

Systematic Method for Determining Intravenous Drug Treatment Strategies Aiding the Humoral Immune Response¹

A. Rundell
School of Electrical and
Computer Engineering

R. DeCarlo
School of Electrical and
Computer Engineering

V. Balakrishnan
School of Electrical and
Computer Engineering
Purdue University, West Lafayette, IN 47906

H. HogenEsch
School of Veterinary
Medicine

Keywords: predator-prey modeling, nonlinear modeling, immune response modeling, intravenous antibiotic treatment, robust control, linear matrix inequalities

Abstract:

This paper delineates a systematic method for determining "optimal" intravenous drug delivery strategies for patients having illnesses that primarily evoke a humoral immune response and are treatable by antibiotics. The method derives from a nonlinear, distributed predator-prey model that captures the dominant antigen and antibody interaction. This model is developed from relevant physiology, past predator-prey-type modeling work, available data, and pertinent parameter identification. Embedding this predator-prey model into a larger class of uncertain systems, by a finite dimensional approximation and a transformation to a linear fractional representation, enables the application of robust control based on linear matrix inequality optimization techniques. The optimization problem is solved by minimizing an upper bound on a measure of the total drug delivered subject to patient recovery (stability to healthy equilibrium state). Specifically, the paper addresses the treatment of *Haemophilus influenzae* through modeling, controller development, and simulations of infected adult patients subjected to typical and proposed intravenous antibiotic treatments. Through simulations the proposed intravenous drug strategy shortens patient recovery time, lowers peak drug concentrations and decreases the total drug administered when compared to standard antibiotic strategies.

I Introduction

In the immune response to antigen, the host and antigen are both predator and prey: the antigen preys on the host and the host mounts an immune response to attack the antigen. The work herein describes a predator-prey model that captures the dominant immune response to the bacterium, *Haemophilus influenzae*, but can be generalized to most antibiotic susceptible antigens that primarily evoke a humoral immune response.

H. influenzae is a Gram negative bacterium which can cause bacterial sepsis, pneumonia, or meningitis. Because it spreads by respiratory droplets, day care centers

and homes for the elderly are often outbreak centers. Standard treatments to combat infection include antibiotics (ampicillin or ceftriaxone for ampicillin resistant strains) or immunization which is only partially successful [3].

Within the context of the predator-prey model, our overall goal is to investigate the feasibility and effectiveness of two antibiotic treatments for *H. Influenzae*: (i) a typical intravenous antibiotic treatment, and (ii) an "optimal" intravenous drug strategy. The consistency of the simulated model response with the clinical response provides a partial model validation. The control strategy is obtained by applying convex optimization techniques based on linear matrix inequalities (LMIs) [2] to reduce the total quantity of drug administered to a level below that of a typical intravenous treatment. Because of the approximations inherent in the LMI problem formulation, the solution strategies are conservative, but nevertheless, provide improvement and represent a first step in obtaining a systematic method for determining optimal drug delivery strategies.

II Relevant Immunology Overview

The host's immune system predominantly responds to *H. influenzae* with a specific humoral response producing antibodies which bind to the bacteria. These bound antibodies are bactericidal (kill the bacteria) and opsonic (promote phagocyte engulfing) [4] thereby eliminating the bacteria threat to the host. The antibodies (types IgG, IgM, and IgA [4]) are produced by plasma cells. Plasma cells are differentiated B cells which have been stimulated by active T-helper cells, stimulatory signals, and antigen.

For hosts with immune deficiencies, immature, or suppressed immune systems, the bacteria may escape early detection and proliferate to debilitating or lethal levels. AIDS patients with compromised immune systems are particularly susceptible to *H. influenzae* induced pneumonia [15]. Consequently, a mathematical model of the immune response to *H. influenzae* provides a tool for illness evaluation plus analysis and development of disease treatment strategies.

¹ This work was supported in part by ONR under contract N00014-97-1-0640.

III Model Development

The dominant disease dynamics for *H. influenzae* are modeled by the predator-prey characteristics of bacteria and antibody serum concentrations. This new predator-prey model evolved from that of Rai, Kumar, Pandé (RKP) [1] into a model quite similar to Bell's model [14]. Enhancements to and differences from Bell's model include a time delay on the antibody production rate, an upper limit on antigen concentration, and the effects of antibiotics. Our new model has an antigen rate equation

$$\frac{dB(t)}{dt} = a_1 B(t) - w \frac{(A(t) - A_{eq})B(t)}{d + \frac{B(t)}{\eta} + A(t) - A_{eq}} - bB^2(t) - \alpha B(t) u(t) \quad (3.1a)$$

and an antibody rate equation

$$\frac{dA(t)}{dt} = \rho \frac{A(t-\tau)B(t-\tau)}{\eta \left(r + A(t-\tau) + \frac{B(t-\tau)}{\eta} \right)} \left[1 - \frac{A(t)}{A^*} \right] 1^+(t-\tau) - w \frac{(A(t) - A_{eq})B(t)}{\eta \left(d + \frac{B(t)}{\eta} + A(t) - A_{eq} \right)} - a_2 (A(t) - A_{eq}) \quad (3.1b)$$

where $1^+(t-\tau) = 1$ for $t \geq \tau$ and 0 for $t < \tau$, and $B(t)$ and $A(t)$ represent antigen (bacteria) and antibody concentrations in the blood respectively. (The bacteria concentration is measured in colony forming units (cfu) per ml and the antibodies are stated in μg per ml.)

3.1 The Antigen Rate Equation

Bacterial growth, modeled by $a_1 B(t)$, with appropriate choice of a_1 , accounts for the rapid proliferation of *H. influenzae* (which in vitro is 2×10^4 cfu/ml to 6.5×10^7 cfu/ml in a matter of hours [6]) as well as the growth inhibiting effects of nonspecific serum components such as acute phase proteins and collectins [7,8]. Other bacterial growth limiting factors are the specific immune system response, resource limitations, and antibiotics.

The specific immune system response produces antibodies which are bactericidal and opsonic for *H. Influenzae*, i.e. antigen removal by antigen-antibody complex formation and phagocytosis. The removal rate is assumed to be proportional to the concentration of bound bacteria

approximated by the fraction: $\frac{(A(t) - A_{eq})B(t)}{d + \frac{B(t)}{\eta} + A(t) - A_{eq}}$

derived from a mass balance equation with the Law of Mass Action [14]. The parameter, w , is the rate of removal of these

bound bacteria. The parameter d is related to antibody avidity and immunity levels (i.e. antibody concentrations which prevent infection); η is a constant accounting for multivalent antigens and unit conversions.

Resource availability, competition for limited resources within the host, limits growth for extremely large bacteria concentrations and is accommodated within the model by a self-interaction term [1]: $-bB^2(t)$. Neglecting the effects of antibiotics and antibodies, this self-interaction term causes bacterial growth to cease as bacteria concentrations approach a_1/b . This follows from the fact that $B = [a_1 - bB(t)]B(t)$ is negative for $B(t) > a_1/b$ and positive for $B(t) < a_1/b$.

The term $-\alpha B(t) u(t)$ represents bacterial growth inhibition due to antibiotics where $u(t)$ is the drug concentration in the blood. The product term, $B(t) u(t)$, reflects the necessity of drug-antigen interaction for halting antigen growth; α is a parameter dependent on the drug's minimum inhibitory concentration (MIC); however, α must be lowered to account for bacteria inaccessible to the blood.

Equation 3.1a differs from the Bell equation in the last two terms which limit growth for extremely large bacteria concentrations, $-bB^2(t)$, and incorporate antibiotics, $\alpha B(t) u(t)$.

3.2 The Antibody Rate Equation

Production of antibodies for *H. influenzae* occurs after specific T-helper and B cells are activated by stimulatory signals and antigen contact. This is assumed to be proportional to the concentration of bound antibodies as

represented by $\rho \frac{A(t-\tau)B(t-\tau)}{\eta \left(r + A(t-\tau) + \frac{B(t-\tau)}{\eta} \right)}$. This term is

derives its form from the Law of Mass action and the associated parameters ρ and r correspond to antibody production rates, the host sensitivity to this particular antigen, and the immune system activation capability. The delay terms, $A(t-\tau)$ and $B(t-\tau)$, (a modification to the Bell model) compensate for the activation, proliferation, and differentiation times of the T-helper and B cells. To simulate saturation antibody concentration levels [14], the antibody production term is multiplied by $[1 - A(t)/A^*]$ so that as $A(t)$ approaches the upper limit A^* , antibody production ceases.

The finite effective life span of an antibody is incorporated by $-a_2(A(t) - A_{eq})$ where a_2 is the inverse of the antibody half-life and A_{eq} represents the equilibrium level of naive B cell membrane surface immunoglobulins available for stimulation at the onset of an immune response. As bound bacteria is removed from the host, the antibodies bound to the bacteria are also removed. This physiological effect is

accounted for by $w \frac{(A(t) - A_{eq})B(t)}{\eta \left(d + \frac{B(t)}{\eta} + A(t) - A_{eq} \right)}$ which

coincides (as expected) with the antigen-antibody complex removal rate in 3.1a except in the parameter, η , which adjusts for the effects of multivalent antigens and unit conversions. This activity is not explicitly represented in the original Bell model since without the delay it can be accommodated only by lowering the antibody production rate appropriately.

3.3 Simulation of Model

Traditional model validation is difficult without an abundance of experimental data. The available experimental biological data for adult infections with *H. Influenzae* was utilized to find model parameters. The model parameters, a_1 , a_2 , b , η , α , A^* , A_{eq} , and τ , were chosen to be consistent with known physiological quantities and the remaining parameters, w , d , ρ , and r , were found by meeting the few immunological observations of a typical adult response for the bacterial and antibody curves as discussed below.

Using the parameter values and initial conditions listed in Appendix I, a typical *H. influenzae* infection for a healthy adult was simulated. Figure 3.1 shows a bacteria concentration that peaks at 234 cfu/ml on about day five. This represents a typical adult response given that children not immune to *H. influenzae* exhibit much higher bacterial levels on the order of 1000 cfu/ml [11]. Figure 3.1 also indicates antibody production for five to seven days plateauing at day 7 in agreement with typical humoral immune responses [12]. Four weeks after the *H. influenzae* infection, the resulting antibody concentration is 53 $\mu\text{g/ml}$, well within the expected concentration range after one month of 35 to 180 $\mu\text{g/ml}$ [4,13].

Such a simplified model (antigen and antibody responses only) from equation 3.1 can only be expected to capture dominant aspects of the humoral immune response. As a validation exercise, simulations run with minor variations in the model parameters gave similar reasonable bacteria and antibody responses. As a further independent validation, we examined the initial bacteria response to various initial conditions on antibody concentrations. Our model indicates that for $A(0) < 0.1 \mu\text{g/ml}$ the bacteria concentration increases (infection occurs) while for initial concentrations greater than 0.1 $\mu\text{g/ml}$ the bacteria concentration decays which is consistent with literature [4, 13] that suggests bacterial growth is inhibited when circulating *H. Influenzae* specific antibody concentrations exceed the immunity level estimated between 0.06 $\mu\text{g/ml}$ to 1 $\mu\text{g/ml}$.

Illnesses which elicit a dominant humoral immune response have similar antigen-antibody dynamics since the underlying physiology is the same. This suggests that the structure of our predator prey model will capture the dynamics of other illnesses similar to *H. influenzae* with appropriate parameter values for antigen growth rate, a_1 , resource availability, b , antibody-antigen avidity, d and w , and antibiotic efficacy, α .

IV Drug Therapy as Control

To establish a baseline for later comparison of recovery time and total drug administered, we evaluate the standard intravenous drug treatment using our model for an AIDS patient with *H. influenzae* induced pneumonia.

4.1 Standard Antibiotic Intravenous Treatment

Ampicillin, an antibiotic commonly used to treat *H. influenzae*, inhibits bacteria proliferation by interfering in the bacterial cell wall synthesis process [3]. It is administered every 6 hours intravenously with dosages ranging from 500mg to 3 g over 10 to 14 days for adults [9,16]. The dominant pharmacokinetics of ampicillin, including its half-life (1 to 1.8 hours), dosage level and schedule, specify the drug concentration in the blood, $u(t)$. With a 10 day regimen administering 3 g of ampicillin four times a day and assuming a half-life of 1.5 hours:

$$u(t) \approx \sum_{k=0}^{4*10-1} 1^+(t-6k)500 \exp\left[\frac{-1}{1.5}(t-6k)\right]$$

assuming that the 3 g of ampicillin will distribute throughout the 6000 ml of blood in a short period of time.

4.2 Evaluation of Standard Antibiotic Intravenous Treatment

The rapid growth of *H. influenzae* requires drug treatment for patients with suppressed immune systems. An adult AIDS patient can contract pneumonia from exposure to the *H. influenzae* bacteria [15]. We model an AIDS patient with a suppressed immune system by making the antibody production rate, ρ , small compared to the normal healthy parameter. (Simulation shown in Figure 4.1.) With bacterial levels exceeding 1000 cfu/ml (greater than sixteen times that of a healthy adult patient), this patient is extremely ill and would probably not survive more than a few days untreated. Since an AIDS patient has a severely depressed immune system, it is reasonable to assume that the administered treatment would be the most aggressive strategy available (3 g dosages every 6 hours.) Applying this standard intravenous drug treatment to our model of an adult AIDS patient results in antigen elimination (less than one cfu/6000ml) after 9.5 days as shown in Figure 4.2. This recovery required a total administration of 114 g of ampicillin which is reasonable.

V Mathematical Formulation of the Control Problem and Solution

By applying numerical LMI optimization techniques we generate an alternative intravenous drug strategy that reduces the total quantity of drug administered to a level below that of the standard intravenous treatment. The model of equations 3.1, must be adapted to the application of LMI techniques since it is nonlinear and distributed (due to the delay). To obtain a finite dimensional model we approximate

the delay with a finite-dimensional linear time-invariant system. The nonlinearities are addressed by taking advantage of their rational nature and transforming the nonlinear model to a linear-fractional representation which consists of a linear system with a feedback loop containing multiple copies of the state variables. The state variables appearing in the feedback loop can be artificially regarded as "structured, bounded uncertainties" and standard LMI techniques from robust control can be employed. In effect, this embeds the nonlinear system in a family of uncertain systems. Controllers are generated that are guaranteed to work for all members of this family, which in turn are guaranteed to work for our specific nonlinear model. Our objective is to determine a strategy for drug delivery that minimizes the total drug administered subject to the constraint that the patient recovers; this is accomplished by minimizing an upper bound for the drug - antigen interaction.

5.1 Expressing Model in Suitable Form for Application of LMI Techniques

A 4th order Bessel filter with linear phase [5] is used to obtain a finite dimensional approximation of the time delay:

$$\begin{aligned} \frac{dx}{dt} &= A_d x(t) + B_d h(t) \\ y(t) &= x_1(t) \approx h(t-\tau) \end{aligned}$$

where $x(t) \in \mathbb{R}^4$ and $y(t)$ approximates the delayed input $h(t)$. (The Bessel filter was chosen to be fourth order so as not to increase the dimension and complexity of the resulting LMIs beyond what is reasonable to formulate and solve.) Incorporating this model for the delay in equations 3.1 results in a model of the form:

$$\frac{dx}{dt} = f(x) + B_u g(x) u \quad (5.1)$$

where $x = [B \ A \ x_1 \ x_2 \ x_3 \ x_4]^T$ and $f(x)$ and $g(x)$ are rational functions. We require the finite dimensional model to approximately match the input/output relationship (antigen infection dose/antigen and antibody responses) of the original nonlinear differential delay model (3.1). This requires adjusting the parameters associated with the antibody production rate, ρ and r , in equation 5.1. Figure 5.1 compares the resulting approximate finite dimensional model and the original model. Appendix II lists the explicit equations of 5.1 with the parameters for the Bessel filter and the adjusted values for ρ and r .

With the substitution of $u = g(x) u$, the rational form of $f(x)$ can be used to obtain an equivalent linear fractional representation (LFR) of 5.1 using techniques from El Ghaoui and Scorletti [10] and Balakrishnan and Boyd [26]. The resulting LFR is given by:

$$\begin{aligned} \frac{dx}{dt} &= A_m x + B_p p + B_u u \\ q &= C_q x + D_{qp} p \\ p &= \Delta(x) q \\ \Delta(x) &= \text{diag}(B(t), B(t), B(t), B(t), A(t) - A_{eq}, A(t) - A_{eq}, A(t) - A_{eq}, A(t) - A_{eq}) \end{aligned} \quad (5.2)$$

where $x = [B \ (A-A_{eq}) \ x_1 \ x_2 \ x_3 \ x_4]^T$. In effect, we have an approximate model of our system which consists of a linear part with multiple copies of the state $x(t)$ appearing in the feedback loop (see Figure 5.2). By bounding the norm of the feedback, $\|\Delta(x)\| \leq 1/\sigma$, the LFR defines a class of uncertain systems. Our original nonlinear model is a member of this class. Models such as these routinely appear in robust control [2, 10] and motivate our use of robust control techniques. Note that system 5.2 has an equilibrium state at $x = 0$ which represents a patient with no infection. Appendix III states the associated LFR matrices.

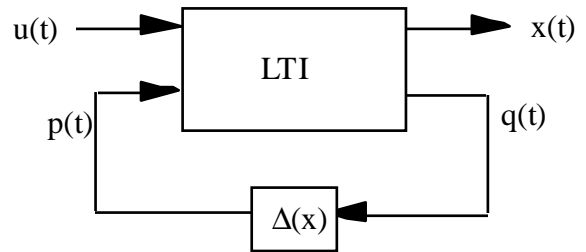


Figure 5.2 Linear Fractional Representation

5.2 LMI based Control Synthesis

There are three steps to generate a controller using LMI techniques: (i) the selection of a Lyapunov function, $V(x) = x^T P x$ with symmetric $P > 0$, and controller architecture, $u(t) = K_1 x + K_2 p$, (ii) the formulation of the conditions on the Lyapunov function and controller parameters that guarantee properties desired of the closed loop system, and (iii) a numerical search to solve the resulting LMIs from which we can find numerical values for P , K_1 and K_2 subject to (i) and (ii).

The objective is to generate a drug delivery strategy that minimizes total drug dosage subject to the patient's recovery. Stability to the zero equilibrium level assures patient recovery, guaranteed when the derivative of the Lyapunov function is negative, $\frac{dV}{dt} < 0$ for $x \neq 0$. One measure for quantifying drug dosage is a bound on the total drug-antigen interaction as represented by $\int (Bu)^2 dt$ and thereby limit the total drug delivered. Under the assumption that the linear portion of the control ($K_1 x$) dominates the controller effort (justified since the bacterial growth rate term in equation 3.1a is linear and is the only positive rate term), we have:

Expressing $u(t) = K_1x + K_2p$ within the context of our model as a combination of static linear and nonlinear feedback terms plus a dynamic linear feedback component yields:

$$u(t) = \kappa_1 B(t) + -\kappa_5 \frac{(A(t) - A_{eq})B(t)}{d + \frac{B(t)}{\eta} + A(t) - A_{eq}} - \kappa_6 B(t)^2 + \kappa_2 X_2 + \kappa_3 X_3 + \kappa_4 X_4. \quad (5.8)$$

This stabilizing controller was generated with a local ‘artificial’ restriction of the state variables in $\Delta(x)$ to a ball of radius $1/\sigma$. Sigma was chosen to be sufficiently large, $\sigma = 1000$, so that a controller existed. If the initial conditions of the states are within the ball ($B(0) < 1/\sigma$ and $A(0) - A_{eq} < 1/\sigma$), the controller maintains the states within the ball and stabilizes the system to the zero bacteria equilibrium ($B = 0$ and $A = A_{eq}$), guaranteeing patient recovery.

The ratio R of the L_2 -norm of the dynamic linear feedback terms of the controller ($\kappa_2 X_2 + \kappa_3 X_3 + \kappa_4 X_4$) to the L_2 -norm of the static linear and nonlinear terms approximates 10^{-10} for our particular model parameters. This negligible influence permits us to ignore these terms (by setting $\kappa_2 = \kappa_3 = \kappa_4 = 0$). It is easy to check that the original model maintains stability about the equilibrium with the truncated control.

Sufficient conditions on the controller parameters to eliminate the antigen for all infection levels are found by examining the bacteria rate equation. Provided the controller parameters satisfy $\kappa_1 > a_1/\alpha$, $\kappa_2 \geq 0$, $\kappa_3 \geq 0$, $\kappa_4 \geq 0$, $\kappa_5 < d/\alpha$,

and $\kappa_6 < b/\alpha$, this controller forces $\frac{dB(t)}{dt}$ negative, for all non negative values of $A(t)$ and $B(t)$, driving $B(t)$ towards zero and ensuring patient recovery from serious infections. For *H. influenzae* the controller parameters meet these conditions and guarantee complete bacterial elimination from the host. Therefore we have recovery for all non-negative values of the state variables outside the ball of radius $1/\sigma$.

The nonlinear control terms have the same structure as the antigen-antibody complex removal term and the self-interaction term on the antigen. These terms reduce the required drug concentration as the antibody concentration increases or as the self-interaction antigen rate term increases. The conservative control of 5.8 is the primary bacterial removal source until the antibody concentration, $A(t)$, reaches inhibitory levels at which point the drug contribution to bacterial removal is reduced and eventually eliminated as $A(t)$ becomes sufficiently large. In such cases, the LMI derived controller, $u(t)$, goes negative unnecessarily eliminating excess antibody by theoretically introducing controlled amounts of antigen for complex formation. Physiologically, $u(t)$ is lower bounded by zero. Incorporation of the constraint $u(t) \geq 0$ in the LMI problem formulation is an area of future research. In keeping with physiology, $u(t) \geq 0$ for all simulations.

VI Simulations and Immunological Interpretation of Results

Since mathematical models merely reflect the dominant characteristics of a system, any simulation must be accompanied by some mathematical interpretation of the physiology, and mathematical assumptions to accommodate unmodeled physiology. For simulation purposes we assume that bacterial levels less than or equal to one cfu in the host ($B(t) \leq 1/6000$ cfu/ml) corresponds to successful bacterial elimination.

We simulate the patient response using the Gear algorithm in Simulink to numerically solve the model of equations 3.1. System parameters and initial conditions can be found in Appendices I. The desired drug concentration, $u(t)$, is implemented as

$$u(t) = \begin{cases} 0 & \text{if } u(t) < 0 \\ \frac{u(t)}{B(t) + \epsilon} & \text{otherwise.} \end{cases} \quad (6.1)$$

This conversion rule from the drug-antigen interaction controller, $u(t)$ of equation 5.8 (recall $\kappa_2 = \kappa_3 = \kappa_4 = 0$), to $u(t)$ helps avoid numerical complications when $B(t)$ is very small by using a small (less than $1/6000$ cfu/ml) positive regularization constant ϵ . Physiologically, once $B(t) < 1/6000$ cfu/ml, the drug dosages may be discontinued ($u(t) = 0$).

Figure 6.1 shows the responses of a healthy adult and an immune suppressed AIDS patient with treatment immediately following infection by 100 cfu. In both cases the bacterial removal is completed within 2.5 days using a continuous constant drug concentration less than $138 \mu\text{g/ml}$ tailing off after one and a half days. Even though patients are not administered an intravenous drug delivery system upon immediate exposure to the bacteria, the simulations provide validation of the effectiveness of the control strategy.

Figure 6.2 profiles our proposed drug strategy, applied four days after bacterial infection, which successfully eliminates the bacteria with a peak drug concentration less than $138 \mu\text{g/ml}$. For the healthy patient, the drug concentration decays rapidly after only one-half day since the antibody concentration has grown large enough to effectively eliminate the bacteria unaided by antibiotics. For an AIDS patient, with a suppressed immune system, the simulation indicates an expected longer treatment duration.

Applying our drug strategy at day 10 to a critically ill AIDS patient (bacteria concentration approaching 4000 cfu/ml) requires a continuous drug delivery as shown in Figure 6.3. Comparison with the standard ampicillin technique (Figure 4.2 and 6.4) demonstrates a shorter recovery time (8 vs. 9.5 days) and a lower peak drug concentration ($138 \mu\text{g/ml}$ vs. $500 \mu\text{g/ml}$). In addition, our proposed treatment required 6% less drug administration

(106.8 g vs. 114 g) where an initial 0.828 g dosage followed by a continuous constant drug delivery rate of .552 g/hr for 8 days approximates $u(t)$.

The LMIs, as stated in problem 5.7, do not explicitly guarantee robustness to any model parameter variations. However, the resulting controller stabilizes a class of uncertain systems containing our nonlinear model, this provides some robustness to parameter variations that maintain the system within this class. With the controller from equation 5.8, we observed robustness to variations in model parameters representing antibody affinity or production rates and somewhat robust to bacterial growth rates and antibiotic efficacy. Simulations (not shown) indicated stability for small deviations of these parameters from their nominal values as would be expected from the sufficient conditions stated in section 5.3 for a stabilizing controller. To explicitly include robustness to certain parameter variations in the controller design one must augment $\Delta(x)$ to include parameter uncertainties: specifically $\Delta(x)$ would become $\Delta(x, \delta a_1, \delta w, \delta p, \text{etc.})$ and would change from an 8 to an $8+n$ diagonal matrix (here n = number of uncertain parameters). This is a standard technique [2] which we have chosen not to pursue since it attaches an additional objective to our goal of minimizing total drug administered and further complicates our procedure without providing any additional insight.

"Optimal" drug treatments for other illnesses similar to *H. influenzae* whose dominant dynamics are captured by our predator-prey model, can be obtained from the numerical solution of the same eigenvalue problem of 5.7 evaluated with appropriate model parameter value modifications. Similar results indicating continuous constant drug delivery until antibody levels exceed inhibitory levels are expected.

VII Conclusions

Although at the current time it is not possible to monitor the bacteria and antibody concentrations continuously, the control techniques presented in this paper provide a benchmark against which other strategies can be compared and indicate that an alternative continuous dosage strategy is preferable to the currently administered one of periodic dosages. In particular, simulation results suggest that a constant drug concentration may be advantageous over the standard strategy due to a decrease in peak drug concentrations, decrease in treatment duration, and a decrease in total drug administered. Patients with severely suppressed immune systems require a longer treatment duration since their antibodies do not contribute significantly to the elimination of bacteria. Due to the conservative nature of the LMI solutions, the drug levels proposed are robust to variations in the antibody affinity or production rates and somewhat robust to bacterial growth rates and antibiotic efficacy. Explicit robustness to parameter variations in the

controller design was not pursued but would only require a few modifications [2].

The current problem formulation within the LMI framework does not fully utilize the structure of our original nonlinear equations. Physiologically, better utilization of the ability of the immune system to respond will allow us to further reduce the total drug delivered. Alternate techniques which take fuller advantage of the nonlinearities (the effects of the antibodies binding to the antigen) are currently under investigation.

VIII References

- [1] Rai, V., V. Kumar, and L. Pandé, "A New Prey-Predator Model," *IEEE Transactions on Systems, Man and Cybernetics*, Vol. 21, No 1, pp. 261-263, Jan./Feb. 1991.
- [2] Boyd, S., L. El Ghaoui, E. Feron, and V. Balakrishnan, *Linear Matrix Inequalities in System and Control Theory*, *Studies in Applied Mathematics SIAM*, Vol. 15, Philadelphia, PA, 1994.
- [3] Hoepflich, P., M. Jordan, and A. Ronald, *Infectious Diseases, a Treatise of Infectious Processes*, Philadelphia: J.B. Lippincott Company, 5th edition, 1994.
- [4] Schreiber, J., V. Barrus, K. Cates, and G. Siber, "Functional Characterization of Human IgG, IgM, and IgA Antibody Directed to the Capsule of Haemophilus influenzae Type b," *Journal of Infectious Diseases*, Vol. 153, No 1, pp. 8-16, Jan. 1986.
- [5] Johnson, D., *Introduction to Filter Theory*, New Jersey: Prentice-Hall, Inc., pp. 133 -153, 1976.
- [6] Langford, P., and E. Moxon, "Growth of Haemophilus influenzae Type b in the Presence of Bovine Aortal Endothelial Cells," *Journal of General Microbiology*, Vol. 137, pp. 1577-1581, 1991.
- [7] Holmskov, U., R. Malhotra, R. Sim, and J. Jensenius, "Collectins: Collagenous C-type Lectins of the Innate Immune Defense System," *Immunology Today*, Vol. 15, No 2, pp. 67-74, 1994.
- [8] Steel, D., and W. Whitehead, "The Major Acute Phase Reactants: C-reactive Protein, Serum Amyloid P Component and Serum Amyloid A Protein," *Immunology Today*, Vol. 15, No 2, pp. 81-88, 1994.
- [9] *Drug Information Handbook*, ed. Charles Lacy, L. Armstrong, R. Lippy, and L. Lance, 2nd Edition, Cleveland: Lexi-comp Inc., 1994.

[10] El Ghaoui, L., and G. Scorletti, "Control of Rational Systems using Linear-Fractional Representations and Linear Matrix Inequalities," *Automatica*, Vol. 132, No 9, Sept. 1996.

[11] Welch, D. R., Clinical Microbiology Laboratories, University Hospitals, Oklahoma City, Personal Communiqué, May 1996.

[12] Roitt, I., Brostoff, J., and D. Male, *Immunology*, Chicago: Mosby, 3rd Ed., 1993.

[13] Griswold, W., A. Lucas, J. Bastian, and G. Garcia, "Functional Affinity of Antibody to the Haemophilus influenzae Type b Polysaccharide," *The Journal of Infectious Diseases*, Vol. 159, No 6, pp. 1083-1087, June 1989.

[14] Bell, G. I., "Predator-Prey Equations Simulating an Immune Response", *Mathematical BioSciences*, Vol. 16, pp. 291-314, 1973.

[15] *Conn's Current Therapy*, ed. Robert E. Rakel, Philadelphia: W. B. Saunders Company, 1996.

[16] Gahart, B., *Intravenous Medications*, 9th Edition, Boston: Mosby Year Book, 1993.

[17] Hiriart-Urruty J-B. and C. Lemaréchal, *Convex Analysis and Minimization Algorithms I & II*, Grundlehren der Mathematischen Wissenschaften, Vol. 305,306, Springer - Verlag, 1993.

[18] Nesterov, Y., and A. Nemirovsky, *Interior-point Polynomial Methods in Convex Programming*, *Studies in Applied Mathematics SIAM*, Vol. 13, Philadelphia, PA, 1994.

[19] LMI Control Toolbox, The MathWorks, Inc., 1995.

[20] El Ghaoui, L., F. Delebecque, and R. Nikoukhah, LMITOOL: A User-friendly Interface for LMI Optimization. ENSTA/INRIA, 1995. Software available via anonymous FTP from ftp.inria.fr, under directory pub/elghaoui/limitool.

[21] S. Boyd and C. Barratt, *Linear Controller Design: Limits of Performance*, Prentice-Hall, 1991.

[22] O. Mangasarian, *Nonlinear Programming*, McGraw-Hill, 1969. Reprinted in 1994 in SIAM Classics in Applied Mathematics series.

[23] A. Packard, "Gain Scheduling via Linear Fractional Transformations", *System and Control Letters*, Vol. 22, pp. 79-92, 1994.

[24] W. M. Lu and K. Zhou and J.C. Doyle, "Stabilization of LFT systems", *Proceedings of the 30th CDC Conference*, pp 1239-1244, 1991.

[25] P. Apkarian, and P. Gahinet, "A convex characterization of Gain-Scheduled H_∞ Controllers", *IEEE Transactions on Automatic Control*, Vol. 40, No. 5, pp. 853-864, 1995.

[26] V. Balakrishnan and S. Boyd, "Global Optimization in Control System Analysis and Design", *Control and Dynamic Systems: Advances in Theory and Applications*, ed. C. T. Leondes, New York, New York: Academic Press, Vol. 53, 1992.

Appendix I: Model Parameters

$a_1 = .09/\text{hr}$, $b = 2.25 \times 10^{-5} \text{ ml/cfu/hr}$, $a_2 = 1.54 \times 10^{-3}/\text{hr}$, $\eta = 4.12 \times 10^{13} \text{ cfu}/\mu\text{g}$, $w = .237/\text{hr}$, $d = .158 \mu\text{g/ml}$, $\rho = 8 \times 10^{11}$, (AIDS 8×10^4)/hr, $r = 8 \times 10^{-5} \mu\text{g/ml}$, $\alpha = .0013 \text{ ml}/\mu\text{g/hr}$, $A^* = 1500 \mu\text{g/ml}$, $A_{\text{eq}} = 1.455 \times 10^{-7} \mu\text{g/ml}$, $\tau = 48 \text{ hr}$, $A(0) = A_{\text{eq}}$, $B(0) = .0167 \text{ cfu/ml}$, $K_1 = [137.5 \ 0 \ 0 \ 0.0001 \ 0.0007 \ 0.0034]$, $K_2 = [-181.0417, 181.0417, -0.0172, 0, 181.0417, 0, 0, 0, 0]$

Appendix II: Parameters for Finite Dimensional Delay Approximation

$\rho = 1.4 \times 10^{12}$ (AIDS 1.5×10^8)/hr, $r = .01$ (AIDS $.2$) $\mu\text{g/ml}$, A_d is a standard companion with bottom row $[-1.978 \times 10^{-5}, -9.49 \times 10^{-4}, -.0195, -.2083]$, $B_d = [0 \ 0 \ 0 \ 1.978 \times 10^{-5}]^T$

$B(t)$ same as 3.1a

$$A(t) = x_1 \left[1 - \frac{A(t)}{A^*} \right] I^+(t - \tau) - a_2(A(t) - A_{\text{eq}}) - \frac{w(A(t) - A_{\text{eq}})B(t)}{\eta(d + B(t)/\eta + A(t) - A_{\text{eq}})}$$

$$h(t) = \frac{\rho A(t)B(t)}{\eta \left(r + A(t) + \frac{B(t)}{\eta} \right)}$$

Appendix III: Matrices for Linear Fractional Representation

$$A_m = \begin{bmatrix} a_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & -a_2 & 1 - \frac{A_{\text{eq}}}{A^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ \frac{\rho b_4}{\eta(r + A_{\text{eq}})} & 0 & -a_{4d} & -a_{3d} & -a_{2d} & -a_{1d} \end{bmatrix}$$

$$B_u = [-\alpha \ 0 \ 0 \ 0 \ 0 \ 0]^T$$

$$\begin{aligned}
\mathbf{B}_p = & \begin{bmatrix} -w & w & -b & 0 & w & 0 & 0 & 0 \\ -w/\eta & w/\eta & 0 & 0 & w/\eta & -1/A^* & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_4 \rho/\eta & 0 & 0 & -b_4 \rho/\eta & b_4 \rho/\eta \end{bmatrix} \quad \mathbf{D}_{qp} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1/d\eta & -1/d\eta & 0 & 0 & -1/d\eta & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1/(r+A_{eq})\eta & 0 & 0 & -1/(r+A_{eq})\eta & 0 \\ 1/d & -1/d & 0 & 0 & -1/d & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1/r+A_{eq} & 0 & 0 & -1/r+A_{eq} & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & -1 & 0 \end{bmatrix} \\
\mathbf{C}_q = & \begin{bmatrix} 0 & 1/d & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ \frac{1}{(r+A_{eq})^2 \eta} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ \frac{1}{(r+A_{eq})^2} & 0 & 0 & 0 & 0 & 0 \\ \frac{1}{r+A_{eq}} & 0 & 0 & 0 & 0 & 0 \end{bmatrix}
\end{aligned}$$

Figure 3.1: Haemophilus Influenzae Infection of Healthy Patient

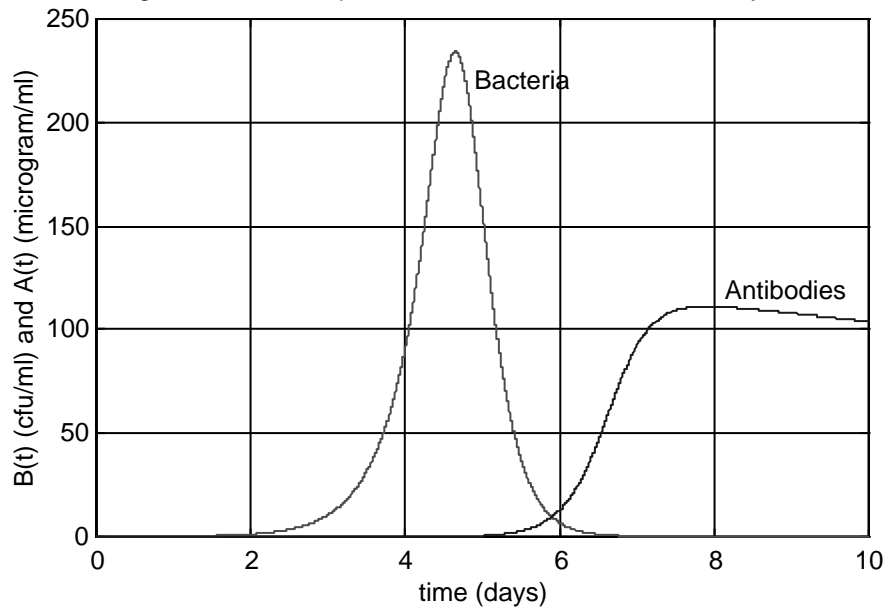


Figure 4.1: Haemophilus Influenzae Infection of AIDS Patient

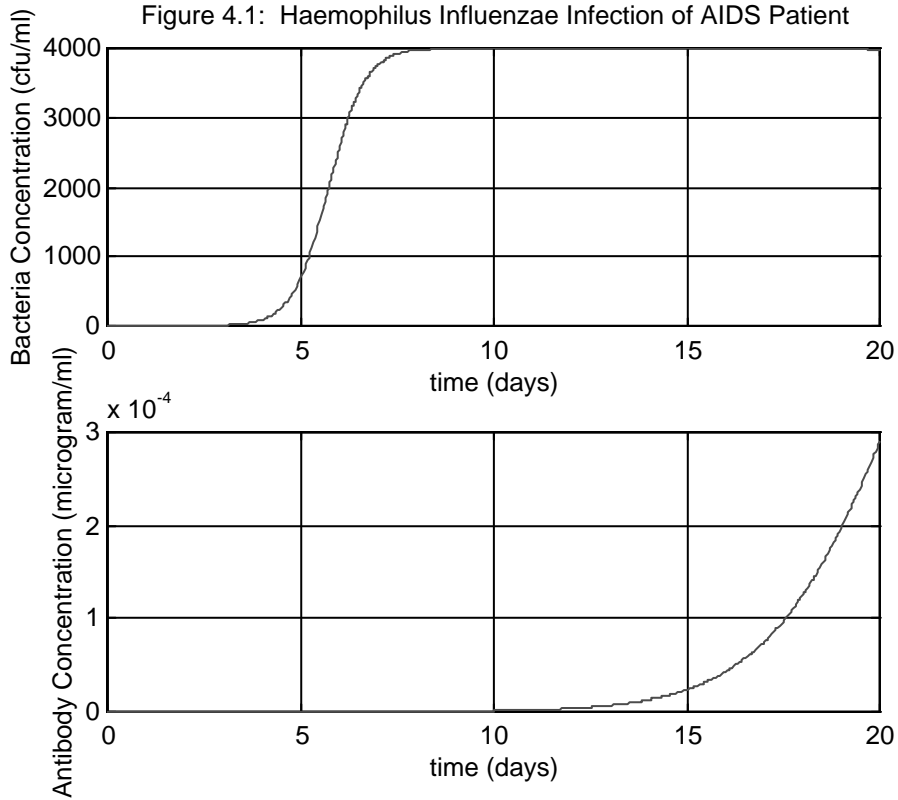


Figure 4.2: Evaluation of Standard Intravenous Treatment

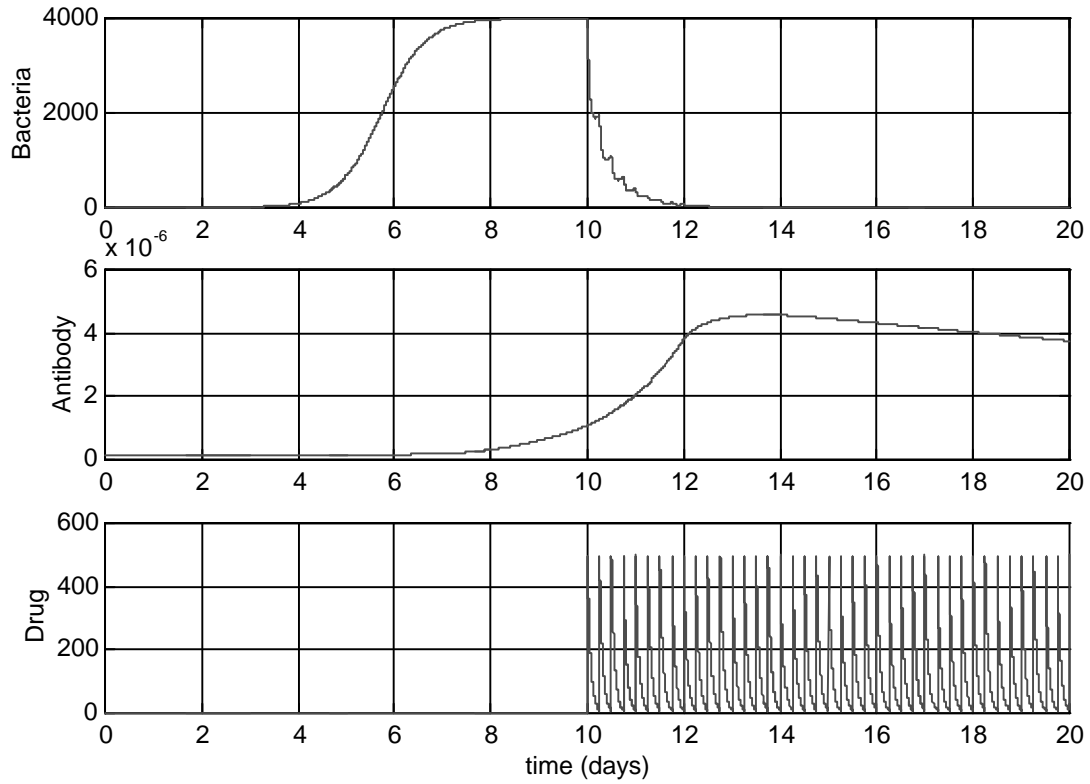


Figure 5.1: Comparison of Finite Dimensional Model and Delay Model

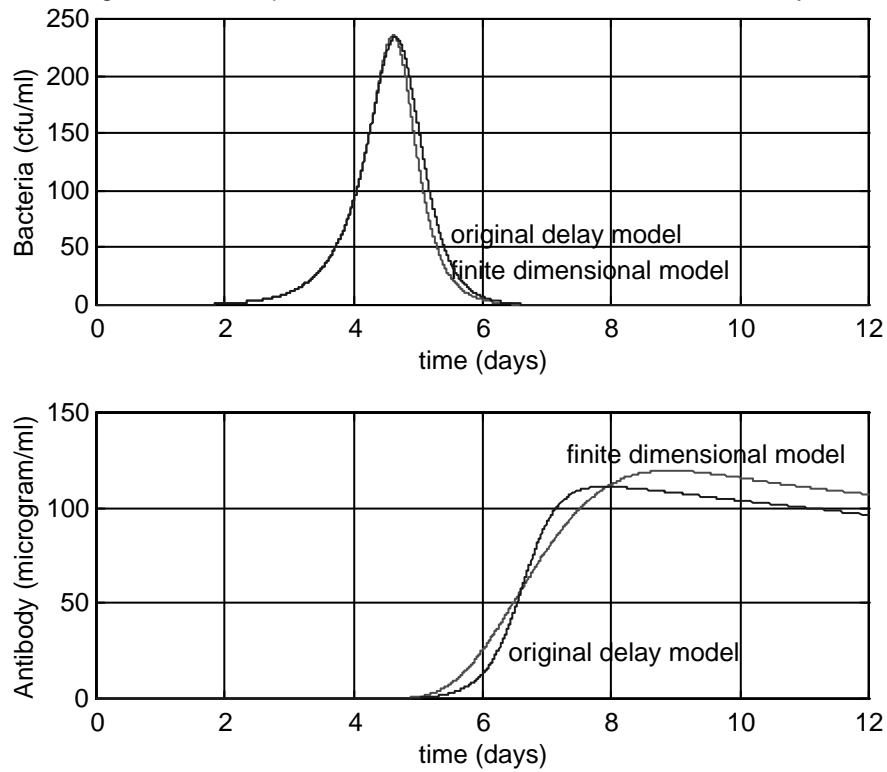


Figure 6.1: Healthy and AIDS Patients with Drug Initiated Immediately

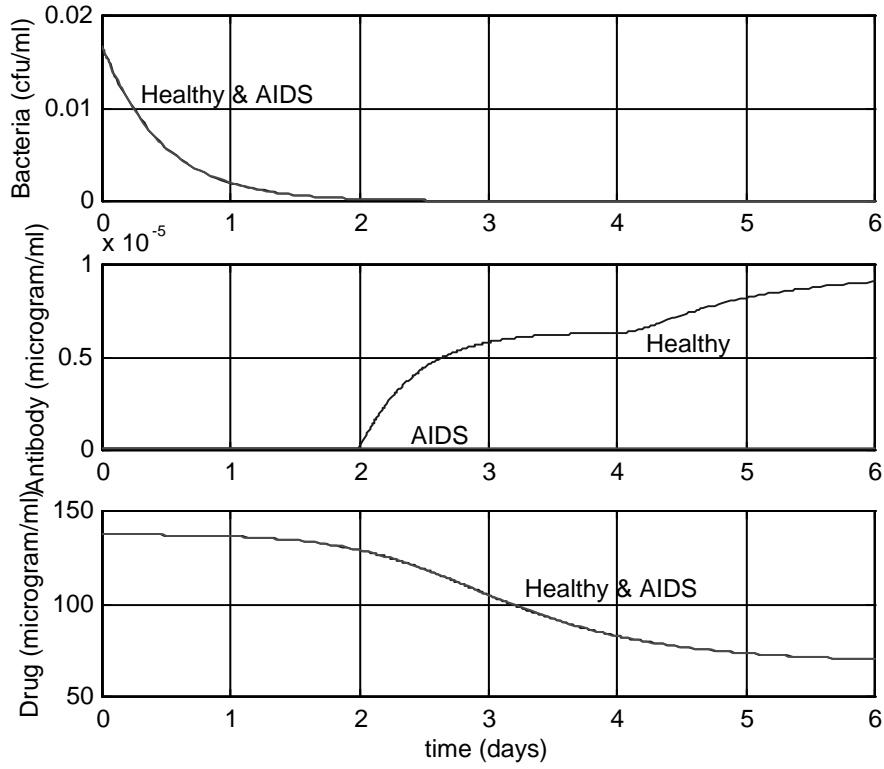


Figure 6.2: Healthy and AIDS Patients with Drug Initiated at Day 4

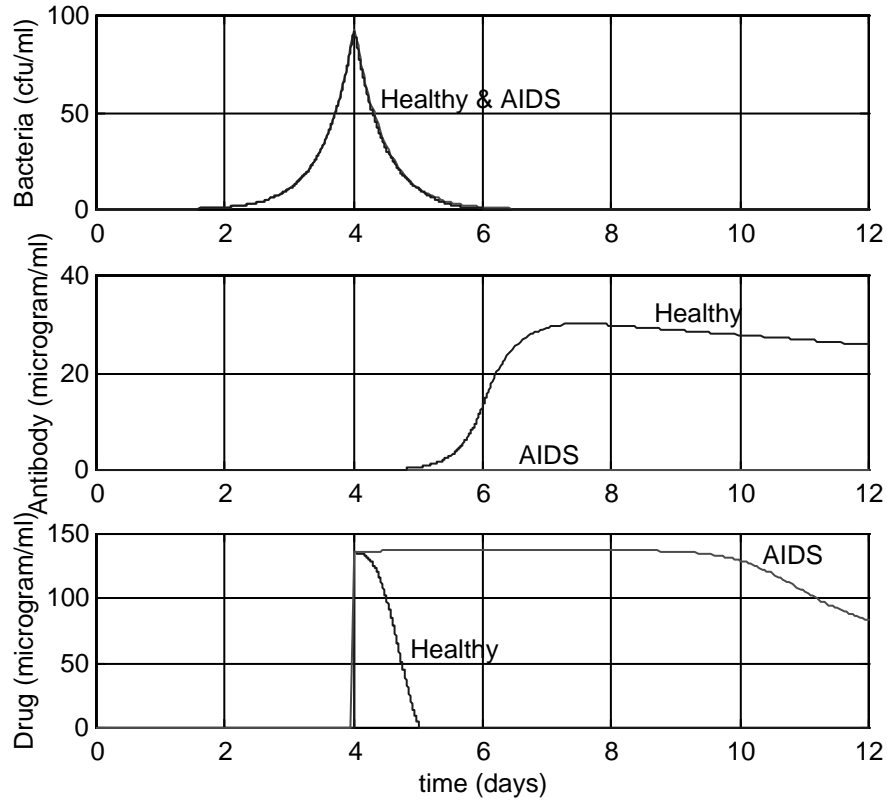
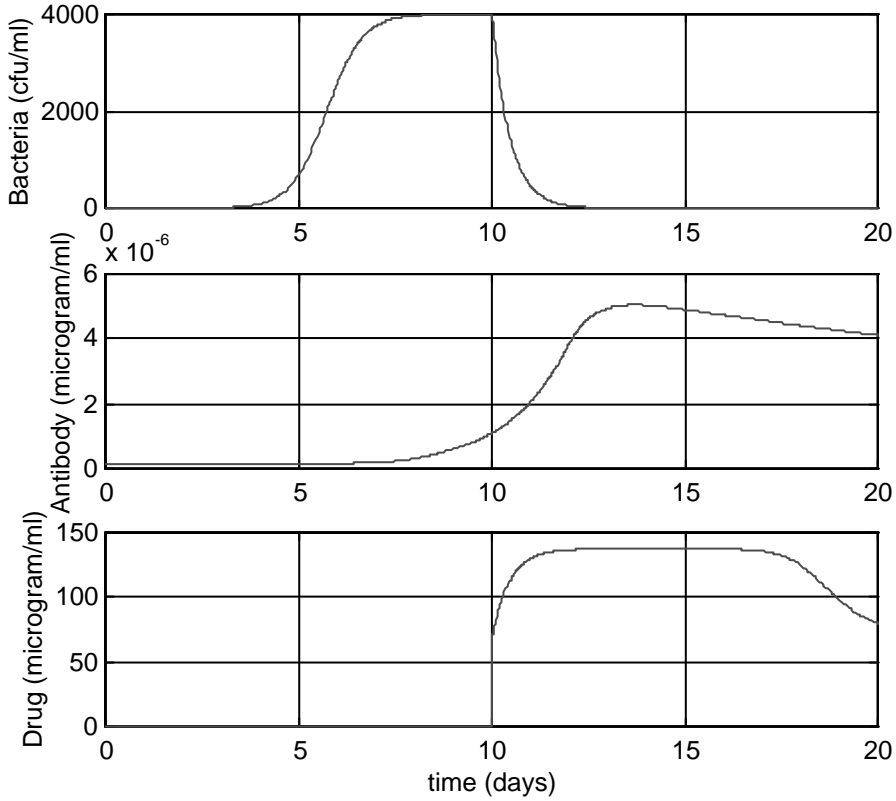


Figure 6.3: AIDS Patient with Drug Initiated at Day 10



$\times 10^{-3}$ Figure 6.4: Comparison of AIDS Patient Recovery

