Investigations into Treatment Strategies Aiding the Immune Response to 
Haemophilus Influenzae

A. Rundell  
School of Electrical and 
Computer Engineering 

R. DeCarlo  
School of Electrical and 
Computer Engineering  

V. Balakrishnan  
School of Electrical and 
Computer Engineering  

H. HogenEsch  
School of Veterinary 
Medicine  

Purdue University, West Lafayette, IN 47906

Abstract
A predator-prey model to reflect the dominant immune response to the bacterium, *Haemophilus Influenzae*, is given. Using our model, we investigate the feasibility and effectiveness of antibiotic treatments by formulating the control problem as an LMI. Given the resulting robust control strategy, simulations demonstrate its superiority.

I Introduction
Predator-prey models capture certain dominant dynamics of the immune response to antigen. Here the host and antigen are both predator and prey. The work herein describes a predator-prey model to reflect the dominant immune response to the bacterium, *Haemophilus Influenzae*. *H. influenzae* is a Gram negative bacterium causing bacterial sepsis, pneumonia, or meningitis; spread by respiratory droplets. Standard treatments to combat infection include antibiotics or immunization which is only partially successful [1].

Using our predator-prey model, we investigate the feasibility and effectiveness of antibiotic treatments for *H. influenzae*. First, we evaluate a typical intravenous antibiotic treatment. Consistency of the clinical response with the simulated model response provides a partial model validation. Next, we look at "optimal" intravenous drug strategies. These strategies are obtained by applying convex optimization techniques to linear matrix inequalities (LMIs) [2] to reduce the total quantity of drug administered below that of the typical intravenous treatment. Approximations inherent in the LMI problem formulation produce conservative strategies. Nevertheless, this is a first step in obtaining a systematic method for determining 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 and opsonic (promote phagocyte engulfing) [3] thereby eliminating the threat to the host. Plasma cells which produce antibodies (types IgG, IgM, and IgA [3]) are differentiated B cells stimulated by active T-helper cells, stimulatory signals, and antigens.

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 [4]. A mathematical model of the immune response to *H. influenzae* provides a tool for illness evaluation plus analysis and development of disease treatment strategies.

III Model Development
The dominant (predator-prey, PP) disease dynamics for *H. influenzae* are modeled by bacteria and antibody serum concentrations. The new PP model evolved from the Rai, Kumar, Pandé (RKP) [5] model into one very similar to Bell’s [6]. 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. The antigen rate equation for the new model is

\[ \dot{B} (t) = a_1 B(t) - \frac{w (A(t) - A_{eq}) B(t)}{d + B(t) / \eta + A(t) - A_{eq}} - b B^2 (t) - \alpha B(t) \dot{u} (t) \]  

(3.1a)

with antibody rate equation

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

(3.1b)

where B(t) and A(t) are antigen (bacteria) and antibody blood concentrations in colony forming units (cfu) per ml and μg per ml respectively.

3.1 The Antigen Rate Equation
Bacterial growth, modeled by \( a_1 B(t) \), accounts for the rapid proliferation [7] as well as the growth inhibiting effects of nonspecific serum components such as acute phase proteins and collectins [8].

The bactericidal and opsonic properties of antibodies is reflected in the term \( \frac{w (A(t) - A_{eq}) B(t)}{d + B(t) / \eta + A(t) - A_{eq}} \) which is a rational approximation derived from the Law of Mass Action [6]. The parameters d and w are related to antibody avidity and protective antibody concentrations; \( \eta \) accounts for multivalent antigens and unit conversions.

The self-interaction term, \( -b B^2 (t) \) [5], accounts for competition of resources within the host and limits unrestricted bacterial growth. The term \( -\alpha B(t) \dot{u} (t) \) represents bacterial growth inhibition due to antibiotics where \( \dot{u} (t) \) is the drug blood concentration. The product term, \( B(t) \dot{u} (t) \), reflects the necessity of drug-antigen
interaction for halting antigen growth. \( \alpha \) depends on the drug’s minimum inhibitory concentration (MIC) but has a reduced value due to antigen inaccessibility from the blood stream.

### 3.2 The Antibody Rate Equation

Antibody production occurs after specific T-helper and B cells are activated by stimulatory signals and antigen contact as:

\[
\frac{\rho A(t - \tau) B(t - \tau)}{\eta (r + A(t - \tau) + B(t - \tau) / \eta)} I^+(t - \tau) \quad \text{where}
\]

\( I^+(t - \tau) = 1 \) for \( t \geq \tau \) and 0 for \( t < \tau \). The delay terms, \( A(t - \tau) \) and \( B(t - \tau) \), (a modification Bell’s model) compensates for the activation, proliferation, and differentiation times for T-helper and B cells. \( \rho \) and \( r \) specify antibody production rates, host sensitivity to this particular antigen, and the immune system activation capability. To limit antibody concentration [6], the antibody production term is multiplied by \([1 - A(t) / A^*] \) so that as \( A(t) \) approaches the upper bound \( A^* \), antibody production ceases. The effective antibody life span is incorporated by \(-a \ (A(t) - A^*_e) \) where \( a \) is the (antibody half-life)\(^1\) and \( A^*_e \) an equilibrium level of naive B cell membrane antibodies available for stimulation at the onset of an immune response.

Once antibodies bind to antigens they cease to interfere with other antigen particles as per the term:

\[
\frac{w (A(t) - A^*_e) B(t)}{\eta (d + B(t) / \eta + A(t) - A^*_e)} \quad \text{which coincides with the}
\]

antigen-antibody complex removal rate in 3.1a except in the parameter, \( \eta \). This activity is not explicitly represented in the original Bell model since without the delay it can be accommodated by lowering the production rate.

### 3.3 Simulation of Model

A typical *H. influenzae* infection for a healthy adult was simulated using the model of equation 3.1 with parameters in Appendix I. Figure 3.1 shows the resulting bacteria concentration peaks at 234 cfu/ml on about day five. This consistent with observed results. Note that children not immune to *H. influenzae* can exhibit much higher bacterial concentrations levels on the order of 1000 cfu/ml [9]. The antibody concentration indicates antibody production for five to seven days, plateauing at day 7. This agrees with typical humoral immune responses [10]. Four weeks after the *H. influenzae* infection, the resulting antibody concentration is 53 \( \mu \)g/ml, well within the expected concentration range after one month of 35 to 180 \( \mu \)g/ml [3,11].

### IV Drug Therapy as Control

Ampicillin inhibits *H. influenzae* bacterial growth by interfering in the cell wall synthesis [1]. Administered is every 6 hours intravenously with dosages ranging from 500 mg to 3 g over 10 to 14 days for adults [12,13]. The dominant pharmacokinetics of ampicillin, its half-life (1 to 1.8 hours), dosage level and schedule, specify its blood concentration. A 10 day regimen administering 3g of ampicillin four times a day with a half-life of 1.5 hours is modeled by the control:

\[
\hat{u}(t) = \sum_{k=0}^{410-1} t^+(t - 6k) 500 e^{-t - 6k}^{1.5}
\]

To establish a baseline intravenous treatment, we considered an adult AIDS patient suffering from *H. influenzae* induced pneumonia [4]. An AIDS patient with a suppressed immune system has a small antibody production rate, \( \rho \). With bacterial levels exceeding 1000 cfu/ml, the patient is extremely ill and would die if left untreated. Simulation of the standard intravenous drug treatment results in antigen elimination (less than one cfu/6000ml) by 9.5 days as shown in Figure 4.1 requiring a total administration of 114 g of ampicillin.

### V Formulation and Solution of the Control Problem

By applying LMI optimization techniques an alternative intravenous drug strategy was found that reduces the total quantity of drug administered. Unfortunately, equation 3.1 does not lend itself to the immediate application of LMI techniques since it is nonlinear and distributed. As such we approximate the delay with a finite-dimensional linear time-invariant system. Also the rational nature of the nonlinearities allows us to rewrite the model in linear-fractional representation (LFR). This equivalent representation models the nonlinear system as a linear system with multiple copies of the state variables appearing in a special feedback loop. This enables us to embed the nonlinearities into an “uncertainty set.” The bounded 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. Controllers that are guaranteed to work for all members of this family are generated, which in turn are guaranteed to work for our nonlinear system. Our objective is to determine a strategy for drug delivery that minimizes the total drug administered subject to the constraint that the patient recovers: accomplished by minimizing an upper bound for the drug-antigen interaction.

#### 5.1 Modeling for the LMI Approach

A 4\textsuperscript{th} order linear phase Bessel filter [14] approximates the time delay with the state model:

\[
\dot{x}(t) = A \dot{x}(t) + B h(t)
\]

\[
y(t) = \tilde{x}(t) = h(t-\tau)
\]

where \( x(t) \in \mathbb{R}^4 \) and \( y(t) \) estimates the delay of the input

\[
h(t) = \frac{\rho A(t) B(t)}{\eta (r + A(t) + B(t) / \eta)}
\]

Incorporating into equations 3.1 yields:

\[
\dot{x} = f(x) + g(x) \hat{u} \quad (5.1)
\]

where \( x = [B A \ \dot{x} \ \dot{x} \ \dot{x} \ \dot{x}]^T \). For appropriately tuned parameters, \( \rho \) and \( r \), the finite dimensional model approximates the input/output relationship (antigen infection dose/antigen and antibody responses) of the original
nonlinear differential delay model (3.1). See Appendix II for details.

With the substitution, \( u = g(x) \dot{u} \), the rational form of \( f(x) \) can be used to obtain an equivalent LFR of 5.1 using techniques from [15]:

\[
\dot{x} = A_n x + B_2 p + B_a u \\
q = C x + D op; \ p = \Delta(x) q
\]

\( \Delta(x) = \text{diag}[B, B, B, A-A_{eq}, A_{eq}, A-A_{eq}, A_{eq}, 1] \)

where \( x = [B(A-A_{eq}) \dot{x}_1, \dot{x}_2, \dot{x}_3, \dot{x}_4]^T \). This approximates our original system in a form suitable for application of robust control techniques [2,15]. Note that system 5.2 has an equilibrium state at \( x = 0 \) which represents no infection.

### 5.2 LMI based Control Synthesis

Three steps generate a controller using LMI techniques: (i) the selection of a Lyapunov function and controller architecture, (ii) the formulation of the conditions on the Lyapunov function and controller parameters that guarantee desired closed loop properties, and (iii) a numerical search for the Lyapunov function and controller parameters.

With a quadratic Lyapunov function, \( V(x) = x^T P x \) and a controller of the form \( u(t) = K_1 x + K_2 p \), we 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 our Lyapunov function is negative for \( x \neq 0 \). One measure to quantify the drug dosage represents the total drug-antigen interaction by \( \int(Bu)^2 \) dt; bounding this measure limits the total drug delivered. Assuming the linear portion of the control \( (K_1 x) \) dominates the controller effort (justified since the linear bacterial growth term in 3.1a is the only positive rate term), we have

\[
\int(Bu)^2 \ dt = \int u^T u \ dt \approx \int[K_1 x]^T K_1 x \ dt
\]

where \( u = B \dot{u} \). To minimize the total drug delivered we propose to minimize the upper bound of the objective \( \int[K_1 x]^T K_1 x \ dt \). Suppose the Lyapunov function, \( V(x) = x^T P x \), satisfies

\[
V < -x^T K_1^T K_1 x
\]

for every state trajectory of \( \Delta(x) \) contained within the ball of radius \( 1/\sigma \) for the system 5.2. Then this system is well posed, stable, and \( x(0)^T P x(0) \) is an upper bound for the objective function as can be shown by integrating both sides of the inequality 5.3. Physiologically this asserts for small infections \( B(t) < 1/\sigma \), the patient will recover since \( V < 0 \) and the total drug delivered is less than \( x(0)^T P x(0) \). A sufficient condition for 5.3, which incorporates the restriction of the norm of \( \Delta \) to \( 1/\sigma \), is:

\[
V - \sigma^2 p^T p \dot{p} + q^T S q < -x^T K_1^T K_1 x
\]

where \( S \) satisfies the following conditions: \( S = S^T > 0, \Delta S = S \Delta \). \( S \) exploits our knowledge of the diagonal structure and real nature of \( \Delta \) [15]. Substituting for \( V \) using equations 5.2 with \( u(t) = K_1 x + K_2 p \) and the following change of variables: \( Q = P^{-1}, Y = K Q, T = (\sigma^2 S)^{-1}, R = K T \), condition 5.4 holds if the following linear matrix inequality is satisfied:

\[
\begin{bmatrix}
QA^T + AQ + B_u Y \\
Y^T B_u^T + B_p^T T \gamma_p^T + B_p^T R^T B_u \\
Q C_q^T + B_p^T D_q^T \\
+ B_u^T R D^T_q \\
R^T B_u^T \\
Y & 0 & 0 & 0 & -I
\end{bmatrix} < 0
\]

by variables \( Q, Y, T, & R \). Minimizing \( x(0)^T Q^T x(0) \), minimizes the upper bound of our objective and is an eigenvalue problem [2]:

\[
\text{minimize } \gamma \text{ subject to } \begin{bmatrix} \gamma & x(0)^T \end{bmatrix} > 0 \text{ and inequality 5.5 } (5.6)
\]

Once minimized, the “optimal” control \( u(t) = K_1 x + K_2 p \) can be recovered from \( K_1 = YQ^{-1} \) and \( K_2 = RT^{-1} \).

### 5.3 Solution to LMIs

LMI optimization can be performed quite efficiently and is ideally suited for linear control system design via numerical methods. LMI problems are convex optimization problems with a finite number of variables [2], solvable in polynomial-time and have every stationary point as a global minimizer. Necessary and sufficient optimality conditions are easily identifiable and there is a well-developed duality theory. Effective and powerful algorithms that rapidly compute the global optimum, with non-heuristic stopping criteria [16, 17] for the solution of LMI problems exist. Recently developed software packages for LMI optimization are [18, 19].

We used LMItool [19] to solve the LMI problem (5.6) for \( Q, T, Y \) and \( R \). The stabilizing controller is given by \( u(t) = K_1 x + K_2 p \) where \( K_1 = YQ^{-1} \) and \( K_2 = RT^{-1} \). We noted, after solving numerous LMI problems each with a different set of model parameters, that the controller matrices have the forms: \( K_1 = [\kappa_1 0 0 0 0 0] \) and \( K_2 = [-\kappa_2 \kappa_2 \kappa_2 0 \kappa_2 0 0 0 0] \). Expressing \( u(t) \) within the context of our original model as a combination of linear and nonlinear feedback terms yields:

\[
u(t) = \kappa_1 B(t) - \frac{\kappa_2 (A(t) - A_{eq}) B(t)}{d + B(t)/\eta + A(t) - A_{eq}} - \kappa_3 B(t)^2.
\]
This stabilizing controller was generated with a local restriction of the state variables in \( \Delta(x) \) to a ball of radius \( 1/\sigma \). So for small infections (\( B(t) < 1/\sigma \) and \( A(t) < 1/\alpha \)), \( u(t) \) guarantees patient recovery. Provided the controller parameters satisfy \( \kappa_1 > a_i/\alpha \), \( \kappa_2 < d/\alpha \), and \( \kappa_i < b/\alpha \), this controller forces \( B \) negative, for all non-negative \( A(t) \) and \( B(t) \), ensuring patient recovery.

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 decrease the required drug concentration as the antibody concentration or the self-interaction antigen rate terms increase. Once the \( A(t) \) reaches inhibitory levels, control (drug therapy) is unnecessary for bacteria removal. This conservative control causes bacterial removal until \( A(t) \) reaches inhibitory levels at which point its contribution is reduced and eventually eliminated as \( A(t) \) becomes sufficiently large (indicated by a negative \( u(t) \)). In practice \( u(t) \) is lower bounded by zero. With small antibody concentrations, the drug-antigen interaction, \( u(t) \), will approach zero as \( B(t) \) approaches zero.

VI. Simulations and Immunological Interpretation

Bacterial levels less than or equal to one cfu in the host indicate successful bacterial elimination (\( B(t) \leq 1/6000 \text{ cfu/ml} \)). Implementing the proposed blood drug concentration \( \dot{u}(t) = B(t) \frac{u(t)}{B(t) + \varepsilon} \) prevents a zero division as \( B(t) \rightarrow 0 \). With small antibody concentrations, the drug concentration will approach a non zero constant level \( \frac{k}{d} \) as \( B(t) \rightarrow \varepsilon (\varepsilon = 1/60000 \text{ cfu/ml}) \); however once \( B(t) < 1/6000 \text{ cfu/ml} \), the ampicillin dosages may be discontinued. In some instances with large antibody levels, the proposed drug concentration is negative indicating the antibody concentration exceeded inhibitory levels and drug administration can be stopped.

Simulink and its Gear integration routines simulate the treatment strategy with the patient response modeled by equation 3.1. See Appendix I for parameters and initial conditions. Figures 6.1 and 6.2 simulate the proposed drug strategy, \( \dot{u} \), applied four days after bacteria infection. A drug concentration \(< 138 \mu g/ml\) eliminates the bacteria. For the healthy patient, the drug concentration decays rapidly after \( \frac{1}{2} \) day since the antibody concentration exceeded inhibitory levels. The negative drug concentration indicates the capability of the healthy patient to recover without ampicillin. For the AIDS patient, Figure 6.2 indicates a longer treatment duration due to a suppressed immune system. Applying the drug strategy at day 10 to an AIDS patient in a critical state (bacteria concentration approaching \( 4000 \text{ cfu/ml} \)) requires a longer drug delivery duration than for the other cases (Figure 6.3). Comparison with the standard ampicillin technique (Figure 4.1) demonstrates a shorter recovery time (8 vs. 9.5 days) and a lower peak drug concentration (138µg/ml vs. 500µg/ml). In addition, our proposed treatment required 6% less drug dosage followed by a continuous constant drug delivery rate of .552g/hr for 8 days achieves \( \dot{u} \).

In practice, the drug strategy would be implemented as:

\[
\dot{u}(t) = \begin{cases} 
0 & \text{if } B(t) < 1/6000 \text{ cfu/ml or } u(t) < 0 \\
\frac{u(t)}{B(t) + \varepsilon} & \text{otherwise}
\end{cases}
\]

which discontinues treatment when bacterial levels are less than 1 cfu (\( B(t) < 1/6000 \text{ cfu/ml} \)) or the antibody level is large enough to eradicate the antigen (\( u(t) < 0 \)).

VII. Conclusions

These control techniques indicate an alternative continuous dosage strategy is optimal to the currently administered one of periodic dosages. Simulation results suggest constant drug concentrations 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 longer treatment duration since their antibodies do not contribute much to bacteria elimination. Due to the conservative nature of the LMI solutions, the drug levels proposed are robust to variations in the antibody affinity and production rates and somewhat robust to bacterial growth rates and antibiotic efficacy.

VIII. References

Appendix I: Model Parameters

\[ a_1 = 0.09/\text{hr}, \quad b = 2.25 \times 10^{-5} \text{cfu}/\text{mg}, \quad a_2 = 1.54 \times 10^{-3} \text{hr}, \quad \eta = 4.12 \times 10^{-12} \text{cfu}/\mu\text{g}, \quad w = 2.37/\text{hr}, \quad d = 0.158 \mu\text{g}/\text{ml}, \quad \rho = 8 \times 10^{-11}, \]  

(AIDS $8 \times 10^{-5})/\text{hr}, \quad r = 8 \times 10^{-4} \mu\text{g}/\text{ml}, \quad \alpha = 0.0013 \text{ ml}/\mu\text{g}/\text{hr}, \quad \Lambda^* = 1500 \mu\text{g}/\text{ml}, \quad A^*_1 = 1.455 \times 10^{-7} \mu\text{g}/\text{ml}, \quad \tau = 48 \text{ hr}, \quad A(0) = A_0^*, \]  

\[ B(0) = 0.0167 \text{ cfu/ml}, \quad K_1 = [137.5 0 0 0 0], \quad K_2 = [-181.0417, 181.0417, 0, 0, 0, 0] \]

Appendix II: Finite Dimensional Delay Approximation

\[ \rho = 1.4 \times 10^{-7} \text{(AIDS $1.5 \times 10^{-5}$)/hr}, \quad r = 0.001 (\text{AIDS} 0.2) \mu\text{g}/\text{ml}, \quad A_0 \]  
is a standard companion with bottom row \( [-1.978 \times 10^{-5}, -9.49 \times 10^{-6}, -0.0195, -0.2083] \),  

\[ B_0 = [0 \ 0 \ 0 \ 1.978 \times 10^{-5}] \]  

\[ B(t) \text{ same as 3.1a} \]

\[ \dot{A}(t) = \hat{x}_1 \left [ 1 - \frac{A(t)}{A^*} \right ] I^+ (t - \tau) - a_1 (A(t) - A_0) \]

\[-\frac{w(A(t) - A_0)}{\eta (d + B(t))} B(t) \]

\[-\frac{\eta (A(t) - A_0)}{\eta + A(t) - A_0} \]