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Global stability of a population dynamics model with inhibition and negative feedback

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Reactions or interactions with the rate which is inhibited by the product or a by-product of the reaction are fairly common in biology and chemical kinetics. Biological examples of such interactions include self-poisoning of bacteria, the non-lytic immune response and the antiviral (and in particular antiretroviral) therapy. As a case study, in this notice, we consider global asymptotic properties for a simple model with negative feedback (the Wodarz model) where the interaction is inhibited by a by-product of the reaction. The objective of this notice is an extending of a technique that was developed during last decade for the global analysis of models with positive feedback to the systems, where the feedback is negative. Using the direct Lyapunov method with Volterra type Lyapunov functions, we establish conditions for the global stability of this model. This result enables us to evaluate the comparative impacts of the lytic and non-lytic components, the efficiency of the antiviral therapy and the possibility of self-poisoning for bacteria. The same approach can be successfully applied to more complex models with negative feedback.

Keywords: kinetics with inhibition; negative feedback; non-lytic immune response; antiretroviral therapy; global stability; direct Lyapunov method; Lyapunov function; virus dynamics; self-poisoning of bacteria; chemostat model; the Wodarz model.

1. Introduction

Processes in chemical kinetics and biology are often inhibited by the product or a by-product of the reactions. The well-known examples of such processes are self-poisoning of bacteria in a chemostat, antiviral non-lytic immune response and antiretroviral therapy. In order to explore the impact of such inhibition on the system dynamics, in this notice, we consider as a case study a simple model of a reaction with inhibition, which is due to Wodarz *et al.* (2002):

$$\begin{aligned}\dot{x} &= \lambda - \beta \frac{xy}{1 + qz} - \mu x, \\ \dot{y} &= \beta \frac{xy}{1 + qz} - \sigma y - pyz, \\ \dot{z} &= \eta + cy - bz.\end{aligned}\tag{1.1}$$

This model is probably the simplest model of a process with inhibition where all three components, namely two reagents, $x(t)$ and $y(t)$, and the inhibitor, $z(t)$, are explicitly present, and the rate of process depends directly on both reagents and inversely on the inhibitor. For this model, we assume that $\eta, c, p, q \geq 0$; that at least one element of each couple, (η, c) and (p, q) , is positive (otherwise the third equation is decoupled from the first two equations) and that all other parameters are positive constants. The initial conditions $x(0), y(0), z(0)$ are assumed to be non-negative. The phase space of system (1.1) is the non-negative octant $\mathbb{R}_{\geq 0}^3$. For the sake of generality, we included in the model a possibility for an inflow of the inhibitor from outside sources at a constant rate η ; this extension makes it possible to apply this model to a wider range of problems, such as antiviral therapy.

Model (1.1), which is essentially a simplification of a model suggested earlier by Wodarz & Nowak (2000), was initially developed for immune response with lytic and non-lytic components. In contrast to the lytic immune response, which kills infected host cells, the non-lytic immune response inhibits viral replication through soluble mediators or simply neutralize free virus particles (Iwasa *et al.*, 2004; Wodarz & Nowak, 2000; Wodarz, 2007). For this particular application, the system variables and parameters should be interpreted as follows: $x(t)$, $y(t)$ and $z(t)$ are populations of the uninfected and infected target cells and the immune response cells, respectively, at time t ; λ and $\mu x(t)$ are the inflow rate and the death rate of the uninfected cells. The infected cells die at the rate $\sigma y(t)$ and are killed by the immune response cells at the rate $py(t)z(t)$ (that corresponds to the lytic effector mechanisms); the non-lytic components of immune response inhibits the incidence rate with a factor $1/(1 + qz(t))$, where the parameter $q \geq 0$ is the efficacy of the non-lytic component. This model does not explicitly include a free virus population, assuming instead that this is proportional to the infected cells population $y(t)$. This assumption is justified if the timescale of free virus is much faster than that of the host cells; in this case, the free virus population quickly converges to a quasiequilibrium level proportional to the infected cells population $y(t)$.

This model can be immediately applied to other processes, which are inhibited by a product or a by-product of a reaction, including self-poisoning of bacteria in a chemostat and antiviral, and in particular antiretroviral, therapy. Bacteria produce metabolic wastes and toxins, which can inhibit their metabolism and reproduction. (It may be worth mentioning that self-poisoning can be a possible mechanism of killing the tuberculosis bacteria *Mycobacterium tuberculosis*; see Kalscheuer *et al.* (2010).) For bacteria self-poisoning, the model variables and parameters can be interpreted as follows: $x(t)$ is the concentration of nutrient, $y(t)$ is the concentration of bacteria, which are dying or are removed at the rate σy , and $z(t)$ is the concentration of the inhibitor (metabolic waste or a toxin). The chemostat is assumed to be well stirred; nutrient inflows at a constant rate λ and is removed from the chemostat at the rate $\mu x(t)$. Toxin $z(t)$ is produced by bacteria at a rate $cy(t)$ and inflows into the chemostat with a constant rate η . Toxin kills the bacteria with the killing rate proportional to the concentrations of toxin and biomass, $py(t)z(t)$, and inhibits their metabolism and reproduction.

The antiretroviral therapy against HIV uses drugs that inhibit replication or transmission of the virus. The drugs that are in common use for HIV treatment are the reverse transcriptase inhibitors and the protease inhibitors which inhibit replication of the virus within a target cell; the fusion or entry inhibitors which inhibit the process of binding to or entering target cells and the integrase inhibitors which inhibit inserting virus genetic material into human cells. Antiviral therapy is also used for hepatitis C virus (HCV) treatment: antiviral drugs, such as interferon, HCV protease inhibitors and polymerase inhibitors, are assumed to reduce virion production (Neumann *et al.*, 1998; Shudo *et al.*, 2008). For the antiviral and antiretroviral therapy, $x(t)$ and $y(t)$ should be interpreted as populations of the uninfected and infected target cells, and $z(t)$ is the concentration of the drug.

Model (1.1) was extensively numerically studied by Wodarz (2005). Later, assuming some constraints on the system parameters, Wang *et al.* (2006) proved global stability using the direct Lyapunov method and the so-called ‘geometric approach’ (Li & Muldowney, 1996; Smith, 1986). Another global stability result, which also assumes some constraints on the parameters, was recently obtained by Muroya *et al.* (2011).

In this notes, our immediate goal is to establish the global asymptotic properties of this model and evaluate the impacts of inhibition on its global dynamics. To do this, we employ the direct Lyapunov method with the Volterra Lyapunov function, which proved to be an extremely effective tool for a variety of problems in mathematical biology (Huang *et al.*, 2010b; Korobeinikov, 2009b, 2010; McCluskey, 2010a,b,c; Melnik & Korobeinikov, 2011; Thieme, 2011), including virus dynamics and immune response models (Huang *et al.*, 2010a, 2011; Korobeinikov, 2004, 2009a; Vargas De León, 2011). However, there is a fundamental difference between the models that were considered in the above-mentioned papers and model (1.1): in the above-mentioned models, all products of a reaction either contribute to an increase of the reaction rate or are neutral, whereas in model (1.1), the ultimate product of the reaction (toxin in chemostat, drug in antiviral therapy or non-lytic immune response) inhibits the reaction. That is, there is a positive feedback in all models that were previously considered, whereas in model (1.1), the feedback is negative. This principal difference prevented a straightforward application of the well-developed technique to model (1.1); a number of attempts yielded results of a rather limited value where some constraints on the system parameters were required. The motivation for this notice, apart from establishing the dynamical properties of model (1.1), is developing a formalism for an extending of the well-developed technique to a new wider class of models with negative feedback. Processes with negative feedback are fairly common in biology and chemical kinetics, and we expect that this result will be of interests for mathematicians and scientists applying mathematical modelling to this kind of problems.

2. Properties of the model

Global qualitative properties of system (1.1) crucially depend on the basic reproduction number of infected cells R_0 . For this system, we define the basic reproduction number as

$$R_0 = \beta \frac{x_0}{(1 + qz_0)(\sigma + pz_0)} = \frac{\beta\lambda}{\mu(1 + q\eta/b)(\sigma + p\eta/b)}. \quad (2.1)$$

At an equilibrium state of system (1.1), the equalities

$$\lambda - \beta \frac{xy}{1 + qz} - \mu x = 0, \quad (2.2)$$

$$\beta \frac{xy}{1 + qz} - \sigma y - pyz = 0, \quad (2.3)$$

$$\eta + cy - bz = 0 \quad (2.4)$$

hold. It is easy to see that the system always has an equilibrium state where $y = 0$ and $x = \lambda/\mu$, $z = \eta/b$. We further refer to this equilibrium state as the microorganisms-free equilibrium state and denote it Q_0 . Apart from this equilibrium state, in the positive octant R_+^3 , the model can also have an equilibrium state Q^* with coordinates $z^* = (\eta + cy^*)/b$, $x^* = (\sigma b + p(\eta + cy^*))(b + q(\eta + cy^*))/\beta b^2$ and y^* which satisfies the quadratic equation $A_1 y^2 + A_2 y - A_3 = 0$, where $A_1 = pc(\beta b + \mu qc) \geq 0$,

$A_2 = ((\beta b + \mu qc)(p\eta + \sigma b) + \mu pc(b + q\eta)) > 0$ and $A_3 = \mu(\sigma b + p\eta)(b + q\eta)(R_0 - 1)$. That is,

$$y^* = \frac{-A_2 + (A_2^2 + 4A_1A_3)^{1/2}}{2A_1}. \quad (2.5)$$

It is easy to see that $A_3 > 0$ for $R_0 > 1$, $A_3 = 0$ when $R_0 = 1$ and $A_3 < 0$ for $R_0 < 1$. Hence, the quadratic equation has a positive root for all $R_0 > 1$ and no positive root when $R_0 < 1$; $y^* = 0$ is the only solution to the equation when $R_0 = 1$. The system can have one more equilibrium state outside of the non-negative octant with $y = -(A_2 + (A_2^2 + 4A_1A_3)^{1/2})/2A_1$. However, this equilibrium is biologically unfeasible and hence is not of our interest.

Global properties of the system are given by following theorem.

THEOREM 2.1 System (1.1) is globally asymptotically stable. That is,

(i) if $R_0 > 1$, then the positive equilibrium state Q^* exists and is globally asymptotically stable in \mathbb{R}_+^3 ;

(ii) if $R_0 \leq 1$, then microorganisms-free equilibrium state Q_0 is globally asymptotically stable in $\mathbb{R}_{\geq 0}^3$.

Proof. We start with an observation that $\dot{x} > 0$ holds at $x = 0$, $\dot{z} > 0$ at $z = 0$ and $\dot{y} = 0$ at $y = 0$, and hence, the positive octant \mathbb{R}_+^3 and the non-negative octant $\mathbb{R}_{\geq 0}^3$ are positive invariant sets of the model.

(i) The existence of positive equilibrium state Q^* for $R_0 > 1$ is proved above. To prove its global stability, we consider a function

$$V = x - x^* \ln x + B(y - y^* \ln y) + D((1 + qz) - (1 + qz^*) \ln(1 + qz)),$$

where $B = 1$ and $Dqcy^* = \frac{py^*(1+qz^*)}{q} + \beta \frac{x^*y^*}{1+qz^*}$. The function is defined in a domain

$$\Sigma = \{(x, y, z) \in \mathbb{R}^3 | x > 0, y > 0, z > -1/q\}$$

and reaches the infinity at its boundaries. It is easy to see that equilibrium Q^* is the global minimum and the only stationary point of the function in Σ .

The function satisfies

$$\begin{aligned} \frac{dV}{dt} &= \lambda - \beta \frac{xy}{1+qz} - \mu x - \lambda \frac{x^*}{x} + \beta \frac{x^*y}{1+qz} + \mu x^* \\ &\quad + B \left(\beta \frac{xy}{1+qz} - \sigma y - pyz - \beta \frac{xy^*}{1+qz} + \sigma y^* + py^*z \right) \\ &\quad + D \left(q\eta + qcy - qbz - q\eta \frac{1+qz^*}{1+qz} - qcy \frac{1+qz^*}{1+qz} + qbz \frac{1+qz^*}{1+qz} \right) \\ &= \mu x^* \left(2 - \frac{x}{x^*} - \frac{x^*}{x} \right) + D(b + q\eta) \left(2 - \frac{1+qz^*}{1+qz} - \frac{1+qz}{1+qz^*} \right) \\ &\quad + \beta \frac{x^*y^*}{1+qz^*} \left(3 - \frac{x}{x^*} \frac{1+qz^*}{1+qz} - \frac{1+qz}{1+qz^*} - \frac{x^*}{x} \right) \\ &\quad + \frac{1}{q} py(1+qz^*) \left(2 - \frac{1+qz}{1+qz^*} - \frac{1+qz^*}{1+qz} \right). \end{aligned}$$

Here, we used $pz = \frac{1}{q}p(1+qz^*)\frac{1+qz}{1+qz^*} - \frac{1}{q}p$, $Dqcy^* = Dq(bz^* - \eta) = \frac{1}{q}py^*(1+qz^*) + \beta \frac{x^*y^*}{1+qz^*}$ and equalities (2.2–2.4). By the theorem that the arithmetic mean is greater than or equal to the geometric

mean, $(2 - \frac{x}{x^*} - \frac{x^*}{x}) \leq 0$, $(2 - \frac{1+qz^*}{1+qz} - \frac{1+qz}{1+qz^*}) \leq 0$ and $(3 - \frac{x}{x^*} \frac{1+qz^*}{1+qz} - \frac{1+qz}{1+qz^*} - \frac{x^*}{x}) \leq 0$ hold for all $x, y, z \geq 0$ and $x^*, y^*, z^* \geq 0$. That is, if a positive equilibrium state exists, then $\frac{d}{dt}V(t) \leq 0$, where the equality $\frac{d}{dt}V(t) = 0$ holds only if $x = x^*$ and $z = z^*$ simultaneously. Hence, by Lyapunov–LaSalle asymptotic stability theorem (LaSalle, 1976), equilibrium state Q^* , if it exists, is globally asymptotically stable.

The uniqueness of positive equilibrium state Q^* follows from the fact that $\frac{d}{dt}V(t) = 0$ necessarily holds at an equilibrium state; however, for this system in the positive octant, this equality holds on the straight line $x = x^*, z = z^*$, and point Q^* is the only equilibrium state of the system on this line.

Furthermore, \mathbb{R}_+^3 is a positive invariant set of the system, and $\mathbb{R}_+^3 \in \Sigma$. Hence, hypothesis (i) is proved.

(ii) For microorganisms-free equilibrium Q_0 , we consider a function

$$W = x - x_0 \ln x + By + D((1 + qz) - (1 + qz_0) \ln(1 + qz)),$$

where $B = 1$ and $Dqc = \frac{1}{q}p(1 + qz_0) + \beta \frac{x_0}{1+qz_0}$. The function reaches its minimum in $\mathbb{R}_{\geq 0}^3$ at Q_0 and satisfies

$$\begin{aligned} \frac{dW}{dt} &= \lambda - \beta \frac{xy}{1+qz} - \mu x - \lambda \frac{x_0}{x} + \beta \frac{x_0 y}{1+qz} + \mu x_0 + B \left(\beta \frac{xy}{1+qz} - \sigma y - pyz \right) \\ &\quad + D \left(q\eta + qcy - qbz - q\eta \frac{1+qz_0}{1+qz} - qcy \frac{1+qz_0}{1+qz} + qbz \frac{1+qz_0}{1+qz} \right) \\ &= \lambda \left(2 - \frac{x_0}{x} - \frac{x}{x_0} \right) + D(q\eta + b) \left(2 - \frac{1+qz}{1+qz_0} - \frac{1+qz_0}{1+qz} \right) \\ &\quad + \frac{1}{q}py(1+qz_0) \left(2 - \frac{1+qz}{1+qz_0} - \frac{1+qz_0}{1+qz} \right) + y(\sigma + pz_0) \left(\beta \frac{x_0}{(1+qz_0)(\sigma + pz_0)} - 1 \right). \end{aligned}$$

(We used $pz = \frac{1}{q}p(1 + qz_0) \frac{1+qz}{1+qz_0} - \frac{1}{q}p$.) Here, $(2 - \frac{x}{x_0} - \frac{x_0}{x}) \leq 0$ and $(2 - \frac{1+qz_0}{1+qz} - \frac{1+qz}{1+qz_0}) \leq 0$ hold for all $x \geq 0$ and $z \geq -1/q$, and, by (2.1),

$$\beta \frac{x_0}{(1+qz_0)(\sigma + pz_0)} - 1 = R_0 - 1.$$

Therefore, $R_0 \leq 1$ ensures that $\frac{d}{dt}W(t) \leq 0$ holds, where equality $\frac{d}{dt}W(t) = 0$ holds only if $x = x_0$, $z = z_0$ and $R_0 = 1$ hold simultaneously. The only invariant set of system (1.1) on the straight line $x = x_0, z = z_0$ is the equilibrium state Q_0 , and hence, by Lyapunov–LaSalle asymptotic stability theorem, equilibrium state Q_0 is globally asymptotically stable when $R_0 \leq 1$.

The absence of positive equilibria when $R_0 \leq 1$ follows from the global stability of Q_0 . Equality $\frac{d}{dt}W(t) = 0$ necessary holds at an equilibrium state. However, as we just mentioned, for this system, the equality holds only if $x = x_0, z = z_0$ and $R_0 = 1$ hold simultaneously, and the point Q_0 is the only equilibrium state on straight line $x = x_0, z = z_0$.

This completes the proof. \square

In conclusion, we have to note that the boundedness of solutions and the uniform persistence of the system immediately follow from theorem and the proof.

3. Discussion and conclusion

In this notice, we investigated global asymptotic properties of a population dynamics model where the interaction has a negative feedback (Wodarz's model). Kinetics with negative feedback is rather common in biology and includes, among other, examples such as self-poisoning of microorganisms, non-lytic immune response and antiretroviral therapy. To study the global dynamics of this model, we employ the direct Lyapunov method with Volterra Lyapunov function. The considered model is globally asymptotically stable for all biologically feasible range of parameters and its global behaviour is completely defined by the basic reproduction number of infected population R_0 . A biologically important consequence of this global stability is the uniform persistence of the system: the condition $R_0 > 1$ ensures that all three species persist near their equilibrium levels, whereas condition $R_0 \leq 1$ implies eventual disappearance of the microorganisms (or infection).

A particular case when the inhibitor is produced only by the microorganisms and there is no inflow of the inhibitor into the system (i.e. when $\eta = 0$) is rather common in the real life and in the literature on immune response (Iwasa *et al.*, 2004; Nowak & May, 2000; Wang *et al.*, 2006; Wodarz & Nowak, 2000; Wodarz *et al.*, 2002; Wodarz, 2007). In this particular case, R_0 does not depend on the inhibitor, and hence, no elimination of the microorganisms or the infection is possible in this model framework. The effects of inhibition in this case are (i) a reduction of the infected cells (or microorganisms) population, (ii) enhancing the system stability (solutions converge an equilibrium state faster) and (iii) slowing the spread of infection. The latter effect, that is slowing the spread, is hardly surprising. Indeed, if we assume that the inhibition acts very fast, then the concentration of inhibitor would be at a quasiequilibrium level proportional to the 'infected population' $y(t)$, and the model can be reduced to a 2D model with respect to variables $x(t)$ and $y(t)$, where the inhibition is given by the Michaelis–Menten kinetics with respect to $y(t)$. The more rapid convergence to an equilibrium state in the presence of inhibitor is hardly surprising either: the negative feedback usually enhances the stability. It is worth mentioning that while no self-elimination is possible in this model framework, a reduction to a dangerously low level, where elimination can occur due to stochastic effects, is still possible.

If there is a constant inflow of the inhibitor, i.e. when $\eta > 0$, then the basic reproduction number is reduced by a factor $(1 + q\eta/b)(1 + p\eta/b\sigma)$; this potentially can lead to a reduction of R_0 below 1 leading to annihilation of the infection. The critical inflow rate η_{cr} that is necessary for the annihilation is a positive root of the quadratic equation $pq\eta_{cr}^2 + b(q\sigma + p)\eta_{cr} - (R_0 - 1)b^2\sigma = 0$; since here $pq \geq 0$ and $b(q\sigma + p) > 0$ hold, this equation always has one positive root for all $R_0 > 1$. If maintaining the critical inflow rate is impossible, then (2.5) gives the rate which is necessary for reduction of the infection load to an acceptable level \bar{y} . For a therapy, it is safe to assume that there is no production of the inhibitor in the system (i.e. $c = 0$) and that all inhibitor is coming from an external source. In this case, assuming that the basic reproduction ratio without the therapy is R_0 , the necessary influx rate $\bar{\eta}$ is a positive root of the equation

$$\mu(R_0 - 1)pq\bar{\eta}^2 + b(\mu(R_0 - 1)(\sigma q + p) - \beta p\bar{y})\bar{\eta} + \sigma b^2[\mu(R_0 - 1) - \beta\bar{y}] = 0.$$

Another conclusion of biological importance is that the contributions of the lytic and non-lytic components to the reduction of R_0 and the infectious level y^* is symmetric, and hence, it is hardly possible to decide which of two components is more efficient in elimination of an infection. The contribution of each component depends on the strength of response (i.e. on the values of coefficients p and q) rather than on its type. The major difference between two components is that the lytic component contribution is proportional to the ratio p/σ , whereas the contribution of the non-lytic response depends

on its strength q alone. Therefore, an increase of the non-lytic response is preferable when the life span of infected cells is short (σ is large), whereas an increase of the lytic component may be a preferable option in the case of long-living infected cells (when $\sigma < 1$). Another conclusion is that in the presence of both lytic and non-lytic components, the basic reproduction number is inversely squared to the influx rate η , and hence, both components are present, a doubling of the influx rate leads to a quadruple reduction of the basic reproduction number. That is, the components cumulative effect is not additive but multiplicative. When a single component of the immune response is active, the basic reproduction number is inversely proportional to η .

In conclusion, we would like to mention that the approach which is used in this paper can be immediately applied to more complex models composed of a larger number of compartments. We also believe that this approach is applicable to models with non-linear reaction rate.

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