GLOBAL PROPERTIES OF BASIC VIRUS DYNAMICS MODELS

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Abstract. Lyapunov functions for basic virus dynamics models are introduced, and global stability of the models are thereby established.

Key words: Direct Lyapunov method, Lyapunov function, equilibrium state, stability.

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1. Basic model

The dynamics of a virus population *in vivo* may be described by a simple three-dimensional model (Bonhoeffer et al., 1997; Nowak and May, 2000)

$$\begin{aligned} \dot{x} &= \lambda - mx - \beta x\nu, \\ \dot{y} &= \beta x\nu - ay, \\ \dot{\nu} &= ky - u\nu. \end{aligned} \tag{1.1}$$

Here we denote uninfected cell population (the susceptible cells) by $x(t)$, infected cells by $y(t)$ and free virus particles by $\nu(t)$. The cells are assumed to reproduce with a constant rate λ, and all the newly produced cells are uninfected (and susceptible). The average life times of the susceptible cells, infected cells and free virus are $1/m, 1/a$ and $1/u$ respectively (naturally, $a \geq m$). Free virus is produced from infected cells at the rate ky and infect the susceptible cells at the rate $\beta x\nu$. Naturally, the system is defined only for non-negative x, y, ν, and all the coefficients are assumed positive.

Apart from an infection-free equilibrium $Q_0 = (\lambda/m, 0, 0)$, the system has an equilibrium $Q^* = (x^*, y^*, \nu^*)$, where

$$x^* = \frac{\lambda}{m}\frac{1}{R_0}, \quad y^* = \frac{mu}{\beta k}\left(R_0 - 1\right), \quad \nu^* = \frac{k}{u}y^* = \frac{m}{\beta}\left(R_0 - 1\right). \tag{1.2}$$

The equilibrium exists and is known to be asymptotically stable if the basic production number $R_0 = \frac{\beta\lambda k}{amu}$ is larger than one (Bonhoeffer et al., 1997; Nowak and May, 2000).

The differential equations (1.1) are equivalent to those of a $SEIR$ epidemiological model with a constant host population size assumption (e.g. Hethcote (2000); Korobeinikov (2004)). Indeed, if the equation for the recovered population R is omitted (the constant population size assumption allows us to do so), the system (1.1) is equivalent to the $SEIR$ model: x corresponds to susceptible population S, y to exposed population E, and ν to infective population I. This equivalence implies that the dynamics of these systems are also similar, and that most of the results known for the $SEIR$ model (which has been well studied) can be straightforwardly extended to the system (1.1).

For the $SEIR$ model there is a global Lyapunov function (Korobeinikov, 2004) which allows a straightforward investigating of global properties of the system (1.1) as well. The following theorem holds for the system.

Theorem 1.1. *(i) If the basic reproduction number $R_0 > 1$ then the positive equilibrium Q^* is globally asymptotically stable.*

(ii) If $R_0 \le 1$ then there is no positive equilibrium Q^*, and the infection free-equilibrium Q_0 is globally asymptotically stable.

Proof. (i) A Lyapunov function

$$V(x,y,\nu) = x^*\left(\frac{x}{x^*} - \ln\frac{x}{x^*}\right) + y^*\left(\frac{y}{y^*} - \ln\frac{y}{y^*}\right) + \frac{a}{k}\nu^*\left(\frac{\nu}{\nu^*} - \ln\frac{\nu}{\nu^*}\right)$$

satisfies

$$\begin{aligned}\frac{dV}{dt} &= \lambda - \beta x\nu - mx - \lambda\frac{x^*}{x} + \beta x^*\nu + mx^* \\ &\quad +\beta x\nu - ay - \beta\frac{x\nu y^*}{y} + ay^* \\ &\quad +ay - u\frac{a}{k}\nu - a\frac{y\nu^*}{\nu} + \frac{a}{k}u\nu^* \\ &= mx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) + ay^*\left(3 - \frac{x^*}{x} - \frac{x\nu y^*}{x^*\nu^* y} - \frac{y\nu^*}{y^*\nu}\right).\end{aligned}$$

(We used (1.2) here.) Since the arithmetical mean is greater then or equal to the geometrical mean, the functions

$$\frac{x}{x^*} + \frac{x^*}{x} - 2 \qquad \text{and} \qquad \frac{x^*}{x} + \frac{x\nu y^*}{x^*\nu^* y} + \frac{y\nu^*}{y^*\nu} - 3$$

are non-negative for all $x, y, \nu > 0$. Hence $x^*, y^* \ge 0$ ensures $\frac{dV}{dt} \le 0$ for all $x, y, \nu > 0$.

(ii) A Lyapunov function

$$U(x,y,\nu) = x_0\left(\frac{x}{x_0} - \ln\frac{x}{x_0}\right) + y + \frac{a}{k}\nu$$

satisfies

$$\frac{dU}{dt} = \lambda\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \frac{au}{k}\left(R_0 - 1\right)\nu.$$

It is obvious that $R_0 \le 1$ ensures $\frac{dU}{dt} \le 0$ for all $x, \nu > 0$. □

2. Model with exposed state

To take into account some features of real systems, such as delay between the moment of infection and the moment when the infected cell begins to produce the virus, additional classes of cells may be added to the system. For instance, for cells in the latent state an additional class, the class of exposed cells $z(t)$, can be used. Then the system equations are

$$\begin{aligned}\dot{x} &= \lambda - mx - \beta x\nu, \\ \dot{z} &= \beta x\nu - (b+c)z, \\ \dot{y} &= cz - ay, \\ \dot{\nu} &= ky - u\nu.\end{aligned} \tag{2.1}$$

Here b is the mortality rate of the exposed cells, and $1/c$ is the average time of the latent state. This system assumes an exponentially-distributed delay between the event of infection and the moment when the infected cell starts to produce the virus.

The system (2.1) has an infection-free equilibrium $Q_0 = (\lambda/m, 0, 0, 0)$ and the co-existing equilibrium $Q^* = (x^*, z^*, y^*, \nu^*)$ with coordinates

(2.2)
$$x^* = \frac{\lambda}{m}\frac{1}{R_0},\ z^* = \frac{aum}{k\beta c}\left(R_0 - 1\right),\ y^* = \frac{um}{\beta k}\left(R_0 - 1\right),\ \nu^* = \frac{m}{\beta}\left(R_0 - 1\right).$$

Here $R_0 = \dfrac{\lambda\beta ck}{aum(b+c)}$ is the basic reproduction number of the system (2.1).

Theorem 1.1 holds for the system (2.1) as well. To prove the first part of the theorem we can use the Lyapunov function

$$\begin{aligned} V(x,y,\nu) &= \left(x - x^*\ln\frac{x}{x^*}\right) + \left(z - z^*\ln\frac{z}{z^*}\right) \\ &+ \frac{b+c}{c}\left(y - y^*\ln\frac{y}{y^*}\right) + \frac{a(b+c)}{ck}\left(\nu - \nu^*\ln\frac{\nu}{\nu^*}\right). \end{aligned}$$

Using (2.2), we obtain

$$\frac{dV}{dt} = mx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) + (b+c)z^*\left(4 - \frac{x^*}{x} - \frac{x\nu z^*}{x^*\nu^* z} - \frac{zy^*}{z^*y} - \frac{y\nu^*}{y^*\nu}\right).$$

It is easy to see that if $x^*, z^* \geq 0$ then $\frac{dV}{dt} \leq 0$ for all $x, y, z, \nu > 0$ (the arithmetical mean is greater then or equal to the geometrical mean).

For the second part of the theorem we apply the Lyapunov function

$$U(x,y,\nu) = x_0\left(\frac{x}{x_0} - \ln\frac{x}{x_0}\right) + \frac{b+c}{c}y + z + \frac{a(b+c)}{ck}\nu,$$

which satisfies

$$\frac{dU}{dt} = \lambda\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \frac{\lambda\beta}{m}\frac{1}{R_0}\left(R_0 - 1\right)\nu.$$

It is obvious that $R_0 \leq 1$ ensures $\frac{dU}{dt} \leq 0$ for all $x, \nu > 0$.

In some cases more complex compartmental model of a virus *in vivo* can be considered. However it appears that a Lyapunov function of the same type, that is, a function of the form

$$V(x_1, x_2, \ldots, x_n) = \sum_{i=1}^{n} A_i\left(x_i - x_i^*\ln\frac{x_i}{x_i^*}\right),$$

where x_i is a number of cells in the ith class (or the number of free virus particles), x_i^* are equilibrium values and A_i are constants, can be successfully applied for such systems. The Lyapunov functions of this type are also proven to be useful for Lotka-Volterra predator-prey systems (see e.g. Goh (1980); Takeuchi (1996)).

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