

**THE EFFECT OF TIME DELAY ON STABILITY IN A
BACTERIA-BACTERIOPHAGE MODEL**

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ABSTRACT.

The stability switch criteria proposed by Beretta and Kuang for delay differential equations is applied to a bacteria-bacteriophage model in order to investigate the effect of delay on stability of the equilibria. It is found that the stability region in the parameters space increases by increasing the replication factor of the virus, but large delay has always a stabilizing effect.

1 The model The first model for phage-bacteria interactions was proposed by Campbell in 1961 [5], to give an answer to how a "virulent phages-susceptible bacteria" system in an open growth system such as a chemostat can approach some stable steady state:

$$(1) \quad \begin{aligned} \frac{dB(t)}{dt} &= \alpha B(t) \left(1 - \frac{B(t)}{C}\right) - DB(t) - KP(t)B(t) \\ \frac{dP(t)}{dt} &= bK [B(t-T)P(t-T)] - KP(t)B(t) - \mu_p P(t) - DP(t) \end{aligned}$$

where $B(t)$ and $P(t)$ are respectively the concentrations of bacteria and phages at time t , $D > 0$ the wash-out rate constant of chemostat, $\alpha > 0$ the logistic growth rate of bacteria and $C > 0$ their carrying capacity, $K > 0$ the effective per bacteria phage absorption rate constant and $\mu_p > 0$ the rate constant of spontaneous inactivation of phages.

It is assumed that each infected bacterium yields b phage particles at time T after infection. Recently Beretta and Kuang [2] considered the phage-host system in an open environment ($D=0$), for example the thermocline layer of the sea in which the phage-bacteria system assumes a relevant role. They assumed that: - B includes both susceptible S and phage infected bacteria I , i.e. $B = I + S$. - The infected bacteria have a proper death rate constant μ_i , ($\mu_i > 0$). - The infected bacteria cannot reproduce themselves and encounter death by lysis after a time T delivering b copies of the phage. The Campbell model was then modified:

$$(2) \quad \begin{aligned} \frac{dS(t)}{dt} &= \alpha S(t) \left(1 - \frac{S(t)}{C}\right) - KS(t)P(t) \\ \frac{dP(t)}{dt} &= -\mu_p P(t) - KS(t)P(t) + b e^{-\mu_i T} KS(t-T)P(t-T) \\ \frac{dI(t)}{dt} &= -\mu_i I(t) + KS(t)P(t) - e^{-\mu_i T} KS(t-T)P(t-T) \end{aligned}$$

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For further biological motivations and for the ranges of parameters see [1] and [7]. For basic theory on delay differential equations see [6]. It is convenient to put equations in dimensionless form, by introducing the dimensionless time $t' = KCt$ and rescaling the variables on the carrying capacity C :

$$s = S/C, \quad i = I/C, \quad p = P/C$$

In dimensionless form the parameters μ_p, μ_i, α are:

$$a = \alpha/KC, \quad m = \mu_p/KC, \quad m_i = \mu_i/KC$$

and the bacteria carrying capacity C corresponds to the value $s = 1$.

The dimensionless latency time is $\tau = KCT$.

For sake of simplicity in the following we denote by t the dimensionless time t' .

The dimensionless equations become

$$(3) \quad \begin{aligned} \frac{ds(t)}{dt} &= as(t)(1-s(t)) - s(t)p(t) \\ \frac{dp(t)}{dt} &= -mp(t) - s(t)p(t) + be^{-m_i\tau}s(t-\tau)p(t-\tau) \\ \frac{di(t)}{dt} &= -m_i i(t) + s(t)p(t) - e^{-m_i\tau}s(t-\tau)p(t-\tau) \end{aligned}$$

or equivalently

$$(4) \quad \begin{aligned} \frac{ds(t)}{dt} &= as(t)(1-s(t)) - s(t)p(t) \\ \frac{dp(t)}{dt} &= -mp(t) - s(t)p(t) + be^{-m_i\tau}s(t-\tau)p(t-\tau) \end{aligned}$$

and

$$(5) \quad i(t) = \int_{t-\tau}^t e^{-m_i(t-\theta)}s(\theta)p(\theta)d\theta.$$

We study the stability properties of the equilibria with respect to the average number of delivered phages by bacteria undergoing lysis and to the latency time, i.e. with respect to parameters space

$$\mathcal{P} = \{(b, \tau) \in (1, +\infty) \times \mathbb{R}_{+0}\}.$$

The stability properties of the model refer to suitable initial conditions:

$$(6) \quad \begin{cases} s(\theta) = \phi_1(\theta), & p(\theta) = \phi_2(\theta) & \theta \in [-\tau, 0] \\ i(0) = \int_{-\tau}^0 e^{m_i\theta}s(\theta)p(\theta)d\theta \\ \phi_i(\theta) \in C([-\tau, 0]) : \phi_i(\theta) \geq 0 & i = 1, 2 \end{cases}$$

where by $C([-\tau, 0])$ we mean the set of real continuous functions on $[-\tau, 0]$. The system admits three nonnegative equilibria. The equilibria

$$E_0 = (0, 0, 0), \quad E_f = (s^* = 1, i^* = 0, p^* = 0)$$

are feasible for all parameters values, whereas the positive or endemic equilibrium

$$(7) \quad E_+ = \left(s^* = \frac{m}{be^{-m_i\tau} - 1}, i^* = \frac{s^*p^*(1 - e^{-m_i\tau})}{m_i}, p^* = a(1 - s^*) \right)$$

is feasible provided that $b > b^*$ and $\tau < T_c$ where

$$b^* := m + 1, \quad T_c = m_i^{-1} \log \frac{b}{b^*}.$$

Note that when $\tau = T_c$ then $s^* = 1$ and $p^* = 0$ thus implying $i^* = 0$, i.e. E_+ coincides with E_f .

2 Global and local stability By suitable Liapunov functionals, we get the following results concerning global asymptotic stability:

Theorem 1 For all values $b \in (1, b^*)$ the free disease equilibrium $E_f = (1, 0, 0)$ is globally asymptotically stable in \mathbb{R}_+^3 .

Theorem 2 Assume $b \geq b^*$. Then the free disease equilibrium $E_f = (1, 0, 0)$ is globally asymptotically stable in \mathbb{R}_+^3 provided that

$$\tau > T_1 = \frac{1}{m_i} \log \left(\frac{b - 1}{b^* - 1} \right).$$

Theorem 3 Assume the parameters satisfy

- i) $m > a + 1$;
- ii) τ is such that $T_c > \tau > T_1^*$ where

$$T_1^* := \frac{1}{m_i} \log \left(\frac{2b}{m + \sqrt{m^2 + 4(2am + 1)}} \right)$$

then the endemic equilibrium $E_+ = (s^*, i^*, p^*)$ is globally asymptotically stable in \mathbb{R}_+^3 .

The proofs of these theorems can be found in [4].

To study local stability, it is sufficient to consider the two equations in (4). The characteristic equation at the equilibrium $\underline{x}^* = (s^*, p^*)$ is:

$$(8) \quad \begin{vmatrix} a(1 - s^*) - as^* - p^* - \Lambda & -s^* \\ -p^*(1 - be^{-(m_i+\Lambda)\tau}) & -m - s^*(1 - be^{-(m_i+\Lambda)\tau}) - \Lambda \end{vmatrix} = 0$$

It follows that

- $E_0 = (0, 0)$ is an unstable saddle point for all parameter values.
- The equilibrium $E_f = (1, 0)$ is locally asymptotically stable when $T > T_c$ ($T_c = m_i^{-1} \log \frac{b}{b^*}$), unstable if $T < T_c$ and critically stable if $T = T_c$.

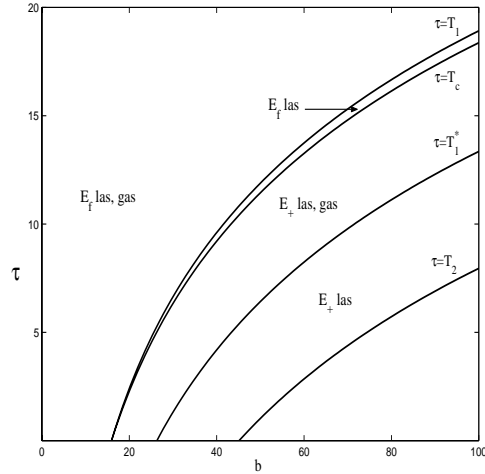


Figure 1: This figure summarizes the dynamical behaviour of model (4) in the parameter space \mathcal{P} . Below the curve T_2 the stability of E_+ can be investigated by the stability switch criterion.

From a mathematical point of view the interesting aspect is the study of the endemic equilibrium stability, since the characteristic equation

$$(9) \quad \Lambda^2 + (as^* + s^* + m)\Lambda - (m + s^*)\Lambda e^{-\Lambda\tau} - a(m + s^*)(1 - 2s^*) + am(1 - s^*) + a(m + s^*)(1 - 2s^*)e^{-\Lambda\tau} = 0$$

has coefficients depending on delay (in fact s^* is function of τ). In this case is not an easy task the study of characteristic roots.

Note that at $\tau = 0$ the characteristic roots of (8) have negative real parts, i.e. the endemic equilibrium $E_+ = (s^*, p^*)$ is locally asymptotically stable. Furthermore, for any delay $\Lambda = 0$ cannot be a characteristic root of (9), i.e. for increasing τ the equilibrium E_+ may lose stability only through a pair of conjugate and purely imaginary characteristic roots, say $\Lambda = \pm i\omega$, $\omega > 0$, which cross the imaginary axis from left to right.

Investigating the existence of characteristic roots $\Lambda = \pm i\omega$, $\omega > 0$, of (9) we find that (see [4]) :

- A value b_c , $b_c > b^*$, exists such that for all $b \in (b^*, b_c]$ the endemic equilibrium remains locally asymptotically stable.
- When $b > b_c$ the positive equilibrium is locally asymptotically stable provided that

$$T_c > \tau \geq T_2 = \frac{1}{m_i} \log \frac{b}{b_c}.$$

The above results concerning local and global stability of E_f and E_+ are summarized in Fig.1. The parameter values have been fixed according to the paper by Beretta and Kuang [1], i.e. $a = 10, m = 14.925, m_i = 0.1$.

The behaviour of E_+ in the parameters space region below the curve T_2 will be studied in Section 3.

3 Stability switches Now we study the occurrence of stability switches in the region

$$\mathcal{P}_1 = \{(b, \tau) \in (b_c, +\infty) \times (0, T_2)\}$$

We use the geometric stability switch criterion proposed by Beretta and Kuang [3] for delay differential equations with delay dependent parameters, with characteristic equation

$$D(\lambda, \tau) = P_n(\lambda, \tau) + Q_m(\lambda, \tau)e^{-\lambda\tau} = 0$$

where $P_n, Q_m, n > m$, are two polynomials in λ

$$P_n(\lambda, \tau) = \sum_{k=0}^n p_k(\tau)\lambda^k; \quad Q_m(\lambda, \tau) = \sum_{k=0}^m q_k(\tau)\lambda^k,$$

with coefficients $p_k(\cdot), q_k(\cdot)$ which are continuous and differentiable functions in τ for $\tau \in \mathbb{R}_{+0}$.

In our case

$$D(\lambda, \tau) = \lambda^2 + a(\tau)\lambda + b(\tau)\lambda e^{-\lambda\tau} + c(\tau) + d(\tau)e^{-\lambda\tau}$$

where, according to (9),

$$a(\tau) = as^* + s^* + m$$

$$b(\tau) = (m + s^*)$$

$$c(\tau) = a(m + s^*)(1 - 2s^*) + am(1 - s^*)$$

$$d(\tau) = a(m + s^*)(1 - 2s^*)$$

with s^* defined in (7). It is easy to check that

$$c(\tau) + d(\tau) \neq 0 \text{ for all } \tau \geq 0.$$

Then no crossing of the imaginary axis can occur with a real λ , i.e. a crossing of the imaginary axis must occur with a pair of conjugate and purely imaginary roots of (9), say $\lambda = \pm i\omega$. Following [3] it is easy to check that ω must be a root of

$$(c(\tau) - \omega^2(\tau))^2 + a^2(\tau)\omega^2(\tau) = \omega^2(\tau)b^2(\tau) + d^2(\tau).$$

Then $\omega(\tau)$ is given by

$$(10) \quad \omega_{\pm}^2(\tau) = \frac{1}{2} \left\{ (b^2(\tau) + 2c(\tau) - a^2(\tau)) \pm \Delta^{1/2}(\tau) \right\}$$

where the nomenclature ω_+, ω_- in (10) is self-evident and

$$(11) \quad \Delta(\tau) := (b^2(\tau) + 2c(\tau) - a^2(\tau))^2 - 4(c^2(\tau) - d^2(\tau)).$$

The stability switches through the characteristic root $\lambda = i\omega(\tau), \omega(\tau) > 0$, occur at τ values given by

$$\tau_n(\tau) = \frac{\theta(\tau) + n2\pi}{\omega(\tau)}, \quad n \in \mathbb{N}_0 := \mathbb{N} \cup \{0\},$$

where $\theta(\tau) \in [0, 2\pi]$ is solution of:

$$\begin{aligned} \sin \theta(\tau) &= \frac{-b(\tau)\omega(\tau)(c(\tau) - \omega^2(\tau)) + \omega(\tau)a(\tau)d(\tau)}{\omega^2(\tau)b^2(\tau) + d^2(\tau)} \\ \cos \theta(\tau) &= -\frac{a(\tau)b(\tau)\omega^2(\tau) + (c(\tau) - \omega^2(\tau))d(\tau)}{\omega^2(\tau)b^2(\tau) + d^2(\tau)} \end{aligned}$$

Since in our case only ω_+ is feasible, the theorem by Beretta and Kuang concerning the existence of stability switches can be simplifying, as follows:

Theorem 4 The characteristic equation (9) has a pair of simple and conjugate roots $\lambda = \pm i\omega(\tau), \omega(\tau) > 0$ at the τ values, say $\tau = \tau^*$, for which

- i) $\tau^* - \tau_n(\tau^*) = 0$ for some $n \in \mathbb{N}_0$.
 Their crossing of imaginary axis occurs according to:

ii)

$$\text{sign} \left\{ \frac{d\Re \lambda}{d\tau} \Big|_{\lambda=i\omega(\tau^*)} \right\} = \text{sign} \left\{ 1 - \frac{d\tau_n(\tau)}{d\tau} \Big|_{\tau=\tau^*} \right\}.$$

Then from i) it follows that stability switches occur at τ values which are zeros of the function $S_n = \tau - \tau_n(\tau)$ and from ii) it follows that the sign of the derivative of S_n is the sign of the derivative of the real part of λ at $\lambda = i\omega$.

These results provide a simple geometric method to find the values of τ at which stability switches occur in \mathcal{P}_1 . We proceed as follows: -we draw by Matlab (or other popular software) the curves $S_n = \tau - \tau_n(\tau)$ -we locate their zeros and see the sign of their derivative at these zeros. For example for $b = 50$ (Fig.2) we see that only the equation $S_0 = 0$ has two roots τ_{01}, τ_{02} and we have two stability switches. At τ_{01} the derivative of S_0 is positive then a couple of complex and conjugate characteristic roots enters in the positive half plane, and the positive equilibrium becomes unstable. E_+ regains stability at τ_{02} , where the derivative of S_0 is negative. (Stability-Instability-Stability).

Fig.3 shows the curves $S_n, n = 0, 1, 2$, for $b = 65$. At τ_{01} we have a switch from stability to instability; at τ_{11} , since the derivative of S_1 is positive a new couple of complex and conjugate eigenvalues enter in the positive half plane; then the equilibrium remains unstable, and only the shape and amplitude of oscillations around it change. The same arguments hold for τ_{21} . Stability will be regained only at τ_{02} .

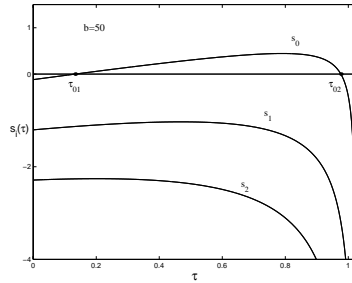


Figure 2: The maps of S_0, S_1 , are drawn for $\tau \in [0, T_2]$ and $b = 50$. The zeros of S_0 determine the values at which stability switches occur.

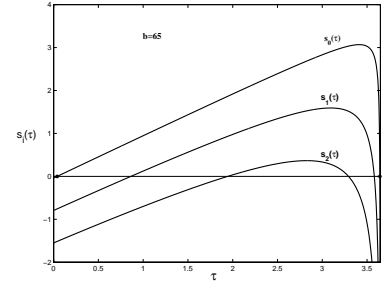


Figure 3: Maps of S_0, S_1, S_2 , for $\tau \in [0, T_2]$ and $b = 65$.

If for each b we plot the stability switched delay values (τ_{01}, τ_{02}) , by repeating this procedure for increasing b , we can numerically define the region of instability of E_+ within the parameters space \mathcal{P}_1 . We see (Fig.4) that the instability region in \mathcal{P}_1 increases by increasing b , but a large delay has always a stabilizing effect.

4 Conclusions We considered a model describing the dynamic of a phage-bacteria system in an open environment, taking into account the incubation time of phages into infected bacteria.

This delay differential system provides an interesting application of the general stability switch criterion by Beretta and Kuang in the case of second order characteristic equations. We found that, varying the incubation time and the virus replication factor, two stability

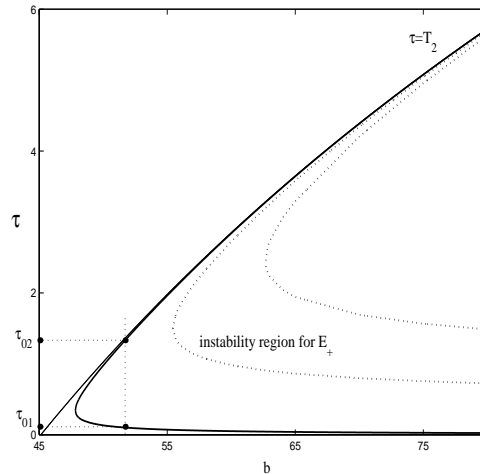


Figure 4: The instability region of E_+ is plotted in the parameters space \mathcal{P}_1 ; the dotted lines delimit the regions determined by the zeros of S_1 , S_2 .

switches occur (from stability to instability and from instability to stability). The instability region increases by increasing the replication factor of virus, but large delay always has a stabilizing effect. Computer simulations confirm these results.

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