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CONSTRUCTION OF LYAPUNOV FUNCTIONS FOR SOME MODELS OF INFECTIOUS DISEASES IN VIVO: FROM SIMPLE MODELS TO COMPLEX MODELS

Tsuyoshi Kajiwara and Toru Sasaki

Graduate School of Environmental and Life Sciences, Okayama University
3-1-1, Tsushima-Naka, Okayama, Japan

Yasuhiro Takeuchi

College of Science and Engineering, Aoyama Gakuin University
5-10-1, Fuchinobe, Sagamihara, Japan

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Abstract. We present a constructive method for Lyapunov functions for ordinary differential equation models of infectious diseases in vivo. We consider models derived from the Nowak-Bangham models. We construct Lyapunov functions for complex models using those of simpler models. Especially, we construct Lyapunov functions for models with an immune variable from those for models without an immune variable, a Lyapunov functions of a model with absorption effect from that for a model without absorption effect. We make the construction clear for Lyapunov functions proposed previously, and present new results with our method.

1. **Introduction.** Infectious diseases in vivo and immune response against infection are investigated using nonlinear ordinary differential equations. It is important to investigate the stability of the equilibrium of the equations to know whether infection is established or not, whether the state of infection after establishment is stable or oscillating, whether immune response exists or not and whether it is stable or oscillating.

While the analysis of local stability using the Jacobi matrix for the stability of equilibria can be used in many cases, we can show the global stability result for the equilibrium if we can construct a Lyapunov function. A Lyapunov function of an ordinary differential equation is a function on the phase space such that it decreases (or does not increase) along each solution of the equation. If we can construct a Lyapunov function, we can prove the global stability using the LaSalle invariance principle in many cases.

But, constructive methods to find Lyapunov functions are not known except for certain particular models, for example, Li *et al.* [9]. In many cases, Volterra type functions are used, and the derivative of the Lyapunov function is shown to be nonpositive using the result that it is expressed as a sum of squared terms with negative coefficients.

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By the limitation of technique, the global stability of the interior equilibrium of the model with three variables in Nowak and Bangham [12] has not been shown for a long time. Korobeinikov [7] showed that Volterra type functions are applicable to many models of epidemiology and virology using arithmetic-geometric mean inequality, and he settled the problem of global stability for the model in Nowak and Bangham [12]. After that, many papers, for example Pang *et al.* [13], Iggidr *et al.* [3], Kajiwara and Sasaki [5], Inoue *et al.* [4], have appeared and Lyapunov functions have been obtained for many models. When a model is modified by some change from a simpler model, it will be better if we can construct a Lyapunov function from that for the original model in a constructive way.

In the present paper, we consider models derived from the models in Nowak and Bangham [12]. We construct Lyapunov functions for more complex models from those for simpler models. Using a Lyapunov function, which are already known (e.g. Korobeinikov [7]) for a model that ignores the immunity, we construct a Lyapunov function for a model that incorporates the immunity. We show that Lyapunov functions, which is already known, are directly obtained by our method, and we also show new results. When a pathogen infects an uninfected cells, the number of pathogens decreases by one, and we call it the absorption effect. We construct a Lyapunov function for a model with absorption effect from a Lyapunov function for a model without absorption effect. We make previous constructions clearer. And we also construct a Lyapunov function for a model of Qesmi *et al.* [14].

The contents of the paper are as follows. In Section 2, we present a method for modifying a Lyapunov function for a model without an immune variable to obtain a Lyapunov function for a model with an immune variable. We state the details of the construction mainly for the model with humoral immunity. In Section 3, we present a method to construct a Lyapunov function for a model with the absorption effect by using that of a model without the absorption effect. We use the method in Section 2 for the model which contains an immune variable and absorption effect.

Using the method which we propose, we also present some new results. We construct Lyapunov functions mainly around the interior equilibrium because the construction for the interior equilibrium is often more difficult.

2. Models with immune variables.

2.1. Formulation and a result.

We will construct a Lyapunov function for a model of infectious diseases in vivo with an immune variable, by using a Lyapunov function for a corresponding model without an immune variable. Since the method of construction can be applied to various models, we consider the following form:

$$\begin{aligned}
\frac{\mathrm{d}x_k}{\mathrm{d}t} &= f_k(x_1, x_2, \ldots, x_n) \qquad (k = 1, 2 \ldots, i-1, i+1, \ldots, n),\\
\frac{\mathrm{d}x_i}{\mathrm{d}t} &= f_i(x_1, x_2, \ldots, x_n) - bx_i - px_{n+1}x_i, \\
\frac{\mathrm{d}x_{n+1}}{\mathrm{d}t} &= x_i q(x_{n+1}) - mx_{n+1}.
\end{aligned} \tag{1}$$

The variables x_k's $(k = 1, 2, \ldots, n)$ express the amount of the uninfected cells, infect cells of several stages, and pathogens. Here we fix i $(1 \leq i \leq n)$, and x_i corresponds to the cells or pathogens that stimulate the immune system and are eliminated by the immune system (the term $-px_{n+1}x_i$ with a positive constant p). The linear clearance term $-bx_i$ $(b > 0)$, which commonly appears in many models, is not included in f_i because of a technical reason. The variable x_{n+1} expresses the amount of the immune cells. We confine ourselves to the case where the immune activation is described in the form $x_i q(x_{n+1})$. We assume that, for $z > 0$, the function $q(z)$ is positive and $z/q(z)$ is monotonously nondecreasing. The positive constant m is the death rate of immune cells.

We will construct a Lyapunov function for (1) using a Lyapunov function for the following model

$$\begin{aligned}\frac{\mathrm{d}x_k}{\mathrm{d}t} &= f_k(x_1, x_2, \ldots, x_n) \qquad (k = 1, 2 \ldots, i-1, i+1, \ldots, n),\\ \frac{\mathrm{d}x_i}{\mathrm{d}t} &= f_i(x_1, x_2, \ldots, x_n) - b' x_i.\end{aligned} \tag{2}$$

The model (2) corresponds to (1), and the meanings and dynamics of x_k's also correspond to those for (1), except the fact that the model (2) dose not explicitly include an immune variable. Here the coefficient b' of the linear clearance term is different from b in (1). If we put $\mathbf{g} = (g_1, g_2, \ldots, g_n)$ with

$$\begin{aligned}g_k(x_1, x_2, \ldots, x_n) &= f_k(x_1, x_2, \ldots, x_n) \qquad (k = 1, 2, \ldots, i-1, i+1, \ldots, n),\\ g_i(x_1, x_2, \ldots, x_n) &= f_i(x_1, x_2, \ldots, x_n) - b' x_i,\end{aligned}$$

and $\mathbf{x} = (x_1, x_2, \ldots, x_n)$, then the system (2) becomes

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{g}(\mathbf{x}).$$

We suppose that the model (1) has a positive equilibrium $(\hat{x}_1, \hat{x}_2, \ldots, \hat{x}_{n+1})$, which satisfies

$$\begin{aligned}&f_k(\hat{x}_1, \hat{x}_2, \ldots, \hat{x}_n) = 0 \qquad (k = 1, 2 \ldots, i-1, i+1, \ldots, n),\\ &f_i(\hat{x}_1, \hat{x}_2, \ldots, \hat{x}_n) - b\hat{x}_i - p\hat{x}_{n+1}\hat{x}_i = 0,\\ &\hat{x}_i q(\hat{x}_{n+1}) - m\hat{x}_{n+1} = 0.\end{aligned} \tag{3}$$

Then, for

$$b' = b + p\hat{x}_{n+1}, \tag{4}$$

$\hat{\mathbf{x}} = (\hat{x}_1, \hat{x}_2, \ldots, \hat{x}_n)$ is a positive equilibrium of (2). We use the notation $(\hat{\mathbf{x}}, \hat{x}_{n+1}) = (\hat{x}_1, \hat{x}_2, \ldots, \hat{x}_{n+1})$ and $\mathbf{R}_+^k = \{\, \mathbf{x} \in \mathbf{R}^k \,|\, x_i > 0,\ i = 1, \ldots, k \,\}$ for each positive integer k.

Theorem 2.1. *We assume that the model (2) has a Lyapunov function of the form*

$$U(\mathbf{x}) = \tilde{U}(x_1, \ldots, x_{i-1}, x_{i+1}, \ldots, x_n) + c(x_i - \hat{x}_i \log x_i) \tag{5}$$

around the positive equilibrium $\hat{\mathbf{x}}$, where c is a positive constant. Then we can construct a Lyapunov function for the model (1), which contains an immune variable, around the positive equilibrium $(\hat{\mathbf{x}}, \hat{x}_{n+1})$ in a constructive way.

We assume $z/q(z)$ is strictly increasing at $\hat{x}_{n+1}$. Then if the largest invariant subset of $\{\mathbf{x} \in \mathbf{R}_+^n \,|\, \dot{U}(\mathbf{x}) = \mathbf{0}\,\}$ for the model (2) is the singleton $\{\hat{\mathbf{x}}\}$, the interior equilibrium $(\hat{\mathbf{x}}, \hat{x}_{n+1})$ of (1) is globally asymptotically stable in $\mathbf{R}_+^n$.

Proof. We introduce a function $W(x_{n+1})$, which will be determined later. We put

$$V(\mathbf{x}, x_{n+1}) = U(\mathbf{x}) + W(x_{n+1}), \tag{6}$$

and will find a condition for W that V is a Lyapunov function of (1) around $(\hat{\mathbf{x}}, \hat{x}_{n+1})$. We note that the inequality

$$\nabla U(\mathbf{x}) \cdot \mathbf{g}(\mathbf{x}) \leq 0 \tag{7}$$

holds.

If we calculate the derivative of V along (1), then we have, by (6), (4) and (5),

$$\begin{aligned}
\dot{V}(\mathbf{x}, x_{n+1}) &= \sum_{\substack{k=1\\k\neq i}}^{n} \frac{\partial V}{\partial x_k}(\mathbf{x}, x_{n+1}) f_k(\mathbf{x}) + \frac{\partial V}{\partial x_i}(\mathbf{x}, x_{n+1})(f_i(\mathbf{x}) - bx_i - px_{n+1}x_i) \\
&\qquad + W'(x_{n+1})(x_i q(x_{n+1}) - mx_{n+1}) \\
&= \sum_{\substack{k=1\\k\neq i}}^{n} \frac{\partial U}{\partial x_k}(\mathbf{x}) f_k(\mathbf{x}) + \frac{\partial U}{\partial x_i}(\mathbf{x})(f_i(\mathbf{x}) - bx_i - p\hat{x}_{n+1}x_i) \\
&\qquad + \frac{\partial U}{\partial x_i}(\mathbf{x})(p\hat{x}_{n+1}x_i - px_{n+1}x_i) + W'(x_{n+1})(x_i q(x_{n+1}) - mx_{n+1}) \\
&= \sum_{\substack{k=1\\k\neq i}}^{n} \frac{\partial U}{\partial x_k}(\mathbf{x}) f_k(\mathbf{x}) + \frac{\partial U}{\partial x_i}(\mathbf{x})(f_i(\mathbf{x}) - b'x_i) \\
&\qquad + \frac{\partial U}{\partial x_i}(\mathbf{x})\, p \cdot (\hat{x}_{n+1} - x_{n+1})x_i + W'(x_{n+1})(x_i q(x_{n+1}) - mx_{n+1}) \\
&= \nabla U(\mathbf{x}) \cdot \mathbf{g}(\mathbf{x}) + c\left(1 - \frac{\hat{x}_i}{x_i}\right) p \cdot (\hat{x}_{n+1} - x_{n+1})x_i \\
&\qquad + W'(x_{n+1})q(x_{n+1})\left(x_i - m\frac{x_{n+1}}{q(x_{n+1})}\right).
\end{aligned}$$

Thus, by the last equality $-\hat{x}_i + m\hat{x}_{n+1}/q(\hat{x}_{n+1}) = 0$ of (3),

$$\begin{aligned}
&\dot{V}(\mathbf{x}, x_{n+1}) \\
=&\nabla U(\mathbf{x}) \cdot \mathbf{g}(\mathbf{x}) + cp \cdot (x_i - \hat{x}_i)(\hat{x}_{n+1} - x_{n+1}) + W'(x_{n+1})q(x_{n+1})(x_i - \hat{x}_i) \\
&\qquad + W'(x_{n+1})q(x_{n+1})m\left(\frac{\hat{x}_{n+1}}{q(\hat{x}_{n+1})} - \frac{x_{n+1}}{q(x_{n+1})}\right).
\end{aligned} \tag{8}$$

Since $(x_i - \hat{x}_i)(\hat{x}_{n+1} - x_{n+1})$ is not definite, we determine $W(x_{n+1})$ as it satisfies

$$cp \cdot (x_i - \hat{x}_i)(\hat{x}_{n+1} - x_{n+1}) + W'(x_{n+1})q(x_{n+1})(x_i - \hat{x}_i) = 0,$$

which implies

$$W'(x_{n+1}) = \frac{cp \cdot (x_{n+1} - \hat{x}_{n+1})}{q(x_{n+1})}.$$

Then (8) becomes

$$\dot{V}(\mathbf{x}, x_{n+1}) = \nabla U(\mathbf{x}) \cdot \mathbf{g}(\mathbf{x}) + cpm(x_{n+1} - \hat{x}_{n+1})\left(\frac{\hat{x}_{n+1}}{q(\hat{x}_{n+1})} - \frac{x_{n+1}}{q(x_{n+1})}\right),$$

and we have

$$W(x_{n+1}) = \int_{\hat{x}_{n+1}}^{x_{n+1}} \frac{cp \cdot (\tau - \hat{x}_{n+1})}{q(\tau)}\, d\tau.$$

Since $z/q(z)$ is assumed to be nondecreasing and (7) holds, $\dot{V}(\mathbf{x}, x_{n+1})$ is nonpositive, and thus $V(\mathbf{x}, x_{n+1})$ is a Lyapunov function for (1) around $(\hat{\mathbf{x}}, \hat{x}_{n+1})$.

We assume $z/q(z)$ is strictly increasing at $\hat{x}_{n+1}$. Then $\dot{V}(\mathbf{x}, x_{n+1}) = 0$ implies $x_{n+1} = \hat{x}_{n+1}$. By the assumption for $U(\mathbf{x})$, the largest invariant subset of $\{\mathbf{x} \in \mathbf{R}_+^{n+1} \,|\, \dot{V}(\mathbf{x}) = \mathbf{0}\,\}$ is the singleton $(\hat{\mathbf{x}}, \hat{x}_{n+1})$. By the LaSalle invariance principle, the interior equilibrium $(\hat{\mathbf{x}}, \hat{x}_{n+1})$ of (1) is globally asymptotically stable. □

Remark 1. When $z/q(z)$ is not strictly increasing near $\hat{x}_{n+1}$, we can not use directly Theorem 2.1 for the global stability of (1). But for some specific examples, we can conclude that the interior equilibrium of (2.1) is globally asymptotically stable, using the specific information of (2) and $U(\mathbf{x})$.

We don't consider the existence of interior equilibria in this section. The existence is a nontrivial matter in many cases, and should be proved for each case. Some results on the existence are described in Appendices B, C and D. The uniqueness of the interior equilibrium follows from its global stability.

2.2. **Some specific models.** We apply Theorem 2.1 in Section 2.1 to specific models in infectious diseases in vivo.

We consider the following model incorporating humoral immunity:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \lambda - dx - \varphi(x,v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x,v) - ay, \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= ary - bv - pzv, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = q(z)v - mz. \end{aligned} \tag{9}$$

Humoral immunity works by killing pathogens outside target cells. In Murase *et al.* [11], models incorporating humoral immunity are investigated. The variable x denotes the amount of uninfected cells, y the amount of infected cells, v the amount of pathogens and z the amount of humoral immunity specific to the pathogens. The function $\varphi(x,v)$ is called an incidence function and nonlinear in general. We assume that $\varphi(x,v)$ and $q(z)$ satisfy the following conditions:

1. $\varphi(x,v)$ is continuous, $\varphi(x,v) > 0$, monotonously increasing with respect to x and v respectively, and $\varphi(x,v)/v$ is monotone nonincreasing, for $x > 0$ and $v > 0$.
2. $\varphi(x,0) = 0$, $\varphi(0,v) = 0$ for $x > 0$ and $v > 0$.
3. $q(z)$ is continuous and positive, and $z/q(z)$ is monotonously nondecreasing for $z > 0$.

When $\varphi(x,v)$ is C^2, the above conditions 1. is satisfied if $\varphi(x,v) > 0$, $\varphi_x(x,v) > 0$, $\varphi_v(x,v) > 0$ and $\varphi_{vv}(x,v) \leq 0$ for $x > 0$ and $v > 0$. We state two important cases for $q(z)$ in Appendix A, which are convenient to show the existence of an interior equilibrium.

We put $x_0 = \lambda/d$. We note that the basic reproductive ratio R_0 for the model is given by

$$R_0 = \frac{r}{b}\frac{\partial\varphi}{\partial v}(x_0, 0).$$

Since $z/q(z)$ is monotonously nondecreasing, $\lim_{z\to+0} z/q(z)$ is zero or positive.

In this section, we assume that an interior equilibrium $(\hat{x},\hat{y},\hat{v},\hat{z})$ exists and construct a Lyapunov function of (9). Some results on the existence of an interior equilibrium are described in Appendix B.

As in Section 2.1, we consider the following model without an immune variable corresponding to (1):

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \varphi(x,v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x,v) - ay, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - bv. \tag{10}$$

We note $i = 3$ in Section 2.1 and the right hand side of the third equation contains a term $-bv$. We use the following modified equation:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \varphi(x,v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x,v) - ay, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - (b + p\hat{z})v. \tag{11}$$

We put $\mathbf{y} = (x, y, v)$ and denote by $\mathbf{k}(\mathbf{y})$ the vector field defined by the right hand side of (11). The equation has an interior equilibrium $(\hat{x}, \hat{y}, \hat{v})$.

We define U by

$$\begin{aligned} U(\mathbf{y}) =& x - \int_{\hat{x}}^{x} \frac{\varphi(\hat{x}, \hat{v})}{\varphi(\tau, \hat{v})} \, \mathrm{d}\tau + (y - \hat{y} \log y) + \frac{1}{r}(v - \hat{v} \log v) \\ =& \frac{1}{r}(v - \hat{v} \log v) + \tilde{U}(\mathbf{y}), \end{aligned}$$

and $\tilde{U}$ does not contain the variable v. The function U is a Lyapunov function of (11) at $(\hat{x}, \hat{y}, \hat{v})$. U is essentially the same as that obtained for SEIR model by Korobeinikov [8]. By Korobeinikov [8], it holds that

$$\begin{aligned} &\dot{U}(\mathbf{y}) = \nabla U(\mathbf{y}) \cdot \mathbf{k}(\mathbf{y}) \\ =& - d \left(1 - \frac{\varphi(\tilde{x}, \tilde{v})}{\varphi(x, \hat{v})}\right)(x - \hat{x}) + \varphi(\hat{x}, \hat{v}) \left(4 - \frac{\varphi(\hat{x}, \hat{v})}{\varphi(x, \hat{v})} - \frac{\hat{y}}{y} \frac{\varphi(x, v)}{\varphi(\hat{x}, \hat{v})} - \frac{\hat{v} y}{v \hat{y}} - \frac{v}{\hat{v}} \frac{\varphi(x, \hat{v})}{\varphi(x, v)}\right) \\ &+ \varphi(\hat{x}, \hat{v}) \left(\frac{\varphi(x, v)}{\varphi(x, \hat{v})} - \frac{v}{\hat{v}} - 1 + \frac{v}{\hat{v}} \frac{\varphi(x, \hat{v})}{\varphi(x, v)}\right) \leq 0. \end{aligned}$$

The first term and the third term are nonpositive from the condition of $\varphi(x, v)$, and the second term is nonpositive from the arithmetic-geometric mean inequality. We put $\mathbf{x} = (x, y, v, z)$, and put

$$\begin{aligned} V(\mathbf{x}) =& U(\mathbf{y}) + W(z) \\ =& x - \int_{\hat{x}}^{x} \frac{\varphi(\hat{x}, \hat{v})}{\varphi(\tau, \hat{v})} \, \mathrm{d}\tau + (y - \hat{y} \log y) + \frac{1}{r}(v - \hat{v} \log v) + \int_{\hat{z}}^{z} \frac{p(\tau - \hat{z})}{r q(\tau)} \, d\tau. \end{aligned}$$

Then by Theorem 2.1, $V(\mathbf{x})$ is a Lyapunov function of (9) at $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$.

Using the LaSalle invariance principle, it is shown that the interior equilibrium $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$ is globally asymptotically stable in the first quadrant, and the interior equilibrium is unique if it exists. When the interior equilibrium does not exist, we can show the global stability of the boundary equilibrium using Lyapunov functions.

Now consider the model incorporating cell-mediated immunity

$$\begin{aligned} &\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \varphi(x, v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x, v) - ay - pzy, \\ &\frac{\mathrm{d}v}{\mathrm{d}t} = ary - bv, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = yq(z) - mz. \end{aligned} \tag{12}$$

We assume that $\varphi(x, v)$ and $q(z)$ satisfy the same conditions as in the humoral immunity model (9). For the model (12), R_0 is given in the same form as (9). We assume $R_0 > 1$. We assume the existence of an interior equilibrium $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$. We consider the following modified equation:

$$\begin{aligned} &\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \varphi(x, v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x, v) - (a + p\hat{z})y, \\ &\frac{\mathrm{d}v}{\mathrm{d}t} = ary - bv. \end{aligned} \tag{13}$$

We put $\mathbf{y} = (x, y, v)$, $\mathbf{x} = (x, y, v, z)$. Let $U(\mathbf{y})$ be the Lyapunov function of (13) at $(\hat{x}, \hat{y}, \hat{v})$ in the same form as humoral immunity model. We put

$$W(z) = \int_{\hat{z}}^{z} \frac{\tau - \hat{z}}{q(\tau)} \, \mathrm{d}\tau.$$

Then as in the humoral immunity model (9), $V(\mathbf{x}) = U(\mathbf{y}) + W(z)$ is a Lyapunov function of (12) at the interior equilibrium $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$. The global stability and the uniqueness of the interior equilibrium also hold.

Putting $\varphi(x, v) = \beta xv$, $q(z) = qz$ in (12), we get the following model given by Nowak and Bangham [12]:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \lambda - dx - \beta xv, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xv - ay - pyz, \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= ary - bv, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = qyz - ez. \end{aligned} \tag{14}$$

For (14), R_0 is given by $\lambda\beta r/(bd)$. When $R_0 > 1 + (are\beta)/(bdq)$, it is easy to show that there exists the unique interior equilibrium. Pang *et al.* [13] constructed a Lyapunov function for the interior equilibrium of (14). Their function is also directly obtained by our method in Section 2.1.

We can incorporate both effects of humoral and cell-mediated immunity to the model (10):

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \lambda - dx - \varphi(x, v), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \varphi(x, v) - ay - pyz, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - bv - svw, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= yq(z) - mz, \quad \frac{\mathrm{d}w}{\mathrm{d}t} = vh(w) - nw. \end{aligned} \tag{15}$$

We put $\mathbf{x} = (x, y, v, z, w)$. The variable z denotes the amount of cell-mediated immunity, and w denotes the the amount of humoral immunity. We assume the existence of an interior equilibrium $\hat{\mathbf{x}} = (\hat{x}, \hat{y}, \hat{v}, \hat{z}, \hat{w})$. We define $V(\mathbf{x})$ by

$$\begin{aligned} V(\mathbf{x}) =& x - \int_{\hat{x}}^{x} \frac{\varphi(\hat{x}, \hat{v})}{\varphi(\tau, \hat{v})}\, d\tau + (y - \hat{y}\log y) + \frac{1}{r}(v - \hat{v}\log v) + \int_{\hat{z}}^{z} \frac{p(\tau - \hat{z})}{rq(z)}\, d\tau \\ &+ \int_{\hat{w}}^{w} \frac{s(\tau - \hat{w})}{h(\tau)}\, d\tau. \end{aligned}$$

Then $V(\mathbf{x})$ is a Lyapunov function for (15). Since the calculation is separated for the z variable part and the w variable part, we omit the detail.

There exist many examples of $q(z)$ satisfying the condition 3 in this section. Nowak and Bangham [12] and Murase *et al.* [11] used $q(z) = qz$. Inoue *et al.* [4] used $q(z) = q$, and they constructed Lyapunov functions which are the same forms as ours. A function in the family of functions $q(z) = qz^a$ $(0 < a < 1)$ satisfies the condition for $q(z)$. The family interpolates the known functions $q(z) = qz$ and $q(z) = q$. Especially, $q(z) = q$ is an idealized form of $q(z) = qz^a$ for small a. The function $W(z)$ for $q(z) = qz^a$ is given by

$$W(z) = \frac{1}{q}\left(\frac{1}{2-a}z^{2-a} - \frac{\hat{z}}{1-a}z^{1-a} + \frac{\hat{z}^{2-a}}{(2-a)(1-a)}\right).$$

Gomez-Acevedo and Li [1] used $q(z) = qz/(z + K)$ and considered the following:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \beta xy, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \sigma\beta xy - ay - pyz, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = \frac{qyz}{z + K} - ez,$$

where we use different notations. The interior equilibrium exists if and only if $\sigma\beta\lambda q < a(dq + \beta eK)$. Gomez-Acevedo and Li [1] used the following Lyapunov function:

$$V(x, y, z) = x - \hat{x}\log x + \frac{1}{\sigma}(y - \hat{y}\log y) + \frac{p(\hat{z} + K)}{\sigma q}(z - \hat{z}\log z),$$

and proved by the Lyapunov function that the interior equilibrium is globally stable. Our Lyapunov function is different from theirs, and it is constructed more constructive way.

If the conditions 3 for $q(z)$ in this section is satisfied, an interior equilibrium can be unstable. The following model

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \beta xy, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \sigma\beta xy - ay - pyz, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = yq(z) - ez$$

is considered in Lang and Li [10], where we use different notations. It is shown that for the case $q(z) = z^n/(z^n + K)$ with $n \geq 2$ interior equilibrium can be unstable. In this case, the condition 3 of $q(z)$ in Section 2.2 is not satisfied.

3. Models with absorption effect.

3.1. Model without an immune variable.

When a pathogen infects an uninfected cell, the number of free pathogens decreases by one. We call it the effect of absorption. We consider the following model whose incidence function is of the form $\varphi(x)v$:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - \rho\psi(x)v - bv. \tag{16}$$

The constant $\rho \geq 0$ with $0 \leq \rho < r$ expresses the strength of absorption effect. The case $\rho = 0$ corresponds to the model without absorption effect, the case $\rho = 1$ corresponds to the model with ordinary absorption effect, and the case $1 < \rho < r$ corresponds to the model with multiple absorption. We assume that the continuous function $\psi(x)$ satisfies the following:

1. The function $\psi(x)$ satisfies $\psi(0) = 0$ and strictly increasing for $x > 0$.
2. The function $\psi(x)$ satisfies
$$\left(\frac{\psi(x_1)}{x_1} - \frac{\psi(x_2)}{x_2}\right)(\psi(x_1) - \psi(x_2)) \leq 0 \tag{17}$$
for $x_1 > 0$, $x_2 > 0$.

When $\psi(x)$ is twice differentiable, the second condition is satisfied if $\phi'(x) \geq 0$ and $\phi''(x) \leq 0$ for $x > 0$. Put $x_0 = \lambda/d$. For the model (16), the basic reproductive ratio R_0 is calculated as follows:

$$R_0 = \frac{r\psi(x_0)}{\rho\psi(x_0) + b}.$$

We assume $R_0 > 1$. We show in Appendix C that the interior equilibrium (x^*, y^*, v^*) of (16) exists.

We construct a Lyapunov function of (16) using a Lyapunov function of the equation without absorption effect. We rewrite (16) as follows:

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay,\\ \frac{\mathrm{d}v}{\mathrm{d}t} &= ary - (\rho\psi(x^*) + b)v + \rho(\psi(x^*) - \psi(x))v.\end{aligned}$$

For the construction of a Lyapunov function, we consider the following modified equation:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - (\rho\psi(x^*) + b)v. \tag{18}$$

The model is of the same form as the model without absorption effect, and also has the interior equilibrium (x^*, y^*, v^*). We put $\mathbf{x} = (x, y, v)$ and denote by $\mathbf{k}(\mathbf{x})$ the vector field defined by the right hand side of (18). Following Korobeinikov [8], we define $U(\mathbf{x})$ by

$$U(\mathbf{x}) = \int_{x^*}^{x} \frac{\psi(\xi) - \psi(x^*)}{\psi(\xi)}\, d\xi + (y - y^* \log y) + \frac{1}{r}(v - v^* \log v).$$

The time derivative of $U(\mathbf{x})$ along (18) is shown in Korobeinikov [8] as

$$\begin{aligned}\dot{U}(\mathbf{x}) &= \nabla U(\mathbf{x}) \cdot \mathbf{k}(\mathbf{x}) \\ &= dx^* \left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right) + \psi(x^*)v^* \left(3 - \frac{\psi(x^*)}{\psi(x)} - \frac{v^* y}{v y^*} - \frac{y^* \psi(x) v}{y \psi(x^*) v^*}\right).\end{aligned}$$

The second term is nonpositive by the arithmetic-geometric inequality.

The time derivative $\dot{U}(\mathbf{x})$ along the original equation (16) is

$$\begin{aligned}\dot{U}(\mathbf{x}) &= \nabla U(\mathbf{x}) \cdot \mathbf{k}(\mathbf{x}) + \frac{1}{r}\left(1 - \frac{v^*}{v}\right)(\rho(\psi(x^*) - \psi(x)))v \\ &= \nabla U(\mathbf{x}) \cdot \mathbf{k}(\mathbf{x}) + \frac{\rho}{r}(v - v^*)(\psi(x^*) - \psi(x)).\end{aligned} \tag{19}$$

The sign of the second term is clearly indefinite. To control the sign of the second term above, we use some unknown differentiable function $T(x)$, which will be determined later. The time derivative of $T(x)$ along (16):

$$\begin{aligned}\dot{T}(x) &= T'(x)(\lambda - dx - \psi(x)v) \\ &= T'(x)\left(-d(x - x^*) + (\psi(x^*)v^* - \psi(x)v)\right) \\ &= -dT'(x)(x - x^*) + T'(x)(\psi(x^*)v^* - \psi(x)v)\end{aligned} \tag{20}$$

We add the second term of (20) and the second term of (19):

$$\begin{aligned}&\frac{\rho}{r}(v - v^*)(\psi(x^*) - \psi(x)) + T'(x)(\psi(x^*)v^* - \psi(x)v) \\ =&\frac{\rho}{r}\left((v - v^*)(\psi(x^*) - \psi(x)) + \frac{r}{\rho}T'(x)(\psi(x^*)v^* - \psi(x)v)\right).\end{aligned}$$

To simplifying the second term, we put $(r/\rho)T'(x) = S(x)(\psi(x^*) - \psi(x))$ using an unknown function $S(x)$. Then

$$\begin{aligned}&(v - v^*)(\psi(x^*) - \psi(x)) + \frac{r}{\rho}T'(x)(\psi(x^*)v^* - \psi(x)v) \\ =&(\psi(x^*) - \psi(x))\left((v - v^*) + S(x)(\psi(x^*)v^* - \psi(x)v)\right) \\ =&(\psi(x^*) - \psi(x))\left((1 - S(x)\psi(x))v + (S(x)\psi(x^*) - 1)v^*\right).\end{aligned}$$

If we put $S(x) = 1/\psi(x)$, then the last expression becomes

$$(\psi(x^*) - \psi(x))\left(\frac{\psi(x^*)}{\psi(x)} - 1\right)v^* = \psi(x^*)v^*\left(1 - \frac{\psi(x)}{\psi(x^*)}\right)\left(\frac{\psi(x^*)}{\psi(x)} - 1\right).$$

Then we have

$$T'(x) = \frac{\rho}{r} \cdot \frac{(\psi(x^*) - \psi(x))}{\psi(x)},$$

and if we require $T(x^*) = 0$, we have

$$T(x) = -\frac{\rho}{r}\int_{x^*}^{x} \frac{\psi(\xi) - \psi(x^*)}{\psi(\xi)}\, d\xi.$$

The condition (17) on $\psi(x)$ can be rewritten as:

$$\text{If } x < x^*, \quad \frac{\psi(x)}{\psi(x^*)} \geq \frac{x}{x^*}, \qquad \text{and if } x > x^*, \quad \frac{\psi(x)}{\psi(x^*)} \leq \frac{x}{x^*}.$$

When $x^* < x$, using $\dfrac{\psi(x^*)}{\psi(x)} - 1 < 0$, it holds that

$$\left(1 - \frac{\psi(x)}{\psi(x^*)}\right)\left(\frac{\psi(x^*)}{\psi(x)} - 1\right) \leq \left(1 - \frac{x}{x^*}\right)\left(\frac{\psi(x^*)}{\psi(x)} - 1\right).$$

When $x < x^*$, the same inequality holds. Then it holds that

$$\begin{aligned}&\frac{\rho}{r}\left((v - v^*)(\psi(x^*) - \psi(x)) - \frac{r}{\rho}T'(x)(\psi(x^*)v^* - \psi(x)v)\right)\\ \leq&\frac{\rho v^*\psi(x^*)}{r}\left(1 - \frac{x}{x^*}\right)\left(\frac{\psi(x^*)}{\psi(x)} - 1\right).\end{aligned}$$

Then we have

$$\begin{aligned}&\frac{\rho}{r}(v - v^*)(\psi(x^*) - \psi(x)) + \dot{T}(x)\\ \leq& -\frac{\rho d x^*}{r}\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right) - \frac{\rho v^*\psi(x^*)}{r}\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right).\end{aligned}$$

We put $V(\mathbf{x}) = U(\mathbf{x}) + T(x)$. The time derivative of $V(\mathbf{x})$ along (16) is

$$\begin{aligned}\dot{V}(\mathbf{x}) =&\nabla U(\mathbf{x}) \cdot \mathbf{k}(\mathbf{x}) + \frac{\rho}{r}(v - v^*)(\psi(x^*) - \psi(x)) + \dot{T}(x)\\ \leq& d x^*\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right) - \frac{\rho d x^*}{r}\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right)\\ &- \frac{\rho v^*\psi(x^*)}{r}\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right)\\ &+ \psi(x^*)v^*\left(3 - \frac{\psi(x^*)}{\psi(x)} - \frac{v^* y}{v y^*} - \frac{y^*\psi(x)v}{y\psi(x^*)v^*}\right)\\ =& d x^*\left(1 - \frac{\rho}{r}\left(1 + \frac{v^*\psi(x^*)}{d x^*}\right)\right)\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right)\\ &+ \psi(x^*)v^*\left(3 - \frac{\psi(x^*)}{\psi(x)} - \frac{v^* y}{v y^*} - \frac{y^*\psi(x)v}{y\psi(x^*)v^*}\right).\end{aligned} \tag{21}$$

When $r > \rho\left(1 + \dfrac{v^*\psi(x^*)}{d x^*}\right)$, it holds $\dot{V}(\mathbf{x}) \leq 0$ and $V(\mathbf{x})$ is a Lyapunov function at (x^*, y^*, v^*). We note that

$$V(\mathbf{x}) = \left(1 - \frac{\rho}{r}\right)\int_{x^*}^{x}\frac{\psi(\xi) - \psi(x^*)}{\psi(\xi)}\,d\xi + (y - y^*\log y) + \frac{1}{r}(v - v^*\log v). \tag{22}$$

By the LaSalle invariance principle, if $r > \rho\left(1 + \dfrac{v^*\psi(x^*)}{d x^*}\right)$, it is shown that (x^*, y^*, v^*) is globally stable. When $R_0 \leq 1$, we can show that disease free equilibrium $(\lambda/d, 0, 0)$ is globally stable using a Lyapunov function. We omit the detail.

Remark 2. When $\psi(x) = \beta x$, then the Lyapunov function constructed in this section coincides with that in Iggidr *et al.* [3].

3.2. **Model with absorption containing an immune variable.** We consider models, with absorption effect, which contain an immune variables explicitly. We consider the following model incorporating humoral immunity:

$$\begin{aligned} &\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay, \\ &\frac{\mathrm{d}v}{\mathrm{d}t} = ary - \rho\psi(x)v - bv - pvz, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = vq(z) - mz, \end{aligned} \tag{23}$$

where $\psi(x)$ satisfies the conditions 1 and 2 in Section 3.1, and $q(z)$ satisfies the condition 3 in Section 2.2.

In the section we assume that an interior equilibrium $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$ exists and construct a Lyapunov function of (23) at $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$. The results on the existence of an interior equilibrium are described in Appendix D.

We put $\mathbf{x} = (x, y, v, z)$ and $\mathbf{y} = (x, y, v)$ here. The following model modified from (16)

$$\begin{aligned} &\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay, \\ &\frac{dv}{\mathrm{d}t} = ary - \rho\psi(x)v - (b + p\hat{z})v \end{aligned} \tag{24}$$

is a model with absorption effect and without an immune variable. It has the same form as the model (16) and has $(\hat{x}, \hat{y}, \hat{v})$ as an interior equilibrium. Then by the argument in Section 3.1, the following function $U(\mathbf{y})$

$$U(\mathbf{y}) = \left(1 - \frac{\rho}{r}\right) \int_{\hat{x}}^{x} \frac{\psi(\xi) - \psi(\hat{x})}{\psi(\xi)}\, d\xi + (y - \hat{y}\log y) + \frac{1}{r}(v - \hat{v}\log v)$$

is a Lyapunov function of (24) at $(\hat{x}, \hat{y}, \hat{v})$ if $r > \rho\left(1 + \frac{\hat{v}\psi(\hat{x})}{d\hat{x}}\right)$ holds.

As in Section 2, we define $V(\mathbf{x})$ by

$$\begin{aligned} V(\mathbf{x}) =& U(\mathbf{y}) + W(z) \\ =& \left(1 - \frac{\rho}{r}\right) \int_{\hat{x}}^{x} \frac{\psi(\xi) - \psi(\hat{x})}{\psi(\xi)}\, d\xi + (y - \hat{y}\log y) + \frac{1}{r}(v - \hat{v}\log v) \\ &+ \int_{\hat{z}}^{z} \frac{p(\tau - \hat{z})}{rq(\tau)}\, d\tau. \end{aligned} \tag{25}$$

By the calculation in the proof of Theorem 2.1 and that in 3.1, the derivative of V along (23) satisfies the following inequality:

$$\begin{aligned} \dot{V}(\mathbf{x}) \leq& d\hat{x}\left(1 - \frac{\rho}{r}\left(1 + \frac{\hat{v}\psi(\hat{x})}{d\hat{x}}\right)\right)\left(1 - \frac{\psi(\hat{x})}{\psi(x)}\right)\left(1 - \frac{x}{\hat{x}}\right) \\ &+ \psi(\hat{x})\hat{v}\left(3 - \frac{\psi(\hat{x})}{\psi(x)} - \frac{\hat{v}y}{v\hat{y}} - \frac{\hat{y}\psi(x)v}{y\psi(\hat{x})\hat{v}}\right) + \frac{p\hat{v}z(z - \hat{z})}{rq(\hat{z})}\left(\frac{q(z)}{z} - \frac{q(\hat{z})}{\hat{z}}\right). \end{aligned} \tag{26}$$

When $r > \rho\left(1 + \frac{\hat{v}\psi(\hat{x})}{d\hat{x}}\right)$, it holds that $\dot{V}(\mathbf{x}) \leq 0$ and $V(\mathbf{x})$ is a Lyapunov function at $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$.

Using the LaSalle invariance principle, it is shown that $(\hat{x}, \hat{y}, \hat{v}, \hat{z})$ is globally asymptotically stable.

When the interior equilibrium does not exist, in Appendix E we construct a Lyapunov functions for some boundary equilibria of the model (23) for some cases.

Remark 3. When $\psi(x) = \beta x$ and $q(z) = qz$, a Lyapunov function is obtained in Kajiwara and Sasaki [5]. Similar results are also obtained for cell-mediated immunity model in Kajiwara and Sasaki [5]. Much calculation is needed in [5], but the same results are directly obtained using models without immunity by our method in the present paper.

3.3. **Qesmi** *et al.***'s model.** In this section, using the Lyapunov function constructed for a simple model (16), we can construct a Lyapunov function for a more complex model.

In Qesmi *et al.* [14], the model which explains relapse after a liver transplant is presented:

$$\begin{aligned}\frac{\mathrm{d}x_1}{\mathrm{d}t} =&\lambda_1 - \beta_1 x_1 v - d_1 x_1, \quad \frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 x_1 v - a_1 y_1,\\ \frac{\mathrm{d}x_2}{\mathrm{d}t} =&\lambda_2 - \beta_2 x_2 v - d_2 x_2, \quad \frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 x_2 v - a_2 y_2,\\ \frac{\mathrm{d}v}{\mathrm{d}t} =&k_1 y_1 + k_2 y_2 - \beta_1 x_1 v - \beta_2 x_2 v - bv.\end{aligned} \tag{27}$$

We change the variables of the original model to fit the equation to our paper. The variable x_1 denotes the amount of uninfected liver cells, y_1 infected liver cells, v hepatitis viruses, x_2 uninfected blood cells and y_2 infected blood cells. In the model, hepatitis viruses infect liver cells and blood cells, and the relapse after a liver transplant can occur. Qesmi *et al.*[14] shows that the backward bifurcation can occur in the model. We put $\mathbf{x}_1 = (x_1, y_1, v)$, $\mathbf{x}_2 = (x_2, y_2, v)$ and $\mathbf{x} = (x_1, y_1, x_2, y_2, v)$.

We assume $k_1 > a_1$, $k_2 > a_2$. By Qesmi *et al.* [14], under some assumption, backward bifurcation does not occur. We also assume that $R_0 > 1$. Then it is shown in Qesmi *et al.* [14] that the interior equilibrium $(\hat{x}_1, \hat{y}_1, \hat{x}_2, \hat{y}_2, \hat{v})$ exists.

By the condition of the equilibrium,

$$b = k_1 \frac{\hat{y}_1}{\hat{v}} + k_2 \frac{\hat{y}_2}{\hat{v}} - \beta_1 \hat{x}_1 - \beta_2 \hat{x}_2, \quad \beta_1 \hat{x}_1 \hat{v} = a_1 \hat{y}_1, \quad \beta_2 \hat{x}_2 \hat{v} = a_2 \hat{y}_2.$$

Using these, we have

$$\begin{aligned}&k_1 y_1 + k_2 y_2 - \beta_1 x_1 v - \beta_2 x_2 v - bv\\ =&\left(k_1 y_1 - \beta_1 x_1 v - \frac{(k_1 - a_1)\hat{y}_1}{\hat{v}} v\right) + \left(k_2 y_2 - \beta_2 x_2 v - \frac{(k_2 - a_2)\hat{y}_2}{\hat{v}} v\right).\end{aligned}$$

We consider

$$\begin{aligned}\frac{\mathrm{d}x_1}{\mathrm{d}t} =&\lambda_1 - \beta_1 x_1 v - d_1 x_1, \quad \frac{\mathrm{d}y_1}{\mathrm{d}t} = \beta_1 x_1 v - a_1 y_1,\\ \frac{\mathrm{d}v}{\mathrm{d}t} =&k_1 y_1 - \beta_1 x_1 v - \frac{(k_1 - a_1)\hat{y}_1}{\hat{v}} v.\end{aligned} \tag{28}$$

We denote by $\mathbf{f}_1(\mathbf{x}_1)$ the vector fields given by (28). We also consider

$$\begin{aligned}\frac{\mathrm{d}x_2}{\mathrm{d}t} =&\lambda_2 - \beta_2 x_2 v - d_2 x_2, \quad \frac{\mathrm{d}y_2}{\mathrm{d}t} = \beta_2 x_2 v - a_2 y_2,\\ \frac{\mathrm{d}v}{\mathrm{d}t} =&k_2 y_2 - \beta_2 x_2 v - \frac{(k_2 - a_2)\hat{y}_2}{\hat{v}} v.\end{aligned} \tag{29}$$

We denote by $\mathbf{f}_2(\mathbf{x}_2)$ the vector fields defined by (29). We put

$$\begin{aligned} U_1(\mathbf{x}_1) &= \left(1 - \frac{a_1}{k_1}\right)(x_1 - \hat{x}_1 \log x_1) + (y_1 - \hat{y}_1 \log y_1) + \frac{a_1}{k_1}(v - \hat{v} \log v) \\ U_2(\mathbf{x}_2) &= \left(1 - \frac{a_2}{k_2}\right)(x_2 - \hat{x}_2 \log x_2) + (y_2 - \hat{y}_2 \log y_2) + \frac{a_2}{k_2}(v - \hat{v} \log v) \\ V(\mathbf{x}) &= \left(\frac{k_1}{a_1} - 1\right)(x_1 - \hat{x}_1 \log x_1) + \left(\frac{k_1}{a_1}\right)(y_1 - \hat{y}_1 \log y_1) + v - \hat{v} \log v \\ &\quad + \left(\frac{k_2}{a_2} - 1\right)(x_2 - \hat{x}_2 \log x_2) + \left(\frac{k_2}{a_2}\right)(y_2 - \hat{y}_2 \log y_2). \end{aligned}$$

The model (28) is obtained from the model (16), if we replace x by x_1, y by y_1, λ by λ_1, d by d_1, $\psi(x)$ by $\beta_1 x_1$, a by a_1, r by k_1/a_1, ρ by 1 and b by $(k_1 - a_1)\hat{y}_1/\hat{v}$. The model (29) is obtained from the model (16) similarly.

If the parameters satisfy

$$k_1 > a_1 \left(1 + \frac{\hat{v}\beta_1}{d_1}\right), \; k_2 > a_2 \left(1 + \frac{\hat{v}\beta_2}{d_2}\right), \tag{30}$$

by using the calculation in Section 3.1, $U_1(\mathbf{x}_1)$ is a Lyapunov function for (28) at the interior equilibrium $(\hat{x}_1, \hat{y}_1, \hat{v})$, and $U_2(\mathbf{x}_2)$ is a Lyapunov function for (29) at the interior equilibrium $(\hat{x}_2, \hat{y}_2, \hat{v})$, and then it holds that

$$\dot{U}_1(\mathbf{x}_1) = \nabla U_1(\mathbf{x}_1) \cdot \mathbf{f}_1(\mathbf{x}_1) \le 0, \; \dot{U}_2(\mathbf{x}_2) = \nabla U_2(\mathbf{x}_2) \cdot \mathbf{f}_2(\mathbf{x}_2) \le 0.$$

Then we have

$$\dot{V}(\mathbf{x}) = \nabla V(\mathbf{x}) \cdot \mathbf{f}(\mathbf{x}) = \frac{k_1}{a_1} \nabla U_1(\mathbf{x}_1) \cdot \mathbf{f}_1(\mathbf{x}_1) + \frac{k_2}{a_2} \nabla U_2(\mathbf{x}_2) \cdot \mathbf{f}_2(\mathbf{x}_2) \le 0.$$

Thus $V(\mathbf{x})$ is a Lyapunov function for $(\hat{x}_1, \hat{y}_1, \hat{x}_2, \hat{y}_2, \hat{v})$. By the LaSalle invariance principle, if (30) is satisfied, $(\hat{x}_1, \hat{y}_1, \hat{x}_2, \hat{y}_2, \hat{v})$ is globally asymptotically stable.

In Qesmi *et al.* [14], the global stability result using a Lyapunov function is not obtained.

4. **Concluding remarks.** In the present paper, we propose a systematic method to construct Lyapunov functions of complex models from Lyapunov functions of simpler equations.

It is not easy to construct directly a Lyapunov function of a complex model. From a simple model without absorption effect and without immunity, we construct a Lyapunov function of more complex models step by step. Each step is clear and easy to understand.

We treat models with nonlinear incidence functions with some reasonable assumptions. But it is not easy to construct Lyapunov functions for models with fully general nonlinear incidence functions especially for models with absorption effect. This is remained as the future problem. For many infectious diseases, there exist a lot of strains in pathogen, and we can consider multistrain models of infectious diseases in vivo. We postpone the construction of Lyapunov functions of multistrain models in a forthcoming paper.

Our method has many applications. We can use similar arguments for the construction of Lyapunov functionals on delay differential equations and age-structured equations. We also postpone these problems in a forthcoming paper.

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Appendix.

Appendix A. For the explicit calculation of the existence of an interior equilibrium, we treat the following two important cases for $q(z)$, Case A and Case B.

Case A. The function $z/q(z)$ is strictly increasing, $\lim_{z\to+0} z/q(z) = 0$ and $\lim_{z\to\infty} z/q(z) = \infty$. In the case, we put $s(z) = mz/q(z)$.

Case B. $q(z) = qz$ for some positive constant q.

Appendix B. We present some results on the existence of an interior equilibrium of the model (9) in Section 2.2 for Case A and Case B.

First we consider Case A. We assume that $R_0 > 1$. We follow the argument in [2]. We consider the following equations:

$$\lambda - dx - \varphi(x,v) = 0, \quad \varphi(x,v) - ay = 0, \quad ary - bv - pzv = 0, \quad vq(z) - mz = 0.$$

From the above equations, we have the following equations of x and v using $z = s^{-1}(v)$:

$$\varphi(x,v) - \frac{1}{r}(bv + ps^{-1}(v)v) = 0,$$
$$x = \frac{1}{d}\{\lambda - \varphi(x,v)\} = \frac{1}{d}\left\{\lambda - \frac{1}{r}(bv + pzv)\right\} = \frac{1}{d}\left\{\lambda - \frac{1}{r}(bv + ps^{-1}(v)v)\right\}.$$

Here $s^{-1}(v)$ is the inverse function of $s(z) = mz/q(z)$. There uniquely exists $v_0 > 0$ such that $\lambda - (1/r)(bv_0 + ps^{-1}(v_0)v_0) = 0$, and it holds $\lambda - (1/r)(bv + ps^{-1}(v)v) > 0$ for $0 < v < v_0$. We put

$$H(v) = f\left(\frac{1}{d}\left(\lambda - \frac{1}{r}(bv + ps^{-1}(v)v)\right), v\right) - \frac{1}{r}(bv + ps^{-1}(v)v).$$

Then we have $H(0) = 0$, $H(v_0) = -(1/r)(bv_0 + s^{-1}(v_0)v_0) < 0$, and the right derivative of H at 0

$$\begin{aligned} H'_+(0) =& \frac{\partial f}{\partial v}(x_0, 0) - \frac{\partial f}{\partial x}(x_0, 0)\frac{b}{dr} - \frac{b}{r} \\ =& \frac{\partial f}{\partial v}(x_0, 0) - \frac{b}{r} = \frac{b}{r}R_0 - \frac{b}{r} = \frac{b}{r}(R_0 - 1) > 0. \end{aligned}$$

We note that the right derivative of $(s^{-1})'_+(v)$ at $v = 0$ is 0 from

$$(s^{-1})'_+(v)(0) = \lim_{v\to+0}\frac{s^{-1}(v)}{v} = \lim_{z\to+0}\frac{z}{s(z)} = \lim_{z\to+0}\frac{q(z)}{m} = 0.$$

Then there exists at least one $0 < \hat{v} < v_0$ with $H(\hat{v}) = 0$. We have $\hat{z} = s^{-1}(\hat{v}) > 0$, $\hat{x} = \frac{1}{d}\left\{\lambda - \frac{1}{r}(b\hat{v} + ps^{-1}(\hat{v})\hat{v})\right\}$, $\hat{y} = (1/a)\varphi(\hat{x}, \hat{v})$. Since $\hat{v} < v_0$, we have $\hat{x} > 0$, then $\hat{y} > 0$. We conclude that if $R_0 > 1$, their exists an interior equilibrium.

Next we consider Case B. We consider the following system of equations:

$$\lambda - dx - \varphi(x,v) = 0, \quad \varphi(x,v) - ay = 0, \quad ary - bv - pzv = 0, \quad vqz - mz = 0.$$

Put $\hat{v} = m/q$. Then there exists unique $0 < \hat{x} < \lambda/d$ with $\lambda - d\hat{x} - \varphi(\hat{x}, \hat{v}) = 0$. The third equation is rewritten as $r(\lambda - dx) - bv - pzv = 0$. Then the interior equilibrium exists if and only if $r(\lambda - d\hat{x}) - b\hat{v} > 0$. It is equivalent to each of the following:

$$\hat{x} < \frac{1}{d}\left(\lambda - \frac{bm}{rq}\right) = \overline{x}, \quad \lambda - d\overline{x} - \varphi(\overline{x}, m/q) < 0.$$

Then the interior equilibrium exists if and only if

$$\frac{bm}{rq} < f\left(\frac{1}{d}\left(\lambda - \frac{bm}{rq}\right), \frac{m}{q}\right).$$

Appendix C. We show the existence of the unique interior equilibrium of the model (16). We consider the equations:

$$\lambda - dx - \psi(x)v = 0, \quad \psi(x)v - ay = 0, \quad ary - u\psi(x)v - bv = 0.$$

From the second equation, it follows $y = \psi(x)v/a$. Substituting it to the third equation, we have $\psi(x) = b/(r-\rho)$. Since $R_0 > 1$ is equivalent to $\psi(x_0) > b/(r-\rho)$, there exists a unique x^* with $\psi(x^*) = b/(r-\rho)$ and $0 < x^* < x_0$. We get $v^* = d(x_0 - x^*)/\psi(x^*) > 0$ by the first equation. We also have $y^* = \psi(x^*)v^*/a > 0$. Then (x^*, y^*, v^*) is the unique interior equilibrium.

Appendix D. We show the existence results of an interior equilibrium of the model (23). We treat case A and case B separately. We note that $R_0 = r\psi(x_0)/(\rho\psi(x_0)+b)$ with $x_0 = \lambda/d$.

We consider Case A. We assume $R_0 > 1$. We use $s(z) = mz/q(z)$ and its inverse $s^{-1}(z)$. We consider the following system of equations:

$$\begin{aligned} &\lambda - dx - \psi(x)v = 0, \quad \psi(x)v - ay = 0, \\ &ary - \rho\psi(x)v - bv - pvz = 0, \quad vq(z) - mz = 0. \end{aligned} \tag{31}$$

From these, assuming $v > 0$ we have

$$\psi(x) = \frac{b + pz}{r - \rho}, \quad \frac{\lambda - dx}{\psi(x)} = s^{-1}(z). \tag{32}$$

We not that we assume $\rho < r$. The first equation is rewritten as:

$$z = \frac{r-\rho}{p}\left(\psi(x) - \frac{b}{r-\rho}\right).$$

We note that the function $(\lambda - dx)/\psi(x)$ of x is strictly decreasing for $0 < x$ and

$$\lim_{x\to+0} \frac{\lambda - dx}{\psi(x)} = +\infty, \quad \left.\frac{\lambda - dx}{\psi(x)}\right|_{x=\lambda/d} = 0.$$

On the other hand, the function $\psi(x) - b/(r-\rho)$ is strictly increasing for $0 < x$ and

$$\left.\frac{r-\rho}{p}\left(\psi(x) - \frac{b}{r-\rho}\right)\right|_{x=0} < 0, \quad \left.\frac{r-\rho}{p}\left(\psi(x) - \frac{b}{r-\rho}\right)\right|_{x=\lambda/d} > 0,$$

because $R_0 > 1$. Then the two curves defined by (32) have a unique intersection in $\{\,(x,z)\,|\,0 < x < \lambda/d,\ z > 0\,\}$. There exist a unique $(\hat{x}, \hat{z})$ satisfying (32) with $\hat{x} > 0$, $\hat{z} > 0$. We can determine $\hat{v} > 0$ and $\hat{y} > 0$ from the second and firth equations in (31). We conclude that if $R_0 > 1$, there exists an interior equilibrium. If $R_0 \leq 1$, there exists no interior equilibrium because

$$\left.\frac{r-\rho}{p}\left(\psi(x) - \frac{b}{r-\rho}\right)\right|_{x=\lambda/d} \leq 0.$$

We consider Case B. When $R_0 > 1$, it is shown in Section 3.1 that the model

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \psi(x)v, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \psi(x)v - ay, \quad \frac{\mathrm{d}v}{\mathrm{d}t} = ary - \rho\psi(x)v - bv \tag{33}$$

without z has an interior equilibrium (x^*, y^*, v^*), where

$$\psi(x^*) = b/(r-\rho), \quad v^* = \frac{\lambda - dx^*}{\psi(x^*)}.$$

We consider the following system of equations:

$$\begin{aligned} &\lambda - dx - \psi(x)v = 0, \quad \psi(x)v - ay = 0, \\ &ary - \rho\psi(x)v - bv - pvz = 0, \quad vqz - mz = 0. \end{aligned} \tag{34}$$

If $z > 0$, v must be $v = m/q (= \hat{v})$. For $v = \hat{v}$, since f is strictly increasing and $\psi(0) = 0$, we have a unique $0 < \hat{x} < \lambda/d = x_0$ with $\lambda - d\hat{x} - \psi(\hat{x})\hat{v} = 0$. From the second and third equation of (34), we have $((r-\rho)\psi(x) - b)v = pvz$. Then there exists a positive $\hat{z}$ if and only if $(r-\rho)\psi(\hat{x}) - b > 0$. The inequality shows that $R_0 > 1$, and $(r-\rho)\psi(\hat{x}) - b > 0 = (r-\rho)\psi(x^*) - b = 0$. The condition is equivalent to $\hat{x} > x^*$. The condition $\hat{x} > x^*$ is rewritten as $\lambda - dx^* - \psi(x^*)\hat{v} > 0$, and using $\psi(x^*) = b(r-\rho)$, $\hat{v} = m/q$, and the monotonously of ψ, we can show that it is equivalent to

$$f\left(\frac{1}{d}\left(\lambda - \frac{m}{q}\frac{b}{(r-\rho)}\right)\right) > \frac{b}{r-\rho}. \tag{35}$$

We conclude that there exists an interior equilibrium if and only if (35) is satisfied.

Appendix E. We construct a Lyapunov function for the model (23) for some boundary equilibrium for Case A and Case B, when an interior equilibrium does not exist.

First we consider case A. If $R_0 \le 1$, then the interior equilibrium does not exist. We put

$$V(\mathbf{x}) = \int_{x_0}^{x} \frac{\psi(s) - \psi(x_0)}{\psi(s)}\,ds + \frac{r}{r-\rho}y + \frac{1}{r-\rho}v + \frac{p}{m(r-\rho)}\int_0^z s(\tau)\,d\tau. \tag{36}$$

Then the time derivative of V along (23) is

$$\dot{V}(\mathbf{x}) = -d\left(1 - \frac{\psi(x_0)}{\psi(x)}\right)(x - x_0) + \left(\psi(x_0) - \frac{b}{r-\rho}\right)v - \frac{p}{r-\rho}s(z)z. \tag{37}$$

If $R_0 \le 1$, $\psi(x_0) - b/(r-\rho) \le 0$. Thus the time derivative of $V(\mathbf{x})$ is nonpositive, and $V(\mathbf{x})$ is a Lyapunov function at $(\lambda/d, 0, 0, 0)$.

Next, we consider Case B. For the case where $R_0 \le 1$, exactly the same Lyapunov function as in Case A for $R_0 \le 1$ works. We assume $1 < R_0$ and the inequality (35) does not hold. Then there exists an equilibrium $(x^*, y^*, v^*, 0)$, which corresponds to the interior equilibrium of (33), where $x^* > 0$, $y^* > 0$ and $v^* > 0$. We use the function $V(\mathbf{x})$ in (22), and define $W(\mathbf{x})$ by

$$W(\mathbf{x}) = \left(1 - \frac{\rho}{r}\right)\int_{x^*}^{x} \frac{\psi(\xi) - \psi(x^*)}{\psi(\xi)}\,d\xi + (y - y^*\log y) + \frac{1}{r}(v - v^*\log v) + \frac{p}{rq}z. \tag{38}$$

Then by (21) the time derivative $\dot{W}(\mathbf{x})$ is

$$\begin{aligned}\dot{W}(\mathbf{x}) =& dx^* \left(1 - \frac{\rho}{r}\left(1 + \frac{v^*\psi(x^*)}{dx^*}\right)\right)\left(1 - \frac{\psi(x^*)}{\psi(x)}\right)\left(1 - \frac{x}{x^*}\right) \\ &+ \psi(x^*)v^*\left(3 - \frac{\psi(x^*)}{\psi(x)} - \frac{v^*y}{vy^*} - \frac{y^*\psi(x)v}{y\psi(x^*)v^*}\right) + \frac{p}{r}(v^* - \hat{v})z.\end{aligned} \tag{39}$$

When (35) is not satisfied, we have $v^* < \hat{v}$. Hence under the condition $r > \rho\left(1 + v^*\psi(x^*)/(dx^*)\right)$, it holds that $\dot{W}(\mathbf{x}) \leq 0$, and $W(\mathbf{x})$ is a Lyapunov function at $(x^*, y^*, v^*, 0)$. It is shown that $(x^*, y^*, v^*, 0)$ is globally asymptotically stable.

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E-mail address: kajiwara@ems.okayama-u.ac.jp
E-mail address: sasaki@ems.okayama-u.ac.jp
E-mail address: takeuchi@gem.aoyama.ac.jp