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Stability Analysis of Viral Dynamics Model with Intracellular Delay and Immune Activation Delay

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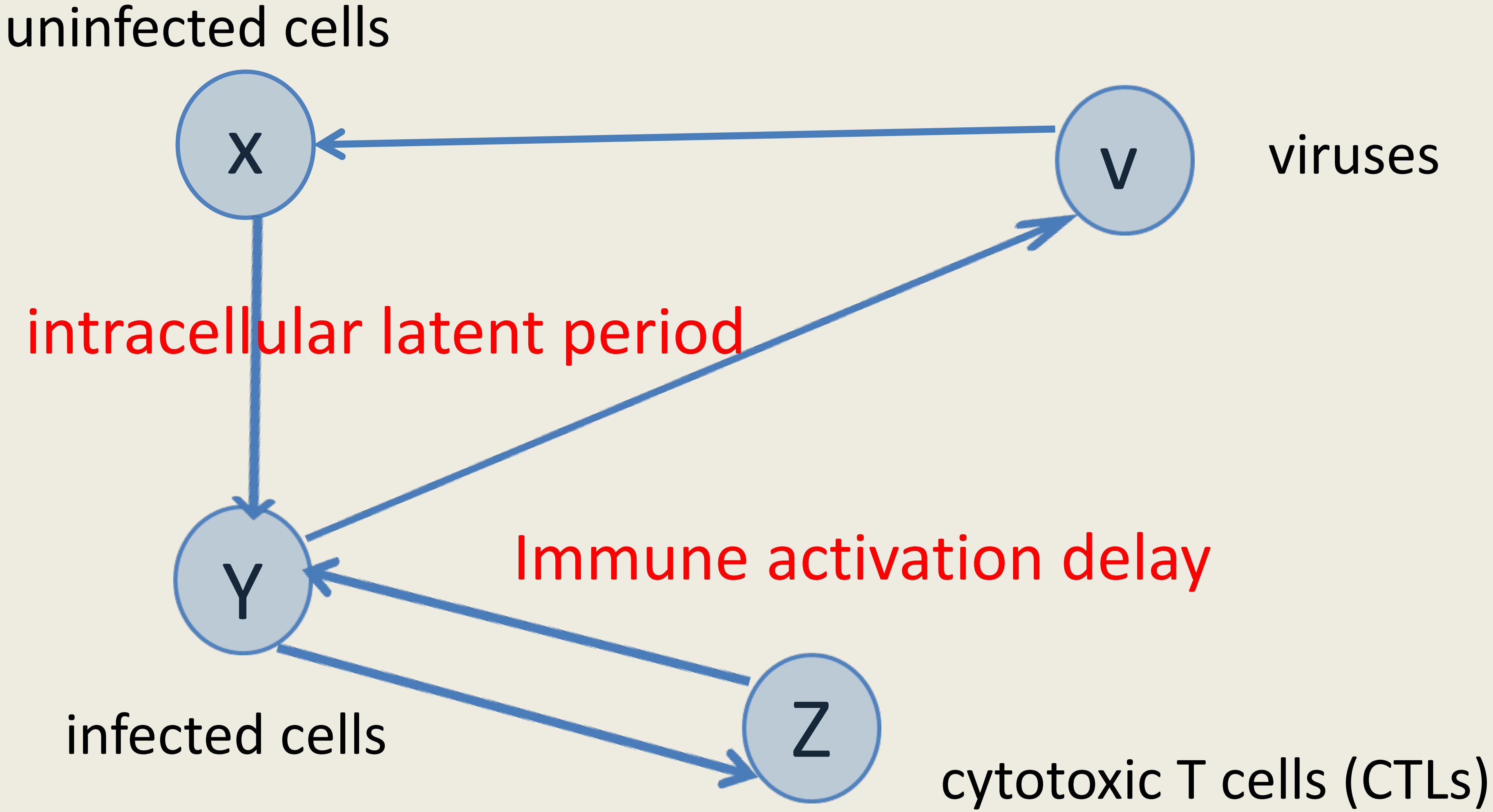
a class of viral infection models with two type discrete delays,



uninfected cells

x

v

viruses

intracellular latent period

y

Immune activation delay

infected cells

z

cytotoxic T cells (CTLs)

1. Model: 1.1: A standard virus dynamics

Nowak and Bangham , Nelson and Perelson

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \beta x(t)\,v(t) \\ \dot{y}(t) &= \beta x(t)\,v(t) - py(t) \\ \dot{v}(t) &= ky(t) - uv(t) \end{aligned} \tag{1.1}$$

- $x(t)$: the concentration of uninfected cells,
- $y(t)$: the concentration of infected cells that produce virus,
- $v(t)$: the concentration of viruses
- $s(s > 0)$: the rate at which new healthy cells are generated.
- $d(d > 0)$: the death rate of uninfected cells
- $\beta(\beta > 0)$: the rate constant characterizing infection of the cells
- $p(p > 0)$: the death rate of the infected due either to virus or immune
- $k(k > 0)$: virsus production rate from the infected cells
- $u(u > 0)$: the rate at which virus particles are removed from the system.

1.2: a nonlinear infection rate

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \underline{\beta x(t)\, v(t)} \\ \dot{y}(t) &= \underline{\beta x(t)\, v(t)} - py(t) \\ \dot{v}(t) &= ky(t) - uv(t) \end{aligned} \qquad (1.1)$$

$$\beta x(t)\, v(t) \longrightarrow g(x(t); v(t)) = \frac{\beta x(t)\, v(t)}{1+\alpha x(t)} \quad (\alpha \geq 0)$$

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \underline{g(x(t); v(t))} \\ \dot{y}(t) &= \underline{g(x(t); v(t))} - py(t) \\ \dot{v}(t) &= ky(t) - uv(t) \end{aligned}$$

★ $\alpha = 0$: $g(x(t); v(t)) = \beta x(t)\, v(t)$

1.3: latent period between the time target cells are infected and the time infected cells start producing virus.

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}$$

$$\dot{y}(t) = e^{-d\tau} \frac{\beta x(t-\tau)\, v(t-\tau)}{1+\alpha x(t-\tau)} - py(t) \qquad (1.2)$$

$$\dot{v}(t) = ky(t) - uv(t)$$

- $e^{-d\tau}$: the survival probability of infected cells during the latent period τ.

1.4: activation rate of CTLs response at time *t* may depend on the population of antigen at time $t-\omega$

$$
\begin{aligned}
\dot{x}(t) &= s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)} \\
\dot{y}(t) &= e^{-d\tau} \frac{\beta x(t-\tau)\, v(t-\tau)}{1+\alpha x(t-\tau)} - py(t) - \underline{ay(t)z(t)} \\
\dot{v}(t) &= ky(t) - uv(t) \qquad (1.3) \\
\underline{\dot{z}(t)} &\underline{= f(y_t, z_t) - bz(t)}
\end{aligned}
$$

$z(t)$: the population of CTLs,

- Case I : $f(y_t, z_t) = cy(t-\omega)z(t-\omega)$ (1.4)

  antigenic stimulation generating CTLs needs a period of time ω

- Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$ (1.5)

  immune system needs some time ω to develop a suitable response after the recognition of non-self cells.

2: Equilibria and stability of model without delay

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}, \quad \dot{y}(t) = \frac{\beta x(t)\, v(t)}{1+\alpha x(t)} - py(t) - ay(t)z(t)$$

$$\dot{v}(t) = ky(t) - uv(t), \qquad \dot{z}(t) = cy(t)z(t) - bz(t) \qquad (2.1)$$

an infection free equilibrium $E0 = (x0; 0; 0; 0)$, where $x0 = s/d$,

an immune free equilibrium $E1 = (x1; y1; v1; 0)$ when $R0>1$

$$x1 = \frac{pu}{k\beta - \alpha pu}, y1 = \frac{(s\alpha + d)u}{k\beta - \alpha pu}(R0 - 1), v1 = \frac{(s\alpha + d)k}{k\beta - \alpha pu}(R0 - 1)$$

$$R0 = \frac{sk\beta}{(s\alpha+d)pu}$$: basic reproductive number of viruses

immune presence equilibrium

$E^* = (x^*; y^*; v^*; z^*)$ when $R1>1$

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}, \quad \dot{y}(t) = \frac{\beta x(t)\, v(t)}{1+\alpha x(t)} - py(t) - ay(t)z(t)$$

$$\dot{v}(t) = ky(t) - uv(t), \qquad \dot{z}(t) = cy(t)z(t) - bz(t) \qquad (2.1)$$

$$x^* = \frac{2s}{\sqrt{(d - \frac{bk\beta}{cu} - \alpha s)^2 + 4\alpha ds} + (d - \frac{bk\beta}{cu} - \alpha s)}$$

$$y^* = b/c, \;\; v^* = bk/cu, \;\; z^* = c(s - dx^*)/ab - p/a$$

$$R1 = R0 - \frac{b(k\beta - \alpha pu)}{(s\alpha + d)cu} > 1$$

$\leftrightarrow 1 < cy_1/b$: basic immune reproductive number

$R0 = \frac{sk\beta}{(s\alpha+d)pu}$: basic reproductive number of viruses

2.1: global stability of the ODEs model

Theorem 1 *(i) When R0 ≤1, E0(x0; 0; 0; 0) is GAS;*
(ii) When R0 > 1 ≥ R1, E1(x1; y1; v1; 0) is GAS;
(iii) When R1 > 1, E(x*; y*; v*; z*) is GAS.*

Proof. (i) Lyapunov function

$$V_1 = x - \int_{x0}^{x} \frac{x0}{1+\alpha x0}\frac{1+\alpha\eta}{\eta}\,d\eta + y + \frac{p}{k}v + \frac{a}{c}z$$

$$\frac{dV_1(t)}{dt} = -\frac{d}{x(1+\alpha x0)}(x-x0)^{2} + \frac{pu}{k}(R0-1)v - \frac{ab}{c}z$$

(ii) Lyapunov function

$$V_2 = x - \int_{x1}^{x} \frac{x1}{1+\alpha x1}\frac{1+\alpha\eta}{\eta}\,d\eta + \underline{y - y1\ln\frac{y}{y1}} + \underline{\frac{p}{k}\left(v - v1\ln\frac{v}{v1}\right)} + \frac{a}{c}z$$

$$\frac{dV_2(t)}{dt} = -\frac{d}{x(1+\alpha x1)}(x-x1)^{2}$$
$$+py1\left(3 - \frac{x1(1+\alpha x)}{x(1+\alpha x1)} - \frac{xy1v(1+\alpha x1)}{x1yv1(1+\alpha x)} - \frac{yv1}{y1v}\right) + az\left(y1 - \frac{b}{c}\right)$$

arithmetical mean ≥ geometrical mean

$R0 > 1 \geq R1 \leftrightarrow 1 > cy_1/b$

Theorem 1 *(iii) When R1 > 1, E*(x*; y*; v*; z*) is GAS.*

Proof. (iii) Lyapunov function

$$V_3 = x - \int_{x^*}^{x} \frac{x^*}{1+\alpha x^*}\frac{1+\alpha\eta}{\eta}\,d\eta + y - y^* ln\frac{y}{y^*} + \frac{p+az^*}{k}\left(v - v^* ln\frac{v}{v^*}\right) + \underline{\frac{a}{c}\left(z - z^* ln\frac{v}{z^*}\right)}$$

$$\frac{dV_3(t)}{dt} = -\frac{d}{x(1+\alpha x^*)}(x - x^*)^{\,2}$$

$$+ (py^* + ay^*z^*)\left(3 - \frac{x^*(1+\alpha x)}{x(1+\alpha x^*)} - \frac{xy^*v(1+\alpha x^*)}{x^*yv^*(1+\alpha x)} - \frac{yv^*}{y^*v}\right)$$

arithmetical mean $\geq$ geometrical mean

Theorem 1 *(i) When $R0 \leq 1$, $E0(x0; 0; 0; 0)$ is GAS;*
(ii) When $R0 > 1 \geq R1$, $E1(x1; y1; v1; 0)$ is GAS;
(iii) When $R1 > 1$, $E^*(x^*; y^*; v^*; z^*)$ is GAS.

- $\beta x(t)\, v(t)$ ↔ $g(x(t); v(t)) = \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}$ when $\alpha=0$

- Nowak and Bangham model ($\alpha=0$) : global stability was proven by Kajiwara and Sasaki[12] and Pang etal [24].

- Theorem 1: nonlinear incidence rate does not affect the stability but change the basic reproductive number and the immune reproductive number.

  $R0 = \frac{sk\beta}{(s\alpha+d)pu}$ becomes smaller for $\alpha>0$.

- Korobeinikov[14,15,16]: gave a plenty of researches on Lyapunov functions and global stability for the ODEs models in vivo with nonlinear or bilinear rate recently. The Lyapunov functions in the proof of Theorem 1 is similar to Korobeinikov type functions.

3: Delay differential equations model

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}$$

$$\dot{y}(t) = e^{-d\tau}\frac{\beta x(t-\tau)\, v(t-\tau)}{1+\alpha x(t-\tau)} - py(t) - ay(t)z(t) \qquad (3.1)$$

$$\dot{v}(t) = ky(t) - uv(t), \qquad \dot{z}(t) = f(y_t, z_t) - bz(t)$$

Case I : $f(y_t, z_t) = cy(t-\omega)z(t-\omega)$
Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$

$x(\theta)=\varphi_1(\theta)$, $y(\theta)=\varphi_2(\theta)$, $v(\theta)=\varphi_3(\theta)$, $z(\theta)=\varphi_4(\theta)$,
for $\forall\theta \in [-\max\{\tau,\omega\}, 0]$ (3.2)
where$\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4)$
$\in C_+ = \{\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in C : \varphi_i \geq 0$ for $\forall\theta \in [-\max\{\tau,\omega\}, 0]\}$
C: the Banach space of continuous functions
$\varphi : [-\max\{\tau,\omega\}, 0] \to R^4$ with sup-norm

3.1: Basic Properties of DDE

Proposition 3.1.

The solution of system (3.1) exists for all $t \geq 0$*, and each variable is non-negative for every* $t > 0$*. Moreover, it holds that* $x(t) > 0$ *for all* $t > 0$*, that* $y(t) > 0$ *and* $v(t) > 0$ *for all* $t > 0$ *if* $y(0) > 0$ *or* $v(0) > 0$*, and that* $z(t) > 0$ *for all* $t > 0$ *if* $z(0) > 0$*.*

Proposition 3.2.

There exists a bounded region $\boldsymbol{\Omega}$ *in the first quadrant of* R4 *such that for each initial condition (3.2), there exists a* $T > 0$ *such that* $(x(t); y(t); v(t); z(t))$ *is contained in* $\boldsymbol{\Omega}$ *for all* $t \geq T$*.*

basic reproductive number and the immune reproductive number for DDE

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}$$

$$\dot{y}(t) = e^{-d\tau} \frac{\beta x(t-\tau)\, v(t-\tau)}{1+\alpha x(t-\tau)} - py(t) - ay(t)z(t)$$

$$\dot{v}(t) = ky(t) - uv(t) \tag{1.3}$$

$$\dot{z}(t) = f(y_t, z_t) - bz(t)$$

Case I : $f(y_t, z_t) = cy(t-\omega)z(t-\omega)$ $\quad$ (1.4)

Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$ $\quad$ (1.5)

$R0^* = \dfrac{sk\beta e^{-d\tau}}{(s\alpha+d)pu}$: basic reproductive number of viruses

$R1^* = R0^* - \dfrac{b(k\beta-\alpha pue^{d\tau})}{(s\alpha+d)cu}$: immune reproductive number

3.2: Stability analysis of the infection-free equilibrium

Theorem 2 : *If* $R0^* < 1$*, E0 is LAS in system (1.3) for Case I or II. Further, E0 of (1.3) in Case I is GAS for any delay* $\tau > 0$ *and* $\omega > 0$ *when* $R0^* \leq 1$*.*

Proof.

LAS: $(\lambda + d)\,(\lambda + b)\,(\lambda^2 + (p + u)\lambda + pu - \frac{k\beta x0}{1+\alpha x0} e^{-d\tau} e^{-\lambda\tau})=0$

GAS: Lyapunov functional

$$U_1 = e^{-d\tau}\left(x - \int_{x0}^{x} \frac{x0}{1+\alpha x0}\frac{1+\alpha\eta}{\eta}\,d\eta\right) + y + \frac{p}{k}v + \frac{a}{c}z$$

$$+\beta e^{-d\tau}\int_0^{\tau}\frac{x(t-\eta)y(t-\eta)}{1+\alpha x(t-\eta)}\,d\eta + \int_0^{\omega} ay(t-\eta)z(t-\eta)\,d\eta$$

$$\frac{dU_1(t)}{dt} = -\frac{de^{-d\tau}}{x(1+\alpha x0)}(x - x0)^2 + \frac{pu}{k}(R0^* - 1)v - \frac{ab}{c}z$$

3.3: Stability analysis of the immune-free equilibrium

Theorem 3 : *If $R1^* < 1 < R0^*$, E1 is LAS in system (1.3) for Case I or II.*

E1 of (1.3) in Case I is GAS for for any $\tau > 0$ and $\omega > 0$ when $R1^* \le 1 < R0^*$.

Proof. GAS: Lyapunov functional

$$U_2 = \widetilde{V_2} + \underline{py1U^+ + \int_0^\omega ay(t-\eta)z(t-\eta)d\eta}$$

$$\widetilde{V_2} = e^{-d\tau}\left(x - \int_{x1}^{x}\frac{x1}{1+\alpha x1}\frac{1+\alpha\eta}{\eta}d\eta\right) + y - y1ln\frac{y}{y1} + \frac{p}{k}(v - v1ln\frac{v}{v1}) + \frac{a}{c}z$$

$$\underline{U^+ = \int_0^\tau\{\frac{x(t-\eta)y(t-\eta)}{1+\alpha x(t-\eta)}\frac{1+\alpha x1}{x1v1} - 1 - ln\frac{x(t-\eta)y(t-\eta)}{1+\alpha x(t-\eta)}\frac{1+\alpha x1}{x1v1}\}d\eta}$$

$$\frac{dU_2(t)}{dt} = -\frac{de^{-d\tau}}{x(1+\alpha x1)}(x-x1)^2 + az\left(y1 - \frac{b}{c}\right)$$

$$+py1(1 - \underline{\frac{x1(1+\alpha x)}{x(1+\alpha x1)} + ln\frac{x1(1+\alpha x)}{x(1+\alpha x1)}}) + py1(1 - \underline{\frac{yv1}{y1v} + ln\frac{yv1}{y1v}})$$

$$+py1\underline{(1 - \frac{y1}{y}\frac{1+\alpha x1}{x1v1}\frac{x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)} + ln\frac{y1}{y}\frac{1+\alpha x1}{x1v1}\frac{x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)})}$$

★$\underline{H(t) = 1 - f(t) + lnf(t) \le 0 \text{ for } \forall\, f(t) > 0,\ H(t) = 0 \leftrightarrow f(t) = 1}$

4: Dynamical analysis for the interior equilibrium :

Global stability of the interior equilibrium when $\tau > 0$ and $\omega = 0$

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}, \quad \dot{y}(t) = e^{-d\tau}\frac{\beta x(t-\tau)\, v(t-\tau)}{1+\alpha x(t-\tau)} - py(t) - ay(t)z(t)$$

$$\dot{v}(t) = ky(t) - uv(t), \qquad \dot{z}(t) = cy(t)z(t) - bz(t)$$

Theorem 4:

If $\omega = 0$ and $R1^* > 1$, E^* of (1.3) is GAS any $\tau > 0$.

Remark 2:

In [32], Zhu and Zou considered the model for a special case $\alpha = 0$ (mass action law), and the local stability of the interior equilibrium E^* is obtained, but its global stability is left as an open question.

Proof of Theorem 4

Theorem 4: *If $\omega = 0$ and $R1^* > 1$, E^* of (1.3) is GAS any $\tau > 0$.*

$$U_3 = e^{-d\tau}\left(x - \int_{x^*}^{x} \frac{x^*}{1+\alpha x^*}\frac{1+\alpha\eta}{\eta}d\eta\right) + y - y^* ln\frac{y}{y^*} + \frac{p+az^*}{k}\left(v - v^* ln\frac{v}{v^*}\right)$$

$$+\frac{a}{c}\left(z - z^* ln\frac{z}{z^*}\right) + \underline{(p+az^*)U\_(t)}$$

$$\underline{U\_ = \int_0^\tau \{\frac{x(t-\eta)y(t-\eta)}{1+\alpha x(t-\eta)}\frac{1+\alpha x^*}{x^*v^*} - 1 - ln\frac{x(t-\eta)y(t-\eta)}{1+\alpha x(t-\eta)}\frac{1+\alpha x^*}{x^*v^*}\}d\eta}$$

$$\frac{dU_3(t)}{dt} = -\frac{de^{-d\tau}}{x(1+\alpha x^*)}(x-x^*)^{2} + (py^*+ay^*z^*)(\underline{1-\frac{yv^*}{y^*v}+ln\frac{yv^*}{y^*v})}$$

$$+(py^*+ay^*z^*)\left(\underline{1-\frac{x^*(1+\alpha x)}{x(1+\alpha x^*)}+ln\frac{x^*(1+\alpha x)}{x(1+\alpha x^*)}}\right)$$

$$+(py^*+ay^*z^*)(1\underline{-\frac{y^*}{y}\frac{1+\alpha x^*}{x^*v^*}\frac{x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)}+ln\frac{y^*}{y}\frac{1+\alpha x^*}{x^*v^*}\frac{x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)})}$$

★$\underline{H(t) = 1 - f(t) + lnf(t) \le 0 \text{ for } \forall f(t) > 0,\ H(t) = 0 \leftrightarrow f(t) = 1}$

4.1: Existence of stability switch when $\tau = 0$ and $\omega > 0$

$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)\, v(t)}{1+\alpha x(t)}$, $\dot{y}(t) = \frac{\beta x(t)\, v(t)}{1+\alpha x(t)} - py(t) - ay(t)z(t)$

$\dot{v}(t) = ky(t) - uv(t)$, $\dot{z}(t) = f(y_t, z_t) - bz(t)$

- Case I : $f(y_t, z_t) = cy(t-\omega)z(t-\omega)$
- Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$

Theorem 5 : *(i) For case I, the stability switch happens at E* as ω increases from zero when the parameters satisfy*

$$\frac{\beta bk(2p+az^*)}{cu(1+\alpha x^*)} < daz^*.$$

(ii) For case II, the stability switch happens at E as ω increases from zero for almost parameters.*

Remark

Li and Shu [18]: a mathematical model of CTL response to HTLV-I infection, which is similar to a special case of our model (1.3) (α=0) with case I.

- Explicit simulation given in [18] describes the coexistence of stable periodic solutions for the same ω.

5. Numerical simulations

- fix the parameter values as

$s = 10.0; d = 0.1; \beta = 0.2; \alpha = 0.01; p = 0.02;$

$a = 10.0; b = 1.0; c = 0.5; k = 1.0; u = 1.0$

- change two delays τ and ω.
- fix the initial values as constant

$x(\theta) = 20; y(\theta) = 1; v(\theta) = 0.1; z(\theta) = 0.1$

for $\theta \in [-\max\{\tau, \omega\}, 0]\}$

Theorem 4: for the infection process without immune activation delay (ω=0) but with intracellular delay τ, *E** is GAS when it exists.

- However

$R0^* = \frac{sk\beta e^{-d\tau}}{(s\alpha+d)pu}$: basic reproductive number of viruses

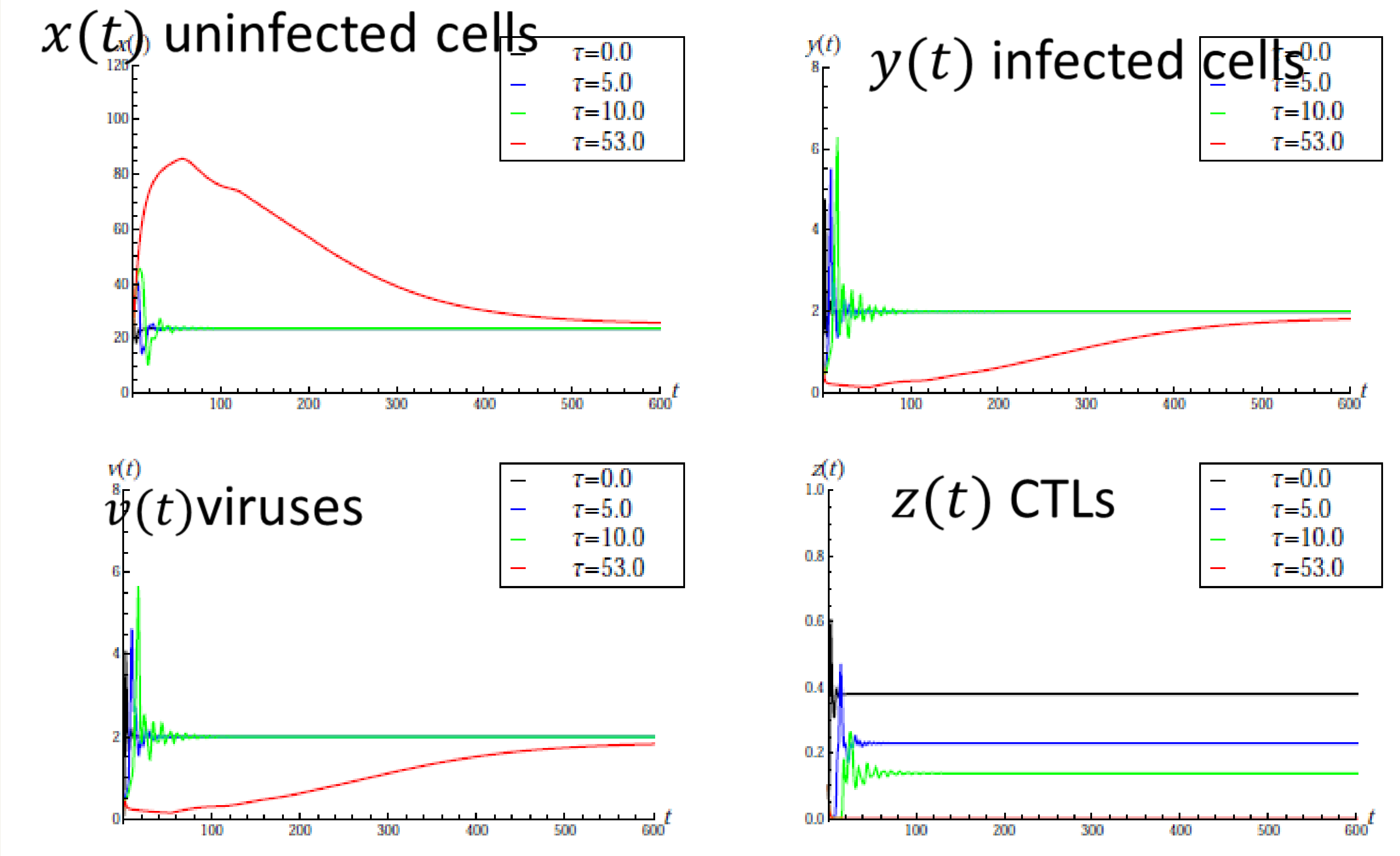
$R1^* = R0^* - \frac{b\left(k\beta - \alpha pue^{d\tau}\right)}{(s\alpha+d)cu}$: immune reproductive number

decreasing functions for $\tau < \frac{1}{2d} ln \frac{cks\beta}{b\alpha up^2}$

- If τ is large enough, the interior equilibrium would disappear and the load of virus would become zero.

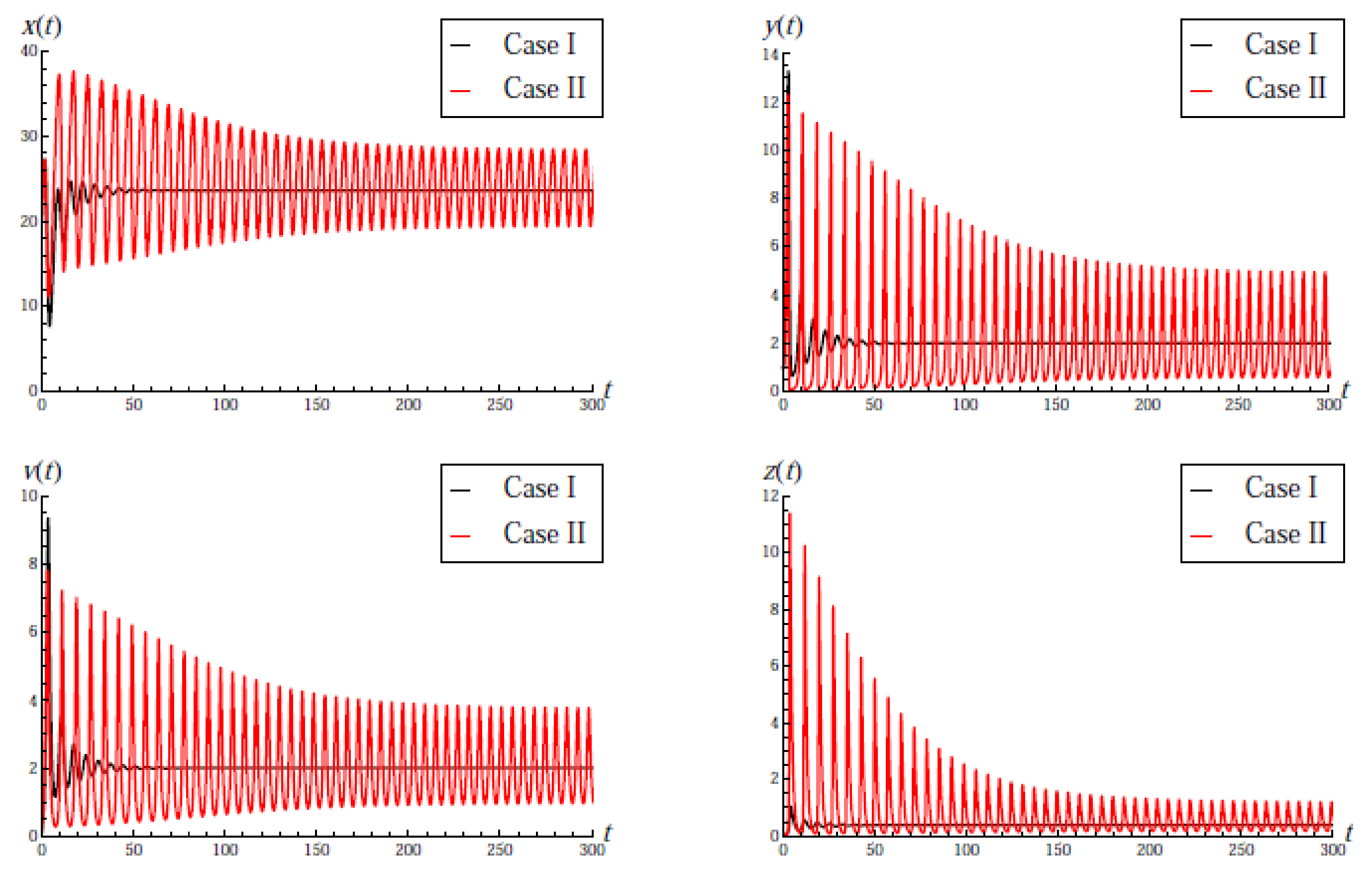
$Fig.1$: impact of the intracellular delay

ω=0, $\tau = 0$; 5.0; 10.0; 53.0



- ★ E^* is GAS for $\tau = 0;\ 5.0; 10.0$: $E1$ is GAS for $\tau = 53.0$.
- ★ z^* is decreasing with respect to τ.

$Fig.$ 2: Comparison Case I (black) and Case II(red) when τ= 0 and ω= 0.57

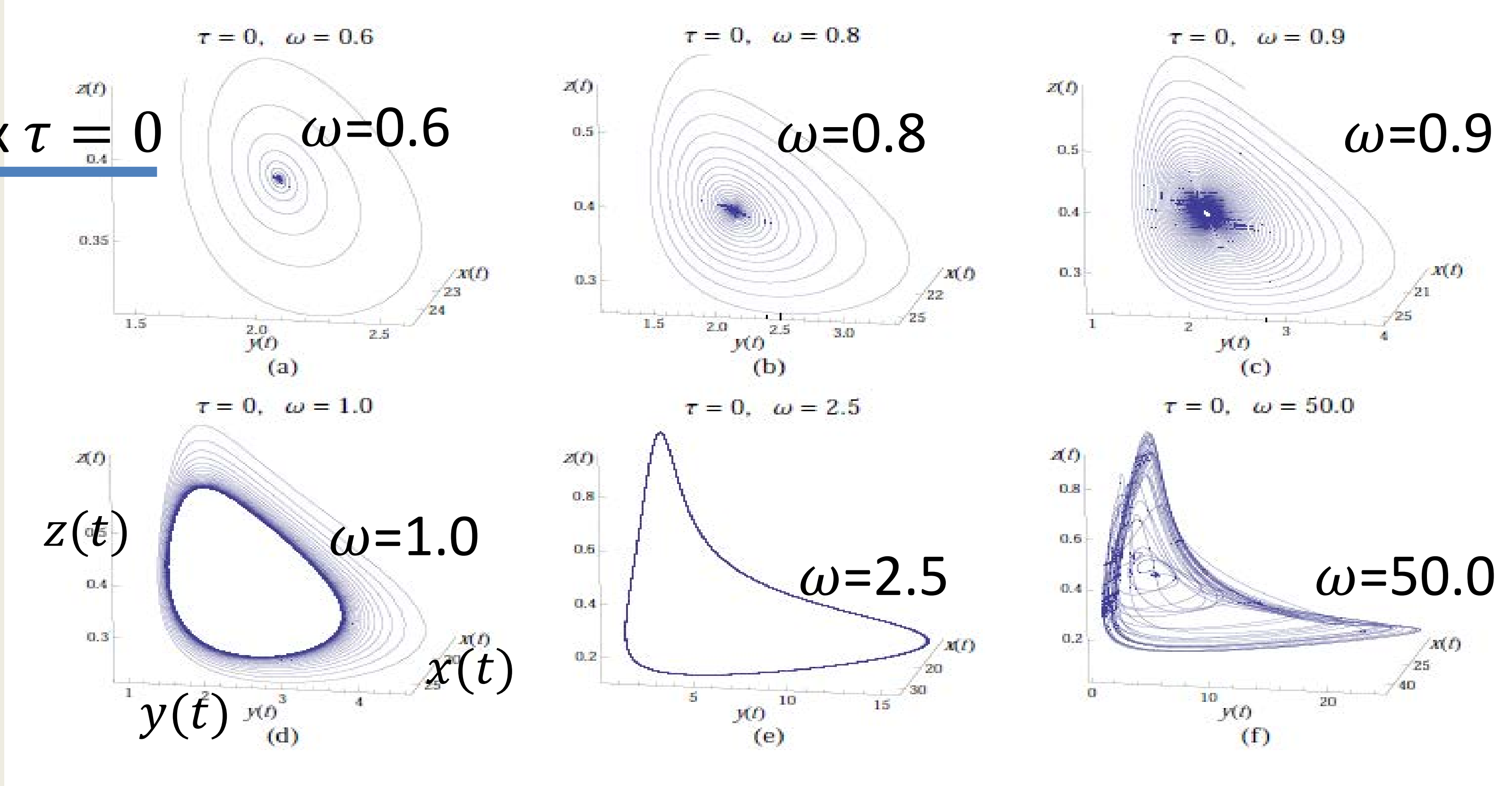


★ E^* is GAS for Case I. Periodic solution for Case II.

Case I : $f(y_t, z_t) = cy(t-\omega)z(t-\omega)$: Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$

$Fig.3$: immune activation delay ω for Case Ⅰ

Fix $\tau = 0$

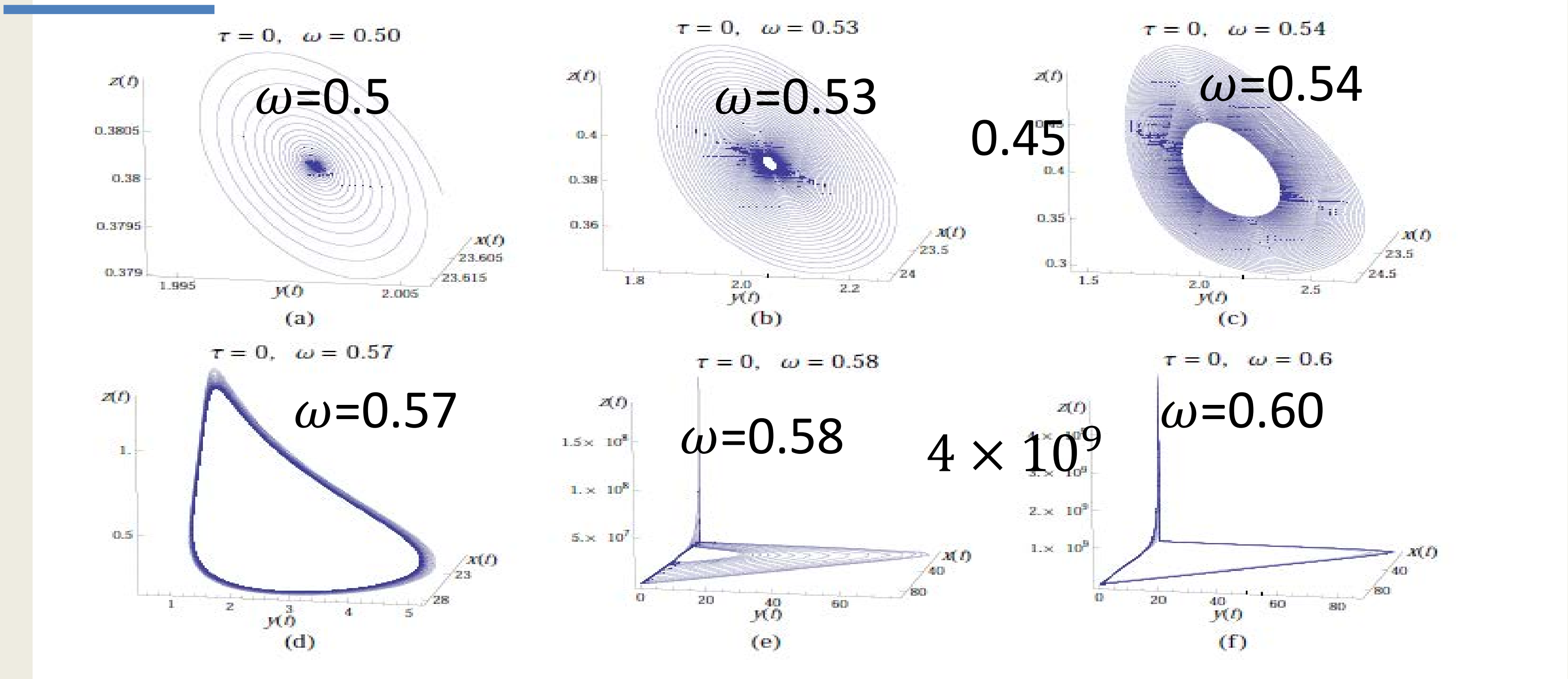


Stability switch at a positive threshold ω_0 ∈(0.8, 0.9).
GAS solution changes to an asymptotically stable periodic solution with the increasing of ω.

Case I : $f(y_t, z_t)$ = $cy(t-\omega)z(t-\omega)$

$Fig.4$: immune activation delay ω for Case II

Fix $\tau = 0$



ω=0.5

ω=0.53

0.45

ω=0.54

ω=0.57

ω=0.58

4×10^9

ω=0.60

Stability switch also happens when ω increases from 0.5 to 0.53.

The time that stability switch happens is earlier in Case II than in I.

After periodic solutions appear and their amplitudes increase.

For further increasing of ω, periodic orbit becomes more twisty.

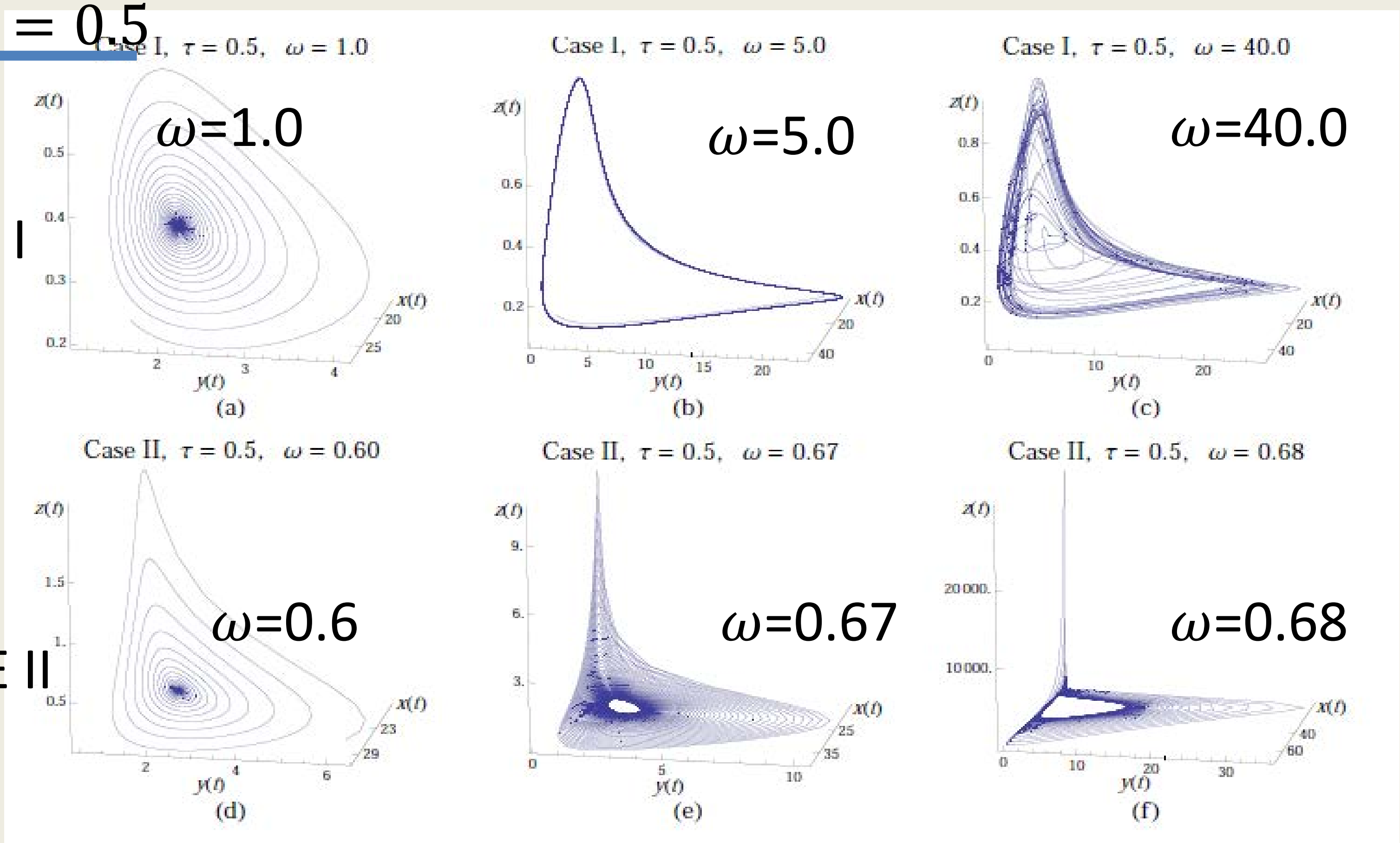
Case II : $f(y_t, z_t) = cy(t-\omega)z(t)$

$Fig. 5$: the dynamics of the model with two delays

Fix $\tau = 0.5$

CASE I

CASE II



ω=1.0

ω=5.0

ω=40.0

ω=0.6

ω=0.67

ω=0.68

delay τ can prolong the stability switch with respect to ω.

τ= 0: a stability switch occurs at ω in (0.8,0.9) for Case I and in (0.5,0.53) for Case II.

τ= 0.5, the switch occurs ω> 1 for Case I and ω> 0.6 for Case II.

Results

1. the global stability of the ODEs model

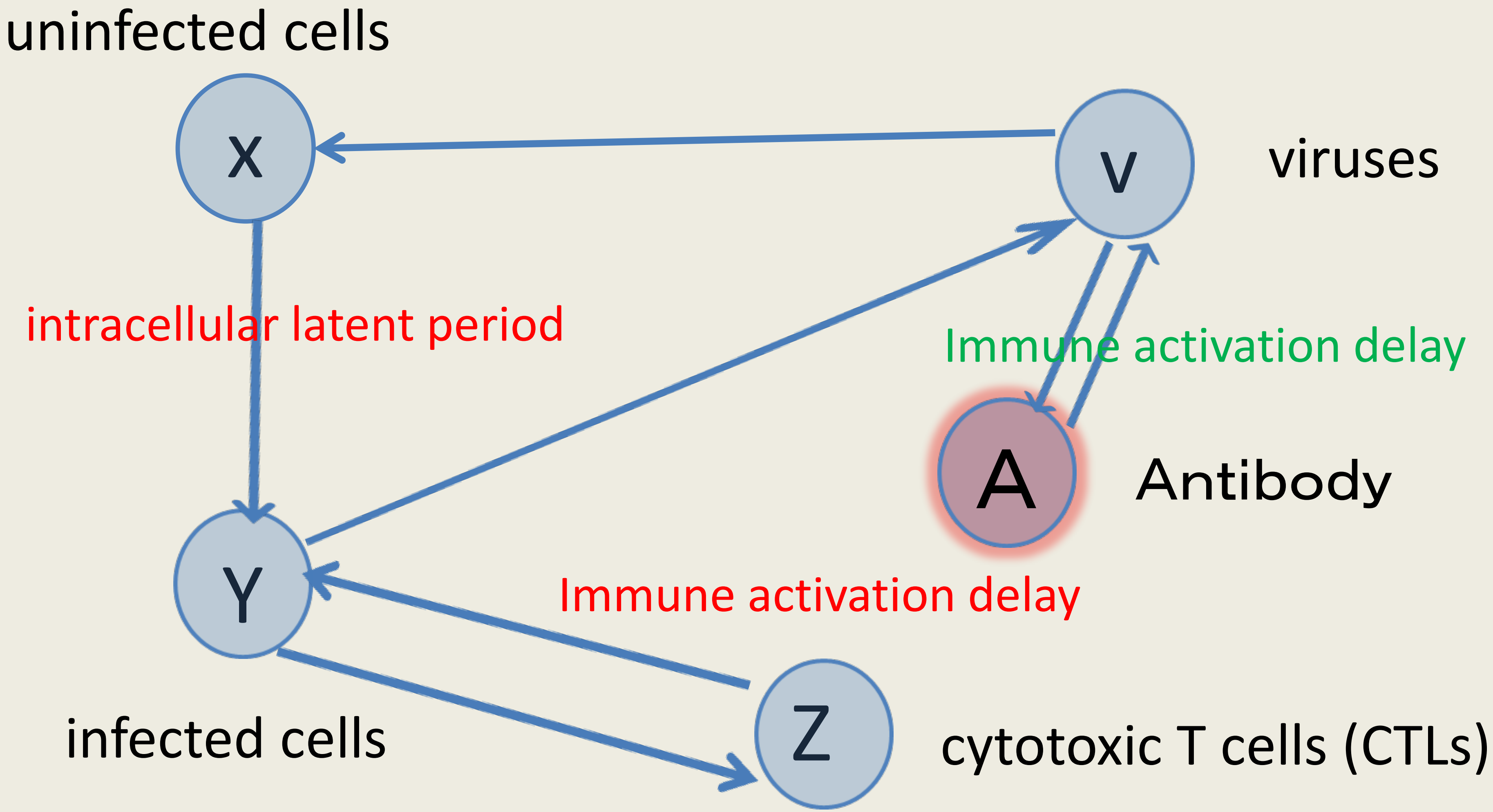
   when the both delays are ignored. (By constructing Lyapunov functions)

2. When both delays are included, the global properties are proved by using Lyapunov-LaSalle invariance theorem and stability switch by bifurcation theory.
3. Our results show that

- intracellular delay would not affect the stability of the model. However,
- the immune activation delay can destabilize the equilibrium and produce periodic solutions.
- The theoretical and numeric analysis give us some useful suggestions on new drugs to fight against viral infection

it is effective for the drugs to prolong the latent period, and/or to reduce the activation delay of CTLs immune response and/or to inhibit infection.

Adding Delayed Antibody response : HCV



uninfected cells

viruses

intracellular latent period

Immune activation delay

Antibody

Immune activation delay

infected cells

cytotoxic T cells (CTLs)

References

1. Anderson, R., May, R.M.: The population dynamics of microparasites and their invertebrate hosts, Philo. T. Roy. Soc. B., 291, 451-524 (1981)
2. Beretta, E., Kuang, Y.: Geometric stability switch criteria in delay differential systems with delay dependent parameters, SIAM J. Math. Anal., 33, 1144-1165 (2002)
3. Beretta, E., Carletti, M., Kirschner, D.E., Marino, S.: Stability analysis of a mathematical model of the immune response with delays, In: Mathematics for life science and medicine, pp177-206 (2007)
4. Buric, N., Mudrinic, M., Vasovic, N.: Time delay in a basic model of the immune response, Chaos,Solutions and Fractals, 12, 483-489 (2001)
5. Canabarro, A.A., Gleria, I.M., Lyra, M.L.: Periodic solutions and chaos in a non-linear model for the delayed celluar immune response, Physica A, 342, 483-489 (2004)
6. Culshaw, R.V., Ruan, S.: A delay-differential equation model of HIV infection of CD4+ T-cells, Math. Biosci., 165, 27-39 (2000)
7. Ebert, D., Zschokke-Rohringer, C.D., Carius, H.J.: Does effects and density-dependent regulation of two microparasites of Daphnia magna, Oecologia, 122, 200-209 (2000)
8. Fenton, A., Lello, J., Bonsall, M.B.: Pathogen responses to host immunity: the impact of time delays and memory on the evolution of virulence, Proc. R. Soc. B, 273, 2083-2090 (2006)

9. Gourley, S.A., Kuang, Y., Nagy, D.: Dynamics of a delay differential model of hepatitis B virus infection, J. Biological Dynamics, 2, 140-153 (2008)

10. Herz, V., Bonhoeffer, S., Anderson, R., May, R.M., Nowak, M.A.: Viral dynamics in vivo: limitations on estimations on intracellular delay and virus delay, Proc. Natl. Acad. Sci. USA, 93, 7247-7251 (1996)

11. Huang, G., Takeuchi, Y., Ma, W.: Lyapunov functionals for delay differential equations model for viral infections, SIAM J. Appl. Math., 70, 2693-2708 (2010)

12. Kajiwara, T., Sasaki, T.: A note on the stability analysis of pathogen-immune interaction dynamics, Disc. and Cont. Dyn. Sys. B, 4, 615-622 (2004)

13. Korobeinikov, A.: Global properties of basic virus dynamics models, Bull. Math. Biol., 66, 879-883 (2004)

14. Korobeinikov, A.: Global asymptotic properties of virus dynamics models with dose dependent parasite reproduction and virulence, and nonlinear incidence rate, Math. Med. Biol., 26, 225-239 (2009)

15. Korobeinikov, A.: Stability of ecosystem: Global properties of a general prey-predator model, Math. Med. Biol., 26, 309-321 (2009)

16. Korobeinikov, A.: Global properties of infectious disease models with non-linear incidence, Bull. Math. Biol., 69, 1871-1886 (2007)

17. Kuang, Y.: Delay Differential Equations with Applications in Population Dynamics, Academics Press, San Diego (1993)

18. Li, M.Y., Shu, H.,: Multiple stable periodic oscillations in a mathematical model of CTL response to HTLV-1 infection, Bull. Math. Biol., in press, DOI 0.1007/sl1538-010-9591-7

19. Mittler, J.E., Sulzer, B., Neumann, A.U., Perelson, A.: Influence of delayed viral production on viral dynamics in HIV-1 infected patients, Math. Biosci., 152, 143-163 (1998)

20. Nelson, P., Murray, J., Perelson, A.: A model of HIV-1 pathogenesis that includes an intracellular delay, Math. Biosci., 163, 201-215 (2000)

21. Nelson, P., Perelson, A.: Mathematical analysis of delay differential equation models of HIV-1 infection, Math. Biosci., 179, 73-94 (2002)

22. Nowak, M.A., Bangham, C.R.M.: Population dynamics of immune responses to persistent virus, Science, 272, 74-79 (1996)

23. Nowak,M.A., May, R.M., Sigmund, K.: Immune responses against multiple epitopes, J. Theoret. Biol., 175, 325-353 (1995)

24. Pang, H., Wang, W., Wang, K. Global properties of virus dynamics with CTL immune response, J. Southwest China Normal Univ., 30, 797-799 (2005)

25. Perelson, A., Kirschner, D.E., De Boer, R.: Dynamics of HIV infection of CD4+T cell, Math. Biosci., 114, 81-125 (1993)

26. Song, X., Wang, S., Zhou, X.: Stability and Hopf bifurcation for a viral infection model with delayed non-lytic immune response, J. Appl. Math. Comput., 33, 251-265 (2010)
27. Tam, J.: Delay effect in a model for virus replication, IMA: J. Math. Appl. Med. Biol., 16, 29-37 (1999)
28. Wang, Y., Zhou, Y., Wu, J., Heffernan, J.: Oscillatory viral dynamics in a delay HIV pathogenesis model, Math. Biosci., 219, 104-112 (2009)
29. Wang, K., Wang, W., Pang, H., Liu, X.: Complex dynamic behavior in a viral model with delay immune response, Physica D, 226, 197-208 (2007)
30. Wodarz, D.: Hepatitis C virus dynamics and pathology: The role of CTL and antibody responses, J. Gen. Virol., 84, 1743-1750 (2003)
31. Xu, R., Ma, Z.: An HBV model with diffusion and time delay, J. Theoret. Biol., 257, 499-509 (2009)
32. Zhu, H., Zuo, X.: Dynamics of an HIV-1 infection model with cell-mediated immune response and intracellular delay, Disc. and Cont. Dyn. Sys. B, 12, 511-524 (2009)