Mathematical models on the dogmas of HIV contagions







Dr. Priti Kumar Roy
Centre for Mathematical Biology and Ecology
Department of Mathematics
Jadavpur University
Kolkata, India.
E-mail: pritiju@gmail.com

Contents of My Talk

- Basics of HIV
- HIV transmission
- Mathematical Models in HIV
- Therapeutic use of IL-2
- Awareness Campaign in HIV

What is AIDS?

- **A**cquired: To come into possession of something new
- **I**mmune **D**eficiency: Decrease or weakness in the body's ability to fight off infections and illnesses
- **S**yndrome: A group of signs and symptoms that occur together and characterize a particular abnormality

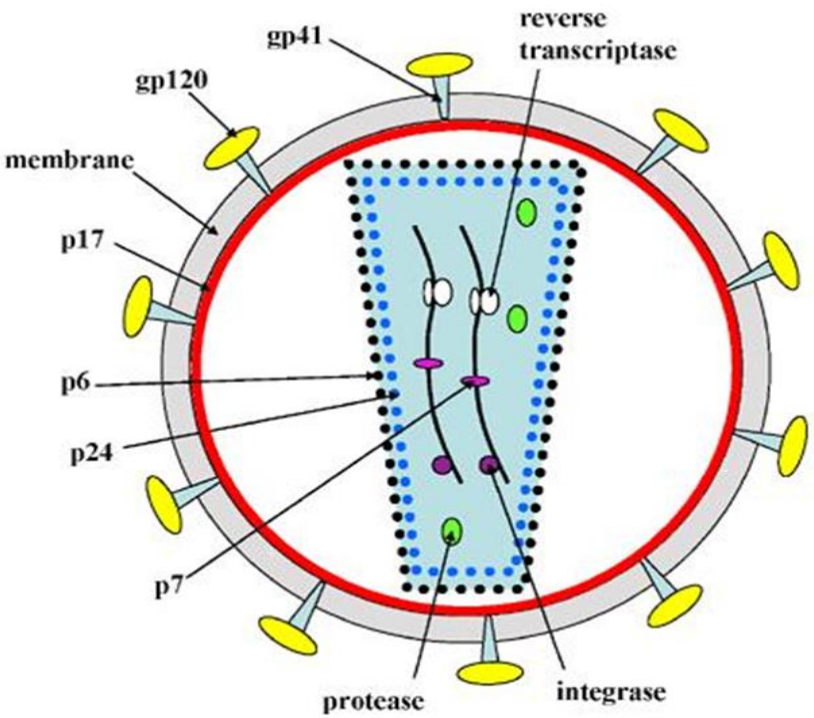
- *HIV is the virus that causes AIDS*
- *Not everyone who is infected with HIV has AIDS*
- *Everyone with AIDS is infected with HIV*
- *AIDS is result of the progression of HIV Infection*
- *Anyone infected with HIV, although healthy, can still transmit the virus to another person*

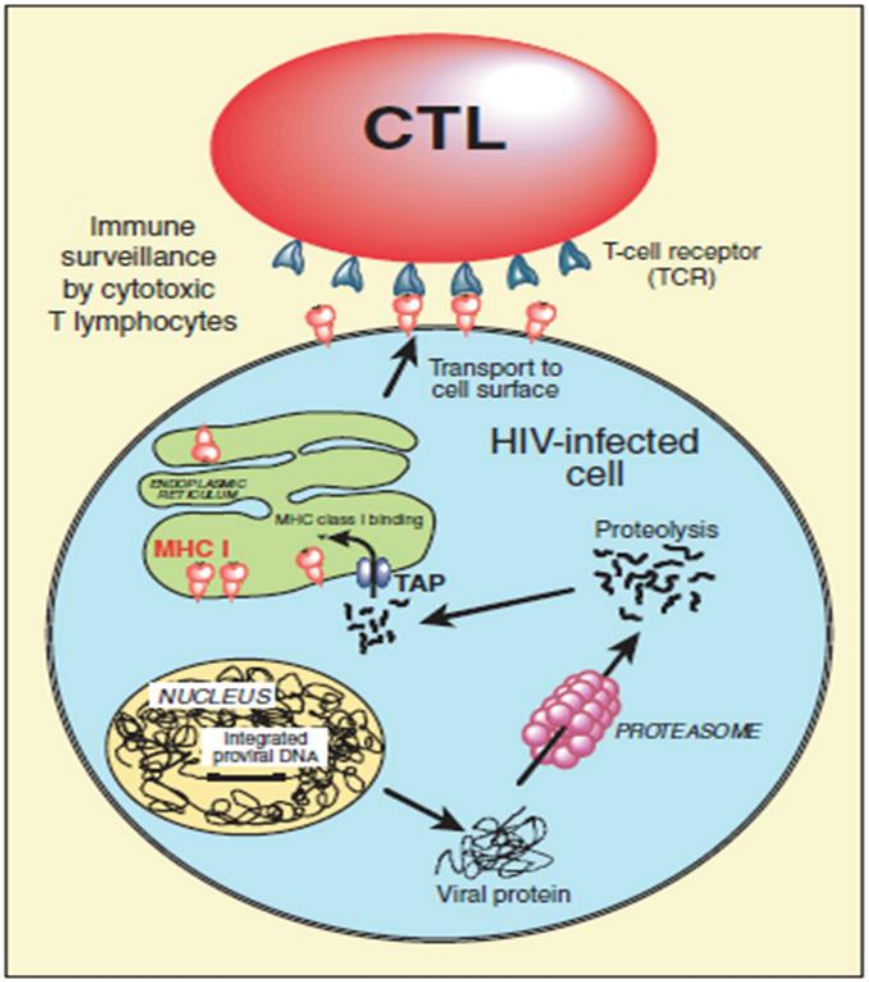
AIDS is the final stage of the disease caused by infection with a type of virus called HIV.

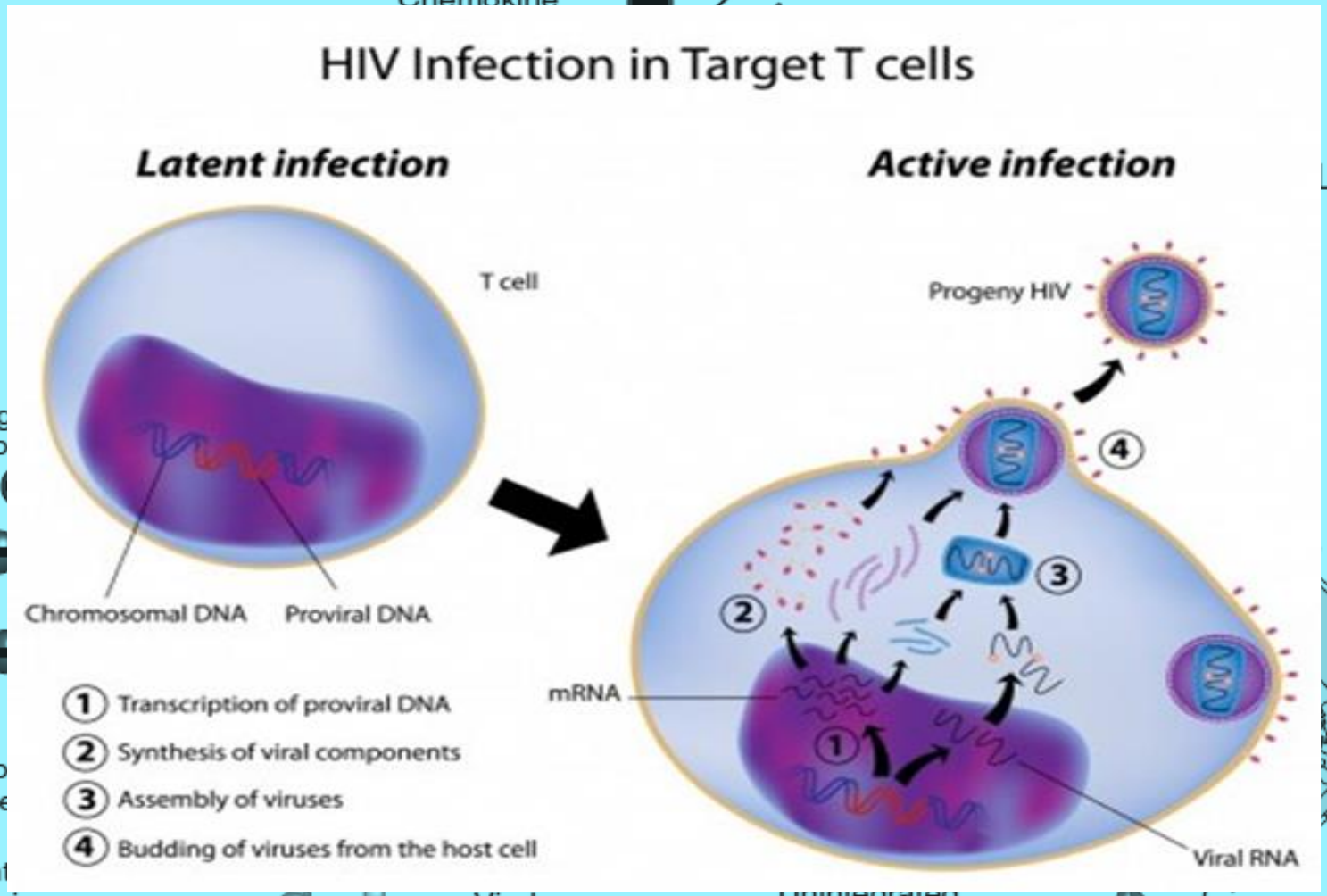
Historical background of HIV/AIDS

- In 1981 AIDS was first recognized in young previously healthy homosexual men in New York City, Los Angeles and San Francisco.
- In 1983 a cytopathic retrovirus was isolated from persons with AIDS and associated condition such as chronic lymphadenopathy.
- In 1985 serological tests had been developed and licensed to make aware of verification of infectivity with HIV.
- In 1987 alteration incorporated HIV encephalopathy, wasting syndrome, and other AIDS indicator diseases were diagnosed presumptively.
- The first AIDS case in India was detected in 1986 and since then HIV infection has been reported in all states and union territories.

Structure & Manifestation of HIV Virion







HIV-1

gp120 binding to CD4

CD4

Chemokine

Budding infectio

Processing to viral prote

Synt protein precursors

Viral peptide-MHC I

Viral mRNAs

Unintegrated proviral DNA

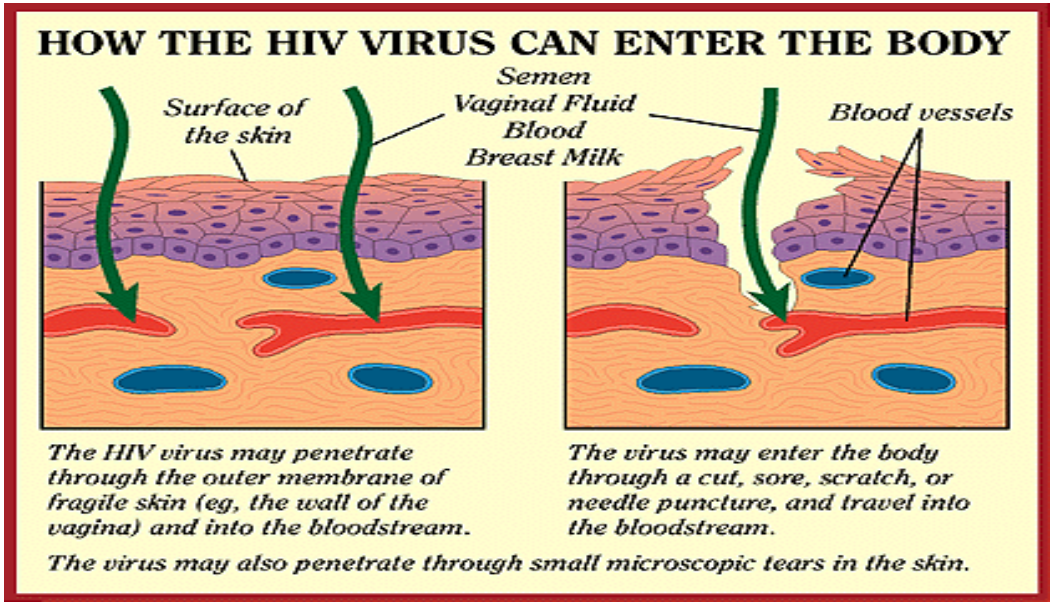
PRODUCTIVELY INFECTED CELL
(Viral peptides presented to CTL)

LATENTLY INFECTED CELL
(No viral peptides presented to CTL)

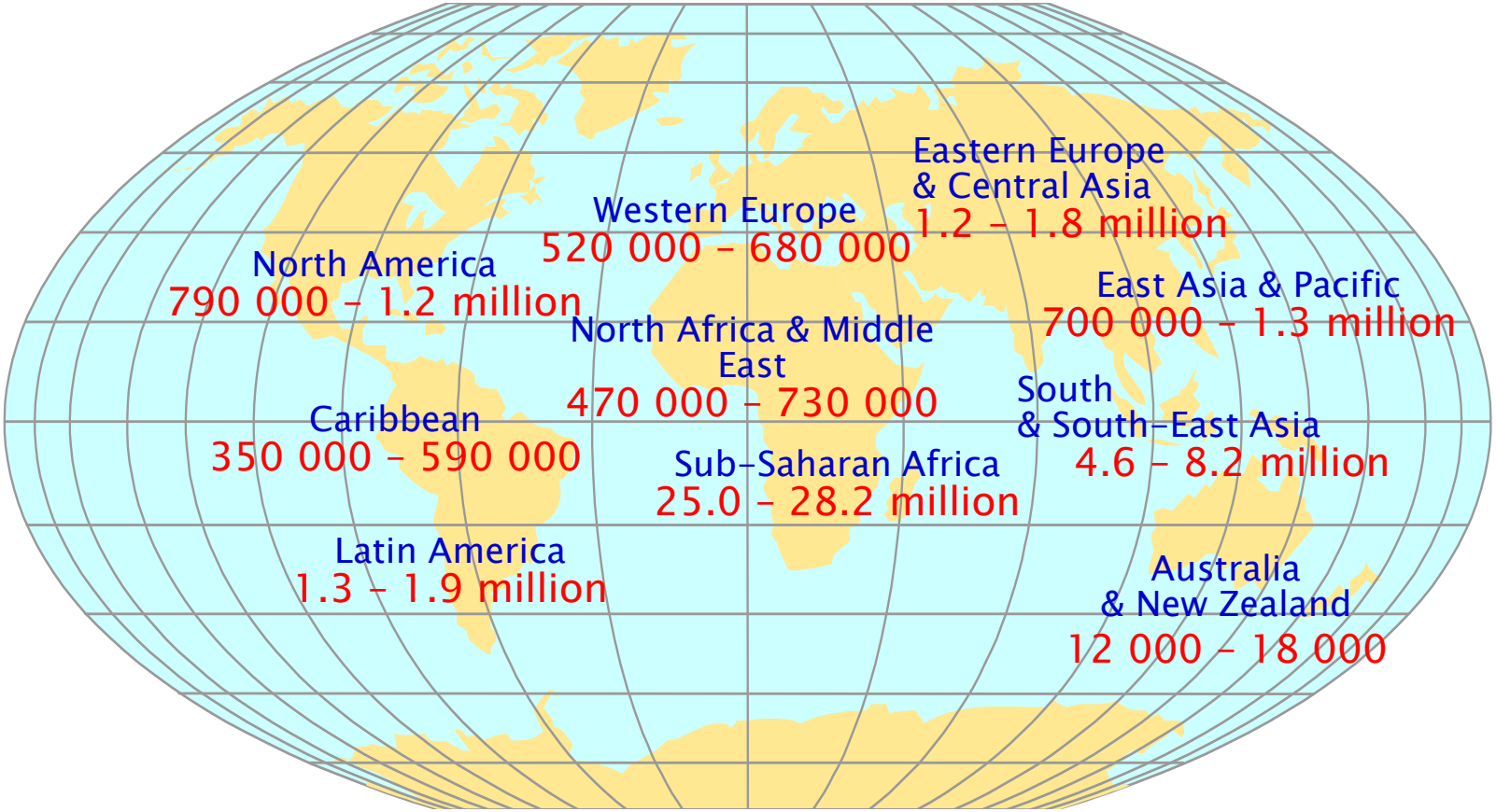
How is HIV Transmitted?

- Unprotected sexual contact with an infected partner
- Exposure of broken skin or wound to infected blood or body fluids
- Transfusion with HIV-infected blood
- Injection with contaminated objects
- Mother to child during pregnancy, birth or breastfeeding





HIV: A Global Pandemic



Adults and children estimated to be living with HIV/AIDS (2003): 34 – 46 million total

Clinical Latency Period

- HIV continues to reproduce, ***CD4*** count gradually declines from its ***normal value of 500-1200***.
- Once ***CD4 count drops below 500***, HIV infected person at risk for **opportunistic infections**.
- ***CD4 count drops below 200*** person is considered to have advanced HIV disease
- If preventative medications not started the HIV infected person is now at risk for infesting secondary infections and achieving death - Most deaths occur with ***CD4 counts below 50***.
- The median incubation period from HIV infection until development of AIDS is estimated at approximately 10 years for young adults.
- Without treatment, people with AIDS typically survive about 3 years.

Modeling the HIV System
Our Approach

Published papers in this field

1.. Roy Priti Kumar; Chattopadhyay B: Mathematical Modelling on the dynamics of CD4+T cell infection by HIV that includes a time delay, International Journal of Evolution Equation, Vol.4, No.2, pp. 227-239, 2009.

2. Roy Priti Kumar, Bairagi N, Chattopadhyay J and Chattopadhyay B: HIV model with intracellular delay -a mathematical study, published in 5th Annual IEEE Conference proceedings on Automation Science and Engineering Bangalore, pp 373-378, 2009

3. Roy Priti Kumar, Chatterjee A N, Chattopadhyay B: " HIV Infection in T-Lymphocytes and Drug Induced CTL Response of a Time Delayed Model", Lecture Notes in Engineering and Computer Science, WCE, UK, Vol. 1, pp. 533-538, 2010.

4. Roy Priti Kumar, Chatterjee A N: "T-cell Proliferation in a Mathematical Model of CTL Activity Through HIV-1 Infection", Lecture Notes in Engineering and Computer Science, WCE, UK, Vol. 1, pp. 615-620, 2010.

5. Roy Priti Kumar, Chatterjee A N: "Delay effect in a Mathematical model of HIV infected T-cell against killing by CTL", Bull. Cal. Math. Soc.,Vol. 102(6), pp. 513-524, 2010.

6. Roy Priti Kumar, Chatterjee A N: "Effect of HAART on CTL Mediated Immune Cells: An Optimal Control Theoretic Approach", Electrical Engineering and Applied Computing, Springer, Vol. 90, pp.595-607, 2011.

7. Roy Priti Kumar, Chatterjee A N: "Reduction of HIV Infection that Includes a Delay of HIV with Cure Rate During Long Term Treatment: A Mathematical Study", Electrical Engineering and Applied Computing", Springer, Vol. 90, pp. 699-713, 2011.

8. Roy Priti Kumar, Sil N, Bhattacharya S: "On the Estimation of Expected Time to Extinction in a Dynamical Model of HIV", International Journal on Mathematical Sciences and Applications, Volume 2, No. 1, pp. 213- 221, 2012.

9. Chatterjee A N, Roy Priti Kumar: "Anti-viral drug treatment along with immune activator IL-2: A control based mathematical approach for HIV infection", International Journal of Control, Volume 85, No. 2, pp. 220- 237, 2012.

10. Roy Priti Kumar, Chowdhury S, Chatterjee A N, Biswas Majee S: "Mathematical Modeling of IL-2 Based Immune Therapy on T Cell Homeostasis in HIV", Insight and Control of Infectious Disease in Global Scenario, InTech Publisher, Chapter 5, pp.79-96, 2012.

11. Chowdhury S, Roy Priti Kumar, "CTL Response Suppression in Chronic Phase of Infection: A Mathematical Study", Acta Analysis Functionalis Applicata, Vol.14, No.1, pp. 46- 54, 2012.

12. Roy Priti Kumar, Chatterjee_A N, Biswas Majee S: "Effect of Chemokine Analog through Perfect Adherence in HIV Treatment: A Model Based Study", International Journal of Applied Mathematics and Applications, Vol. 4, No. 2, pp. 121-145, 2012.

13. Roy Priti Kumar, Nandi S, Sil N, Bhattacharya S: "Insight of T Cell Proliferation in the Estimation of Expected Time to Extinction of the Disease HIV/AIDS", International Journal of Applied Mathematics, Volume 25, No. 6, pp.779-792, 2012.

14. Mondal J, Roy Priti Kumar, Biswas Majee S, Bhattacharya R.: "MATHEMATICAL MODELING OF IMPACT FOR ANTIGENIC STIMULATION ON T-CELL HOMEOSTASIS DURING PRIMARY HIV INFECTION", Bulletin of Calcutta Mathematical Society, Volume 104, No. 5, pp. 393- 408, 2012.

15. **Roy Priti Kumar**, Chowdhury S: "Mathematical Modeling of Enfuvirtide - IL-2 Administration in Impulsive Mode for HIV-1 Treatment, American Journal of Mathematics and Sciences, Vol.2, No.1, pp. 93- 103, 2013.

16. **Roy Priti Kumar**, Chatterjee A. N., Greenhalgh D., Khan Q. J. A., "Long term dynamics in a mathematical model of HIV-1 infection with delay in different variants of the basic drug therapy model", Nonlinear Analysis: Real World Applications, Vol.14, Issue 3, pp. 1621-1633, 2013.

17. **Roy Priti Kumar**, Chatterjee A. N., Biswas Majee S, "Immune Cell Response to Negative Feedback Effect on HIV", Biomedical Engineering Research, Vol.2, Issue 1, pp. 37-47, 2013.

18. **Roy Priti Kumar**, Chowdhury S, Xue-Zhi Li: "Saturation Effects for CTL Mediated Control of HIV-1 Infection: A Mathematical Study", International Journal of Biomathematics, Vol. 6, No. 3, pp 1350013-1-19, 2013.

19. **Roy Priti Kumar**, Chowdhury S, Chatterjee A, Chattopadhyay J, Rachel Norman: "A Mathematical Model on CTL Mediated Control of HIV Infection in a Long Term Drug Therapy", Journal of Biological Systems, Vol. 21, No. 3 (2013) 1350019 (25 pages), 2013.

20. Chatterjee A N, **Roy Priti Kumar**, Biswas Majee S: Negative Feedback Effect in HIV Progression: An Optimal Control Therapeutic Approach. Journal of Algorithms and Optimization (Accepted), 2013.

21. Chatterjee A N, **Roy Priti Kumar**: The Effect of Perfect Drug Adherence to Dendritic Cell and Immune Cell Interaction in HIV-1 Disease Progression. International Journal of Biomathematics. Vol. 9, No. 1 (2016) 1650005 (20 pages)

Anti-viral drug treatment along with immune activator IL-2: a control based mathematical approach for HIV infection

- The effect of *combination of drug therapy* (Reverse Transcriptase Inhibitors (RTI) and Interleukin -2 (IL-2).
- How the drugs act to reduce the cellular infection and simultaneously to activate the immune system?
- The effect of latently infected CD4+T cell population and the effect of IL-2 therapy.
- The control effectiveness of RTI and IL-2 in different approaches.
- The effectiveness of the drugs to make an impact on the immune system.
- The effect of perfect adherence to antiretroviral therapy as studied in respect of our basic mathematical model.

Formulation of the basic model as implicit form

$$\begin{aligned}
\dot{x} &= \lambda - d_1 x - (1 - \eta_1 u_1)\beta_1 x y_i + \eta_2 u_2 x \\
\dot{y}_i &= (1 - \eta_1 u_1)\beta_1 x y_i - d_2 y_i - \beta_2 y_i z + \delta y_l \\
\dot{y}_l &= \nu y_i - d_3 y_l - \delta y_l \\
\dot{z} &= s y_i - d_4 z + \eta_3 u_2 z.
\end{aligned} \tag{1}$$



The work has been published in "International Journal of Control, Vol. 85, No. 2, February 2012, 220-237"

Drug therapy with perfect adherence in explicit form

$$
\begin{aligned}
\dot{x} &= \lambda - d_1 x - \beta_1 x y_i - p_1 x R + q_1 x I, \\
\dot{y_i} &= \beta_1 x y_i - d_2 y_i - \beta_2 y_i z - p_2 y_i R + \delta y_i I, \\
\dot{y_t} &= \nu y_i - d_3 y_t - \delta y_t I, \\
\dot{z} &= s y_i - d_4 z + q_2 z I, \\
\dot{x'} &= p_1 x R - d_1 x', \\
\dot{y_i'} &= p_2 y_i R - d_2 y_i'.
\end{aligned}
$$

Here R(t) and I(t) denotes the drug concentration in the plasma of RTIs and IL-2 respectively. The dynamics of the drugs are given by:

$$
\begin{aligned}
\frac{dR}{dt} &= -d_R R, \quad t \neq t_k \\
\frac{dI}{dt} &= -d_I I, \quad t \neq T_l.
\end{aligned}
$$

$$
\begin{aligned}
\Delta R &= R_d, \quad t = t_k \\
\Delta I &= I_d, \quad t = T_l.
\end{aligned}
$$

Numerical Simulation of both explicit and implicit model

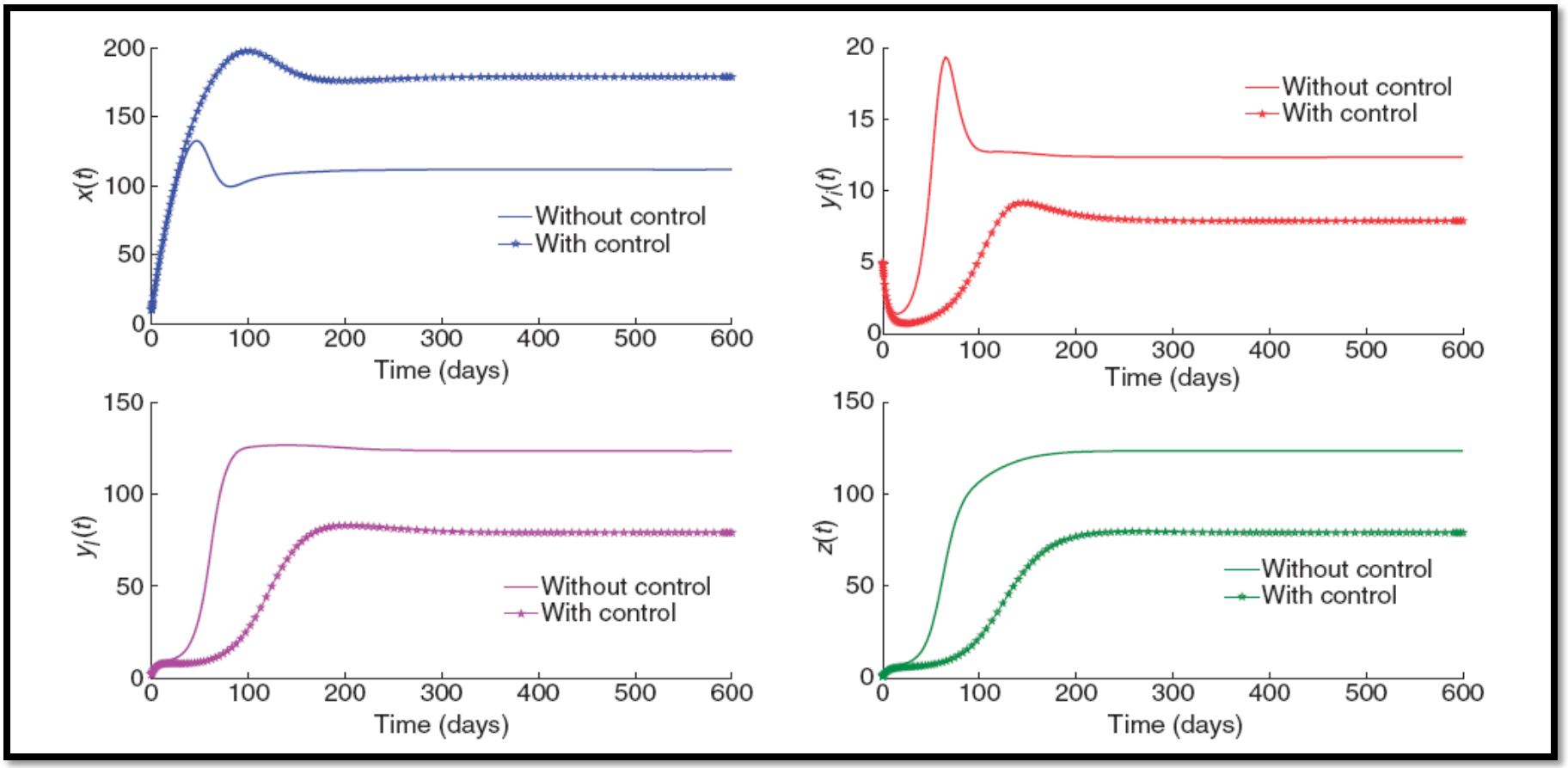


Figure 2. The system behaviour for without control ($u_1 = 0$, and $u_2 = 0$) and with control ($u_1 = 0.5$ and $u_2 = 0$).

Numerical Simulation of both explicit and implicit model

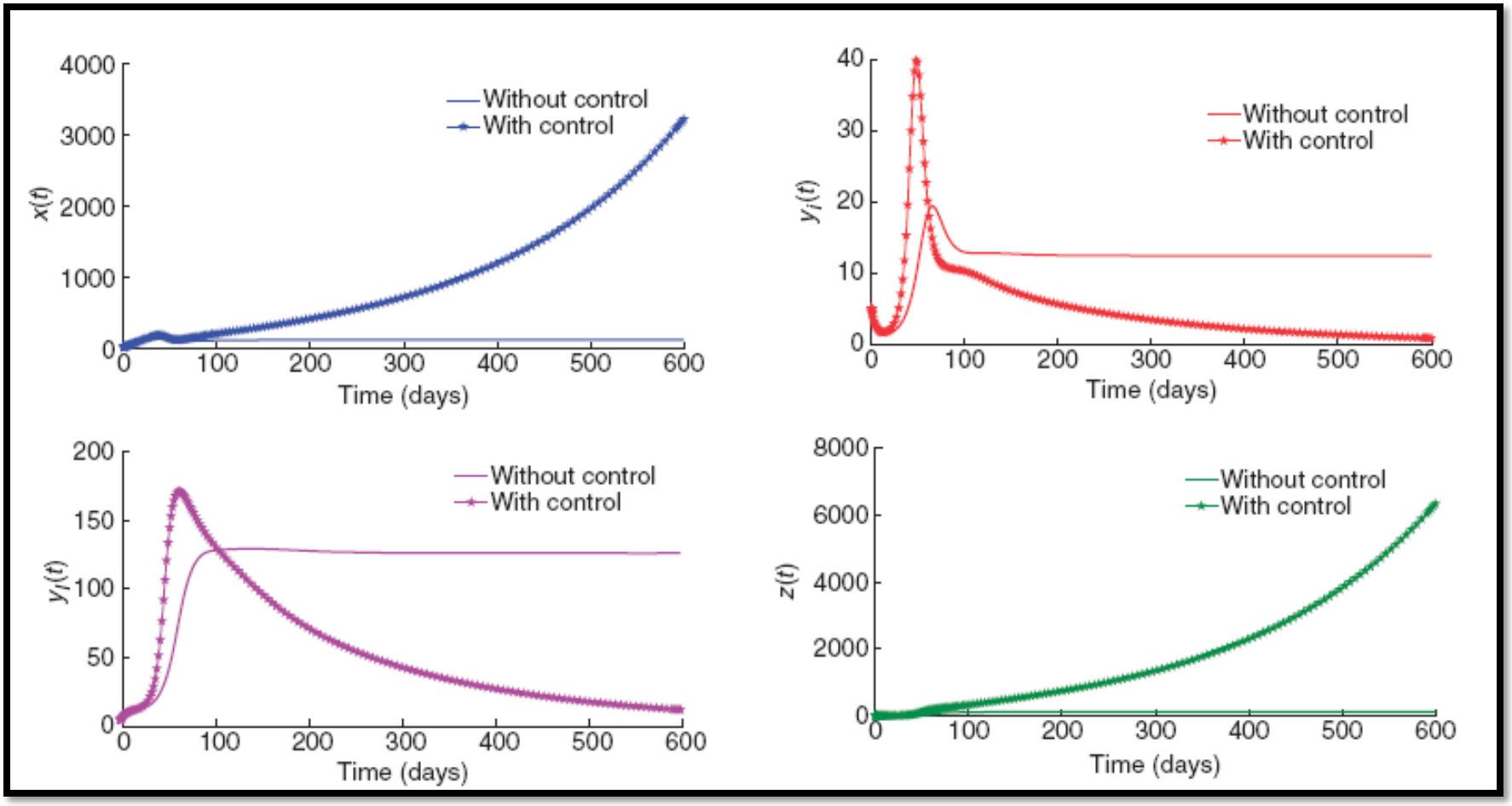


Figure 3. The system behaviour for without control ($u_1 = 0$, and $u_2 = 0$) and with control ($u_1 = 0$ and $u_2 = 0.025$).

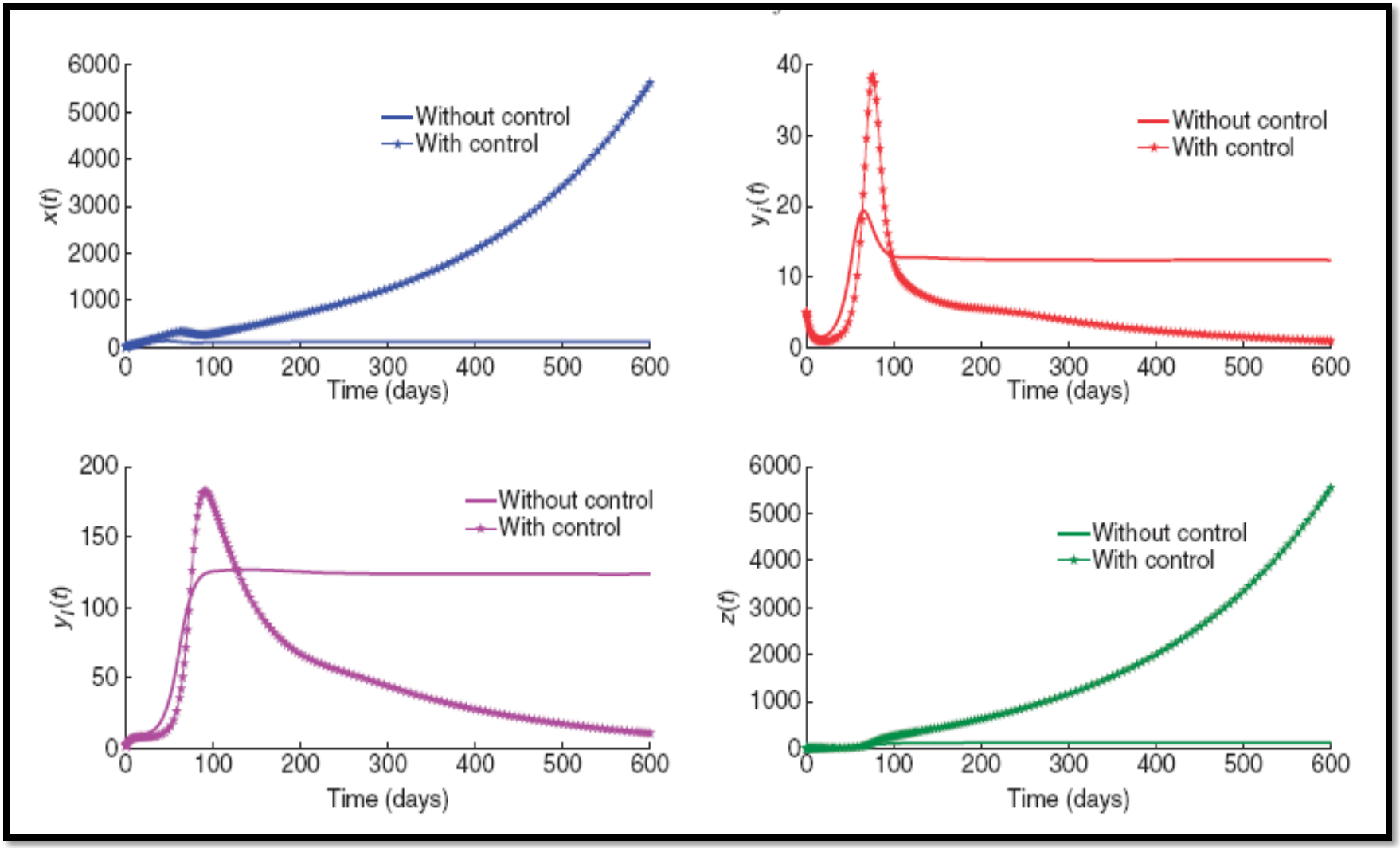


Figure 4. The system behaviour for without control ($u_1 = 0$, and $u_2 = 0$) and with control ($u_1 = 0.5$ and $u_2 = 0.025$).

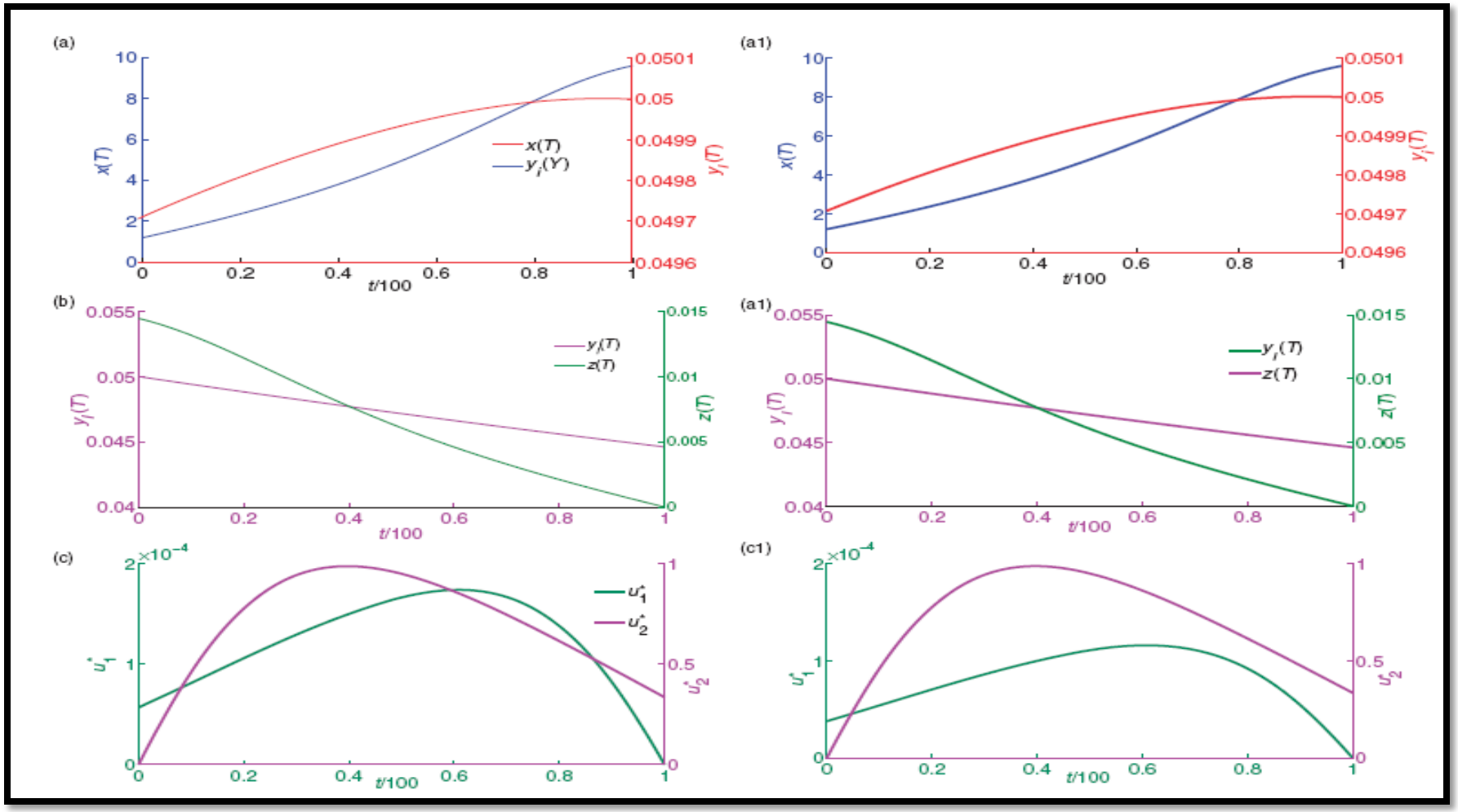


Figure 5. The system behaviour for the optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $P=10$, $Q=18$ (left panel), and for $P=15$ and $Q=18$ (right panel).

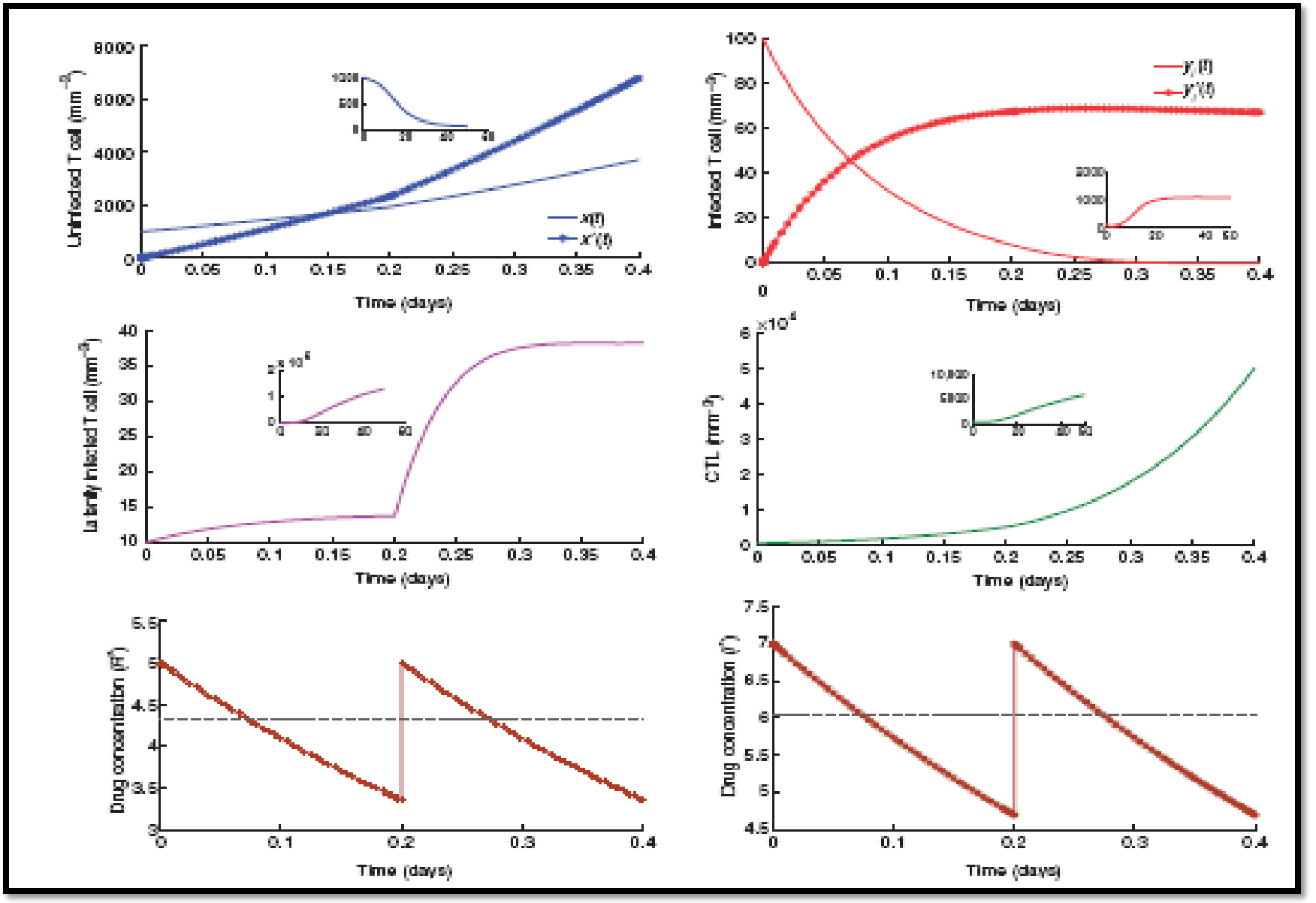


Figure 6.6: The impulsive system behaviour for the perfect adherence with R_d = 5, I_d = 7 and $\tau = \sigma = 0.2$. Inset: Trajectories for the system in absence of therapy.

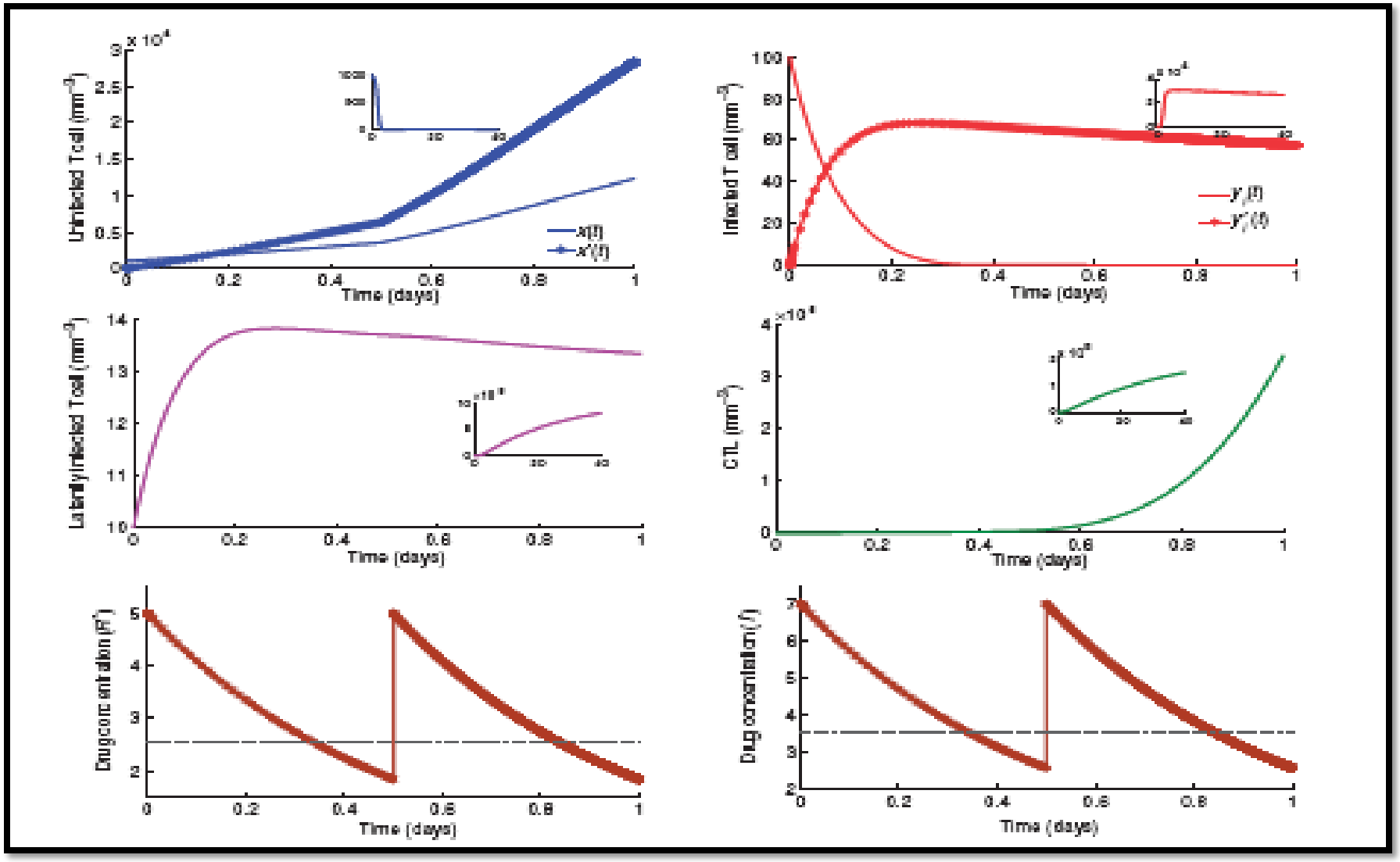


Figure 6.7: The impulsive system behaviour for the perfect adherence with R_d = 5, I_d = 7 and τ =σ= 0.5. Inset: Trajectories for the system in absence of therapy.

Discussions

- During the disease progression the antigenic response of the body is totally collapsed. Thus, only RTIs can not totally control the disease.
- Far better results will appear using immune activator IL-2, compared to only using of RTIs, because IL-2 stimulate the immune system to act properly.
- Fixed dosing interval (dosage interval for IL-2) if RTIs are taken with sufficient frequency. The infected CD4T cell population approaches towards extinction.
- If the drug dosage are taken with perfect adherence on considering the derived condition of drug doses interval and drug dosage, then cellular infection can be controlled and immune system acts properly.



Effect of awareness programs in controlling the disease HIV/AIDS: an optimal control theoretic approach

Human awareness results in the reduction of susceptibility to infection, naturally, in the epidemiological study this factor should be included





Research reveals that most HIV infections come from undiagnosed people and untreated people, but principally from **unaware people.**

Broadcast media have tremendous reach and influence, particularly with young people, so in this study, we incorporate the influence of media and investigate the effect of awareness program in disease outbreaks.

In this present study, we have analyzed a simple SI network epidemic model to study the **impact of awareness programs** conducted through media campaigning **on the spread of HIV/AIDS** in a variable population with immigration. However, these results will fall into the non-network epidemic models category



We consider a basic HIV model

$$\frac{dS}{dt} = \Pi - \beta SI - dS, \qquad (1)$$

$$\frac{dI}{dt} = \beta SI - (d + \delta_I)I,$$

where $S(t)$ and $I(t)$ are the densities of the susceptible and infected populations, respectively, in the region under consideration at any time t. Therefore, the total population is $N(t) = S(t) + I(t)$. Π is the constant recruitment rate in the susceptible population either by birth or immigration; β is the disease transmission rate; d is the natural death rate of

On the basis of the above assumptions, system (1) reduces to

$$\frac{dS_-}{dt} = \Pi - \beta S_- I_- - \alpha_1 S_- M + \lambda_1 S_+ - dS_-,$$

$$\frac{dS_+}{dt} = \alpha_1 S_- M - \lambda_1 S_+ - dS_+,$$

$$\frac{dI_-}{dt} = \beta S_- I_- - \alpha_2 I_- M + \lambda_2 I_+ - (d + \delta_I)I_-,$$

$$\frac{dI_+}{dt} = \alpha_2 I_- M - \lambda_2 I_+ - (d + \delta_I)I_+,$$

$$\frac{dM}{dt} = \eta I_- - \eta_0 M$$

with the initial conditions $S_-(0) = S_{0-}$, $S_+(0) = S_{0+}$, $I_-(0) = I_{0-}$, $I_+(0) = I_{0+}$, $M(0) = M_0$, where α_i $(i = 1, 2)$ is the contact rate between unaware individuals and media.

RESEARCH Open Access

Effect of awareness programs in controlling the disease HIV/AIDS: an optimal control theoretic approach

Springer

Advances in Difference Equations
a SpringerOpen Journal

Roy et al. Advances in Difference Equations (2015) 2015:217
DOI 10.1186/s13662-015-0549-9

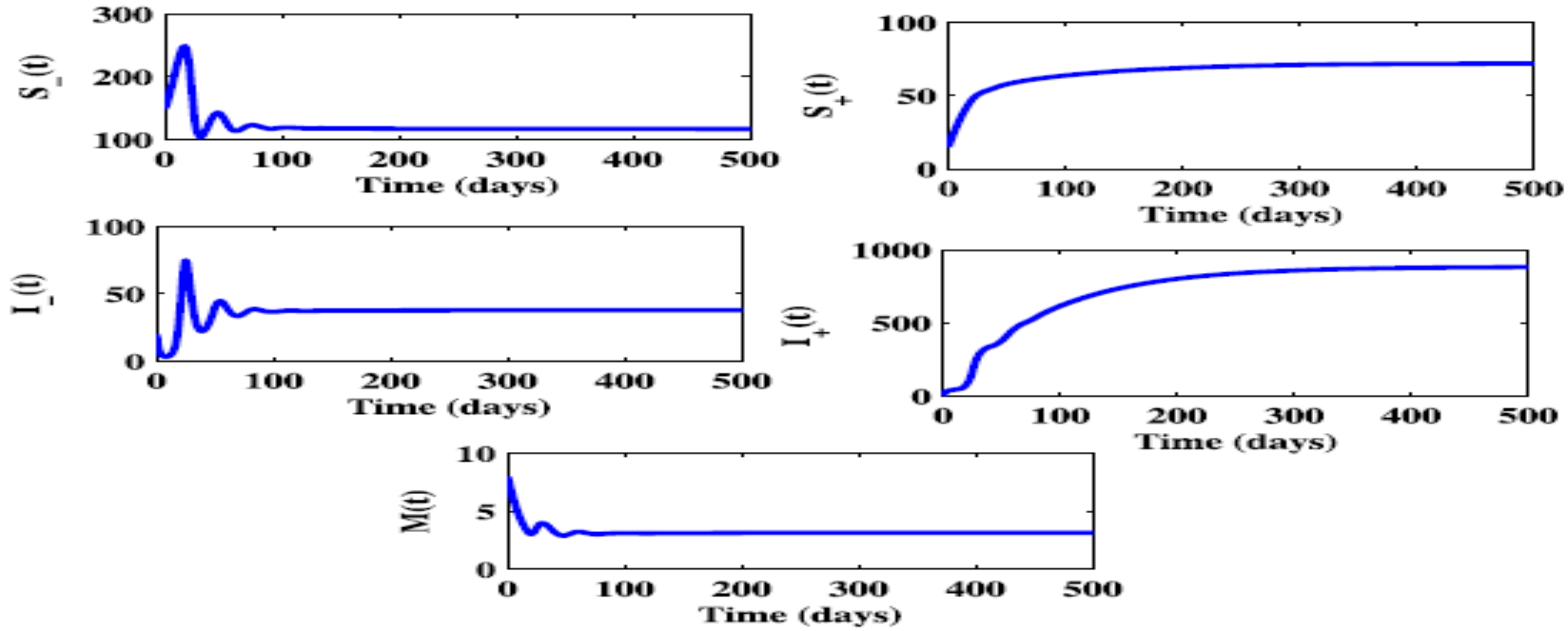


Figure 1 Variations of populations with time.

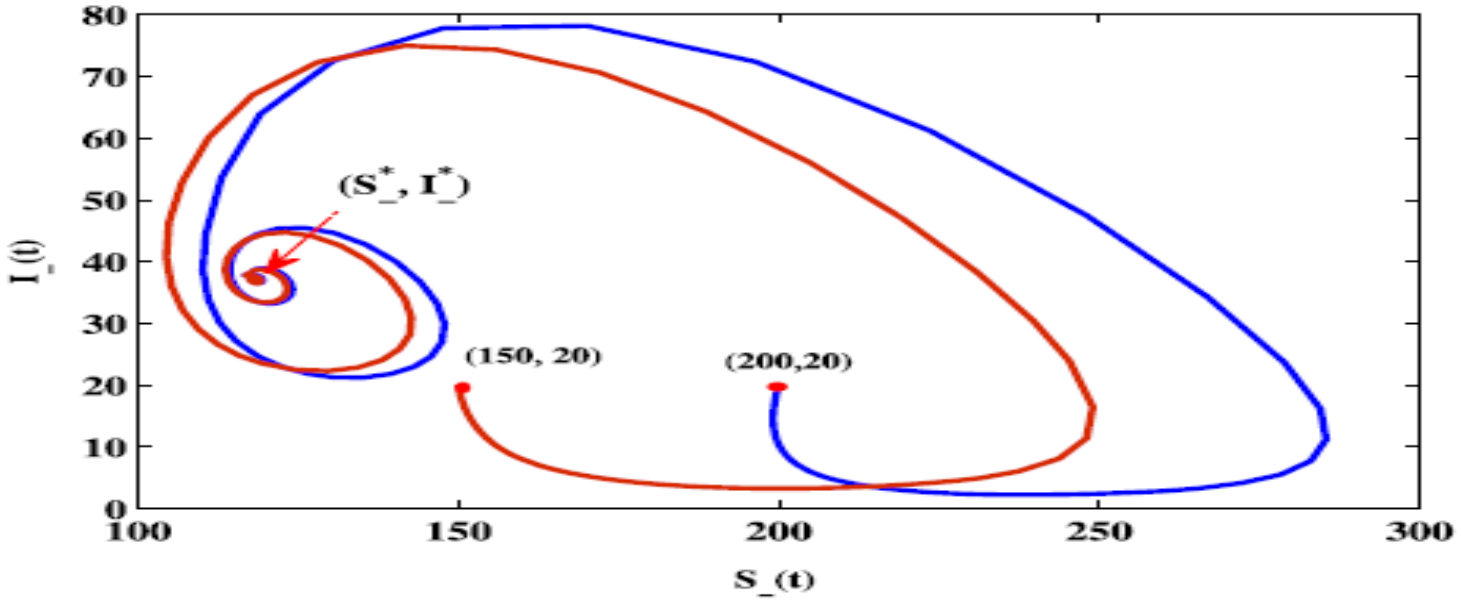


Figure 2 Non-linear stability of (S_-^*, I_-^*) in $S_-^* - I_-^*$ plane.

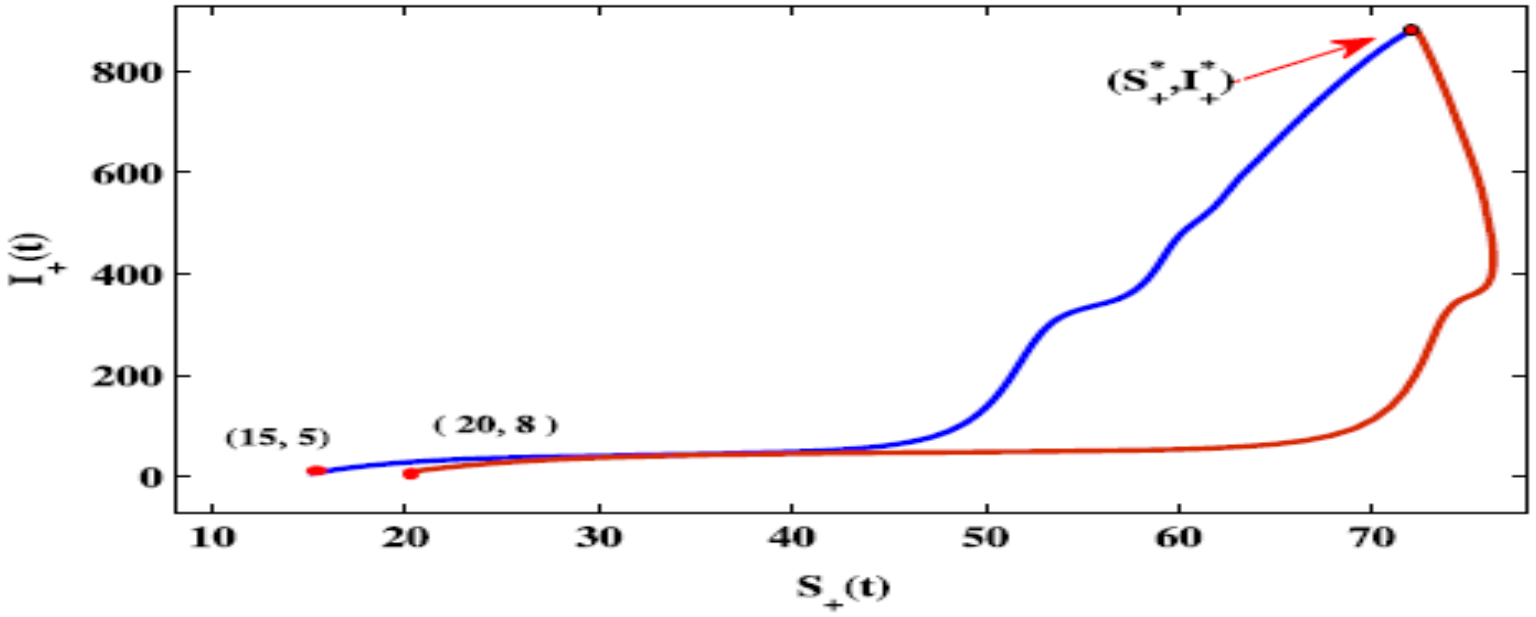


Figure 3 Non-linear stability of (S_+^*, I_+^*) in $S_+^* - I_+^*$ plane.

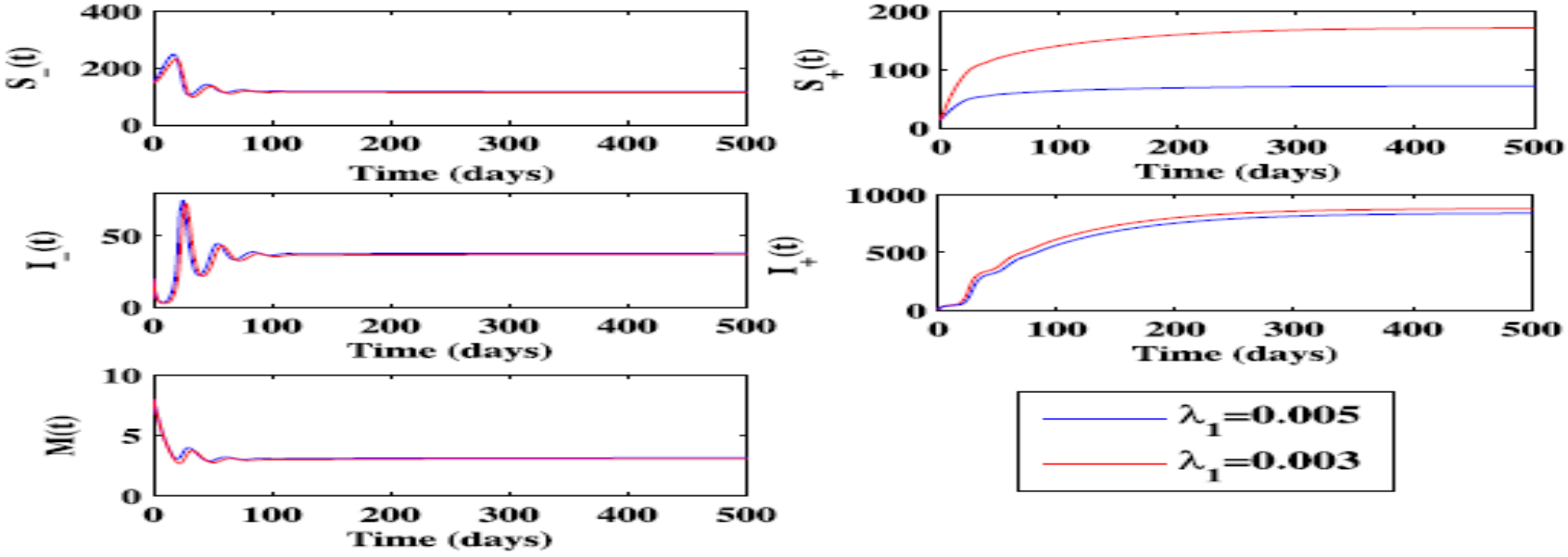


Figure 4 Variation of infected population and other populations with different values of λ_1.

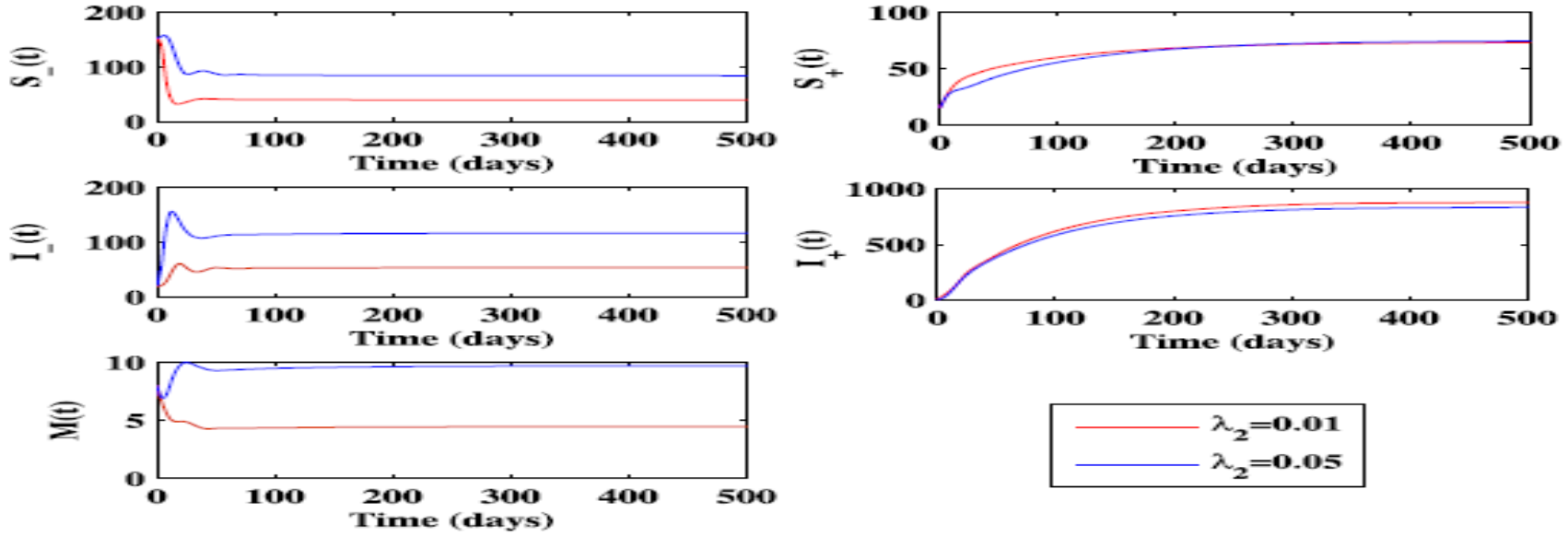


Figure 5 Variation of infected population and other populations with different values of λ_2.

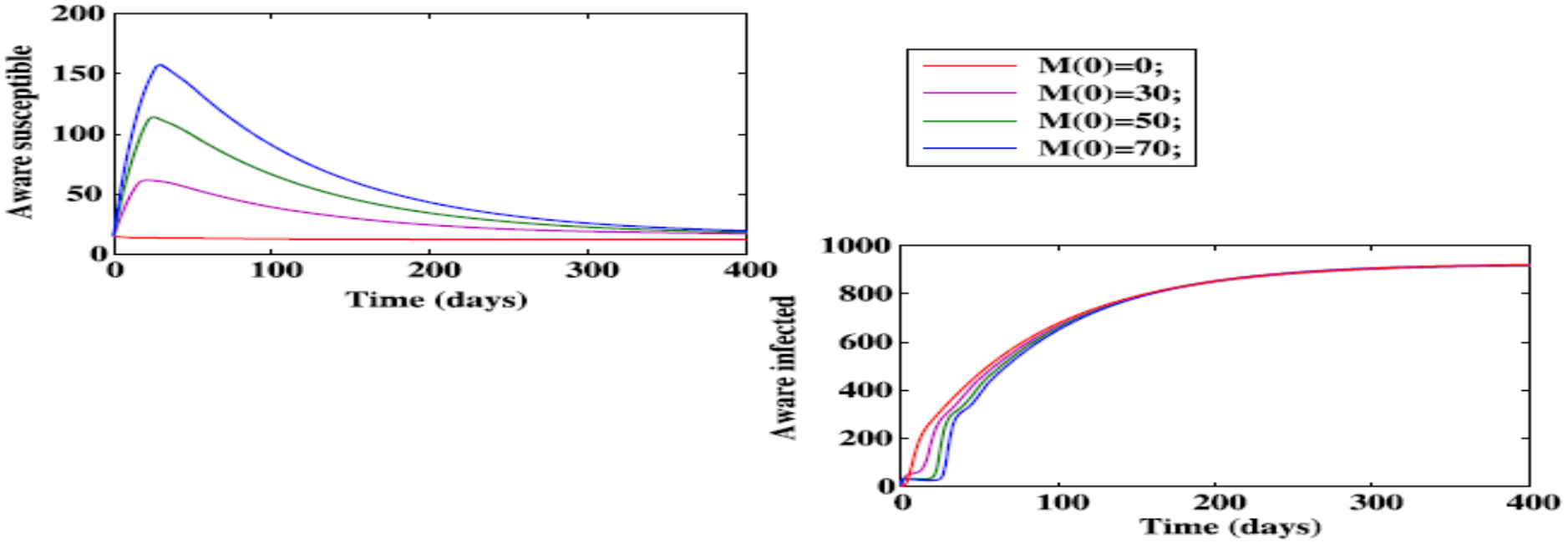


Figure 6 Awareness performance for different values of media campaign, M_0 under high infection scenario ($0.002 < \beta < 0.007$).

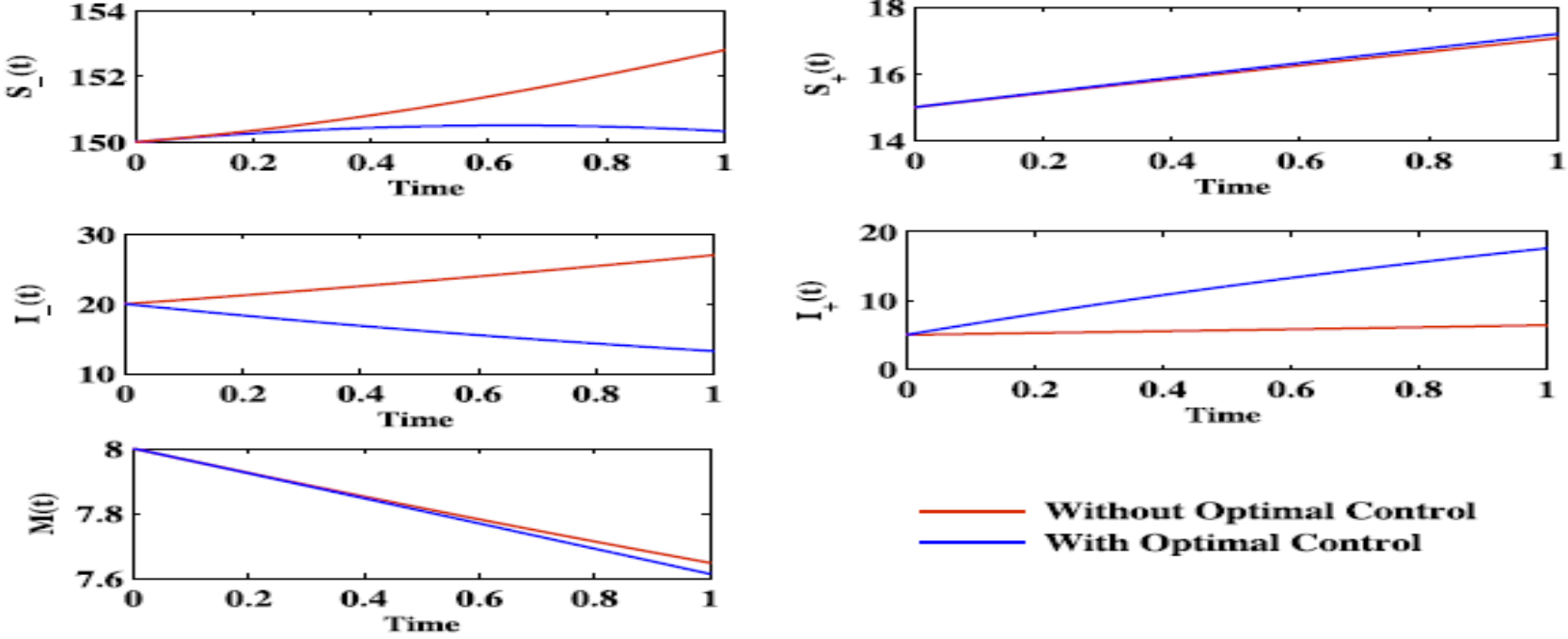


Figure 7 The system behavior for optimal control when final time is $t_f = 1$ (keeping all other parameters same as before considered).

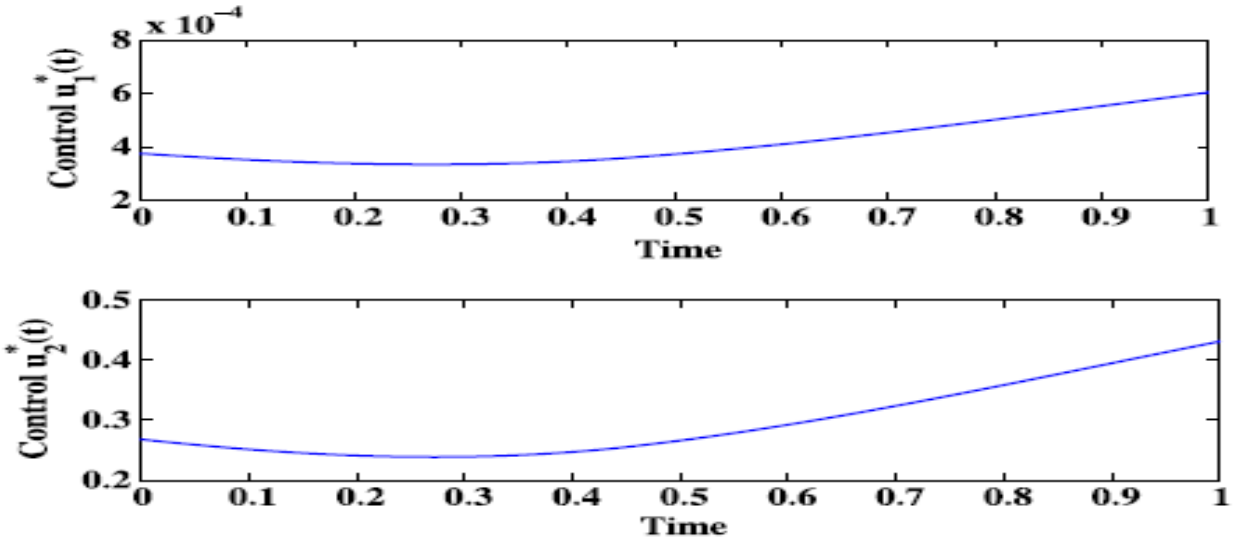


Figure 8 Optimal control parameters u_1^* and u_2^* are plotted as the functions of time, keeping all other parameters same.

Discussions

- ✓ **In the modeling process, it is assumed that media campaigns create awareness regarding personal protection as well as control AIDS.**
- ✓ **Individuals of this class not only protect themselves from the infection, but being aware they also take part in reducing AIDS by taking precautions.**
- ✓ **Awareness programs reduce the infection rate, shorten the rate of disease transmission and cut down the size of the disease.**

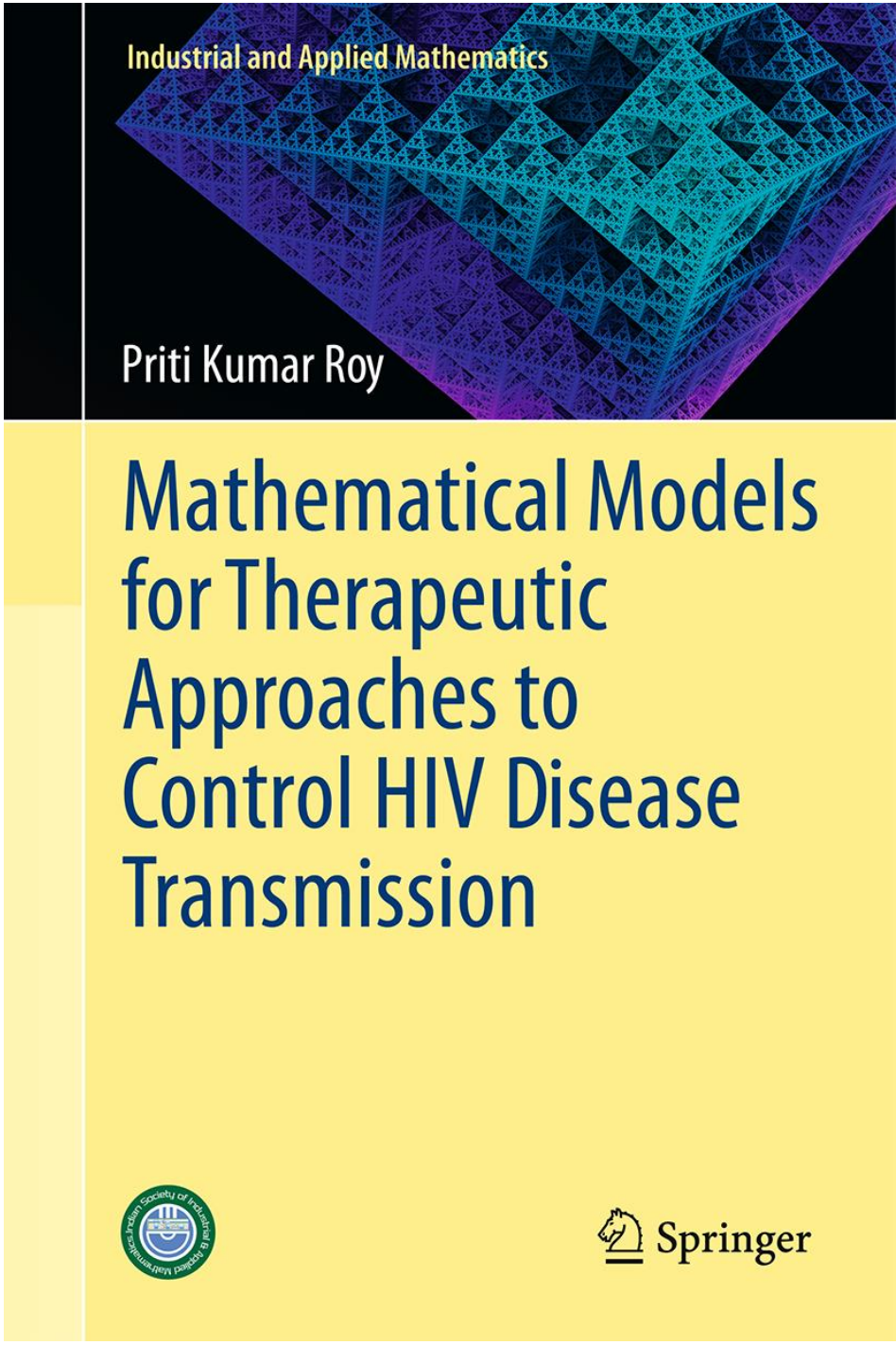






The book discusses different therapeutic approaches based on different mathematical models to control the HIV/AIDS disease transmission. It uses clinical data, collected from different cited sources, to formulate the deterministic as well as stochastic mathematical models of HIV/AIDS. It provides complementary approaches, from deterministic and stochastic points of view, to optimal control strategy with perfect drug adherence and also tries to seek viewpoints of the same issue from different angles with various mathematical models to computer simulations. The book presents essential methods and techniques for students who are interested in designing epidemiological models on HIV/AIDS. It also guides research scientists, working in the periphery of mathematical modeling, and helps them to explore a hypothetical method by examining its consequences in the form of a mathematical modeling and making some scientific predictions.

The model equations, mathematical analysis and several numerical simulations that are presented in the book would serve to reveal the consequences of the logical structure of the disease transmission, quantitatively as well as qualitatively. One of the chapters introduces the optimal control approach towards the mathematical models, describing the optimal drug dosage process that is discussed with the basic deterministic models dealing with stability analysis. Another one chapter deals with the mathematical analysis for the perfect drug adherence for different drug dynamics during the treatment management. The last chapter of the book consists the stochastic approach to the disease dynamics on HIV/AIDS. This method helps to move the disease HIV/AIDS to extinction as the time to increase. This book will appeal to undergraduate and postgraduate students, as well as researchers, who are studying and working in the field of bio-mathematical modeling on infectious diseases, applied mathematics, health informatics, applied statistics and qualitative public health, etc. Social workers, who are working in the field of HIV, will also find the book useful for complements.




Thank
You!