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As a significant class of nonlinear systems, bilinear systems (BLS) are extensively developed in the past years. In addition to their advantages over linear systems which are often not adequate to represent accurately many control processes, the BLS are particularly appealing in modeling biological systems in which parametric controls are of fundamental importance.

This dissertation is aimed at making a contribution to the theory of bilinear control systems via Lie algebraic methods, and the application of accomplished results in immunology. To this end, the input-output relationship of BLS is studied in terms of Volterra series expansion which provides a convenient tool in examining the BLS stability as well as controllability. Moreover, the Volterra series associated with a BLS is in general an infinite series,

and thus in practice, it is important to know how many terms are required to prevent the truncation error from exceeding the maximum allowance. Criteria of acquiring prescribed accuracy in terms of finite Volterra series are derived for BLS with uniformly bounded input or with exponentially stable linear subsystems.

The problem of inverse system design which is capable of identifying both the input function and the state variables based upon the output data, is also considered. The observer theory of constant linear systems is then extended into a special class of bilinear systems with input matrices of rank one.

In view of the functional similarity between immune processes and parametric control systems, a mathematical model of humoral immune response is presented and analyzed. The structural aspects of this nonlinear immune model is examined with the aid of bilinear control theory. Approximate immune models which are amenable to the control-theoretic analysis via foregoingly developed techniques are proposed. Some computer simulations are performed to show that the form of model responses is reasonable by comparing with the experimental data.

Bilinear Control Processes with Application to Immunology

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BILINEAR CONTROL PROCESSES WITH APPLICATION TO IMMUNOLOGY

I. INTRODUCTION

1.1 Motivation and Objective

The development of bilinear system 'theory' has been growing very fast. This is prompted by many reasons. The bilinear control systems are general enough to model various physical and biological processes on the one hand, but they are specific enough to allow elegant mathematical analysis. Recently, it is even shown that every nonlinear control system with control entering linearly is locally almost bilinear [1]. Unfortunately, most of these theoretical contributions require sophisticated mathematical tools with which practicing engineers are not familiar. Even worse, many techniques proposed in past research are often either too complicated or convenient for few particular situations, and rarely feasible in tackling practical problems.

The objective of this thesis is two-fold. One is to investigate some theoretical aspects of bilinear systems, which are potentially useful in applications. The mathematics employed is limited to be minimal in the sense that only rudimentary concepts in Lie algebra and well-known linear system theory are required. The other is to analyze the immune response which is shown to involve bilinear processes. It is intended to show the advantage of apply-

ing control theory to facilitate understanding the immunological process.

1.2 Mathematical Models

1.2.1 System Methodology

Throughout this thesis, the so-called 'dynamic systems approach' is adopted. The system methodology in general conceptual terms is outlined here, putting off the precise definitions and interpretation in appropriate sections.

A dynamic system is conventionally defined to be a collection of interacting components (objects) which as a whole represent the realistic processes or tempo-spatial behavior. Each component (or subsystem) is based upon the physico-chemical principles by a mathematical equation. In order that the whole system may function as desired, all components should be interconnected in a suitable manner. Hence a dynamic system is a mathematical representation or model (usually a set of mathematical equations) from which we are able to extract, via mathematical analysis with the aid of computer simulation, the essence of phenomena of concern. A dynamic system christened as above is said to be 'closed' due to the neglect of its mutual interaction with the environment. In order to take interaction between the system and its environment into account, the notions of input and output to the system are introduced.

In the context of mathematical representation modeled for engineering design, the inputs to the system are called control variables, control policies or simply controls. Therefore a dynamic system endowed with input-output will be called a 'dynamic control system.' Hereafter the word 'system' is used to mean a dynamic control system.

It will be seen that the theoretical contribution of this research is to offer innovative mathematical techniques in the study of nonlinear control systems while the applicative contribution is to apply them to facilitate the understanding of immune responses viewed as an adaptive control system.

1.2.2 System Representations

The characteristics of different processes vary from one to another. Hence specific mathematical models are only convenient for representing specific processes. In what follows, only lumped models interpreted within the framework by ordinary deterministic differential equations are considered. This by no means implies that other models are not practically important, but this assumption is made to keep the complex analysis as simple as possible.

Standard formulation of modern control theory is supplied in order. A dynamic process or a plant will be modeled by a nonlinear ordinary differential equation,

$$\dot{\underline{x}}(t) = \underline{f}(\underline{x}(t),\ \underline{u}(t),\ t), \quad \dot{\underline{x}}(t) \triangleq \frac{d\underline{x}(t)}{dt} \tag{1.1}$$

where $\underline{x}(t)$ is the state vector at time t, $\underline{x} \in R^n$

$\underline{u}(t)$ is the input or control function, $\underline{u} \in R^m$

$\underline{f}$ is the function that represents the system dynamics

$\underline{f}$: $R^n x\ R^m x\ [0,\ T] \longrightarrow R^n$

It will be assumed that $\underline{f}$ is sufficiently smooth so as to guarantee the existence of a unique solution for each initial state $\underline{x}_0 \in R^n$ and each input $\underline{u}(t) \in R^m$ on $0 \leq t \leq T$. Constraints on input class such as piecewise continuous or piecewise constant will be specified when this distinction is significant in underlying discussion.

Systems as described by (1.1) are quite general. As far as this research is concerned, there will be assumptions imposed upon the vector-valued function $\underline{f}$ to make the model mathematically tractable via only standard functional analysis and Lie algebra. Necessary background on Lie algebra will be presented in Section 2.3 and Appendix A. Control systems which are studied in this thesis will be confined to three main classes, namely, linear time-variant, bilinear and quadratic bilinear systems. Examples of these models are presented in Section 1.3. Here the notations and terminology are defined by:

a) Linear time-variant systems,

$$\dot{\underline{x}}(t)=A(t)\underline{x}(t)+B(t)\underline{u}(t), \quad \underline{x}\varepsilon R^n, \quad \underline{u}\varepsilon R^m \tag{1.2}$$

b) Bilinear systems,

$$\dot{\underline{x}}(t)=A(t)\underline{x}(t)+\sum_{i=1}^{m} B_i(t)u_i(t)\underline{x}(t)+C\underline{u}(t) \tag{1.3}$$

c) Quadratic bilinear systems,

$$\dot{\underline{x}}(t)=A(t)\underline{x}(t)+\sum_{i=1}^{m} B_i(t)u_i(t)\underline{x}(t)+C\underline{u}(t) + \sum_{i=1}^{q} \delta_i \underline{x}^T(t)Q_i(t)\underline{x}(t) \tag{1.4}$$

where $A(t)$, $B_i(t)$, $Q_i(t)$ are square matrices of proper dimensions

C is a nxm matrix

δ_i denotes the standard basis vector, i.e. 1 in i-th component and zero elsewhere $\delta_i=(0,0,\ldots,1,0,\ldots,0)^T$

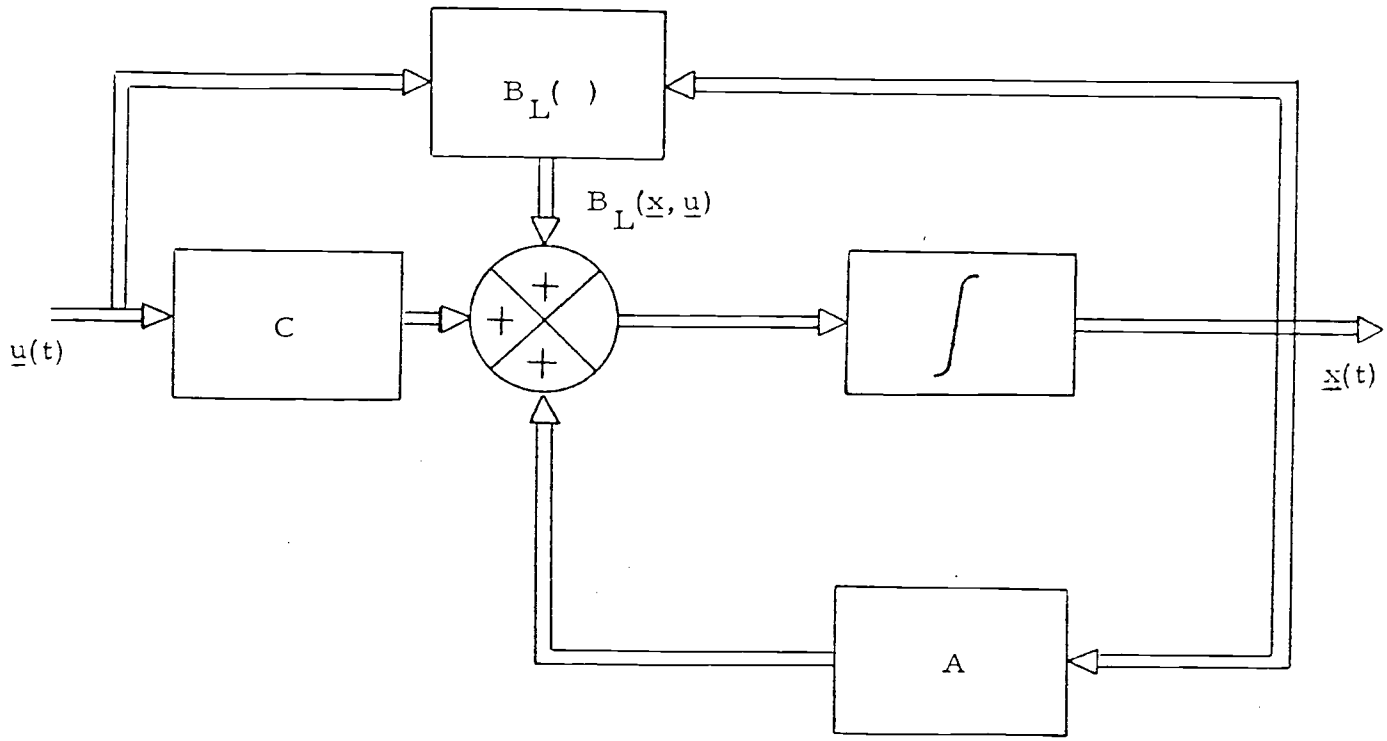
Comments on these specific models are in order.

a') Time-variant linear system (TVLS) are direct extensions of the well-known time-invariant linear systems (i.e. A(t) and B(t) are constant matrices) which are fully developed. It is recognized that time-variant systems often provide better performance than time-invariant systems do. This will be put further systematically by employing Lie algebraic techniques. Another interesting observation is that TVLS are closely related to the

constant bilinear systems. This inherent relationship as well as the significant difference will be investigated in the next chapter.

b') Bilinear systems are featured by the fact that the models are linear in the state $\underline{x}(t)$ and linear in the input $\underline{u}(t)$ but not jointly so. A schematic block diagram for a bilinear system is illustrated in Figure 1.1. Many significant (most of them theoretical) results have been developed for last decade since the study was initiated by Mohler [2, 3]. However, there are still many important topics left open which deserve to be more deeply investigated; for example, these include general estimation and identification procedures, with related problems of identifiability and observability, stability and optimal control. Effective contributions to the application of bilinear systems theory to the solution of practical modeling problems in the areas of biology, ecology, social-economics and biomedicine are still far from satisfactory [4]. The main purpose of this research is to present new contributions to some of the above mentioned issues with particular emphasis on immunology.

c') Though bilinear systems are often appropriate models for representing the dynamic processes



$$B_L(\underline{x},\underline{u}) = \sum_{i=1}^{m} B_i u_i \underline{x}$$

Figure 1.1. Bilinear state diagram [11].

studied here, quadratic systems (i.e. B_i's are null matrices in (1.4)) are often used as models for predator-prey systems or rigid body motion among many others. For such systems, the study from standpoint of control theory has just begun and only very few results are available. Some significant progress out of non-associative algebra was made recently by Frayman [5]. It is of interest to notice here that quadratic systems can be constructed as a bilinear system with a linear feedback [6]. Beyond quadratic systems, quadratic bilinear systems are among the most important from applicative point of view [7]. An example in optimal control of pest management will be presented in Section 1.3.2. A mathematical model in immunology, which naturally fits into this class, will be discussed in Chapter IV.

1.2.3 System Properties

Once a dynamic system is modeled by a set of mathematical equations, the next step is to investigate the attributes of the model. Before proceeding with such a model analysis, several necessary terms are recalled [8].

a) Controllability: A dynamic system is said to be completely controllable if it can be transferred from any initial state $\underline{x}_i \in R^n$ to any prescribed

final state $\underline{x}_f \in R^n$ by some admissible control $\underline{u}(t)$ in a finite interval of time. Otherwise, the system is said to be uncontrollable. In practice, the state space of interest will only be a subset in R^n. For example, in analyzing biological systems, the state variables concerned may be nonnegative and hence the state space may be the positive octant in R^n. Also, the magnitude of the input cannot be as large as desired.

b) Zero-input stability: A state $\underline{x}_e$ such that $f(x_e, t)=0$ for all t is called an equilibrium state of the system. An equilibrium state $\underline{x}_e$ is said to be: 1) stable i.s.L. (in the sense of Lyapunov), if for any positive ε, there exists a positive $\delta(\varepsilon, t_0)$ such that $\| \underline{x}_0 - \underline{x}_e \| < \delta$ implies $\| \phi(t; \underline{x}_0, t_0) - \underline{x}_e \| \leq \varepsilon$ for all $t \geq t_0$, where $\phi(t; \underline{x}_0, t_0)$ denotes the solution of the given system and $\phi(t; \underline{x}_0, t_0) = \underline{x}_0$ (The notation $\| \quad \|$ represents the usual Euclidean norm), and 2) asymptotically stable if it is stable i.s.L. and if every motion starting sufficiently near $\underline{x}_e$ converges to $\underline{x}_e$ as $t \longrightarrow \infty$.

c) Bounded-input stability: a system is said to be BIBO stable (bounded-input-bounded-output stable), if for any bounded input, the output is bounded, that is, $\| \underline{u}(t) \| < M$ implies $\| \underline{x}(t) \| < \infty$ for all t.

The concept of controllability or stability as well as their interrelationship is of practical importance. They are well developed at least for linear time-invariant systems [9]. But extensive research is still continuing for bilinear and more general nonlinear systems [10]. A variety of different definitions and criteria were proposed in the past. Part of this thesis is to derive new results pertaining to this.

1.3 Examples of Control Systems

1.3.1 Bilinear Systems

Linear models are frequently used to approximate the dynamic nature of nonlinear processes due to their mathematical tractability. However, in many cases, linear models are not adequate, especially in modeling biological mechanisms. The analysis of bilinear systems has received much attention in recent years primarily attempting to overcome the difficulty that linear systems present. Various theoretical and practical aspects of bilinear systems can be found from Mohler's monograph [11], which includes both natural and artificial systems such as the populations in

biological species, the neutron population in nuclear fission, the regulation of CO_2 in the respiratory system and thermal exchange...etc. An excellent survey paper by Bruni, et al. [4] summarizes most of significant results up to 1973.

In this section, a recent application of bilinear system to biological control problems is illustrated, which presents a bilinear model describing microbial cell growth and product synthesis in continuous cultures [12]. (See Figure 1.2)

Let

$x_1(t)$=concentration of cells in a continuous mass culture

$u(t)$= flow rate of fresh nutrient into the growth vessel of unit volume $0 \leq u(t) \leq m_o$

$x_2(t)$=substrate concentration in growth vessel

s_r=constant concentration of nutrient flowing into growth vessel

$r(t)$=specific growth rate of $x_1(t)$

$x_3(t)$=product concentration (i.e. penicillin productions)

Based on the mass conservation and approximations such as constant environmental conditions (i.e. temperature and pH) and unlimited supply of nutrient substrate $x_2(t)$, a bilinear model is formulated as follows:

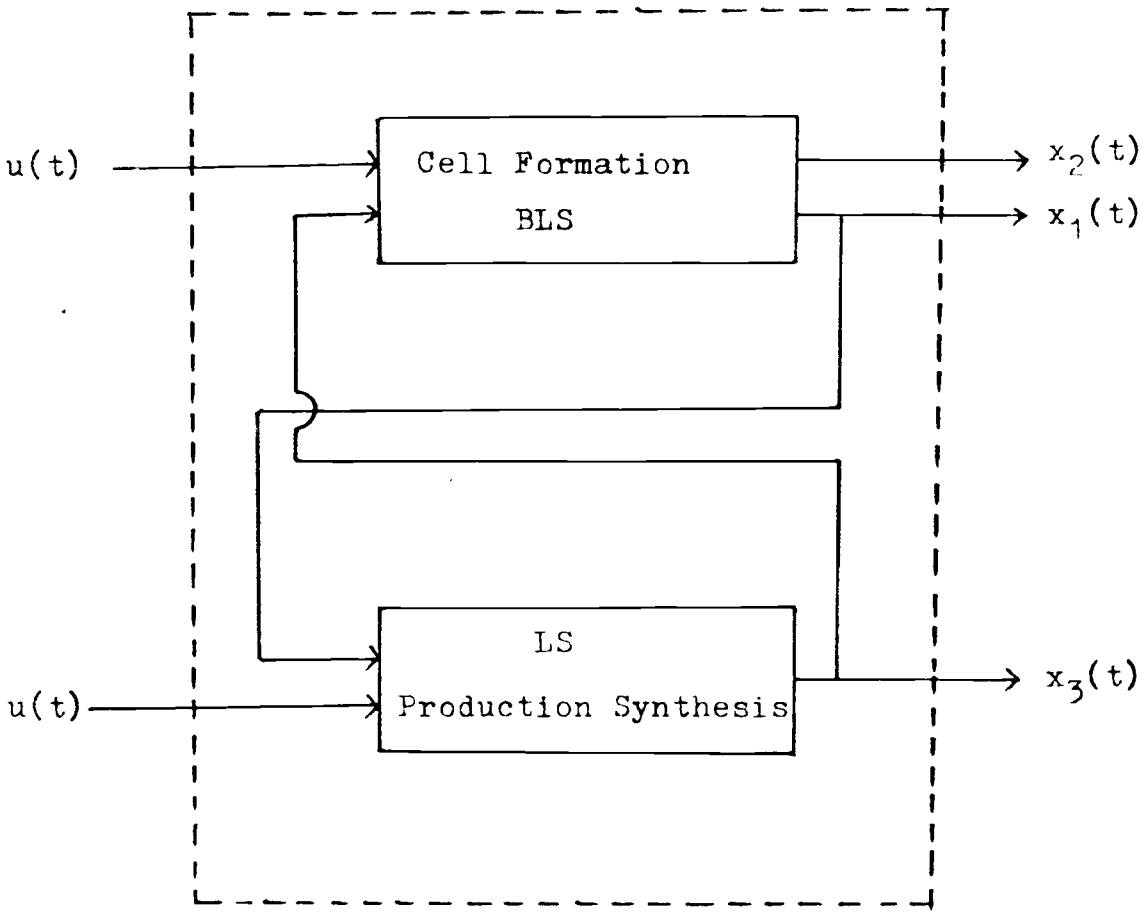


Figure 1.2. A Bilinear model of microbial growth.

$$\dot{x}_1(t)=r(t)x_1(t)-u(t)x_1(t)-k_3x_3(t)$$

$$\dot{x}_2(t)=-\frac{r(t)}{k_1}x_1(t)-u(t)x_2(t)+s_ru(t)$$

$$\dot{x}_3(t)=\alpha\dot{x}_1(t)+\beta x_1(t)-\delta x_3(t)+k_2u(t)$$

or $$\dot{x}_3(t)=(\alpha r(t)+\beta)x_1(t)-\alpha u(t)x_1(t)-\delta' x_3(t)+k_2u(t)$$

where $-\delta x_3(t)$ represents a first order penicillin destruction mechanism and $-k_3x_3(t)$ represents the formation of products which inhibit the production of cells; k_1, α, β are suitable constants. It is straightforward to put the above equations into standard form:

$$\underline{x}=(x_1,\ x_2,\ x_3)^T$$

$$\dot{\underline{x}}(t)=A(t)\underline{x}(t)+u(t)B\underline{x}(t)+\underline{c}u(t)$$

with

$$A(t)=\begin{pmatrix} r(t) & 0 & -k_3 \\ -r(t)/k_1 & 0 & 0 \\ \alpha r(t)+\beta & 0 & -\delta' \end{pmatrix},\quad B=\begin{pmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ -\alpha & 0 & 0 \end{pmatrix},\quad \underline{c}=\begin{pmatrix} 0 \\ s_r \\ k_2 \end{pmatrix}$$

where $\delta'=\delta+\alpha k_3$

1.3.2 Quadratic Bilinear Systems

The uncontrolled prey-predator Lotka-Volterra models used to study the population problems of interacting biological species abound in the literature [13, 14]. These models are quadratic in state variables and characterized by a set of Riccati euqations. Particularly in ecology and

enzyme kinetics many results are available. However, there is limited literature on the actual use of optimal control theory for ecosystem management. In this section, a simple model represented by a quadratic bilinear equation relevant to optimal control of prey-predator system is illustrated [15].

Consider the classical Lotka-Volterra model introduced with biological and insecticide controls u & v, respectively. The cost of control efforts is assumed to include: the cost associated with the presence of prey on the crop, the cost associated with using insecticide and the cost associated with using biological controls. Then an approximate optimization model, after nondimensionalizing all of the variables, is of the form

$$\dot{x}_1(t)=x_1(t)(1-x_2(t))-v(t)x_1(t)$$

$$\dot{x}_2(t)=x_2(t)(x_1(t)-K)-\ell v(t)x_2(t)+u(t)$$

$$\text{cost}=\int_0^T (ax_1(\tau)+bu(\tau)+cv(\tau))d\tau$$

where $x_1(t)$: number of preys (pests) at time t

$x_2(t)$: number of predators at time t

u(t): rate of introducing predators, $0\leq u(t)\leq u_m$

v(t): rate of application of the insecticide, $0\leq v(t)\leq v_m$

a,b,c: appropriate constants associated with the particular system under investigation

ℓ : a constant proportional to the relative effectiveness of the insecticide on the predator compared with the prey (i.e. $\ell=0$ corresponds to a pesticide harmless to the predator)

After formulating as above, the problem then is to to determine how to drive the system using admissible controls u and v to the equilibrium point (K, 1), so that the total cost of operations is minimized. Of course, the well-established theory of optimal control (viz. nonlinear control systems with controls entering multiplicatively) [16] can be applied here. But the structural theory as well as the higher dimensional situations still present serious problems to establish the realistic control strategies. Optimal control theory of quadratic bilinear systems is yet in its infancy. The conventional Lie algebraic techniques which are convenient in dealing with systems of matrix Riccati equations fail to be applicable in the vectorial Riccati models [17].

Rewriting the model offers

$$\dot{\underline{x}}(t)=A\underline{x}(t)+\sum_{i=1}^{2} B_i\underline{x}(t)u_i+C\underline{u}(t)+\sum_{i=1}^{2}\delta_i\underline{x}^T(t)Q_i\underline{x}(t)$$

with $\underline{x}(t)=(x_1, x_2)^T$, $\underline{u}(t)=(u, v)^T$

$$A=\begin{pmatrix}1 & 0\\ 0 & -K\end{pmatrix},\quad B_1=\begin{pmatrix}0 & 0\\ 0 & 0\end{pmatrix},\quad B_2=\begin{pmatrix}-1 & 0\\ 0 & -\ell\end{pmatrix},\quad C=\begin{pmatrix}0 & 0\\ 1 & 0\end{pmatrix},$$

$$Q_1=\begin{pmatrix}0 & -1\\ 0 & 0\end{pmatrix},\quad Q_2=\begin{pmatrix}0 & 1\\ 0 & 0\end{pmatrix}$$

The decomposition of such quadratic bilinear systems into feedback combination of BLS is quite apparent, and consequently optimal control of BLS may be useful in solving these.

1.3.3 Quasi-nonlinear System

In this section, two examples which are nonlinear but can be reduced into simpler ones are introduced. The first example is to consider the problem of guiding an aircraft in minimal time from an arbitrary point in the terminal area to the outer marker [18, 19]. The second example is a scalar nonlinear system which is chosen only for its simplicity to illustrate the benefit of bilinear modeling. These two examples are shown to possess, after introducing new state variables, structures of bilinear and quadratic bilinear systems, respectively.

Assuming that the thrust is equal to the drag and the flight path angle is small, the centrifugal force due to the turn and the weight of the aircraft are balanced by the horizontal and vertical components of the lift, respectively. Under these assumptions, no slideslip occurs and the equations of motion of the aircraft in the horizontal plane are

$$\dot{x}(t) = \cos \psi(t), \qquad x(0)=x^{o}$$

$$\dot{y}(t) = \sin \psi(t), \qquad y(0)=y^{o}$$

$$\dot{\psi}(t) = -\frac{g}{v(t)} \tan \phi(t), \qquad \psi(0)=\psi^{o}$$

where $x(t)$, $y(t)$ and $\psi(t)$ are the current coordinates and heading angle of the aircraft, $v(t)$ is the speed, $\phi(t)$ is the bank angle and g is the acceleration due to gravity. See Figure 1.3. In addition, the speed is assumed constant so that the control function can be normalized and defined as follows:

$$u(t) = \frac{g}{v(t)} \tan \phi(t) = \frac{v}{R(t)}$$

where $R(t)$ denotes the radius of curvature of the flight path.

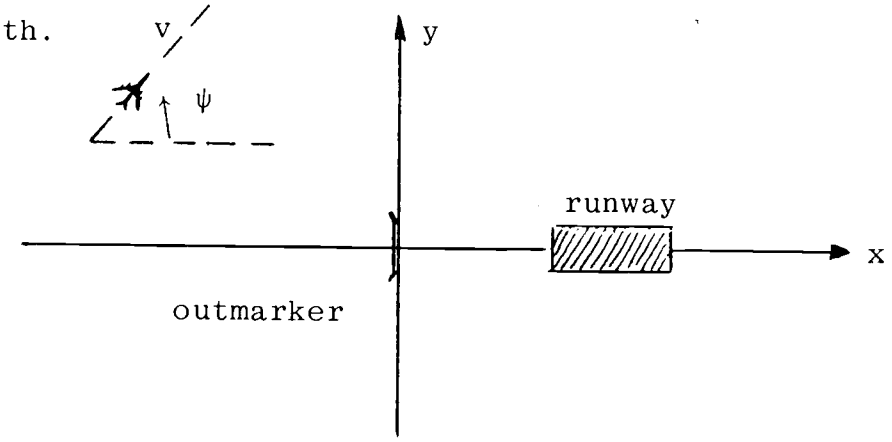


Figure 1.3. Top view of aircraft in terminal area.

Introducing additional state variables, $z(t)=\cos \psi(t)$, $w(t)=\sin \psi(t)$ gives

$$\dot{x}(t)=z(t)$$

$$\dot{y}(t)=w(t)$$

$$\dot{z}(t)=u(t)w(t)$$

$$\dot{w}(t)=-u(t)z(t)$$

$$\dot{\psi}(t)=-u(t)$$

In standard form, this is a bilinear system

$$\dot{\underline{x}}(t)=A\underline{x}(t)+B\underline{x}(t)u(t)+\underline{c}u(t), \qquad \underline{x}(0)=\underline{x}_o$$

with

$$\underline{x}(t)=\begin{pmatrix} x(t) \\ y(t) \\ z(t) \\ w(t) \\ \psi(t) \end{pmatrix}, \quad A=\begin{pmatrix} 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad B=\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\underline{c}=\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \end{pmatrix}, \quad \text{and} \quad \underline{x}_o=\begin{pmatrix} x^o \\ y^o \\ \cos\ \psi^o \\ \sin\ \psi^o \\ \psi^o \end{pmatrix}$$

Next, consider a scalar nonlinear system which is described as

$$\dot{x}_1(t)=\sin\ x_1(t)+u(t), \qquad x_1(0)=0$$

Introducing new state variables $x_2(t)=\sin\ x_1(t)$, $x_3(t)=\cos\ x_1(t)$ gives

$$\dot{x}_1(t)=x_2(t)+u(t)$$

$$\dot{x}_2(t)=x_2(t)x_3(t)+u(t)x_3(t)$$

$$\dot{x}_3(t)=-x_2^2(t)-u(t)x_2(t)$$

In standard form, this is a quadratic bilinear system

$$\dot{\underline{x}}(t)=A\underline{x}(t)+Bu(t)\underline{x}(t)+\sum_{i=1}^{3}\delta_i\underline{x}^T(t)Q_i\underline{x}(t)$$

with

$$\underline{x}(t)=(x_1(t),\ x_2(t),\ x_3(t))^T,\ \text{and}$$

$$A=\begin{pmatrix}0&1&0\\0&0&0\\0&0&0\end{pmatrix},\quad B=\begin{pmatrix}0&0&0\\0&0&1\\0&-1&0\end{pmatrix},\quad Q_1=\begin{pmatrix}0&0&0\\0&0&0\\0&0&0\end{pmatrix},$$

$$Q_2=\begin{pmatrix}0&0&0\\0&0&0\\0&0&0\end{pmatrix},\quad Q_3=\begin{pmatrix}0&0&0\\0&-1&0\\0&0&0\end{pmatrix}$$

Therefore, there are special classes of nonlinear systems which are inherently bilinear or quadratic bilinear. For such quasi-nonlinear systems, techniques developed for bilinear and quadratic bilinear systems can be employed, though unfortunately the number of state variables in the system is increased and computation becomes much more involved.

The examples presented above are much simplified. In fact, there are much larger class of more complex aircraft dynamics in which BLS theory may be useful by considering the aerodynamic coefficient control, e.g. by wing flaps etc. [20].

1.4 Outline of Thesis

The next chapter, Chapter II, introduces Lie algebraic methods in control theory with the intent of preparing sufficient technical background for the rest of the thesis. Volterra series and global solutions of bilinear systems are selected as heuristic examples to aid illustrating the mathematical concepts.

Chapter III develops the main theoretical results, which include the structural decomposition, Volterra series representation, as well as inverse system design of bilinear control systems. In addition, the Lie algebraic conditions on finiteness of Volterra series associated with bilinear systems are investigated pertaining to the bilinear state observer.

Chapter IV is devoted to the modeling of humoral immune responses. A mathematical model of B cell dynamics stimulated by T-independent antigens is presented. The positive invariance and stability of the B Model are investigated. Computer simulations are contained to assess model validity in comparison with the experimental data.

Finally, approximated versions of the B Model are derived. Optimization criterion assumed in conjunction with the simplified immune model leads to a time-optimal control problem from which foregoing techniques can be applied.

II. LIE ALGEBRAIC METHODS IN CONTROL THEORY

2.1 Lie Algebraic Methods

2.1.1 Review of Past Research

Dynamic control systems are very frequently modeled by a set of ordinary differential equations. It is well-known that there are versatile methods that are appropriate for dealing with the theory of differential equations such as functional-theoretic, algebro-geometric and differential-topologic methods among many others. Hence it is of no surprise in control theory that there are many different branches of mathematics at our disposal. In what follows, a brief review is given on the development of applying Lie algebras to the study of control theory, especially those relevant to the bilinear systems. No complete survey is attempted in order not to be lead too far afield. A basic introduction of this issue may be found in the survey papers of Bruni et al. [4] and Mohler [21]; other more mathematically involved results may be consulted from the conference proceedings [22, 23]. Terminology and basic facts to be used in the rest of this thesis are summarized in Appendix A.

Hermann [24] first studied the accessibility[1] problem

[1]Accessibility is referred to as the property that, for any given state, the set of points attainable from that state has a nonempty interior.

in control theory via differential-geometric approach. His result is based upon Chow's theorem which is a generalization of a famous theorem of Caratheodory in thermodynamics giving a geometric condition that a Pfaffian form be completely integrable. Kucera [25] was the first to analyze a particular class of control constrained bilinear systems with the theory of Lie groups. He shows that for his problem, the attainable states form a maximal integral manifold and they can be reached with piecewise constant control of values -1, 0, 1 for an admissible set defined such that $\sum_{k=1}^{m} |u_k| = 1$. Since 1970, Lie algebra in contrast to the linear algebra was extensively adopted as a mathematical tool to tackle theoretical problems of bilinear and linear-analytic systems. Significant results are often accredited to Brockett [26], Elliott [27], Sussmann [28], Krener [29, 30] among many others. Many of these results are applicable for those control systems defined on group manifolds which are out of the scope of this study. Hence, we will not discuss details here but simply mention that:

a) the Lie algebraic approach was successful in investigating the complete controllability and observability, as well as structural decomposition problems, but are less convenient in dealing with the optimal control and system identification problems;

b) the criteria derived via Lie algebras for checking controllability and observability require calculating the dimension and classifying the Lie algebra associated with the underlying control systems. This is by no means a simple task, particularly difficult for high dimensional systems.

The research of control theory utilizing the concept of Lie algebra as well as other related branches of mathematics is still active, and it may very well have an impetus on control theory and applications in the future.

2.1.2 New Directions of This Study

By examining the specific structure of bilinear systems, the tools of linear algebra are seen no longer convenient in many respects. For instance, if we are aiming at decomposing bilinear systems for finding canonical forms, then a set of matrices has to be simultaneously dealt with in contrast to that of linear time-invariant systems where only a single matrix should be considered. It will be recognized that the study of bilinear systems is intimately connected with a set of matrices which are closed under vector space and Lie bracket operation (i.e. Lie algebra). Two main advantages that Lie algebraic methods provide in control theory are realized as follows. Firstly, it carries as far as possible the well-known

results in linear time-invariant systems over to bilinear systems such as 'rank test' for controllability analysis in the form of Lie algebraic criterion. Secondly, it provides the global results up to linear-analytic control systems while classical methods give only the local results. Here the notions of 'global' and 'local' are vaguely referred in the context of localization or approximation problems of non-linear systems.

In the next section, some basic topics in control theory in which Lie algebra plays a significant role are posed. Solutions to these problems as well as new results originate from them form the theoretical contribution of this research. Then in Section 2.3, a brief review on Lie algebra is presented. The well-known Baker-Campbell-Hausdorff formula as well as the notion of adjoint operator are introduced. Armed with these algebraic concepts, the Lie algebra associated with bilinear systems is given and some relevant theorems presented in Section 2.4. Section 2.5 is devoted to the global solution of matrix bilinear equations with the aid of Wei-Norman's [31] and Wichmann's decomposition theorems [32]. Finally, the techniques developed in previous sections are envisaged with practical control problems. Analysis of closed-form expression of Volterra kernels for time-variant bilinear systems is established via a global solution approach. Concluding with Section 2.6 is alternative design of a single-input

bilinear system to illustrate Kucera's mathematical result from an adaptive control-theoretic viewpoint.

In short, the purpose of Chapter II is to prepare a technical background for the main results in the next chapter and control analysis of immunological models following it.

2.2 Examples and Questions

2.2.1 Controllability

To begin with, constant bilinear systems of the following form are considered,

$$\dot{\underline{x}}(t) = (A + \sum_{k=1}^{m} u_k B_k)\underline{x}(t) + C\underline{u}(t) \qquad (2.1)$$

$$\underline{y}(t) = D\underline{x}(t) \qquad (2.2)$$

where $\underline{x}(t) \in R^n$, $\underline{u}(t) \in R^m$, $\underline{y}(t) \in R^r$, the matrices A, D, C and B_k, $k=1,2,\ldots,m$ are of appropriate dimensions; the controls $u_i(t)$ are piecewise continuous and $|u_i(t)| \leq 1$.

It is of practical importance to know the sufficient and/or necessary conditions under which the transfer of one state into another state is possible within a finite time interval. The sufficient conditions are derived by Mohler and Rink [3, 11] by the equilibrium point approach. While the original result is applicable for general BLS, here only a specific but simple result is stated. Formally,

if C is a nonzero matrix, if the BLS is in phase-variable canonical form, and if all eigenvalues of the system matrix $A+\sum_{k=1}^{m} u_k B_k$ can be shifted across the imaginary axis of the complex plane without passing through zero, as $\underline{u}$ ranges continuously over a subset of the input space $\mathcal{U}$, then system (2.1) is completely controllable. It is seen that this criterion also suggests some relationship between BLS stability and controllability. This will be furthermore elaborated in Section 3.1.3.

A question of interest that may be asked is what are the conditions which $\{A, B_1,\ldots,B_m, C\}$ should satisfy in order that the system (2.1) to be completely controllable. Of course, it is more convenient that the answer should not require the computation of eigenvalues. The answer to this question was partially resolved for special BLS in the literature, e.g. the following result is due to Kucera [25].

Lemma 2.1

Consider the homogeneous BLS with scalar input

$$\dot{\underline{x}}(t) = A\underline{x}(t) + Bu(t)\underline{x}(t) \qquad (2.3)$$

If the system (2.3) is controllable, then the Lie algebra $\mathcal{L}$ associated with (2.3) is transitive, that is,

$$\text{rank } (P_1\underline{x}, P_2\underline{x},\ldots,P_\ell\underline{x})=n \quad \text{for all } \underline{x}\in R^n-\{0\} \qquad (2.4)$$

where $\{P_1, P_2,\ldots,P_\ell\}$ is a basis of $\mathcal{L}$.

Condition (2.4) is also a sufficient condition for (2.3) to have accessibility property.

2.2.2 Observer Design

It frequently occurs that not all the state variables of a control system are directly measurable. In order to estimate the states based on the measurable outputs, observer design may be used. For constant linear systems, the observer theory is a well-developed topic [33]. However, observer design for bilinear systems recently attracts attention and few methods have been proposed [12, 34]. If the input of a BLS is a priori known, then its states can be estimated in the same way as linear time-variant systems. Thus a state observer for a single-input single-output (SISO) bilinear system

$$\dot{\underline{x}}(t) = (A+u(t)B)\underline{x}(t) + \underline{b}u(t), \quad \underline{x}(t)\varepsilon R^n \tag{2.5}$$

$$y(t) = \underline{c}^T\underline{x}(t)$$

can be constructed as follows [18]:

$$\dot{\hat{\underline{x}}}(t) = K_1(t)\hat{\underline{x}}(t) + \underline{k}_2(t)y(t) + \underline{b}u(t) \tag{2.6}$$

where

$$K_1(t) = (A+u(t)B) - \underline{k}_2(t)\underline{c}^T$$

$$k_2(t) = \tfrac{1}{2}L^{-1}(t)\underline{c}$$

and $\dot{L}(t) = -L(t)(A+u(t)B) - (A+u(t)B)^T L(t) - R(t) + \underline{c}\,\underline{c}^T$

R(t) is an arbitrary real, symmetric, positive-definite nxn matrix.

Implementing this observer requires finding L(t) explicitly which cannot be done in general. Thus it is of interest to ask:

(1) What is the 'maximal' class of SISO bilinear systems for which a state observer can be constructed as in (2.6)?

(2) If the input u(t) is inaccessible, then how to estimate the unmeasurable states using only output data?

These questions will be answered in Section 2.5 and Chapter III, respectively.

2.2.3 Volterra Series

Under some regularity conditions, the output of a nonlinear system may be directly expressed in terms of input by a functional series [35]. This approach is particularly appropriate for many aspects in the study of bilinear systems. Bruni et al. [36] show that the input-output relationship of system (2.1) and (2.2) can be expressed as a Volterra series which consists of a uniformly convergent sequence $\{\underline{x}_i(t),\ i=1,2,3,\ldots\}$,

i.e. $\lim_{i\to\infty} \underline{x}_i(t) = \underline{x}(t)$, where $\underline{x}_i(t)$ satisfies

$$\begin{aligned} \dot{\underline{x}}_0 &= A\underline{x}_0 + C\underline{u}, \quad \underline{x}_0(0)=\hat{\underline{x}}_0 \\ \dot{\underline{x}}_i &= A\underline{x}_i + \sum_{k=1}^{m} B_k u_k \underline{x}_{i-1} + C\underline{u} \end{aligned} \tag{2.7}$$

with $\underline{x}_i(0)=\hat{\underline{x}}_0$, and i=1,2,3,...

Thus

$$y(t)=De^{At}[I+\sum_{i=1}^{\infty}\sum_{1=k_1,k_2,\ldots k_i}^{m}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}}\prod_{j=1}^{i}$$

$$e^{-A\tau_j}B_{k_j}e^{A\tau_j}u_{k_j}(\tau_j)d\underline{\tau}]\hat{\underline{x}}_0$$

$$+De^{At}\sum_{i=1}^{\infty}\sum_{1=k_1,k_2\ldots k_{i+1}}^{m}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_i}\prod_{j=1}^{i}$$

$$(e^{-A\tau_j}B_{k_j}e^{A\tau_j})e^{-A\tau_{j+1}}$$

$$\prod_{j=1}^{i+1}u_{k_j}(\tau_j)d\hat{\underline{\tau}}\,\underline{c}_{k_{i+1}} \qquad (2.8)$$

where $d\underline{\tau} = d\tau_i d\tau_{i-1}\cdots d\tau_1$

$d\hat{\underline{\tau}} = d\tau_{i+1}d\underline{\tau}$

$C = [\underline{c}_1, \underline{c}_2, \cdots, \underline{c}_k, \cdots, \underline{c}_m]$, $\underline{c}_j$'s are column vectors.

In general, the Volterra series (2.8) for a bilinear system is an infinite series which characterizes the output depends multilinearly on the input. Truncation is usually used to approximate the input-output relationship. Recently, Brockett [37] developed a necessary Lie algebraic condition for a bilinear system to have only finite Volterra kernels. Now it is significant to ask:

Under what conditions is 'truncation' a reasonable procedure? What does 'truncation' mean with respect to

the structure of bilinear systems? These problems will be further studied in Chapter III.

2.3 Brief Review of Lie Algebra

The mathematical background and some preliminary facts in Lie algebra required throughout the text are summarized here. More profound Lie algebraic theorems can be found in Appendix A with details in Reference 49. Throughout this thesis, only finite dimensional matrix Lie algebras over a real field are considered. Recall that a set of matrices $\mathcal{L} = \{A_1, A_2, \ldots, A_m\}$ form a matrix Lie algebra if its elements are closed under the nonassociative Lie bracket or commutator operator, $[X, Y] = XY - YX$, $X, Y \in \mathcal{L}$. A subset of $\mathcal{L}$, $\mathcal{B} = \{B_1, B_2, \ldots, B_\ell\}$, $\ell \leq m$, is called a basis of $\mathcal{L}$ if every element in $\mathcal{L}$ can be expressed as a linear combination of B_i's, $i=1,2,\ldots\ell$, where ℓ is referred as the dimension of $\mathcal{L}$. Moreover,

$$[A_i, A_j] = \sum_k \alpha_{ij}^k A_k, \qquad A_i, A_j, A_k \in \mathcal{L} \tag{2.9}$$

where the constants α_{ij}^k which uniquely characterize $\mathcal{L}$ are called the structure constants of the algebra $\mathcal{L}$.

A most important operator in Lie algebra is now introduced, that is, the adjoint operator. The adjoint operator, denoted by 'ad', is a linear mapping from the Lie algebra into itself, and can be defined inductively as

$$\text{ad}: \mathcal{L} \longrightarrow \mathcal{L}$$

$$\text{ad}_A^0 B = B, \qquad \text{ad}_A^1 B = [A, B]$$

$$\text{ad}_A^k B = [A, \text{ad}_A^{k-1} B], \quad A, B \in \mathcal{L} \tag{2.10}$$

A significant property of the adjoint operator is that it has a matrix representation consisting of entries specified by structure constants of the corresponding Lie algebra.

One version of the well-known Baker-Campbell-Hausdorff formula [38] (abbreviated hereafter BCH formula) is stated below,

$$\begin{aligned} e^A B e^{-A} &= B + [A, B] + \frac{1}{2!}[A, [A, B]] + \cdots \\ &= \text{ad}_A^0 B + \text{ad}_A^1 B + \frac{1}{2!}\text{ad}_A^2 B + \cdots \\ &= \sum_{k=0}^{\infty} \frac{\text{ad}_A^k B}{k!} \\ &= e^{\text{ad}_A} B \end{aligned} \tag{2.11}$$

2.4 Bilinear Systems and Lie Algebras

Important results on bilinear systems using Lie algebra as a tool are depicted here without proof, however adequate references are supplied.

To begin with, equivalent state space representations are examined. A constant bilinear system as represented in (2.1) can be reformulated into the homogeneous form by

introducing an additional state variable, $x_{n+1}=1$, such that

$$\dot{\underline{y}}(t) = \tilde{A}\underline{y}(t) + \sum_{i=1}^{m} \tilde{B}_i u_i(t)\underline{y}(t) \qquad (2.12)$$

$$\underline{y}(0) = (\underline{x}_0, 1)^T$$

where $\tilde{A} = \begin{bmatrix} A & 0 \\ 0 & 0 \end{bmatrix}$, $\tilde{B}_i = \begin{bmatrix} B_i & 0 \\ 0 & 0 \end{bmatrix}$

As a consequence, only multiplicative input to the bilinear systems is indicated with additive input presumably suppressed. The solution to (2.1) with C=0 is often conveniently expressed as $\underline{x}(t)=X(t)\underline{x}_0$ [39], where $X(t)$ is an nxn matrix-valued function of t which is the corresponding matrix bilinear system

$$\dot{X}(t) = AX(t) + \sum_{i=1}^{m} u_i(t)B_iX(t) \qquad (2.13)$$

$$X(0) = X_0$$

If X_0 is assumed to be nonsingular, then $X(t)$ evolves in GL(n,R), the general linear group of nonsingular nxn real matrices.

It is well-documented that the reachable set for (2.1) is related to the structure of the Lie algebras:

$$\mathcal{L} = \{A, B_1, B_2, \ldots, B_m\}_{LA}$$

$$\mathcal{L}_0 = \{ad_A^k B_i, \ k=0,1,2,\ldots; \ i=1,2,\ldots,m\}_{LA}$$

$$\mathcal{B} = \{B_1, B_2, \ldots, B_m\}_{LA}$$

where $\{M_1,\ldots,M_\ell\}_{LA}$ denotes the smallest Lie algebra generated by M_i, $i=1,2,\ldots,\ell$. Obviously, the following inclusion relationship holds

$$\mathcal{B}\subset\mathcal{L}_0\subset\mathcal{L}$$

More concisely, it is shown that [39]

Theorem 2.1

Associated with the matrix bilinear system (2.13) is the triple Lie algebra $\{\mathcal{L},\mathcal{L}_0,\mathcal{B}\}$. $X(t)$ is reachable from X_0 at time t if

$$X(t)\in e^{At}\{\exp\mathcal{L}_0\}_G X_0 \tag{2.14}$$

Moreover, if $\mathcal{B}$ is an ideal[1] in $\mathcal{L}_0$, then the reachable set of X_0 at time t is $e^{At}\{\exp\mathcal{L}_0\}_G X_0$, where $\{\exp\mathcal{L}_0\}_G$ denotes the Lie group consisting of elements in the form exp M, i.e.

$$\{\exp\mathcal{L}_0\}_G \triangleq \{\exp M:\ M\in\mathcal{L}_0\}_G$$

Theorem 2.2

Suppose that $\{\mathcal{L},\mathcal{L}_0,\mathcal{B}\}$ is the triple Lie algebra associated with the system (2.1), and $\mathcal{B}$ is an ideal in $\mathcal{L}_0$, then the set of vectors reachable from $\underline{x}_0$ at time t, $\mathcal{R}(t)$, is

$$\mathcal{R}(t) = e^{At}\{\exp\mathcal{L}_0\}_G\underline{x}_0 \tag{2.15}$$

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[1] A subalgebra S is an ideal of $\mathcal{L}$, if $[S,\mathcal{L}]\in S$, or, in other words, if $X\in S$, $Y\in\mathcal{L}$ implies $[X, Y]\in S$.

Applying this result to linear systems, i.e. (2.1) with $B_1=B_2=\ldots=B_m=0$, it is readily deduced that $\mathcal{R}(t)=e^{At}\underline{x}_0+\text{Range}\ (C,\ AC,\ldots,A^{n-1}C)$ which is the usual rank test [40]; i.e. a linear system, $\dot{\underline{x}}(t)=A\underline{x}(t)+C\underline{u}$, is completely controllable if and only if Rank $(C,\ AC,\ldots,A^{n-1}C)=n$.

2.5 Global Solution of Bilinear Systems

Since the bilinear system with input $\underline{u}(t)$ specified a priori is a linear though generally time-variant system, certain techniques for linear time-variant systems may be useful. In what follows, rudimentary Lie algebraic theorems which are useful in linear time-variant systems are introduced.

Keeping in mind the resemblance between bilinear and linear time-variant systems, it is convenient to write a homogeneous BLS in the form

$$\dot{\underline{x}}(t) = (A+\sum_{i=1}^{m} u_i(t)B_i)\underline{x}(t) \tag{2.16}$$

$$\underline{x}(0) = \underline{x}_0$$

or equivalently for given $u_i(t)$

$$\dot{\underline{x}}(t) = A(t)\underline{x}(t) \tag{2.17}$$

where $A(t) = A + \sum_{i=1}^{m} u_i(t)B_i$

Let $\Phi(t,0)$ denote the state transition matrix for (2.17), then $\underline{x}(t)=\Phi(t, 0)\underline{x}_0$ and

$$\dot{\Phi}(t, 0) = A(t)\Phi(t,0), \quad \Phi(0,0)=I \tag{2.18}$$

It is significant to observe that (2.18) is nothing but the matrix bilinear system (2.13) if $u_i(t)$ is specified ($i=1,2,\ldots,m$).

Now a well-known assumption is that unless $A(t)$ possesses some specific properties, an explicit solution to (2.18), in general, cannot be found with known techniques. A specific exception is that $A(t)$ commutes with its integral, i.e. $[A(t), \int_0^t A(\tau)d\tau]=0$ for all t, yielding

$$\Phi(t,0) = \exp\left(\int_0^t A(\tau)d\tau \right) \tag{2.19}$$

More recently, Freedman and Lawson [41] derive a sufficient condition for the above commutativity to hold, that is, $A(t)$ is a diagonizable matrix and has a set of constant eigen-vectors for all t.

A convenient mathematical tool to find the maximal class of $A(t)$ which gives explicit solution in the form of product of exponentials (global solution) seems to be Lie algebra. Though this is well-developed in algebraic theory of differential equations and its application to physical problems, a thorough treatment in the context of control theory is yet not completely established.

In the rest of this section, two fundamental Lie

algebraic theorems on the global solution to the matrix bilinear equation with specified controls are introduced, namely, the Wei-Norman theorem [31] and the Wichmann's theorem [32].

For convenience, equation (2.18) is rewritten as

$$\dot{X}(t) = A(t)X(t), \qquad X(0) = I, \ t \geq 0 \tag{2.20}$$

where

$$A(t) = \sum_{i=0}^{m} u_i(t)A_i .$$

Then, the famous theorem of Frobenius [42] implies that for small $|t|$ and suitable $g_i(t)$'s,

$$X(t) = \prod_{i=0}^{m} e^{A_i \, g_i(t)} \tag{2.21}$$

This local solution may be furthermore elaborated with the aid of the implicit function theorem [43] to develop global solutions by imposing conditions on the structure of the set of matrices $\{A_0, A_1, \ldots, A_m\}$.

Theorem 2.3 (Wei-Norman [31])

If $\{A_i, i=0,1,2,\ldots,m\}$ generate a solvable Lie algebra , then $X(t)$ admits a global solution

$$X(t) = \prod_{i=1}^{\ell} e^{g_i(t)M_i} \tag{2.22}$$

where $\{M_i, i=1,2,\ldots,\ell\}$ denotes a basis for the ℓ-dimensional $\mathcal{L}$ and $g_i(t)$'s which are functions of $u_i(t)$ can be found by solving a set of differential equations.

In particular, if $\{A_i,\ i=0,1,2,\ldots,m\}$ itself is a basis for $\mathcal{L}$ (i.e. $\ell=m+1$), then

$$X(t) = \prod_{i=0}^{m} e^{g_i(t)A_i} \tag{2.23}$$

A derivation of differential equations which $g_i(t)$'s must satisfy is given in order. Rigorous proof can be found in the original paper of Wei and Norman [31].

By equation (2.23),

$$\begin{aligned}
\dot{X}(t)=&\dot{g}_0(t)A_0 \prod_{i=0}^{m} e^{g_i(t)A_i}+\dot{g}_1(t)e^{g_0(t)A_0}A_1 \prod_{i=1}^{m} e^{g_i(t)A_i}+\ldots \\
&+\dot{g}_m(t)e^{g_0(t)A_0}\ldots.e^{g_{m-1}(t)A_{m-1}}A_m e^{g_m(t)A_m} \\
=&\dot{g}_0(t)A_0X(t)+\dot{g}_1(t)e^{g_0(t)A_0}A_1e^{-g_0(t)A_0}X(t)+\ldots. \\
&+\dot{g}_m(t)e^{g_0(t)A_0}\ldots.e^{g_{m-1}(t)A_{m-1}}A_m e^{-g_{m-1}(t)A_{m-1}} \\
&e^{-g_0(t)A_0}X(t) \\
=&(\dot{g}_0(t)A_0+\dot{g}_1(t)e^{g_0(t)\mathrm{ad}_{A_0}}A_1+\ldots. \\
&+\dot{g}_m(t)\prod_{i=1}^{m} e^{g_{m-1}(t)\mathrm{ad}_{A_{i-1}}}A_j)X(t)
\end{aligned} \tag{2.24}$$

Comparing (2.24) and (2.21) yields

$$\dot{g}_0(t) = u_0(t) \equiv 1$$

$$\dot{g}_1(t)e^{g_0(t)A_0}A_1e^{-g_0(t)A_0} = u_1(t)A_1$$

.

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$$\dot{g}_i(t)\prod_{j=1}^{i} e^{g_{j-1}(t)\mathrm{ad}_{A_{j-1}}A_j} = u_i(t)A_i \qquad (2.25)$$

which is a set of nonlinear differential equations that $g_i(t)$ must satisfy and can be solved in terms of the input $\underline{u}(t)$ and A_i, $i=0,1,2,\ldots,m$.

A particular class of solvable Lie algebra is the abelian (commutative) Lie algebra. If $\{A_i,\ i=0,1,\ldots,m\}$ generates an abelian Lie algebra, i.e. $A_iA_j=A_jA_i\ \forall i$, $j=0,1,\ldots,m$, then (2.25) becomes $\dot{g}_i(t)=u_i(t)$ $i=0,1,\ldots,m$. Thus,

$$X(t) = \prod_{i=0}^{m} e^{A_i g_i(t)} = \prod_{i=0}^{m} e^{A_i \int_0^t u_i(\tau)d\tau}$$

$$= \exp \sum_{i=0}^{m} \int_0^t u_i(\tau)A_i d\tau = \exp\left(\int_0^t \sum_{i=0}^{m} u_i(\tau)A_i d\tau \right)$$

which is of course the same as (2.19).

While abelian bilinear systems are a very special class of bilinear systems, there are some significant results in the literature. Sussmann shows that the reachable set of abelian BLS with bang-bang controls is <u>closed</u>

[44]. Wei and Pearson studied the minimum energy control of abelian BLS and its applications in a two-dimensional missile intercept problem [45].

Moreover, abelian bilinear systems are particularly appealing in modeling biocontrol processes for which it is convenient that $X(t)$ has only nonnegative entries if the off-diagonal entries of $A(t)$ and the initial condition are nonnegative [46]. From the control-theoretic viewpoint, this implies that the reachable set is confined to the first orthant under any positive perturbation, ——— a property that many biocontrol models should possess [47].

In applications, not all and possibly very few Lie algebras generated by $A(t)$ are solvable. A most important class of Lie algebras which are not solvable directly but can be algebraically solved indirectly as shown below is the semisimple Lie algebra [48]. Recall that the Levy-Malcev theorem [49] which says that any semisimple Lie algebra S can be factored as a direct sum of simple ideals, i.e. $S = S_1 \oplus S_2 \oplus \ldots \oplus S_k$, where the elements of distinct S_j must commute. Based on this algebraic decomposition, one can then find the solution to (2.20) in terms of simpler structures of the Lie algebra generated by $A(t)$. This may be illustrated by

Theorem 2.4 (Wichmann [32])

Consider the matrix differential equation

$$\dot{X}(t) = A(t)X(t), \qquad X(0) = I$$

with $$A(t) = \sum_{i=0}^{m} u_i(t)A_i$$

Decomposing the system matrix $A(t)$ into

$$A(t) = A_r(t) + A_s(t)$$

$$= A_r(t) + \sum_{j=1}^{k} A_{s_j}(t), \quad A_{s_j} \in S_j, \quad S = S_1 \oplus S_2 \oplus \ldots \oplus S_k$$

where $A_r(t)$ and $A_s(t)$ generate the <u>radical</u> R[1] and the semisimple subalgebra S of the Lie algebra $\mathcal{L} \triangleq \{A_i : i=0,1,\ldots,m\}_{LA}$. respectively. Then

$$X(t) = \hat{X}_r(t)X_s(t)$$

where $$X_s(t) = \prod_{j=1}^{k} X_{s_j}(t)$$

and $$\dot{X}_{s_j}(t) = A_{s_j}(t)X_{s_j}(t), \qquad X_{s_j}(0) = I$$

$$\dot{\hat{X}}_r(t) = [\, X_s^{-1}(t)A_r(t)X_s(t) \,]\, \hat{X}_r(t), \qquad X_r(0) = I \quad (2.26)$$

It merits attention that once $X_s(t)$ is obtained, then (2.26) can be solved by quadrature, since $A_r(t)$ generates the radical of $\mathcal{L}$.

The following example shows a semisimple Lie algebra associated with a bilinear system. Consider a BLS

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[1]The radical R of a Lie algebra $\mathcal{L}$ is the maximal solvable ideal (containing all solvable ideals) in $\mathcal{L}$.

$$\dot{x}_1 = x_2$$

$$\dot{x}_2 = -x_1 + u(t)x_1$$

i.e. $\dot{\underline{x}} = A\underline{x} + u(t)B\underline{x}$ with

$$A = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}, \qquad \text{and} \qquad B = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}$$

Then

$$[A, B] = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}, \qquad [A, [A, B]] = \begin{pmatrix} 0 & -2 \\ -2 & 0 \end{pmatrix}$$

It can be checked that $\{B, [A,B], [A,[A,B]]\}$ is a basis of the Lie algebra $\mathcal{L} = \{A, B\}_{LA}$ which is indeed a 3-dimensional special linear Lie algebra with zero traces, i.e. $s\ell(2,R)$. After some calculation, it is seen that $\mathcal{L}$ has no abelian ideals except 0 and itself. Thus $\mathcal{L}$, by definition, is a semisimple Lie algebra. This example will be further discussed in Section 3.1.3.

2.6 Applications in Control Systems

2.6.1 Volterra Series of Time-Variant Bilinear Systems

The intent of this section is to apply previous theorems to develop preliminary results concerning the SISO bilinear systems.

$$\dot{\underline{x}}(t) = A(t)\underline{x}(t) + u(t)B(t)\underline{x}(t), \quad \underline{x}(0) = \underline{x}_0 \qquad (2.27)$$

$\underline{x}(t) \in R^n$, $A(t), B(t) \in R^{nxn}$

The coefficient matrices in (2.27) are now allowed to be time-dependent, unless otherwise specified. As stated in Section 2.2.3, the internal representation of a constant bilinear system can be characterized by a sequence of Volterra kernels. Here the Volterra series expansion is extended into a class of time-variant bilinear systems, while instead of using a set of recursive linear differential equations, the Peano-Baker series approach is undertaken [37].

Making a change of variable, $\underline{z}(t)=\Phi(t,0)\underline{x}(t)$ reduces (2.27) into

$$\dot{\underline{z}}(t) = u(t)\hat{B}(t)\underline{z}(t) \tag{2.28}$$

where $\hat{B}(t) = \Phi(0,t)B(t)\Phi(t,0)$, and

$$\dot{\Phi}(t,0) = A(t)\Phi(t,0), \quad \Phi(0,0) = I$$

Hence, by Peano-Baker series, (2.28) yields

$$\underline{z}(t)=[I+ \int_0^t u(\sigma_1)B(\sigma_1)d\sigma_1+\int_0^t\int_0^{\sigma_1} u(\sigma_1)\hat{B}(\sigma_1)u(\sigma_2)\hat{B}(\sigma_2) d\sigma_2 d\sigma_1+....+.....] \underline{z}(0) \tag{2.29}$$

Therefore, the Volterra series for (2.27) is

$$\underline{x}(t)=\Phi(0,t)[I+\int_0^t u(\sigma_1)\Phi(0,\sigma_1)B(\sigma_1)\Phi(\sigma_1,0)\, d\sigma_1+.....] \underline{x}_o \tag{2.30}$$

In general, closed form expression for Volterra kernels is not available, due to the difficulty that $A(t)$ is a time-variant matrix. However, by Wei-Norman theorem, Volterra kernels can be explicitly calculated if $A(t)$ generates a solvable Lie algebra. There are two special

classes of bilinear systems for which the corresponding Volterra series can be explicitly found. These are the constant BLS (A(t)=A, B(t)=B) and quasi time-variant BLS (A(t)=A). The Volterra series for the constant BLS has been developed in Section 2.2.3, here the quasi time-variant case is treated. Deducing from (2.30) leads to

$$\underline{x}(t)=e^{At}[I+\int_0^t u(\sigma_1)e^{-A\sigma_1}B(\sigma_1)e^{A\sigma_1}d\sigma_1+ \dots]\underline{x}_0 \quad (2.31)$$

It is remarkable that all Volterra kernels of a bilinear system are related to the expression $e^{At}B(t)e^{-At}$ or its integrals. By introducing the notion of adjoint operator, (2.31) can be put into a more concise form.

$$\begin{aligned}\underline{x}(t)=e^{At}[I&+\int_0^t e^{-\sigma_1 ad_A}B(\sigma_1)u(\sigma_1)d\sigma_1\\ &+\int_0^t\int_0^{\sigma_1} e^{-\sigma_1 ad_A}B(\sigma_1)e^{-\sigma_2 ad_A}B(\sigma_2)u(\sigma_2)u(\sigma_1)\\ &d\sigma_2 d\sigma_1+\dots]\underline{x}_0\\ &= e^{At}[I+\sum_{i=1}^{\infty}\int_0^t\int_0^{\sigma_1}\cdots\int_0^{\sigma_{i-1}}\prod_{j=1}^{i}\\ &(e^{-\sigma_j ad_A}B(\sigma_j)u(\sigma_j)d\sigma_j)]\ \underline{x}_0 \end{aligned} \quad (2.32)$$

In particular, the Volterra series for a constant BLS is

$$\begin{aligned}x(t)=e^{At}[I&+\sum_{j=1}^{\infty}\int_0^t\int_0^{\sigma_1}\cdots\int_0^{\sigma_{i-1}}\prod_{j=1}^{i}\\ &(e^{-\sigma_j ad_A}Bu(\sigma_j)d\sigma_j)]\ \underline{x}_0\end{aligned} \quad (2.33)$$

By examining the above equations, it is now apparent that the structure of bilinear systems is closely related to the Lie algebra $\{ad_A, B\}_{LA}$, i.e. smallest Lie algebra containing B and closed under the adjoint operator ad_A. More details on this relationship will be presented in Section 3.1.3.

2.6.2 Adaptive Design of Constant BLS with Single Input

In practice, it is often important to reformulate the mathematical models within equivalence in favor of more tractable analysis. Derivation of various canonical forms is a concrete example in linear system theory. Meanwhile, model reformulation also provides alternative design techniques for maneuvering adaptive systems subject to structural variations. Bilinear models allow more flexibility from a design point of view than do linear models. Therefore, the above equivalence concept merits further investigation. The rest of this section is devoted to a preliminary development concerning single input bilinear systems.

The paper of Kucera cited in Section 2.2.1 deals with certain aspects of controllability of a bilinear system of the form:

$$\dot{x}(t) = [A(1-u)+Bu]\, x(t), \qquad |u(t)| \leq 1 \tag{2.34}$$

In contrast to the representation of single-input BLS as to be given below, (2.34) possesses distinctive

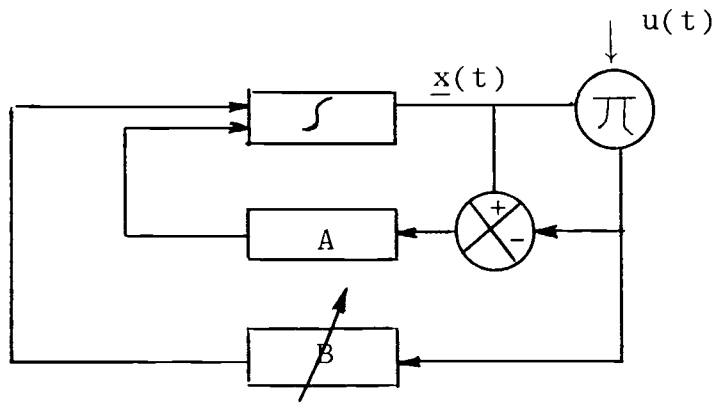
properties. For example, the matrices A and B can be viewed as linear operators mapping from the convex input space into itself. However, as far as controllability is concerned, system (2.34) is equivalent to

$$\dot{\underline{x}}(t)=A\underline{x}(t)+N\underline{x}(t)u \tag{2.35}$$

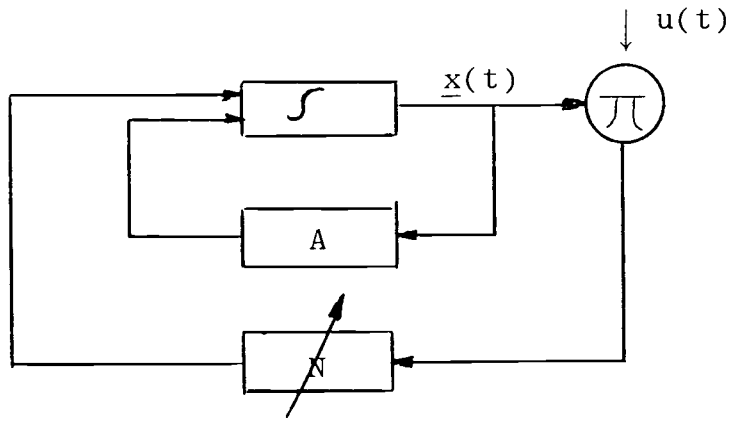
where N is decomposed as B-A.

As a consequence of the commutator [A,N] and [A,B] are identical, the corresponding adjoint operators $ad_A^k B$, and $ad_A^k N, \forall k$, are also identical. Keeping in mind the reachable set for a BLS is determined by the associated Lie algebra and hence the adjoint operator (see Theorem 2.1), the controllability equivalence between (2.34) and (2.35) is at hand established. State diagrams for these two different representations are given in Figure 2.1 to illustrate the structural designs.

It is significant to observe that the structural variation of bilinear systems can be accomplished by augmenting either the subsystem N or the subsystem B.



(a)



(b)

Figure 2.1 (a) Bilinear state diagram for (2.34)
(b) Bilinear state diagram for (2.35)

2.6.3 A Biocontrol Example

Analysis of a bilinear control system with single input is presented here to illustrate the foregoing techniques. This example is in fact a simplified model of immune response. Only theoretical aspects are considered here, and the biological interpretation on the model itself and parameters will be deferred until Chapter IV and references therein.

Consider the following bilinear model as also shown in Figure 2.2,

$$\dot{x}_1(t)=kx_2(t)+rkx_3(t) \tag{2.36a}$$

$$\dot{x}_2(t)=bu(t)x_2(t)-d(1-u(t))x_2(t)-\mu_2 x_2(t) \tag{2.36b}$$

$$\dot{x}_3(t)=d(1-u(t))x_2(t)-\mu_3 x_3(t) \tag{2.36c}$$

with $0\leq u(t)\leq 1$

and initial condition $x_1(0)=x_3(0)=0, \quad x_2(0)=x_{20}$

In standard form, (2.36) can be rewritten as

$$\dot{\underline{x}}(t)=A\underline{x}(t)+u(t)B\underline{x}(t) \tag{2.37}$$

with $$A=\begin{pmatrix} 0 & k & rk \\ 0 & -d-\mu_2 & 0 \\ 0 & d & -\mu_3 \end{pmatrix}, \qquad B=\begin{pmatrix} 0 & 0 & 0 \\ 0 & b+d & 0 \\ 0 & -d & 0 \end{pmatrix}$$

and $\underline{x}(t)=(x_1(t),\ x_2(t),\ x_3(t))^T$, $\underline{x}(0)=(0,\ x_{20},\ 0)^T$

After some manipulation, it can be verified that A and B generate a 4-dimensional solvable Lie algebra $\mathcal{L}$.

More precisely,

$\mathcal{L} = \{A, B\}_{LA}$ has a basis $\{A, B, C_1, C_2\}$

$\mathcal{L}_0 = \{ad_A^k B, k=0,1,2,\ldots\}_{LA}$ has a basis $\{B, C_1, C_2\}$

$\mathcal{B} = \{B\}_{LA}$ has a basis $\{B\}$

where

$$C_1 = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad C_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}$$

Obviously $\mathcal{B}$ is not an ideal $\mathcal{L}_0$ (i.e. $[B, C_1] = -(b+d)C_1 \notin \mathcal{B}$), and hence the bilinear model (2.37) does not satisfy the hypothesis of Theorem 2.2. In fact, the reachable set which will be calculated in Section 5.2.2 is confined to the first quadrant in R^3 so that the system (2.37) is not completely controllable. Moreover, thanks to the solvability and Wei-Norman theorem, system (2.37) admits a global solution as follows:

$$x_2(t) = x_{20} e^{-\beta t + \alpha v(t)} \tag{2.38a}$$

$$x_3(t) = dx_{20} e^{-\mu_3 t} \int_0^t e^{\beta\tau - \alpha v(\tau)} (1-u(\tau)) d\tau \tag{2.38b}$$

$$x_1(t) = kx_{20} \Big[\int_0^t e^{-\beta\tau + \alpha v(\tau)} d\tau + rd \int_0^t e^{-\mu,\sigma} \int_0^t e^{\beta\tau - \alpha v(\tau)} (1-u(\tau)) d\tau d\sigma \Big] \tag{2.38c}$$

where $\alpha \triangleq b+d$, $\beta \triangleq d+\mu_2$, $v(t) = \int_0^t u(\tau)d\tau$.

A significant observation is made here. The existence of global solution attributed to the fact that $\mathcal{L}$ is solvable, is a consequence of the specific structure of bilinear model, that is, the model is 'partially decoupled'. This may be seen readily from the fact that (2.36b) is independent of the equations (2.36a) and (2.36c). The Figure 2.2 also shows that this multivariate model is composed of a scalar BLS followed by two scalar linear systems in series. The problem of decoupling a BLS into simpler subsystems is thus conceivably resolved by examining the structural properties of the Lie algebra associated with the BLS as will be discussed in the next chapter.

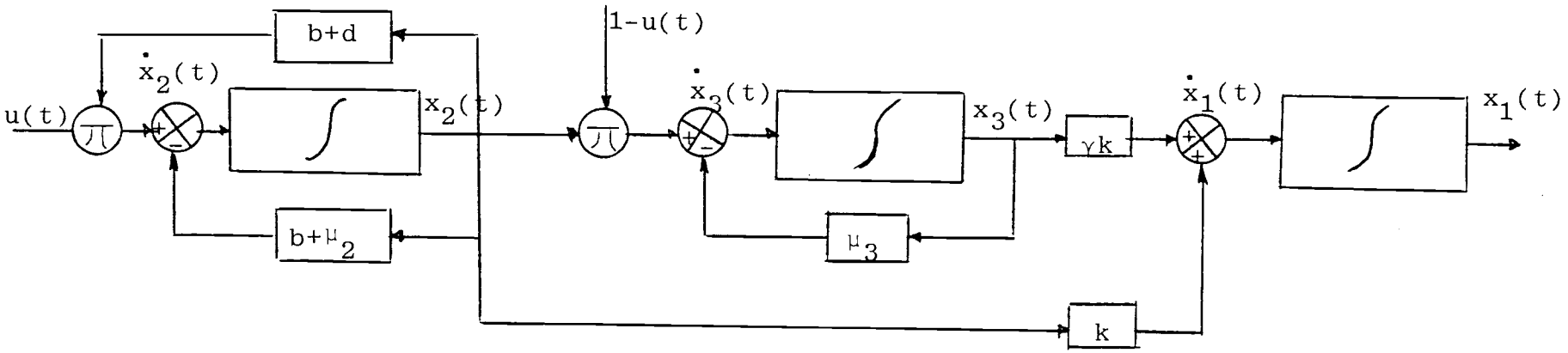


Figure 2.2. Structural decoupling of a bilinear model.

III. ANALYSIS OF BILINEAR SYSTEMS

3.1 BLS Analysis via Volterra Series

3.1.1 Convergence and Boundedness

As discussed in the preceding chapters, Volterra series is a convenient tool in studying some special classes of bilinear systems. This section is devoted to the examination of several properties of BLS via Volterra series expansion. As far as the convergence and boundedness of Volterra series on a finite time interval are concerned, basic results are at hand in literature [50, 51]. These will be summarized here as Lemmas (to be given below) While these lemmas are significant, they fail to be useful if the time domain of interest is allowed to be infinite. A particularly important situation is relevant to the asymptotic stability of bilinear systems —— a property that will be proved useful in analyzing immune models of the next chapter.

For simplicity, some notations are defined in order. A constant BLS is described by the following state and output equations:

$$\dot{\underline{x}}(t)=(A+\sum_{k=1}^{m} u_k B_k)\underline{x}(t)+C\underline{u}(t), \quad \underline{x}(0)=\underline{x}_0 \tag{3.1}$$

$$\underline{y}(t)=D\underline{x}(t) \tag{3.2}$$

where $\underline{x}(t) \in R^n$, $\underline{u}(t) \in R^m$, $\underline{y}(t) \in R^r$, the matrices A, C, D

and B_k, $k=1,2,\ldots,m$ are of appropriate dimensions, $\underline{u}(t)$ is bounded and measurable on $[0, \infty)$. The following norms are used; $\|\underline{x}(t)\| = \sum_{i=1}^{n} |x_i(t)|$ and $\|A\| = \max_j \sum_{i=1}^{n} |a_{ij}|$ with $A=[a_{ij}]$. The Volterra series representation of the above system has been developed as (2.9) in Section 2.2.3.

Lemma 3.1 [50]

The Volterra series for (3.1) and (3.2) is uniformly convergent on $[0, T]$ if the input $\underline{u}(t)$ is in $C[0,T]$, where $C[0, T]$ denotes the space of continuous functions on $[0, T]$, $T<\infty$.

Lemma 3.2 [51]

If the conditions in Lemma 3.1 are met and $\max_k \|B_k\| \leq M_1$, $\max_k \|\underline{u}_k\| \leq \ell$, $\max_k \|\underline{c}_k\| \leq M_2$, then for all $t\in[0, T]$

$$\|\underline{y}(t)\| \leq \|D\| \left(\|\underline{x}_0\| + \frac{1}{w} m\ell M_2\right) e^{(w+m\ell M_1)t} - \|D\| \frac{1}{w} m\ell M_2 \qquad (3.3)$$

where $w = \|A\|$.

It is seen from (3.3) that the upper bound for the output $\underline{y}(t)$ becomes very conservative if t approaches a very large value, i.e. $T \longrightarrow \infty$. To establish an upper bound for $\underline{y}(t)$ which remains valid as $T \longrightarrow \infty$, more restrictive conditions on the coefficient matrices and input are desirable.

Theorem 3.1

Given any finite dimensional BLS as (3.1) and (3.2). Assume that for $t>0$

(1) $\| e^{At} \| \leq s_1 e^{-s_2 t}$, $s_1, s_2 > 0$

(2) $\| \underline{u}(t) \| \leq \nu_1 e^{-\nu_2 t}$, $\nu_1, \nu_2 > 0$

(3) $\| C \| \leq M_2$, $\max_k \| B_k \| \leq M_1$

Then, for each initial condition, there exists a positive constant μ such that for the solution to (3.1) it holds:

$$\| \underline{y}(t) \| \leq \mu e^{-t \min(s_2, \nu_2)} \tag{3.4}$$

where μ is an appropriate positive constant.

Proof —— The proof is similar to that given in Reference 52 in which the counterpart of this theorem for infinite dimensional BLS is provided. Consider the sequence $\{\underline{x}_i(t)\}$ of solutions of the equations:

$$\dot{\underline{x}}_1(t) = A\underline{x}_1(t) + C\underline{u}(t), \quad \underline{x}_1(0) = \underline{x}_0 \tag{3.5}$$

$$\dot{\underline{x}}_i(t) = A\underline{x}_i(t) + \sum_{k=1}^{m} B_k u_k(t) \underline{x}_{i-1}(t), \quad \underline{x}_i(0) = \underline{0}, \; i>1 \tag{3.6}$$

Without loss of generality, assuming $s_2 < \nu_2$ gives

$$\begin{aligned} \| \underline{x}_1(t) \| &= \| e^{At}\underline{x}(0) + \int_0^t e^{A\tau} C\underline{u}(t-\tau) d\tau \| \\ &\leq s_1 \| \underline{x}(0) \| e^{-s_2 t} + \| C \| \nu_1 s_1 \int_0^t e^{-s_2 \tau} e^{\nu_2 \tau} d\tau \\ &\leq \mu_1 e^{-s_2 t}, \left(\mu_1 \triangleq s_1 \| \underline{x}_1(0) \| + \frac{s_1 \nu_1 M_2}{\nu_2 - s_2} \right) \end{aligned} \tag{3.7}$$

Using (3.6),

$$\| \underline{x}_2(t) \| = \| \int_0^t e^{A\tau} \sum_{k=1}^{m} B_k u_k(t-\tau) \underline{x}_1(t-\tau) d\tau \|$$

$$\leq s_1 m M_1 \nu_1 \mu_1 \int_0^t e^{-s_2\tau} e^{\nu_2\tau} e^{-s_2(t-\tau)} d\tau$$

$$\leq s_1 m M_1 \nu_1 \mu_1 e^{-s_2 t} \int_0^t e^{\nu_2\tau} d\tau$$

$$\leq \mu_2 \mu_1 e^{-s_2 t} (1-e^{-\nu_2 t}), \quad (\mu_2 \triangleq \frac{s_1 m M_1 \nu_1}{\nu_2}) \qquad (3.8)$$

Similarly,

$$\| \underline{x}_i(t) \| \leq \frac{1}{(i-1)!} \mu_1 e^{-s_2 t} (1-e^{-\nu_2 t})^{i-1} \mu_2^{i-1} \qquad (3.9)$$

Combining (3.7)——(3.9) and the fact $\lim_{j\to\infty} \sum_{i=1}^{j} \underline{x}_i(t) = \underline{x}(t)$ results in

$$\| \underline{x}(t) \| \leq \sum_{i=1}^{\infty} \| \underline{x}_i(t) \| \leq \mu_1 e^{-s_2 t} e^{\mu_2 (1-e^{-\nu_2 t})}$$

$$\leq \mu_1 e^{\mu_2} e^{-s_2 t}$$

or $\| \underline{y}(t) \| \leq \| D \| \mu_1 e^{\mu_2} e^{-s_2 t} = \mu e^{-s_2 t}$ (3.10)

where $\mu \triangleq \| D \| \mu_1 e^{\mu_2}$ Q.E.D.

By examining the assumption (1) in Theorem 3.1 and recalling that this assumption holds if A is a stable matrix (meaning that the eigenvalues of A have negative real

parts [53]), it follows

Corollary 3.1

A constant BLS in R^n with exponentially bounded input and stable matrix A is BIBO stable.

If the assumption (2) in Theorem 3.1 is relaxed to be $\|\underline{u}(t)\| \leq \nu_1$, i.e. uniformly bounded rather than exponentially bounded and the system is initially at rest, i.e. $\underline{x}(0)=\underline{0}$, then in line with the proof given above, it immediately yields:

Corollary 3.2

A constant BLS in R^n with stable matrix A is bounded-input-bounded-output (BIBO) stable, if $s_1 m M_1/s_2 < 1/\nu_1$ with output bounded by

$$\|\underline{y}(t)\| = M_2 \frac{\|D\| \nu_1 s_1 (1-e^{-s_2 t})}{s_2 (1-\frac{s_1 m M_1 \nu_1}{s_2})} \qquad (3.11)$$

It is easily seen now that the Volterra series provides a convenient tool for examining the stability behavior of a constant BLS via the coefficient matrices as well as input classes. An example is given below (which is in fact a subsystem of the immune model to be derived in Chapter IV) to illustrate these stability criteria.

Example 3.1

Consider a bilinear system with state equations,

$$\dot{x}_1 = \alpha u_1(t)x_1 - \frac{x_1}{\tau_1} + \beta, \quad x_1(0) = \tau_1\beta$$

$$\dot{x}_2 = 2\alpha u_2(t)x_1 - \frac{x_2}{\tau_2}, \quad x_2(0) = 0 \tag{3.12}$$

and with output equation $y(t) = x_2(t)$, where $-1 \leq u_1(t) \leq 1$, $0 \leq u_2(t) \leq 1$, and α, β, τ_1 and τ_2 are suitable positive constants. By defining $\hat{x}_1 = x_1 - \tau_1\beta$, $\hat{x}_2 = x_2$, (3.12) is recast into

$$\dot{\hat{\underline{x}}} = A\hat{\underline{x}} + \sum_{k=1}^{2} B_k u_k(t)\hat{\underline{x}} + C\underline{u}(t), \quad \hat{\underline{x}}(0) = \underline{0} \tag{3.13}$$

with

$$A = \begin{pmatrix} -\frac{1}{\tau_1} & 0 \\ 0 & -\frac{1}{\tau_2} \end{pmatrix}, \quad B_1 = \begin{pmatrix} \alpha & 0 \\ 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 2\alpha & 0 \\ 0 & 0 \end{pmatrix},$$

$$C = \begin{pmatrix} \alpha\tau_1\beta & 0 \\ 0 & 2\alpha\tau_1\beta \end{pmatrix}$$

Using Lemma 3.2, it can be shown that for $0 < t < \infty$

$$\| x_2(t) \| \leq (4\alpha\tau_1\tau_2\beta)e^{(\frac{1}{\tau_2} + 4\alpha)t} - 4\alpha\tau_1\tau_2\beta \tag{3.14}$$

If the multiplicative inputs are moreover restricted by $u_i(t) = 0$, if $t > t_2$ or $t < t_1$, $i = 1,2$, then those conditions in Theorem 3.1 are satisfied. And therefore after some algebraic manipulation, it can be shown that

$$\| x_2(t) \| \leq \mu_1 e^{\mu_2} e^{-s_2 t} \qquad (3.15)$$

with $\mu_1 = \frac{2\alpha\tau_1\beta\nu_1}{\nu_2 - s_2}$, $\nu_1 >> 1$

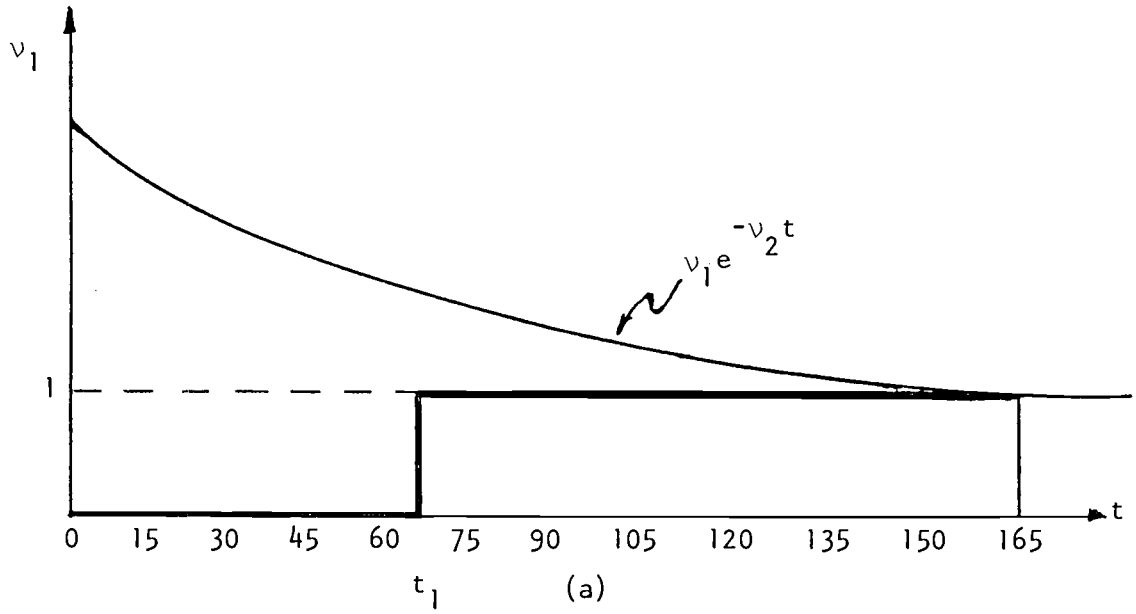
$$\mu_2 = \frac{4\alpha}{\nu_2} \ , \ \nu_2 = \frac{1}{t_2} \ln\nu_1 \quad \text{and} \quad s_2 = \frac{1}{\tau_1}$$

Figure 3.1 shows the upper bounds for $x_2(t)$ in (3.14) and (3.15) by using data of immunological relevance which will be explained later.

3.1.2 Finite Volterra Series

Up to now, three different methods of generating Volterra series for a constant BLS have been presented, namely, the Peano-Baker series, (Section 2.6.1), and other two in terms of a set of recursive linear equations (3.5) and (3.6) as well as (2.8), respectively. The latter two methods seem similar, but are significantly different with each other in view of Volterra kernel synthesis with respect to the structure of bilinear systems [54].

Associated with a BLS, there is, in general, an infinite number of Volterra kernels. Hence, it is natural to pose two questions. One is for practical purposes how many terms are sufficient to accurately represent a BLS? The other is for what class of bilinear systems, the corresponding Volterra series has only finite terms.



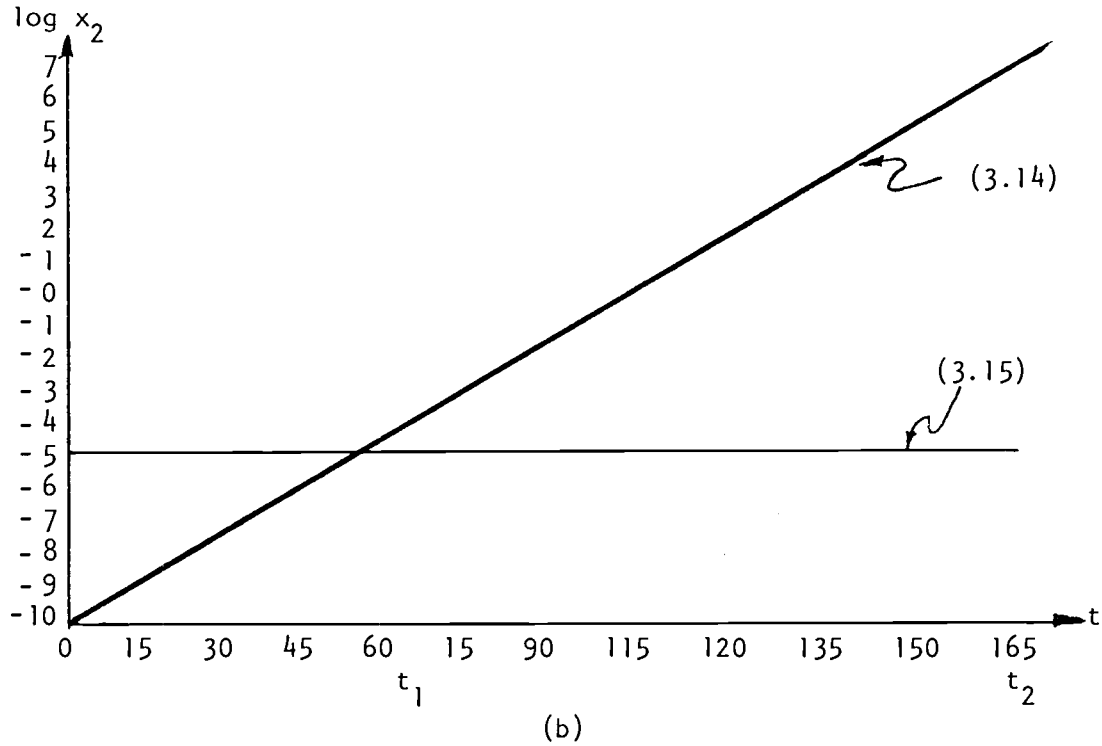


Figure 3.1. A simulation result for (3.14) and (3.15)
(a) upper bounds of $u_i(t)$, i=1,2
(b) upper bounds of $x_2(t)$ by (3.14) and (3.15); α=0.0578, τ_1=7140, τ_2=72, β=8.262x10^{-17}, t_1=65, t_2=165, ν_1=30.

To resolve these two problems, for instance, may lead to a better understanding of the structural aspects of bilinear systems. The first problem involving the truncation accuracy will be studied in this section, while the second is more intricate and will be dealt with the aid of Lie algebras in Section 3.1.4.

To simplify the exposition, all notations follow the last section, and it is understood that $\underline{x}(t)=\sum_{i=1}^{\infty}\underline{x}_i(t)$, where $\underline{x}_i(t)$'s are defined in (3.5) and (3.6).

Lemma 3.3 [51]

If the assumptions on Lemma 3.2 are kept the same and the Volterra series is truncated after r terms, then the output truncation error, $\tilde{\underline{y}}(t)=D\sum_{i=r+1}^{\infty}\underline{x}_i(t)$ is bounded by

$$\|\tilde{\underline{y}}(t)\| = \|D\sum_{i=r+1}^{\infty}\underline{x}_i(t)\| \leq \|D\|\left(\|\underline{x}_0\| + \frac{1}{w}\, m\ell M_2\right)$$

$$e^{(w+m\ell M_1)t}\,\frac{(m\ell M_1)^r t^r}{r!}, \quad r\geq 1 \qquad (3.16)$$

It is acknowledged here that the above error bound is very conservative, if t approaches a very large value. However, for the class of BLS as specified in Theorem 3.1, more accuracy can be established by,

Theorem 3.2

For a constant finite dimensional BLS with stable

matrix A and exponentially bounded input, the truncation error is bounded by

$$\| \tilde{\underline{y}}(t) \| \leq \mu_1 e^{-s_2 t} \frac{e^{\theta} \theta^r}{r!} \tag{3.17}$$

where $\theta = \mu_2(1-e^{-\nu_2 t})$

Proof: $\| \tilde{\underline{y}}(t) \| = \| D \sum_{i=r+1}^{\infty} \underline{x}_i(t) \| \leq \| D \| \, \| \sum_{i=r}^{\infty} \underline{x}_{i+1}(t) \|$

$$\leq \| D \| \, \mu_1 e^{-s_2 t} \| \sum_{i=r}^{\infty} \frac{\mu_2^{\,i}(1-e^{-\nu_2 t})^i}{i!} \|$$

(using (3.9))

$$\leq \| D \| \, \mu_1 \mu_2^{\,r} e^{-s_2 t} \frac{e^{\mu_2(1-e^{-\nu_2 t})}(1-e^{-\nu_2 t})^r}{r!} \tag{3.18}$$

The last step follows from Taylor's theorem [55]:

$$e^{\theta} = \sum_{i=0}^{r-1} \frac{\theta^i}{i!} + \frac{e^{\phi} \theta^r}{r!}$$

for some ϕ between 0 and θ; therefore

$$e^{\theta} - \sum_{i=0}^{r-1} \frac{\theta^i}{i!} = \sum_{i=r}^{\infty} \frac{\theta^i}{i!} = \frac{e^{\phi} \theta^r}{r!} \leq \frac{e^{\theta} \theta^r}{r!}$$

which is used to arrive at (3.18). Q.E.D.

Corresponding to Corollary 3.2, which is obtained by summing an infinite geometric series, the following can be easily obtained by summing the series with first r terms deleted.

Corollary 3.3

The truncation error for a constant BLS with stable matrix A and uniformly bounded input is

$$\| \tilde{y}(t) \| \leq M_2 \frac{\| D \| \nu_1 s_1 (1-e^{-s_2 t})}{s_2} \frac{Q^{r+1}}{1-Q},$$

$$Q \triangleq \frac{s_1 m M_1 \nu_1}{s_2}, \quad \text{if} \quad Q<1. \tag{3.19}$$

Based on the above analysis, if the required accuracy on the output is assigned, then sufficiently many Volterra kernels can be appropriately chosen to achieve the accuracy. This can be verified from (3.16) or (3.17) or (3.19) in which the error apporaches zero as $r \to \infty$. These truncation errors are shown in Figure 3.2, where the direction of the arrow corresponds to the error reduction as r increases.

3.1.3 Controllability and Stability

Controllability is a basic property of systems which is indicative of the ability to control. A most harsh requirement of a system would be to specify that it must be completely controllable. Formally, a system is said to be completely controllable if it can be driven from any finite initial state $\underline{x}_0 \in R^n$ to any prescribed finite terminal state $\underline{x}_f \in R^n$ in finite time with an admissible control. The precise definition has been given in Section 1.2.3.

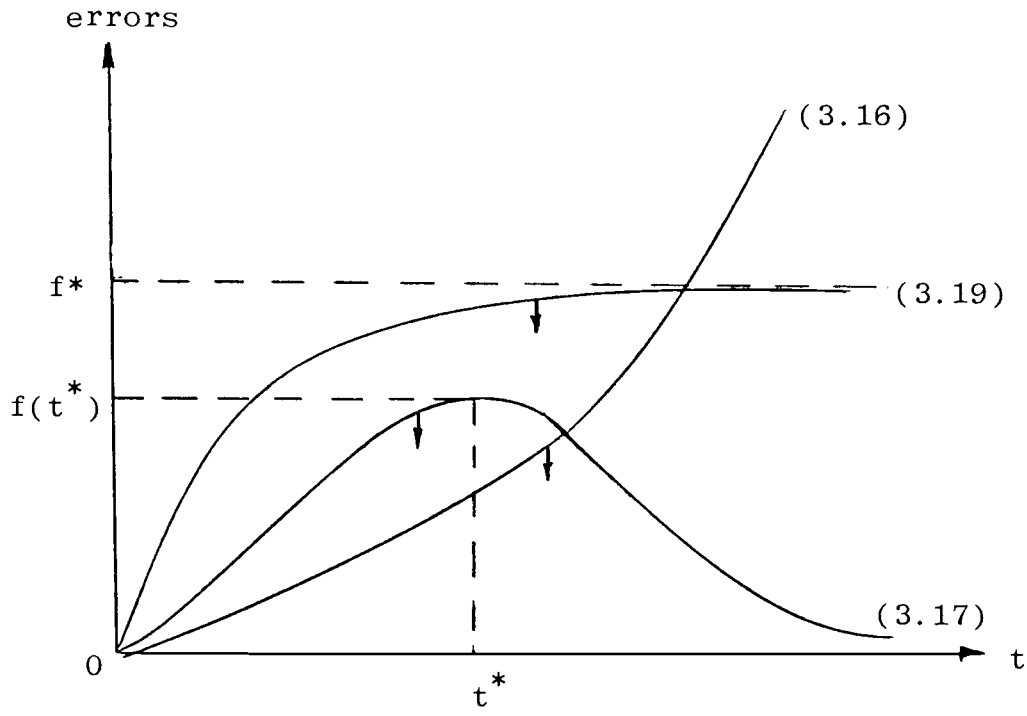


Figure 3.2. Comparison of truncation errors

$$t^* = \frac{-\ln m}{\nu_2}$$

$$\text{with } m = \frac{(\nu_2+s_2+r\nu_2)-\sqrt{(\nu_2-s_2)^2+r^2\nu_2^2+2r\nu_2^2+2rs_2\nu_2}}{2\nu_2}$$

$$f(t^*) = \frac{\mu_1\mu_2^r}{r!}\,(1-m)^r e^{\mu_2(1-m)}\, m^{s_2/\nu_2}$$

$$f^* = \frac{Q^{r+1}}{1-Q}\,\frac{||D||\nu_1 s_1}{s_2}\,M_2$$

Apparently, there is some inherent relationship between stability and controllability. Such a connection is well exploited for constant linear systems [8]. For constant BLS, the work was initiated by Mohler and Rink who derived sufficient conditions for complete controllability [3]. Their criterion, while especially useful for phase-variable canonical BLS, is to check if all eigenvalues of the system matrix $A+\sum_{k=1}^{m} u_k(t)B_k$ can be shifted across the imaginary axis of the complex plane without passing through the origin, as $\underline{u}(t)$ ranges continuously over an admissible subset of $\mathcal{U}$. This work suggested the connection between controllability and stability and has recently attracted much attention. Some interesting results with applications in nonconservative elastic systems are now available due to Jurdjevic and Quinn [56], and Slemrod [57].

The above remarks are made not only because the connection stays a fruitful research arena, but more importantly, the conceptually simple analysis developed in the preceding sections provides insight and new link as far as the controllability and stability of BLS are concerned. This will be explained in more detail in the next section.

A well-known criterion concerning the uncontrollability of a constant linear system is

Theorem 3.3 [11]

A constant linear system with uniformly bounded input $\underline{u}(t)$,

$$\dot{\underline{x}}(t) = A\underline{x}(t) + C\underline{u}(t) \tag{3.20}$$

is not completely controllable if the eigenvalues of A have only negative real parts, i.e. A is a stable matrix.

By recalling the definition of complete controllability as well as the results developed so far on the boundedness property of BLS with constrained inputs, the above theorem can be easily extended. All parameters are defined the same as in the previous section.

Theorem 3.4

A constant BLS with uniformly bounded input $\underline{u}(t)$

$$\dot{\underline{x}}(t) = A\underline{x}(t) + \sum_{k=1}^{m} u_k(t)B_k\underline{x}(t) + C\underline{u}(t) \tag{3.21}$$

is not completely controllable if A is a stable matrix and $s_1 m M_1 / s_2 < 1/\nu_1$.

It is easily understood that just the same as the stability, the controllability depends crucially on the input classes. As a consequence of Theorem 3.1, it follows that

Theorem 3.5

A constant BLS with exponentially bounded input $\underline{u}(t)$,

viz, (3.21) is not completely controllable if A is a stable matrix.

It is of interest to note that the condition on A in Theorem 3.3 cannot be relaxed because it is readily seen, for example, that the second-order linear system with imaginary eigenvalues (e.g. linear harmonic oscillator) is completely controllable with bounded control if a sufficiently large number of switchings are permitted with a bang-bang control [58]. Similarly, the eigenvalue condition on A in Theorem 3.4 cannot be relaxed in view of Lemma 3.2 which immediately implies that if A is not a stable matrix (A has purely imaginary eigenvalues is a special case of this), then the reachable set of $\underline{x}(0)$ may be unconstrained. In other words, such a BLS may be completely controllable as expected.

It is seen from the above that control systems, linear or bilinear, whose system matrix A has only purely imaginary eigenvalues merit particular attention in control theory and applications. For the sake of completeness, the theorem of Jurdjevic and Quinn [56] is stated with an example to substantiate the link between BLS controllability and stability via eigen modes of BLS.

Theorem 3.6 [56]

Consider the control system

$$\dot{\underline{x}}(t) = A\underline{x}(t) + u(t)B\underline{x}(t), \quad \underline{x}(t)\in R^n - \{0\} \qquad (3.22)$$

where the control u(t) is a piecewise continuous function defined on $[0, \infty)$, and A is a constant matrix with real entries such that its eigenvalues are purely imaginary and distinct. If

$$\text{Span } \{A\underline{x},\ ad_A^0 B\underline{x},\ ad_A^1 B\underline{x}, \ldots\} = R^n \tag{3.23}$$

for all $\underline{x} \in R^n - \{0\}$, then (3.22) is completely controllable.

Concluding with this section, bilinear models proposed by Mohler [11] are selected as examples to illustrate and compare the use of above theorems.

Example 3.3(a)

Consider the bilinear system

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= -2x_1 - x_2 + u + x_1 u + 2x_2 u \end{aligned} \tag{3.24}$$

or in concise form, $\dot{\underline{x}}(t) = A\underline{x}(t) + Bu(t)\underline{x}(t) + \underline{c}u(t)$ with

$$A = \begin{pmatrix} 0 & 1 \\ -2 & -1 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & 0 \\ 1 & 2 \end{pmatrix}, \quad \underline{c} = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$$

It is easily checked that the linear part of (3.24), that is, $\dot{\underline{x}}(t) = A\underline{x}(t) + \underline{c}u(t)$, is completely controllable if input u(t) is unconstrained. However, by Theorem 3.3, this linear system is not completely controllable if the input u(t) is bounded, for instance, $|u(t)| \leq 1$, because A is a stable matrix (with eigenvalues $(-1+\sqrt{7}\ i)/2$ and $(-1-\sqrt{7}\ i)/2$). Even though the matrix A is stable and

the input is bounded, by employing the theorem of Mohler and Rink, the BLS (3.24) can be shown to be completely controllable. This can be further verified by the fact that the condition $s_1 m M_1/s_2 < 1/\nu_1$ in Theorem 3.4 is violated (with $m=1$, $M_1=2$, $s_1=1$, and $s_2=1/2$ for this example).

Example 3.3(b)

Consider the bilinear system (3.22) with

$$A = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}, \quad \text{and} \quad B = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

The eigenvalues of A are $\pm i$. To show that the condition (3.23) is satisfied, let $\underline{x}=(a, b)^T \in R^2$, and use the fact that $[A, B] = 0$ so as $ad_A^i B = 0 \ \forall\ i \geq 1$,

$$\text{Span } \{A\underline{x}, ad_A^0 B\underline{x}, ad_A^1 B\underline{x}, \ldots\}$$

$$= \text{Span } \{A\underline{x}, B\underline{x}\} = R^2 \ \forall\ \underline{x} \neq \underline{0}, \quad \text{since}$$

$$\det \begin{pmatrix} b & a \\ -a & b \end{pmatrix} = b^2 + a^2 \neq 0 \text{ unless } a=b=0.$$

Thus by Theorem 3.6, this BLS is completely controllable. It is of some interest to observe here that the eigenvalues of $(A+u(t)B)$ are $u \pm i$, which can be shifted across the imaginary axis without passing through the origin by ranging $u(t)$ from negative to positive or vice versa. The complete controllability is therefore verified by the theorem of Mohler and Rink.

Example 3.3(c)

The BLS example presented in Section 2.5 is again considered,

$$\dot{\underline{x}} = A\underline{x} + u(t)B\underline{x}, \qquad \underline{x}(0) = (0,\ 1)^T$$

with

$$A = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \qquad B = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}$$

It is easily seen that $\underline{x}(t) \geq \underline{0}\ \forall t$, if $u(t)$ is restricted to be greater or equal to one. In this case, the system is not completely controllable. Moreover, the eigenvalues of $A+uB$ are $\pm j\sqrt{1-u}$ if $u(t)$ is less than or equal to one. If $\underline{x}=(a,\ b)^T$, then $\det\{A\underline{x},\ B\underline{x}\} = ab$ which can be zero when either a or b is zero. Thus both the theorem of Mohler and Rink and Theorem 3.6 are not appropriate to apply for this particular example. Though the above situation may arise from the semi-simplicity of the Lie algebra $\{A,\ B\}_{LA}$, this will not be pursued here [27, 28].

3.1.4 Structural Aspects of Bilinear Systems

It is apparent that the BLS structure is determined by the coefficient matrices, $S=\{A,\ B_i,\ i=1,\ 2,\ldots,m,\ C\}$. In this section, the second question raised in Section 3.1.2, what class of BLS has only finite terms of Volterra series, will be answered. Here the Lie algebra provides

a convenient tool demarcating Volterra series and consequently shed light on the intrinsic link between algebraic structure of the set S and internal structure of a bilinear system. For convenience, a BLS which can be fully represented by a finite Volterra series is said to have F.V.S. property.

It has been shown in Section 3.1.2 that for a BLS without FVS property, special care should be taken to the problem of truncation accuracy. However, if a BLS has FVS property, then truncation is no longer meaningful in practice, unless the truncation is inevitable out of numerical difficulty such as large scale BLS, etc.

Recalling that solving (3.5) and (3.6) explicitly will give the Volterra series corresponding to the BLS (3.1). Without loss of generality, only homogeneous BLS with scalar input (with the output equation $y(t)=\underline{d}^T\underline{x}(t)$ understood),

$$\dot{\underline{x}}(t) = A\underline{x}(t) + u(t)B\underline{x}(t), \quad \underline{x}(0)=\underline{x}_0\neq\underline{0} \tag{3.25}$$

will be considered. The vectorial input case is not pursued since it does not introduce any conceptual difficulty but does complicate notations considerably.

The Volterra series for (3.25) is obtained as

$$\underline{x}(t) = \sum_{i=1}^{\infty} \underline{x}_i(t) \text{ from}$$

$$\begin{aligned} &\dot{\underline{x}}_1(t)=A\underline{x}_1(t), \quad \underline{x}_1(0)=\underline{x}_0 \\ &\dot{\underline{x}}_i(t)=A\underline{x}_i(t)+B\underline{x}_{i-1}(t)u(t), \quad \underline{x}_i(0)=\underline{0}, \quad i=1,2,\ldots \end{aligned} \tag{3.26}$$

By (3.26)

$$\underline{x}_1(t)=e^{At}\underline{x}_1(0)=e^{At}\underline{x}_0$$

$$\underline{x}_2(t)=\int_0^t e^{A(t-\tau)}Be^{A\tau}u(\tau)d\tau\cdot\underline{x}_0$$

$$\underline{x}_3(t)=\int_0^t\int_0^{\tau_1} e^{A(t-\tau_1)}Be^{A(\tau_1-\tau_2)}Be^{A\tau_2}u(\tau_1)u(\tau_2)d\tau_1d\tau_2\cdot\underline{x}_0$$

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Hence, $\underline{x}(t)=\sum_{i=1}^{\infty}\underline{x}_i(t)$

$$=e^{At}\underline{x}_0+\sum_{i=1}^{\infty}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}} e^{A(t-\tau_1)}Be^{A(\tau_1-\tau_2)}$$

$$B\cdot e^{A\tau_i}\cdot\underline{x}_0\prod_{j=1}^{i}u(\tau_j)d\tau_j \qquad (3.27)$$

Employing the notion of adjoint operator and BCH formula in Section 2.3, (3.27) can be concisely expressed as

$$\underline{x}(t)=e^{At}\underline{x}_0+\sum_{i=1}^{\infty}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}} e^{At}e^{-\tau_1 ad_A}Be^{-\tau_2 ad_A}B\cdots$$

$$e^{-\tau_i ad_A}B\prod_{j=1}^{i}u(\tau_j)d\tau_j\cdot\underline{x}_0$$

or

$$\underline{x}(t)=e^{At}\underline{x}_0+\sum_{i=1}^{\infty}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}}$$

$$e^{At}\prod_{j=1}^{i}(e^{-\tau_j ad_A}B)u(\tau_j)d\tau_j\cdot\underline{x}_0 \qquad (3.28)$$

The above equation gives clue to the fact that whether a BLS has FVS property critically depends on matrices A and B, more precisely, on the algebraic property of the set $\{ad_A, B\}$.

The following theorems due to Brockett [37] and Crouch [59] relate the algebraic structure of $\{ad_A, B\}$ with the finiteness of Volterra series for BLS.

Theorem 3.7

The nilpotency of the Lie algebra $\mathcal{L} = \{ad_A, B\}_{LA}$ is necessary for the Volterra series of the system (3.25) to be finite, where $\mathcal{L}$ denotes the smallest Lie algebra containing B and closed over the operation $ad_A: \mathcal{L} \rightarrow [A, \mathcal{L}]$.

Theorem 3.8

The nilpotency of the algebra $\mathcal{A} = \{B, ad_A^k B\}_{AA}$ is a necessary and sufficient condition for the Volterra series of the system (3.25) to be finite, where $\mathcal{A}$ denotes the

smallest associative algebra[1] that contains B and $ad_A^k B$, k=0,1,2,$\cdots$.

As a consequence of these general results and the global solution technique presented in Section 2.5, structural aspects of BLS can be thoroughly examined, at least, in theory. This argument is further furnished by,

Example 3.4

Suppose that a BLS is commutative (abelian), i.e. [A, B]= AB-BA = 0, then by (3.28),

$$\underline{x}(t)=e^{At}\underline{x}_0 + \sum_{i=1}^{\infty} \int_0^t \int_0^{\tau_1} \cdots \int_0^{\tau_{i-1}} e^{At} B^i \prod_{j=1}^{i} u(\tau_j)d\tau_j \cdot \underline{x}_0 \qquad (3.29)$$

It is seen that the R.H.S. of (3.29) is a finite series if and only if B is nilpotent (that is, there exists a positive integer n such that $B^n=0$). However, owing to the assumption of [A, B]=0, the nilpotency of B implies that A is transformable to upper-triangular form.

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[1]That is, the smallest vector space of matrices, closed under usual multiplication. An associative algebra is nilpotent if there exists a positive integer n such that the product of any n elements of the associative algebra vanishes.

Thus for abelian BLS having FVS property, they are fully represented by

$$\underline{x}(t)=e^{At}\underline{x}_0+\sum_{i=1}^{q-1}\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}} e^{At}B^i\prod_{j=1}^{i}u(\tau_j)d\tau_j\cdot\underline{x}_0 \qquad (3.30)$$

where q denotes the index of the nilpotent matrix B (i.e. $B^{q-1}\neq 0$, but $B^q=0$). It is apparent that this particular BLS class can be structurally decoupled as a cascade of linear systems. For example, a second-order SISO abelian BLS with a finite Volterra series is representable by the equations:

$$\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\end{pmatrix}=\begin{pmatrix}a_{11} & a_{12}\\ 0 & a_{22}\end{pmatrix}\begin{pmatrix}x_1\\ x_2\end{pmatrix}+u(t)\begin{pmatrix}0 & b\\ 0 & 0\end{pmatrix}\begin{pmatrix}x_1\\ x_2\end{pmatrix} \qquad (3.31)$$

$$y(t)=\begin{pmatrix}c_1, & c_2\end{pmatrix}\begin{pmatrix}x_1\\ x_2\end{pmatrix}$$

It is easily seen that (3.31) can be decomposed in terms of two linear systems in cascade. The Volterra series (3.29) can also be obtained directly from the global solution of the abelian BLS, that is,

$$\underline{x}(t)=\exp\int_0^t (A+u(\tau)B)d\tau\underline{x}_0$$

$$=e^{At}\exp(B\int_0^t u(\tau)d\tau)\underline{x}_0$$

$$=e^{At}\sum_{i=0}^{\infty}\frac{B^i v^i(t)}{i!}\underline{x}_0, \qquad (v(t)\triangleq\int_0^t u(\tau)d\tau)$$

$$=\sum_{i=0}^{\infty} e^{At}B^i\int_0^t\int_0^{\tau_1}\cdots\int_0^{\tau_{i-1}}\prod_{j=1}^{i}u(\tau_j)d\tau_j\cdot\underline{x}_0$$

Where the last equality is arrived by using the identity

$$[\int_0^t u(\tau)d\tau]^n = n!\int_0^t\int_0^{\tau_1}\int_0^{\tau_{n-1}} u(\tau_{n-1})u(\tau_{n-2})\cdots u(\tau_1)$$

$$d\tau_{n-1}d\tau_{n-2}\cdots d\tau_1 \qquad (3.32)$$

As shown in the previous example, some BLS with FVS property may be synthesized as linear systems in cascade. However, such BLS may also be decomposed into other interconnection of linear subsystems for which the linear system theory can be advantageously applied. An interesting class of linear composite systems, called factorable Volterra systems and developed by Harper and Rugh [60] for approximating nonlinear systems, are closely related to such decomposable bilinear systems.

Example 3.5

The factorable Volterra system π_k (Figure 3.3)

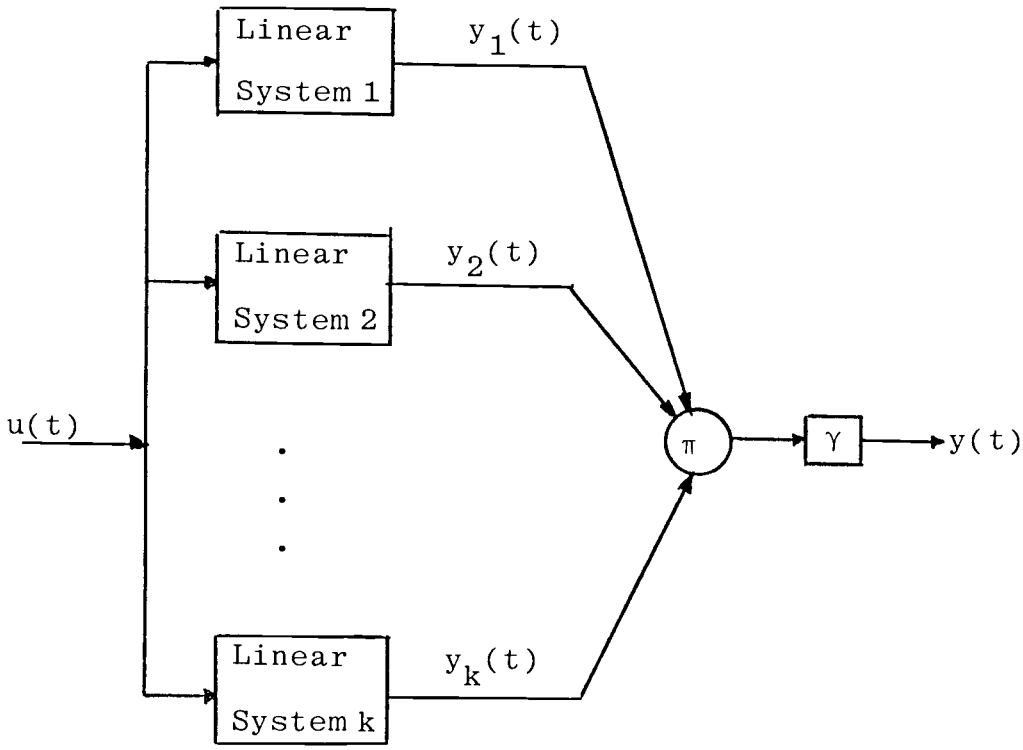

Figure 3.3. The factorable Volterra system π_k [60].

composed of k linear dynamic subsystems connected in parallel with the outputs multiplied (in the time domain) are defined by

$$\dot{\underline{x}}(t)=A\underline{x}(t)+\underline{b}u(t)$$
$$y(t)=\gamma\prod_{i=1}^{k}\underline{c}_i^T\underline{x}_i(t)=\gamma\prod_{i=1}^{k}y_i(t) \qquad (3.33)$$

where

$$\underline{x}(t)=\begin{pmatrix}\underline{x}_1(t)\\ \underline{x}_2(t)\\ \cdot\\ \underline{x}_k(t)\end{pmatrix},\quad A=\begin{pmatrix}A_1 & & & \\ & A_2 & & \\ & & \cdot & \\ & & & A_k\end{pmatrix},\quad \underline{b}=\begin{pmatrix}\underline{b}_1\\ \underline{b}_2\\ \cdot\\ \underline{b}_k\end{pmatrix},\quad \underline{c}_i=\begin{pmatrix}c_1\\ c_2\\ \cdot\\ c_{n_i}\end{pmatrix}$$

i.e.,

$$\dot{\underline{x}}_i(t)=A_i\underline{x}_i(t)+\underline{b}_i u(t),\ A_i\varepsilon R^{n_i xn_i},\ \underline{b}_i\varepsilon R^{n_i},\ i=1,2,\ldots,k$$

$$y_i(t)=\underline{c}_i^T\underline{x}_i(t),$$

and the vector $\underline{x}(t)$ is of dimension $n=n_1+n_2+\ \ldots\ +n_k$.

It can be seen that the system π_k can be represented by a Volterra series and also can be realized as a BLS which is nevertheless not a natural representation.
As an example, consider the π_2 system with transfer functions

$$H_1(s) = \frac{b_1}{s + a_1} \quad \text{and} \quad H_2(s) = \frac{b_2}{s + a_2}$$

A bilinear system which has the same input/output behavior as the π_2 system, with $x_3(t)=x_1(t)x_2(t)$ is as follows:

$$\begin{aligned}\dot{\underline{x}}(t)&=A\underline{x}(t)+uB\underline{x}(t)+\underline{c}u,\quad \underline{x}(t)\varepsilon R^3\\ y(t)&=\underline{d}^T\underline{x}(t)\end{aligned} \tag{3.34}$$

where

$$A=\begin{pmatrix} -a_1 & 0 & 0 \\ 0 & -a_2 & 0 \\ 0 & 0 & -(a_1+a_2) \end{pmatrix},$$

$$B=\begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ b_2 & b_1 & 0 \end{pmatrix} \quad \underline{c}=\begin{pmatrix} b_1 \\ b_2 \\ 0 \end{pmatrix} \quad \text{and} \quad \underline{d}=\begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

The homogeneous BLS associated with (3.34) is

$$\begin{aligned} \dot{\hat{\underline{x}}}(t) &= \hat{A}\hat{\underline{x}}(t) + u\hat{B}\hat{\underline{x}}(t), \quad \hat{\underline{x}}(t)\in R^4 \\ y(t) &= \hat{\underline{d}}^T\hat{\underline{x}}(t) \end{aligned} \tag{3.35}$$

where $\hat{\underline{x}}(t) = (x_1(t),\ x_2(t),\ x_1(t)x_2(t),\ 1)^T$

and

$$\hat{A}=\begin{pmatrix} -a_1 & 0 & 0 & 0 \\ 0 & -a_2 & 0 & 0 \\ 0 & 0 & -(a_1+a_2) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad \hat{B}=\begin{pmatrix} 0 & 0 & 0 & b_1 \\ 0 & 0 & 0 & b_2 \\ b_2 & b_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\hat{\underline{d}}=\begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}$$

It can be shown that the associative algebra $\{B, ad_A^k B\}_{AA}$, k=0, 1,2,... is nilpotent, hence by Theorem 3.8, the BLS (3.35) has the FVS property. Consequently, the Volterra system π_2 has also the FVS property.

3.2 Inverse of Bilinear System

3.2.1 Concept of the Inverse System

Investigation of a 'system' employing a mathematical model normally grants that the input (control) and output (measurement) are known, at least in the probabilistic sense. This is the essence of the well-known 'black-box approach'. Formally speaking, the object is to construct a model that will accurately represent the underlying system by way of, for instance, estimating the parameters, realizing the system structure, etc. However, very often the situation is not so. The communication system is an illustrative example. The main concern is to retrieve the message (input) based on the output (the received signal which may be corrupted by noises).

To this, it is remarkable that the question of invertibility — when the output of a control system uniquely determines the input — is of practical as well as theoretical interest. The construction of an 'inverse model' which is able to predict the unknown input of a model from measured output data, is particularly important in biolog-

ical modeling [61]. Fish [62] made a model of the movement of uranium in the body, in which uranium was picked up by the body from the surroundings and appeared in the urine. The output could be measured, but the history of the input was unknown. In immunology, the measurable output data usually is the antibody concentration in the serum, the threshold (input or parametric control) which determines the cell stimulations and differentiations is unknown [63, 64]. This issue of considerable importance in understanding the immune system will be furthermore studied in Chapter V.

There is a considerable amount of literature dealing with the construction of an inverse system for a linear system (references [65, 66] and other references therein). The main result is summarized as follows without proof.

Theorem 3.9

Consider the SISO completely controllable linear system.

$$\dot{\underline{x}}(t)=A\underline{x}(t) + \underline{b}u(t) \quad ; \quad \underline{x}(0)=\underline{x}_0, \ \underline{x}(t)\varepsilon R^n$$
$$y(t)=\underline{c}^T\underline{x}(t) \tag{3.36}$$

If the relative order α[1] of (3.36) is finite, i.e.

[1]The relative order of a linear system is referred to as the difference in the degree of numerator and denominator polynomials of its transfer function $G(s)=\underline{c}^T(Is-A)^{-1}\underline{b}$.

$\alpha<\infty$, then there is a unique inverse system which is also completely controllable and is defined by,

$$\begin{aligned}\dot{\hat{\underline{x}}}(t)&=[A-(\underline{b}\ \underline{c}^TA^{\alpha}/\underline{c}^TA^{\alpha-1}\underline{b})]\ \hat{\underline{x}}(t)+\\&\quad+(1/\underline{c}^TA^{\alpha-1}\underline{b})\underline{b}\tilde{u}(t),\hat{\underline{x}}(0)=\underline{x}_0\\\hat{y}(t)&=-(\underline{c}^TA^{\alpha}/\underline{c}^TA^{\alpha-1}\underline{b})\hat{\underline{x}}(t)+(1/\underline{c}^TA^{\alpha-1}\underline{b})\hat{u}(t)\end{aligned}\tag{3.37}$$

Let $\hat{u}(t)=y^{(\alpha)}(t)$, then $\hat{y}(t)=u(t)$

3.2.2 Inverse of a Class of BLS

In the last section, the design of the inverse system of a given linear system is shown to be available if certain conditions are met (see Theorem 3.9). The extension of constructing the inverse system for a bilinear system is a much more difficult task. A significant contribution in BLS analysis owing to Hirschorn [67] generalized the Theorem 3.9, which states:

Theorem 3.10 [67]

Consider the SISO BLS,

$$\begin{aligned}\dot{\underline{x}}(t)&=A\underline{x}(t)+u(t)B\underline{x}(t),\ \underline{x}(0)=\underline{x}_0\in R^n\\y(t)&=\underline{c}^T\underline{x}(t)\end{aligned}\tag{3.38}$$

If the BLS (3.38) is invertible, then its relative order[1] is $\alpha<\infty$.

---

[1] The relative order of a BLS is referred to the least positive integer k such that $\underline{c}^TAd_A^{k-1}B\neq 0$ or $\alpha=\infty$ if $\underline{c}^TAd_A^kB=0$ for all $k>0$.

If $\alpha<\infty$ and $\underline{c}^T ad_A^{\alpha-1} B\underline{x}_0 \neq 0$, then the BLS is invertible with inverse system defined by

$$\begin{aligned} \dot{\hat{\underline{x}}}(t) &= \underline{a}(\hat{\underline{x}}(t)) + \hat{u}(t)\underline{b}(\hat{\underline{x}}(t)), \quad \hat{\underline{x}}(0)=\hat{\underline{x}}_0=\underline{x}_0 \in R^n \\ \hat{y}(t) &= d(\hat{\underline{x}}(t)) + \hat{u}(t)e(\hat{\underline{x}}(t)) \end{aligned} \tag{3.39}$$

where

$$\begin{aligned} \underline{a}(\hat{\underline{x}}(t)) &= A\hat{\underline{x}}(t) - (\underline{c}^T A^{\alpha}\hat{\underline{x}}(t)/\underline{c}^T A^{\alpha-1} B\hat{\underline{x}}(t))B\hat{\underline{x}}(t) \\ \underline{b}(\hat{\underline{x}}(t)) &= (1/\underline{c}^T A^{\alpha-1} B\hat{\underline{x}}(t))B\hat{\underline{x}}(t) \\ d(\hat{\underline{x}}(t)) &= -(\underline{c}^T A^{\alpha}\hat{\underline{x}}(t)/\underline{c}^T A^{\alpha-1} B\hat{\underline{x}}(t)) \\ e(\hat{\underline{x}}(t)) &= 1/\underline{c}^T A^{\alpha-1} B\hat{\underline{x}}(t) \end{aligned} \tag{3.40}$$

If $\hat{u}(t) = y^{(\alpha)}(t)$, then $\hat{y}(t) = u(t)$

Proof of this theorem is omitted here since it is quite lengthy and involves mathematical machineries outside of the scope of this thesis. Reader who is interested in the proof is referred to the original paper [67]. There are a few consequences of Theorem 3.10 which are of particular relevance to this research. Firstly, it can be proved that when $\hat{u}(t) = y^{(\alpha)}(t)$, the state $\hat{x}(t) = x(t)$, the state of the original BLS (3.38). Thus the inverse system (3.39) acts as state observer (defined in Section 2.2.2) for the BLS, a result which itself is of practical importance. Secondly, the inverse system (3.39) is in general a highly nonlinear system. The vector fields $\underline{a}$ $(\hat{\underline{x}}(t))$ and $\underline{b}$ $(\hat{\underline{x}}(t))$ may not be complete, that is, the integral curves for these vector fields need not be defined for all time.

In other words, there is a possibility that the solution to (3.39) may go without bound at a certain finite time. Thirdly, the above theorem presents a sufficient condition for inverting vector BLS (3.38) in case where $\alpha<\infty$, but this condition is far from being necessary. Fourthly, Hirschorn raises the question whether or not an invertible BLS has a bilinear inverse system. This is indeed only a specific question of the more subtle one, that is, what is the connection (if any) of BLS and its inverse as far as their structural aspects are concerned. For instance, the inverse system is linear and controllable if and only if the original system is linear and controllable (see Theorem 3.9). Can this connection be carried over to bilinear systems? While aforementioned problems are interesting of their own right, the last question is treated here, leaving the description of using inverse system as a state observer to the next section.

The inverse system (3.39) is obviously a linear-analytic system which includes BLS as a special case. In order to have the inverse system of simpler structure, it is reasonable to impose conditions on the matrices A and B of the original BLS (3.38). It is shown here that if the rank of B is unity, then the inverse system (3.39) is much simplified.

First consider the following fact in matrix theory [68].

Lemma 3.4

Any n-dimensional square matrix of rank one can be uniquely (within a scalar factor) expressed as a product of a column and a row n-vector.

Theorem 3.11

Consider the SISO BLS (3.38) with relative order α if the system is invertible and rank (B) = 1, then the inverse system of (3.38) is a linear time-invariant system with nonlinear output defined by (3.39) with

$$\underline{a}(\hat{\underline{x}}(t)) = (A - \frac{\underline{\ell}\ \underline{c}^T A^{\alpha}}{\underline{c}^T A^{\alpha-1}\underline{\ell}})\hat{\underline{x}}(t) \qquad (3.41a)$$

$$\underline{b}(\hat{\underline{x}}(t)) = \frac{1}{\underline{c}^T A^{\alpha-1}\underline{\ell}}\ \underline{\ell} \qquad (3.41b)$$

$$d(\hat{\underline{x}}(t)) = -\frac{\underline{c}^T A^{\alpha}\hat{\underline{x}}(t)}{\underline{c}^T A^{\alpha-1}\underline{\ell}\ \underline{m}^T\hat{\underline{x}}(t)} \qquad (3.41c)$$

$$e(\hat{\underline{x}}(t)) = \frac{1}{\underline{c}^T A^{\alpha-1}\underline{\ell}\ \underline{m}^T\hat{\underline{x}}(t)} \qquad (3.41d)$$

where $B = \underline{\ell}\ \underline{m}^T$

The assumption that rank (B)=1 seems very restrictive, but BLS with this property stands out as a special BLS of particular interest both in theory and in practice. For instance, discrete BLS with rank (B)=1 has been extensively studied as far as the controllability and optimal control are concerned [69, 70, 71]. Many natural

bilinear systems do satisfy this rank assumption as can be found in the next section and elsewhere [11, 72].

It is observed from this theorem that the inverse system (3.41a) and (3.41b) is exactly the same as that for the constant linear system (see Theorem 3.9). The following stronger result can be established,

Theorem 3.12

Consider the BLS (3.38) as described in Theorem 3.11, then the inverse system of (3.38) is a linear time-invariant system which is completely controllable if the original system is completely controllable.

The proof of this theorem is based on the following two remarks, and is somewhat straightforward:

Remark 1 [66]

Rank $(\underline{\ell}, A\underline{\ell}, \ldots, A^{n-1}\underline{\ell})$ = Rank $(\underline{\ell}, \hat{A}\underline{\ell}, \ldots, \hat{A}^{n-1}\underline{\ell})$

where $\hat{A} = A - (\underline{\ell}\underline{c}^T A^{\alpha})/\underline{c}^T A^{\alpha-1}\underline{\ell}$.

Remark 2 [69]

If the BLS (3.38) with rank (B)=1 is completely controllable, then Rank $(\underline{\ell}, A\underline{\ell}, \ldots, A^{n-1}\underline{\ell}) = n$.

In other words, if BLS (3.38) with rank(B)=1 is completely controllable, then by the above remarks Rank $(\underline{\ell}, \hat{A}\underline{\ell}, \ldots, \hat{A}^{n-1}\underline{\ell})=n$. The inverse system of (3.38), which is a constant linear system by Theorem 3.11, is thus completely controllable as a consequence of the well-known rank test.

3.2.3 Numerical Examples

Example 3.6

The biocontrol example (a simplified immune model) presented in Section 2.6.3 is adopted here again for the purpose of illustrating the inverse system of BLS. For convenience, the model described in (2.36) is transformed by $\underline{z}(t)=P\underline{x}(t)$, b=d and $u(t)=\frac{1}{2}(1+\tilde{u}(t))$, into

$$\dot{\underline{z}}(t) = \tilde{A}\underline{z}(t) + \tilde{u}(t)\tilde{B}\underline{z}(t), \quad \underline{z}(0)=(z_{10}, 0, 0)^T \qquad (3.42)$$

where

$$\tilde{A}=\begin{pmatrix} -\mu_2 & 0 & 0 \\ \frac{1}{2}b & -\mu_3 & 0 \\ k & rk & 0 \end{pmatrix}, \quad \tilde{B}=\begin{pmatrix} b & 0 & 0 \\ -\frac{1}{2}b & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \text{and}$$

$$P=\begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{pmatrix}$$

If the input $\tilde{u}(t)$ is not known and $z_3(t)$ is the only measurable state, viz, $y(t)=\underline{c}^T\underline{z}(t)=(0, 0, 1)\underline{z}(t)$, then the BLS observer theory developed in the previous section can be applied to estimate the inaccessible input and states. For this particular example, rank $(\tilde{B})=1$, the relative order $\alpha = 2$[1], and therefore by Theorem 3.11, the inverse

[1] It should be noted here that $\alpha=2$ only if $r\neq 2$, otherwise $\alpha=\infty$, i.e. $\underline{c}^T ad_A^k B\underline{z}_0=0$ for all k=0, 1,2,... . By Theorem 3.10, if $\alpha=\infty$, then the BLS (3.42) is not invertible. This can also be seen from the inverse system (3.43) and (3.44).

system of (3.42) is via (3.41) a constant linear system:

$$\dot{\hat{\underline{z}}}(t) = \hat{A}\hat{\underline{z}}(t)+\hat{u}(t)\hat{\underline{b}}, \quad \hat{\underline{z}}(0)=(z_{10}, 0, 0)^T \tag{3.43}$$

$$\hat{y}(t) = \frac{\delta\mu_3 rk\hat{z}_2(t)-\delta(-\mu_2 k+\frac{1}{2}brk)\hat{z}_1(t)}{b\hat{\underline{z}}_1(t)} + \hat{u}(t)\frac{\delta}{b\hat{\underline{z}}_1(t)} \tag{3.44}$$

where $\delta \triangleq 1/(k-\frac{1}{2}rk)$

$$\hat{A} = \begin{pmatrix} -\mu_2+\delta k(\mu_2-\frac{1}{2}br) & \delta\mu_3 rk & 0 \\ \frac{1}{2}b-\frac{1}{2}\delta k(\mu_2-\frac{1}{2}br) & -\mu_3-\frac{1}{2}\delta\mu_3 rk & 0 \\ k & rk & 0 \end{pmatrix} \qquad \hat{\underline{b}} = \begin{pmatrix} \delta \\ -\frac{1}{2}\delta \\ 0 \end{pmatrix}$$

Since the relative order of (3.42) is equal to two, it follows that if $\hat{u}(t)=z_3^{(2)}(t)$, then $\tilde{u}(t)=\hat{y}(t)$.

Since the input to inverse system (3.43) involves second derivative, a first-order approximation is used for the numerical simulation. The procedure of simulation is shown in Figure 3.4. Figure 3.5 shows the simulation result using a set of immunological data. It is seen that the inverse system favorably estimate the state variables. The input function $\tilde{u}(t)$ is recovered from the inverse system, basing on the second derivative of the output from the original system (Figure 3.6).

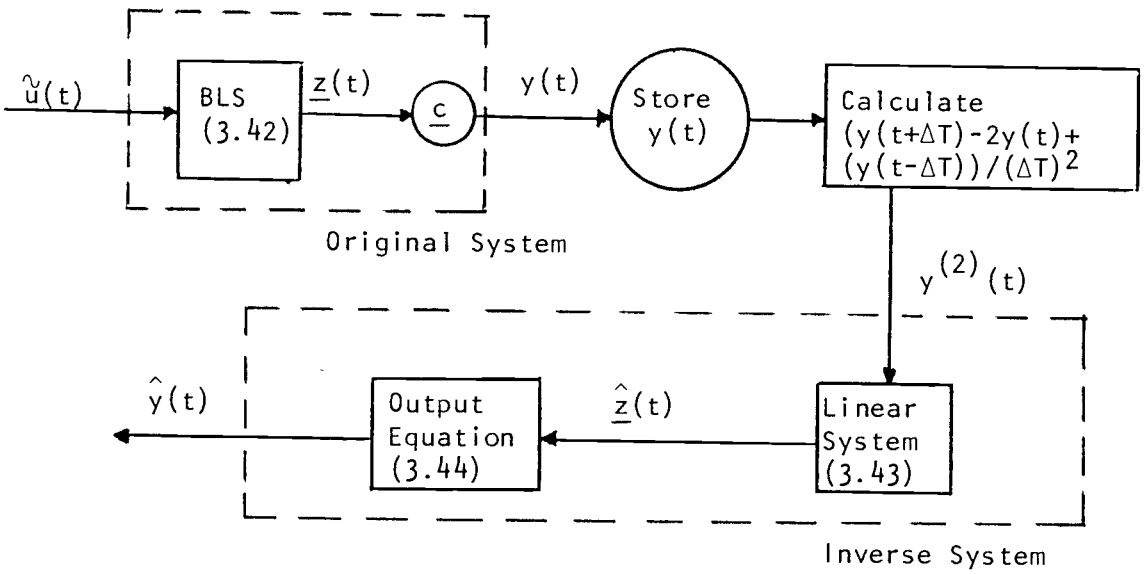

Figure 3.4. Flowchart of Simulation in Example 3.6.

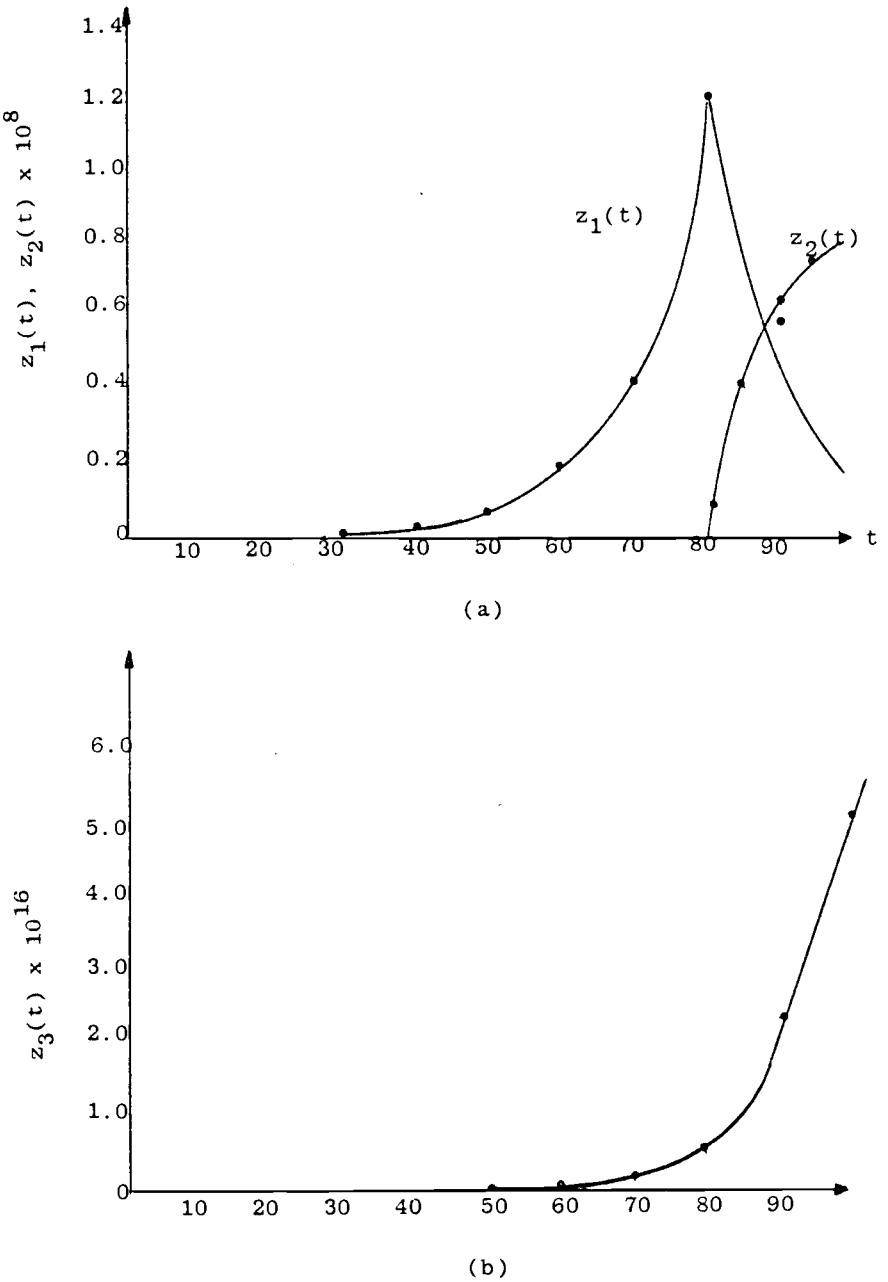

Figure 3.5. Simulation of BLS (3.42) and its inverse system (3.43) and (3.44), the dots denote the estimated values.
Data: $k=3.6\times10^6$, $r=10$, $b=0.1$, $\mu_2=10^{-5}$, $\mu_3=0.02$ and $z_1(0)=4\times10^4$, $z_2(0)=0$, $z_3(0)=0$.

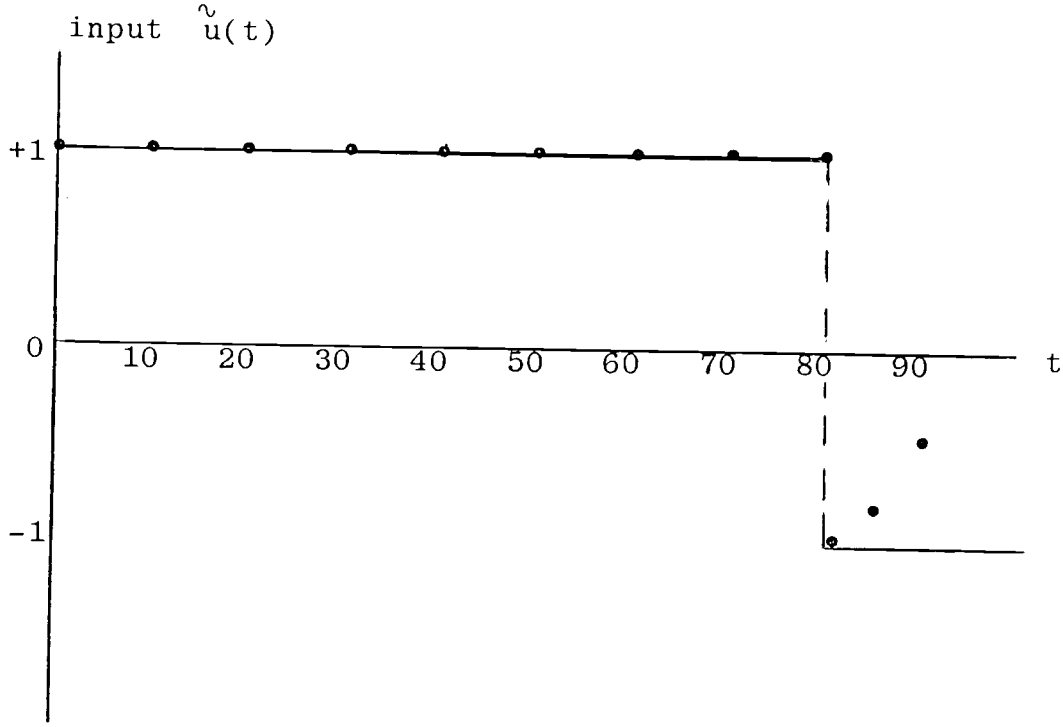

Figure 3.6 Input function $\tilde{u}(t)$ reproduced from the output of the original system (3.42). Data used is the same specified in Figure 3.5.

Example 3.7

The Volterra system π_2 described in Section 3.14 is studied here to furthermore illustrate the role of the inverse system of a BLS acting as a state observer. The output of a π_2 system is inherently nonlinear in the form of product of state variables. However, as shown in Example 3.5, the Volterra system is transformable to a decomposable BLS. And therefore in view of the BLS inverse design, each state variable of π_k can be estimated from the available output without knowing the input function.

Recall the homogeneous BLS (3.35) which is associated with a π_2 system with transfer functions $H_1(s)=b_1/(s+a_1)$ and $H_2(s)=b_2/(s+a_2)$. It can be easily shown that the relative order of BLS (3.35) is unity and rank $(\hat{B})=2$. Employing Theorem 3.10, the inverse system of (3.35) is readily derived as

$$\dot{\hat{x}}_1 = -a_1\hat{x}_1 + \frac{b_1(a_1+a_2)\hat{x}_3\,\hat{x}_4}{b_2\hat{x}_1+b_1\hat{x}_2} + \hat{u}(t)\,\frac{b_1\hat{x}_4}{b_2\hat{x}_1+b_1\hat{x}_2} \qquad (3.45a)$$

$$\dot{\hat{x}}_2 = -a_2\hat{x}_2 + \frac{b_2(a_1+a_2)\hat{x}_3\hat{x}_4}{b_2\hat{x}_1+b_1\hat{x}_2} + \hat{u}(t)\,\frac{b_2\hat{x}_4}{b_2\hat{x}_1+b_1\hat{x}_2} \qquad (3.45b)$$

$$\dot{\hat{x}}_3 = \hat{u}(t) \qquad (3.45c)$$

$$\dot{\hat{x}}_4 = 0 \qquad (3.45d)$$

$$\hat{\underline{x}}(0) = (x_{10},\ x_{20},\ x_{10}x_{20},\ 1)^T$$

$$\hat{y}(t) = \frac{(a_1+a_2)\hat{x}_3}{b_2\hat{x}_1+b_1\hat{x}_2} + \hat{u}(t)\frac{1}{b_2\hat{x}_1+b_1\hat{x}_2} \tag{3.45e}$$

Using (3.45d) and (3.45e), and the fact that $x_3(t)=x_1(t)x_2(t)=y(t)$, the above equations are simplified into,

$$\dot{\hat{x}}_1 = -a_1\hat{x}_1 + \frac{b_1(a_1+a_2)y(t)}{b_2\hat{x}_1+b_1\hat{x}_2} + \frac{b_1\dot{y}(t)}{b_2\hat{x}_1+b_1\hat{x}_2} \tag{3.46a}$$

$$\dot{\hat{x}}_2 = -a_2\hat{x}_2 + \frac{b_2(a_1+a_2)y(t)}{b_2\hat{x}_1+b_1\hat{x}_2} + \frac{b_2\dot{y}(t)}{b_2\hat{x}_1+b_1\hat{x}_2} \tag{3.46b}$$

with $\hat{x}_1(0)=x_{10}$ and $\hat{x}_2(0)=x_{20}$.

It is seen from this equation that the state variables $x_1(t)$ and $x_2(t)$ can be found from the available output $y(t)$ and its first derivative $\dot{y}(t)$. This fact can be verified directly from the original system π_2 in which the input function $u(t)$ can be found as $u(t)=(\dot{y}(t)+(a_1+a_2)x_1x_2)/(b_2x_1+b_1x_2)$. The state observer (3.46) is obviously a nonlinear dynamic system which is of course a consequence of rank $(\hat{B})=2>1$ (Theorem 3.11).

IV. MODELING OF IMMUNE PROCESSES

4.1 Essentials of Immunology

4.1.1 Outline of Immune System

The immune system of an organism is a collection of organs, cells, and proteins (macromolecules) working as a whole to maintain the functional integrity of itself via elimination of the intruded alien substance. A very simplified theory to delineate the immune system is presented here. After being attacked by foreign substance (antigen), the immune cells (committed lymphocytes) are stimulated to divide themselves or differentiate into plasma cells. Plasma cells are short-lived and nondividing, but can produce significant amount of immunoglobulins I_gM, I_gG, etc. (antibody) to combine with the antigen to form immune complexes, which in turn are removed by scanvenger cells (macrophages). The immune response is an extremely complex phenomenon of which many internal mechanisms are still uncertain.

In general, the immune response can be divided into two major types — humoral response and cell mediated response [73]. The former is referred to the immunity mediated by specific antibodies which are present in the blood serum and tissue fluids of the body. The latter is pertaining to sensitized thymus-dependent lymphocytes

which are responsible to graft-rejection and delayed hyper-sensitivity and so on.

There are three particular classes of cells participating in the immune reaction, namely, B cells, T cells and accessory cells:

a) B cells—immunocompetent cells (ICC) which, while not yet making an active immune response, are capable of being immediately stimulated by antigen to generate effector offspring. ICC arise from stem cells of bone marrow, processed through the bursa of Fabricius or its equivalent in mammals. B cells are also called bone marrow-derived lymphocytes.

b) T cells—these cells are derived from uncommitted stem cells which migrate into the thymus, and proliferate and differentiate there. T cells have a variety of functions, which not only play an important role in cell-mediated immunity, but also are decisive in the regulation of B-cell dynamics. T cells are also called thymus-derived lymphocytes.

c) Accessory cells—macrophages and other mononuclear phagocytes elicit phagocytosis and lysis on antigens. Macrophages participate in immune response in various aspects, the most important functions of which is to cooperate with T cells in regulating the B cell dynamics.

Figure 4.1 illustrates a simplified version of cell lineages involved in humoral immune response.

It is understood now that the immune system consists of various types of cells and molecules to perform defense mechanism against hostile environment. As one of the most rapidly progressing branch in biomedicine, it is prohibitive even to present here a less satisfactory outline. A comprehensive overview of modern immunology and its ramifications may be referred to the excellent text by Cunningham [74].

Concluding with this section, a general description on the immune system by Nobel Laureate Burnet is excerpted for better appreciating the essence of immunology [76]:

> "From all these perspectives, then, we arrive at a concept of the immune system as a homeostatic and self-monitoring unit with a control system reminiscent of the computerized control of a modern petrochemical complex with its sensors constantly monitoring for change in vital parameters and automatically calling positive or negative feedback mechanisms into action. The immunological controls differ from this computerized control in their flexibility and their need to respond to major calamities as well as to the minor fluctuations in average functioning, and control is of course limited to processes that are possible with biological material. I like to think of this system as an immensely complex interacting network of mobile lymphocytes comprising thousands of distinguishable sub-populations. Control involves the impact of patterned macromolecules, carrying genetically coded information, on receptors they can recognize and, depending on circumstances, can stimulate to give synthesizing, proliferative, or destructive signals to the cell."

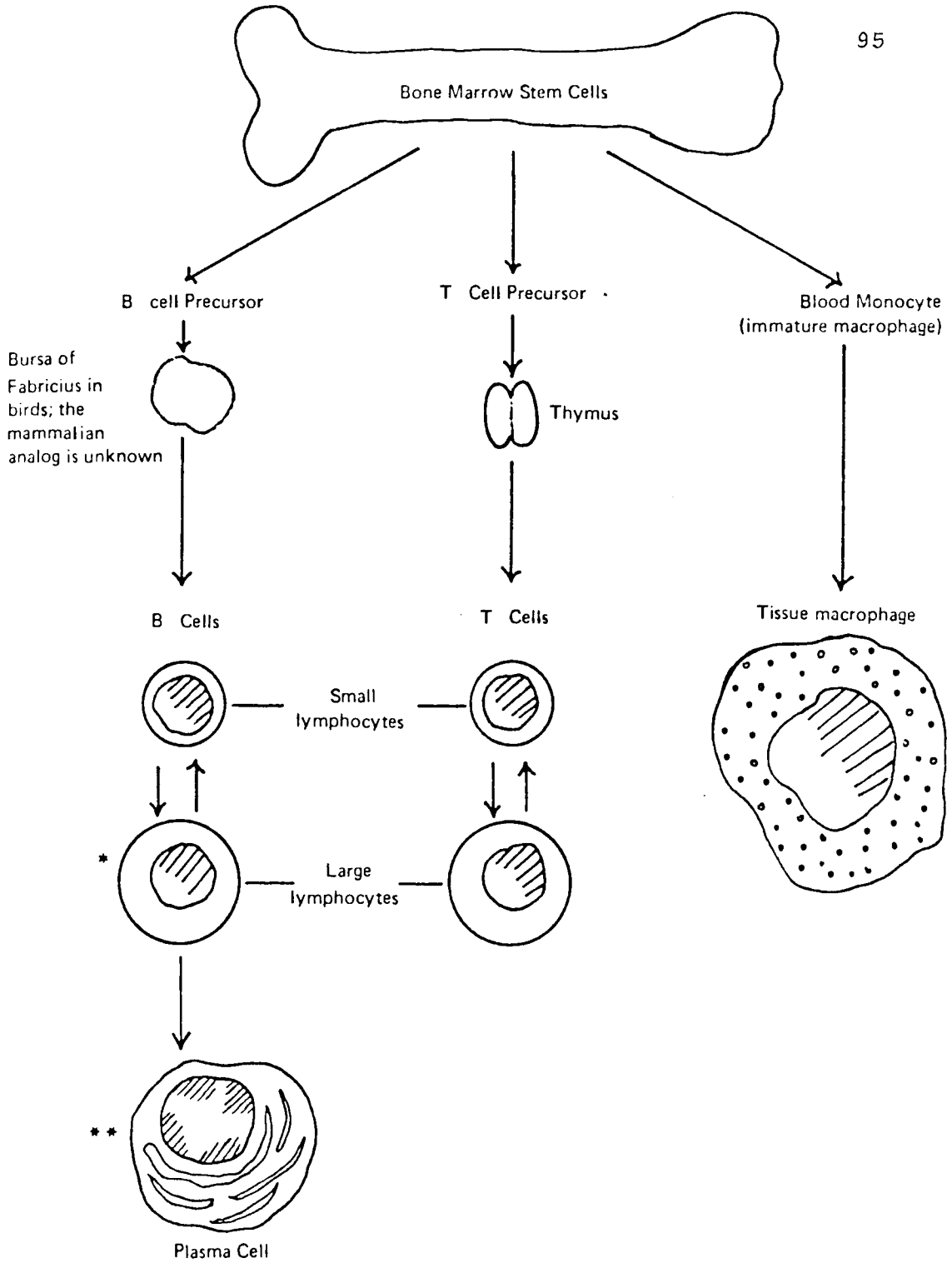

Figure 4.1 Maturation pathways of the principal cells in the immune response. Antibody molecules are secreted by large lymphocytes (*) and especially by plasma cells (**) in the B-cell lineage. (After Eisen, Reference 75)

4.1.2 Mathematical Models in Immunology

Applying the concept of mathematical modeling to the study of immune system have attracted much attention ever since Bell presented an interesting model of the antibody production of humoral response about 1970 [77]. His model consists of six nonlinear differential equations, and so not amenable to mathematical analysis, though the model is successful in simulating several immunological phenomena. Later on, many different models are proposed including prey-predator model, network model, compartmental model, and functional differential model, just to name a few. Various mathematical techniques are called upon to analyze these models, for instance, Hopf bifurcation theorem, optimal control theory as well as the catastrophe theory. A brief survey up to 1976 may be found in a technical report by Merrill [78]. A more expository collection of immune models can be referred to the recently published monograph edited by Bell, Perelson, and Pimbley [79].

In this section, immune models proposed by Merrill [80] and Perelson et al. [81] are discussed in order to compare them later with the model developed by Mohler, Barton and the author [82] and the main results of this thesis.

To determine the possible regulatory mechanisms for B-cell proliferation and differentiation when the immune

system responds to an antigenic challenge, a very simple model was formulated as a BLS with a scalar input,

$$\dot{x}_1(t)=\alpha(2u(t)-1)x_1(t)-\frac{1}{\tau_1}x_1(t)$$

$$\dot{x}_2(t)=\alpha(1-u(t))x_1(t)-\frac{1}{\tau_2}x_2(t) \qquad (4.1)$$

$$\dot{x}_3(t)=\alpha' x_1(t)+\alpha'' x_2(t), \quad t\in[0,T]$$

$$x_1(0)=x_{10}>0, \quad x_2(0)=0, \quad x_3(0)=0$$

where $x_1(t)$, $x_2(t)$ and $x_3(t)$ respectively denote the population of large lymphocytes, plasma cells and antibody. The input $u(t)$ is the fraction of cells that remain large lymphocytes (i.e. $0\leq u(t)\leq 1$), $1-u(t)$ is the fraction that differentiates into plasma cells. Definitions of rate constants α, τ_1, τ_2, α', and α'' are obvious from the context.

It has been shown that the optimal input to minimize the total time T required to secrete a specified amount of antibody x_3^* is bang-bang. However, it should be observed that in model (4.1), it is assumed that the injection of antigen has caused a fraction of the virgin B lymphocytes to undergo blast transformation resulting in x_{10} large lymphocytes. Based upon this crucial assumption, no antigen dynamics is considered and hence the model is bilinear rather than quadratic bilinear as would be without this assumption. In fact, model (4.1) is a very particular

class of bilinear systems, which will be furthermore investigated in the next chapter.

Merrill [80] derived a nonlinear model for immune response which is similar to the well-known model of heartbeat and nerve impulse by Zeeman [83]. This model enjoys dynamic characteristics that can be geometrically interpreted via catastrophe theory. For instance, the primary immune response is visualized as a path around the cusp. His model is rewritten as below,

$$
\begin{aligned}
\varepsilon\dot{x}_1(t) &= -(x_1^3(t)+(x_2(t)-\tfrac{1}{2})x_1(t)+x_3(t)x_4(t)-\tfrac{1}{2}) \\
\dot{x}_2(t) &= \tfrac{\delta}{2}(1-x_1(t))-x_2(t)-\gamma_1 x_2(t)x_3(t) \\
\dot{x}_3(t) &= -\gamma_1 x_2(t)x_3(t)-\gamma_2 x_3(t) \\
\dot{x}_4(t) &= \gamma_3 x_4(t)(x_3(t)-x_2(t))(x_{4max}-x_4(t)) \\
x_1(0)&=1, \quad x_2(0)=0, \quad x_3(0)=x_{30}\leq 1, \quad x_4(0)=x_{40}\leq x_{4max}
\end{aligned}
\tag{4.2}
$$

where $x_1(t) = \dfrac{y(t)-z(t)}{y(t)+z(t)}$, considered as a stimulation parameter $-1\leq x_1(t)\leq 1$ (+1 when unstimulated, -1 when stimulated)

$y(t)$= number of unstimulated B-cells which can respond to a particular antigen

$z(t)$= number of stimulated B-cells which have been stimulated by the presence of that antigen

$x_2(t)$= concentration of free antibody

$x_3(t)$= concentration of unbound antigen (sites)

$x_4(t)$= $\dfrac{\text{number of small B-cells + memory cells}}{\text{original number of small B cells}}$

All other parameters are obvious from the context, except ε, $1>>\varepsilon>0$, which indicates the fact that the cell stimulation itself is taking place on a much faster time scale than the time scale of other responses in (4.2). Moreover, all numerical values including the time scale are normalized. Merrill showed that model (4.2) has the following properties: $h(x_{4max}) \leq x_1(t) \leq 1$, $0 \leq x_2(t) \leq \frac{\delta}{2}(1-h(x_{4max}))$, $0 \leq x_3(t) \leq x_{30} \leq 1$, and $0 \leq x_4(t) \leq x_{4max}$ for all $t\varepsilon[0,\infty)$, where $h(x_{4max})$ is the unique real root of the equation $x_1^3 - \frac{1}{2}x_1 + x_{4max} - \frac{1}{2} = 0$ (assume $x_{4max} > 1$).

Though model (4.2) is capable of simulating primary and secondary response as well as low-zone and high-zone tolerance, it is not derived from basic mechanisms of immune response. For instance, the nonlinear term $x_1^3(t)$ in (4.2) seems to be chosen just in favor of mathematical convenience (more precisely, to have a cusp singularity). Another drawback is $h(x_{4max})$ may be less than -1; i.e. $x_1(t)$ is no longer restricted to [-1, 1]; the definition for $x_1(t)$ given as above fails to hold and needs ramification. It will be shown later that the models to be presented can overcome this and other shortcomings.

Simulation results for a particular set of data are shown in Figure 4.2 and Figure 4.3 to illustrate the dynamic behavior of mathematical models (4.1) and (4.2).

The simulation of model (4.2) which is not included in Merrill's paper is preformed by the author.

It is of some interest to compare these two simulation responses. The antibody production in Figure 4.1 (b) is exponentially increasing, while that in Figure 4.2 (b) is increasing first and then decreasing. Moreover, model (4.2) includes the dynamics of antigens $x_3(t)$ and a stimulation factor $x_1(t)$, both of which model (4.1) does not take into account. It is seen that response behavior of (4.2) is more immunologically realistic than that of (4.1), at the expense of model complexity. This will be furthermore discussed in Chapter V.

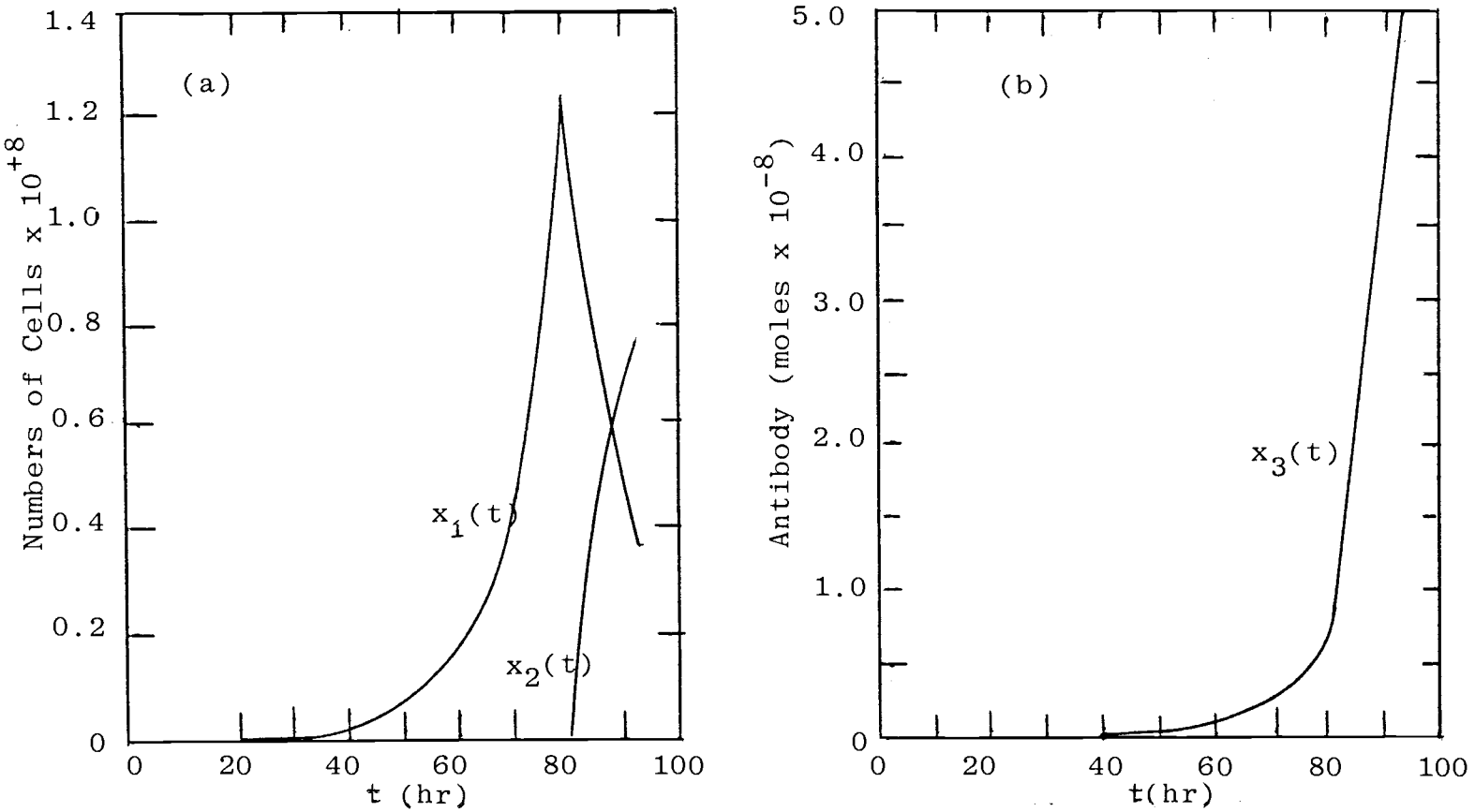

Figure 4.2. Simulation of Model (4.1).

(a) The number of large lymphocytes $x_1(t)$ and plasma cells $x_2(t)$

(b) The number of moles of antibody secreted as a function of time with $\tau_1=10^5$hr, $\tau_2=50$hr, $\alpha=0.1\text{hr}^{-1}$, $\alpha'=3.6\text{x}10^6\text{hr}^{-1}$, $\alpha''=3.6\text{x}10^7\text{hr}^{-1}$ $x_1(0)=4\text{x}10^4$cells and $u(t)=1$, $0\leq t<80$, $u(t)=0$, $80\leq t\leq 100$.
(After Perelson et al. reference 81)

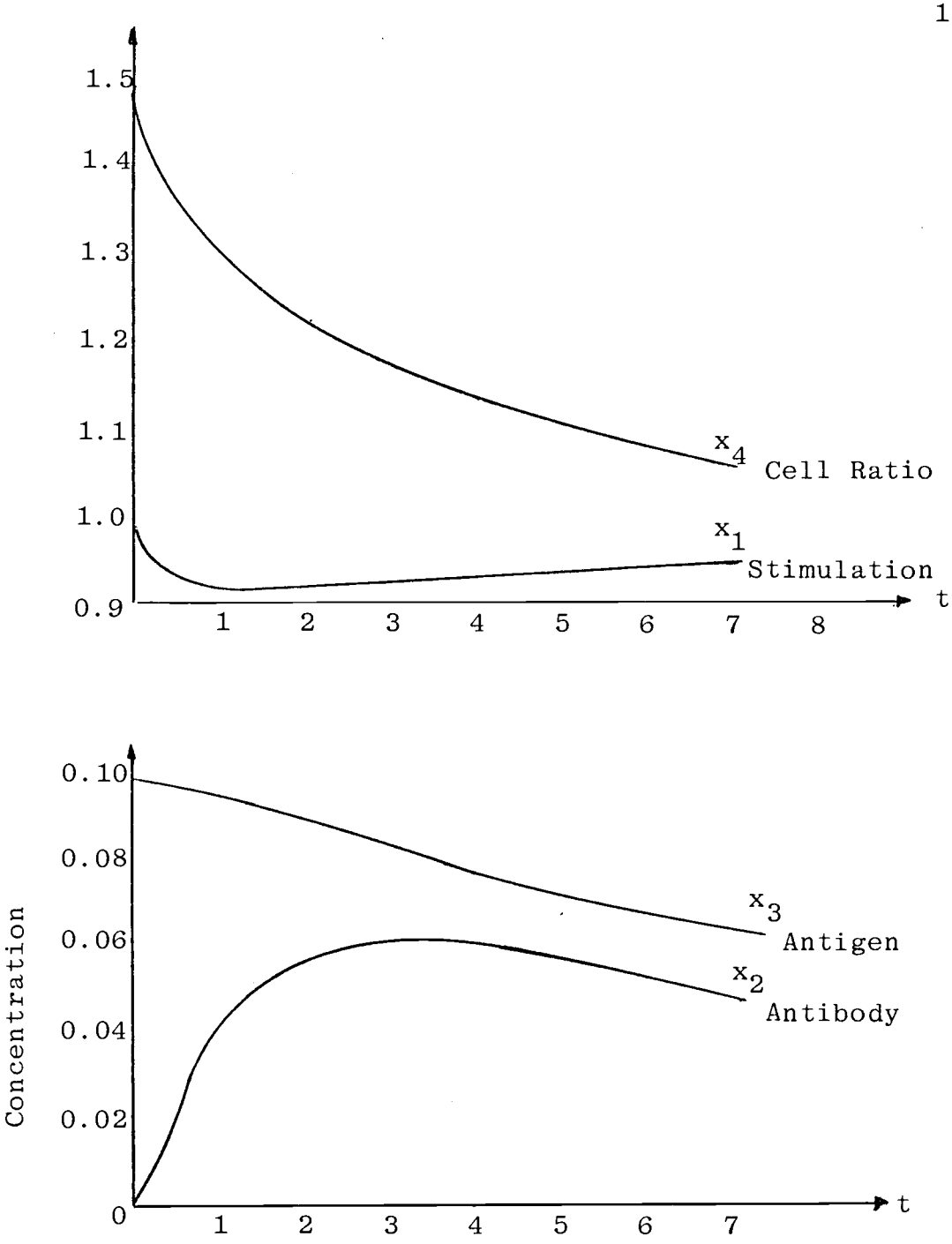

Figure 4.3. Simulation of model (4.2) with
$\varepsilon=0.01$, $\delta=2.0$, $\gamma_1=1.0$, $\gamma_2=0.01$,
$\gamma_3=1.0$, and $x_{4max}=3.0$
$x_1(0)=1$, $x_2(0)=0.0$, $x_3(0)=0.1$, $x_4(0)=1.5$

4.1.3 A Systems Approach to Immunology

This section is devoted to elaborating the research methodology and objective of the rest of this thesis. Figure 4.4 gives a functional description of the inter-relationships of experimentation, immune theory, modeling and simulation. In contrast to the conventional approach, the 'systems approach' requires formulation of a mathematical model based upon assumptions and immunological phenomena which clearly illustrates the interacting sub-systems. With the aid of computer simulation and control theory, an effective experimental plan may be designed to provide time-series data for identifying the parameters upon which the understanding of the homeostatic mechanisms of the immune system faithfully depends.

This study began with the viewpoint of applying optimal control and system theory (with special emphasis on bilinear processes) to the investigation of immune system. What is to be presented is confined to the B-cell dynamics stimulated by non-replicating antigens. The generally accepted clonal selection theory is adopted. The humoral immune response involves both cellular and molecular reactions, it is not surprising that the model initially developed (see next section) is highly nonlinear. This first model (hereafter called B Model) is simulated with a set of parameters and initial conditions. The

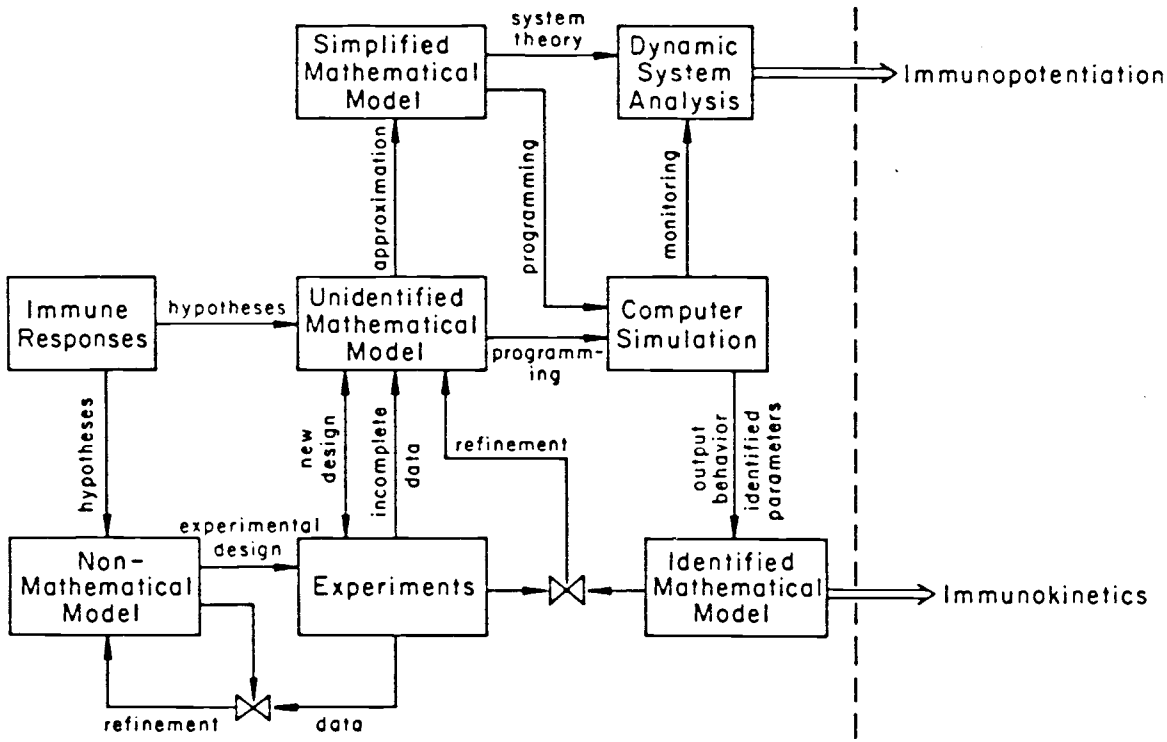

Figure 4.4 Role of mathematical models in immunology.

simulation result is then compared with the experimental data available in the literature. The mathematical analysis of the B Model is carried out to validate the model equations. This encompasses the existence and uniqueness of solution to the mathematical model. Moreover, asymptotic stability and positive-invariance (to be defined later) are proved.

The B Model itself, as will be derived in detail in the next section, is a fairly complete model of humoral immune response for T-independent antigens. However, it is a 5-dimensional bilinear system with two nonlinear feedback controls entering multiplicatively. This nonlinearity plus high dimensionality render the rigorous control-theoretic analysis infeasible (if not impossible). In order to overcome this disadvantage, some assumptions are made to seek a simplified version of B Model. The effort ends up with a 3-dimensional bilinear system with scalar input. This new approximated B Model enjoys also other structural aspects which make it very convenient to be investigated via the techniques developed in Chapter III.

Finally, immunological implication arising from the acquired results is discussed.

4.2 B Model

4.2.1 Derivation of B Model

A mathematical model of B-cell kinetics is presented to explain the dynamic behavior of the humoral immune response. This model is based on the clonal selection theory, classical birth-death cell population balances and law of mass action. Only the consequence of an animal injected with thymus independent antigen is considered.

Before modeling the B-cell dynamics, elementary phenomena of B-cell stimulation and differentiation are discussed. The mechanisms that determine whether an immunocompetent cell can be stimulated and can differentiate into a plasma cell have not been fully elucidated. The initiation of an immune response critically depends on these two basic cellular events. As suggested by some experimental results, it is assumed that stimulation occurs only when the fraction of receptors which is occupied by the antigen falls between two values σ_1 and σ_2. Also the probability of differentiation into plasma cells is assumed to be proportional to that fraction of occupancy. Equipped with these assumptions, probabilities for stimulation and differentiation are derived and shown to be functions of free antigen concentration and antibody affinity, due to Bruni et al. [84].

If $F(k,t)$ and $B(k,t)$ are respectively the number of free and bound receptors on the cell surface per unit volume, then at given concentration of antigen $h(t)$,

$$\frac{B(k,t)}{F(k,t)h(t)} = k$$

where k is the affinity of B-cell receptor with respect to determinants of antigens. The probability that a receptor of affinity k be occupied is

$$p(kh) = \frac{B(k,t)}{B(k,t)+F(k,t)} = \frac{kh(t)}{1+kh(t)} \tag{4.3}$$

The probability that n receptors, out of a total number m per cell, be occupied as expressed by binomial distribution

$$p^{(n)}(kh) = \binom{m}{n} p^n(kh)(1-p(kh))^{m-n}$$

The probability that a cell with affinity k be stimulated is therefore

$$p_s(kh) = \sum_{n=n_1}^{n_2} p^{(n)}(kh) = \frac{\sum_{n=n_1}^{n_2}\binom{m}{n}(kh)^n}{(1+kh)^m} \tag{4.4}$$

where n_1 is the smallest integer such that $n_1 \geq m\sigma_1$, and n_2 is the largest integer such that $n_2 \leq m\sigma_2$. Because of the high value of m (usually $m \simeq 10^5$), the distribution (4.4) can be approximated by

$$p_s(kh) = \begin{cases} 1 & \text{if } \dfrac{\sigma_1}{1-\sigma_1} \leq kh \leq \dfrac{\sigma_2}{1-\sigma_2} \\ 0 & \text{otherwise} \end{cases} \tag{4.5}$$

The probability that a cell of affinity k with n occupied receptors to be differentiated has been taken equal to the ratio $\frac{n}{m}$, and therefore

$$p_d(kh) = \sum_{n=0}^{m} \frac{n}{m} p^{(n)}(kh) = \frac{kh}{1+kh} \qquad (4.6)$$

Equations (4.5) and (4.6) are important for modeling B-cell dynamics as will be presented next. A word of caution is that the numerical values of σ_1 and σ_2 are not known a priori, except by definition $0 \leq \sigma_1 \leq \sigma_2 \leq 1$. While this may be considered as a drawback, it consolidates the necessity of computer simulations as well as control-theoretic analysis beyond modeling the immune system. The following derivation follows that of Mohler, Barton and Hsu [82].

The primary humoral immune process is described by the following variables with the arguments (t, time and k, affinity or association constant) omitted for brevity:

x_1, population density of immunocompetent cells (ICC), which are sensitized lymphocytes with particular surface receptors which in turn have affinity (or association constant), k, for antigen. They may differentiate into plasma cells or proliferate into memory cells. The latter may further divide and enter the pool of immunocompetent cells.

x_2, population density of plasma cells which are non-reproducing offspring of stimulated immuno-

competent cells.

x_3, population density of "antibody sites," unbound to antigen.

x_4, population density of immune complexes, which individually include antibody sites and antigen.

h, antigen concentration, unbound to antibody, which triggers the response mechanism.

Consideration of immunocompetent cells first leads to a change of population density, Δx_1, on an interval Δt due to mitosis, given by

$$\{2\alpha(1-p_d)\, p_s x_1 - \alpha p_s x_1\}\, \Delta t,$$

where α is the birth-rate constant of stimulated immunocompetent cells, p_d and p_s are respectively the probability that an immunocompetent cell differentiates into a plasma cell and the probability that antigen stimulates a cell. These probability terms are function of antigen h, and affinity k as given in (4.5) and (4.6).

To this must be added the source of new stem cells $\beta_k \Delta t$ and the death of cells $x_1 \Delta t/\tau_1$, where β_k is the rate of generation of new immunocompetent cells (from bone marrow), and τ_1 is the mean lifetime of immunocompetent cells. In the limit, the process is described by an ordinary differential equation of form

$$\dot{x}_1 = \alpha u_1 x_1 - \frac{x_1}{\tau_1} + \beta_k, \qquad (4.7)$$

where $u_1 = p_s(1-2p_d)$. Similarly, plasma cells, antibody sites and immune complex generation for each k may be approximated by birth-rate minus death-rate equations as follows:

$$\dot{x}_2 = 2\alpha u_2 x_1 - \frac{x_2}{\tau_2} , \tag{4.8}$$

$$\dot{x}_3 = \alpha' x_1 + \alpha'' x_2 - \frac{x_3}{\tau_3} - kc_k x_3 h + c_k x_4 \tag{4.9}$$

$$\dot{x}_4 = kc_k x_3 h - \frac{x_4}{\tau_4} - c_k x_4 \tag{4.10}$$

where τ_2, τ_3, τ_4 are appropriate life times,

$u_2 = p_s p_d$

α' is plasma-cell antibody production rate, α'' is ICC antibody production rate, and c_k, kc_k are dissociation rate and association rate constants of immune complex, respectively.

After inoculation of the antigen population $dh_i(t) = \dot{h}_i(t)dt$, the rate of generation of a free antigen density may be approximated by the inoculation rate minus rate of catabolism minus net rate of immuno-complex formation,

$$\dot{h} = \dot{h}_i(t) - \frac{h}{\tau_h} - \sum_k kc_k x_3 h + \sum_k c_k x_4 \tag{4.11}$$

where τ_h is the average lifetime, and k extends over the whole range of the association constants of antibodies.

Antigens administrated into an animal is often mixed with Freund's complete adjuvant (an emulsion of mineral

oil, detergent, and mycobacteria), which may enhance the immune response by increasing the local recirculation of lymphocytes, and slow, continual release of antigen. Consequently, the antigen inoculation rate $\dot{h}_i(t)$ may be represented by the sum of two functions; a step function δ_{-1} accounting for two-thirds of the total amount of antigen injected and an exponential function accounting for the remaining one-third. So that, for convenience, it is assumed that

$$\dot{h}_i(t) = \frac{Q}{3\tau_u V} e^{-t/\tau_u} + \frac{2}{3}\frac{Q}{T_u V}\delta_{-1}(T_u - t), \qquad (4.12)$$

$$\delta_{-1}(T_u - t) = \begin{cases} 1, & \text{if } 0 \leq t \leq T_u \\ 0, & \text{otherwise} \end{cases}$$

where Q is the total inoculation of antigen, V is the estimated volume of circulating animal fluids in which the antigen distributes itself and T_u is the interval of time for which the constant level of antigen is diffused from Freund's adjuvant. If antigen is injected without Freund's adjuvant, the inoculation of antigen may be represented by h(0) with amount

$$\int_0^\infty \dot{h}_i(t)dt = \int_0^\infty \frac{Q}{3\tau_u V} e^{-t/\tau_u} dt + \frac{2}{3}\frac{Q}{T_u V} T_u = \frac{Q}{V}$$

Equations (4.5) - (4.12) comprises a mathematical model for B cell dynamics, if appropriate initial concition is provided. An interesting structural feature of

this model is that the model is a bilinear system with two nonlinear state feedbacks entering multiplicatively (i.e. a quadratic bilinear system). In addition to this feedback nonlinearity, there is quadratic nonlinearity arising from antigen-antibody reaction characterized by law of mass action. Recalling that a quadratic system may be decomposed as a BLS with a linear state feedback (see Section 1.2.2), B Model can also be viewed as a cascade of two BLS's with one linear and two nonlinear feedbacks. Figure 4.5 illustrates such decomposition. The first BLS describes the cellular dynamics (x_1 and x_2), while the second represents the molecular dynamics (x_3, x_4 and h). The interaction between these two subsystems is apparently taken by the nonlinear feedbacks. Though only structural decomposition is heuristically touched upon here, more details will be given in Section 4.3.

4.2.2 Data Interpretation in B Model

Before proceeding with simulation and mathematical analysis of the B Model, the immunological relevance of the model is discussed by examining numerical values of initial conditions, parameters, as well as input variables. Numerical data collected from animal experiments usually vary considerably among different species and different antigens. Of particular concern here is the data from

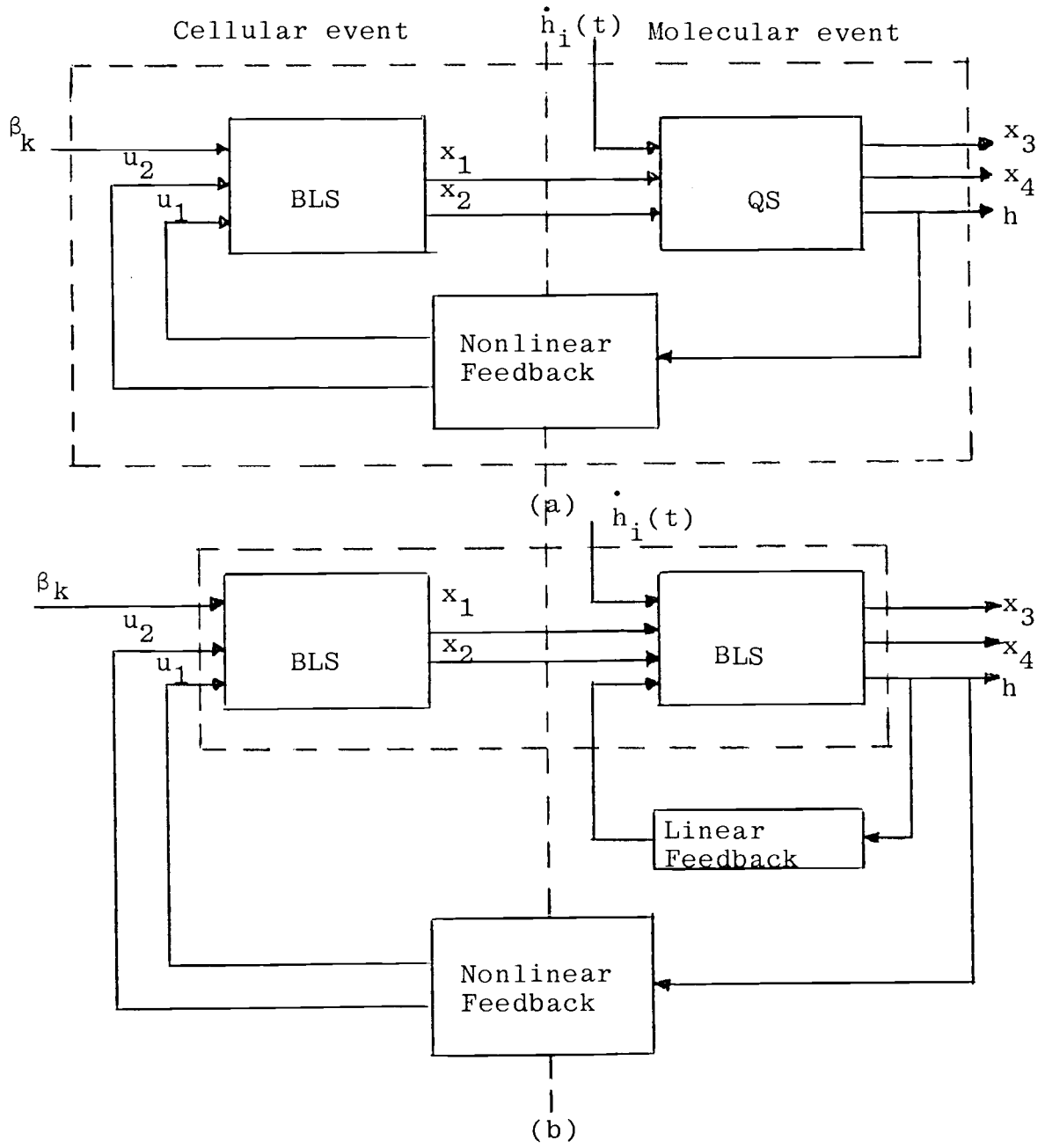

Figure 4.5. Structural Decomposition of B Model
(a) B Model viewed as a quadratic bilinear system
(b) B Model viewed as a BLS with nonlinear feedback

rabbit immunized with DNP-BGG (2,4-dinitrophenyl bovine γ-globulin) in complete Freund's adjuvant.

One outstanding feature of the immune response is of course the antibody-antigen reaction, symbolically, it is

$$Ag + Ab \underset{c_k}{\overset{kc_k}{\rightleftharpoons}} Ag\text{-}Ab \qquad (4.13)$$

where Ag, Ab and Ag-Ab stand for antigen, antibody, and immune complex, respectively. At equilibrium, the rates of forward and reverse reactions are the same, which may be characterized by the ratio of association and dissociation constants, i.e. k, the average affinity. Values of k and c_k may be experimentally determined but not precisely. The value of k may range from 10^3 liter/mole to 10^{10} liter/mole, while c_k from 1 sec^{-1} to 100 sec^{-1}. The discussion above holds only for in vitro situation. In vivo, the immune complex is normally removed out of circulation shortly after it is formed. And therefore only local equilibrium can be established. Accumulation of immune complexes within the immune system is harmful to the body, because they not only cause the so-called serum sickness disease, but also possibly act as a blocking factor to the destruction of tumor cells [85]. However, this pathological consequence cannot be deduced from B Model as will be shown in Section 4.3, because the antigen injected is not replicable. Immune models for replicable

antigens are more complicated and will not be pursued since experimental data is rarely available.

The B Model assumes that the rates of antibody production by ICC, α', and plasma cells, α'', are constant, though they may be affected by specific hormones or cell cycle. Experimental results shows that plasma cells attribute much more antibody than ICC. Jerne estimated that at full synthetic rate a cell may turn out 2000 antibodies per second [86]. And so the numerical values of α'' and α' may be taken to the order of $6x10^{-17}$ and $6x10^{-19}$ moles Ab cell $^{-1}hr^{-1}$, respectively.

The average lifetimes from τ_1 to τ_5 are now discussed. T-independent antigens tend to persist in body tissue and are only slowly degraded by metabolic processes. The elimination of free antigen is largely due to its combination with antibody. In addition to the dissociation, the soluble immune complexes are normally taken out of the immune system pretty soon by phagocytic cells. The metabolic turnover of antibody is about ten days [87]. The mean lifetimes of ICC and plasma cells are more thoroughly studied. Plasma cells are nondividing and survive at most only a few weeks, while ICC may persist more than one year [88]. Based on this, it is not unreasonable to take values as $\tau_1=10^4$hr, $\tau_2=72$ hr, $\tau_3=200$hr, $\tau_4=50$hr, and $\tau_5=100$hr. There are two external inputs

β_k and $\dot{h}_i(t)$ appearing additively in B Model. It is known that the bone marrow continually replenishes the B-cell population at a rate which is slow compared to the time course of the response to a T-independent antigen [89]. The input β_k takes this into account and its value is around $2x10^6$ cells/hour. The other input $\dot{h}_i(t)$ has been discussed in the last section and will not be repeated here.

It is recalled that, if free antigen concentration is within some range, ICC may be stimulated and then proliferate itself or differentiate into plasma cells. The proliferation rate of stimulated ICC is estimated to be about 0.05~0,2 hr^{-1}, in other words, estimates of the average time between ICC cell divisions vary, but are mostly from 5 to 20 hours [90].

Since only primary response is concerned, the initial populations of plasma cells, antibody, immune complex and free antigen are all taken to be zero. The initial concentration of ICC population for rabbit is estimated to be $5x10^8$ cells/liter, about one percent of total lymphocytes.

It should be admitted here that all numerical values presented above are only roughly deduced from experimental data, which is often not so consistent among different experiments.

4.2.3 Simulations and Implication

In the previous subsections, model of B cell dynamics and its immunological relevance has been given. It is seen that the B Model is high-dimensional and nonlinear, information on qualitative properties can only be surmized from numerical simulations. However, this does not imply that partial but rigorous mathematical analysis of the B Model is out of the question. Indeed, analysis will be carried out in the next section to justify the B Model and also confirm the simulation results presented in this section.

B Model deals with both the molecular (antigen, antibody, and immune complex) and cellular (ICC and plasma cells) events. This immediately gives rise to two computational problems. One is to have consistent units for the model, the other is the wide separation of different response times. The former can be resolved by expressing the number of cells and concentration of molecules in a homogeneous manner, say, moles per liter. To do so, the number of cells per unit volume must be divided by Avogadro number (6.02217×10^{23}), while molecular concentration (usually expressed in mg/ml) must be divided by appropriate molecular weight. The time scale for all simulations is with unit 'hours'.

The widely different response times may cause computa-

tional difficulty, if the numerical integration formula is not appropriate for the model. The notion of stiffness of differential equations has been demonstrated to be particularly important for simulating biomedical models [91]. Experience of the B Model simulation concurs this argument. Stiffness associated with the B Model is brought about here, because the simulation results to be presented are actually obtained by using the DVOGER SUBROUTINE (a modified Gear's algorithm [92]) rather than the familiar Runge-Kutta 4th order formula. Numerical computations are carried out by CDC Cyber 73 NOS 1.2 Version at Oregon State University.

The B Model is simulated with the data set given in Table 4.1 and the result is shown in Figure 4.6. The probability terms p_s and p_d induced by the antigenic injection $\dot{h}_i(t)$ are shown in Figure 4.7. From the time response of antibody production, it is observed that the model predicts with some accuracy the experimental concentration of antibody [93]. While experimental data on the other variables have not been obtained, their kinetics seems reasonable and consistent with known immunological phenomena.

If Freund's complete adjuvant is not used for antigenic injection, the initial free antigen is taken by $h(0) = \frac{Q}{V}$. Simulation of B Model using nonzero $h(0)$ is presented in Figure 4.8. If the dissociation of immune

TABLE 4.1

Parameters Used in the Simulation

α	5.780×10^{-2}	hr^{-1}
α'	0.2×10^{7}	hr^{-1}
α''	10^{8}	hr^{-1}
β_k	1.627×10^{-22}	mole/hr
τ_1	7140	hr
τ_2	72	hr
τ_3	200	hr
τ_4	50	hr
τ_h	100	hr
τ_u	100	hr
T_u	1000	hr
k	10^{6}	liter/mole
c_k	3.6×10^{3}	hr^{-1}
Q	3.33×10^{-8}	mole
V	0.2	liter
σ_1	0.01	
σ_2	0.10	
$x_1(0)$	0.8262×10^{-16}	mole/liter

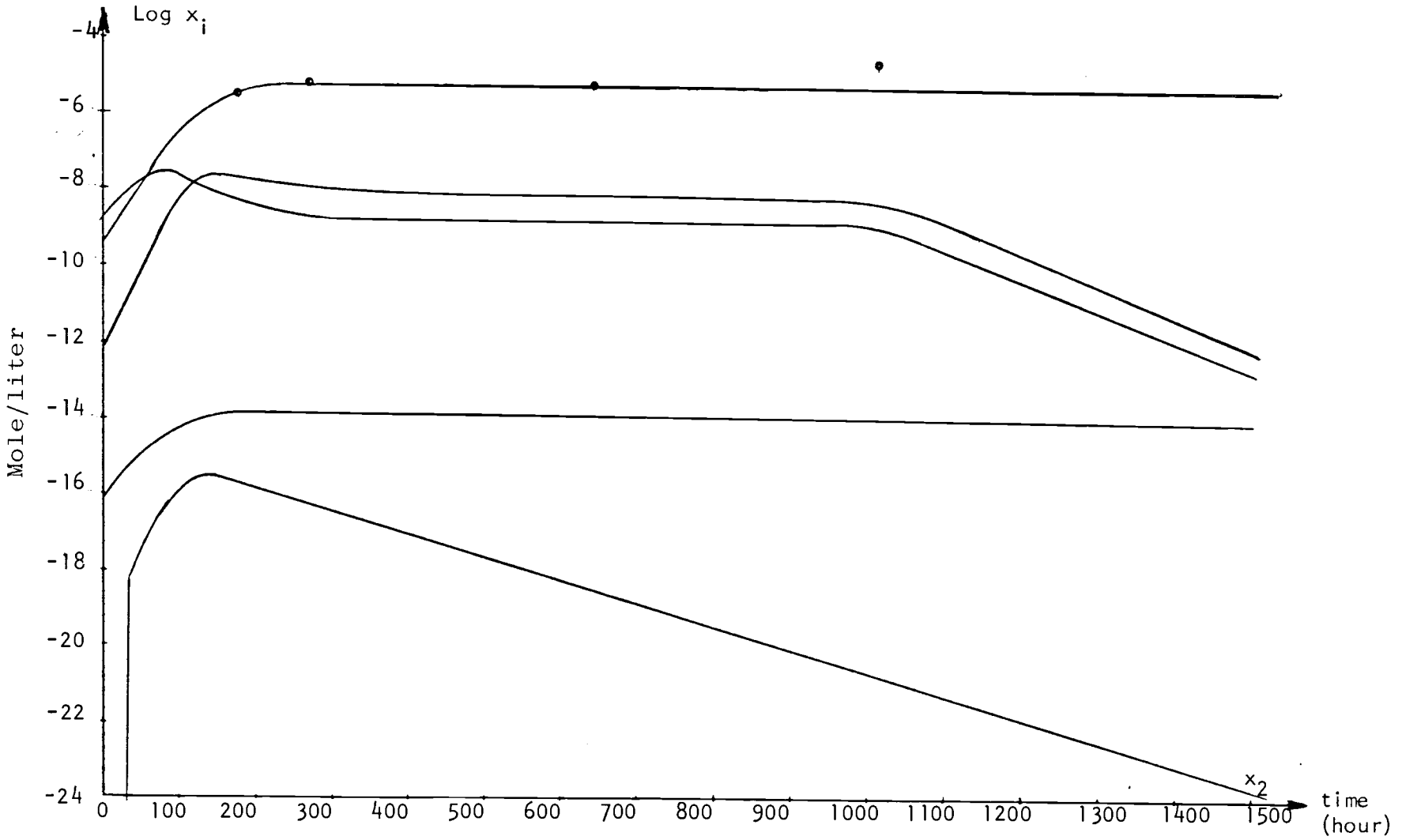

Figure 4.6. Simulation response of the B Model with Freund's adjuvant.

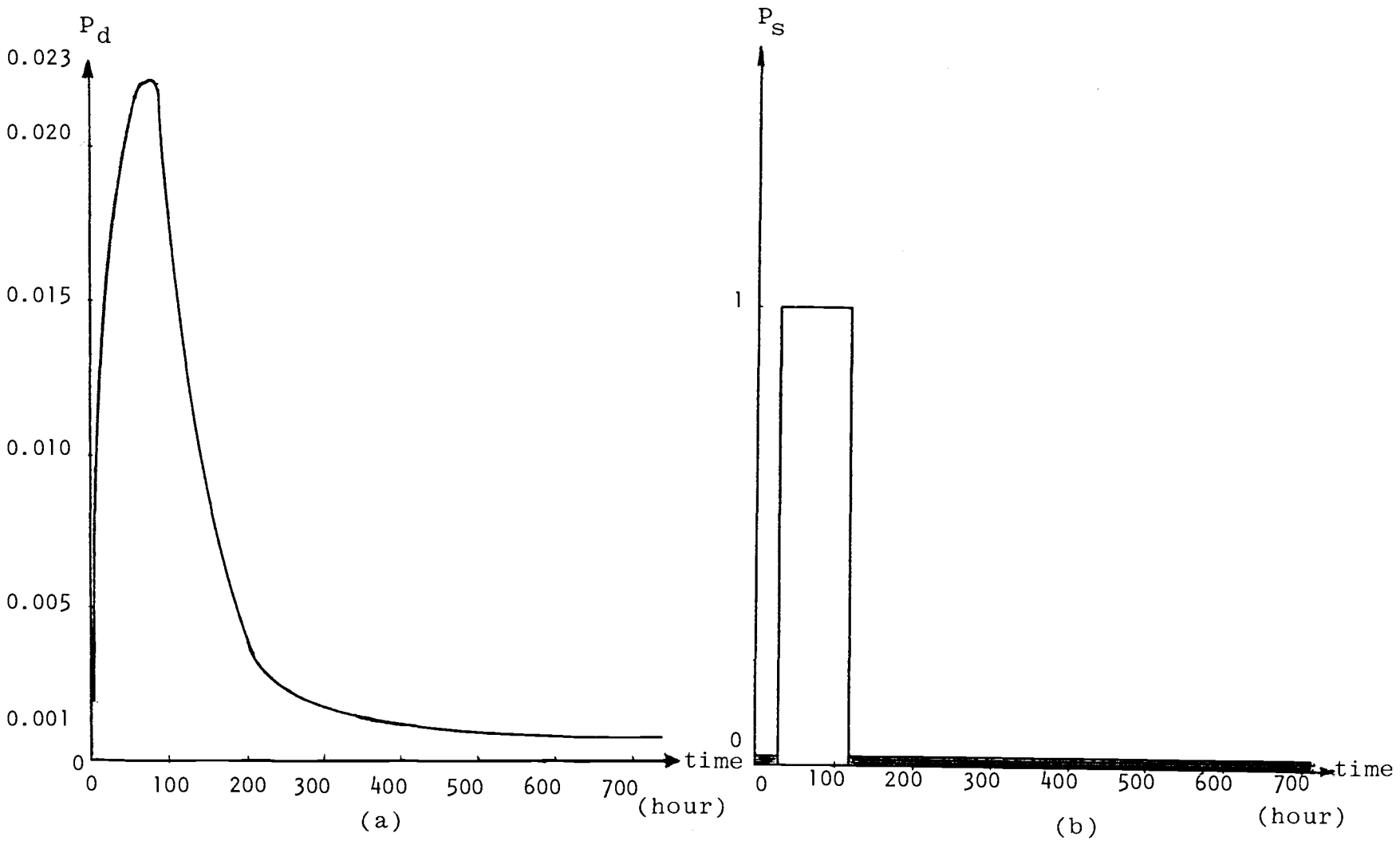

Figure 4.7. Probabilities of ICC differentiation and stimulation.

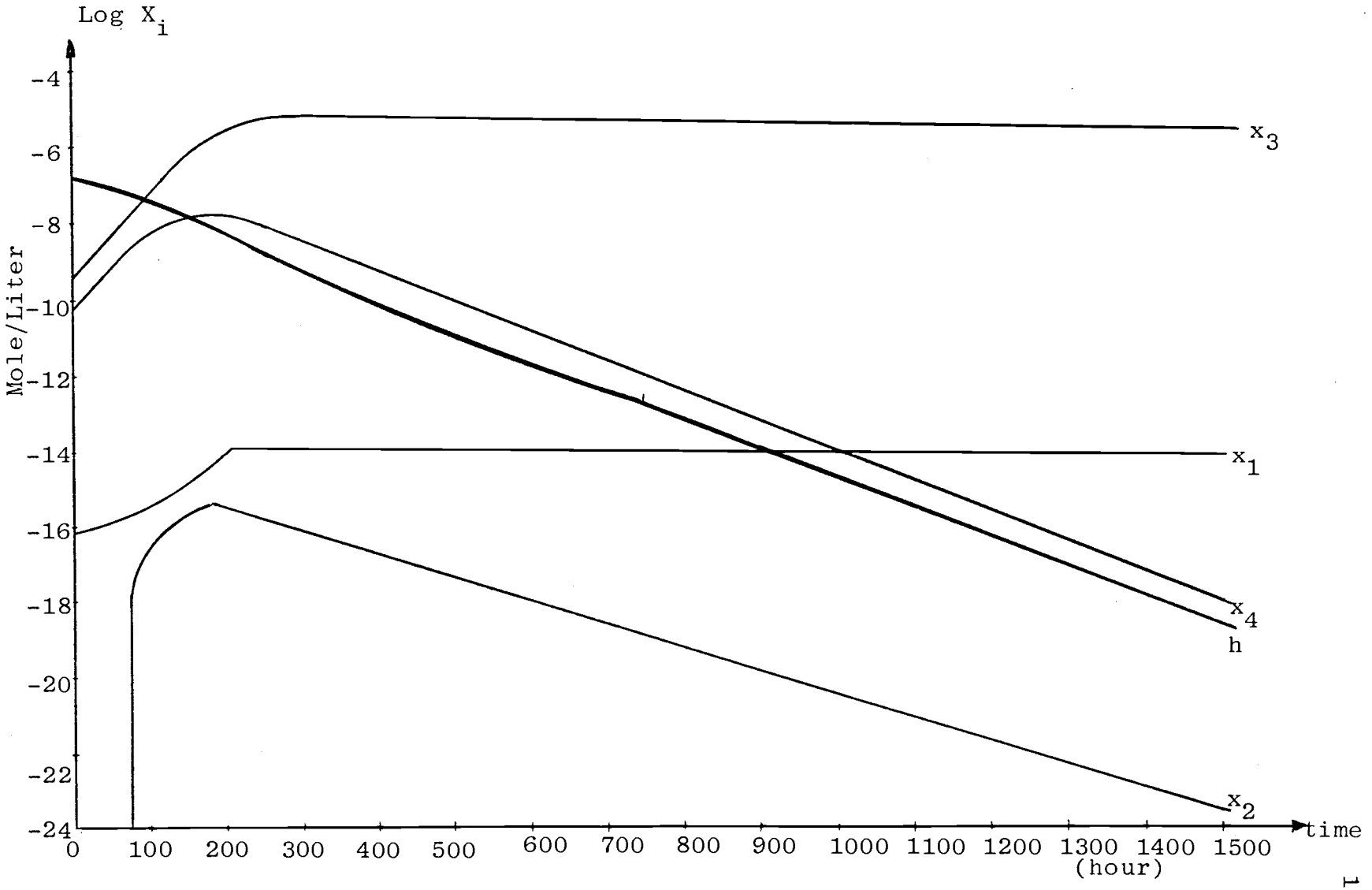

Figure 4.8. Simulation response of the B Model without Freund's adjuvant.

complex is assumed to be negligible, then B Model may be simplified by taking the term $c_k x_4$ out of equations (4.8), (4.9) and (4.10).

The results presented as above confirm that the B Model is in favor of the available experimental data and the clonal selection theory on which the model itself is founded.

4.3 Analysis of B Model

4.3.1 Existence and Uniqueness of Solution to Model Equations

Several fundamental system-theoretic properties of the B Model are studied to confirm the numerical simulations presented in the last section. Among many system-theoretic characteristics on which the quality of a biomedical model crucially depends, perhaps the most important are the existence, uniqueness, positive invariance as well as stability of solution to the model equations. To investigate mathematically whether the B Model satisifes all of these properties is the main concern in the rest of this chapter.

The B Model endowed with initial condition forms an initial value problem. Equations (4.7) —— (4.11) may be written as

$$\dot{\underline{x}}(t) = \underline{f}(\underline{x}, \underline{u}(t), \underline{v}(t)), \quad \underline{x}(0) = \underline{x}_0, \ 0 \leq t < \infty \qquad (4.14)$$

where $\underline{x}(t) \triangleq (x_1(t),\ x_2(t),\ x_3(t),\ x_4(t),\ h(t))^T$

$\underline{u}(t) \triangleq (u_1(t),\ u_2(t))^T$

$\underline{v}(t) = (\beta_k,\ \dot{h}_i(t))^T$

$\underline{f}$ is a 5-vector nonlinear function of $\underline{x}(t)$

and $\underline{x}(0) = (x_1(0),\ 0,\ 0,\ 0,\ 0)^T$

It is straightforward to show that $u_1(t)$ and $u_2(t)$ are uniformly bounded, recalling that $u_1(t)=p_s(1-2p_d)$, $u_2(t)=p_s p_d$ and equations (4.4) and (4.6),

$$|u_1(t)| = \left| \frac{\sum_{n=n_1}^{n_2} \binom{m}{n} (kh)^n}{(1+kh)^m} \cdot \frac{1-kh}{1+kh} \right| \leq \left| \frac{(1+kh)^m}{(1+kh)^m} \right| \left| \frac{1-kh}{1+kh} \right| \leq 1$$

$$|u_2(t)| = \left| \frac{\sum_{n=n_1}^{n_1} \binom{m}{n} (kh)^n}{(1+kh)^m} \cdot \frac{kh}{1+kh} \right| \leq 1$$

The above inequalities hold only when h is non-negative, which will be proved later.

The local existence and uniqueness of solution to (4.14) can be guaranteed if $u_1(t)$ and $u_2(t)$ are also Lipschitzian [94].

$$|u_2(h_2) - u_2(h_1)|$$

$$= \left| \frac{\sum_{n=n_1}^{n_2} \binom{m}{n}(kh_2)^n}{(1+kh_2)^m} \cdot \frac{kh_2}{1+kh_2} - \frac{\sum_{n=n_1}^{n_2} \binom{m}{n}(kh_1)^n}{(1+kh_1)^m} \cdot \frac{kh_1}{(1+kh_1)} \right| .$$

$$= \left| \frac{\sum_{n=n_1}^{n_2} \binom{m}{n} [(kh_2)^{n+1}(1+kh_1)^{m+1} - (kh_1)^{n+1}(1+kh_2)^{m+1}]}{|(1+kh_2)^{m+1}(1+kh_1)^{m+1}|} \right|$$

$$\leq \left| \sum_{n=n_1}^{n_2} k^{n+1} \binom{m}{n} [(h_2)^{n+1}(1+kh_1)^{m+1} - (h_1)^{n+1}(1+kh_2)^{m+1}] \right|$$

$$= \left| \sum_{n=n_1}^{n_2} k^{n+1} \binom{m}{n} [\sum_{j=0}^{m+1} h_2^{n+1} \binom{m+1}{j}(kh_1)^j - \sum_{j=0}^{m+1} h_1^{n+1} \binom{m+1}{j}(kh_2)^j] \right|$$

$$= \left| \sum_{n=n_1}^{n_2} k^{n+1} \binom{m}{n} \sum_{j=0}^{m+1} k^j \binom{m+1}{j}(h_2^{n+1}h_1^j - h_1^{n+1}h_2^j) \right|$$

$$\leq \sum_{n=n_1}^{n_2} \binom{m}{n} \sum_{j=0}^{m+1} k^{n+j+1} \binom{m+1}{j} |F_{n+j}(h_2, h_1)| \, |h_2 - h_1|$$

$$\leq M|h_2 - h_1|$$

where $F_{n+j}(h_2, h_1)$ is a homogeneous form of degree $n+j$ in h_2 and h_1, M is a suitable constant. A similar proof holds for $u_1(t)$. Consequently, it is seen that:

Lemma 4.1

There exists (in some interval $t \in [0, a], a>0$) a unique solution to the B Model if the free antigen concen-

tration h(t) is nonnegative, as it is in reality.

The global existence and uniqueness of solution to (4.14) can be established by showing that the solution is uniformly bounded for all t>0 [95]. This will be investigated in the next section.

4.3.2 Positive Invariance and Stability

A most obvious and striking property of a biomedical model is that all state variables which describe poupla-tions, chemical or biochemical concentrations, etc. must be nonnegative for all t. That is, it makes no sense to speak of negative populations, negative chemical concentrations, etc. A dynamic bio-control model is even more restrictive, and expected to possess nonnegativity under all possible control perturbations. Usually, such perturbations are constrained owing to their physical realizability. Another advantage of examining nonnegativity comes from the simulation of the stiff model equations. When a numerical integration formula used is not appropriate for simulated model, the errors accumulate rapidly and the system 'blows up' or fails to provide any further meaningful answers. Experience of simulating the B Model shows that whenever one of the state variables becomes negative, the error starts accumulating and the simulation 'blows up'. Thus, if a model is proved to be positively invariant (to be defined below), then this unsuccessful simulation can be

blamed on numerical integration rather than the model itself.

Definition 4.1

A mathematical model is said to be positively invariant if its solution (all state variables) is nonnegative for all $t \geq 0$, provided that the initial condition is non-negative.

Definition 4.2

A dynamic control system is said to be positively invariant if its state space (reachable set) is confined to the positive quadrant, for all admissible controls, provided that the initial condition is nonnegative.

Lemma 4.2

The B Model is positively invariant if β_k and $\dot{h}_i(t)$ are nonnegative for all $t \geq 0$.

Proof of Lemma 2 may be easily done by applying the following theorem [96]:

Theorem 4.1

Consider the initial value problem of a system of a n-dimensional autonomous differential equation,

$$\dot{\underline{x}} = \underline{f}(\underline{x}), \quad \underline{x}(0)=\underline{x}_0 \tag{4.15}$$

in $J = [0, T]$, $0<T<+\infty$. Assume that

(1) there is a solution of (4.15) in J and is uniquely determined

(2) $\underline{x}(0)=\underline{x}_0 \geq \underline{0}$

(3) for any $i=1,2,\ldots,n$ if $x_i=0$ and $x_j \geq 0$ $(j\neq i)$, then $f_i(\underline{x}) \geq 0$

Then the solutions of system (4.15) are all nonnegative.

The above theorem is also applicable for control sytem such as (4.14), if control(s) is differentiable and considered as another state variable. Two things merit attention; one is the theorem gives only sufficient but not necessary conditions, the other is the theorem may be thought as an extension of the well-known nonnegativity criterion for linear system. That is, a linear system is positively invariant if the off-diagonal entries of system matrix and the initial condition are nonnegative.

Stability consideration of the B Model is now presented. To begin with, it is observed that with $\dot{h}_i(t)=0$, the B Model has a unique equilibrium point,

$$\underline{x}_e=(\beta_k\tau_1,\ 0,\ \alpha'\tau_3\tau_1\beta_k,\ 0,\ 0)^T.$$

Lemma 4.3

The unique equilibrium point x_e of the B Model is asymptotically stable.

The proof of this lemma may be carried out along these lines:

(1) Recall that B Model is decomposed as a bilinear system and a quadratic system with nonlinear feedbacks (Section 4.2.1). By Corollary 3.2, the BLS (i.e. (4.7) and (4.8)) is BIBO stable owing to the fact that the matrix A has only negative eigenvalues $-1/\tau_1$ and $-1/\tau_2$, as well as $|u_1(t)| \leq 1$ and $|u_2(t)| \leq 1$. If the probability of stimulation p_s is approximated as in (4.5), then Theorem 3.1 holds and thus the BLS is BIBO stable.

(2) By (1), $x_1(t)$ and $x_2(t)$ as bounded inputs to the quadratic system, combining (4.10) and (4.11) gives

$$\dot{x}_4 + \dot{h} = -\frac{x_4}{\tau_4} - \frac{h}{\tau_h} + \dot{h}_i(t) \qquad (4.16)$$

Then $\dot{x}_4+\dot{h} \leq -d(x_4+h) + \dot{h}_i(t)$; $d \triangleq 1/\max(\tau_4, \tau_h)$, which is a differential inequality. Solving this with $x_4(0) = h(0) = 0$,

$$x_4(t)+h(t) \leq \int_0^t e^{-d(t-s)}\dot{h}_i(s)ds \leq \int_0^\infty \dot{h}_i(s)ds = \frac{Q}{V} \qquad (4.17)$$

But $x_4(t)$ and $h(t)$ have been shown to be non-negative for $t \geq 0$, and therefore $x_4(t)$ and $h(t)$ are both bounded by Q/V.

(3) Using (1) and (2), it is straightforward to have the boundedness of $x_3(t)$. Put $t \longrightarrow \infty$ in (4.17)

and a little algebraic calculation completes the proof of Lemma 4.3.

The system-theoretic properties of B Model can now be summarized by the following:

Theorem 4.2

For each nonnegative initial state, and each bounded β_k, and $\dot{h}_i(t)$, there exists a unique solution of B Model for all $t \geq 0$. Moreover, the solution is positively invariant and asymptotically stable with respect to the unique equilibrium point.

4.3.3 More About B Model

Until now the B Model is shown to be a special class of variable structure system. Structural decomposition is given in light of cellular and molecular subsystems. The control aspects are also discussed together with system-theoretic properties. As emphasized earlier, this research is aiming to apply modern control theory to facilitate understanding the immune systems. The B Model is moreover exploited qualitatively to examine its dynamic behavior and immunological interpretations.

The B Model comprising from equations (4.5) to (4.12) can be represented by

$$\dot{\underline{x}}(t)=A_1\underline{x}(t)+\sum_{i=1}^{2} B_i u_i(t)\underline{x}(t)+\underline{c}_1 v_1 \qquad (4.18)$$

$$\dot{\underline{y}}(t)=A_2\underline{y}(t)+\langle \underline{y},Q\underline{y}\rangle\ \underline{p}+C\underline{v}(t) \tag{4.19}$$

where $\underline{x}(t)=(x_1(t),\ x_2(t))^T$, $\underline{y}(t)=(x_3(t),\ x_4(t),\ h(t))^T$, $v_1\triangleq\beta_k$, $\underline{v}(t)=(x_1(t),\ x_2(t),\ \dot{h}_i(t))^T$ and $\underline{c}_1=(1,\ 0)^T$, $\underline{p}=(-1,1,-1)^T$

$$A_1=\begin{pmatrix} -\frac{1}{\tau_1} & 0 \\ 0 & -\frac{1}{\tau_2} \end{pmatrix},\quad B_1=\begin{pmatrix} \alpha & 0 \\ 0 & 0 \end{pmatrix},\quad B_2=\begin{pmatrix} 0 & 0 \\ 2\alpha & 0 \end{pmatrix},$$

$$A_2=\begin{pmatrix} -\frac{1}{\tau_3} & c_k & 0 \\ 0 & -\frac{1}{\tau_4}-c_k & 0 \\ 0 & c_k & -\frac{1}{\tau_h} \end{pmatrix},\qquad C=\begin{pmatrix} \alpha' & \alpha'' & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

$$Q=\begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ kc_k & 0 & 0 \end{pmatrix}$$

It is seen that (4.18) is a 2-dimensional BLS with two multiplicative and one constant additive inputs. This BLS may also be realized as a cascade of two scalar BLS. Hence it can be explicitly solved (obviously, $\{A_1,\ B_1,\ B_2\}$ generates a solvable Lie algebra),

$$x_1(t) = x_{10}\exp\int_0^t r(s)ds+\beta_k\int_0^t \exp(\exp\int_0^t r(s)ds)ds \tag{4.20}$$

$$x_2(t) = 2\alpha e^{\frac{-t}{\tau_2}} \int_0^t e^{\frac{s}{\tau_2}} u_2(s)x_1(s)ds \qquad (4.21)$$

where $r(t) = \alpha u_1(t) - \frac{1}{\tau_1}$

Since $r(t)$ is function of $u_1(t)$ which in turn is a nonlinear function of $h(t)$, not much information can be conveyed from these explicit solutions. But taking the approximation of p_s into account, i.e. (4.5), provides interesting interpretation on B Model dynamics. For convenience, the overall primary immune response is divided into three periods, namely, latent state, active immune state and memory state [97].

In the latent state, concentration of free antigen is below the threshold of ICC stimulation, so the immune system as defined in B Model remains unaffected, e.g. $u_1(t)=u_2(t)=0$. Equations (4.20) and (4.21) reduces to

$$x_1(t) = x_{10} e^{\frac{-t}{\tau_1} + \tau_1\beta_k(1-e^{\frac{-t}{\tau_1}})}, \qquad (4.22)$$

$$x_2(t) = 0, \quad 0 \leq t \leq t_1$$

ICC population decays exponentially as a consequence of catabolism, but nonsignificantly ($\tau_1 >> t_1$), and no plasma cells are generated.

If ICC is stimulated, the immune response is active and the underlying dynamics is much more complicated. During this period,

$$r(t) = \alpha\frac{1-kh(t)}{1+kh(t)} - \frac{1}{\tau_1}, \qquad u_2(t) = \frac{kh(t)}{1+kh(t)}$$

Unless $h(t)$ is known explicitly, it seems difficult to accurately predict the time course of lymphocytes. A way to undertake this problem is to do B Model approximation which will be studied later. However, it is not unreasonable to expect that ICC and plasma cell populations would be rising up until $kh(t)$ surpasses $\sigma_2/1-\sigma_2$ (see (4.5)). Suppose that at $t=t_2$, values of x_1 and x_2 are A and B, respectively.

As soon as free antigen concentration reaches the upper limit, ICC is saturated and stimulation is blocked. The active immune response is diminished and ensues <u>memory state</u> for the next antigenic attack. Again $u_1(t)=u_2(t)=0$, so

$$x_1(t) = Ae^{\frac{-(t-t_2)}{\tau_1}} + \tau_1\beta_k(1-e^{\frac{-(t-t_2)}{\tau_1}})$$

$$x_2(t) = Be^{-\frac{(t-t_2)}{\tau_2}}, \qquad t \geq t_2 \tag{4.23}$$

Population of plasma cells decays significantly (owing to its short life time), while ICC (more precisely, memory cells) levels off slowly due to large value of τ_1.

A moment of reflection shows that (4.19) is similar to some sort of prey-predator model. Analogy of immune system and prey-predator system can be simply interpreted in the manner that the antigen acts as 'food' for the antibody and the antibody is stimulated by that antigen.

Bell and Pimbley presented some interesting immune models from this point of view but for the replicating antigens [98, 99].

In the latent state there is no ICC stimulation, and (4.19) becomes

$$\dot{x}_3 = \alpha' [x_{10} e^{\frac{-t}{\tau_1}} + \tau_1 \beta_k (1-e^{\frac{-t}{\tau_1}})] - \frac{x_3}{\tau_3} - kc_k x_3 h + c_k x_4$$

$$\dot{x}_4 = kc_k x_3 h - \frac{x_4}{\tau_4} - c_k x_4 \qquad 0 \leq t \leq t_1 \qquad (4.24)$$

$$\dot{h} = \dot{h}_i(t) - \frac{h}{\tau_h} - k\, c_k x_3 h + c_k x_4$$

To simplify the analysis, $\dot{h}_i(t)$ is replaced by non-zero h(0), (see Section 4.2.3) and τ_1 is known to be very large compared to other lifetimes, $\tau_1 >> t_1$. Hence equation (4.24) may be approximated by

$$\dot{x}_3 = \alpha' x_{10} - \frac{x_3}{\tau_3} - kc_k x_3 h + c_k x_4, \quad x_3(0) = 0$$

$$\dot{x}_4 = kc_k x_3 h - \frac{x_4}{\tau_4} - c_k x_4, \quad x_4(0) = 0 \qquad (4.25)$$

$$\dot{h} = -\frac{h}{\tau_h} - kc_k x_3 h + c_k x_4, \quad h(0) \neq 0; \quad 0 \leq t \leq t_1$$

The only antibody production comes from the basal unstimulated ICC, which is usually much less than that in active response. Eliminating the second equation of (4.25) gives $(c_k' \triangleq \frac{1}{\tau_4} + c_k)$,

$$\dot{x}_3=\alpha' x_{10} - \frac{x_3}{\tau_3} - kc_k x_3 h + kc_k^2 e^{-c_k' t} \int_0^t e^{c_k' s} x_3(s)h(s)ds$$

$$\dot{h} = - \frac{h}{\tau_h} - kc_k x_3 h + kc_k^2 e^{-c_k' t} \int_0^t e^{c_k' s} x_3(s)h(s)ds \qquad (4.26)$$

Unfortunately the closed-form solution for (4.26) is not available. It is of some interest to notice that (4.26) which represents the antibody-antigen reaction is in fact a model of two competing species —— one of which has a constant rate of introduction (i.e. $\alpha' x_{10}$), the other has no progeny. Recall that c_k is quite large ($3.6\times10^3 hr^{-1} \sim 3.6\times10^5 hr^{-1}$) and $0 \leq t \leq t_1$. For sufficiently small t_1 (the latent state is not long) the integral terms in (4.26) may be neglected, and the equation becomes

$$\dot{x}_3 = \alpha' x_{10} - \frac{x_3}{\tau_3} - kc_k x_3 h$$

$$\dot{h} = - \frac{h}{\tau_h} - kc_k x_3 h \qquad (4.27)$$

Now it is obvious that the free antigen concentration decreases, while the antibody production increases during the latent period.

If the immune response is active ($t_1 \leq t \leq t_2$) accurate prediction on its dynamics is not acquired. What may be expected is the decrease of antigen and the increase of antibody will be faster than that of the latent period.

Assume that $x_3(t_2)=C$, $x_4(t_2)=D$, and $h(t_2)=E$, then, by (4.23),

$$\dot{x}_3 = \alpha'[Ae^{\frac{-s}{\tau_1}}+\tau_1\beta_k(1-e^{\frac{-s}{\tau_1}})]+\alpha''Be^{\frac{-s}{\tau_2}}-\frac{x_3}{\tau_3} - kc_kx_3h$$

$$+c_k[De^{-c_k's}+kc_ke^{-c_k's}\int_{t_2}^{t} e^{c_k'\sigma} x_3(\sigma)h(\sigma)d\sigma] \quad (4.28)$$

$$\dot{h}=-\frac{h}{\tau_h} - kc_kx_3h+c_k[De^{-c_k's}+kc_ke^{-c_k's}\int_{t_2}^{t} e^{c_k'\sigma} x_3(\sigma)h(\sigma)d\sigma]$$

where $s \triangleq t - t_2$

Dynamic behavior of the molecular subsystem of the B Model is summarized in Figure 4.9(b). Comparison of Figure 4.9 with simulation result in Figure 4.8, shows that response curves of the latter are fairly reasonable.

Partial analysis of the B Model is now accomplished. What needs to be resolved boils down to the investigation of active immune state, which is the theme of the next chapter.

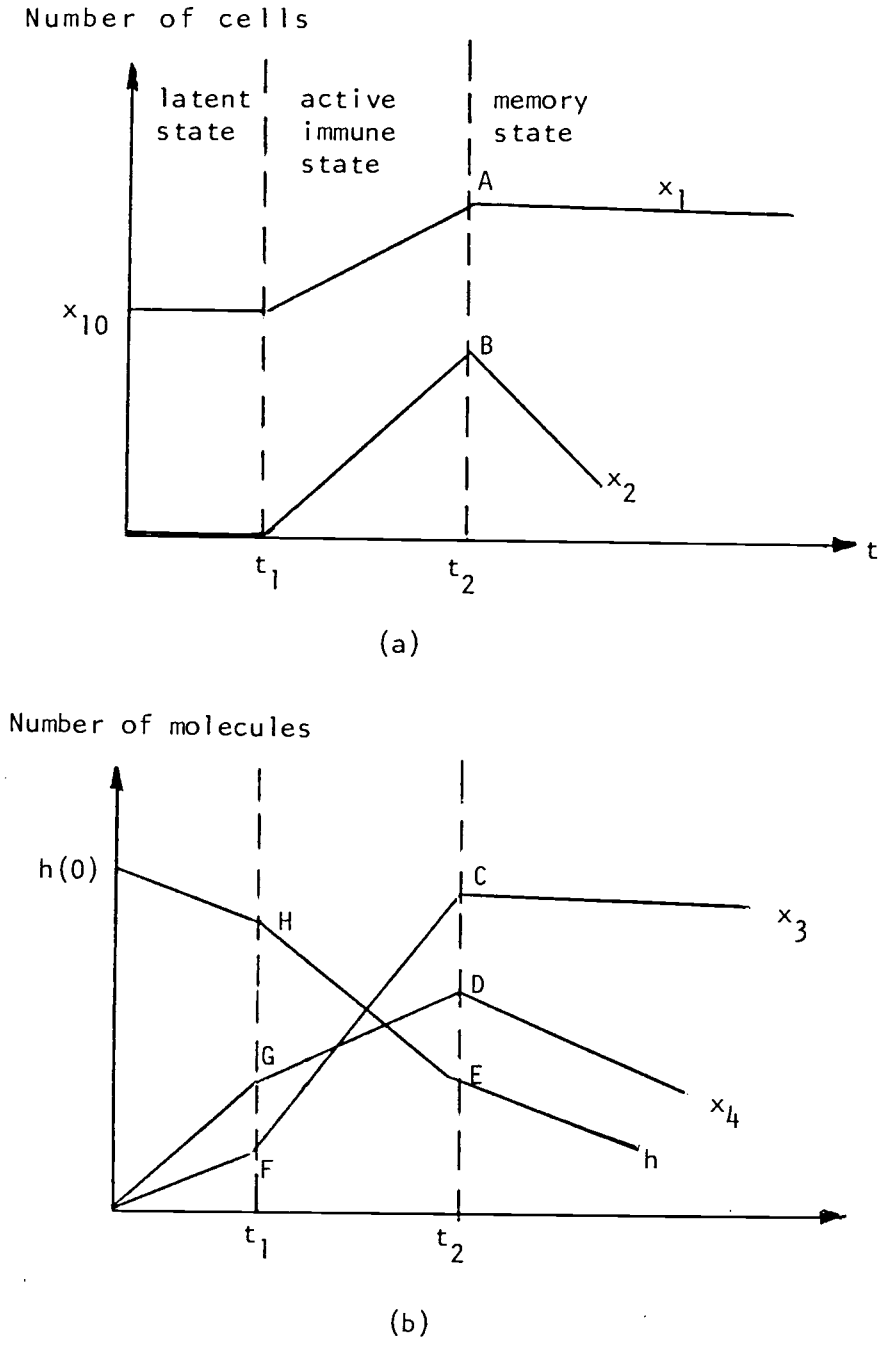

Figure 4.9. Approximate dynamic behavior of primary immune response

(a) time course response of cellular subsystem
(b) time course response of molecular subsystem

V. SYSTEM-THEORETIC CONTROL IN IMMUNOLOGY

5.1 Approximated B Models

5.1.1 A Simplified Model of Active Immune Response

In the previous Chapter, the B Model has been presented and its dynamic behavior in the latent and memory states is discussed. This section is devoted to the simplification of the B Model so as to arrive at approximated immune models which are amenable to dynamic analysis, in particular, in the active state. The simplified models presented below will be shown to possess specific structures which make it more convenient to characterize their dynamic behavior via BLS theory.

For convenience, the B Model is restated by

$$\dot{x}_1 = p_s \hat{u}_1(t) x_1 + \beta_k \tag{5.1a}$$

$$\dot{x}_2 = 2\alpha p_s \hat{u}_2(t) x_1 - \frac{x_2}{\tau_2} \tag{5.1b}$$

$$\dot{x}_3 = \alpha' x_1 + \alpha'' x_2 - \frac{x_3}{\tau_3} - k c_k x_3 h + c_k x_4 \tag{5.1c}$$

$$\dot{x}_4 = k c_k x_3 h - \frac{x_4}{\tau_4} - c_k x_4 \tag{5.1d}$$

$$\dot{h} = -k c_k x_3 h - \frac{h}{\tau_h} + c_k x_4 + \dot{h}_i(t) \tag{5.1e}$$

where $\hat{u}_1(t) = \alpha u_1(t) - \frac{1}{\tau_1} = \alpha \frac{1-kh}{1+kh} - \frac{1}{\tau_1}$,

$$\hat{u}_2(t) = \frac{kh}{1+kh} = \tfrac{1}{2}(1-u_1(t)),$$

and the initial conditions are

$$x_1(0)=x_{10},\ x_2(0)=x_3(0)=x_4(0)=h(0)=0.$$

It is seen from the model equations that the complicating nonlinearity arises from multiplicative inputs (parametric controls) $\hat{u}_1(t)$ and $\hat{u}_2(t)$. For some situations, the term kh may be much less than one, i.e. $kh<<1$, then $\hat{u}_1(t)$ and $\hat{u}_2(t)$ can be approximated by $\alpha-\frac{1}{\tau_1}$ and kh, respectively. As far as the immune response in the active state is concerned, the probability of stimulation, p_s, is equal to one (see (4.5)), and thus (5.1a) and (5.1b) can be simplified as

$$\dot{x}_1 = (\alpha - \frac{1}{\tau_1})x_1+\beta_k \qquad (5.2a)$$

$$\dot{x}_2 = 2\alpha kh x_1 - \frac{x_2}{\tau_2} \qquad (5.2b)$$

These two equations together with (5.1c)——(5.1e) form a model of active immune response, $t_1\leq t\leq t_2$, with initial data $x_1(t_1)=x_{10}e^{-t_1/\tau_1}+\tau_1\beta_k(1-e^{-t_1/\tau_1})\triangleq x_{10}'$, $x_2(t_1) = 0$, $x_3(t_1)=F$, $x_4(t_1) = G$, $h(t_1) = H$, where F, G, H are final values at $t=t_1$ of (4.25). The simulation result (with data the same as in B Model simulation) is given in Figure 5.1.

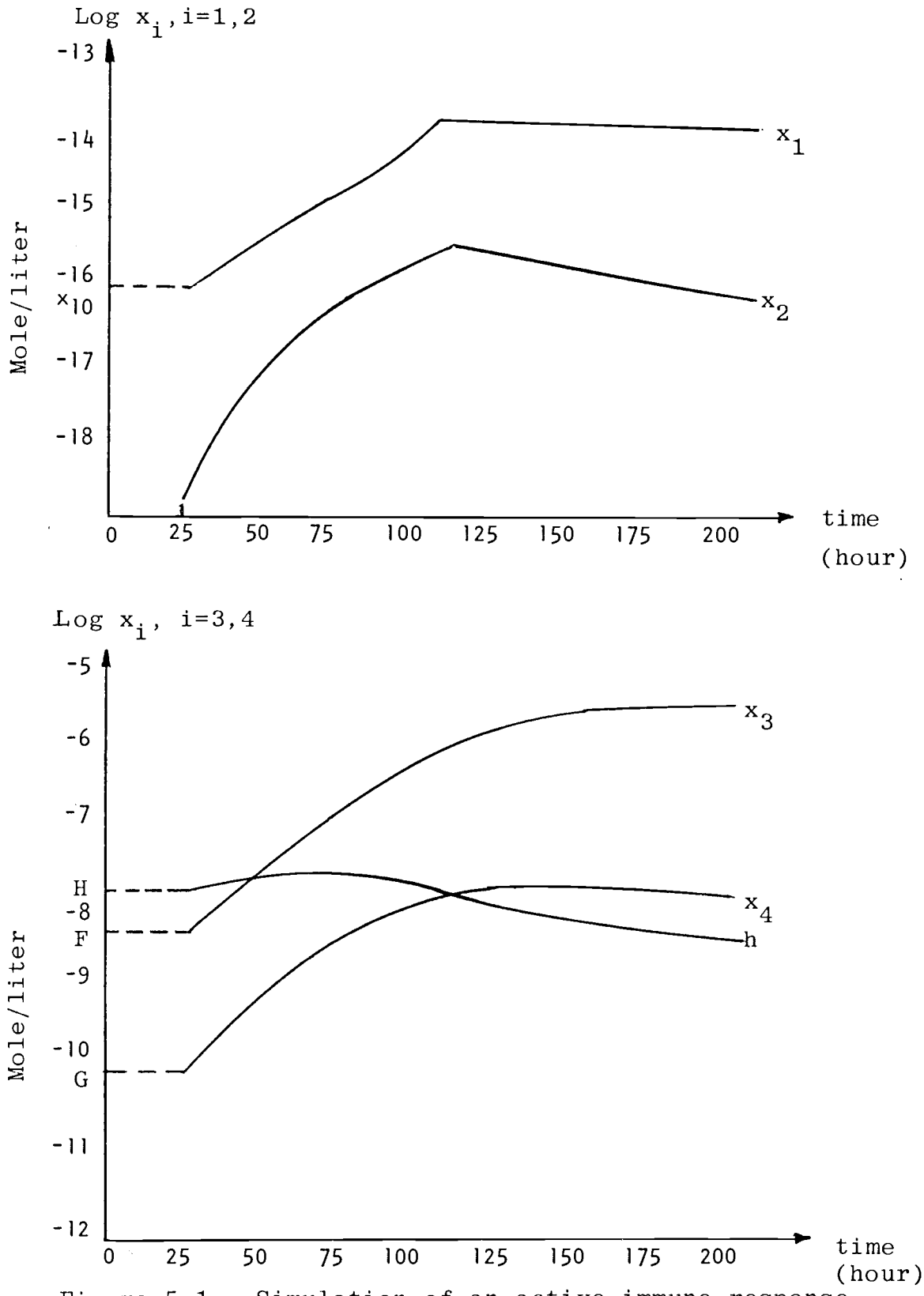

Figure 5.1. Simulation of an active immune response.

Explicit solutions to (5.2a) and (5.2b) are

$$x_1(t) = \exp(\hat{\alpha}(t-t_1))[x_{10}' + \beta_k \int_{t_1}^{t} \exp(-\hat{\alpha}(t_1-\tau))d\tau]$$

$$x_2(t) = 2\alpha k e^{-t/\tau_2} \int_{t_1}^{t} e^{\tau/\tau_2} h(\tau) x_1(\tau) d\tau \qquad (5.3)$$

where $\hat{\alpha} = \alpha - \frac{1}{\tau_1}$

It is observed that $x_1(t)$ in (5.3) is no longer a function of $h(t)$ and can be explicitly solved, that is,

$$x_1(t) = e^{\hat{\alpha}(t-t_1)} x_{10}' + \frac{\beta_k}{\hat{\alpha}} (e^{\hat{\alpha}(t-t_1)} - 1) \triangleq f_1(t) \qquad (5.4)$$

This is not unreasonable, because as stated earlier that the antibody production comes mostly from plasma cells not ICC. Coordination of (5.3) and (5.4) as well as the assumption that immune complexes are removed out of the immune system immediately after they are formed, will give the following simplified model which characterizes the antibody-antigen dynamics,

$$\dot{x}_3 = \alpha' f_1(t) - \frac{x_3}{\tau_3} + 2\alpha'' \alpha k e^{-t/\tau_2} \int_{t_1}^{t} e^{\tau/\tau_2} h(\tau) f_1(\tau) d\tau$$

$$- k c_k x_3 h$$

$$\dot{h} = -\frac{h}{\tau_h} - k c_k x_3 h + \dot{h}_i(t), \qquad t_1 \leq t \leq t_2$$

The integral term can be eliminated by redefining state variables $y_1(t)=x_3(t)$, $y_2(t)=\dot{x}_3(t)$, and $y_3(t)=h(t)$, that

is, y_1, y_2 and y_3 denote the antibody concentration, the rate of change of antibody concentration, and the free antigen concentration, respectively. Then an equivalent model is obtained as,

$$\begin{aligned}
\dot{y}_1 &= y_2 \\
\dot{y}_2 &= S(t)\,\frac{y_1}{\tau_2\tau_3} - \left(\frac{1}{\tau_3}+\frac{1}{\tau_2}\right)y_2 + 2\alpha''\alpha k f_1(t) y_3 \\
&\quad - kc_k y_2 y_3 - \left(\frac{1}{\tau_2}-\frac{1}{\tau_h}\right)y_1 y_3 + k^2 c_k^2 y_1^2 y_3 \\
\dot{y}_3 &= \frac{y_3}{\tau_h} - kc_k y_1 y_3, \quad t_1 \le t \le t_2
\end{aligned} \tag{5.5}$$

where $S(t) \triangleq \alpha' \dot{f}_1(t) + \frac{\alpha'}{\tau_2} f_1(t)$, $f_1(t)$ is defined in (5.4). The initial condition of model (5.5) is $y_1(t_1)=F$, $y_3(t_1)=H$, and $y_2(t_1)=\alpha' x_{10}' - kc_k FH - \frac{F}{\tau_3}$, where $y_2(t_1)$ is obtained from (5.3).

Though (5.5) may be used as an approximate model to represent the active immune response, its cubic nonlinearity and time-varying property still make it difficult for analytical study, and it is not pursued further here.

It may be appropriate to compare here the simplified model (5.5) with Merrill's model (4.2). It is easily seen that both models have cubic nonlinearity. In Merrill's model, one state variable (i.e. $x_1(t)$) is referred to the 'stimulation factor', others are concentrations of molecules and cells. The dynamic equation for this 'stimula-

tion factor' is a nonlinear cubic equation which is nothing but the well-known Van der Pol equation [100]. The cubic nonlinearity contributes several qualitative characteristics of Merrill's model, which describes some features of humoral immune response [80]. However, two disadvantages are easily singled out. One is that it seems obscured that the Van der Pol equation can be derived from biological assumptions (immune mechanism). The other is that it is difficult to test the model against the experimental data. The B Model and the model (5.5) overcome these shortcomings but only by increasing the complexity of the model equations (compare the second equation of (5.5) and the first equation of (4.2)). In contrast to the 'stimulation factor', the corresponding state variable in (5.5) is $y_2(t)$, which stands for the rate of change of antibody production. This observation is particularly significant in the sense that the model (5.5) may be used to help interpret part of the theory, proposed by Rosen [101], that states: the features of rate-sensitive chemoreceptors automatically possess many of the basic features of an immune mechanism, such as tolerance inducibility, memory, biosynthesis of antibody-like material, cellular proliferation and possibility of co-operative interaction between cells.

5.1.2 A Simple Model for Antibody Formation

The B Model as well as its simplified version proposed so far, are seen to be nonlinear. Direct application of control theory to such immune models is difficult and rare results can be expected. The rest of this chapter is devoted to the construction of simplified immune models, which are more tractable from the viewpoint of control applications. These simplified models will be derived as based on some stronger hypotheses. In fact, a very simple model (4.1) of immune response, which only include immunocompetent cells (ICC), plasma cells and antibodies as state variables, has been studied in Section 2.6.3, Section 3.2.3 and Section 4.1.2.

For convenience of comparison, the model (4.1) is repeated here,

$$\begin{aligned}
\dot{x}_1 &= \alpha(1-2u_1(t))x_1 - \frac{x_1}{\tau_1}, \quad x_1(0)=x_{10} \\
\dot{x}_2 &= 2\alpha u_1(t)x_1 - \frac{x_2}{\tau_2}, \quad x_2(0)=0 \qquad (5.6) \\
\dot{x}_3 &= \alpha' x_1 + \alpha'' x_2, \quad x_3(0)=0
\end{aligned}$$

where x_1, x_2, and x_3 denote the concentrations of ICC, plasma cells, and antibody, respectively. The input $u_1(t)$ is the probability of differentiation from ICC to plasma cells, $0 \leq u_1(t) \leq 1$ (p_d in the B Model).

This model is a homogeneous BLS with scalar input $u_1(t)$ which is simulated with immunological data and shown in Figure 3.5 and Figure 4.2. From these simulations, it is seen that the antibody production is unlimited due to only one switching of the input function. In contrast to this behavior, the B Model simulation shows that the antibody production is a saturated curve, as a consequence of two switchings of its input function (Figure 4.7).

In addition to the negligence of antigen dynamics, the catabolism of antibody as well as the generation of stem cells from bone marrow are also neglected in model (5.6). Removing the later two assumptions leads to the following immune model.

$$\begin{aligned}
\dot{x}_1 &= \alpha(1-2u_1(t))x_1 - \frac{x_1}{\tau_1} + \beta_k, \quad x_1(0) = x_{10} \\
\dot{x}_2 &= 2\alpha u_1(t)x_1 - \frac{x_2}{\tau_2}, \quad x_2(0) = 0 \qquad (5.7) \\
\dot{x}_3 &= \alpha' x_1 + \alpha'' x_2 - \frac{x_3}{\tau_3}, \quad x_3(0) = 0
\end{aligned}$$

where $u_1(t)$, $0 \leq u_1(t) \leq 1$, denotes the probability of differentiation (p_d in the B Model); β_k is the rate of generation of ICC from bone marrow, and τ_3 is the mean lifetime of free antibody sites.

Model (5.7) is more realistic than model (5.6) as can be seen that there is an additional <u>additive input</u> β_k in the model. Moreover, the main assumption of not consid-

ering the antigen can be partially offset by redefining $1/\tau_3$ as another multiplicative input, say $u_2(t)$. Both inputs $u_1(t)$ and $u_2(t)$ may be viewed as parametric controls in the immune response, which are functions of the injected antigens. From the above argument, model (5.7) is revised as

$$\dot{x}_1 = \alpha(1-2u_1(t))x_1 - \frac{x_1}{\tau_1} + \beta_k, \quad x_1(0) = x_{10}$$

$$\dot{x}_2 = 2\alpha u_1(t)x_1 - \frac{x_2}{\tau_2}, \quad x_2(0) = 0 \qquad (5.8)$$

$$\dot{x}_3 = \alpha' x_1 + \alpha'' x_2 - u_2(t)x_3, \quad x_3(0) = 0$$

Though models (5.7) and (5.8) are less realistic than the B Model, they are more amenable to control-theoretic analysis and may provide insight to the more complete system. For example, as pointed out by Perelson et al. [81], if the performance index of the immune system is chosen to be the minimal time interval in which a prescribed amount of antibodies can be produced, then an optimal strategy can be found. This will be elaborated in more detail in the next section.

The above models are obtained by assuming that antigens have already stimulated the ICC. This may also be interpreted as these models are for the immune response in the <u>active</u> state, i.e. $p_s=1$. Moreover, the model (5.7) can be considered as a specific case of the B Model.

To be precise, the notion of instantaneous equilibrium is introduced. In view of the rate constants for association and dissociation of the immune complex, they are higher than those relative to the other immune phenomena (compare the rate constants in Table 4.1). Consequently, it is not unreasonable in studying the long-range (slow transients) to assume that a condition of instantaneous equilibrium between antigen, antibody and immune complex is established so that (5.1d) can be substituted by the instantaneous relationship:

$$x_4 = kx_3h \tag{5.9}$$

It is seen that the model (5.7) follows immediately from the B Model by using (5.9). It should also be noted here that the assumption of instantaneous equilibrium reduces the state equation of free antigen concentration, (5.1e), into

$$\dot{h} = -\frac{h}{\tau_h} + \dot{h}_i(t), \quad h(0) = 0 \tag{5.10a}$$

whose solution can be explicitly found if the rate of releasing the injected antigen $\dot{h}_i(t)$ is a priori known. This is consistent with the fact that in immunological experiments, the free antigen concentration is a directly measurable quantity [102].

However, the assumption of instantaneous equilibrium is a very strong one so as the free antigen concentration is independent of antibody. This is not quite realistic,

though this may probably be explained by that 'at equilibrium' there is no 'net' reaction between free antigen and antibody. It is known from immunological experiments that the free antigen is distributed with respect to the association constant k which may range from 10^3 liter mole^{-1} to 10^{10} liter mole^{-1} [87]. Thus total free antigen for all k is more accurately described as given by (4.11). While (5.10a) may be used to approximate the dynamic behavior of total free antigen $h(t)$, it is not accurate due to large number of small terms which are neglected. But assuming $\dot{x}_4 = 0$ such that $x_4 \simeq khx_3$ ($c_k >> 1/\tau_4$) [82], somewhat more accurate approximation seems to be

$$\dot{h} \simeq \dot{h}_i - \frac{h}{\tau_h} - \sum_k \frac{x_4}{\tau_4} \qquad (5.10b)$$

5.2 Control-theoretic Analysis of Immune Models

5.2.1 Optimization of an Immune Model

The mathematical immune models proposed in the last section are 3-dimensional bilinear systems with particular structure. The optimal control theory of bilinear systems may be readily applied to exploit the homeostatic immune system which seems to be endowed with the evolutionary goal of eliminating antigen in some optimal manner. However, optimization of immune models may be somewhat

speculative, since it can be very difficult to ascertain the optimization criteria which may include minimum response time, minimum control effort, and minimum likelihood of failure as well as other criteria [82, 103, 104]. The following quotation, however, does seem reasonable:

> "Although there is not a priori reason which assures that the immune system responds to antigen in an optimal way, the mammalian immune system has been evolutionarily static for a long time. It is quite possible that the system has become static because it has evolved to the point where it performs optimally" [105].

To illustrate the application of bilinear optimal regulation to the approximate model (5.6), a time-optimal control problem is formulated and resolved below. It will be shown that the structure of BLS as emphasized previously is important in the determination of optimal strategy.

The performance index (optimization criterion) is to choose $u_1(t)$ so as to minimize the total time, T, required to secrete an amount of antibody, x_3^*, sufficient to neutralize a given antigenic assault. This can be formally stated as

$$\min_{u_1(t)} \int_0^t dt, \; x_3(T) = x_3^*.$$

The matrix B of model (5.6) is seen to have rank one, and hence this time-optimal problem can be solved via the following:

Theorem 5.1 [19, 106]

Consider the BLS $\dot{\underline{x}}=A\underline{x}+u(t)B\underline{x}$, $\underline{x}(0)\in R^n-\{0\}$, with the input $u(t)\in\mathcal{U}=\{u(t);\ s_1\leq u(t)\leq s_2$, measurable on $t\in[0, T]\}$. If rank $(B)=1$, i.e. $B=\underline{\ell}\ \underline{m}^T$, and rank $(\underline{\ell}:A\underline{\ell}:\ldots:A^{n-1}\underline{\ell})=n$, then

(a) there exists a bang-bang time-optimal control strategy $u^0(t)$ which transfers $\underline{x}(0)$ to the prescribed $\underline{x}(T)$.

(b) if, furthermore, the BLS is positively invariant (defined in Section 4.3.2), and all components of $\underline{m}$ are nonnegative, $u^0(t)$ is uniquely defined (almost everywhere) by

$$u^0(t)=\begin{cases} s_2 & \text{if } \underline{\lambda}^T\cdot e^{-At}\underline{\ell}<0 \\ s_1 & \text{if } \underline{\lambda}^T\cdot e^{-At}\underline{\ell}>0 \end{cases} \qquad (5.11)$$

where the costate vector $\underline{\lambda}$ is the outward normal to the terminal manifold $\theta(\underline{x}(T))$ at $t=T$.

(c) the optimal singular trajectories (i.e. $\underline{\lambda}^T\cdot e^{-At}\underline{\ell}=0$, for a nonzero time interval), if they exist, lie completely on the hypersurface defined by $\underline{m}^T\underline{x}=0$.

This theorem is stated in a different format without proof in the references cited above. For the sake of completeness, the proof is outlined as follows:

Proof of Theorem 5.1

It can be shown that the BLS, $\dot{\underline{x}}=A\underline{x}+u(t)B\underline{x}$ is equivalent to $\dot{\underline{y}}=u(t)e^{-At}Be^{At}\underline{y}$ by the transformation $\underline{x}=e^{At}\underline{y}$. Hence by the rank assumption on B

$$\dot{\underline{y}}(t) = u(t)e^{-At}\underline{\ell}\ \underline{m}^T e^{At}\underline{y}(t) \tag{5.12}$$

The Hamiltonian, H, associated with the BLS (5.12) is

$$H = \lambda_0 + (\underline{\lambda}^T e^{-At}\underline{\ell}\ \underline{m}^T e^{At}\underline{y}(t))u(t) \tag{5.13}$$

Owing to the assumption of rank $(\underline{\ell} \vdots A\underline{\ell} \vdots \ldots \vdots A^{n-1}\underline{\ell})=n$, $\underline{\lambda}^T e^{-At}\underline{\ell}$ is a nonzero scalar unless $\underline{\lambda}\equiv\underline{0}$. With the aid of assumptions on positive invariance of the BLS, the proof is then established by direct application of the Pontryagin Maximum Principle [107] to (5.13).

By Theorem 5.1, the time-optimal strategy of model (5.6) is seen to be bang-bang, namely, $(r\triangleq\alpha''/\alpha')$,

$$u^0(t) = \begin{cases} 0, & 0\le t\le T \quad \text{if} \quad r\le 2 \\ 1, & 0\le t\le T \text{ small} \quad \text{if} \quad r>2 \quad \text{and} \quad x_3^* \text{ is sufficiently} \end{cases}$$

If x_3^* is sufficiently large and $r>2$, then a switching is needed, that is, $u^0(t)=0$, $0\le t<t^*$; $u^0(t)=1$, $t^*\le t\le T$.

The value of r (by definition the ratio of antibody production rates of plasma cells and ICC) is pivotal when r=2. This is 'no accident', but instead reminiscent of the fact stated in Section 3.2.3 that the relative order of (5.6) is infinite if r=2.

An interpretation of the above optimal strategy is given below in view of immunological relevance, mostly following the work of Perelson et al. [81]. If $r \leq 2$, then plasma cells hold no advantage over ICC and the optimal policy is $u^0(t)=0$, $0 \leq t \leq T$; i.e. no production of plasma cells, $p_d=0$. If $r>2$, then over some time interval it is advantageous to differentiate ICC into plasma cells. The time at which this differentiation occurs depends upon the antigen concentration. If x_3^* is sufficiently small that a single generation of plasma cells could produce x_3^*, then clearly the control should be $u^0(t)=1$, $0 \leq t \leq T$. In the case of x_3^* is sufficiently large, the optimal strategy consists of a single switching: $u^0(t)=0$, $0 \leq t < t^*$, $u^0(t)=1$, $t^* \leq t \leq T$. In other words, the lymphocyte population proliferates, producing antibody at a rate, $\alpha' x_1$, until a critical time, t^*, is reached. Then all proliferation ceases and all ICC differentiate into plasma cells until the antibody required x_3^* is reached. The switching time, t^*, can be found from the switching equation

$$\underline{\lambda}^T \cdot e^{-At} \underline{\ell}\ \underline{m}^T e^{At} \underline{y}(t)=0, \text{ where } \dot{\underline{\lambda}} = -\frac{\partial H}{\partial \underline{x}} .$$

In general, the maximum principle only gives necessary conditions for optimality of a control. However, in this case the extremal controls satisfy a sufficient condition as well [81]. Thus no intermediate 'graded' response is

more efficient ——— a fact that is perhaps not intuitively obvious.

The control of bang-bang type is frequently used in engineering systems, for example, flip-flop in switching circuits, etc. It may be said with some reservation that the bang-bang control is analogous to the all-or-none principle in neurophysiology [108]. The analogy in the expression of the immune system and nervous system has been a great impetus in contemporatory immunology since it was introduced by Jerne [109, 110]. Mathematical immune models proposed by Richter [111] and Hoffmann [112] which are now called network models, are relevant to this analogy, that is, regarding the immune system as a lymphocyte-antibody network similar to neural network in the nervous system.

5.2.2 Reachability Analysis

The simplified immune models in Section 5.1.2 are studied here from the viewpoint of BLS controllability theory. The foregoingly developed results are used to achieve a more complete analysis of these immune models so as to acquire some immunological implication.

To begin with, it is recalled that the model (5.6) is equivalent to the biocontrol example (2.36) with b=d (Section 2.6.3). This model has also been studied in Section 3.2.3 (Example 3.6), Section 4.1.2 (Figure 4.2) and Section 5.2.1 (time-optimal control). It has been

shown that this BLS model is positively invariant and satisfies the rank assumption. As a consequence of its positive invariance, the model is not completely controllable, while the same conclusion may also be easily verified from the results presented in Section 3.1.3. The uncontrollability is expected for this model in the sense that all state variables must stay positive under any admissible control. Based upon this argument, the complete controllability which often plays no role in biological models with constrained control(s) will be replaced by the consideration of reachability. Formally speaking, a state $\underline{x}_1$ of a control system is said to be reachable from another state $\underline{x}_2$ if there exists an admissible input function that transfers $\underline{x}_2$ into $\underline{x}_1$ in a finite interval of time. The collection of all states that are reachable from a state is referred as the reachable set of that state. Hence, it is of practical interest to characterize the reachable set of the equilibrium state(s), so as to know explicitly the effect of admissible control on the state variables of concern [2]. For an immune model such as (5.6), reachability study makes it possible to predict the dynamics of the immune system after being applied with control p_d. More important, the control p_d is not only a function of free antigen concentration $h(t)$, but can be augmented by nonspecific factors [113].

The theory of BLS reachability is presented in Section 2.4, where the results are obtained from Lie algebraic techniques. By examining the specific structure of the model (5.6), the following result is readily applicable.

Theorem 5.2 [106]

Let $A(t)$, $\underline{b}_i(t)$ and $\underline{c}_i(t)$ be measurable and the components of $\underline{c}_i(t)$ be nonnegative for all $t \geq 0$. Suppose that $\underline{x}$ satisfies the R^n-valued differential equation

$$\dot{\underline{x}}(t) = A(t)\underline{x}(t) + \sum_{i=1}^{m} u_i(t)\underline{b}_i(t)\underline{c}_i^T(t)\underline{x}(t); \quad \underline{x}(0) \in R_+^n$$

$$\alpha_i \leq u_i(t) \leq \beta_i \tag{5.14}$$

and assume for each admissible u_i and all $t>0$ the matrix $A(t) + \sum_{i=1}^{m} u_i(t)\underline{b}_i(t)\underline{c}_i^T(t)$ is nonnegative off the diagonal. Then the reachable set at time t, $\mathcal{R}(t)$, is convex for all positive t. R_+^n denotes the open subset of R^n consisting of those n-tuple having positive entries.

An immediate consequence of the above theorem is

Corollary 5.1

Consider the BLS with scalar input $u(t)$, $0 \leq u(t) \leq 1$

$$\dot{\underline{x}} = A\underline{x} + u(t)B\underline{x}, \quad \underline{x}(0) \in R_+^n \tag{5.15}$$

If the BLS is positively invariant, and Rank $(B)=1$, then $\mathcal{R}(t)$ is convex for all $t \geq 0$.

It can be easily checked that the model (5.6) is positively invariant and rank (B)=1. Therefore, by the above corollary, the immune system represented by (5.6) can be regulated by varying the probability of differentiation p_d within a convex set in R_+^n. This seems obvious that, for example, if the immune system is capable of producing two levels of antibodies, then it is theoretically possible to regulate the antibody production falling between these two levels. Other state variables, ICC and plasma cells can be similarly controlled.

The above analysis confirms the convexity of the reachable set of a simplified immune model, while the problem of finding the reachable set $\mathcal{R}(t)$ remains. This is resolved as below with the aid of material presented in Section 2.4.

It is known from Theorem 2.2 that the reachable set $\mathcal{R}(t)$ for (5.15) can be expressed as $e^{At}\{\exp\mathcal{L}_0\}_G x_0$ where $\{\exp\mathcal{L}_0\}_G$ denotes the Lie group consisting of elements in the form exp M, i.e. $\{\exp\mathcal{L}_0\}_G \triangleq \{\exp M: M\varepsilon\mathcal{L}_0\}_G$. Computation of $\mathcal{R}(t)$ for (5.6) is shown:

$$A = \begin{pmatrix} \alpha - \frac{1}{\tau_1} & 0 & 0 \\ 0 & -\frac{1}{\tau_2} & 0 \\ \alpha' & \alpha'' & 0 \end{pmatrix}, \qquad B = \begin{pmatrix} -\alpha & 0 & 0 \\ 2\alpha & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$[A, B] = \begin{pmatrix} 0 & 0 & 0 \\ -\frac{2\alpha}{\tau_2} - 2\alpha^2 + \frac{2\alpha}{\tau_1} & 0 & 0 \\ -\alpha\alpha' + 2\alpha\alpha'' & 0 & 0 \end{pmatrix}$$

$$[[A, B], B] = -\alpha[A, B]$$

$$[A, [A, B]] = \begin{pmatrix} 0 & 0 & 0 \\ \delta_1 & 0 & 0 \\ \delta_2 & 0 & 0 \end{pmatrix}$$

$$\delta_1 \triangleq 2\alpha(\alpha + \frac{1}{\tau_2} - \frac{1}{\tau_1})^2$$

$$\delta_2 \triangleq \alpha[(\alpha - \frac{1}{\tau_1})(\alpha' - 4\alpha'') - \frac{2\alpha''}{\tau_2}]$$

Hence $\mathcal{L}_0 \triangleq \{ad_A^k B,\ k=0,1,2,\ldots\}_{LA}$ has basis $\{B, C_1, C_2\}$, where

$$C_1 = \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad C_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix}$$

$$\{\exp \mathcal{L}_0\}_G = \left\{ \begin{bmatrix} e^{-\theta_1^\alpha} & 0 & 0 \\ (2+\frac{\theta_2}{\theta_1^\alpha})(1-e^{-\theta_1^\alpha}) & 1 & 0 \\ \frac{\theta_3}{\theta_1^\alpha}(1-e^{-\theta_1^\alpha}) & 0 & 1 \end{bmatrix} \theta_1,\ \theta_2,\ \theta_3 \varepsilon R_+^1 \right\}_G$$

(5.16)

$$e^{At} = \begin{bmatrix} e^{(\alpha - 1/\tau_1)t} & 0 & 0 \\ 0 & e^{-t/\tau_2} & 0 \\ \Delta_1(t) & \Delta_2(t) & 1 \end{bmatrix}, \qquad (5.17)$$

where $\Delta_1(t) \triangleq \alpha' \dfrac{e^{(\alpha - 1/\tau_1)t} - 1}{\alpha - 1/\tau_1}$

$$\Delta_2(t) \triangleq \alpha'' \tau_2 (1 - e^{-t/\tau_2})$$

Consequently, the reachable set at time t is found via (5.16), (5.17) and $\underline{x}_0 = (x_{10}, 0, 0)^T$, that is,

$$\mathcal{R}(t) = \left\{ \begin{bmatrix} e^{(\alpha - \frac{1}{\tau_1})t - \theta_1^\alpha} x_{10} \\ e^{-\frac{t}{\tau_2}}(2+\frac{\theta_2}{\theta_1^\alpha})(1-e^{-\theta_1^\alpha})x_{10} \\ x_{10}(e^{-\theta_1^\alpha}\Delta_3 + \Delta_2(2+\frac{\theta_2}{\theta_1^\alpha}) + \frac{\theta_3}{\theta_1^\alpha}) \end{bmatrix} , \quad \begin{matrix} \theta_1, \theta_2, \theta_3 \varepsilon R_+^1 \\ \Delta_3 = \Delta_1 - \Delta_2(2+ \\ \frac{\theta_2}{\theta_1^\alpha}) - \frac{\theta_3}{\theta_1^\alpha} \end{matrix} \right\}$$

(5.18)

The characterization of the reachable set for the simplified immune model (5.6) is now completed. The same

approach can be extended to models (5.7) and (5.8), though the computation is expected to be more involved.

In addition to providing the insight of the immunological regulation, the task conducted in this section also elicits an interesting issue, namely, the link between $\mathcal{R}(t)$ and the Volterra series representation of BLS. Both results arising from characterizing the reachable set as presented here and from deriving the Volterra series of BLS as presented in Section 3.1.1 lead to the boundedness criteria of BLS. It seems worthwhile to clarify this connection in a future study.

VI. CONCLUSIONS

In this thesis, bilinear systems and their applications in analyzing immune models are studied with the aid of Lie algebraic techniques. The results accomplished are now summarized:

1) Analysis of bilinear systems is presented via Volterra series. Stability criteria are derived for specific classes of BLS. Estimates on the bound of the system output and on the truncation error are developed. The results obtained are used to examine the connection of BLS controllability and stability as well as the structural aspects of BLS.

2) The inverse system design for a special class of bilinear systems with input matrices of rank one is established. It has been shown that for such BLS, their corresponding inverse systems are constant linear systems with nonlinear outputs. Moreover, in view of the inverse system as a state observer, a simplified immune model is used as an example to illustrate the estimates of unmeasurable states and unknown input from the known output data. The implication of this approach in immunology is the estimate of dynamic behavior of ICC and

plasma cells from the antibody production which is assumed as a measurable quantity.

3) A mathematical model of humoral immune response stimulated by T-independent antigens is presented. The model is shown to be acceptable in the sense that with respect to the equilibrium state, it possesses a unique solution, positive invariance and globally asymptotic stability. Results of computer simulations are provided to conclude that the model behavior is consistent with the experimental data available from the literature.

4) Simplified immune models are proposed, which are shown to be BLS with particular structure so that theoretical results developed earlier can be advantageously applied. The reachability analysis and a time-optimal control problem of an approximate immune model are presented and interpreted from the immunological viewpoint.

Possible future study which may extend and take advantage of this research is suggested as the following:

a) It is known (see Figure 4.1) that the humoral immune response is also regulated by thymus-dependent lymphocytes (T cells) and phagocytic cells (macrophages). However, the detailed mechanism of this cellular interaction is not

certain. A mathematical model which takes this into account and contains the B Model as a sub-system, may be invaluable to help unravel many a multi-cellular event in immunology.

b) The inverse system of a BLS is in general highly nonlinear. The current research investigates a specific class of BLS which possess inverse systems of simpler structure. However, for general BLS, much remains to be developed. In theory, the control-theoretic properties of the inverse system of a general BLS need to be exploited. In application, available data from immunological experiments may be used to study more realistically the dynamic behavior of an immune system. The biomedical significance of designing inverse systems is already given in 2).

BIBLIOGRAPHY

1 Sussmann, H. J.,"Semigroup Representations, Bilinear Approximation of Input-Output Maps, and Generalized Inputs," in Mathematical System Theory, (A. Marchesini and S. K. Mitter, Eds.) Springer-Verlag, New York, 1976.

2 Mohler, R. R. and R. E. Rink, "Reachable Zones for Equicontinuous Bilinear Control Processes," Intern. J. Control, Vol. 14, pp. 331-339, 1971.

3 Rink, R. E. and R. R. Mohler, "Completely Controllable Bilinear System," SIAM J. Contr., Vol. 6, No. 3, pp. 477-486, 1968.

4 Bruni, C., G. DiPillo and G. Koch, "Bilinear Systems: An Appealing Class of 'Nearly Linear' Systems in Theory and Applications," IEEE Trans. Automat. Contr., Vol. AC-19, No. 4, pp. 334-348, 1974.

5 Frayman, M., Quadratic Differential Systems: A Study in Nonlinear Systems Theory, Ph.D. Dissertation, Univ. of Maryland, 1974.

6 Frayman, M., "On the Relationship Between Bilinear and Quadratic Systems," IEEE Trans. Automat. Contr., Vol. AC-20, No. 4, pp. 567-568, 1975.

7 Jacobson, D. H., "On the Optimal Control of Systems of Quadratic and Bilinear Differential Equations," Proc. IFAC 6th World Congress, Boston/Cambridge, Mass., 1975.

8 Chen, C. T., Introduction to Linear System Theory, Holt, Rinehart and Winston, Inc., 1970.

9 Wonham, W. M., Linear Multivariable Control: A Geometric Approach, Springer-Verlag, 1974.

10 Hermann, R. and A. J. Krener, "Nonlinear Controllability and Observability," IEEE Trans. Automat. Contr., Vol. Ac-22, No. 5, pp. 728-740, 1977.

11 Mohler, R. R., Bilinear Control Processes with Applications to Engineering, Ecology and Medicine, Academic Press, New York, 1973.

12 Williamson, D., "Observation of Bilinear Systems with Application to Biological Control," Automatica, Vol. 13, pp. 243-254, 1977.

13 Goel, N. S., S. C. Maitra and E. W. Montoll, Nonlinear Models of Interacting Populations, Academic Press, New York, 1972.

14 May, R. M., Stability and Complexity in Model Ecosystems, Princeton University Press, Princeton, N. J., 1973.

15 Goh, B. S., G. Leitmann and T. L. Vincent, "Optimal Control of the Prey-Predator System," Math. Biosciences, Vol. 19, pp. 263-286, 1974.

16 Zager, E. and D. Tabak, "Optimal Control of a Class of Unconstrained Bilinear Systems," Int. J. Syst. Sci., Vol. 7, No. 12, pp. 1349-1354, 1976.

17 Jacobson, D. H., Extensions of Linear-Quadratic Control, Optimization and Matrix Theory, Academic Press, New York, 1977.

18 Pecsvaradi, T., "Optimal Horizontal Guidance Law for Aircraft in the Terminal Area," IEEE Trans. Auto. Contr., Vol, AC-17, No. 6, pp. 763-772, 1972.

19 Arimoto, S. and M. Y. Gaafar, "On the Structure of Optimal Control for Certain Systems Linear in Control," Int. J. Control, Vol. 25, No. 4, pp. 545-555, 1977.

20 Hsu, J. C. and A. U. Meyer, Modern Control Principles and Applications, McGraw Hill, New York, 1968.

21 Mohler, R. R., "Bilinear Systems: Genesis and Development" 12th Allerton Conf. on Circuit and System Theory, Univ. of Ill., Urbana, Champaign, pp. 814-822, 1974.

22 Mayne, D. Q., and R. W. Brockett (eds.), Geometric Methods in System Theory, D. Reidel Publishing Company, Dordrecht, Holland, 1973.

23 Martin C. and R. Hermann (eds.), Proc. of the 1976 Ames Research Center (NASA) Conf. on Geometric Control Theory, Math Sci Press, Brookline, Mass., 1977.

24 Hermann, R., "On the Accessibility Problem in Control Theory," in Internat. Sympos. Nonlinear Differential Equations and Nonlinear Mechanics, Academic Press, New York, pp. 325-332, 1963.

25 Kucera, J., "Solution in Large of Control Problem $\dot{x}=[A(1-u)+Bu]x$," Czecholovak Math. J., Vol. 16, pp. 600-622, 1966.

26 Brockett, R. W., "On the Algebraic Structure of Bilinear Systems," pp. 153-168 in Theory and Application of Variable Structure Systems (R. R. Mohler and A. Ruberti, eds.), Academic Press, New York, 1972.

27 Elliott, D. L. and T. J. Tarn, "Controllability and Observability for Bilinear Systems," SIAM Natl. Meeting, Seattle, WA., 1971.

28 Sussmann, H. J. and V. Jurdjevic, "Controllability of Nonlinear Systems," J. of Differential Equations, Vol. 12, pp. 95-116, 1972.

29 Krener, A. J., "Bilinear and Nonlinear Realizations of Input-Output Maps," SIAM J. Control, Vol. 13, No. 4, pp. 827-834, 1975.

30 Krener, A. J., "The High Order Maximal Principle and its Application to Singular Extremals," SIAM J. Contr., Vol. 15, No. 2, pp. 256-293, 1977.

31 Wei, J. and E. Norman, "On Global Representations of the Solutions of Linear Differential Equations as a Product of Exponentials," Proc. Am. Math. Soc., pp. 327-334, 1964.

32 Wichmann, E. H., "Note on the Algebraic Aspect of the Integration of a System of Ordinary Linear Differential Equations," J. of Math. Physics, Vol. 2, No. 6, pp. 876-880, 1961.

33 Luenberger, D. G., "An Introduction to Observers," IEEE Trans. Automat. Contr., Vol. AC - 16, No. 6, pp. 596-602, 1971.

34 Hara, S. and K. Kuruta, "Minimal Order State Observer for Bilinear Systems," Int. J. Contr., Vol. 24, pp. 705-718, 1976.

35 Gilbert, E. G., "Functional Expansions for the Response of Nonlinear Differential Systems," IEEE Trans. Auto. Contr., Vol. AC-22, pp. 909-921, 1977.

36 Bruni, C., G. DiPillo and G. Koch, "On the Mathematical Models of Bilinear Systems," Ricerche Automat., Vol. 2, No. 1, pp. 11-26, 1971.

37 Brockett, R. W., "Volterra Series and Geometric Control Theory," Automatica, Vol. 12, pp. 167-176, 1976.

38 Boothby, W. M., An Introduction to Differential Manifolds and Riemannian Geometry, Academic Press, New York, 1975.

39 Hirschorn, R., "Topological Semigroups, Sets of Generators, and Controllability," Duke Math. J., Vol. 40, No. 4, pp. 937-947, 1973.

40 Wolovich, W. A., Linear Multivariable Systems, Springer-Verlag, New York, 1974.

41 Freedman, H. I. and J. D. Lawson, "Systems with Constant Eigenvectors with Applications to Exact and Numerical Solutions of Ordinary Differential Equations," Linear Algebra and Applications, Vol. 8, pp. 369-374, 1974.

42 Flanders, H., Differential Forms with Applications to the Physical Sciences, Academic Press, New York, 1963.

43 Apostol, T. M., Mathematical Analysis, 2nd ed., Addison-Wesley, Reading, MA. 1974.

44 Sussmann, H. J., "The Bang-Bang Problem for Certain Control Systems in GL(n,R)," SIAM J. Control, Vol. 10, pp. 470-476, 1972.

45 Wei, K. C. and A. E. Pearson, "On Minimum Energy Control of Commutative Bilinear Systems," pp. 839-846, JACC, San Francisco, 1977.

46 Bellman, R., Introduction to Matrix Analysis, 2nd ed., McGraw-Hill, New York, 1970.

47 Sandberg, I. W., "On the Mathematical Foundations of Compartmental Analysis in Biology, Medicine, and Ecology," IEEE Trans. on Circuits and Systems, Vol. CAS-25, No. 5, pp. 273-279, 1978.

48 Belinfante, J. and B. Kolman, Lie Groups and Lie Algebras, SIAM, Philadelphia, 1972.

49 Gilmore, R., Lie Groups, Lie Algebras, and Some of Their Applications, John Wiley and Sons, New York, 1974.

50 Ruberti, A., A. Isidori and P. d'Alessandro, Theory of Bilinear Dynamical Systems, Springer-Verlag, New York, 1972.

51 Karanam, V. R., Functional Expansions in Bilinear System Analysis, Ph.D. Dissertation, Oregon State University, 1978.

52 Bruni, C., M. A. Giovenco, G. Koch and R. Strom, "The Immune Response as a Variable Structure System," in Variable Structure Systems with Application to Economics and Biology, (A. Ruberti and R. R. Mohler, eds.), Springer-Verlag, New York, pp. 244-264, 1975.

53 Silverman, L. M., and B. D. O. Anderson, "Controllability, Observability and Stability of Linear Systems," SIAM J. Control, Vol. 6, No. 1, pp. 121-129, 1968.

54 Rao, K. V. and R. R. Mohler, "On the Synthesis of Volterra Kernels of Bilinear Systems," Auto. Control Theory and Appl., Vol. 3, pp. 44-46, 1975.

55 Goldberg, R. R., Methods of Real Analysis, 2nd edition, John Wiley and Sons, Inc., New York, 1976.

56 Jurdjevic, V. and J. P. Quinn, "Controllability and Stability," J. of Differential Equations, Vol. 28, pp. 381-389, 1978.

57 Slemrod, M., "Stabilization of Bilinear Control Systems with Applications to Nonconservative Problems in Elasticity," SIAM J. Control and Optimization, Vol. 16, No. 1, pp. 131-141, 1978.

58 Lee, E. B., and L. Markus, Foundations of Optimal Control Theory, John Wiley and Sons, Inc., New York, 1967.

59 Crouch, P. E., Dynamic Realizations of Finite Volterra Series, Ph.D. Thesis, Harvard University, 1977.

60 Harper, T. R. and W. J. Rugh, "Structural Features of Factorable Volterra Systems," IEEE Trans. Auto. Contr., Vol. AC-21, pp. 822-832, 1976.

61 Osburn, J. O., "Biological Modeling: A Program to Calculate the Input from Observations on the Output," Proc. Iowa Acad. Sci., Vol. 80, No. 2, pp. 87-90, 1973.

62 Fish, B. R., "Applications of an Analog Computer to Analysis of Distribution and Excretion Data," Health Physics, Vol. 1, pp. 276-281, 1958.

63 Waltman, P. and E. Butz, "A Threshold Model of Antigen-Antibody Dynamics," J. Theor. Biol., Vol. 65, pp. 499-512, 1977.

64 DeLisi, C., "Some Mathematical Problems in the Initiation and Regulation of the Immune Response," Math. Biosciences, Vol. 35, pp. 1-26, 1977.

65 Orner, P. A., "Construction of Inverse Sytems," IEEE Trans. Auto. Contr., Vol. AC-17, pp. 151-153, 1972.

66 Brockett, R. W., "Poles, Zeros, and Feedback: State Space Interpretation," IEEE Trans. Auto. Contr., Vol. AC-10, pp. 129-135, 1965.

67 Hirschorn, R. M., "Invertibility of Control Sytems on Lie Groups," SIAM J. Control and Optimization, Vol. 15, No. 6, pp. 1034-1049, 1977.

68 Shilov, G. E., Linear Algebra, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1971.

69 Goka, T., T. J. Tarn and J. Zaborszky, "On the Controllability of a Class of Discrete Bilinear Systems," Automatica, Vol. 9, pp. 615-622, 1973.

70 Swamy, K. N. and T. J. Tarn, "Optimal Control of Discrete Bilinear Systems," in Geometric Methods in System Theory, (D. Q. Mayne, R. W. Brockett, eds.), D. Reidel Publishing Co., Dordrecht, pp. 275-284, 1973.

71 Evans, M. E. and D. N. P. Murphy, "Controllability of Discrete Time Inhomogeneous Bilinear Systems," Automatica, Vol. 14, pp. 147-151, 1978.

72 Smith, J. M., Mathematical Ideas in Biology, Cambridge University Press, London, 1968.

73 Roitt, I. M., Essential Immunology, 2nd ed. Blackwell Scientific Publ., Oxford, 1974.

74 Cunningham, A. J., Understanding Immunology, Academic Press, New York, 1978.

75 Eisen, H. N., Immunology: An Introduction to Molecular and Cellular Principles of the Immune Response, Harper and Row, New York, 1974.

76 Burnet, F. M., Immunology, Aging, and Cancer — Medical Aspects of Mutation and Selection, W. H. Freeman and Company, San Francisco, 1976.

77 Bell, G. I., "Mathematical Model of Clonal Selection and Antibody Production," in three parts, J. Theor. Biol., 29 (1970), 191-232; 33 (1971), 339-378; 33 (1971), 379-398.

78 Merrill, S. J., "Mathematical Models of Humoral Immune Response," Technical Report IM76-1, Dept. of Math., Univ. of Iowa, Jan. 1976.

79 Bell, G. I., A. S. Perelson, and G. H. Pimbley, Jr., (editors), Theoretical Immunology, Marcel Dekker, New York, 1978.

80 Merrill, S. J., "A Geometrical Study of B-Cell Stimulation and Humoral Immune Response," pp. 611-630 in Nonlinear Systems and Applications, edited by V. Lakshmikantham, Academic Press, New York, 1977.

81 Perelson, A. S., M. Mirmirani, and G. F. Oster, "Optimal Strategies in Immunology. I. B-cell Differentiation and Proliferation," J. Math. Biol., 3: 325-367, 1976.

82 Mohler, R. R., C. F. Barton and C. S. Hsu, "T and B Cells in the Immune System," pp. 415-435 in Theoretical Immunology, op. cit. 1978.

83 Zeeman, E. C., "Differential Equations for the Heartbeat and Nerve Impulse," pp. 683-741 in Dynamical Sytems, M. M. Peixoto, Ed., Academic Press, 1973.

84 Bruni, C., M. A. Giovenco, G. Koch, and R. Strom, "A Dynamical Model of Humoral Immune Response," Math. Biosciences, Vol. 27, pp. 191-211, 1975.

85 Braun, A. C., The Biology of Cancer, Addison-Wesley Reading, Massachusetts, 1974.

86 Jerne, N. K., "Summary: waiting for the end", Cold Spring Harbor Symp. Quant. Biol. Vol. 32, pp. 591-603, 1967.

87 Weir, D. M., Handbook of Experimental Immunology, 2nd ed. Blackwell Scientific Publ., Oxford, 1973.

88 Greaves, M. F., J. Owen, and M. Raff, T and B Lymphocytes: Their Origins, Properties and Roles in Immune Responses, North Holland, Amsterdam, 1974.

89 Hay, J. B., R. N. P. Cahill and Z. Trnka, "The Kinetics of Antigen-Reactive Cells during Lymphocyte Recruitment," Cellular Immunology, Vol. 10, pp. 145-153, 1974.

90 Melchers, F. and J. Anderson, "Proliferation and Maturation of Bone-marrow Derived Lymphocytes," in Cellular Selection and Regulation in the Immune Response, edited by G. M. Edelman, Raven Press, New York, 1974.

91 Garfinkel, D., C. B. Marbach, and N. Z. Shapiro, "Stiff Differential Equations," pp. 525-542, in Ann. Rev. Biophys. Bioeng., Vol. 6, 1977.

92 DVOGER Subroutine in the International Mathematical and Statistical Library, available from IMSL cooperation.

93 Werblin, T. P., Y. T. Kim, F. Quagliata and G. W. Siskind, "Changes in Heterogeneity of Antibody Affinity during the Course of the Immune Response," Immunology, Vol. 24, pp. 477-492, 1973.

94 Coddington, E. A. and N. Levinson, Theory of Ordinary Differential Equations, McGraw-Hill, New York, 1955.

95 Ladas, G. E. and V. Lakshmikantham, Differential Equations in Abstract Spaces, Academic Press, 1972.

96 Takeuchi, Y., N. Adachi, and H. Tokumaru, "The Stability of Generalized Volterra Equations," in JMAA, Vol. 62, No. 3, pp. 453-473, 1978.

97 Abramoff, P. and M. F. La Via, Biology of the Immune Response, McGraw Hill Co., New York, 1970.

98 G. I. Bell, "Predator-Prey Equations Simulating an Immune Response," Math. Biosciences, Vol. 16, pp. 291-314, 1973.

99 Pimbley, Jr. G. H., "Bifurcation Behavior of Periodic Solutions for an Immune Response Problem," ARMA, Vol. 64, No. 2, pp. 169-192, 1977.

100 Hirsch, M. W. and S. Smale, Differential Equations, Dynamical Systems, and Linear Algebra, Academic Press, New York, 1974.

101 Rosen, R., "On Rate-sensitive Chemoreceptor Systems and the Origin of the Immune Response," J. Theor. Biol., Vol. 62, pp. 429-445, 1976.

102 Bertuzzi, A., C. Bruni, A. Gandolfi, and G. Koch, "Maximum Likelihood Identification of an Immune Response Model," in Working Conference on Modeling and Optimization of Complex Systems, IFIP-TC, Novosibirsk, 1978.

103 Manning, J. T., "The Optimization of Immune System 'Decision'," J. Theor. Biol., Vol. 52, pp. 219-222, 1975.

104 Perelson, A. S., "The IgM-IgG Switch Looked at From a Control Theoretic Viewpoint," Proc. of IFIP Optimization Conference in Wurzburg, Germany, September, 1977.

105 Goldstein, B., "Some Mathematical Models in Immunology, II," pp, 25-56, in Lectures on Mathematics in the Life Sciences, Vol. 9, American Math. Society, 1977.

106 Brockett, R. W., "On the Reachable Set for Bilinear Systems," in Variable Structure Systems (Ruberti and Mohler, eds.), pp. 54-63, Srpinger-Verlag, 1975.

107 Sage, A. P. and C. C. White III, Optimum Systems Control, 2nd edition, Prentice-Hall, Englewood Cliffs, New Jersey, 1977.

108 Rosen, R., Dynamic System Theory in Biology: Stability Theory and Its Applications, Wiley-Interscience, 1970.

109 Jerne, N. K., "The Immune System," Scientific American, 229/1: pp. 52-60, 1973.

110 Jerne, N. K., "Toward a Network Theory of the Immune System," Ann. Immunol. Inst. Pasteur, 125c; 373-389, 1974.

111 Richter, P. H., "A Network Theory of the Immune System," Eur. J. Immunol., Vol. 5, pp. 350-354, 1975.

112 Hoffmann, G. W., "A Theory of Regulation and Self-nonself Discrimination in an Immune Network," Eur. J. Immunol., Vol. 5, pp. 638-647, 1975.

113 Fahey, J. L., "Control of Proliferation in the Immune System," in Control of Proliferation in Animal Cells, B. Clarkson and R. Baserga (editors), pp. 379-392, Cold Spring Harbor Lab., New York, 1974.

APPENDIX A

APPENDIX A

Some Definitions and Facts on Lie Algebra

Basic facts on Lie algebra which are needed in this thesis are summarized here. Details can be found in References 1 and 2. Throughout this appendix, only finite dimensional (matrix) Lie algebras over the field R of real numbers are considered.

Part A: Definitions

1. Let $\mathcal{L}$ be a linear space over a field R. Suppose that $\mathcal{L}$ admits an operation denoted by $[x, y]$, which satisfies the following conditions

   a) bilinearity: $[\lambda_1 x_1+\lambda_2 x_2, y] = \lambda_1[x_1, y]+ \lambda_2[x_2, y] \forall x,y \in \mathcal{L}$

   b) antisymmetry: $[x, y]= -[y, x] \forall x,y \in \mathcal{L}$

   c) the Jacobi identity:

   $$[[x, y], z]+[[y, z], x]+[[z, x], y]= 0 \quad \forall x,y,z \in \mathcal{L}$$

   then $\mathcal{L}$ is called a Lie algebra.

2. A Lie subalgebra I is an ideal of $\mathcal{L}$ if $[x, y] \in I$ whenever $x \in \mathcal{L}$ and $y \in I$.

3. The derived series of $\mathcal{L}$ is the decreasing sequence of ideals $D^0\mathcal{L}, D^1\mathcal{L}, D^2\mathcal{L}, \cdots$ of $\mathcal{L}$ defined inductively by $D^0\mathcal{L}=\mathcal{L}$, $D^{p+1}\mathcal{L} =[D^p\mathcal{L}, D^p\mathcal{L}]$

4. The descending central series of $\mathcal{L}$ is the decreasing sequence of ideals $C^0\mathcal{L}$, $C^1\mathcal{L}, \cdots$ of $\mathcal{L}$ defined inductively by $C^0\mathcal{L}=\mathcal{L}$, $C^{p+1}\mathcal{L} = [\mathcal{L}, C^p\mathcal{L}]$

5. The Lie algebra $\mathcal{L}$ is said to be
abelian (commutative) if $D^1\mathcal{L} = 0$
nilpotent if $C^p\mathcal{L} = 0$ for some p
solvable if $D^p\mathcal{L} = 0$ for some p
simple if it contains no nontrivial ideals
semisimple if it contains no nontrivial abelian ideals.

6. The <u>radical</u> R of a Lie algebra $\mathcal{L}$ is the unique maximal solvable ideal $\mathcal{L}$ (i.e. R is the sum of the solvable ideals of $\mathcal{L}$)

7. The <u>center</u> of a Lie algebra $\mathcal{L}$ is the set of all elements $x\varepsilon\mathcal{L}$ such that $[x, y] = 0 \forall y\varepsilon\mathcal{L}$

8. The <u>adjoint operator</u> on $\mathcal{L}$ is defined by $ad_x^0 y=y$, $ad_x^1 y =[x, y]$, $ad_x^{i+1} y=[x, ad_x^i y]$ where $x,y\varepsilon\mathcal{L}$

9. A group G is said to act <u>transitively</u> on a linear space X if every point of X can be carried into every other point of X by some element in G. i.e. for every pair of points x, y in X, there exists $T\varepsilon G$ such that $Tx = y$.

Part B: Basic Facts

1. $$\begin{array}{ccccccccc} C^1 & \supset & C^2 & \supset & C^3 & \supset \cdots & \supset C^n & \supset \cdots \\ \| & & \cup & & \cup & & \cup & \\ D^1 & \supset & D^2 & \supset & D^3 & \supset \cdots & \supset D^n & \supset \cdots \end{array}$$

   Hence abelian (commutative) $\Rightarrow$ nilpotent $\Rightarrow$ solvable, but none of the reverse implications holds in general.

2. If $\mathcal{L}$ is solvable, then the subalgebra $[\mathcal{L},\mathcal{L}]$ is nilpotent.

3. Engel's Theorem: A Lie algebra is nilpotent iff the $\mathrm{ad}x$ is nilpotent $\forall x \in \mathcal{L}$ (i.e. $(\mathrm{ad}x)^n = 0$ for some n)

4. Levy-Malcev Theorem: Any Lie algebra can be decomposed as the direct sum, in the sense of vector spaces, of its radical R and a semi-simple subalgebra S: $\mathcal{L} = R \oplus S$; Any semisimple Lie algebra S can be written as a direct sum of simple ideals: $S = S_1 \oplus S_2 \oplus \cdots \oplus S_k$ where the elements of distinct S_j must commute.

   Hence $\mathcal{L} = R \oplus (S_1 \oplus S_2 \oplus \cdots \oplus S_k)$

5. A matrix Lie algebra $\mathcal{L}$ is solvable, iff there exists a (possibly complex-valued) nonsingular matrix P such that PxP^{-1} is in upper triangular form for all $x \in \mathcal{L}$.

6. Let $\mathcal{L}$ be a solvable Lie algebra, acting on the

vector space V (both over C); then there exists a simultaneous eigenvector for all x of $\mathcal{L}$.

7. A matrix Lie algebra $\mathcal{L}$ is nilpotent iff there exists a (possibly complex-valued) nonsingular matrix P such that for all $x \in \mathcal{L}$, PxP^{-1} has the nilpotent canonical form. i.e. $PxP^{-1} = \text{diag}\,(\Phi_1(x), \Phi_2(x), \cdots)$ where each $\Phi_i(x)$ is a matrix of the form

$$\begin{pmatrix} \phi_1(x) & & * \\ & \phi_2(x) & \\ & & \cdot \\ 0 & & \phi_i(x) \end{pmatrix}$$

and ϕ_i's are linear mappings: $\phi_k : \mathcal{L} \to \mathcal{L}$, $\phi_k([\mathcal{L}, \mathcal{L}]) = \{0\}$.

References:

(1) Sagle, A. A. and R. E. Walde, Introduction to Lie Groups and Lie Algebras, Academic Press, New York, 1973.

(2) Samelson, H, Notes on Lie Algebra, Van Nostrand Reinhold Company, New York, 1969.