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Within-host dynamics of lysogen and non-lysogen bacteria with spontaneous prophage induction phenomenon

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Abstract

Bacteriophages or phages (viruses of bacteria) play numerous roles in shaping the diversity of bacterial communities within the human gut. Either a phage-infected bacterial cell immediately starts a lysis mechanisms (virulent/lytic infection), or it enters a stable state within the host as a prophage (lysogeny), until a trigger event, called Spontaneous Prophage Induction (SPI), allows the lysis phenomenon. We develop an approach to address the role of SPI within phage-bacteria interactions and the influence of lysogeny on the success of phage therapy. This is based on a model structure in terms of time since infection. Our analysis suggests that SPI allows lysogen bacteria to have a competitive advantage over their non-lysogenic counterparts. Moreover, the model exhibits the bistability phenomenon such that, depending on the initial conditions, the dynamic can either converge towards a purely temperate state (only lysogens and temperate phages persist) or a purely lytic state (only non-lysogens and virulent phages persist). We also highlight the existence of SPI's critical values leading to the coexistence of all states through periodic oscillations. Finally, the model suggests that efficient bacteria control through phage therapy can be achieved by minimizing lysogens' offspring.

Keywords: Within-host competition; Nonlinear dynamical systems; SPI; Age structured model; Phage therapy; Hopf bifurcation.

1 Introduction

Antimicrobial resistance (AMR) is a worldwide major crisis [1]. The lack of effective treatments to control pathogenic vibrios resistant to antibiotics has led to the exploration of new alternatives. One of the most promising options, called phage therapy, is the use of lytic bacteriophages to kill pathogenic bacteria [14, 24]. These infections can lead to lysis and death of the infected bacteria, and new infections by progeny virus particles can drive down bacterial populations leading to endogenous oscillations in population densities [17]. However, for many bacteriophages, lysis is not the only possible infection outcome. Infection by temperate bacteriophages such as phage λ , μ , and P22 can lead to cell lysis or lysogeny. Lysogenic conversion refers to the integration of a temperate phage into the bacterial genome and forms a prophage. As a genetic material, prophage might constitute up to 20% of the bacterial genome, with variation between species and strains. These prophages propagate vertically together with bacterial cell division and induce spontaneously to enter the lytic cycle to form new bacteriophage particles either spontaneously or under the influence of various inducers. These new phages can then lyse or lysogenize other susceptible non-lysogens, thereby restarting the process and impacting the competition between lysogens and non-lysogens [4].

Small intestines are highly polluted by phages. One estimates that 1015 phages reside in the human gut, which accounts for approximately 108–1010 phages per gram of human stool depending on the

extraction method used [9, 19]. In the human gut, phages are capable to eradicate bacterial populations by lysis (virulent infection), but can also carry out horizontal gene transfer (HGT) through prophage integration (lysogenic infection). The acquisition of new genes provided by prophage can be favourable to the bacterial host with benefits including improved colonization of the gut, virulence factors, improved stress tolerance, biofilm formation, motility, or immunity in the case of prophages [10, 12]. Whenever gut commensals acquire genes conducive to virulence, they can evolve to become pathogens, thus, phages can contribute to the spread of virulence and disease development in the human gut. Indeed, prophages or phage genes have been detected in many pathogens. A classic example of this is some nonpathogenic *E. coli* strains residing in the human gut, but, which through the acquisition of phage-encoded Shiga toxins, can evolve into pathogens [12, 13, 21, 23]. These complex relationships between phages and their bacterial hosts in the human gut urge us to investigate the following research questions: (i) What is the impact of lysogeny on the success of phage therapy? (ii) What is the role of SPI in the competition of lysogen and non-lysogen bacteria? In other words, in a typical scenario with different growth rates, will SPI be favourable or detrimental to the lysogens (as it kills the host cell but also attacks non-lysogenic competitors, by either lysing or lysogenizing them)?

The life cycles of phages within the human gut can be described by splitting phages and bacteria populations into different state variables: susceptible or non-lysogen bacteria (B_S), lysogen bacteria (B_T), lytic fated infected bacteria (B_L), induced infected bacteria (B_{Ti}), purely lytic phages (P_L) and temperate phages (P_T) (Figure 1). The proposed model reads as

$$\left\{ \begin{array}{l} \dot{B}_S(t) = r_S B_S(t) \mathcal{W}(B_S(t) + B_T(t)) - (\beta_L P_L(t) + \beta_T P_T(t)) B_S(t) - \delta_S B_S(t), \\ \dot{B}_T(t) = r_T B_T(t) \mathcal{W}(B_S(t) + B_T(t)) + (1 - \pi) \beta_T B_S(t) P_T(t) - (\delta_T + \alpha) B_T(t), \\ (\partial_t + \partial_a) B_L(t, a) = -(\mu_L(a) + \delta_S) B_L(t, a), \\ B_L(t, 0) = \beta_L B_S(t) P_L(t) + \pi \beta_T B_S(t) P_T(t), \\ (\partial_t + \partial_a) B_{Ti}(t, a) = -(\mu_T(a) + \delta_T) B_{Ti}(t, a), \\ B_{Ti}(t, 0) = \alpha B_T(t), \\ \dot{P}_L(t) = \int_0^\infty \theta_L \mu_L(a) B_L(t, a) da - \delta P_L(t) - \beta_L B_S(t) P_L(t), \\ \dot{P}_T(t) = \int_0^\infty \theta_T \mu_T(a) B_{Ti}(t, a) da - \delta P_T(t) - \beta_T B_S(t) P_T(t). \end{array} \right. \quad (1.1)$$

The function \mathcal{W} accounts for the regulation factor of the bacteria growth. We assume that \mathcal{W} is continuous, decreasing and there exists w_0 (either a positive constant or ∞) such that

$$\mathcal{W}([0, w_0)) = (0, 1].$$

The function \mathcal{W} encompasses the classical logistic growth $\mathcal{W}(B) = 1 - \kappa B$, or functions of the form $\mathcal{W}(B) = (1 + B)^{-\kappa}$, with κ a positive constant. Therefore, the growth factors for lysogen and non-lysogen populations are then $r_j B_j \mathcal{W}(B_S + B_T)$, $j \in \{S, T\}$, where $r_{j,s}$ are intrinsic growth rates of susceptible and lysogen populations. Moreover, we assume that immune responses eliminate non-lysogens and lysogens at constant rates δ_S and δ_T , respectively. Susceptible bacteria are those that are not yet infected by a phage. When infected by purely lytic phage at rate $\beta_L P_L(t)$, susceptible bacteria move to newly lytic-fated bacteria class $B_L(t, 0)$. By contrast, when susceptible bacteria are infected by temperate phages at rate $\beta_T P_T(t)$, a proportion (π) of them moves to the newly lytic-fated bacteria class, while the remainder $(1 - \pi)$ moves to lysogens class B_T . The rupture of lytic-fated bacteria, which are infected since time a , results in the release of an average number θ_L of virulent phages; so that lytic-fated bacteria, infected since time a , produce virulent phages at the net rate $\theta_L \mu_L(a)$, where $\mu_L(a)$ denotes the additional death rate of lytic-fated bacteria –due to the rupture (burst)– and infected since time a . Together with this description, the quantity $\int_0^\infty \theta_L \mu_L(a) B_L(t, a) da$ corresponds to the total number of virulent phages

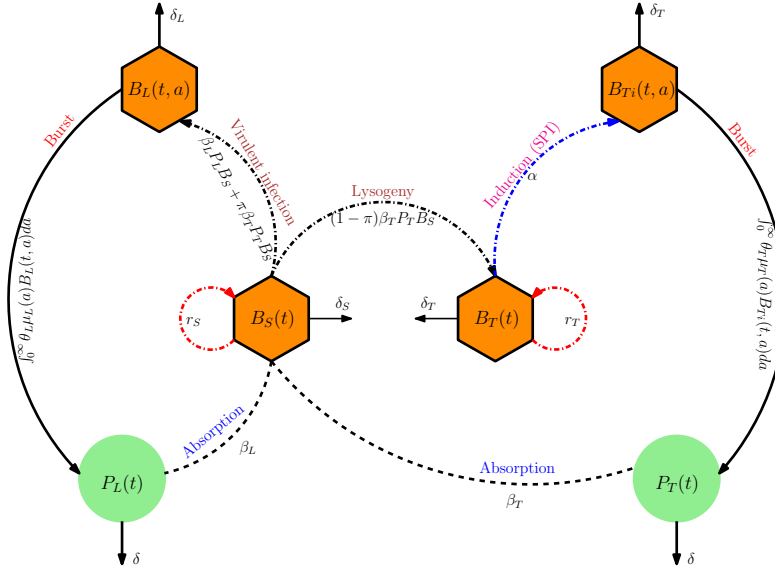


Figure 1: Phage-bacteria interaction with both horizontal and vertical transmissions. The figure illustrates interactions, at any time t , between: susceptible or non-lysogen bacteria, $B_S(t)$, lysogen bacteria, $B_T(t)$, lytic-fated infected bacteria since time a , $B_L(t, a)$, induced infected bacteria since time a , $B_{Ti}(t, a)$, purely lytic phages, $P_L(t)$, and temperate phages, $P_T(t)$.

produced by lytic-fated bacteria at time t . Furthermore, lysogens bacteria B_T are those keeping prophage in their chromosome and will transmit this genetic material to their offspring through vertical transmission [10, 22, 29]. The SPI phenomenon allows this class to undergo lytic cycle and become induced infected bacteria that will then produce temperate phages. The SPI phenomenon occurs at rate α and leads to newly induced lytic-fated bacteria $B_{Ti}(t, 0)$. The rupture of induced-lytic-fated bacteria, which are infected since time a , results in the release of an average number θ_T of temperate phages such that, the quantity $\int_0^\infty \theta_T \mu_T(a) B_{Ti}(t, a) da$ corresponds to the total number of temperate phages produced by induced-lytic-fated bacteria at time t . Both temperate and virulent phages decay at rate δ . System (1.1) is appended with the initial data:

$$\begin{aligned} (B_L(0, \cdot), B_{Ti}(0, \cdot)) &= (B_{L0}(\cdot), B_{Ti0}(\cdot)) \in L^1(0, \infty, \mathbb{R}_+^2), \\ (B_S(0), B_T(0), P_L(0), P_T(0)) &= (B_{S0}, B_{T0}, P_{L0}, P_{T0}) \in \mathbb{R}_+^4. \end{aligned}$$

Several models have been developed to study the role of SPI on the dynamic of phages and bacteria. But few models have considered both virulent and lysogenic infection as in our modelling framework. For instance, in [4, 11, 22, 23, 26] authors derived an ordinary differential equation describing the temperate phages dynamics and focusing on the role of SPI. However, taking into account both types of infections is relevant since some bacteria can be infected by virulent or temperate phage. For instance, *E. coli* is infected by temperate phage λ but also by phage T_4 which is a purely lytic virus. Moreover, experiments showed the existence of a delay or latent period (≈ 20 min) which is the interval between phage adsorption to a bacterium and subsequent lysis of the bacterium. The latent period has a constant range for given human gut conditions and our model explicitly tracks the "age" of the infected cell to properly capture the lysis phenomenon (*eg.*, see [2, 7] for more discussion).

The manuscript is organized as follows. Section 2 is devoted to some preliminaries including some notations, the existence and properties of globally defined and positive semiflow of Model (1.1). In Section 3, we introduce the main results of the manuscript. Those results include the existence and stability of the model's stationary states. Furthermore, we highlight the existence of a Hopf-bifurcation around the positive stationary state (the coexistence of all state variables) with the SPI rate as the bifurcation

parameter. Our results are then discussed in Section 4. Finally, in Sections 5-9, we provide detailed proofs of our main results.

2 Preliminary remarks

This section is devoted to some preliminaries including the abstract formulation of Model (1.1), the existence and properties of the associated semiflow. We will make use of the following assumption

Assumption 2.1 $\pi \in (0, 1)$, and $\delta, \theta_j, \beta_j, \delta_j$ are positive constants, $\alpha \geq 0$, and functions $\mu_j \in L_+^\infty(0, \infty)$; $j \in \{L, T\}$.

Notice that the average number of susceptible/non-lysogen and lysogenic bacteria produced by a single bacterium during its entire lifespan is respectively quantified by

$$\mathcal{T}_S = \frac{r_S}{\delta_S}, \quad \text{and} \quad \mathcal{T}_T = \frac{r_T}{\delta_T + \alpha}, \quad (2.1)$$

For mathematical elegance, we introduce the following quantities:

$$F_j(a) = e^{-\int_0^a \mu_j(\tau) d\tau}, \quad d_j(a) = e^{-\delta_j a} F_j(a), \quad K_j = \int_0^\infty \theta_j \mu_j(a) d_j(a) da, \quad j \in \{L, T\}.$$

Note that, $F_j(a)$ is the probability that a lytic-fated bacteria of concern has not yet lysed a -time after infection, and $d_j(a)$ is the probability of such a bacteria to remain alive a -time after infection. The parameters K_L and K_T are respectively the total numbers of virulent and temperate phages produced after the burst. It is natural to assume that $K_L > 1$ and $K_T > 1$.

Furthermore, by the next-generation operator approach (e.g., [6, 16]) we compute the average number of phages produced by a single temperate (resp. virulent) phage in an entirely susceptible bacterial population, denoted \mathcal{R}_{0T} (resp. \mathcal{R}_{0L}) as (see Section 6 for details)

$$\mathcal{R}_{0L} = K_L \frac{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1})}{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta}, \quad \text{and} \quad \mathcal{R}_{0T} = K_T \frac{(1 - \pi) \beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1})}{\left(1 - \frac{\mathcal{T}_T}{\mathcal{T}_S}\right) (\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)} \frac{\alpha}{\delta_T + \alpha}.$$

In the above expression of \mathcal{R}_{0L} , a total number of K_L virulent phages is produced by a single phage during its lifespan, and those phages are absorbed, by a susceptible bacteria population of size $\mathcal{W}^{-1}(\mathcal{T}_S^{-1})$, with the probability $\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) / (\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)$. Similarly, for the quantity \mathcal{R}_{0T} , a total number of K_T temperate phages is produced by a single phage during its lifespan, and those phages are absorbed, by a susceptible bacteria population of size $\mathcal{W}^{-1}(\mathcal{T}_S^{-1})$, at the probability $\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) / (\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)$. Among those absorbed temperate phages by susceptible bacteria, only the proportion $(1 - \pi)$ will become lysogens, and will be induced by the probability $\alpha / (\delta_T + \alpha)$ to produce temperate phages. Similarly, \mathcal{R}_{0L} accounts for a total number of K_L virulent phages produced by a single phage during its lifetime, and those phages are absorbed, in a susceptible bacteria population of size $\mathcal{W}^{-1}(\mathcal{T}_S^{-1})$, by the probability $\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) / (\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)$. Similarly, for the quantity \mathcal{R}_{0T} , a total number of K_T temperate phages is produced by a single phage during its lifetime, and those phages are absorbed, in a susceptible bacteria population of size $\mathcal{W}^{-1}(\mathcal{T}_S^{-1})$, by the probability $\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) / (\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)$. Among those absorbed temperate phages by susceptible bacteria, only a proportion $(1 - \pi) / \left(1 - \frac{\mathcal{T}_T}{\mathcal{T}_S}\right)$ will become lysogens, and will be induced by the probability $\alpha / (\delta_T + \alpha)$ to produce temperate phages.

For convenience, we use a compact form of System (1.1). Setting $x = (B_S, B_T)^T$, $y = (B_L, B_{Ti})^T$, $P = (P_L, P_T)^T$, and defining

$$\begin{aligned} R(x) &= \text{diag}(r_S \mathcal{W}(B_S + B_T), r_T \mathcal{W}(B_S + B_T)), \gamma = \text{diag}(\delta_S, \delta_T), \quad I = \text{diag}(0, 1), \\ \Phi(x) &= \begin{pmatrix} -\beta_L B_S & -\beta_T B_S \\ 0 & (1 - \pi) \beta_T B_S \end{pmatrix}, \quad \Psi(x) = \begin{pmatrix} \beta_L B_S & \pi \beta_T B_S \\ 0 & 0 \end{pmatrix}, \beta(x) = \begin{pmatrix} \beta_L B_S & 0 \\ 0 & \beta_T B_S \end{pmatrix}, \\ \mu &= \text{diag}(\mu_L, \mu_T), \quad \theta = \text{diag}(\theta_L, \theta_T), \quad K = \text{diag}(K_L, K_T), \quad \mathcal{D} = \text{diag}(d_L, d_T). \end{aligned}$$

Model (1.1) rewrites

$$\begin{cases} \dot{x}(t) = (R(x(t)) - \gamma)x(t) + \Phi(x(t))P(t) - \alpha Ix(t), \\ y(t, 0) = \Psi(x(t))P(t) + \alpha Ix(t), \\ (\partial_t + \partial_a)y(t, a) = -(\mu(a) + \gamma)y(t, a), \\ \dot{P}(t) = \int_0^\infty \theta\mu(a)y(t, a)da - \delta P(t) - \beta(x(t))P(t). \end{cases} \quad (2.2)$$

Next, let us denote by $\mathbb{X} := \mathbb{R}^2 \times \mathbb{R}^2 \times L^1(0, \infty, \mathbb{R}^2) \times \mathbb{R}^2$ the Banach space endowed with its usual product norm $\|\cdot\|_{\mathbb{X}}$. Let $\mathbb{X}_+ := \mathbb{R}_+^2 \times \mathbb{R}_+^2 \times L_+^1(0, \infty, \mathbb{R}^2) \times \mathbb{R}_+^2$ be the positive cone of \mathbb{X} . Set $u = (x, 0, y(\cdot), P) \in \mathbb{X}$, and define the linear operator $A : D(A) \subset \mathbb{X} \rightarrow \mathbb{X}$ by $D(A) = \mathbb{R}^2 \times \{0_{\mathbb{R}^2}\} \times W^{1,1}(0, \infty, \mathbb{R}^2) \times \mathbb{R}^2$ and

$$A(u) = \begin{pmatrix} -\gamma x \\ -y(0) \\ -y' - \mu y \\ -\delta P \end{pmatrix}, \quad (2.3)$$

We also define the nonlinear map $F : \overline{D(A)} \rightarrow \mathbb{X}$

$$F(u) = \begin{pmatrix} R(x)x + \Phi(x)P - \alpha Ix \\ \Psi(x)P + \alpha Ix \\ 0 \\ \int_0^\infty \theta\mu(a)y(a)da - \beta(x)P \end{pmatrix}.$$

Thus, by setting $\mathcal{X}_0 = \overline{D(A)}$ and $\mathcal{X}_0^+ = \mathcal{X}_0 \cap \mathbb{X}_+$, the abstract Cauchy problem associated with (2.2) writes

$$\frac{du(t)}{dt} = Au(t) + F(u(t)), \quad \text{and} \quad u(0) = u_0 \in \mathcal{X}_0^+. \quad (2.4)$$

The above abstract Cauchy problem generates a unique globally defined and positive semiflow as follows.

Theorem 2.2 *There exists a unique strongly continuous semiflow $\{U(t) : \mathcal{X}_0^+ \rightarrow \mathcal{X}_0^+\}_{t \geq 0}$ such that, for all $u_0 \in \mathcal{X}_0^+$, the map $u \in \mathcal{C}([0, \infty), \mathcal{X}_0^+)$ defined by $u = U(\cdot)u_0$ is a mild solution of (2.4) and satisfies for all $t \geq 0$*

$$\int_0^t u(s)ds \in D(A), \quad u(t) = u_0 + A \int_0^t u(s)ds + \int_0^t F(u(s))ds.$$

Moreover, setting $U(t, u_0) = (x(t), 0_{\mathbb{R}^2}, y(t, \cdot), P(t))$, for all $u_0 \in \mathcal{X}_0^+$. The semiflow $\{U(t)\}_{t \geq 0}$ is such that

(i) *The following Volterra formulation holds:*

$$\begin{aligned} B_L(t, a) &= \begin{cases} (\beta_L B_S(t-a)P_L(t-a) + \pi\beta_T B_S(t-a)P_T(t-a))d_L(a), & a < t \\ B_L(0, a-t)\frac{d_L(a)}{d_L(a-t)}, & a > t \end{cases} \\ \text{and} & \\ B_{Ti}(t, a) &= \begin{cases} \alpha B_T(t-a)d_T(a), & a < t \\ B_{Ti}(0, a-t)\frac{d_T(a)}{d_T(a-t)}, & a > t \end{cases} \end{aligned} \quad (2.5)$$

coupled with x and P equations of (2.2).

(ii) The semiflow $\{U(t)\}_{t \geq 0}$ is bounded dissipative and asymptotically smooth in the sense that

Bounded dissipative: there exists a bounded set $\mathcal{B} \subset \mathcal{X}_0$ such that for any bounded set $\mathcal{C} \subset \mathcal{X}_0$, there exists $\tau = \tau(\mathcal{C}, \mathcal{B}) \geq 0$ such that $U(t, \mathcal{C}) \subset \mathcal{B}$ for $t \geq \tau$.

Asymptotically smooth: for any nonempty, closed, bounded set $\mathcal{C} \subset \mathcal{X}_0$, there exists a nonempty compact set $J = J(\mathcal{C})$ such that J attracts the set $\{\varphi \in \mathcal{C} : U(t, \varphi) \in \mathcal{C}, \forall t \geq 0\}$.

Recall that a nonempty set $J \subset \mathcal{X}$ is said to attract a nonempty set $C \subset \mathcal{X}$ if $\delta_{\mathcal{X}}(U(t, C), J) \rightarrow 0$ as $t \rightarrow +\infty$, where $\delta_{\mathcal{X}}(C, J) = \sup_{u \in C} \inf_{v \in J} \|u - v\|_{\mathcal{X}}$ is a semi-distance on \mathcal{X} . We refer the reader to Section 5 for the proof of Theorem 2.2.

3 Main results

We show that Model (1.1) has many trivial stationary states as opposed to a positive stationary state where all the variables are positive. Those stationary states lead to many bi-stability regions that are precisely determined. Moreover, we show that Model (1.1) exhibits a Hopf-bifurcation around the positive stationary state (the coexistence of all state variables) with the SPI rate α as the bifurcation parameter.

Our first main result is about the existence and stability of trivial stationary states. Such a result reads

Theorem 3.1 *Let Assumption 2.1 be satisfied, and set $(B_S, B_T, B_L(a), B_{Ti}(a), P_L, P_T)$ the state variables of the solution of model (1.1). We also recall the parameters $\mathcal{T}_{j,s}$ defined by (2.1). Then,*

- (i) *The null state $\mathcal{O} = (0, 0, 0, 0, 0, 0)$ is always an equilibrium of Model (1.1). It is the unique equilibrium of Model (1.1) if and only if $\max\{\mathcal{T}_S, \mathcal{T}_T\} < 1$.*
- (ii) *When $\mathcal{T}_S > 1$, $\mathcal{E}_0 = (B_S, 0, 0, 0, 0, 0)$ is an equilibrium of Model (1.1), with $B_S = \mathcal{W}^{-1}(\mathcal{T}_S^{-1})$.*
- (iii) *When $\mathcal{T}_T > 1$, $\mathcal{E}_T = (0, B_T, 0, B_{Ti}(\cdot), 0, P_T)$ is an equilibrium of Model (1.1), with $B_T = \mathcal{W}^{-1}(\mathcal{T}_T^{-1})$, $B_{Ti}(\cdot) = \alpha \mathcal{W}^{-1}(\mathcal{T}_T^{-1}) d_T(\cdot)$, and $P_T = \alpha K_T \mathcal{W}^{-1}(\mathcal{T}_T^{-1}) \delta^{-1}$.*
- (iv) *When $\mathcal{T}_S > \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L - 1)}\right)\right)^{-1}$, $\mathcal{E}_L = (B_S, 0, B_L(\cdot), 0, P_L, 0)$ is an equilibrium of Model (1.1), with $B_S = \delta((K_L - 1)\beta_L)^{-1}$, $B_L(\cdot) = \beta_L B_S P_L d_L(\cdot)$ and $P_L = \delta \beta_L^{-1} \mathcal{W}(B_S) \left(\mathcal{T}_S - (\mathcal{W}(B_S))^{-1}\right)$.*

At the equilibrium \mathcal{E}_0 , only susceptible or non-lysogen bacteria (B_S) are present. Susceptible bacteria can co-exist at the equilibrium \mathcal{E}_L with lytic-fated infected bacteria (B_L) and purely lytic phages (P_L). Finally, lysogen bacteria (B_T) and temperate phages (P_T) are only present at the equilibrium \mathcal{E}_T . Therefore, equilibrium \mathcal{E}_0 , \mathcal{E}_L and \mathcal{E}_T can be referred to as: purely susceptible, purely lytic (*ie.*, without temperate phages), and purely temperate equilibrium, respectively.

Next, to investigate the stability of equilibria \mathcal{O} and $\mathcal{E}_{j,s}$, we introduce the following functions:

$$\begin{aligned} h(\mathcal{T}_S) &= \left(1 - \frac{\alpha(1 - \pi)\beta_T K_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1})}{(\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)(\delta_T + \alpha)}\right) \mathcal{T}_S, \\ g(\mathcal{T}_T) &= \left(1 + \frac{\beta_T \alpha K_T \mathcal{W}^{-1}(\mathcal{T}_T^{-1})}{\delta_S \delta}\right) \mathcal{T}_T, \\ l(\mathcal{T}_S) &= \left(1 - \frac{\alpha(1 - \pi)\beta_T K_T (\beta_L(K_L - 1))^{-1}}{(\delta_T + \alpha) \left(1 + \beta_T (\beta_L(K_L - 1))^{-1}\right)}\right) \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L - 1)}\right)\right)^{-1}. \end{aligned}$$

Although the above functions do not seem to have a precise biological meaning, they allow us to precisely determine the local asymptotic stability (l.a.s) of the equilibria \mathcal{O} and $\mathcal{E}_{j,s}$ within the $(\mathcal{T}_S, \mathcal{T}_T)$ -plane. Consequently, our second main result is stated in Theorem 3.2 below.

Theorem 3.2 *Let Assumption 2.1 be satisfied. Recall the equilibria \mathcal{O} and $\mathcal{E}_{j,s}$ given by Theorem 3.1. Then,*

- (i) *The null equilibrium \mathcal{O} is globally asymptotically stable if and only if $\max\{\mathcal{T}_S, \mathcal{T}_T\} < 1$.*
- (ii) *The purely susceptible equilibrium \mathcal{E}_0 is l.a.s if and only if $1 < \mathcal{T}_S < \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$ and $\mathcal{T}_T < h(\mathcal{T}_S)$.*
- (iii) *Let $\mathcal{T}_T > 1$. The purely temperate equilibrium \mathcal{E}_T is l.a.s if and only if $\mathcal{T}_S < g(\mathcal{T}_T)$.*
- (iv) *Let $\mathcal{T}_S > \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$. The purely lytic equilibrium \mathcal{E}_L is l.a.s if and only if $\mathcal{T}_T < l(\mathcal{T}_S)$.*

Note that the local stability condition of the purely susceptible equilibrium \mathcal{E}_0 is equivalent to $\mathcal{R}_0 := \max\{\mathcal{R}_{0_L}, \mathcal{R}_{0_T}\} < 1$. The latter inequality highlights the invasion capability of phages in a phage-free environment. We refer the reader to Section 7 for the proof of Theorem 3.2.

A positive stationary state of Model (1.1) is difficult to handle in general. Indeed, let $x^* = (B_S^*, B_T^*)$, $y^* = (B_L^*, B_{Ti}^*)$, $P^* = (P_L^*, P_T^*)$ be a positive equilibrium of Model (1.1). Then by the compact formulation (2.2) we have,

$$(R(x^*) - \gamma)x^* + \Phi(x^*)P^* - \alpha x^* = 0, \quad (3.1)$$

$$\delta^{-1}[K\Psi(x^*) - \beta(x^*)]P^* = P^* - \alpha\delta^{-1}KIx^*, \quad (3.2)$$

$$y^*(\cdot) = \exp\left(-\int_0^\cdot (\mu(\sigma) + \gamma)d\sigma\right)[\Psi(x^*)P^* + \alpha Ix^*].$$

Assuming that the induction rate α is sufficiently small, we can proceed by precisely characterizing such a positive stationary state. Note that in the absence of external interventions (use of inducers), the induction phenomenon can be so rare that its rate α is sufficiently small compared to other parameters of the interactive dynamics of bacteria and phages (eg., [4]). Therefore, thanks to a generalized implicit function theorem-type argument, we have our third main result regarding the existence of a positive equilibrium of Model (1.1) stated as follows:

Theorem 3.3 *Let Assumption 2.1 be satisfied. Assume that*

$$\left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1} < \mathcal{T}_T < \mathcal{T}_S. \quad (3.3)$$

Then, for sufficiently small induction rate α , Model (1.1) has a positive stationary state \mathcal{E}^ such that*

$$\begin{aligned} B_S^* &= B_S^0 + \alpha B_S^1 + \mathcal{O}(\alpha^2), \\ B_T^* &= B_T^0 + \alpha B_T^1 + \mathcal{O}(\alpha^2), \\ P_L^* &= P_L^0 + \alpha P_L^1 + \mathcal{O}(\alpha^2), \\ P_T^* &= \alpha P_T^1 + \mathcal{O}(\alpha^2), \\ B_L^*(a) &= B_L^0(a) + \alpha B_L^1(a) + \mathcal{O}(\alpha^2), \\ B_{Ti}^*(a) &= \alpha B_{Ti}^1(a) + \mathcal{O}(\alpha^2), \end{aligned} \quad (3.4)$$

where

$$\begin{aligned}
B_S^0 &= \delta((K_L - 1)\beta_L)^{-1}, \quad B_T^0 = \mathcal{W}^{-1}(\mathcal{T}_T^{-1}) - \delta((K_L - 1)\beta_L)^{-1}, \\
P_L^0 &= \frac{\delta_S}{\beta_L} \left(\frac{\mathcal{T}_S}{\mathcal{T}_T} - 1 \right), \quad B_L^0(a) = \beta_L P_L^0 B_S^0 d_L(a), \quad B_{Ti}^1(a) = B_T^0 d_T(a), \\
B_S^1 &= r_S r_T^{-1} \left(\frac{\beta_T \delta K_T (r_T B_T^0 + r_S B_S^0)}{\beta_T B_S^0 + \delta} - 1 \right) \pi K_L \beta_T (\beta_L^2 (K_L - 1) P_L^0)^{-1}, \\
B_T^1 &= \frac{\left(\frac{\beta_L (K_L - 1) \beta_L P_L^0}{\pi K_L \beta_T} - r_S B_S^0 B_T^0 \mathcal{W}'(B_S^0 + B_T^0) \right) \left(1 - \frac{(1 - \pi) \beta_T B_S^0 \delta K_T}{\beta_T B_S^0 + \delta} \right) - \frac{r_T B_T^0 B_S^0 \beta_T \delta K_T}{\beta_T B_S^0 + \delta} \mathcal{W}'(B_S^0 + B_T^0)}{r_T \mathcal{W}'(B_S^0 + B_T^0) \frac{\beta_L^2 (K_L - 1) P_L^0}{\pi K_L \beta_T}}, \\
P_L^1 &= \frac{(1 - K_L) \beta_L P_L^0}{\pi K_L \beta_T B_S^0} B_S^1, \quad P_T^1 = \frac{\delta K_T B_T^0}{\beta_T B_S^0 + \delta}.
\end{aligned}$$

Details on the proof of Theorem 3.3 are given in Section 8. Condition (3.3) is interesting in the sense that a full coexistence within Model (1.1) occurs when the reproduction capability of lysogens bacteria (\mathcal{T}_T) is sufficiently large but does not exceed that of non-lysogens bacteria (\mathcal{T}_S).

The qualitative dynamics of Model (1.1), stated by Theorem 3.2 and Theorem 3.3, is summarized in the $(\mathcal{T}_S, \mathcal{T}_T)$ -plane in Figure 2.

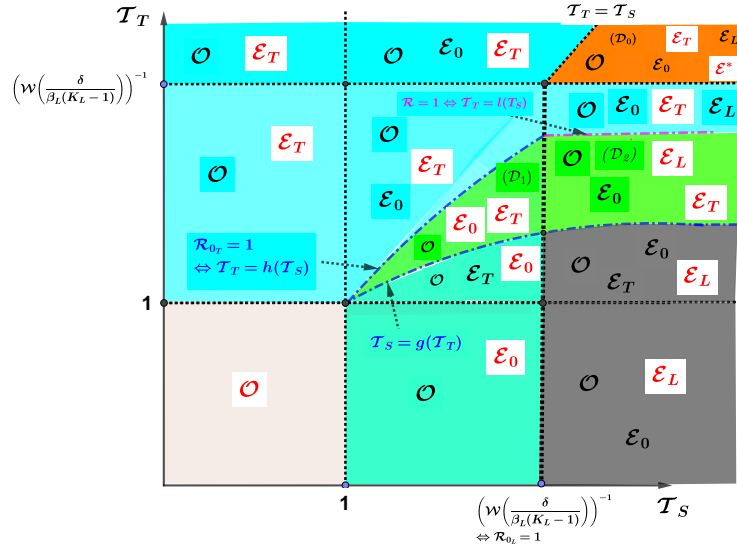


Figure 2: Qualitative analysis of Model (1.1). In the $(\mathcal{T}_S, \mathcal{T}_T)$ -plane the positive orthant is divided into several regions. In each of them, plausible stationary states are illustrated. The local stability of stationary states is marked within a box. The bistability phenomenon occurs in regions (\mathcal{D}_1) and (\mathcal{D}_2) . (\mathcal{D}_1) : \mathcal{E}_0 and \mathcal{E}_T are locally asymptotically stable. (\mathcal{D}_2) : \mathcal{E}_T and \mathcal{E}_L are locally asymptotically stable. In the region (\mathcal{D}_0) , we have the existence of a positive stationary state \mathcal{E}^* . Both stationary states \mathcal{E}_T and \mathcal{E}^* may be locally asymptotically stable, and a Hopf-bifurcation occurs around \mathcal{E}^* under a certain condition (Theorem 3.4). Note that $\mathcal{R}_{0T} = 1 \Leftrightarrow \mathcal{T}_T = h(\mathcal{T}_S)$ and $\mathcal{R}_{0L} = 1 \Leftrightarrow \mathcal{T}_S = \left(\mathcal{W} \left(\frac{\delta}{\beta_L (K_L - 1)} \right) \right)^{-1}$. The threshold quantity \mathcal{R} is such that $\mathcal{R} = \frac{(1 - \pi) \beta_T \alpha K_T ((K_L - 1) \beta_L)^{-1}}{(\delta_T + \alpha) (1 + \beta_T ((K_L - 1) \beta_L)^{-1})} + \mathcal{T}_T \mathcal{W}(\delta ((K_L - 1) \beta_L)^{-1})$, and $\mathcal{R} = 1 \Leftrightarrow \mathcal{T}_T = l(\mathcal{T}_S)$.

We now focus on the local asymptotic behaviour of Model (1.1) around the positive equilibrium \mathcal{E}^* for $\alpha \ll 1$. In this regard, we naturally set by $\tau > 0$, the time delay between phage adsorption and lysis

and consider (without loss of generality) that the rupture functions $\mu_{j,s}$ ($j \in \{L, T\}$) take the following form

$$\mu_j(a) = \begin{cases} 0 & \text{for } a < \tau \\ \mu_{j_0} & \text{for } a \geq \tau \end{cases}. \quad (3.5)$$

Next, for any spectrum point λ (with $\text{Re}(\lambda) > -\min\{\gamma, \mu, \delta\}$) of the System (1.1), linearized around the positive equilibrium \mathcal{E}^* ,

$$p(\lambda, \alpha) + q(\lambda, \alpha)e^{-\lambda\tau} = 0, \quad (3.6)$$

where $p(\lambda, \alpha)$ and $q(\lambda, \alpha)$ are of the form $p(\lambda, \alpha) = \lambda^6 + \sum_{l=0}^5 p_l(\alpha)\lambda^l$, $q(\lambda, \alpha) = \sum_{l=0}^3 q_l(\alpha)\lambda^l$. Moreover, by the expansion (3.4) of \mathcal{E}^* , $p_l(\alpha) = p_l^0 + \alpha p_l^1 + \mathcal{O}(\alpha^2)$, and $q_l(\alpha) = q_l^0 + \alpha q_l^1 + \mathcal{O}(\alpha^2)$, with coefficients p_l^j, s and q_l^j, s detailed in Section 9 (to facilitate the readability). Finally, any solution of the form $\lambda = i\omega$ ($\omega \in \mathbb{R}$) of the characteristic equation (3.6) around \mathcal{E}^* is characterized by any pairing (ω, α) satisfying

$$\begin{cases} \Gamma(\omega, \alpha) := \omega^{12} + \sum_{k=0}^5 f_k \omega^{2k} - 2\alpha \sum_{k=0}^5 g_k \omega^{2k} = 0, \\ \Gamma_1(\omega, \alpha) := \cos \omega\tau - \mathcal{Q}(\omega, \alpha) = 0, \end{cases} \quad (3.7)$$

where $\mathcal{Q} = \mathcal{Q}(\omega, \alpha)$ is a rational function defined by (9.6) and, $f_{k,s}$; $g_{k,s}$ are precisely given in Section 9 as coefficients depending (only) on p_l^j, s and q_l^j, s . We then have our fourth main result stated as follows:

Theorem 3.4 *Let Assumption 2.1 be satisfied. Assume that (3.3) and (3.5) hold. Let $(\omega_c > 0, \alpha_c > 0)$ such that condition (3.7) holds. Then, Model (1.1) undergoes a Hopf bifurcation, at the positive equilibrium \mathcal{E}^* , for the critical value α_c , whenever we have*

$$\mathcal{M}_c(\omega, \alpha) := (5p_5(\alpha_c)\omega_c^4 - 3p_3(\alpha_c)\omega_c^2 + p_1(\alpha_c))M_1(\omega_c) + (6\omega_c^5 - 4p_4(\alpha_c) + 2p_2(\alpha_c))M_2(\omega_c) \neq 0, \quad (3.8)$$

where

$$\begin{aligned} M_1(\omega_c) &= p_0^1 - p_2^1\omega_c^2 + p_4^1\omega_c^4 + (q_0^1 - q_2^1\omega_c^2) \cos \omega_c\tau + (q_1^1\omega_c - q_3^1\omega_c^3) \sin \omega_c\tau, \\ M_2(\omega_c) &= p_1^1\omega_c - p_3^1\omega_c^3 + p_5^1\omega_c^5 + (q_1^1\tau\omega_c - q_3^1\tau\omega_c^3) \cos \omega_c\tau - (q_0^1 - q_2^1\omega_c^2) \sin \omega_c\tau. \end{aligned}$$

Note that (3.8) ensures the transversality condition of the Hopf bifurcation theorem. We refer the interested reader to Section 9 for the proof of Theorem 3.4.

We end this section with numerical simulations which illustrate the Hopf bifurcation phenomenon. For all the figures, we assume that the regulation growth function takes the form $\mathcal{W}(B) = (1 + B)^{-\kappa}$, with $\kappa > 0$. All the model parameters are fixed, except the bifurcation parameter α which is assumed to be variable. Figure 3 (right) illustrates a possible critical pairing $(\omega_c > 0, \alpha_c > 0)$ given by the intersection of the level sets $\Gamma(\omega, \alpha) = 0$ and $\Gamma_1(\omega, \alpha) = 0$. Figure 3 (left) then highlights the first bifurcation threshold value $\alpha_c \approx 0.0023$. Finally, Figures 4-5 illustrate a supercritical Hopf bifurcation, *ie.*, the appearance of a limit cycle which is stable for values $\alpha < \alpha_c$ (Figure 4) and unstable for some values $\alpha > \alpha_c$, giving rise to the stable endemic equilibrium \mathcal{E}^* (Figure 5).

4 Discussion

Bacteriophages (viruses of bacteria) are an alternative and efficient biocontrol agent of bacteria (in the human gut) through a treatment protocol known as phage therapy. We address the role of Spontaneous Prophage Induction (SPI) within phage-bacteria interactions and the influence of lysogeny on the success of phage therapy. Our approach is based on an age-structured mathematical model accounting for the time since infection (Model (1.1)). Such a modeling framework allows a refined description of the cell lysis phenomenon (*eg.*, [7]). The model developed exhibits the bistability phenomenon such that, depending on the initial conditions, the dynamics can either converge towards a purely temperate state (where only lysogens and temperate phages are persistent), or a purely lytic state (where only non-lysogens and

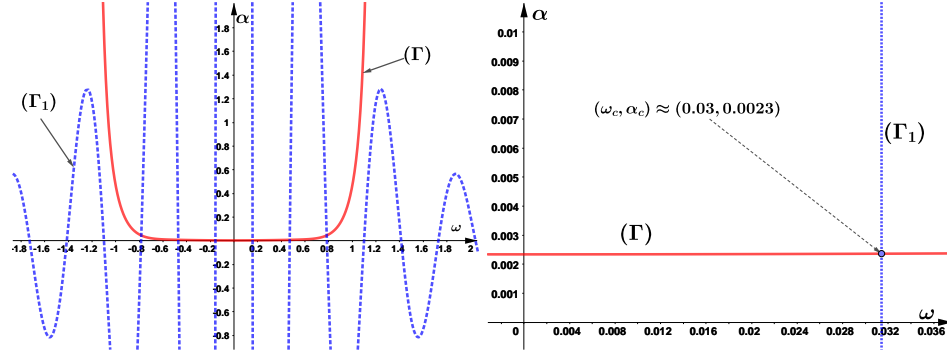


Figure 3: Level sets (Γ) and (Γ_1) for the set of parameter's values: $r_S = 20$; $r_T = 20$; $\beta_T = 1e - 8$; $\beta_L = 1e - 3$; $\delta_S = 1e - 4$; $\delta_T = 1e - 4$; $\delta = 0.2$; $\pi = 0.1$; $\kappa = 2$; $\theta_L = \theta_T = 50$, $\mu_{L_0} = \mu_{T_0} = 10$, $\tau = 10$.

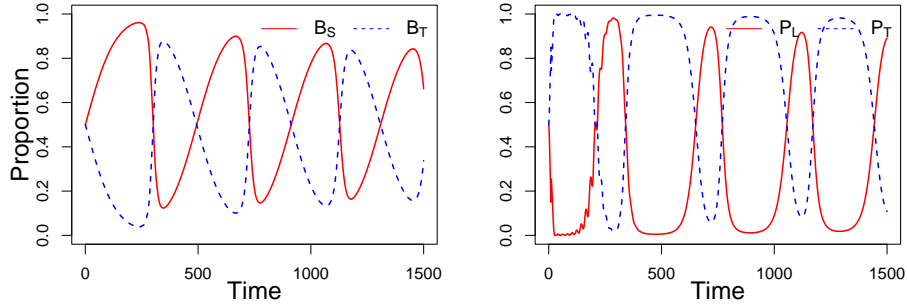


Figure 4: Periodic solutions for $\alpha = 0.0015 < \alpha_c$; $r_S = 20$; $r_T = 20$; $\beta_T = 1e - 8$; $\beta_L = 1e - 3$; $\delta_S = 1e - 4$; $\delta_T = 1e - 4$; $\delta = 0.2$; $\pi = 0.1$; $\kappa = 2$; $B_S(0) = 1$, $B_T(0) = 1$; $P_L(0) = 1$; $P_T(0) = 1$; $\theta_L = \theta_T = 50$, $\mu_{L_0} = \mu_{T_0} = 10$, $\tau = 10$.

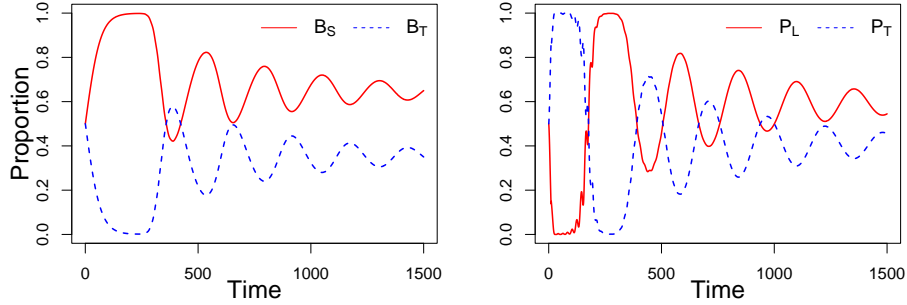


Figure 5: Local asymptotic stability of \mathcal{E}^* , for $\alpha = 0.003 > \alpha_c$; $r_S = 20$; $r_T = 20$; $\beta_T = 1e - 8$; $\beta_L = 1e - 3$; $\delta_S = 1e - 4$; $\delta_T = 1e - 4$; $\delta = 0.2$; $\pi = 0.1$; $\kappa = 2$; $B_S(0) = 1$, $B_T(0) = 1$; $P_L(0) = 1$; $P_T(0) = 1$; $\theta_L = \theta_T = 50$, $\mu_{L_0} = \mu_{T_0} = 10$, $\tau = 10$.

virulent phages are persistent). The dynamical behaviour of Model (1.1) is summarized into $(\mathcal{T}_S, \mathcal{T}_T)$ -plane (Figure 2), where \mathcal{T}_S and \mathcal{T}_T are the growth thresholds of non-lysogens and lysogens strains respectively.

As long as $\mathcal{T}_T > \mathcal{T}_S$, the purely temperate equilibrium is the only stable equilibrium, *ie.*, only lysogens bacteria and temperate phages are persistent within the host. Since lysogens bacteria are already infected

by temperate phages (and thus immunise for a second phage's infection), ingestion of selected lytic phages is not recommended for phage therapy, because those lytic phages can no longer infect the lysogen bacteria which are already persistent in the human gut. In such a configuration, our analysis suggests the use of inducers (such as acyl-homoserine lactones) to trigger the burst of lysogens bacteria. Achieving the non-persistence of lysogens bacteria is then one of the key targets to phage therapy success, and to reach this objective through the analysis of our model is to sufficiently reduce the growth threshold \mathcal{T}_T of lysogens bacteria such that $\mathcal{T}_S > g(\mathcal{T}_T)$ is achieved. The latter can be done as suggested in [3], where authors recommended the use of antibiotics such as ciprofloxacin to eradicate *E. coli* in vitro through depletion of lysogens. Such an approach is in a favour of the combination of both phage therapy and antibiotherapy to fight against antibiotic-resistant bacteria.

On the other hand, when $\mathcal{T}_T < \mathcal{T}_S$, the configuration becomes less simple. Indeed, in such a situation, Model (1.1) exhibits the bistability phenomenon, *ie.* the asymptotic behaviour of the system is strongly related to the initial conditions. More precisely, whenever $\max\{\mathcal{T}_T, \mathcal{T}_S\} < \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$ (or equivalently $\mathcal{R}_{0_L} < 1$), System (1.1) either converges to the purely susceptible equilibrium (\mathcal{E}_0), or to the purely temperate equilibrium (\mathcal{E}_T). Conversely, if $\mathcal{T}_T < \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$ and $\mathcal{T}_S > \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$ (or equivalently $\mathcal{R}_{0_L} > 1$), System (1.1) either converges to the purely temperate equilibrium (\mathcal{E}_T) or to the purely lytic equilibrium (\mathcal{E}_L). On the other note, for sufficiently high values of the growth threshold \mathcal{T}_T , *ie.* $\mathcal{T}_T > \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$, our analysis also highlights the existence of critical values of SPI leading to the coexistence of all states through periodic oscillations. For such configurations, where lysogens bacteria are persistent, the single action of phage therapy (through the ingestion of selected lytic phages) is not enough for effective control of the bacterial population. In this context, using inducers as suggested above may not be an efficient strategy to supplement the actions of phages to fight against bacterial infections.

Within the human gut, intestinal environmental factors such as temperature, gastrointestinal transit, intestinal diseases, and oxidative stress, have been recognized as crucial factors in regulating prophage induction, as well as the microbiome and phageome. Some previous studies (*eg.* [14]), indicated that prophage induction could mainly be associated with high temperature. Consequently, SPI is a random phenomenon that can be considered a stochastic process. In this work, we've assumed that the proportion of temperate bacteria (following virulent infections) produces 100% of virulent phages after the lysis. However, it could be interesting to account for the mutation process that allows some temperate phages to lysogenize susceptible bacteria. Another limitation of our work is that the modelling approach did not explicitly consider the effect of the human immune system on the overall dynamics. A complete round-up will be to address the challenging modelling framework by combining antibiotics and phage-bacteria dynamics and the human immune system in a single (but more realistic for the implementation of phage therapy) within-host mathematical model. This is particularly important within the context of phage therapy as an alternative approach to the challenging fight against antibiotic multi-resistance diseases.

5 Proof of Theorem 2.2

The existence and uniqueness of a semiflow associated with System (1.1) is a quite standard result (*eg.*, [20, 27]), as well as the Volterra formulation (*eg.*, [15, 28]).

For estimate (ii), let $u_0 \in \mathcal{X}_{0+}$; then

$$\frac{d}{dt}(B_S + B_T) \leq \max(r_S, r_R)(B_S + B_T)\mathcal{W}(B_S + B_T) - \min(\delta_S, \delta_T)(B_S + B_T),$$

Recalling that $\mathcal{W}(w) \in (0, 1]$ for all $w \in [0, w_0)$, it follows that

$$B_S(t) + B_T(t) \leq \begin{cases} \max\left(B_S(0) + B_T(0), \mathcal{W}^{-1}\left(\frac{\min(\delta_S, \delta_T)}{\max(r_S, r_R)}\right)\right) & \text{if } \frac{\min(\delta_S, \delta_T)}{\max(r_S, r_R)} \leq 1 \\ B_S(0) + B_T(0) & \text{if } \frac{\min(\delta_S, \delta_T)}{\max(r_S, r_R)} > 1 \end{cases}$$

that is

$$B_S(t) + B_T(t) \leq \max(B_S(0) + B_T(0), \mathcal{W}^{-1}(\delta^\diamond)),$$

with $\delta^\diamond := \min\left(1, \frac{\min(\delta_S, \delta_T)}{\max(r_S, r_R)}\right)$. Next, by setting $B = B_S + B_T + \int (B_L + B_{Ti})(a)da$, it comes

$$\dot{B}(t) \leq \Lambda - \min(\delta_S, \delta_T)B(t),$$

with $\Lambda = \max(B_S(0) + B_T(0), \mathcal{W}^{-1}(\delta^\diamond))$. From where

$$B(t) \leq \max\left\{\frac{\Lambda}{\min(\delta_S, \delta_T)}, B(0)\right\}. \quad (5.1)$$

Finally, by setting $P = P_T + P_L$, we similarly find that

$$P(t) \leq \max\left\{\frac{\max(\theta_L \|\mu_L\|_\infty, \theta_T \|\mu_T\|_\infty)}{\delta} \max\left(\frac{\Lambda}{\min(\delta_S, \delta_T)}, B(0)\right), P(0)\right\}. \quad (5.2)$$

Therefore, the bounded dissipativity of the semiflow $\{U(t) : \mathcal{X}_0^+ \rightarrow \mathcal{X}_0^+\}_{t \geq 0}$ is a consequence of estimates (5.1) and (5.2).

To prove the asymptotic smoothness, let C be a forward invariant bounded subset of \mathcal{X}_{0+} . By the results in [25], it is then sufficient to show that the semiflow U is asymptotically compact on the subset C . Let us introduce a sequence of solutions $(B_S^n, B_T^n, B_L^n, B_{Ti}^n, P_L^n, P_T^n)_n$ that is equibounded in \mathcal{X}_{0+} and a sequence $\{t_n\}_n$ such that $t_n \rightarrow +\infty$. Since the sequences B_S^n, B_T^n, P_L^n , and P_T^n are uniformly bounded in the Lipschitz norm, the Arzela-Ascoli theorem implies that, possibly along a subsequence, we can assume that the above sequence is such that $B_S^n(t + t_n) \rightarrow \tilde{B}_S(t)$, $B_T^n(t + t_n) \rightarrow \tilde{B}_T(t)$, $P_L^n(t + t_n) \rightarrow \tilde{P}_L(t)$, and $P_T^n(t + t_n) \rightarrow \tilde{P}_T(t)$ locally uniformly for $t \in \mathbb{R}$. For the sequences $\{B_L^n, B_{Ti}^n\}_n$, we only detail the case of $\{B_{Ti}^n\}_n$, because $\{B_L^n\}_n$ can be obtain similarly. Denote $\tilde{B}_{Ti}^n(t, \cdot) = B_{Ti}^n(t + t_n, \cdot)$. Then, the Volterra formulation (2.5) gives

$$\tilde{B}_{Ti}^n(t, a) = \begin{cases} \alpha B_T^n(t - a + t_n) d_T(a), & a < t + t_n \\ B_{Ti}(0, a - t - t_n) \frac{d_T(a)}{d_T(a - t - t_n)}, & a > t + t_n \end{cases}$$

Since $B_T^n(t - a + t_n) d_T(a)$ converges locally and uniformly towards the function $\tilde{B}_T(t - a) d_T(a)$ as $t_n \rightarrow +\infty$, it comes

$$B_{Ti}^n(t_n, \cdot) = \tilde{B}_{Ti}^n(0, \cdot) \rightarrow \alpha \tilde{B}_T(t - \cdot) d_T(\cdot) \text{ in } L^1(0, \infty, \mathbb{R}).$$

From where the asymptotic smoothness of the semiflow U holds. Finally, the above estimates show that the semiflow U is bounded dissipative, eventually bounded on bounded sets, and asymptotically smooth.

6 The basic reproduction number of phage infections

Let $N_T(t)$ and $N_L(t)$ be the number of newly produced temperate and virulent phages at time t , respectively. We have

$$N_L(t) = \int_0^\infty \theta_L \mu_L(a) B_L(t, a) da, \quad N_T(t) = \int_0^\infty \theta_T \mu_T(a) B_{Ti}(t, a) da.$$

By the Volterra formulation (2.5) linearized at the purely susceptible equilibrium \mathcal{E}_0 , we find that

$$N_L(t) = B_S^0 \int_0^t \theta_L \mu_L(a) [(\beta_L P_L(t - a) + \pi \beta_T P_T(t - a)) d_L(a)] da + \int_t^\infty \theta_L \mu_L(a) B_L(0, a - t) \frac{d_L(a)}{d_L(a - t)} da, \quad (6.1)$$

and

$$N_T(t) = \int_0^t \theta_T \mu_T(a) \alpha B_T(t-a) d_T(a) da + \int_t^\infty \theta_T \mu_T(a) B_{Ti}(0, a-t) \frac{d_T(a)}{d_T(a-t)} da,$$

with $B_S^0 = \mathcal{W}^{-1}(\mathcal{T}_S^{-1})$. Since

$$B_T(t) = B_S^0(1-\pi)\beta_T \int_0^t e^{\left(\frac{r_T}{\mathcal{T}_S} - \delta_T - \alpha\right)(t-s)} P_T(t-s) ds + B_T(0) e^{\left(\frac{r_T}{\mathcal{T}_S} - \delta_T - \alpha\right)t},$$

it comes

$$N_T(t) = \alpha \theta_T (1-\pi) \beta_T B_S^0 \int_0^t \left(\int_0^a \mu_T(\sigma) d_T(\sigma) e^{\left(\frac{r_T}{\mathcal{T}_S} - \delta_T - \alpha\right)(a-\sigma)} d\sigma \right) P_T(t-a) da + N_{T0}(t), \quad (6.2)$$

where N_{T0} is accounting for the initial conditions.

Next, the P_L - and P_T -equation of (1.1) linearized at \mathcal{E}_0 lead to

$$P_j(t) = \int_0^t e^{-(\beta_j B_S^0 + \delta)(t-s)} N_j(s) ds + e^{-(\beta_j B_S^0 + \delta)t} P_j(0),$$

for $j = L, T$. Therefore, (6.1) and (6.2) respectively give

$$\begin{aligned} N_L(t) &= \theta_L \beta_L B_S^0 \int_0^t \left(\int_0^{t-a} e^{-(\beta_L B_S^0 + \delta)(t-a-s)} N_L(s) ds \right) \mu_L(a) d_L(a) da \\ &\quad + \pi \theta_L \beta_T B_S^0 \int_0^t \left(\int_0^{t-a} e^{-(\beta_T B_S^0 + \delta)(t-a-s)} N_T(s) ds \right) \mu_L(a) d_L(a) da + N_{L0}(t), \\ &= \theta_L \beta_L B_S^0 \int_0^t N_L(t-a) \left(\int_0^a e^{-(\beta_L B_S^0 + \delta)(a-s)} \mu_L(s) d_L(s) ds \right) da \\ &\quad + \pi \theta_L \beta_T B_S^0 \int_0^t N_T(t-a) \left(\int_0^a e^{-(\beta_T B_S^0 + \delta)(a-s)} \mu_L(s) d_L(s) ds \right) da + N_{L0}(t), \end{aligned}$$

and

$$\begin{aligned} N_T(t) &= \alpha \theta_T (1-\pi) \beta_T B_S^0 \int_0^t \Gamma(a) \left(\int_0^{t-a} e^{-(\beta_T B_S^0 + \delta)(t-a-s)} N_T(s) ds \right) da + N_{T0}(t), \\ &= \alpha \theta_T (1-\pi) \beta_T B_S^0 \int_0^t N_T(t-a) \left(\int_0^a e^{-(\beta_T B_S^0 + \delta)(a-s)} \Gamma(s) ds \right) da + N_{T0}(t), \end{aligned}$$

where $\Gamma(a) = \int_0^a \mu_T(\sigma) d_T(\sigma) e^{\left(\frac{r_T}{\mathcal{T}_S} - \delta_T - \alpha\right)(a-\sigma)} d\sigma$, and N_{T0} , N_{L0} are set again to account for the initial conditions.

It then follows (*eg.*, see [6, 16]), that the next generation operator \mathcal{U} is given by

$$\mathcal{U} \begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} \mathcal{U}_{11}u & \mathcal{U}_{12}v \\ 0 & \mathcal{U}_{22}v \end{pmatrix},$$

with

$$\begin{aligned} \mathcal{U}_{11}u &= \theta_L \beta_L B_S^0 \int_0^\infty u(a) \left(\int_0^a e^{-(\beta_L B_S^0 + \delta)(a-s)} \mu_L(s) d_L(s) ds \right) da, \\ \mathcal{U}_{12}v &= \pi \theta_L \beta_T B_S^0 \int_0^\infty v(a) \left(\int_0^a e^{-(\beta_T B_S^0 + \delta)(a-s)} \mu_L(s) d_L(s) ds \right) da, \\ \mathcal{U}_{22}v &= \alpha \theta_T (1-\pi) \beta_T B_S^0 \int_0^\infty v(a) \left(\int_0^a e^{-(\beta_T B_S^0 + \delta)(a-s)} \Gamma(s) ds \right) da. \end{aligned}$$

From where the basic reproduction number \mathcal{R}_0 is calculated as the spectral radius $r(\mathcal{U})$ of \mathcal{U} , *ie.*,

$$\mathcal{R}_0 = \max \{ \mathcal{R}_{0T}, \mathcal{R}_{0L} \},$$

where

$$\mathcal{R}_{0L} = K_L \frac{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1})}{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta}, \quad \text{and} \quad \mathcal{R}_{0T} = K_T \frac{\alpha(1-\pi)\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1})}{(\delta_T + \alpha) \left(1 - \frac{\mathcal{T}_T}{\mathcal{T}_S} \right) (\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)}.$$

7 The characteristic equation and proof of Theorem 3.2

7.1 The characteristic equation of Model (1.1)

Let $u^* = (x^*, 0_{\mathbb{R}^2}, y^*(\cdot), P^*) \in \mathcal{X}_0^+$ be any equilibrium of problem (2.4). The linearized system at u^* reads as:

$$\frac{du}{dt} = (A + G[u^*])u(t),$$

where A is the linear operator defined by (2.3), and $G[u^*]$ is such that

$$G[u^*]u = \begin{pmatrix} J_{f(x^*)}x + \Phi(x^*)P + \Phi(x)P^* - \alpha Ix \\ \Psi(x^*)P + \Psi(x)P^* + \alpha Ix \\ 0_{L^1(0, \infty, \mathbb{R}^2)} \\ \int_0^\infty \theta \mu(a)y(a)da - \beta(x^*)P - \beta(x)P^* \end{pmatrix},$$

with $J_{f(x^*)}$ is the Jacobian matrix of $f(x) = R(x)x$ at x^* . Set

$$K_j(\lambda) = \int_0^\infty \theta(a)\mu_j(a)e^{-\int_0^a(\lambda + \mu_j(\tau))d\tau}da, \quad j \in \{T, L\} \quad K(\lambda) = \text{diag}(K_L(\lambda), K_T(\lambda)), \quad (7.1)$$

$$F(P) = \begin{pmatrix} -(\beta_L P_L + \beta_T P_T) & 0 \\ (1 - \pi)P_T & 0 \end{pmatrix}, \quad E(P) = \begin{pmatrix} \beta_L P_L - K_L(\lambda)(\beta_L P_L + \pi \beta_T P_T) & 0 \\ \beta_T P_T & 0 \end{pmatrix}.$$

and $M_{ij} \in \mathcal{M}_2(\mathbb{R})$ such that

$$\begin{cases} M_{11}(\lambda, u^*) = I_d + (\lambda I_d + \gamma)^{-1}(\alpha I - J_{f(x^*)} - F(P^*)), \\ M_{12}(\lambda, u^*) = -(\lambda I_d + \gamma)^{-1}\Phi(x^*), \\ M_{21}(\lambda, u^*) = (\lambda I_d + \delta)^{-1}(E(P^*) - \alpha I K(\lambda)), \\ M_{22}(\lambda, u^*) = I_d + (\lambda I_d + \delta)^{-1}(\beta(x^*) - K(\lambda)\Psi(x^*)). \end{cases}$$

Defining

$$\Delta(\lambda, u^*) = \begin{pmatrix} M_{11}(\lambda, u^*), & M_{12}(\lambda, u^*) \\ M_{21}(\lambda, u^*), & M_{22}(\lambda, u^*) \end{pmatrix}, \quad (7.2)$$

we have the following lemma

Lemma 7.1 *Let*

$$\zeta = \min\{\gamma, \mu, \delta\} \quad \text{and} \quad \Omega = \{\lambda \in \mathbb{C} : \text{Re}(\lambda) > -\zeta\},$$

then the spectrum $\sigma(A + G[u^]) \cap \Omega \neq \emptyset$ and it is only composed of point spectrum of $A + G[u^*]$ and*

$$\sigma(A + G[u^*]) \cap \Omega = \{\lambda \in \Omega : \det \Delta(\lambda, u^*) = 0\}$$

with $\Delta(\lambda, u^)$ defined in (7.2).*

Proof: Let denote by $A_0 : D(A_0) \subset \mathcal{X}_0$ the part of A in \mathcal{X}_0 which is defined

$$A_0 u = Au \quad \forall u \in D(A_0) = \{u \in D(A) : Au \in D(A)\},$$

then it is the infinitesimal generator of a C_0 -semigroup on \mathcal{X}_0 denoted by $\{S_{A_0}(t)\}_{t \geq 0}$. Let $u = (x, 0_{\mathbb{R}^2}, y(\cdot), P)$, we have,

$$S_{A_0}(t)u = \begin{cases} (e^{-\gamma t}x, 0_{\mathbb{R}^2}, \mathcal{D}(a-t)y(a-t), e^{-\delta t}P), & a \geq t \\ (e^{-\gamma t}x, 0_{\mathbb{R}^2}, 0_{L^1(0, \infty, \mathbb{R}^2)}, e^{-\delta t}P), & a < t. \end{cases}$$

Then, for $t \geq t_0$ we have,

$$\|S_{A_0}(t - t_0)\|_{\mathcal{X}} \leq e^{-\zeta(t-t_0)} \|u\|_{\mathcal{X}}, t \geq t_0.$$

We deduce that the growth rate of the semigroup satisfies

$$\omega_0(A_0) = \lim_{t \rightarrow \infty} \frac{\ln \left(\|S_{A_0}(t)\|_{\mathcal{L}(\mathcal{X})} \right)}{t} \leq -\zeta.$$

Since the operator $G[u^*]$ is compact, the essential growth rate of $\{S_{(A+G[u^*])}(t)\}_{t \geq 0}$, the C_0 -semigroup generated by the part of $(A + G[u^*])$ in \mathcal{X}_0 satisfies ([8])

$$\omega_{0,ess}(A + G[u^*]) \leq \omega_{0,ess}(A_0) < \omega_0(A_0) \leq -\zeta.$$

The latter inequality implies that $\Omega \cap \sigma(A + G[u^*]) \neq \emptyset$ and it is composed of the spectrum of $(A + G[u^*])$.

7.2 Proof of Theorem 3.2

For a given equilibrium u^* of Model (1.1), recall that $\sigma(A + G[u^*])$ is the spectrum of the linearized system at u^* . Such a spectrum is characterized by Lemma 7.1.

(i) The spectrum $\sigma(A + G[\mathcal{O}]) \cap \Omega = \{\delta_S(\mathcal{T}_S - 1), (\delta_T + \alpha)(\mathcal{T}_T - 1)\}$. Then, \mathcal{O} is locally asymptotically stable if and only if $\max\{\delta_S(\mathcal{T}_S - 1), (\delta_T + \alpha)(\mathcal{T}_T - 1)\} < 0$, that is $\mathcal{T}_S < 1$ and $\mathcal{T}_T < 1$.

(ii) Let $\lambda \in \sigma(A + G[\mathcal{E}_0]) \cap \Omega$. Some computations give $\lambda_0 = r_S \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) \mathcal{W}'(\mathcal{W}^{-1}(\mathcal{T}_S^{-1})) \in \sigma(A + G[\mathcal{E}_0])$ or

$$\lambda + \delta = -\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1})(1 - K_L(\lambda)), \quad (7.3)$$

$$\left(\lambda + (\delta_T + \alpha) \left(1 - \frac{\mathcal{T}_T}{\mathcal{T}_S} \right) \right) (\lambda + \delta + \beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1})) - \alpha(1 - \pi) \beta_T K_T(\lambda) \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) = 0. \quad (7.4)$$

Since \mathcal{W} is decreasing, $\lambda_0 < 0$. Equations (7.3)-(7.4) are equivalent to:

$$\mathcal{H}_L(\lambda) = 1, \quad \text{and} \quad \mathcal{V}(\lambda) = \mathcal{H}_T(\lambda) \quad (7.5)$$

with

$$\mathcal{H}_L(\lambda) = \frac{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) K_L(\lambda)}{\lambda + \beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta}, \quad \mathcal{H}_T(\lambda) = \frac{\alpha(1 - \pi) \beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) K_T(\lambda)}{(\delta_T + \alpha)(\lambda + \beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta)} + \frac{\mathcal{T}_T}{\mathcal{T}_S}, \quad \mathcal{V}(\lambda) = \frac{\lambda}{\delta_T + \alpha} + 1.$$

Note that, $\forall \lambda \in \mathbb{R}$ $\lim_{\lambda \rightarrow -\infty} \mathcal{H}_L(\lambda) = +\infty$, $\lim_{\lambda \rightarrow +\infty} \mathcal{H}_L(\lambda) = 0$, $\partial \mathcal{H}_L / \partial \lambda < 0$, $\lim_{\lambda \rightarrow -\infty} \mathcal{H}_T(\lambda) = +\infty$, $\lim_{\lambda \rightarrow +\infty} \mathcal{H}_T(\lambda) = \mathcal{T}_T / \mathcal{T}_S$, $\partial \mathcal{H}_T / \partial \lambda < 0$.

Therefore \mathcal{H}_L , \mathcal{H}_T , are decreasing functions on \mathbb{R} . Hence, any real solution of (7.5) is negative if $\max\{\mathcal{H}_L(0), \mathcal{H}_T(0)\} < 1$ and positive if $\max\{\mathcal{H}_L(0), \mathcal{H}_T(0)\} > 1$. Thus, if $\max\{\mathcal{H}_L(0), \mathcal{H}_T(0)\} > 1$ the trivial equilibrium \mathcal{E}_0 is unstable. Note that, $\text{sign}(\max\{\mathcal{H}_L(0), \mathcal{H}_T(0)\} - 1) = \text{sign}(\max\{\mathcal{R}_{0_L}, \mathcal{R}_{0_T}\} - 1)$.

Next, we show that equations (7.5) has no complex solutions with non-negative real part whenever $\max\{\mathcal{R}_{0_L}, \mathcal{R}_{0_T}\} < 1$. By contradiction, assume that we can find $\lambda_0 \in \sigma(A + G[\mathcal{E}_0])$ such that $\Re(\lambda_0) \geq 0$.

Set $\lambda_0 = x + iy$, with $x > 0, y \in \mathbb{R}$. $|\mathcal{V}(\lambda_0)| = \left| \frac{x + iy}{\delta_T + \alpha} + 1 \right| > 1$. Therefore,

$$1 = |\mathcal{H}_L(\lambda_0)| \leq \frac{\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) \theta_L \int_0^\infty \mu_L(a) d_L(a) e^{-ax} da}{(x + (\beta_L \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta))} = \mathcal{H}_L(x) \leq \mathcal{H}_L(0) < 1, \text{ and}$$

$$|\mathcal{V}(\lambda_0)| = |\mathcal{H}_T(\lambda_0)| \leq \frac{\alpha(1 - \pi) \beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) \theta_T \int_0^\infty \mu_T(a) d_T(a) e^{-ax} da}{(\delta_T + \alpha)(x + (\beta_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) + \delta))} + \frac{\mathcal{T}_T}{\mathcal{T}_S} = \mathcal{H}_T(x) \leq \mathcal{H}_T(0) < 1.$$

A contradiction holds. Consequently, any solution of (7.5) has negative real part if $\max\{\mathcal{R}_{0_L}, \mathcal{R}_{0_T}\} < 1$, that is $\mathcal{T}_S < \left(\mathcal{W}\left(\frac{\delta}{\beta_L(K_L-1)}\right)\right)^{-1}$, $\mathcal{T}_T < h(\mathcal{T}_S)$.

(iii) We have, $\sigma(A + G[\mathcal{E}_T]) \cap \Omega = \left\{ \delta_S \left(\frac{\mathcal{T}_S}{\mathcal{T}_T} - 1 \right) - \beta_T \alpha K_T \mathcal{W}^{-1}(\mathcal{T}_T^{-1}) \delta^{-1}, r_T \mathcal{W}^{-1}(\mathcal{T}_S^{-1}) \mathcal{W}'(\mathcal{W}^{-1}(\mathcal{T}_S^{-1})) \right\}$.

Since \mathcal{W} is decreasing, \mathcal{E}_T is locally asymptotically stable if and only if

$\delta_S \left(\frac{\mathcal{T}_S}{\mathcal{T}_T} - 1 \right) - \beta_T \alpha K_T \mathcal{W}^{-1}(\mathcal{T}_T^{-1}) \delta^{-1} < 0$ equivalent to $\mathcal{T}_S < g(\mathcal{T}_T)$.

(iv) Let $\lambda \in \sigma(A + G[\mathcal{E}_L])$, $\det \Delta(\lambda, \mathcal{E}_L) = 0$ if and only if $D_T(\lambda) D_L(\lambda) = 0$ with

$$\begin{aligned} D_T(\lambda) &= (\lambda + (\delta_T + \alpha) (1 - \mathcal{T}_T \mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}))) (\lambda + \delta + \beta_T \delta(\beta_L(K_L - 1))^{-1}) \\ &\quad - \alpha(1 - \pi) \beta_T \delta(\beta_L(K_L - 1))^{-1} K_T(\lambda) \\ D_L(\lambda) &= \frac{\beta_L^2 (\delta(\beta_L(K_L - 1))^{-1} \delta_S \beta_L^{-1} \mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}) (\mathcal{T}_S - (\mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}))^{-1}))}{\delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} \\ &\quad + (\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1})) \\ &\quad - (\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1})) \frac{\beta_L \delta(\beta_L(K_L - 1))^{-1} K_L(\lambda)}{\lambda + \delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}}. \end{aligned}$$

Recall that $\mathcal{W}'(B_S) < 0$. For the equation

$$D_L(\lambda) = 0, \tag{7.6}$$

if $\Re(\lambda) > 0$, then, $\left| \frac{\beta_L \delta(\beta_L(K_L - 1))^{-1} K_L(\lambda)}{\lambda + \delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} \right| < \frac{\beta_L \delta(\beta_L(K_L - 1))^{-1} K_L}{\delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} = 1$. On the one hand

$$\begin{aligned} &\left| (\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1})) \frac{\beta_L \delta(\beta_L(K_L - 1))^{-1} K_L(\lambda)}{\lambda + \delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} \right| \\ &< \left| (\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1})) \frac{\beta_L \delta(\beta_L(K_L - 1))^{-1} K_L}{\delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} \right| \\ &= |(\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1}))|. \end{aligned}$$

On the other hand,

$$\begin{aligned} &\left| \frac{\beta_L^2 (\delta(\beta_L(K_L - 1))^{-1} \delta_S \beta_L^{-1} \mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}) (\mathcal{T}_S - (\mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}))^{-1}))}{\delta + \beta_L \delta(\beta_L(K_L - 1))^{-1}} \right. \\ &\quad \left. + (\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1})) \right| > |(\lambda - r_S \delta(\beta_L(K_L - 1))^{-1} \mathcal{W}'(\delta(\beta_L(K_L - 1))^{-1}))|. \end{aligned}$$

A contradiction holds. Thus, every root of (7.6) has a negative real part.

$$D_T(\lambda) = 0 \Leftrightarrow \frac{\lambda}{\delta_T + \alpha} + 1 = \frac{\alpha(1 - \pi) \beta_T K_T(\lambda) \delta(\beta_L(K_L - 1))^{-1}}{(\delta_T + \alpha) (\lambda + \delta + \beta_T \delta(\beta_L(K_L - 1))^{-1})} + \mathcal{T}_T \mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}). \tag{7.7}$$

Using same arguments as in (7.5), every root of (7.7), has negative real if and only if

$$\mathcal{R} = \frac{(1 - \pi) \beta_T \alpha K_T(\beta_L(K_L - 1))^{-1}}{(\delta_T + \alpha) (1 + \beta_T(\beta_L(K_L - 1))^{-1})} + \mathcal{T}_T \mathcal{W}(\delta(\beta_L(K_L - 1))^{-1}) < 1.$$

Otherwise, there is at least one root with non-negative real part. Above inequality $\mathcal{R} < 1$ is equivalent to $\mathcal{T}_T < l(\mathcal{T}_S)$.

8 Existence of a positive equilibrium

At a positive equilibrium, (2.2) gives

$$\begin{cases} (R(x) - \gamma)x + \Phi(x)P - \alpha x = 0, \\ y(a) = \mathcal{D}(a)[\Psi(x)P + \alpha Ix], \\ \int_0^\infty \theta\mu(a)y(a)da - \delta P - \beta(x)P = 0, \end{cases}$$

such that the positive equilibrium of (2.2) is strongly related to the system (3.1)-(3.2).

Next, set

$$D(x) = \delta^{-1}[K\Psi(x) - \beta(x)] = \delta^{-1} \begin{pmatrix} (K_L - 1)\beta_L B_S & \pi K_L \beta_T B_S \\ 0 & -\beta_T B_S \end{pmatrix}.$$

For all $x > 0$, the unique positive eigenvalue of $D(x)$ is $\sigma(D(x)) = \delta^{-1}(K_L - 1)\beta_L B_S$, with the associated eigenvector $e = (1, 0)$.

Case $\alpha = 0$. By (3.2), we necessary have $\sigma(D(x)) = \delta^{-1}(K_L - 1)\beta_L B_S = 1$, and $P = (c, 0)$, where c is as positive constant, *i.e.*,

$$B_S = B_S^0 = \delta((K_L - 1)\beta_L)^{-1}.$$

By (3.1), it comes

$$(\mathcal{W}(B_S^0 + B_T^0))^{-1} = \mathcal{T}_T, \quad c = \frac{\delta_S}{\beta_L} \left(\frac{\mathcal{T}_S}{\mathcal{T}_T} - 1 \right).$$

Case $\alpha > 0$. Here we introduce a parametric representation of the positive equilibrium of Model (2.2) with respect to the small parameter α . Using Theorem B.2.1 in [5], the expanded variables are

$$x = x^0 + \alpha x^1 + \dots, \tag{8.1}$$

$$y(\cdot) = y^0(\cdot) + \alpha y^1(\cdot) + \dots,$$

$$P = P^0 + \alpha P^1 + \dots, \tag{8.2}$$

where the subscript 0 is set for the equilibrium of the model when $\alpha = 0$. We are investigating on the existence of $u^1 = (x^1, y^1(\cdot), P^1)$ with $x^1 = (B_S^1, B_T^1)$, $y(\cdot)^1 = (B_L(\cdot)^1, B_{Ti}(\cdot)^1)$, $P^1 = (P_L^1, P_T^1)$. Plugging above expansion of x , P into (3.1)-(3.2), one has

$$(R(x^0 + \alpha x^1) - \gamma)(x^0 + \alpha x^1) + \Phi(x^0 + \alpha x^1)(P^0 + \alpha P^1) - \alpha(x^0 + \alpha x^1) = 0$$

$$D(x^0)P^0 + \alpha D(x^0)P^1 + \alpha D(x^1)P^0 = P^0 + \alpha P^1 - \alpha M I x^0.$$

For $\alpha = 0$ $(R(x^0) - \gamma)x^0 + \Phi(x^0)P^0 = 0$ and $D(x^0)P^0 = P^0$

For $\alpha = 1$, we have

$$(J_{f(x^0)})x^1 - \gamma x^1 + \Phi(x^0)P^1 + \Phi(x^1)P^0 - x^0 = 0 \tag{8.3}$$

$$D(x^0)P^1 + D(x^1)P^0 = P^1 - M I x^0. \tag{8.4}$$

Our problem is reduced to System (8.3)-(8.4). Expanding (8.4) gives

$$P_L^1 = -\frac{(K_L - 1)\beta_L P_L^0}{\pi K_L \beta_T B_S^0} B_S^1, \quad P_T^1 = \frac{\delta K_T B_T^0}{\beta_T B_S^0 + \delta}$$

Expansion of (8.3) yields

$$\begin{cases} \left(r_S B_S^0 \mathcal{W}'(B_S^0 + B_T^0) - \delta_S - \beta_L P_L^0 + \frac{\beta_L(K_L-1)\beta_L P_L^0}{\pi K_L \beta_T} \right) B_S^1 + r_S B_S^0 \mathcal{W}'(B_S^0 + B_T^0) B_T^1 = \frac{\beta_T B_S^0 \delta K_T B_T^0}{\beta_T B_S^0 + \delta} \\ r_T B_T^0 \mathcal{W}'(B_S^0 + B_T^0) B_S^1 + (r_T B_T^0 \mathcal{W}'(B_S^0 + B_T^0) - \delta_T) B_T^1 = B_T^0 \left(1 - \frac{(1-\pi)\beta_T B_S^0 \delta K_T}{\beta_T B_S^0 + \delta} \right) \end{cases} \quad (8.5)$$

Equation (8.5) becomes

$$\begin{cases} \left(\frac{\beta_L^2(K_L-1)P_L^0}{\pi K_L \beta_T} + r_S B_S^0 \mathcal{W}'(B_S^0 + B_T^0) \right) B_S^1 + r_S B_S^0 \mathcal{W}'(B_S^0 + B_T^0) B_T^1 = \frac{\beta_T B_S^0 \delta K_T B_T^0}{\beta_T B_S^0 + \delta} \\ r_T B_T^0 \mathcal{W}'(B_S^0 + B_T^0) B_S^1 + r_T B_T^0 \mathcal{W}'(B_S^0 + B_T^0) B_T^1 = B_T^0 \left(1 - \frac{(1-\pi)\beta_T B_S^0 \delta K_T}{\beta_T B_S^0 + \delta} \right) \end{cases}$$

Set,

$$\begin{cases} \Delta = r_T B_T^0 \mathcal{W}'(B_S^0 + B_T^0) \frac{\beta_L^2(K_L-1)P_L^0}{\pi K_L \beta_T} \\ \Delta_{B_S} = r_S B_S^0 B_T^0 \mathcal{W}'(B_S^0 + B_T^0) \left(\frac{\beta_T \delta K_T (r_T B_T^0 + r_S B_S^0)}{\beta_T B_S^0 + \delta} - 1 \right) \\ \Delta_{B_T} = B_T^0 \left(\left(\frac{\beta_L(K_L-1)\beta_L P_L^0}{\pi K_L \beta_T} - r_S B_S^0 B_T^0 \mathcal{W}'(B_S^0 + B_T^0) \right) \left(1 - \frac{(1-\pi)\beta_T B_S^0 \delta K_T}{\beta_T B_S^0 + \delta} \right) - \frac{r_T B_T^0 B_S^0 \beta_T \delta K_T}{\beta_T B_S^0 + \delta} \mathcal{W}'(B_S^0 + B_T^0) \right) \end{cases}$$

then

$$B_S^1 = \frac{\Delta_{B_S}}{\Delta} \quad \text{and} \quad B_T^1 = \frac{\Delta_{B_T}}{\Delta}$$

Thus (2.2) has a unique positive stationary state in the form (8.1)-(8.2).

9 Hopf bifurcation around the positive equilibrium

The proof of the bifurcation Theorem 3.4 is mainly based on the results in [18]. Let $\lambda \in \sigma(A + G[\mathcal{E}^*]) \cap \Omega$. By Lemma 7.1, and recalling the functions $K_{j,s}$ defined by (7.1), as well as the rupture functions $\mu_{j,s}$ given by (3.5), it comes

$$\det \Delta(\lambda, \mathcal{E}^*) = \frac{p(\lambda, \alpha) + q(\lambda, \alpha)e^{-\lambda\tau}}{(\lambda + \delta_S)(\lambda + \delta_T)(\lambda + \delta)^2(\lambda + \delta_S + \mu_{L_0})(\lambda + \delta_T + \mu_{T_0})} = 0$$

with

$$\begin{cases} p(\lambda, \alpha) = p_0(\alpha) + p_1(\alpha)\lambda + p_2(\alpha)\lambda^2 + p_3(\alpha)\lambda^3 + p_4(\alpha)\lambda^4 + p_5(\alpha)\lambda^5 + \lambda^6, \\ q(\lambda, \alpha) = q_0(\alpha) + q_1(\alpha)\lambda + q_2(\alpha)\lambda^2 + q_3(\alpha)\lambda^3. \end{cases}$$

Coefficients $p_i(\alpha) = p_i(\alpha, \mathcal{E}^*)$ $q_i(\alpha) = q_i(\alpha, \mathcal{E}^*)$; $i = 1, \dots, 5$; are derived in Appendix A. Taking into account Taylor expansions in (3.4), the above coefficients take the form:

$$\begin{aligned} p_5(\alpha) &= p_5^0 + \alpha p_5^1 + O(\alpha^2), & p_4(\alpha) &= p_4^0 + \alpha p_4^1 + O(\alpha^2), & p_3(\alpha) &= p_3^0 + \alpha p_3^1 + O(\alpha^2) \\ p_2(\alpha) &= p_2^0 + \alpha p_2^1 + O(\alpha^2), & p_1(\alpha) &= p_1^0 + \alpha p_1^1 + O(\alpha^2), & p_0(\alpha) &= p_0^0 + \alpha p_0^1 + O(\alpha^2) \\ q_3(\alpha) &= q_3^0 + \alpha q_3^1 + O(\alpha^2), & q_2(\alpha) &= q_2^0 + \alpha q_2^1 + O(\alpha^2), & q_1(\alpha) &= q_1^0 + \alpha q_1^1 + O(\alpha^2), \\ q_0(\alpha) &= q_0^0 + \alpha q_0^1 + O(\alpha^2). \end{aligned}$$

Set $\lambda = i\omega$, with $\omega > 0$. $\Delta(i\omega, \mathcal{E}^*) = 0$ if and only if $p(i\omega, \alpha) = -q(i\omega, \alpha)e^{-i\omega\tau}$, that is

$$-\omega^6 + p_4(\alpha)\omega^4 - p_2(\alpha)\omega^2 + p_0(\alpha) = (q_0(\alpha) - (q_2(\alpha))\omega^2) \cos \omega\tau + (q_1(\alpha)\omega - (q_3(\alpha)\omega^3) \sin \omega\tau, \quad (9.1)$$

$$p_5(\alpha)\omega^5 - p_3(\alpha)\omega^3 + p_1(\alpha)\omega = (q_1(\alpha)\omega - (q_3(\alpha)\omega^3) \cos \omega\tau - (q_0(\alpha) - (q_2(\alpha))\omega^2) \sin \omega\tau. \quad (9.2)$$

Moreover, $|p(i\omega, \alpha)| = |q(i\omega, \alpha)e^{-i\omega\tau}|$ leads to

$$\begin{aligned} & (-\omega^6 + p_4(\alpha)\omega^4 - p_2(\alpha)\omega^2 + p_0(\alpha))^2 + (p_5(\alpha)\omega^5 - p_3(\alpha)\omega^3 + p_1(\alpha)\omega)^2 \\ & = (q_0(\alpha))^2 + ((q_1(\alpha))^2 - 2q_0(\alpha)q_2(\alpha))\omega^2 + (q_2(\alpha))^2\omega^4 - 2q_1(\alpha)q_3(\alpha)\omega^4 + (q_3(\alpha))^2\omega^6, \end{aligned}$$

that is

$$F(\omega^2, \alpha) := \omega^{12} + a_{10}(\alpha)\omega^{10} + a_8(\alpha)\omega^8 + a_6(\alpha)\omega^6 + a_4(\alpha)\omega^4 + a_2(\alpha)\omega^2 + a_0(\alpha) = 0 \quad (9.3)$$

where

$$\begin{aligned} a_{10}(\alpha) &= (p_5(\alpha))^2 - 2p_4(\alpha) = (p_5^0)^2 - 2p_4^0 + \alpha(2p_5^0p_5^1 - 2p_4^1) + \dots \\ a_8(\alpha) &= (p_4(\alpha))^2 + 2p_2(\alpha) - 2p_3(\alpha)p_5(\alpha) = (p_4^0)^2 + 2p_2^0 - 2p_3^0p_5^0 + \alpha(2p_4^0p_4^1 + 2p_2^1 - 2p_3^1p_5^0 - 2p_5^1p_3^0) + \dots \\ a_6(\alpha) &= (p_3(\alpha))^2 + 2p_1(\alpha)p_5(\alpha) - 2p_0(\alpha) - 2p_2(\alpha)p_4(\alpha) - (q_3(\alpha))^2 \\ &= (p_3^0)^2 - (q_3^0)^2 + 2p_1^0p_5^0 - 2p_0^0 - 2p_2^0p_4^0 + \alpha(2p_3^0p_3^1 + 2p_1^0p_5^1 + 2p_5^0p_3^1 - 2p_0^1 - 2p_2^0p_4^1 - 2p_4^0p_2^1 - 2q_3^0q_3^1) + \dots \\ a_4(\alpha) &= (p_2(\alpha))^2 + 2p_0(\alpha)p_4(\alpha) - 2p_1(\alpha)p_3(\alpha) - (q_2(\alpha))^2 + 2q_1(\alpha)q_3(\alpha) \\ &= (p_2^0)^2 - (q_2^0)^2 + 2p_0^0p_4^0 - 2p_1^0p_3^0 + \alpha(2p_2^0p_2^1 + 2p_0^0p_4^1 + 2p_4^0p_0^1 - 2p_1^0p_3^1 - 2p_3^0p_1^1 - 2q_2^0q_2^1) + \dots \\ a_2(\alpha) &= (p_1(\alpha))^2 - 2p_0(\alpha)p_2(\alpha) - (q_1(\alpha))^2 + 2q_0(\alpha)q_2(\alpha) \\ &= (p_1^0)^2 - (q_1^0)^2 - 2p_0^0p_2^1 + \alpha(2p_1^0p_1^1 - 2p_1^0p_2^1 - 2p_2^0p_1^1 - 2q_1^0q_1^1) + \dots \\ a_0(\alpha) &= (p_0(\alpha))^2 - (q_0(\alpha))^2 = (p_0^0)^2 - (q_0^0)^2 + \alpha(2p_0^0p_0^1 - 2q_0^0q_0^1) + \dots \end{aligned}$$

We are interesting on the existence of ω_c^2 , $\alpha_c > 0$ such that $F(\omega_c^2, \alpha_c) = 0$. Note that $F(\omega_c^2, \alpha_c) = 0$ if and only if

$$\Gamma(\omega_c, \alpha_c) := f(\omega_c^2) - 2\alpha_c g(\omega_c^2) = 0,$$

with

$$\begin{aligned} f(z) &= z^6 + \sum_{k=0}^5 f_k z^k \\ &= \left((p_5^0)^2 - 2p_4^0\right) z^5 + \left((p_4^0)^2 + 2p_2^0 - 2p_3^0p_5^0\right) z^4 + \left((p_3^0)^2 - (q_3^0)^2 + 2p_1^0p_5^0 - 2p_0^0 - 2p_2^0p_4^0\right) z^3 \\ &\quad + \left((p_2^0)^2 - (q_2^0)^2 + 2p_0^0p_4^0 - 2p_1^0p_3^0\right) z^2 + \left((p_1^0)^2 - (q_1^0)^2 - 2p_0^0p_2^1\right) z + (p_0^0)^2 - (q_0^0)^2, \\ g(z) &= \sum_{k=0}^5 g_k z^k \\ &= (p_4^1 - p_5^0p_5^1) z^5 + (p_3^1p_5^0 + p_5^1p_3^0 - p_4^0p_4^1 - p_2^1) z^4 + (p_0^1 + p_2^0p_4^1 + p_4^0p_2^1 + q_3^0q_3^1 - p_3^0p_3^1 - p_1^0p_5^1 - p_5^0p_3^1) z^3 \\ &\quad + (p_1^0p_3^1 + p_3^0p_1^1 + q_2^0q_2^1 - p_2^0p_2^1 - p_0^0p_4^1 - p_4^0p_0^1) z^2 + (p_1^0p_2^1 + p_2^0p_1^1 + q_1^0q_1^1 - p_1^0p_1^1) z + (q_0^0q_0^1 - p_0^0p_0^1). \end{aligned}$$

Assume

$$\min_{k=1,2,3,4,5} \{f_k, g_k\} > 0, \quad (9.4)$$

Fixing $z_c = \omega_c^2 > 0$, one find

$$\alpha_c = \frac{f(z_c)}{2g(z_c)} > 0, \quad (9.5)$$

so that $F(z_c, \alpha_c) = 0$. Thus for $\omega_c = \pm\sqrt{z_c}$, the pairing (ω_c, α_c) is solution of (9.3).

Moreover, from (9.1) and (9.2), for the fixed value of τ , one has:

$$\Gamma_1(\omega_c, \alpha_c) := \cos \omega_c \tau - \frac{(-\omega_c^6 + p_4(\alpha_c)\omega_c^4 - p_2(\alpha_c)\omega_c^2 + p_0(\alpha_c)(q_0(\alpha_c) - (q_2(\alpha_c))\omega_c^2))}{(q_0(\alpha_c) - (q_2(\alpha_c))\omega_c^2)^2 + (q_1(\alpha_c)\omega_c - (q_3(\alpha_c)\omega_c^3))^2} - \frac{(p_5(\alpha_c)\omega_c^5 - p_3(\alpha_c)\omega_c^3 + p_1(\alpha_c)\omega_c)(q_1(\alpha_c)\omega_c - (q_3(\alpha_c)\omega_c^3))}{(q_0(\alpha_c) - (q_2(\alpha_c))\omega_c^2)^2 + (q_1(\alpha_c)\omega_c - (q_3(\alpha_c)\omega_c^3))^2} = 0. \quad (9.6)$$

Transversality condition. Assume that (9.4) is satisfied, and let $\lambda(\alpha) = \zeta(\alpha) + i\omega(\alpha)$ be the root of $\Phi(\lambda, \alpha) = 0$ satisfying $\zeta(\alpha_c) = 0$, $\omega(\alpha_c) = \omega_c$, where α_c is defined in (9.5). Let's prove that $\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right) \neq 0$. Taking the derivative with respect to α on $\Phi(\lambda, \alpha)$, we get

$$\begin{aligned} & p_0^1 + p_1^1\lambda + p_2^1\lambda^2 + p_3^1\lambda^3 + p_4^1\lambda^4 + p_5^1\lambda^5 + (q_0^1 + q_1^1\lambda + q_2^1\lambda^2 + q_3^1\lambda^3) e^{-\lambda\tau} \\ &= (6\lambda^5 + 5p_5(\alpha)\lambda^4 + 4p_4(\alpha)\lambda^3 + 3p_3(\alpha)\lambda^2 + 2p_2(\alpha)\lambda + p_1(\alpha)) \frac{d\lambda}{d\alpha} \\ & (-\tau(q_0(\alpha) + q_1(\alpha)\lambda + q_2(\alpha)\lambda^2 + q_3(\alpha)\lambda^3) + q_1(\alpha) + 2q_2(\alpha) + 3q_3(\alpha)\lambda^2) e^{-\lambda\tau} \frac{d\lambda}{d\alpha} \end{aligned}$$

then

$$\begin{aligned} \left(\frac{d\lambda(\alpha)}{d\alpha}\right)^{-1} &= \frac{6\lambda^5 + 5p_5(\alpha)\lambda^4 + 4p_4(\alpha)\lambda^3 + 3p_3(\alpha)\lambda^2 + 2p_2(\alpha)\lambda + p_1(\alpha)}{p_0^1 + p_1^1\lambda + p_2^1\lambda^2 + p_3^1\lambda^3 + p_4^1\lambda^4 + p_5^1\lambda^5 + (q_0^1 + q_1^1\lambda + q_2^1\lambda^2 + q_3^1\lambda^3) e^{-\lambda\tau}} \\ &+ \frac{(-\tau(q_0(\alpha) + q_1(\alpha)\lambda + q_2(\alpha)\lambda^2 + q_3(\alpha)\lambda^3) + q_1(\alpha) + 2q_2(\alpha) + 3q_3(\alpha)\lambda^2) e^{-\lambda\tau}}{p_0^1 + p_1^1\lambda + p_2^1\lambda^2 + p_3^1\lambda^3 + p_4^1\lambda^4 + p_5^1\lambda^5 + (q_0^1 + q_1^1\lambda + q_2^1\lambda^2 + q_3^1\lambda^3) e^{-\lambda\tau}} \end{aligned}$$

Then substitute $\lambda = i\omega_c$ to obtain that

$$\Re\left\{\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)^{-1}\right\} = \frac{(5p_5(\alpha_c)\omega_c^4 - 3p_3(\alpha_c)\omega_c^2 + p_1(\alpha_c))M_1 + (6\omega_c^5 - 4p_4(\alpha_c) + 2p_2(\alpha_c))M_2}{M_1^2 + M_2^2}$$

$$\begin{aligned} M_1^2 &= [p_0^1 - p_2^1\omega_c^2 + p_4^1\omega_c^4 + (q_0^1 - q_2^1\omega_c^2) \cos \omega_0\tau + (q_1^1\omega_c - q_3^1\omega_c^3) \sin \omega_c\tau]^2 \\ M_2^2 &= [p_1^1\omega_0 - p_3^1\omega_c^3 + p_5^1\omega_c^5 + (q_1^1\tau\omega_c - q_3^1\tau\omega_c^3) \cos \omega_c\tau - (q_0^1 - q_2^1\omega_c^2) \sin \omega_0\tau]^2 \end{aligned}$$

$$\text{sign}\left(\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)^{-1}\right) = \text{sign}\left(\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)\right)$$

Set

$$\mathcal{M}_0(\alpha_c, \omega_c) = (5p_5(\alpha_c)\omega_c^4 - 3p_3(\alpha_c)\omega_c^2 + p_1(\alpha_c))M_1 + (6\omega_c^5 - 4p_4(\alpha_c) + 2p_2(\alpha_c))M_2$$

the transversality condition holds if

$$\mathcal{M}_c(\alpha_c, \omega_c) \neq 0.$$

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Conflict of interest disclosure

The authors of this article declare that they have no financial conflict of interest with the content of this article.

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A Coefficients $p_i(\alpha), s$ and $q_i(\alpha), s$.

Set $B^* = B_S^* + B_T^*$

$$\begin{aligned}
p_5(\alpha) &= \delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + 2\delta + (\beta_L + \beta_T) B_S^* + \delta_S + \mu_{L_0} + \delta_T + \mu_{T_0} \\
p_4(\alpha) &= (\delta_T + \alpha - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) - r_S B_S^* \mathcal{W}'(B^*) (\delta + \beta_L B_S^* + (1 - \pi) P_T - r_T B_T^* \mathcal{W}'(B^*)) \\
&\quad - (r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) - \beta_L^2 B_S^* P_L^* \\
&\quad + (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) + 2\delta + (\beta_L + \beta_T) B_S^* (\delta_S + \mu_{L_0} + \delta_T + \mu_{T_0}) \\
&\quad + (\delta_S + \mu_{L_0}) (\delta_T + \mu_{T_0}) \\
p_3(\alpha) &= (-r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) + r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) \\
&\quad - r_S B_S^* \mathcal{W}'(B^*) (\delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \\
&\quad + r_S B_S^* \mathcal{W}'(B^*) (r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) (2\delta + (\beta_L + \beta_T) B_S^*) \\
&\quad - \beta_L^2 B_S^* P_L^* (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \\
&\quad + (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) (\delta_S + \mu_{L_0} + \delta_T + \mu_{T_0}) \\
&\quad + (-r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) - \beta_L^2 B_S^* P_L^* \\
&\quad + (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) + 2\delta + (\beta_L + \beta_T) B_S^* (\delta_S + \mu_{L_0}) (\delta_T + \mu_{T_0}) \\
p_2(\alpha) &= (-r_S B_S^* \mathcal{W}'(B^*) (\delta + \beta_L B_S^*) - \beta_L^2 B_S^* P_L^*) (\delta + \beta_T B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) \\
&\quad + r_S B_S^* \mathcal{W}'(B^*) (\delta + \beta_L B_S^*) (\delta + \beta_T B_S^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T) \\
&\quad + \left\{ (-r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) \right. \\
&\quad - r_S B_S^* \mathcal{W}'(B^*) (\delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \\
&\quad - r_S B_S^* \mathcal{W}'(B^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) (2\delta + (\beta_L + \beta_T) B_S^*) \\
&\quad \left. - \beta_L^2 B_S^* P_L^* (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \right\} (\delta_S + \mu_{L_0} + \delta_T + \mu_{T_0}) \\
&\quad + (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) \\
&\quad + (-r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) - \beta_L^2 B_S^* P_L^*
\end{aligned}$$

$$\begin{aligned}
p_1(\alpha) &= \left\{ (-r_S B_S^* \mathcal{W}'(B^*)(\delta + \beta_L B_S^*) - \beta_L^2 B_S^* P_L^*) (\delta + \beta_T B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) \right. \\
&\quad \left. + r_S B_S^* \mathcal{W}'(B^*)(\delta + \beta_L B_S^*)(\delta + \beta_T B_S^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) \right\} (\delta_S + \mu_{L_0} + \delta_T + \mu_{T_0}) \\
&\quad + \left\{ (-r_S B_S^* \mathcal{W}'(B^*) + \delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) \right. \\
&\quad - r_S B_S^* \mathcal{W}'(B^*)(\delta + \beta_L B_S^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \\
&\quad + r_S B_S^* \mathcal{W}'(B^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) (2\delta + (\beta_L + \beta_T) B_S^*) \\
&\quad \left. - \beta_L^2 B_S^* P_L^* (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \right\} (\delta_S + \mu_{L_0})(\delta_T + \mu_{T_0}) \\
p_0(\alpha) &= \left\{ (-r_S B_S^* \mathcal{W}'(B^*)(\delta + \beta_L B_S^*) - \beta_L^2 B_S^* P_L^*) (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) \right. \\
&\quad \left. + r_S B_S^* \mathcal{W}'(B^*)(\delta + \beta_L B_S^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) \right\} (\delta_S + \mu_{L_0})(\delta_T + \mu_{T_0})(\delta + \beta_T B_S^*) \\
q_3(\alpha) &= \theta_L \mu_{L_0} \beta_L B_S^* e^{-\delta_S \tau} \\
q_2(\alpha) &= (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^* - \beta_L P_L^*) \theta_L \mu_{L_0} \beta_L B_S^* e^{-\delta_S \tau} - \pi \theta_T \beta_T \beta_L B_S^* e^{-\delta_T \tau} \\
q_1(\alpha) &= ((\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*)) (\delta + \beta_T B_S^*) + r_S B_S^* \mathcal{W}'(B^*) (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*)) \\
&\quad + (\delta_T + \alpha - r_S B_S^* \mathcal{W}'(B^*) - r_T B_T^* \mathcal{W}'(B^*) + \delta + \beta_T B_S^*) \left((-r_S B_S^* \mathcal{W}'(B^*) - \beta_L P_L^*) \beta_L \theta_L \mu_{L_0} e^{-\delta_S \tau} \right) \beta_L B_S^* \\
&\quad + \alpha (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) \beta_T \theta_T \mu_{T_0} e^{-\delta_T \tau} \\
q_0(\alpha) &= (\delta + \beta_T B_S^*) \left((-r_S B_S^* \mathcal{W}'(B^*) - \beta_L P_L^*) \beta_L \theta_L \mu_{L_0} e^{-\delta_S \tau} - \pi \beta_T P_T^* \theta_T e^{-\delta_T \tau} \right) \beta_L B_S^* \\
&\quad + (-r_T B_T^* \mathcal{W}'(B^*) - (1 - \pi) P_T^*) (\delta + \beta_L B_S^*) \left(\theta_T \alpha \beta_T P_T^* \mu_{T_0} e^{-\delta_T \tau} + r_S B_S^* \mathcal{W}'(B^*) \beta_L \theta_L \mu_{L_0} B_S^* e^{-\delta_S \tau} \right)
\end{aligned}$$