数理解析研究所講究録
第1853巻 2013年 11-18

A dynamical model of two type influenza-A virus replication in human epithelial cells

Noppharat Chaifong
Graduate School of Science and Engineering, Chuo University

1. Introduction

Nowadays, influenza has vigorously evolved and mutated into different variations. Many diseases are transmitted by virus particles. Influenza is caused by a virus that can be of three different type (A, B and C). Among these types, the virus A is epidemiologically the most important for humans, since it can recombine its genes with those of strains circulating in animal populations (birds, swine and horses). These relatively rare recombination give rise every few decades to new viral subtypes via the so called *antigenic shift* mechanism. The new subtypes, classified according to the antigenic and genetic nature of their surface glycoprotiens HA (hemagglutinin) and NA (neuraminidase), are usually antigenically so different from their ancestors to escape completely the defenses of the immune system of the previously infected hosts. Consequently, every antigenic shift is associated potentially with particularly severe pandemics.

Many mathematical models have been proposed in the literature to describe the inter-pandemic ecology of influenza A in humans and used to be a valuable tool in the understanding of immune response to infectious diseases which helps in clarifying and testing hypotheses.

2. The model

This research represents a dynamical model of influenza virus replication in human epithelial cells. For a spread of two diseases by effects of two type of influenza virus, we developed a simplified dynamical model, which focuses on the control of the infections by innate and adaptive immunity. Innate immunity is represent by interferon-induced resistance to infection of respiratory epithelial cells and by removal of infected cells by effector cells. Adaptive immunity is represented by virus specific antibodies. The model does not include effects of time delays and assumed that *antigenic shift* is not included in this model. This model is constructed as a system of 13 ordinary differential equations with 35 parameters characterizing the rate of various processes contributing to the course of disease. The parameters are derived from published experimental data. Then we will show the existence of solutions and bounded of solutions and investigate the behavior of systems.

The general flow diagram is show in Fig.1, the proportion of susceptible $H(t)$, i.e., those cells do not have specific immune defenses against that particular strain; the fraction $I_1(t), I_2(t)$of those individuals that are infected by virus A subtype1, 2 the two classes of those cells resistant to infection by virus A subtype 1, 2 to that strain (i.e. recovered $R(t)$); $D(t)$ is a number of dead cells at time t. $V_1(t), V_2(t)$ is a number of free virus A subtype1, 2 particles.

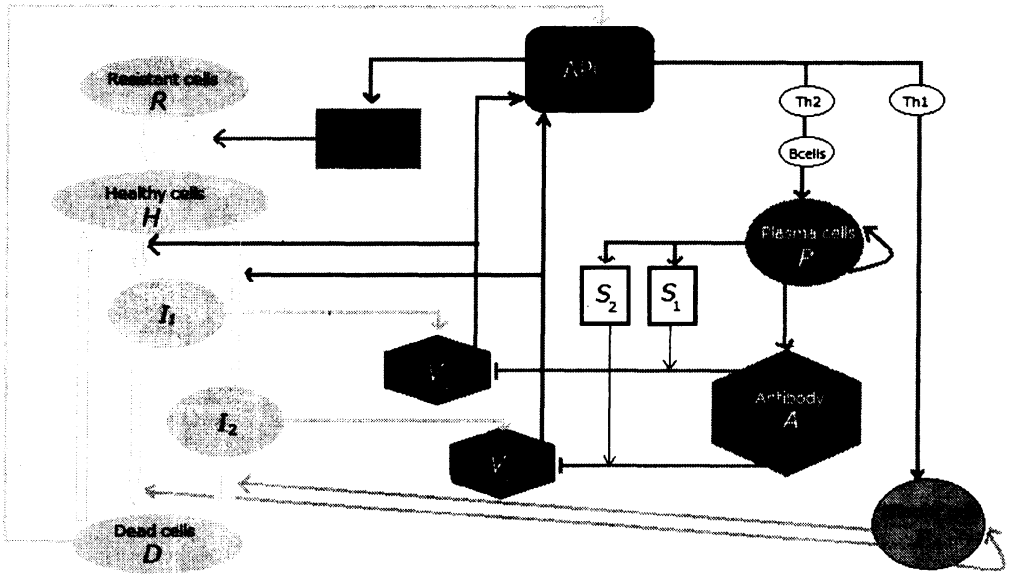


Fig.1 General flow diagram of the model.

Table1. Model variables and scaling factors

Variables	Descriptions	Scaling factor
H	Proportion of healthy cells without immunity	H^*=1.7x10^{-11}M
I_1, I_2	Proportion of infected cells by virus A subtype 1, 2	H^*=1.7x10^{-11}M
R	Proportion of resistant cells	H^*=1.7x10^{-11}M
V_1, V_2	Viral load per epithelial cell* subtype 1, 2	H^*=1.7x10^{-11}M
D	Proportion of dead cells	H^*=1.7x10^{-11}M
M	Activated antigen presenting cells per homeostatic level	M^*=10^{-15}M
F	Interferons per homeostatic level of macrophages	M^*=10^{-15}M
E	Effector cells per homeostatic level	E^*=10^{-16}M
P	Plasma cells per homeostatic level	P^*=1.8139x10^{-20}M
A	Antibodies per homeostatic level	A^*=7.2x10^{-11}M
S_1, S_2	Antigenic distance	

* V_1, V_2=1 corresponds to 10^{10} particles/ml respiratory epithelial cells

The model of human immune response against influenza virus infection we consider is a simplified model of population dynamics type with consists of the following interactions (see fig.1). The epithelial cells of respiratory tract are assumed to be in one of five possible states; healthy (H), Infected (I_1, I_2), dead (D) or resistant (R) to infection. The virus particles

(V_1, V_2) interact with healthy cells and infect them. Infected cells release new virus particles upon their death. Proliferation of healthy cells causes regeneration and decrease in proportion of dead cells.

These interactions were used in the construction of a system of 13 ordinary differential equations describing the dynamics of the main variables, list in Table1, which correspond to the components of the immune response shown in fig.1

$$\frac{dV_1}{dt} = \gamma_{V1} I_1 - \gamma_{VA1} S_1 A V_1 - \gamma_{VH1} H V_1 - \alpha_{V1} V_1 - \frac{a_v V_1}{1 + a_v' V_1} \quad (1)$$

$$\frac{dV_2}{dt} = \gamma_{V2} I_2 - \gamma_{VA2} S_2 A V_2 - \gamma_{VH2} H V_2 - \alpha_{V2} V_2 - \frac{a_v V_2}{1 + a_v' V_2} \quad (2)$$

$$\frac{dH}{dt} = b_{HD} D(H + R) + a_R R - \gamma_{HV1} V_1 H - \gamma_{HV2} V_2 H - b_{HF} F H \quad (3)$$

$$\frac{dI_1}{dt} = \gamma_{HV1} V_1 H - b_{IE} E I_1 - a_{I1} I_1 \quad (4)$$

$$\frac{dI_2}{dt} = \gamma_{HV2} V_2 H - b_{IE} E I_2 - a_{I2} I_2 \quad (5)$$

$$\frac{dM}{dt} = [b_{MD} D + b_{MV}(V_1 + V_2)](1 - M) - a_M M \quad (6)$$

$$\frac{dF}{dt} = b_F M + C_F(I_1 + I_2) - a_F F - b_{FH} H F \quad (7)$$

$$\frac{dR}{dt} = b_{HF} F H - a_R R \quad (8)$$

$$\frac{dE}{dt} = b_{EM} M E - b_{EI}(I_1 + I_2) E + a_E(1 - E) \quad (9)$$

$$\frac{dP}{dt} = b_{PM} M P + a_p(1 - P) \quad (10)$$

$$\frac{dA}{dt} = b_A P - \gamma_{AV1} S_1 A V_1 - \gamma_{VA2} S_2 A V_2 - a_A A \quad (11)$$

$$\frac{dS_1}{dt} = r_1 P(1 - S_1) \quad (12)$$

$$\frac{dS_2}{dt} = r_2 P(1 - S_2) \quad (13)$$

$$D = 1 - H - R - I_1 - I_2 \quad (14)$$

The variable D serves as a maker for issue damage and an indicator of the severity of disease. We assume that $H + I_1 + I_2 + R + D = 1$.

Infected cells by virus 1, 2 can be destroyed by the same effector cell. The production rate of effector cells (E) and plasma cells (P) are stimulated by the same APC (M). And hence the system *(1)-(14)* is dimensionless.

The interactions are based on clonal selection theory, mass-action kinetics, characteristics of interactions and the birth-death balance of population of cells and molecules.

Eq. *(1), (2)* of the system describes the rate of change of virus 1, 2 concentration V_1, V_2.It expresses the production rate of a viral particle by infected cells, rate of neutralization of influenza A type 1 and 2 virus by specific antibodies, the rate adsorption of viral particles by uninfected cells, the natural decay of viral particle and the rate of nonspecific mucociliary removal of virions supported by cough and other mechanisms.

Eq. *(3)* determines the time rate of change of healthy cells H. During recovery, new healthy cells are generated as a result of proliferation of both healthy and resistant cells (the offspring of resistant cells lose resistance) and hence the proliferation term is proportional to

$(H + R)$, and to D (in a logistic fashion) since regeneration can only occur in the presence of damage. Resistant cells R gradually lose their resistance to infection and return into their initial sensitive state (healthy state), which is characterized by the term $a_R R$ The terms $\gamma_{HV1} V_1 H, \gamma_{HV2} V_2 H$ are the loss of healthy cells due to infection and the term $b_{HF} FH$ characterizes transition of the healthy cells into resistant state.

Eq. *(4), (5)* characterize the time rate of change of infected cells I_1, I_2. The infection of healthy cells and resistant cells by virus 1, 2 are described in the terms $\gamma_{HV1} V_1 H$, $\gamma_{HV2} V_2 H$. The term $b_{IE} EI_1, b_{IE} EI_2$ characterizes the destruction of infected cells by effector cells during which no new virus produced. The last term indicates the natural death, damage by virus and recovery of infected cells during which new virus particles are produced.

Eq. *(6)* establishes that the time rate of increase of activated APC (M) is proportional to the amount of the each virus and the amount of dead cells by each virus. The natural decay of activated state of APC is represented by the last term.

Eq. *(7)* describes the time rate of change of interferons which depends on the production rate of F by APC and by infected cells, on the rate of interferons which blinding uninfected cells and the nonspecific decay of interferons represented by $a_F F$.

Eq. *(8)* shows that resistant cells R are induced from healthy cells and by resistant cells R gradually lose their resistance and convert back to healthy cells with finite lifetime. The terms $b_{HF} FH$ characterize transition of the healthy cells into resistant R state.

Eq. *(9),(10)* characterizes the rate of change of effector cells E concentration and takes into account the production rate of effector cells stimulated by APC and the destruction rate of infected cells by effector cells. The terms $a_E(1 - E)$, $a_p(1 - P)$ in Eqs. *(9), (10)* are approximated expressions for homeostatic maintenance of the levels of active effectors and plasma cells. The first term in Eq. *(10)* characterizes the activation process of plasma cells stimulated by APC.

Eq. *(11)* stands for the time rate of change of the concentration of antibodies describing the production rate by plasma cells, the neutralization rate of free viral particles by specific antibodies and the natural decay rate (last term)

Eq. *(12), (13)* The variable S_1, S_2 represents the compatibility between antibodies and the virus strain in an individual and ranges from 0 (no compatibility) to 1 (maximal compatibility) and can be interpreted as a measure of blinding affinity of the antibody and the virus. The rate of increase of S_1, S_2 is approximated by term $rP(1 - S_1), rP(1 - S_2)$ which accounts for two natural observation : (i) the increase in S_1, S_2 are stimulated by plasma cells and (ii) S_1, S_2 cannot increase beyond 1. By adjusting the time evolution of S_1, S_2 we may observe how the course of the disease depends on the evolution of antigenic distance.

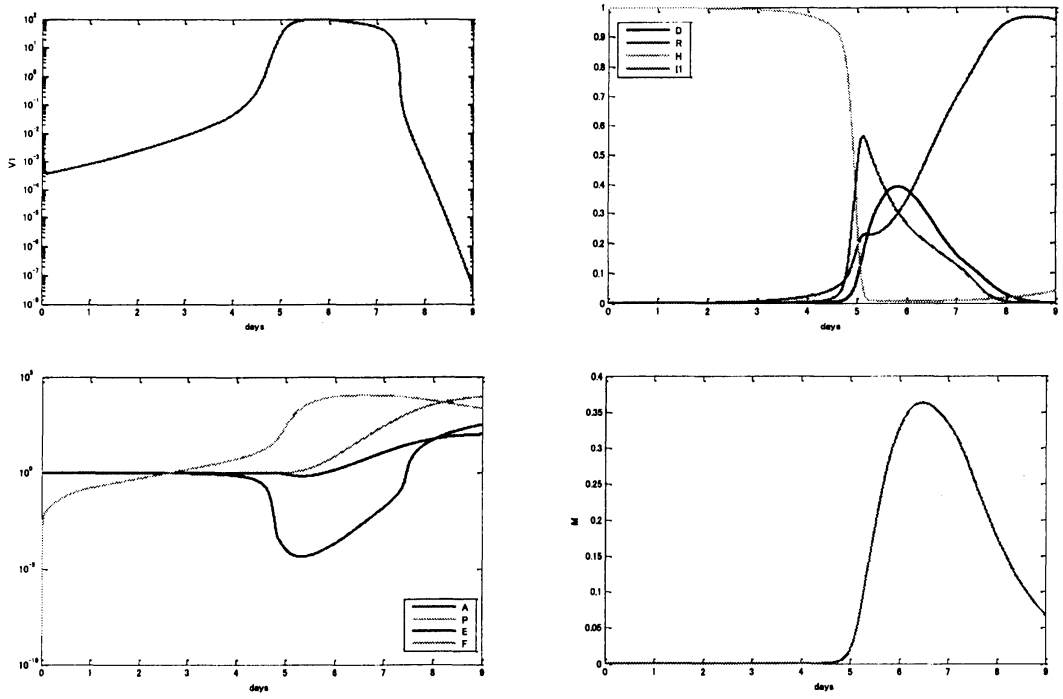
Table2. Model parameters used for the baseline case

Parameters	Values	Descriptions
γ_{V1}	510	Rate constant of influenza A subtype1 particles secretion per infected cells
γ_{V2}	430	Rate constant of influenza A subtype2 particles secretion per infected cells
γ_{VA1}	619.12	Rate constant of neutralization of influenza A subtype1 by antibodies
γ_{VA2}	453.4	Rate constant of neutralization of influenza A subtype2 by antibodies
$\gamma_{VH1}, \gamma_{VH2}$	1.02	Rate constant of adsorption of influenza A subtype1, 2 by infected cells
α_V	1.7	Rate constant of nonspecific influenza virus removal
a_V	100	Rate constant of nonspecific influenza virus removal
a'_V	23000	Rate constant of nonspecific influenza virus removal
b_{HD}	4	Rate constant of regeneration of epithelial cells
a_R	1	Rate constant of epithelial cells virus resistance decay
γ_{HV1}	0.34	Rate constant of epithelial cells infected by influenza A subtype1
γ_{HV2}	0.27	Rate constant of epithelial cells infected by influenza A subtype2
b_{HF}	0.01	Rate constant of epithelial cells virus resistant state induction
b_{IE}	0.066	Rate constant of infected epithelial cells that CTL damage
a_{I1}	1.5	Rate constant of infected cells damage by cytopathicity of influenza A subtype1
a_{I2}	1.2	Rate constant of infected cells damage by cytopathicity of influenza A subtype2
b_{MD}	1	Rate constant of simulation of antigen presenting cells by dead cells
b_{MV}	0.0037	Rate constant of stimulation of antigen presenting cells by virus particles
a_M	1	Rate constant of stimulated state loss of antigen presenting cells
b_F	250,000	Interferon (IFN) production rate per APC
C_F	2000	Interferon (IFN) production rate per infected cell
b_{FH}	17	Rate constant of epithelial cells that IFN binds
a_F	8	Rate constant of IFN`s natural decay
b_{EM}	8.3	Rate constant of stimulation of effector cells
b_{EI}	2.72	Rate constant of death of effectors by lytic interactions with infected cells
a_E	0.4	Rate constant of natural death of effector cells
b_{PM}	11.5	Rate constant of plasma cells production
a_p	0.4	Rate constant of natural death of effector cells
b_A	0.043	Antibody production rate per plasma cells
$\gamma_{AV1}, \gamma_{AV2}$	146.2	Rate constant of antibodies which binds to influenza A subtype1, 2
a_A	0.043	Rate constant of natural death of antibodies
r	3e-5	Rate constant of S_1, S_2 variable

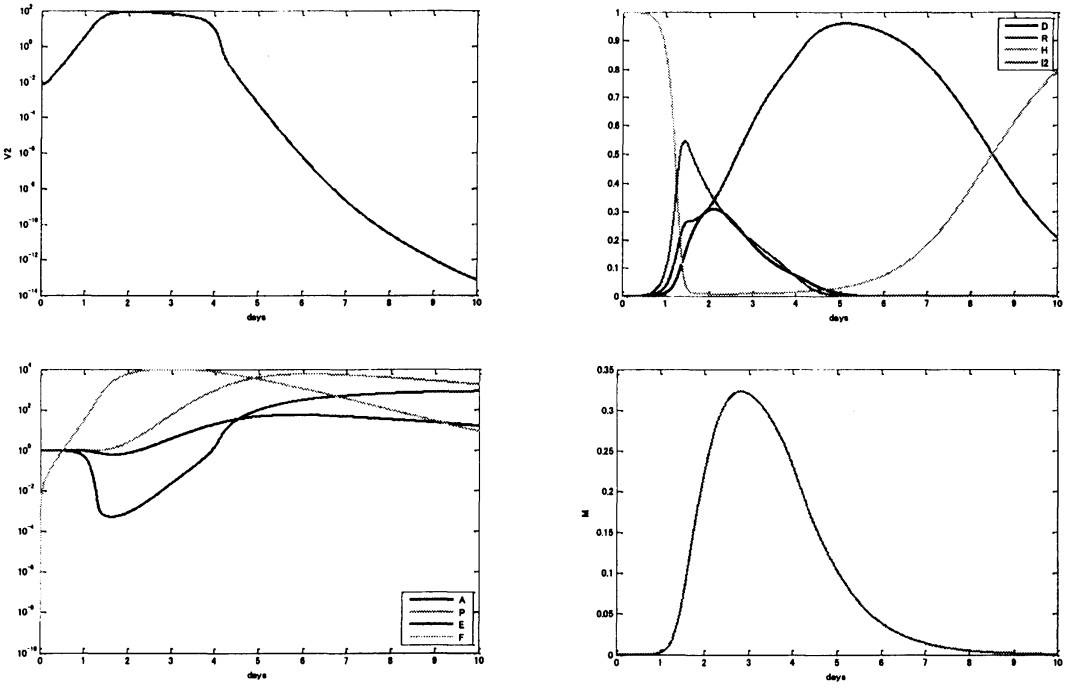
where each of the parameters has a clear epidemiological meaning, thus can be estimated from data.

3. Simulation

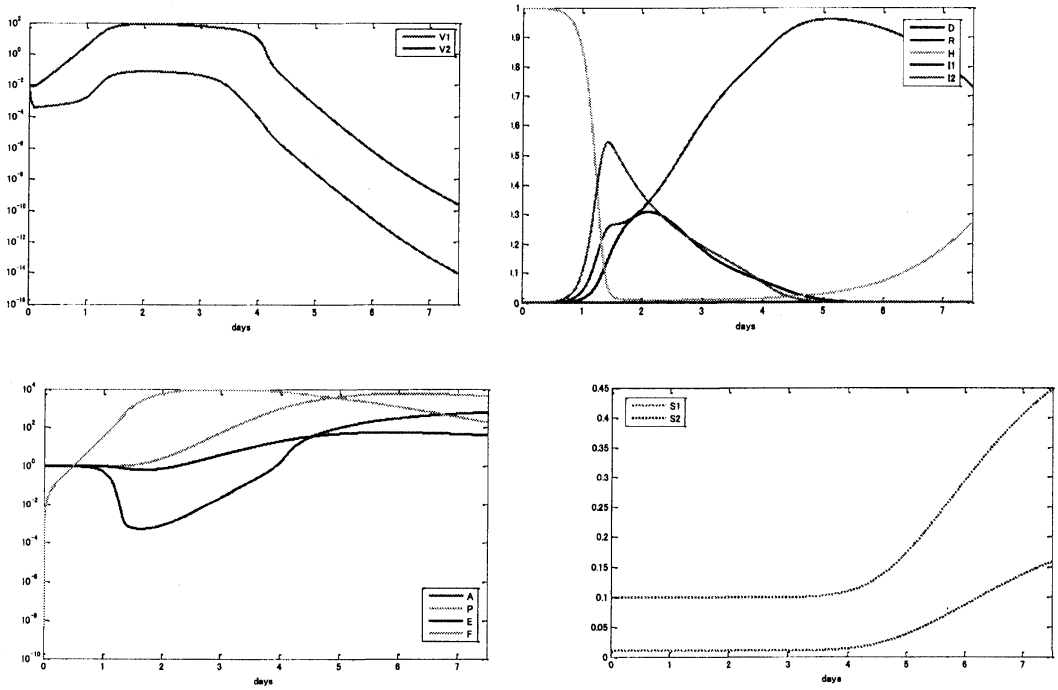
We use software XPPAUT to run all simulations. The time courses of variables were obtained by numerical integration using parameters provided in Table2. following clinical data.



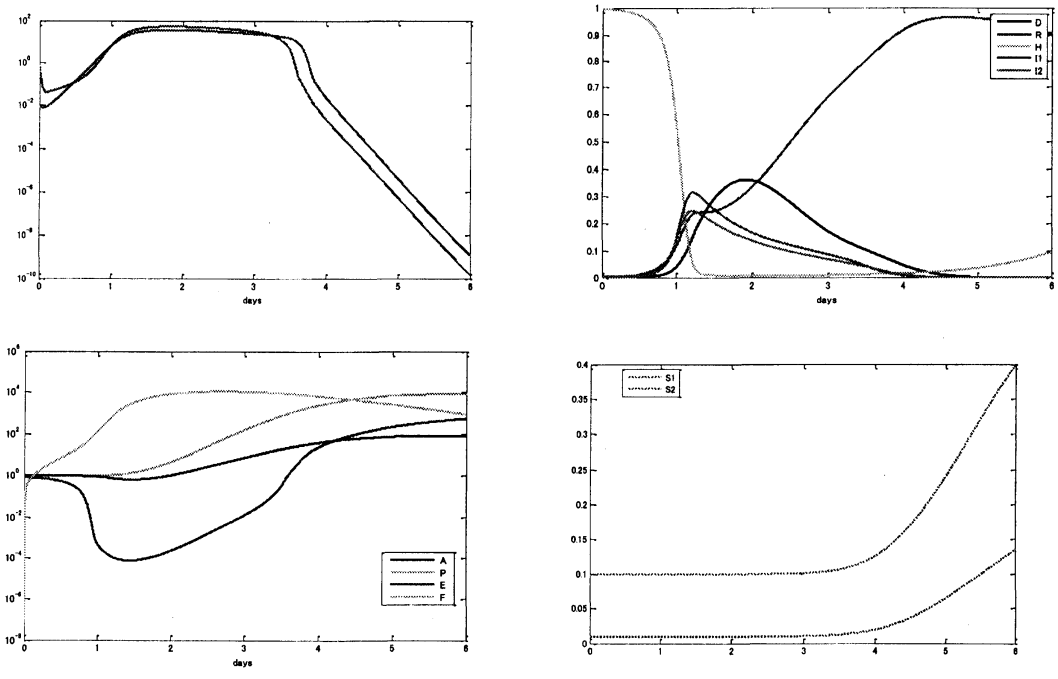
$V_1(0) = 0.01, V_2(0) = 0, S_1(0) = 0.01, S_2(0) = 0, r_1 = 000003, r_2 = 0$



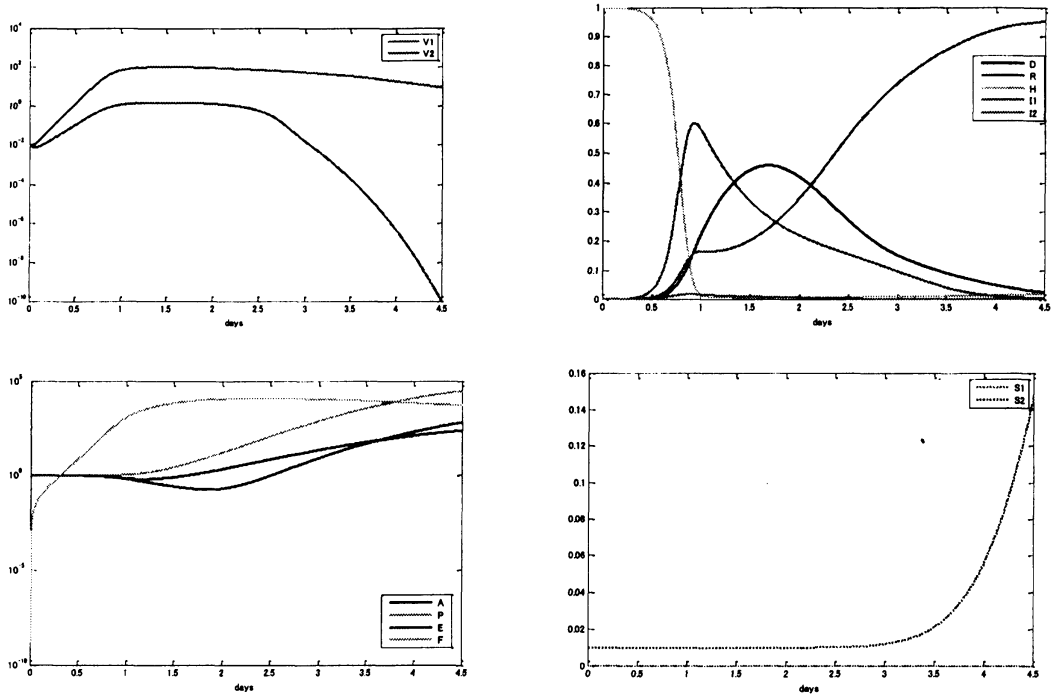
$V_1(0) = 0, V_2(0) = 0.01, S_1(0) = 0, S_2(0) = 0.01, r_1 = 0, r_2 = 0.00001$



$V_1(0) = 0.01, V_2(0) = 0.01, S_1(0) = 0.1, S_2(0) = 0.01, r_1 = 0.00003, r_2 = 0.00001$



$V_1(0) = 0.7, V_2(0) = 0.01, S_1(0) = 0.1, S_2(0) = 0.01, r_1 = 0.00003, r_2 = 0.00001$



$V_1(0) = 0.01, V_2(0) = 0.01, S_1(0) = 0, S_2(0) = 0.01, r_1 = 0, r_2 = 0.00001$

References

[1] D.Earn, J. Dushoff, S. Levin, Ecology and evolution of the flu, Trends Ecol. Evol. 17 (2002) 334

[2] Hayden, F.G., Fritz, R., Lobo, M.C., Alvord, W., Strober, W., Straus, S.E., 1998.Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. J. Clin. Invest. 101, 643-649

[3] Zdanov, V.M., Bukrinskaja, A.G., 1969. Myxoviruses Reproducton. Medicina, Moscow, Russia.

[4] Hancioglu, B., et al., A dynamical model of human immune response to influenza A virus infection. Journal of Theoretical Biology (2007), doi:10.1016/j.jtbi.2006.12.015

[5] Marchuk, G.I., Petrov, R.V., Romanyukha, A.A., Bocharov, G.A., 1991. Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for hepatitis B. J. Theor. Biol. 151, 1-40

Graduate School of Science and Engineering
Chuo University
Tokyo 112-8551
Japan
E-mail address: s10001@gug.math.chuo-u.ac.jp