can be summarized as the following lemma.

Lemma 6.6 *Assume that $c \geq 1$, then for each $n \geq 0$ there exists a C^1 map $\widetilde{\lambda}_n : [\nu_n - \varepsilon_n, \nu_n + \varepsilon_n] \to \mathbb{C}$ such that*

$$
\widetilde{\lambda}_n(\nu_n) = \lambda_n = \omega_n i, \;\; \Delta_1(\nu, \widetilde{\lambda}_n(\nu)) = 0, \; \forall \nu \in [\nu_n - \varepsilon_n, \nu_n + \varepsilon_n],
$$

and

$$
\operatorname{Re}\left(\frac{d\widetilde{\lambda}_n(\nu_n)}{d\nu}\right) > 0.
$$

For the symmetric case (6.5), we have $h(\nu) = \nu\widehat{\kappa}(c)$ and $\widehat{\Delta}_1(\nu,\lambda) := \lambda\left[\lambda+\nu\widehat{\kappa}(c)\right]+\nu^2\widehat{\kappa}(c)\left(1-e^{-\lambda}\right)$, where

$$
\widehat{\kappa}(c) = \frac{\left(\frac{1}{c}\right)^2}{1+\sqrt{1-\frac{1}{c^2}}} > 0.
$$

Similarly, we have the following lemma.

Lemma 6.7 *Assume that $c \geq 1$, then for each $n \geq 0$ there exists a C^1 map $\lambda_n^* : [\widehat{\nu}_n - \varepsilon_n, \widehat{\nu}_n + \varepsilon_n] \to \mathbb{C}$ such that*

$$\lambda_n^*(\widehat{\nu}_n) = \lambda_n = \widehat{\omega}_n i, \quad \widehat{\Delta}_1(\nu, \lambda_n^*(\nu)) = 0, \ \forall \nu \in [\widehat{\nu}_n - \varepsilon_n, \widehat{\nu}_n + \varepsilon_n],$$

and

$$\operatorname{Re}\left(\frac{d\lambda_n^*(\widehat{\nu}_n)}{d\nu}\right) > 0.$$

6.3 Hopf bifurcation

By combining the results on the essential growth rate of the linearized equations (equation (4.3)), the simplicity of the imaginary eigenvalues (Lemma 4.9), the existence of purely imaginary eigenvalues (Lemma 6.4), and the transversality condition (Lemma 6.6), we are in a position to apply the center manifold Theorem 4.21 and Proposition 4.22 in Magal and Ruan [33]. Applying the Hopf bifurcation theorem proved in Hassard et al. [16] to the reduced system, we obtain the following theorem.

Theorem 6.8 *Consider the curves defined by (6.4) in the (ν, δ)-plan for some $c \geq 1$. Then for each $n \geq 0$,*

$$\nu_n = c\left(\arcsin\left(-\frac{1}{c}\right) + 2(n+1)\pi\right)$$

is an Hopf bifurcation point for the system

$$\frac{du(t)}{dt} = Av(t) + F(\nu, \delta(\nu), u(t)), \ t \geq 0, \ u(0) = x \in \overline{D(A)} \tag{6.6}$$

around the branch of equilibrium points $\overline{s} = \overline{s}_{(\nu,\delta)}$. Moreover, the period of the bifurcating periodic orbits is close to

$$\omega = c \arcsin\left(-\frac{1}{c}\right) + \pi + 2n\pi.$$

By using the same arguments as above (that is, combining equation (4.3), Lemma 4.9, Lemma 6.5, and Lemma 6.7), we also obtain the following theorem.

Theorem 6.9 *Consider the curves defined by (6.5) in the (ν, δ)-plan for some $c \geq 1$. Then for each $n \geq 0$,*

$$\nu_n = c\left(\arcsin\left(\frac{1}{c}\right) + \pi + 2n\pi\right)$$

is an Hopf bifurcation point for the system (6.6) around the branch of equilibrium points $\overline{s} = \overline{s}_{(\nu,\delta)}$. Moreover, the period of the bifurcating periodic orbits is close to

$$\omega = c \arcsin\left(\frac{1}{c}\right) + \pi + 2n\pi.$$

We would like to point out that we have studied the existence of Hopf bifurcation, while the stability of the bifurcating periodic solutions remains open.

7 Numerical Simulations

In this section we present some numerical simulations for model (3.1). We consider the percentage of the population in a community. Recall that by Assumption 2.2, $\gamma(ka)$ is equal to δ if $a \geq \rho$ and 0 if $0 < a < \rho$, where $\rho = \tau/k$. Here we fix $\tau = 30, \nu = 1/5$ day^{-1}, $\delta = 0.0034$. and let ρ vary from 0 to 365 days.

When $\rho = 30$ days, there is an endemic equilibrium which is asymptotically stable (see Figure 7.1, left). When $\rho = 100$ days, the endemic equilibrium becomes unstable and there are periodic solutions via Hopf bifurcation (see Figure 7.1, right). The oscillations are amplified when $\rho = 200$ days (see Figure 7.2, left) and irregular when $\rho = 365$ days (see Figure 7.2, right).

Recall that τ is the average number of amino acid substitutions before re-infection and k is the average number of amino acid substitutions per unit of time, that is, the mutation rate. Thus, the threshold ρ represents the time necessary to be re-infected after one infection. The simulations in Figures 7.1-7.2 indicate that for given mutation rate, oscillations can start as early as 100 days after the previous infection and become irregular after about a year. It should be emphasized that ρ depends on the average number of amino acid substitutions after one infection and the mutation rate.

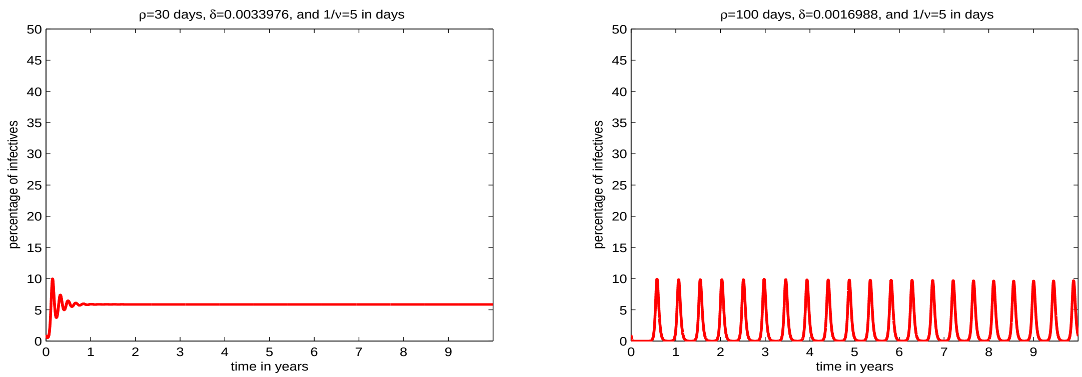

Figure 7.1: *Left*: When $\rho = 30$ days, the trajectories converge to the positive equilibrium value. *Right*: There are sustained oscillations when $\rho = 100$ days via Hopf bifurcation.

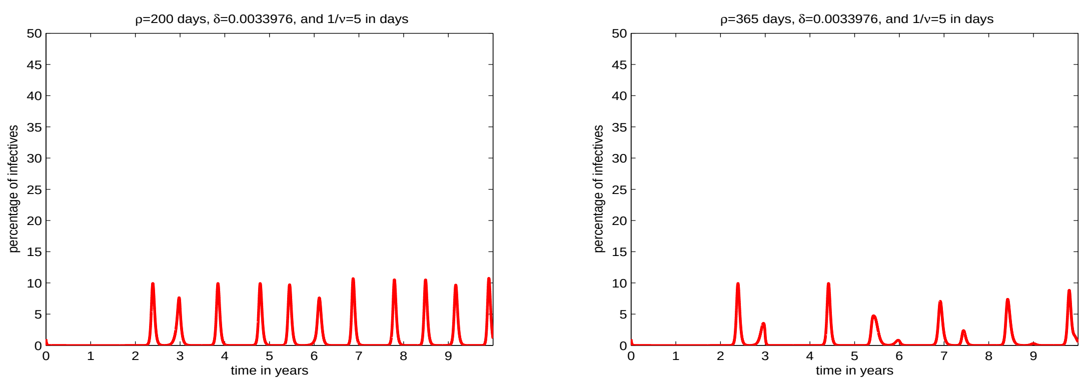

Figure 7.2: *Left*: The oscillations are amplified when $\rho = 200$ days. *Right*: Irregular oscillations when $\rho = 365$ days.

8 Discussion

Understanding the seasonal/periodic reoccurrence of influenza will be very helpful in designing successful vaccine programs and introducing public health interventions. However, the reasons for seasonal/periodic influenza epidemics are still not clear even though various explanations have been proposed (Fine [14], Dushoff et al. [11], Levin et al. [28]).

Deterministic SIR models for some infectious diseases with permanent immunity have been shown to have an intrinsic tendency to oscillate periodically (Dushoff et al. [11], Hethcote et al. [18], Hethcote and Levin [17], Ruan and Wang [39], Tang et al. [43], etc.). However, this type of models do not apply directly to influenza since immunity is not permanent for influenza. Dushoff et al. [11] modelled antigenic drift by allowing individuals to lose their resistance to the circulating virus and re-enter the susceptible class after a few years and used a periodic incidence function to describe seasonal changes. They showed that the large oscillations in incidence may be caused by undetectably small seasonal changes in the influenza transmission rate that are amplified by dynamical resonance. Castillo-Chavez et al. [7], Andreasen et al. [3], Lin et al. [30], Andreasen [1] and Nuño et al. [37] developed multiple influenza A strain models with partial cross-immunity and showed that such models exhibit sustained oscillations. Note that Castillo-Chavez et al. [7] observed that sustained oscillations do not seem possible for a single-strain model even with age-specific mortalities. For sustained oscillations to occur, they required at least an age-structured population and two or more co-circulating viral strains.

Pease [38] used an age-structured type model to describe the evolutionary epidemiological mechanism of influenza A drift, in which the susceptible class is continually replenished because the pathogen changes genetically and immunologically from one epidemic to the next, causing previously immune hosts to become susceptible. However, applied to influenza A the model only predicted damped oscillations. Inaba [22] modified the model of Pease [38] and conjectured that for realistic parameter values, the modified model may exhibit sustained oscillations due to Hopf bifurcation. In this paper, we first modified the model of Pease [38] and Inaba [22] by using the age of infection (instead of the number of amino acid substitutions) as a variable. Then we applied our recent established center manifold theory for semilinear equations with non-dense domain (Magal and Ruan [33]) to show that Hopf bifurcation occurs in the modified model. This demonstrates that the age-structured type evolutionary epidemiological model of influenza A drift has an intrinsic tendency to oscillate due to the evolutionary and/or immunological changes of the influenza viruses.

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