2009

A shooting algorithm for complex immunodominance control problems

Xiaopeng Zhao
University of Tennessee - Knoxville

R Yang

M Zhang

Recommended Citation
Conf Proc IEEE Eng Med Biol Soc. 2009;2009:3897-900. doi: 10.1109/IEMBS.2009.5333566

31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

A Shooting Algorithm for Complex Immunodominance Control Problems

Xiaopeng Zhao, *Member, IEEE*, Ruoting Yang, *Member, IEEE*, and Mingjun Zhang, *Senior Member, IEEE*

***Abstract*—Although T cells are able to recognize a wide variety of target peptides, they are often strongly focused on a few of the peptides and leave the rest of them unattended. This phenomenon of strongly biased immune response is known as immunodominance. Mathematically, an immunodominance problem can be formulated using optimal control principles as a two-point boundary-value problem. The solution of this problem is challenging especially when the control variables are bounded. In this work, we develop a numerical algorithm based on the shooting technique for bounded optimal control problems. The algorithm is applied to a group of immunodominance problems. Numerical simulations reveal that the immune system selects either a broad or a specific strategy of immunodominance based on different optimization goals. The shooting algorithm can also be utilized to solve other complex optimal control problems.**

I. Introduction

WHEN a pathogen (bacterium or virus) invades a human body, it is phagocytosed by APCs (Antigen Presenting Cells). The pathogen's proteins are broken down by proteolytic enzymes, generating many amino acid sequences, or peptides, of various lengths and sequences. Some peptides bind to MHC (Major Histocompatibility Complex) molecules and present on the surface of the APCs, called epitopes. Any pathogen may give rise to many different epitopes, but only a few of them may be recognized by T lymphocytes and stimulate immune responses [1-7]. This extremely narrow targeting behavior is known as immunodominance. For example, an HIV virus contains 10-30 epitopes that can be seen by a patient's CTLs, but the immune response concentrates its forces against a single epitope.

How the immune system chooses the immunodominant epitopes from hundreds of candidates is still a challenging question in immunology research. Recently, both experimental [8-11] and theoretical [12-15] efforts have been directed at understanding the physicochemical and immunological factors that determine whether or not an epitope will become immunodominant. Many researchers believe that the immunodominance is the optimal choice of the immune system. In particular, the breadth and specificity of the immune response have significant impact on the speed and efficiency of viral clearance from the host. For example, a focused immune response with only one or two immunodominant epitopes often offer effective defense against a particular pathogen, but they are incapable of controlling any pathogen that rapidly mutates its immunodominant epitopes [16]. As a result, a broader albeit weaker response may be optimal against rapid mutant pathogens, like RNA viruses [17]. Optimal control theory has been successfully applied to theoretically understand the immune system, such as B-cell [18-21] and cytotoxic T lymphocyte. Yang et al [22] applied optimal control theory to understand immune response in identifying the optimal breadth and specificity of the immune response. Two important questions arise in understanding the immunodominance: 1) why does the immune system target a specific epitope instead of a broader response? 2) when does the immune system switch from a narrow response to a broader response?

In general, the immune system exhibits optimal strategy in choosing narrow or broad target epitopes. However, due to high complexity of the process, its analytical solution is very difficult to obtain. The objective of this article is to develop a computational approach to solve complex optimal control problems and to apply the method to understand the mechanisms of immunodominance.

II. Problem Formulation

A same type of pathogens can have several mutants recognized by the immune system as antigenically distinct pathogens. Consider the following scenario, two groups of antigenically distinct pathogens, each with a common epitope and a mutating epitope. In this case, however, we consider mutation from the first pathogen population to the second population. In other words, we assume that the first variant of the mutating epitope, which is referred as the active epitope, exhibits constant mutation to the second variant, which is referred to as the passive epitope, we assume that there is no backwards mutation from the passive epitope to the active epitope. These scenarios can be collectively described by the following differential equations:

$$\dot{x}_1(t) = [r_1(1-\varepsilon) - k_{11}u_1(t) - k_2u_2(t)]x_1(t)$$
$$\dot{x}_2(t) = [r_2 - k_{12}u_2(t) - k_2u_2(t)]x_2(t) + r_1\varepsilon x_1(t). \quad (1)$$

Here, x_1 and x_2 are the pathogen loads of the first and the second antigenically distinct pathogens. The coefficients r_1 and r_2 represent the per pathogen growth rates. And k_{11}, k_{12}

Manuscript received April 7, 2009. This work was supported in part by the National Science Foundation under Grant CMMI 0845753.

X. Zhao, R. Yang, and M. Zhang are with the Mechanical, Aerospace and Biomedical Engineering Department, University of Tennessee, Knoxville, TN 37996 USA (corresponding author: X. Zhao; phone: 865-974-7682; e-mail: xzhao9@utk.edu).

and k_2 represent immune system killing rates for the active and passive mutating epitopes, and the stable epitope, respectively. The mutation rate $0 < \varepsilon < 1$ represents the rate of mutation from the active epitope to the passive epitope.

The above equations can also be rewritten in a compact form as follows:

$$\dot{x} = (\bar{A} + u_1\bar{B}_1 + u_2\bar{B}_2)x,\ x(0) = x_0$$

where, $x = \{x_1, x_2\}^T$,

$$\bar{A} = \begin{bmatrix} r_1(1-\varepsilon) & 0 \\ r_1\varepsilon & r_2 - k_{12} \end{bmatrix},\ \bar{B}_1 = \begin{bmatrix} -k_{11} & 0 \\ 0 & k_{12} \end{bmatrix},\ \text{and } \bar{B}_2 = \begin{bmatrix} -k_2 & 0 \\ 0 & k_{12} - k_2 \end{bmatrix}.$$

The question, then, is how the immune system partition efforts against the various epitopes in order to annihilate the total pathogen load as efficiently as possible. This can be described as an optimal problem:

$$\min \int_0^T \sum_{i=1}^{2} \alpha_i x_i^{\,2} + \sum_{j=1}^{3} \beta_j u_j^{\,2} dt$$

subject to the dynamics equation of (1). Regardless of the specific weighted average, though, the control objective is always to reduce measure of the host cost associated with an elevated pathogen load. The time T corresponds to the time at which the system reaches the minimum pathogen load possible, and is not a fixed time period, but rather, depends on the specific model and model parameters considered.

The solution of this problem can be obtained using Pontryagin Minimum Principle [26]. If u^* is an optimal control with corresponding trajectory X^*, we can define the Hamiltonian for the system as follows:

$$H = \sum_{i=1}^{2} \alpha_i x_i^{\,2} + \sum_{j}^{3} \beta_j u_j^{\,2} + \lambda(A + \sum u_j B_j)X,$$

where the absolutely continuous co-state function λ is a row vector that satisfies the adjoint equation:

$$\dot{\lambda} = -\frac{\partial H}{\partial X} = -2\alpha^T X - \lambda(A + \sum u_j B_j),$$

and subject to the end condition $\lambda(T) = 0$.

Thus, the solution of the immunodominance problem is to look for the solution of the two-point boundary-value problem of x and λ.

III. Numerical Algorithm

As described in the previous section, the immunodominance phenomenon can be represented as a two-point boundary-value problem. Such a problem can often be solved using a shooting algorithm. We consider the following sets of differential equations:

$$\dot{x} = g(x, u),$$

$$\dot{\lambda} = f(x, \lambda, u),$$

subject to the initial condition: $x(0) = x_0$ and the ending condition: $r(\lambda(T)) = 0$. The problem is to find the initial condition $\lambda(0) = \lambda_*$ that satisfies the above equations and conditions. Given an arbitrarily guessed initial condition $\lambda(0) = y_0$, then the value of $\lambda(T)$ can be regarded as an implicit function of y_0, defined through the solution of the differential equation. Thus, λ_* can be regarded as a root of the nonlinear function r and λ_* is the result of the following iteration:

$$\begin{aligned} \mathrm{y}_{n+1} &= \mathrm{y}_n - \left(\frac{\partial \mathrm{r}}{\partial \mathrm{y}_n}\right)^{-1} \mathrm{r}(\lambda(T))\Big|_{\mathrm{y}_n} \\ &= \mathrm{y}_n - \left(\frac{\partial \mathrm{r}}{\partial \lambda(T)}\frac{\partial \lambda(T)}{\partial \mathrm{y}_n}\right)^{-1} \mathrm{r}(\lambda(T))\Big|_{\mathrm{y}_n}. \end{aligned}$$

The key in this iteration is to find $\lambda(T)$ and $\partial\lambda(T)/\partial \mathrm{y}_n$ for any given y_n. The former can be easily obtained by integrating the differential equation with the initial condition $\lambda(0) = \mathrm{y}_n$. The computation of the latter relies on the variational equation:

$$\frac{d}{dt}\frac{\partial \lambda}{\partial \mathrm{y}_n} = \frac{\partial \mathrm{f}(\mathrm{x}, \lambda, \mathrm{u})}{\partial \mathrm{y}_n}\frac{\partial \lambda}{\partial \mathrm{y}_n}. \quad (2)$$

Since $\lambda(0) = \mathrm{y}_n$, it follows that $\partial\lambda(0)/\partial \mathrm{y}_n = I$. Now, one can compute $\partial\lambda(T)/\partial \mathrm{y}_n$ by integrating the variational equation.

For bounded optimal control problems, oftentimes the control inputs piecewise continuous due to restrictions imposed by the boundaries. Shooting mechanism for such a discontinuous problem is challenging for a number of reasons. First, when a trajectory encounters a discontinuity surface, the subsequent flow may either slides along the discontinuity surface or crosses the discontinuity surface. For optimal control problems, a sliding surface is referred to singular control whereas a crossing surface is referred to as bang-bang control. After the singular and bang-bang control have been identified, the next question is when to switch between the controls. Finding numerical solutions of optimal control becomes development of a criterion to distinguish between a sliding surface and a crossing one.

Define the normal of the discontinuity surface at the intersection point as n and the vector fields evaluated at the different sides of the surface by f_1 and f_2, respectively. For a sliding surface, it can be shown that $(\mathrm{f}_1 \cdot \mathrm{n})(\mathrm{f}_2 \cdot \mathrm{n}) < 0$. For a crossing surface, it follows that $(\mathrm{f}_1 \cdot \mathrm{n})(\mathrm{f}_2 \cdot \mathrm{n}) > 0$. Note that the critical case $(\mathrm{f}_1 \cdot \mathrm{n})(\mathrm{f}_2 \cdot \mathrm{n}) = 0$ corresponds to a tangent contact between the flow trajectory and the discontinuity surface, the so-called grazing contact [24-26].

IV. Results

As an example, we consider an immunodominance problem with the following parameters: $r_1 = 0.3, r_2 = 0.1, \varepsilon = 0.1, k_{11} = 0.7, k_{12} = 0.5, k_2 = 0.3$. We study the optimal solution of the problem for two different control boundaries: 1.) $0 \le u_1 \le 1$ and $0 \le u_2 \le 1$; and 2.)

$0 \le u_1 \le 1$, $0 \le u_2 \le 1$, and $0 \le u_1 + u_2 \le 1$.

We first consider the objective function to be the integration of $x_1^2 + x_2^2 + u_1^2 + u_2^2$ from 0 to 1. The optimal solution for square boundary is 4.43288 and that for triangular boundary is 4.7296; see Figures 1 and 2, respectively.

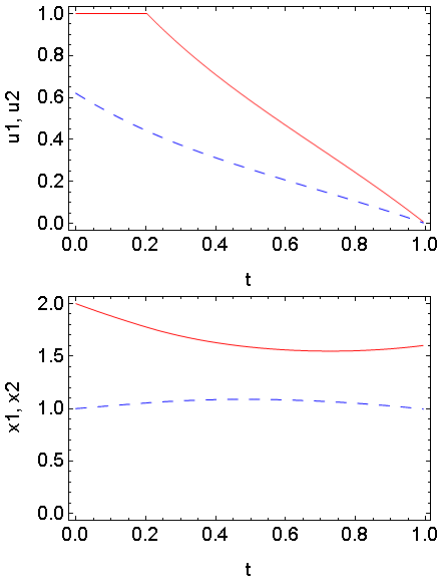

Figure 1. Optimal solution of an immunodominance problem. Top figure: solid curves correspond to u_1 and dashed u_2. Bottom figure: solid curves correspond to x_1 and dashed x_2.

Then, we consider the objective function to be the integration of $x_1^2 + x_2^2$ from 0 to 1. The optimal solution for square boundary is 3.53585 and that for triangular boundary is 3.84873; see Figures 3 and 4, respectively.

V. Conclusion and Discussion

Quantitative analysis has proven to be an ideal tool to better understand immune responses in identifying the optimal breadth and specificity of the immune response. The understanding of immunodominance control will greatly benefit the development of effective therapy and, in particular, effective vaccination schemes designed to stimulate the immune system for viral control.

Optimal control theories have been well developed in the literature and successfully applied to many fields, including biological sciences, medicine, economics, management, and engineering, etc. However, while turning to complex optimal control problems, the major challenge is to find proper solutions. It is very difficult or almost impossible to find closed-form analytical solutions for many practical problems. Even numerical solutions of optimal control problems can be very hard to find for complex optimal control problems. Especially, the solution becomes cumbersome when the dimension of the system becomes large. Real-world problems are often complex. Although analysis of simplified models is able to yield great insight, a full-scale solution of the complex problem is essential in thorough understanding of the system. Advancements in numerical methods for optimal control problems will not only foster the development of control techniques, but also have enormous impacts in science, engineering, and society through the applications. Thus, the numerical algorithm targeted towards complex optimal control problems will make significant impacts through its applications in important problems such as immunodominance.

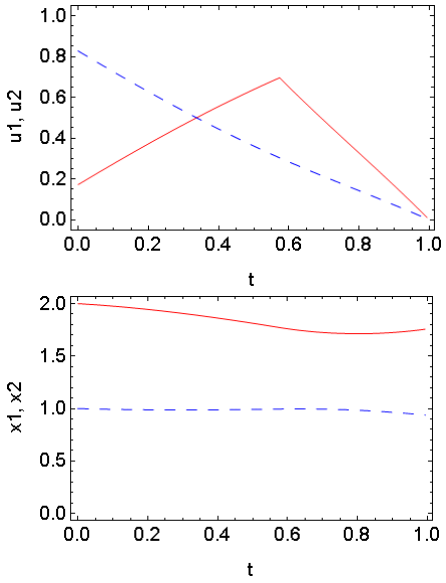

Figure 2. Optimal solution of an immunodominance problem. Top figure: solid curve corresponds to u_1 and dashed curve represents u_2. Bottom figure: solid curve corresponds to x_1 and dashed curve represents x_2.

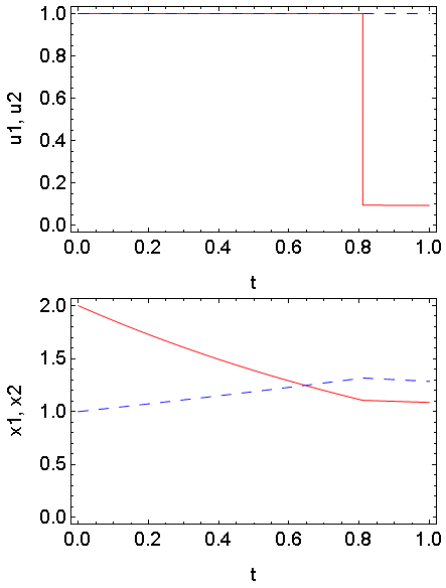

Figure 3. Optimal solution of an immunodominance problem. Top figure: solid curve corresponds to u_1 and dashed curve represents u_2. Bottom figure: solid curve corresponds to x_1 and dashed curve represents x_2.

The immune system is a complex biological problem. From system and control theory perspective, the immunodominance phenomenon shows unique features of optimal control, such as optimal feedback and dynamics response. Optimal control has been widely accepted and used to understand biological problems. The approach has brought powerful insights for many complex biological problems. Introducing optimal control to understand the immunodominance will bring unique understanding for the complex immunodominance problem. The insight brought into the understanding will be long term and significant for understanding the immune system dynamics and control mechanism in general.

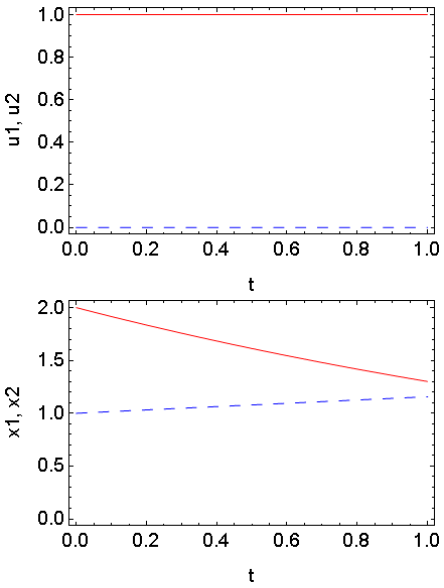

Figure 4. Optimal solution of an immunodominance problem. Top figure: solid curve corresponds to u_1 and dashed curve represents u_2. Bottom figure: solid curves correspond to x_1 and dashed curve represents x_2.

REFERENCES

[1] L. Adorini, E. Appella, D. G., and Z. Nagy, "Mechanisms influencing the immunodominance of T cell determinants," J. Exp. Med., vol. 168, pp. 2091-2104, 1988.

[2] L. Vijayakrishnan, V. Kumar, J. N. Agrewala, G. C. Mishra, and K. V. Rao, "Antigen-specific early primary humoral responses modulate immunodominance of B cell epitopes," J. Immunol., vol. 153, pp. 1613-1625, 1994.

[3] B. P. Nayak, R. Tuteja, V. Manivel, R. P. Roy, R. A. Vishwakarma, and K. V. Rao, "B cell responses to a peptide epitope. V. Kinetic regulation of repertoire discrimination and antibody optimization for epitope," J. Immunol., vol. 161, pp. 3510-3519, 1998.

[4] P. Nakra, V. Manivel, R. A. Vishwakarma, and K. V. Rao, "B cell responses to a peptide epitope. X. Epitope selection in a primary response is thermodynamically regulated," J. Immunol., vol. 164, pp. 5615-5625, 2000.

[5] A. Gallimore, H. Hengartner, and R. Zinkernagel, "Hierarchies of antigen-specific cytotoxic T-cell responses," Immunol. Rev., vol. 164, pp. 29-36, 1998.

[6] J. Yewdell, "Confronting Complexity: Real-World Immunodominance in Antiviral CD8+ T Cell Responses," Immunity, vol. 25, pp. 533-543, 2006.

[7] J. Yewdell and J. Bennink, "Immunodomoniance in Major Histocompatibility Complex Class I Restricted T Lymphocyte Responses," Annu Rev Immunol., vol. 17, pp. 51-88, 1999.

[8] W. Chen, L. C. Antón, J. R. Bennink, and J. W. Yewdell, "Dissecting the Multifactorial Causes of Immunodominance in Class I–Restricted T Cell Responses to Viruses," Immunity, vol. 12, pp. 83-93, 2000.

[9] W. Kastenmuller, G. Gasteiger, J. H. Gronau, R. Baier, R. Ljapoci, D. H. Busch, and I. Drexler, "Cross-competition of CD8+ T cells shapes the immunodominance hierarchy during boost vaccination," J. Exp. Med., vol. 204, pp. 2187-2198, 2007.

[10] J. Ishizuka, G. Stewart-Jones, v. d. M. A., J. Bell, A. McMichael, and E. Jones, "The Structural Dynamics and Energetics of an Immunodominant T Cell Receptor Are Programmed by Its Vβ Domain," Immunity, vol. 28, pp. 171-182, 2008.

[11] E. Assarsson, J. Sidney, C. Oseroff, V. Pasquetto, H. Bui, N. Frahm, C. Brander, B. Peters, H. Grey, and A. Sette, "A quantitative analysis of the variables affecting the repertoire of T cell specificities recognized after vaccinia virus infection," J. Immunol., vol. 178, pp. 7890-7901, 2007.

[12] M. A. Nowak, R. M. May, R. E. Phillips, S. Rowland-Jones, D. G. Lalloo, S. McAdam, P. Klenerman, B. Köppe, K. Sigmund, C. R. M. Bangham, and A. J. McMichael, "Antigenic oscillations and shifting immunodominance in HIV-1 infections," Nature, vol. 375, pp. 606-611, 1995.

[13] A. Handel and R. Antia, "A simple mathematical model helps explain immunodominance of CD8 T-cells in influenza virus A infections," J. Virol., vol. Epub ahead of print, 2008.

[14] M. A. Nowak, "Immune responses against multiple epitopes: A theory for immunodominance and antigenic variation," Seminars in Virology, vol. 7, pp. 83-92, 1996.

[15] D. Wodarz, Killer Cell Dynamics. New York: Springer, 2006.

[16] D. E. Gaddis, M. J. Fuller, and A. J. Zajac, "CD8 T-cell Immunodominance, Repertoire, and Memory," in Immunodominance - The Choice of the Immune System, J. A. Frelinger, Ed. Weinheim: Wiley-VCH, 2006, pp. 109-145.

[17] J. Holland, "Genetic Diversity of RNA Viruses," New York: Springer-Verlag, 1992.

[18] A. Perelson, B. Goldstein, and S. Rocklin, "Optimal strategies in immunology, III: the IgM-IgG switch," Journal of Mathmatical Biology, vol. 10, pp. 209-256, 1980.

[19] A. Perelson, M. Mirmirani, and G. Oster, "Optimal strategies in immunology, I: B-cell differentiation and proliferation," Journal of Mathmatical Biology, vol. 3, pp. 325-367, 1976.

[20] A. Perelson, M. Mirmirani, and G. Oster, "Optimal strategies in immunology, II: B-memory cell production," Journal of Mathmatical Biology, vol. 5, pp. 213-256, 1978.

[21] A. Van Den Berg, "Expansion and Contraction of the Cytotoxic T Lymphocyte Response—An Optimal Control Approach," Bulletin of Mathematical Biology, vol. 66, pp. 1345-1369, 2004.

[22] R. T. Yang, S. Bewick and M. J. Zhang. Optimal Control in Immunodominance. IEEE Transactions on Control System Technology, under review.

[23] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze, and E. F. Mishchenko, The Mathematical Theory of Optimal Processes. New York: MacMillan, 1964.

[24] X. Zhao, H. Dankowicz, C.K. Reddy, and A.H. Nayfeh, "Modeling and Simulation Methodology for Impact Microactuators", Journal of Micromechanics and Microengineering, Vol. 14, pp. 775-784, 2004

[25] X. Zhao, C.K. Reddy, and A.H. Nayfeh, "Nonlinear Dynamics of an Electrically Driven Impact Microactuator", Nonlinear Dynamics, Vol. 40, pp. 227-239, 2005

[26] H. Dankowicz and X. Zhao, "Local Analysis of Co-dimension-one and Co-dimension-two grazing bifurcations in Impact Microatuators", Physica D, Vol. 202, pp. 238-257, 2005