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R. R. Mohler

A compartmental model of the immune system is simulated. Chapter I discusses the importance of such a model, reviews past immune system models, and summaries the immunological theory the model is based upon. In Chapter II, the compartmental representation of the immune system is developed from immunological and physiological theory. A simplified system of three compartments, the blood, the spleen, and the lymph and lymph nodes is derived. The mathematical model is derived in Chapter III based upon the simplified compartmental system, and immune system kinetics. The simulation results are compared to literature data in Chapter IV, and it is concluded that modeling and simulation of the immune system may result in significant advances in immunological theory.

Compartmental Analysis of the Immune System

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COMPARTMENTAL ANALYSIS OF THE IMMUNE SYSTEM

I. INTRODUCTION

The purpose of this study is to develop a model which, when simulated, mimics the behavior of the immune system. A model is defined by Calligan [1, p. 17] to be a comprehensive mathematical statement which describes the system elements and the theory of their interactions. Modeling and simulation are effective tools in studying a system, because they are easily manipulated and are not dependent on real time. For example, a computer can simulate hundreds of years in a few seconds. As a result, simulation is less costly than experimentation with the system. The mouse is one of the most studied animals in immunology. Therefore, the mouse immune system will be modeled here. Experimentation suggests that the same mechanisms and interactions are involved in the mouse and human immune systems, so parameter values involving the circulation of cells throughout the body, cellular division rates, and cell life times determine whether the model represents the mouse or human system. These similarities allow simulation results for the mouse model to be generalized to the human system. Modeling and simulation of the immune system may help resolve conflicting hypotheses, lead to more effective immunotherapy, determine the most important variables of the system, and result in a more systematic

approach to experimentation.

The model presented here is a compartmental model. This approach was chosen, because the contained nature of the immune system and the individual roles of its tissues and fluids form a natural compartmental system. The multicompartmental model simulated in this study is an improvement over previous models, discussed below, because it includes more detail of the immune system, as well as accommodating the restrictions imposed by experimental methods. The data obtained for an immune response are usually measured in the organs and fluids which are defined as compartments in the simplified model considered here. The choice of compartments is important because the data from any one component of the immune system does not represent the response of the whole system. Other models have considered the immune system to be a homogenous unit, or in other words a single compartment.

Previous Work

The first mathematical model of the immune response was presented by Hege and Cole [2]. Many papers followed, each considering something new. Jilek [3, 4] derived a probability model for cellular contact with antigens using a Poisson distribution and Monte Carlo simulation. Bruni, et al. [5] formulated the probabilities for cell stimulation and differentiation during the immune response.

Perelson, et al. [6] derived a model for B cell differentiation and proliferation using the optimal strategy of bang-bang control. Mohler, et al. [7, 8] considered T cell kinetics in the immune response. Bell [9, 10, 11, 12] included heterogenity of antibodies, affinity distributions, and the secondary response. Bell and DeLisi [13] considered nonspecific antigen binding and competition.

Models for individual organs of the immune system have also been published. Lajtha, et al. [14] derived a model for bone marrow stem cell kinetics. Lumb [15] modeled the kinetics of the development and later degeneration of the thymus. Prothero and Tyler [16] published a compartmental model of thymocyte proliferation with the proliferation represented by a feedback amplifier. Hammond [17] derived a compartmental model of lymphocyte circulation in the spleen using the marginal zone, red pulp, and white pulp as compartments.

Bystryn et al. have discussed compartmentation in the immune system, but have not derived a model [18].

Immunological Theory

A system is defined by Calligan [1, p. 16] to be a collection of interacting components, elements, or entities having a unifying purpose. The immune system consists of the cells and the tissues involved in the elimination of antigen from the body. An antigen is any substance which

the body recognizes as foreign. This ability to distinguish the antigen from the environment is the foundation of the immune system.

The bone marrow is the source of all the cells involved in the immune response. The stem cells released by the bone marrow differentiate into the many cell types found in the blood. One of these are the lymphocytes, which are white blood cells. There are two classes of lymphocytes, bursa derived cells (B cells) and thymus derived cells (T cells). These cells are so named because of the two organs, the bursa of Fabricus, and the thymus which respectively regulate their development. The bursa of Fabricus is present in avians, but the equivalent has not yet been identified in mammals. Macrophages function in the immune response as helper cells and phagocytes. Phagocytes are cells which ingest and destroy particular substances. These cells, their precursors, antigen, and antibody, the molecules formed to neutralize antigen, are distributed throughout the body by the blood and lymph.

Cells involved in the immune response are in a constant state of flux, recirculating throughout the body, primarily in the spleen, lymph nodes, and gut associated lymphoid tissue, by set pathways. These fluxes are called cellular migration streams. The concept of cellular migration streams was first formulated by Yoffey, et al. [19] and was originally applied to lymphocytes. There are

two types of cellular migration streams, haemopoietic and immunological. Haemopoietic streams consist of stem cells, whereas immunological streams consist of differentiated cells.

Antigen can initiate two different but closely associated immunological reactions, the humoral immune response or cell-mediated immunity. The humoral immune response stimulates B cells which results in the production of antibodies. Cell-mediated immunity results in the production of T cells which have antibody-like molecules on their surface.

Antibody is composed of proteins called immunoglobulins, which are subdivided into classes on the basis of their molecular structure. In the mouse for example, the major classes are IgG, IgM, and IgA, where Ig is an abbreviation for immunoglobulin [20]. Man also has significant amounts of IgD, and IgE. IgG and IgM are the major immunoglobulins produced against antigen. The IgA system is a local immune system of the gut associated lymphoid tissue. The functions of IgD have not been established. IgE is involved in the allergic response. Gamma globulin, IgG, is the largest component of the several globulin classes.

The clonal selection theory of Burnet [21] is widely regarded as a working model for antibody synthesis. This theory proposes that the small lymphocytes are committed

genetically to react with a specific antigen. The stimulated cells differentiate and divide to form a clone of cells producing antibodies against the same antigen which the parent cell recognized.

The induction of humoral antibody formation by many antigens requires specific interaction of B cells with T cells and macrophages, with the T cells regulating the proliferation and differentiation of B cells into antibody producing cells (plasma cells), and memory cells. Macrophages process the antigen and then present it to the lymphocytes. A review of the many proposed modes of B cell, T cell, macrophage, and antigen interactions is given in Greaves et al.[23]. Some of the B cell progeny revert to small lymphocytes and become memory cells. These relationships are shown in Figure 1. Memory cells have a long life and as a result are ready to quickly initiate the production of antibody if the same antigen which triggered the reaction reappears later. The larger and more rapid response to a second exposure to an antigen is called the secondary response.

Low and high zone tolerance are phenomena in which antigen levels above or below certain limits do not initiate an immune response. These limits vary with the antigen. Tolerance affects both the cellular and humoral response mechanisms. When low levels of antigen are injected, T cells become tolerant. At high antigen doses, both B and

and T cells are unresponsive [22, p. 19]. Tolerance continues as long as the antigen exceeds the low or high zone limits thereby blocking the immune response [23, p. 188].

Antigens are neutralized when antibody reacts with antigen to form an antigen-antibody complex. Antibodies react only against the antigen which triggered the immune response. The sites on the antigen surface which stimulate antibody production are called antigenic determinants, and become bound in the antigen-antibody complex preventing further stimulation. Macrophages destroy the antigen-antibody complex by phagocytosis.

Immunology, physiology, compartmental analysis, and experimental data are used to derive the immune system model presented in this thesis. The second chapter develops the immune system as a compartmental system. The mathematical model of the compartmental system is derived in chapter three, then simulation of the model is described in chapter four.

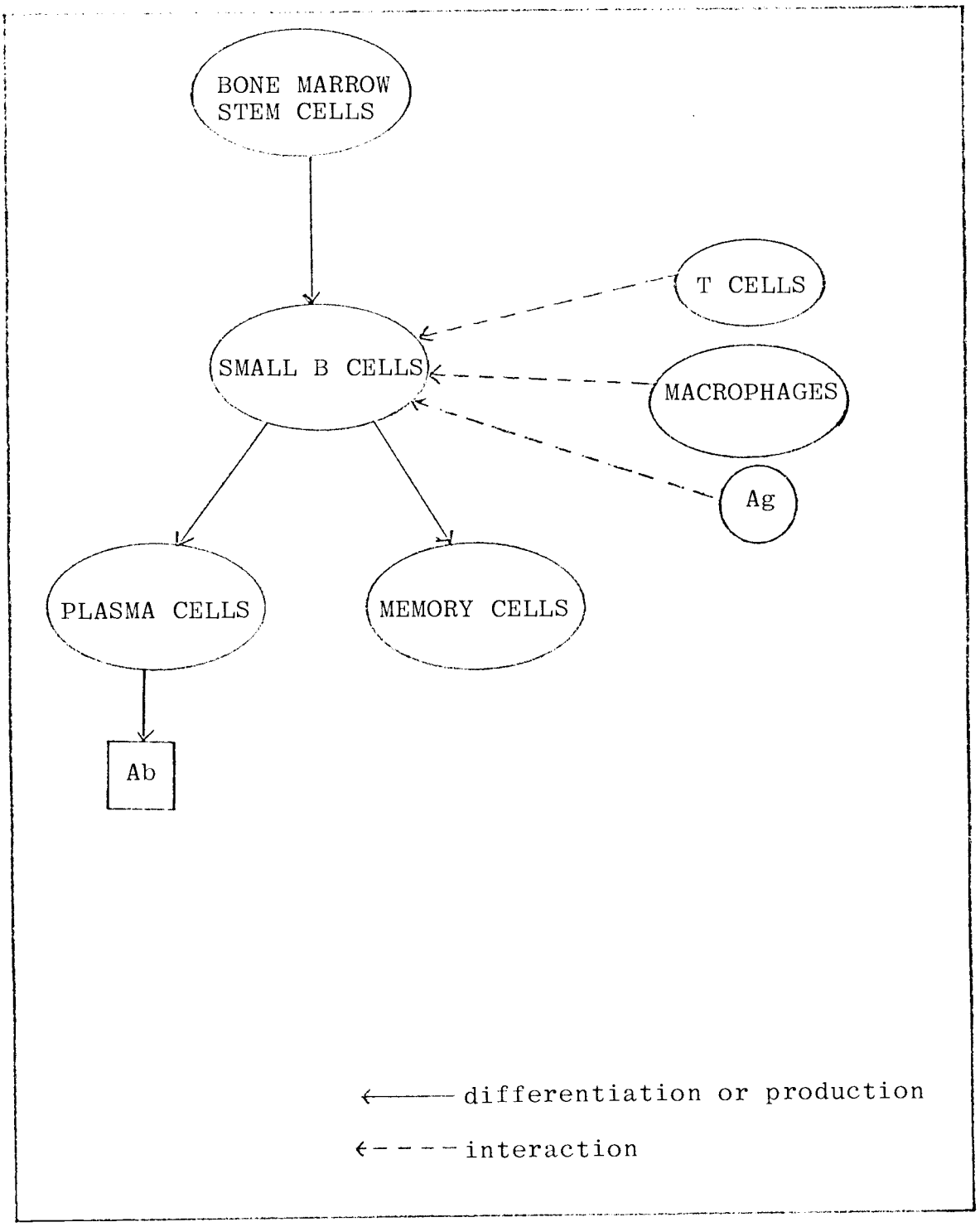

Figure 1. Illustration of humoral immune reaction

II. COMPARTMENTAL SYSTEM

A compartment can be a grouping of anything which is homogenous and has distinct kinetics. Compartments can represent such diverse things as age, temperature, volume, population, and mass. In this study, populations of cells and molecules are defined as compartments. A compartment intereacts with other compartments or the environment by exchanging material. A group of compartments which are interconnected comprise a compartmental system. The mathematical study of these interactions is called compartmental analysis, for which Jacquez [24] is an excellent reference.

Compartmental analysis has become an important investigative tool since the introduction of radioactive tracers. They are widely used to determine the parameters, compartmental size, and order of compartmental systems. Dyes predate isotopes in circulation studies, but radioactive tracers have made it possible to study other systems such as transmembrane flow rates, electrolyte kinetics, blood-tissue perfusion rates, and hemopoiesis [25]. The systems studies with the aid of isotopes must be in steady state. The tracer added to a compartment must be a negligible amount, and it must mix rapidly and completely with the unlabeled material. Sheppard [26] gives a thorough discussion of radioactive tracer methodology.

Compartmental Representation of the Immune System

The functions of the immune system are affected throughout the body by various tissues and fluids. Body organs and fluids can be considered to be compartments, because they have individual functions, composition, and kinetics. Therefore, the tissues, and fluids involved in the immune response will be defined as compartments. They are:

1. the bone marrow, which is the source of all precursor cells,
2. the thymus, where T cells mature,
3. the spleen, one place where antigen and antibody react,
4. the lymph nodes, another site of the antigen-antibody reactions,
5. the gut associated lymphoid tissue, GALT, which consists of the tonsils, appendix, and Peyer's patches. These tissues are all part of the gut epithelium, therefore they will be considered to be one compartment. The antigen-antibody reaction also occurs in these tissues,
6. the blood which transports the cells and molecules of the immune system between compartments as well as being a holding area for them, and
7. the lymph which is also a transport mechanism

and holding area for the system's cells and molecules.

Within each of these physiologically separate regions various stages of the immune response occur. The immune response involves various cells and molecules, so all of the regions defined as compartments do not have a homogenous population and must be subdivided. Each previously defined compartment will be divided into new compartments for each cell and molecule type involved in the immune response that it contains. The cells and molecules involved in the immune response are:

1. the T cells, effectors of cell-mediated immunity and helper cells in the humoral immune response,
2. the B cells, which differentiate into plasma cells,
3. the plasma cells, producers of antibody,
4. monocytes, the precursors of macrophages,
5. macrophages, which contribute in the humoral immune response as well as phagocytize antigen and the antigen-antibody complex,
6. antigen, the foreign substance which triggers the immune response,
7. antibody, the molecule which is produced to neutralize antigen, and
8. the antigen-antibody complex, the result of

antibody neutralizing antigen. It is the formation of this complex which initiates allergic symptons, transplant rejection, and protection against various diseases.

The compartmental system defined above is best described by schematic diagrams showing the movement of cells and molecules through the tissues and fluids. When no immune reaction is occurring, the body's kinetics are at their normal levels, so there are no net changes in cell or molecule populations. The symbolic representation of the compartmental immune system is shown in Figures 2 through 9.

Figure 2 is similar to that formulated by Yoeffey [27, p. 42].

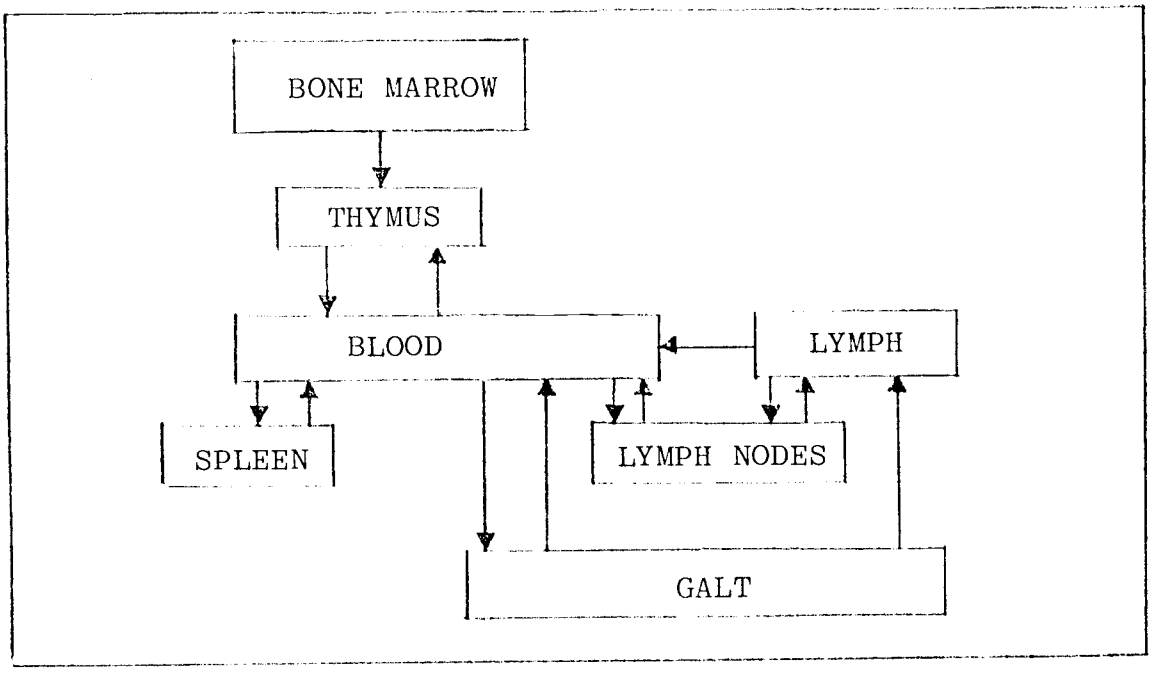

Figure 2. Circulation of T cells among the T cell compartments contained in the tissues and fluids

Gowans [27] was the first to establish that there is a large pool of recirculating lymphocytes. The bone marrow is the source of stem cells which migrate to the thymus where they mature into T cells. The thymus releases these cells into the blood. Lymphocytes enter and leave the spleen by the blood. Lymphocytes can enter or leave the lymph nodes via the lymph or blood. Those leaving by way of the lymph enter the blood from the lymphatic ducts, primarily the thoracic duct. The lymph nodes found throughout the body are connected by lymphatic vessels. Lymphocytes recirculate thru GALT as in the lymph nodes [27, p. 591]. A more detailed discussion of these cellular migration streams is found in Yoffey and Courtice [27].

B cells directly enter the blood from the bone marrow. They recirculate through the blood, spleen, lymph nodes, GALT, and lymph as shown in Figure 3.

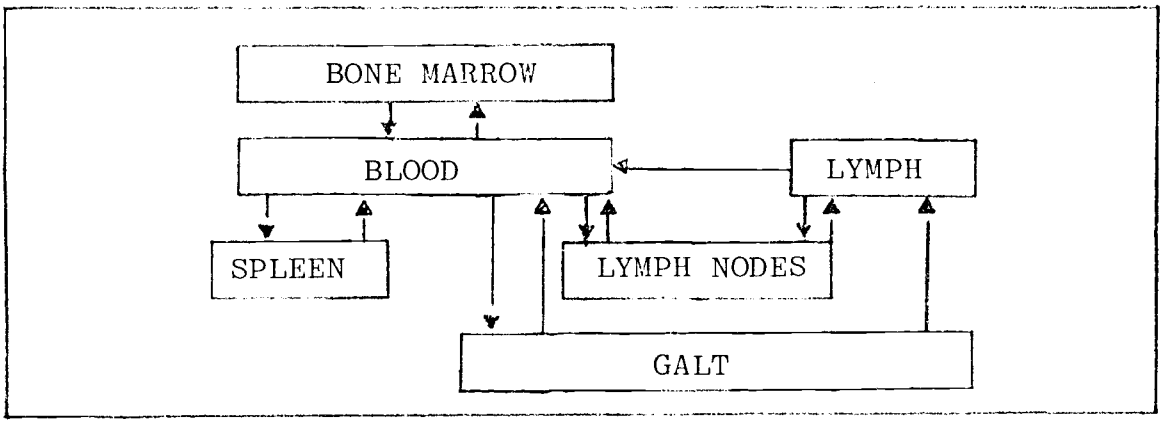

Figure 3. Circulation of B cells among the B cell compartments contained in the tissues and fluids

B and T cell migration in these compartments vary only in kinetics and the portions of the lymphoid tissue involved [23, p. 59]. The spleen, the lymph nodes, and the GALT have separate areas of circulation for B and T cells.

Monocytes originate in the bone marrow, and are transported throughout the body by blood and lymph as shown in Figure 4. Monocytes have a short circulation time before they become sequestered in the tissues [30, p. 119].

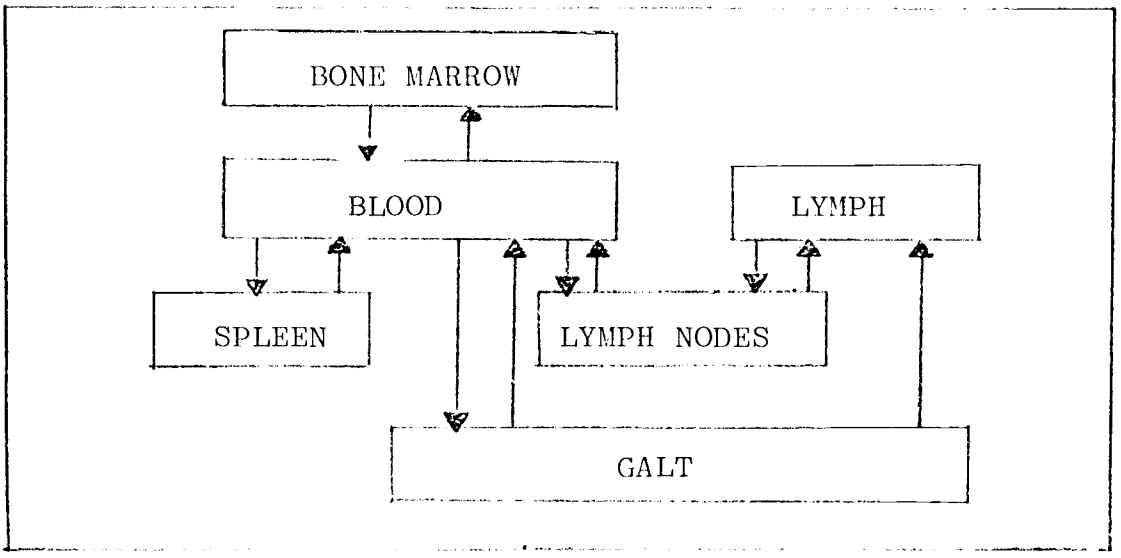

Figure 4. Circulation of monocytes among the monocyte compartments contained in the tissues and fluids

Macrophages are produced by monocyte differentiation or by division of pre-existing macrophages [29, p. 116]. There is some evidence that lymphocytes may differentiate into macrophage-like cells [27, p. 701]. The mechanism controlling macrophage production is not known. Almost no macrophages are found in the blood [29, p. 119], so

therefore it is assumed that macrophages arise in the tissues and do not circulate as shown in Figure 5.

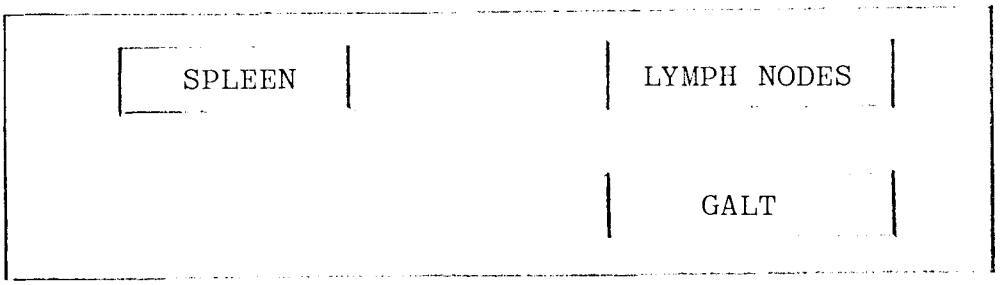

Figure 5. Tissues containing macrophage compartments

Plasma cells are mainly concentrated in the spleen, lymph nodes, and GALT as shown in Figure 6 [29, p. 151].

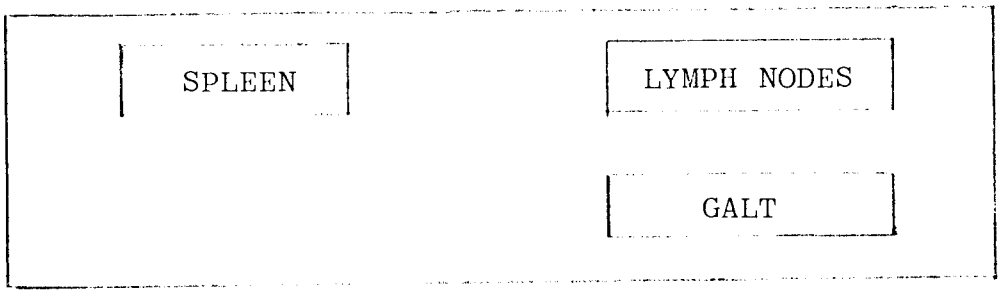

Figure 6. Tissues containing plasma cell compartments

Mature plasma cells do not circulate, while immature plasma cells do enter the blood stream for a short time before becoming trapped in the tissues [27, p. 706]. Immature plasma cell is an arbitrary designation for the transitional stage between the small B lymphocyte and the fully differentiated plasma cell [31, p. 470]. The model derived from this compartmental system assumes that all plasma cells are capable of producing antibody, i.e. are mature cells, so it will be assumed that plasma cells do not

circulate.

Antigen becomes trapped in the spleen, lymph nodes, and GALT after a very short circulation time. For example, the highest amount of sheep red blood cells, the antigen used in this study, in mouse tissues are observed at four hours. This is a short time compared to the nine days required for the maximum antibody production to be reached [32]. The reticular meshwork of these tissues act as a mechanical filter to trap the antigen from the blood or lymph [29, p. 49]. This short time delay will be disregarded, so antigen, Figure 7, is not shown as a recirculating entity.

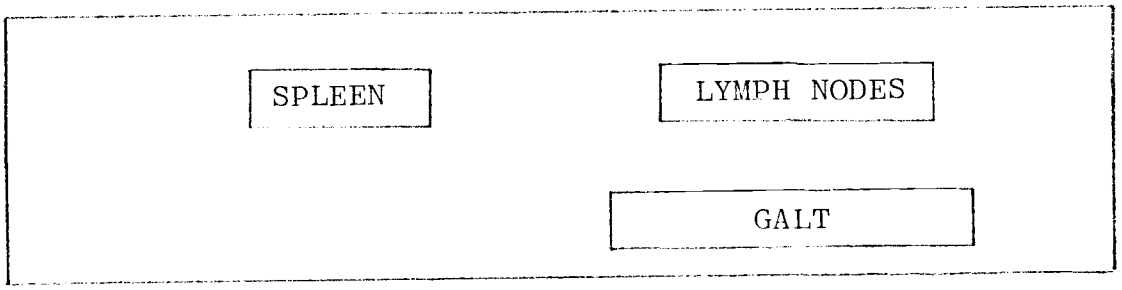

Figure 7. Tissues containing antigen compartments

Antibody is produced by the plasma cells in the spleen, lymph nodes, and GALT. Antibody molecules are too large to pass through the capillary pores to enter the blood directly from the tissues, so they leave through the lymphatic channels which later drain into the blood. Antibody recirculates by leaking out of the blood into the tissues [31, p. 483]. This is shown in Figure 8.

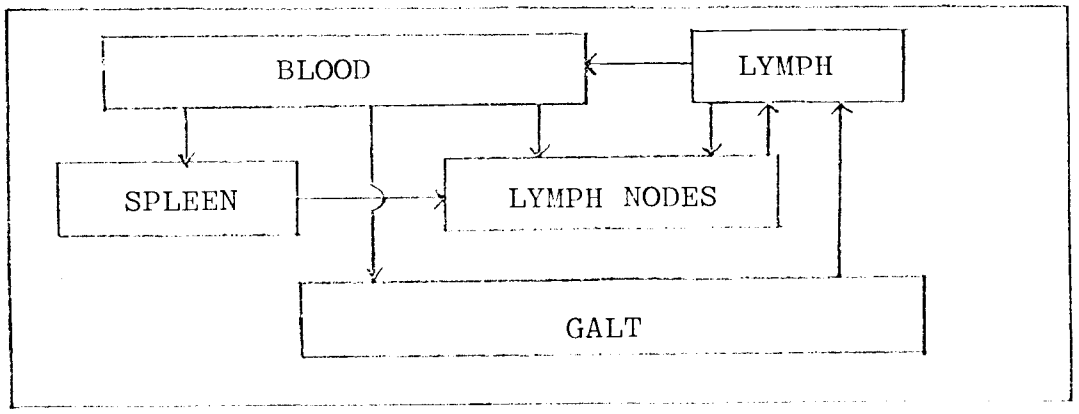

Figure 8. Circulation of antibody among the antibody compartments contained in the tissues and fluids.

The antigen-antibody complex is located in the spleen, lymph nodes, and GALT, as shown in Figure 9, and does not circulate. Antibody reacts with the trapped antigen to form this complex. Macrophages then destroy the complex.

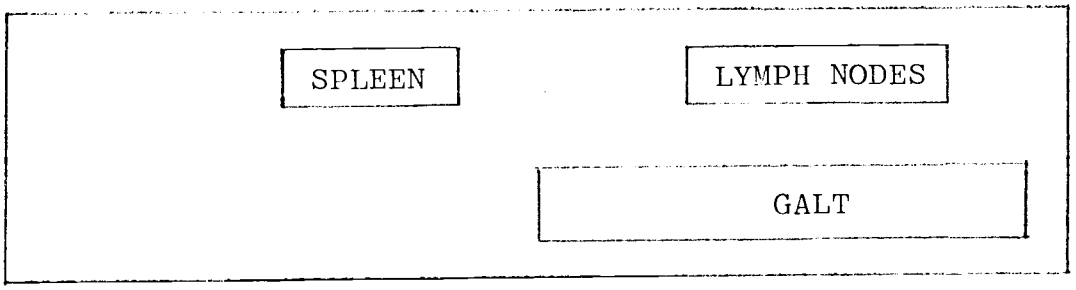

Figure 9. Tissues containing antigen-antibody complex compartments

Simplified Compartmental System

The humoral immune response will be modeled in this study. In particular, the production of gamma globulin (IgG) in the mouse as a result of antigenic stimulation by sheep red blood cells will be analyzed. This animal and

antigen were chosen because there is a great deal of data available in the literature for this combination. T cells and macrophages are required for B cells to respond to this antigen [29, p. 207]. It is desirable to simplify the system shown in Figures 2 through 9, because all of the theory and data are not available at this time. In the simplified system presented in Figure 10 (the notation is explained in Chapter 3) it is assumed that T cells are present in the needed ratio of T to B cells for the immune response to proceed, and likewise that macrophages are present in sufficient numbers. These are reasonable assumptions because the dynamics of the B cells and their progeny which result in antibody production can still be effectively modeled. The GALT is ignored since the IgA produced by its plasma cells is not considered in this model. The lymph nodes consist of a long series of individual nodes connected by lymph channels. Lymph leaving organs (other than lymph nodes) contains no lymphocytes. The more nodes the lymph passes through, the more lymphocytes it picks up. The thoracic duct is the main end point of the system and contains the largest lymph cell density of the lymph [27, p. 542]. The lymph and lymph nodes will be assigned as one compartment, since it would not be feasible to obtain data for them as separate compartments. It is not known what percentage of the total antibody leaving the blood to enter the tissues enters the spleen.

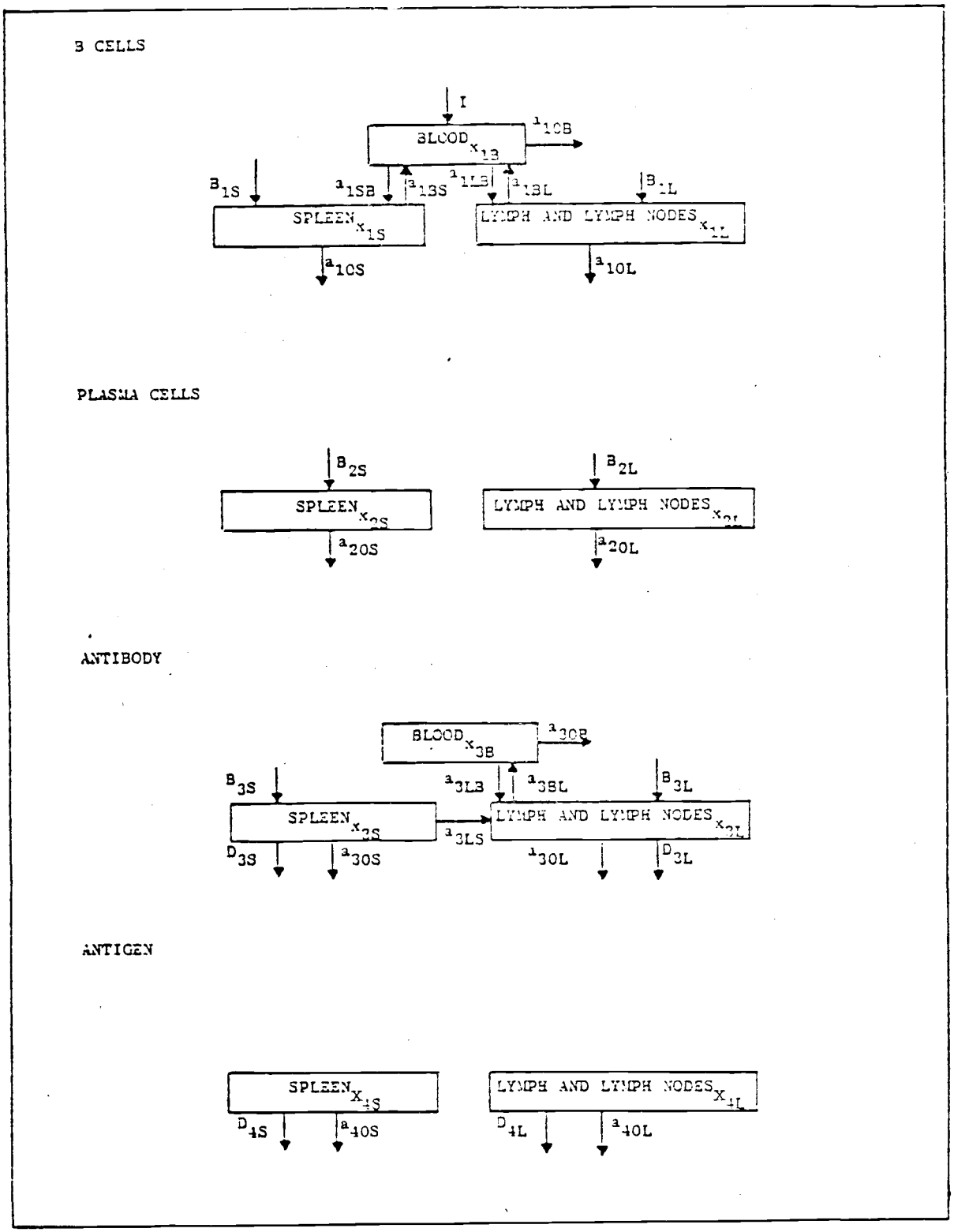

Figure 10. Symbolic representation of the simplified immune system compartmental model

Key Figure 10:

x_{1B} Compartment representing B cells in the blood.

x_{1S} Compartment representing B cells in the spleen.

x_{1L} Compartment representing B cells in the lymph and lymph nodes.

x_{2S} Compartment representing plasma cells in the spleen.

x_{2L} Compartment representing plasma cells in the lymph and lymph nodes.

x_{3B} Compartment representing antibody in the blood.

x_{3S} Compartment representing antibody in the spleen.

x_{3L} Compartment representing antibody in the lymph and lymph nodes.

x_{4S} Compartment representing antigen in the spleen.

x_{4L} Compartment representing antigen in the lymph and lymph nodes.

I Release of B cells into the blood from the bone marrow.

B_{1S} Net birth of splenic B cells due to memory cell production.

B_{1L} Net birth of lymph and lymph node B cells due to memory cell production.

B_{2S} Birth of splenic plasma cells due to B cell differentiation.

B_{2L} Birth of lymph and lymph node plasma cells due to B cell differentiation.

B_{3S} Birth of splenic antibody produced by plasma cells.

B_{3L} Birth of lymph and lymph node antibody produced by plasma cells.

D_{3S} Death of splenic antibody due to antigen antibody complex formation.

D_{3L} Death of lymph and lymph node antibody due to antigen antibody complex formation.

D_{4S} Death of splenic antigen due to antigen antibody complex formation.

D_{4L} Death of lymph and lymph node antigen due to antigen antibody complex formation.

a_{1OB} The fraction of population in x_{1B} leaving to enter the environment.

a_{1SB} The fraction of population in x_{1B} leaving to enter x_{1S}.

a_{1BS} The fraction of population in x_{1S} leaving to enter x_{1B}.

a_{1OS} The fraction of population in x_{1S} leaving to enter the environment.

a_{1LB} The fraction of population in x_{1B} leaving to enter x_{1L}.

a_{1BL} The fraction of population in x_{1L} leaving to enter x_{1B}.

a_{1OL} The fraction of population in x_{1L} leaving to enter the environment.

a_{2OS} The fraction of population in x_{2S} leaving to enter the environment.

a_{2OL} The fraction of population in x_{2L} leaving to enter the environment.

a_{3OB} The fraction of population in x_{3B} leaving to enter the environment.

a_{3OS} The fraction of population in x_{3S} leaving to enter the environment.

a_{3LS} The fraction of population in x_{3S} leaving to enter x_{3L}.

a_{3LB} The fraction of population in x_{3B} leaving to enter x_{3L}.

a_{3BL} The fraction of population in x_{3L} leaving to enter x_{3B}.

a_{3OL} The fraction of population in x_{3L} leaving to enter the environment.

a_{4OS} The fraction of population in x_{4S} leaving to enter the environment.

a_{4OL} The fraction of population in x_{4L} leaving to enter the environment.

The lymph drains all of the tissues, so it will be assumed that the antibody leaving the blood compartments enters only the lymph and lymph node compartment. The cells which recirculate to the bone marrow are disregarded because they only constitute about three percent of the total lymphocyte population of the bone marrow. It will be assumed that no compartment is either a source or a sink, so the flux of cells from the bone marrow will be treated as an input from the environment. In order to simplify the compartmental system, the antigen-antibody complex compartments will be eliminated since only free antigen can initiate the immune reaction. However, Bell [9], Bruni, et. al., [5] and Mohler, et. al. [8], consider the complex in their model because the dissociation of the antigen-antibody complex releases free antibodies. The values for the association and dissociation constants for the antigen-antibody complex are obtained by in vitro experiments which have reached equilibrium. The other studies cited above have approximated the dissociation in various ways, using the constant obtained from the equilibrium studies. Bruni et. al. [5] assumed instantaneous equilibrium. However, as discussed in Chapter 3, this reaction may not be in equilibrium in an animal and the dissociation constant will be neglected. Inclusion of this term in this model would result in lengthening the time response. Association of the antigen-antibody complex will be treated as antigen and antibody death terms.

The interactions of the compartments within the tissues and fluids is shown in Figure 11.

It is necessary to be careful when referring to the compartments, for example the B cells in the blood compartment describes the compartment consisting of the B cells in the blood, not just the blood. This type of compartmental description is used throughout this paper.

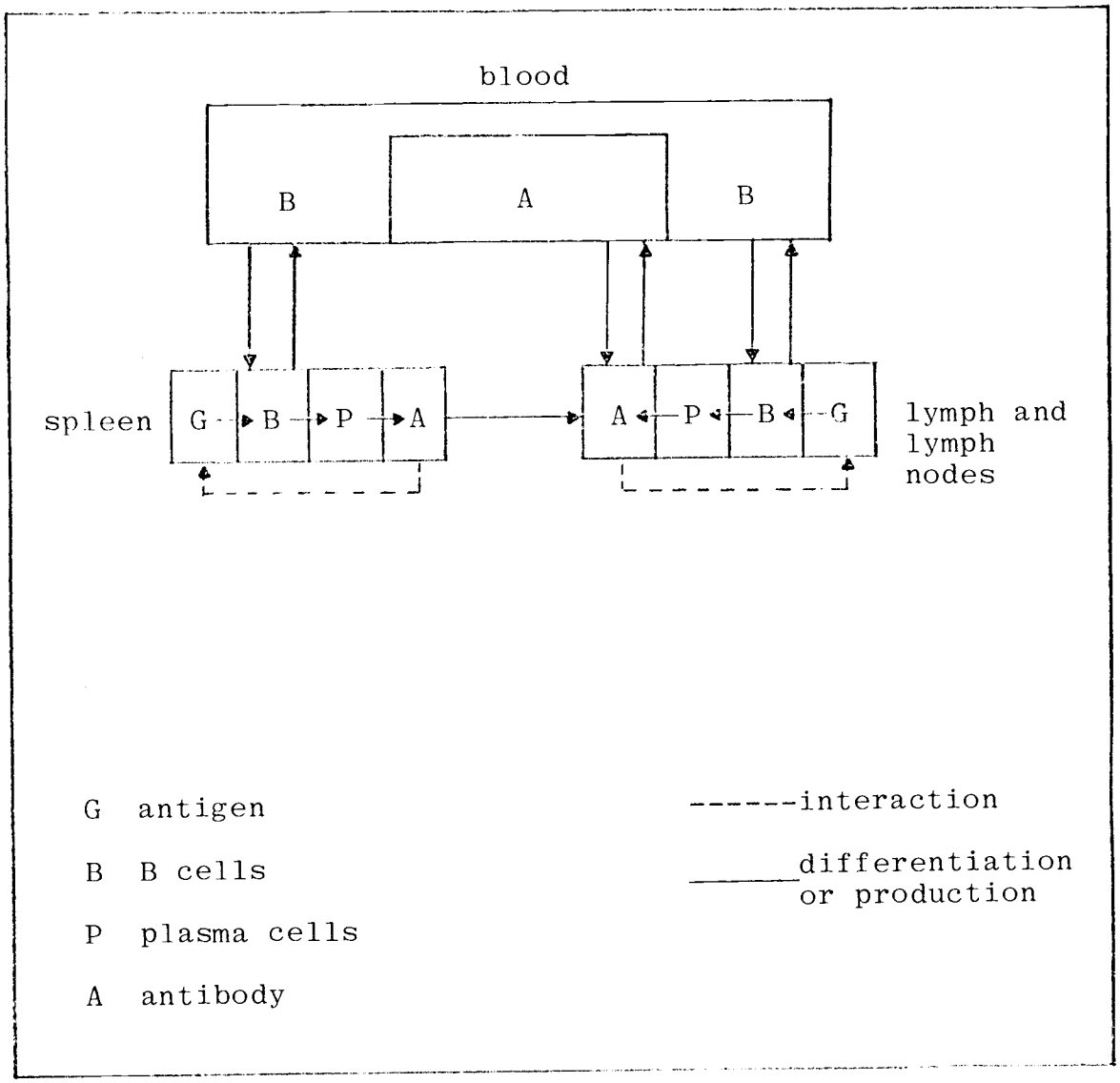

Figure 11. Interaction of compartments within organs

III. MATHEMATICAL MODEL

Most mathematical models of the immune system have considered the body to be one uniform compartment, with a homogenous mixture of cell types. The multicompartmental model discussed in this thesis is based upon the same immunological principles as a whole body model, but also considers the circulation of cells and molecules throughout the body, and the separate functions of tissues and fluids. It is instructive to derive the equations for a single compartment before considering the multicompartmental model, because the immune response occurs in each compartment of a multicompartmental model in the same manner but to a varying degree as the response occurs in the whole body model. In the single compartmental model considered here, the contributors of T cells, macrophages, and antibody classes, the dependence of parameters on cell populations, and the secondary response are ignored. The derivation of this model follows that of the B cell model of Mohler, Barton, and Hsu [8].

Single Compartmental Model

The state variables representing B and plasma cell populations are in units of cells, and state variables representing antigen or antibody have units of molecules unless otherwise noted.

The kinetics of small B cells in the body is derived from classical cell birth and death population balances. When the small B cell population , x_1, is stimulated by antigen, x_4, they become either plasma cells or memory cells. $\alpha p_s x_1$ B cells differentiate into $2\alpha p_s p_d x_1$ plasma cells or $2\alpha p_s(1-p_d)\ x_1$ memory cells, where α is the birth constant of stimulated B cells. The probability that a B cell is stimulated, is derived and approximated by Bruni, et al. [5] to be

$$p_s = 1 \quad \gamma_1 \leq kx_4 \leq \gamma_2$$

$$= 0 \text{ otherwise}$$

where k is the association constant, and γ_1 and γ_2 are the bounds of a low zone high zone tolerance sensitivity interval. The probability that a B cell differentiates into a plasma cell, p_d, is shown by Bruni, et al. [5] to be

$$p_d = \frac{kx_4}{1+kx_4}$$

which is the probability that an antigen receptor is bound and represents the ratio of bound to total receptors on the antigen. This model does not consider the secondary immune response, therefore memory cells are assumed to be part of the small B cell pool. Memory cells behave and morphologically look like small B cells.

The change of population, Δx_1, due to antigenic stimulation on the interval Δt is therefore given by

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

the sum of B cell birth and death during the interval Δt which reduces to

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

There is another source of B cells, I, the input of new cells from the bone marrow. The death of B cells is given by

$$\frac{x_1}{\tau_1}\ \Delta t$$

where τ_1 is the mean lifetime of small B cells. As Δt approaches zero, the time change of the small B cell population is described by the net birth rate equation

$$\frac{dx_1}{dt} = I + \alpha p_s(1-2p_d)\, x_1 - \frac{x_1}{\tau_1}$$

The remaining equations are derived in a similar manner.

B cells are the only source of plasma cells, the x_2 population. B cells differentiate after antigenic stimulation into plasma cells at the rate $2\alpha p_s p_d x_1$. Plasma cells die at the rate x_2/τ_2, where τ_2 is the mean lifetime of plasma cells. Consequently, the net birth rate of this population is

$$\frac{dx_2}{dt} = 2\alpha p_s p_d\, x_1 - \frac{x_2}{\tau_2}$$

Antibody is produced by the plasma cells at the rate βx_2 where β is the antibody production per plasma cell. The free antibody population is the population of antigen which is not bound by antigen in the antigen-antibody complex. The bound antibody population must be subtracted from the total antibody population to get the free antibody population. The B cell binding sites are antibody molecules which coat the cells [22, p. 102]. Therefore, the probability that antigen will bind to antibody will be considered to be the same as the probability that antigen binds to B cells. p_d is about equal to kx_4 because kx_4 is a small number. Therefore, $p_d x_3$ approximates the complex population. Antigen and antibody react to form the antigen-antibody complex according to the law of mass action.

$$Ag + Ab \underset{k_d}{\overset{k_a}{\rightleftharpoons}} AgAb$$

Macrophages act to remove the antigen-antibody complex from the body. This drives the reaction to the right, resulting in an association rate which is much larger than the dissociation rate. Therefore, the dissociation rate of the antigen-antibody complex will be neglected. The concentration of bound antibody is $k_a[Ag][Ab]$ in the units moles per liter. Since the model is in the units of cells, $k_a[Ag][Ab]$ is multiplied by a conversion factor changing the units to cells. The rate of formation of the antigen-antibody is thus $p_d x_3$. The dynamics of free antibody is

$$\frac{dx_3}{dt} = \beta x_2 - p_d x_3 - \frac{x_3}{\tau_3}$$

where βx_2 is the rate of formation of free antibody, $p_d x_3$ is the rate at which antibody is bound and x_3/τ_3 is the death rate of free antibody. x_4 is the population of free antigen and τ_3 is the mean lifetime of free antibody.

The dynamic of the antigen depends upon the type of antigen used and its mode of introduction into the animal. An intravenous or intraperitoneal injection can be represented as an impulse function. An adjuvant injection would be written as a distribution, because adjuvant slowly releases antigen over a period of time. x_4 is the population of free antigen. The free antigen population is found by subtracting the population bound antigen from total antigen population. $\rho(t)$ represents the antigen birth rate, where $\rho(t)$ is a factor depending on the rate of antigen administration which regulates the release of antigen into the system. $p_d x_3$ is the rate of formation of antigen bound in the antigen-antibody complex, and x_4/τ_4 is the death rate of free antigen, where τ_4 is the mean lifetime of free antigen. Therefore, the time change of the free antigen population is

$$\frac{dx_4}{dt} = (p(t) + p_d x_3) - \frac{x_4}{\tau_4}$$

Physiological Controls

In the multicompartmental model of the immune system, the dynamics of the immune response is affected by the changes in B cell, plasma cell, antigen and antibody populations as well as their movement between compartments. The fluxes between organs are regulated by the physiological controls which maintain the body's steady states. These controls are represented in the model by the fractional transfer coefficient. A fractional transfer coefficient represents the fraction of a compartment which is transferred per unit time. The following discussion considers the sensitivity of the physiological controls in relation to the immune response.

The characteristics of the blood are not greatly affected by the immune response. Blood is composed of cells and plasma. More than 99% of the cells are red blood cells, so the lymphocytes contribute little to the physical properties of the blood [33, p. 204]. Albumin is the most important protein in capillary dynamics. The albumin fraction of the plasma causes about 70% of the total colloid osmotic pressure. The remaining 30% is due to the various globulin and fibrinogen fractions [33, p. 237]. The amount of antibody produced in an immune reaction is small when compared to the total blood globulins, therefore it has a minimal effect on the colloid

osmotic pressure of the blood.

Fluid filtration in the spleen is controlled by pressure differences which are directly proportional to the protein concentration in the blood [33, p. 236]. These pressures are minimally affected by the immune response as explained above. Blood enters the spleen by arterial capillaries and leaves by venous capillaries. The capillary pressure is greater in the arterial capillaries than in the venous capillaries, and because of this fluid filters out of the arterial capillaries and flows to the venous capillaries where it is reabsorbed. This fluid flow into, through, and out of the spleen carries cells and molecules with it.

The forces controlling lymphocyte movement in the spleen are not completely understood. The splenic capillaries are very permeable therefore lymphocytes enter the pulp by diapedesis, that is by sliding thru a capillary pore a small portion at a time. In this manner lymphocytes migrate from the blood into the spleen at a rate proportional to their concentrations in the blood [34]. Lymphocytes are moved thru the tissue by the fluid flow between capillaries and by their own ameboid motion. Ameboid motion can be initiated by chemotaxic substances which act by causing action potentials in the cell membrane. However, there is no known chemotaxic substance which affects lymphocytes. The lymphocytes then enter the venous

capillaries by diapedesis and are returned to the circulation [33, p. 112].

Protein also leaks out of the splenic capillaries into the pulp. While most of the escaped fluid is reabsorbed, antibody is too large to be reabsorbed by the venous capillaries. The antibody which leaks into the splenic pulp is a small portion of the total antibody leakage. Proteins become concentrated in the interstitial fluid until the pressure is sufficiently raised to force the fluid and the excess proteins it contains into the lymphatic channels, returning the protein concentration to its normal value [33, p. 244]. The tissue fluid that flows into the lymph vessels becomes lymph. The faster protein accumulates, the more frequently it flows into the lymphatic channels. In this way the protein concentration in the spleen is maintained at a low level. The pressure difference between the two ends of a vessel, not the absolute pressure in the vessel, causes fluid to flow from the high to low pressure area [33, p. 237]. There are currently no techniques to measure the pressures at the splenic and node ends of the draining lymphatic vessel discussed above in the mouse.

Blood is the main source of incoming lymphocytes when the lymph and lymph nodes are considered to be one compartment. Lymphocytes in the lymph nodes can return to the blood directly or via the thoracic duct [27, p. 543].

Lymphocytes migrate from the blood into the lymph nodes at a rate proportional to their concentration in the blood [35]. The force which propels lymphocytes through the lymph nodes from the post capillary venules to the efferent lymphatics is unknown [34].

Since the factors controlling cell movement appear to be minimally affected by the immune response, the fractional transfer coefficients for B cells are written as simple percentages in the multicompartmental model. The values used are the steady state values. This allows the fluxes (amount entering and leaving compartments) to increase as the cells proliferate as the immune response proceeds and later return to the initial flux values.

The fractional transfer coefficients for antibody are more complicated. Antibody produced during an immune reaction does not build up in the spleen, but is released into the lymph as described earlier. Therefore, the sum of the fractional transfer coefficient regulating the antibody fluxes leaving the spleen must be equal to one. At steady state, the blood and lymph and lymph node compartments contain the same amount of "natural" antibody. An animal always produces some antibody against antigens introduced by the environment. These "natural" antibodies are not considered in this model, but they do give some clues about the dynamics of antibody circulation. Eisen [29, p. 483] indicates that the flux of antibody

leaving the blood compartment to enter the lymph and lymph node compartment equals the flux of antibody entering the blood compartment from the lymph and lymph node compartment.

Multicompartmental Model

The equations for the multicompartmental model shown in Figure 10 follow directly from the model representation. They represent the population changes due to the net flux balances and the net birth rates which follow from the single compartmental model. The state terms are represented by x_{ki}, where subscript k indicates the contents of the compartment and subscript i denotes the compartment. Subscript k can have the value 1 for B cells, 2 for plasma cells, 3 for antibody or 4 for antigen. Subscript i can be B for blood, S for spleen, L for lymph and lymph nodes, or 0 for the environment. The constant fractional transfer coefficient is written as a_{kji} indicating that material k is being transferred from compartment i to compartment j. All fractional transfer coefficients are defined to be positive terms. Subscript j has the same representation as i. The rate of transfer of material k from the ith to the jth compartment is $a_{kji}\ x_{ki}$. B_{ki} is the birth of material k in compartment i and D_{ki} is the death of material k in compartment i.

The dynamics in the blood compartment for small B cells, derived from a balance of flow rates, is

$$\frac{dx_{1B}}{dt} = I + a_{1BS}x_{1S} + a_{1BL}x_{1L} - (a_{1SB} + a_{1LB} + a_{10B})\, x_{1B}$$

where I is the rate input of new B cells from the bone marrow. It is usually assumed to be constant which is reasonable unless the animal is trying to repopulate its stem cell centers after irradiation, or unless bone marrow has been injected into the animal. For example, bone marrow injections are a part of leukemia thereapy. $a_{1BS}x_{1S}$ is the rate of transfer of B cells from the spleen to the blood. $a_{1BL}x_{1L}$ is the rate of transfer of B cells from the lymph and lymph nodes to the blood. $(a_{1SB} + a_{1LB} + a_{10L})x_{1B}$ is the rate of transfer of B cells out of the blood.

The balance of antibody flow rates in the blood compartment is

$$\frac{dx_{3B}}{dt} = a_{3BL}x_{3L} - (a_{3LB} + a_{30B})\, x_{3B}$$

$a_{3BL}x_{3L}$ is the rate of transfer of antibody from the lymph and lymph nodes to the blood via thoracic duct. Antibody leaves the blood at the rate $(a_{3LB} + a_{30B})\, x_{3B}$.

The dynamics of small B cell flow rates in the spleen compartment is given by

$$\frac{dx_{1S}}{dt} = B_{1S} + a_{1SB}\, x_{1B} - (a_{1BS} + a_{10S})\, x_{1S}$$

where $B_{1S} = \alpha p_{ss}(1-2p_{ds})\, x_{1S}$ is the internal birth rate of new B cells due to antigenic stimulations. This internal

birth rate is derived from the single compartment model where the birth of new B cells due to antigenic stimulation is

$$\alpha p_s (1-2p_d) \quad x_1$$

p_{ss} is the probability that antigen stimulate small B cells in the spleen. p_{ds} is the probability that a small B cell differentiates into a plasma cell in the spleen. $a_{1SB}x_{1B}$ is the rate of transfer of B cells from the blood to the spleen. $(a_{1BS} + a_{10S})x_{1S}$ is the rate of transfer of B cells out of the splenic white pulp.

The net flow rate of plasma cells in the spleen compartment is given by

$$\frac{dx_{2S}}{dt} = B_{2S} - a_{20S}x_{2S}$$

where $B_{2S} = 2\ \alpha p_{ss} p_{ds} x_{1S}$ is the internal birth rate of plasma cells due to antigenic stimulation derived from the single compartment model. $a_{20S}x_{2S}$ is the death rate of plasma cells in the spleen.

The balance of antibody flow rates in the spleen compartment is given by

$$\frac{dx_{3S}}{dt} = B_{3S} - (a_{3LS} + a_{30S})x_{3S} - D_{3S}$$

where $B_{3S} = \beta x_{2S}$ is the internal birth rate of antibody, and $D_{3S} = p_{ds}x_{3S}$ is the formation rate of the antigen-antibody complex which are derived from the single compartment model. β is the antibody production rate per

plasma cell. $(a_{3LS} + a_{30S})\, x_{3S}$ is the rate at which antibody leaves the splenic white pulp compartment.

The dynamics of antigen in the spleen compartment derived from a balance of flow rates is

$$\frac{dx_{4S}}{dt} = -a_{40S}x_{4S} - D_{4S}$$

where $D_{4S} = p_{ds}x_{3S}$ is derived from the single compartment model.

The net flux of small B cells in the lymph and lymph node compartment is

$$\frac{dx_{1L}}{dt} = B_{1L} + a_{1LB}x_{1B} - (a_{1BL} + a_{10L})\, x_{1L}$$

where $B_{1L} = \alpha p_{sl}(1-2p_{dl})\, x_{1L}$ is the internal birth rate of new B cells due to antigenic stimulation derived from the single compartment model. p_{sl} is the probability that antigen stimulates small B cells in the lymph and lymph nodes. p_{dl} is the probability that a small B cell differentiates into a plasma cell in the lymph and lymph nodes. $a_{1LB}x_{1B}$ is the rate of transfer of B cells from the blood to the lymph and lymph nodes. $(a_{1BL} + a_{10L})\, x_{1L}$ is the rate of transfer of B cells out of the lymph and lymph node compartment.

The net flow of plasma cells in the lymph and lymph node compartment is

$$\frac{dx_{2L}}{dt} = B_{2L} - a_{20L}x_{2L}$$

where $B_{2L} = 2\alpha p_{sl}p_{dl}x_{1L}$ is the internal birth rate of

plasma cells due to antigenic stimulation derived from the single compartment model. $a_{20L}x_{2L}$ is the death rate of plasma cells in the lymph and lymph nodes.

The dynamics of antibody fluxes in the lymph and lymph node compartment is

$$\frac{dx_{3L}}{dt} = B_{3L}+a_{3LB}x_{3B}+a_{3LS}x_{3S}-(a_{3BL}+a_{30L})x_{3L}-D_{3L}$$

where $B_{3L} = \beta x_{2L}$ is the internal birth rate of antibody and $D_{3L} = p_{d1}x_{3L}$ the rate of formation of the antigen-antibody complex, which are derived from the single compartment model.

The dynamics of antigen in the lymph and lymph node compartment derived from a balance of flow rates is

$$\frac{dx_{4L}}{dt} = -a_{40L}x_{4L}-D_{4L}$$

where $D_{4L} = p_{d1}x_{3L}$. $a_{40L}x_{40L}$ is the death rate of antigen derived from the single compartment model.

The entire model is listed below.

$$\frac{dx_{1B}}{dt} = I+a_{1BS}x_{1S}+a_{1BL}x_{1L}-(a_{1SB}+a_{1LB}+a_{10B})x_{1B}$$

$$\frac{dx_{1S}}{dt} = B_{1S}+a_{1SB}x_{1B}-(a_{1BS}+a_{10S})x_{1S}$$

$$\frac{dx_{1L}}{dt} = B_{1L}+a_{1LB}x_{1B}-(a_{1BL}+a_{10L})x_{1L}$$

$$\frac{dx_{2S}}{dt} = B_{2S}-a_{20S}x_{2S}$$

$$\frac{dx_{2L}}{dt} = B_{2L}-a_{20L}x_{2L}$$

$$\frac{dx_{3B}}{dt} = a_{3BL}x_{3L}-(a_{3LB}+a_{30B})x_{3B}$$

$$\frac{dx_{3S}}{dt} = B_{3S}-(a_{3LS}+a_{30S})x_{3S}-D_{3S}$$

$$\frac{dx_{3L}}{dt} = B_{3L}+a_{3LS}x_{3S}+a_{3LB}x_{3B}-(a_{3BL}+a_{30L})x_{3L}-D_{3L}$$

$$\frac{dx_{4S}}{dt} = -a_{40S}x_{4S}-D_{4S}$$

$$\frac{dx_{4L}}{dt} = -a_{40L}x_{4L}-D_{4L}$$

Data

The data used in this model are for the mouse and are obtained from the literature. It would have been desirable to use data for only one strain, since not all strains react in the same manner when given the same antigen under the same conditions. An extensive literature search indicated that sufficient data for one strain is not available. However, the differences in the immunological responses between strains is small when compared to the differences between species.

In an animal who has not been immunized, there are no net changes in the populations of the compartments defined earlier. This lack of net change is called steady state. The initial values of the state variables are the steady state values. It is not possible to isolate an animal from all antigenic substances, so there is a "natural level" of plasma cells and antibody [20]. In this study only the response to SRBC is considered, so the effects of environmental antigens is neglected. Therefore, only the B cell compartments and the antigen compartments, as a result of the SRBC injection, have initial populations as shown in Table 1. The initial antigen populations are actually the number of antigenic determinances retained in the tissues. Bell [9] discusses the use of the antigenic determinant population in place of the antigen population for multivalent antigen.

TABLE 1

Initial Population of Compartments

Compartment	Value	Reference
x_{1B}	1.60×10^{6}	14, 15
x_{1S}	6.30×10^{7}	30, 15
x_{1L}	1.32×10^{7}	1, 15
x_{2S}	0	
x_{2L}	0	
x_{3B}	0	
x_{3S}	0	
x_{3L}	0	
x_{4S}	$(.0043)(10)(1 \times 10^{8})$	22, 32, 37
x_{4L}	$(.0067)(10)(1 \times 10^{8})$	22, 32, 37

The steady state population of B cells in the blood, spleen, and lymph and lymph node compartments are determined by multiplying the number of lymphocytes in each compartment by the percentage of B cells in each compartment as given in Eisen [31, p. 459]. Dittmer [36, p. 5] gives the number of lymphocytes in the blood, Metcalf [30, p. 11] for the spleen, and Alder [37, p. 35] for the lymph nodes. The number of lymphocytes in the lymph cannot be determined, so the value for the lymph nodes will be used for the lymph and lymph node compartment.

The initial value of the compartments containing antigen, x_{4S} and x_{4L}, depend upon the mode of introduction into the animal. This model will consider intravenous (i.v.) injections, because this is the most common method of introducing SRBC into mice. Perkins [32, p. 567] gives the percentage of SRBC present in the spleen several hours after an i.v. dose is given. The majority of SRBC are destroyed by macrophages as discussed by Perkins [32]. It is assumed for this model that all antigen migrates to the spleen and lymph nodes or has been destroyed by macrophages. These assumptions allow the initial amount of antigen in the lymph and lymph node compartment to be calculated. The time delay for antigen to reach the spleen and lymph and lymph node compartments is ignored, as discussed earlier.

There is rapid large-scale production of lymphocytes in the bone marrow. Many of these cells are discharged into the blood. The number of B cells entering the blood from the bone marrow is determined from the equation describing the kinetics of B cells in the blood. At steady state the equation is

$$0 = I+a_{1BS}x_{IS}+a_{1BL}x_{1L}-(a_{1SB}+a_{1LB}+a_{10B})x_{1B}$$

which reduces to

$$I = a_{10B}x_{1B}+a_{10S}x_{1S}+a_{10L}x_{1L}$$

where I is the only term with an unknown value. The value of I determined from the equations above is about 60% of the B cells produced in the bone marrow each hour [30, p. 22].

The thoracic duct is the main pathway through which cells enter the blood from the lymph and lymph nodes. The number of lymphocytes entering the blood via the thoracic duct is found in Allman [38, p. 441]. The percentage being B cells is given by Eisen [31, p. 459], giving the value for $a_{IBL}x_{1L}$.

The lifetime of B cells in the blood is given by Yoffey and Courtice [27, p. 45]. There is no difference between the B cells of the three compartments, therefore the lifetime of B cells is assumed to be the same in the spleen and lymph nodes as in the blood.

Therefore (B cell lifetime in hours)$^{-1}$ is the fractional coefficient for B cells entering the environment a_{10B}, a_{10S} and a_{10L}.

a_{1LB} is calculated from the steady state equation of the lymph and lymph node compartment, so

$$a_{1LB} = (a_{1BL}+a_{10L})\frac{x_{1L}}{x_{1B}}$$

The flux of lymphocytes from the blood to the spleen is about ten times the flux from the blood to the lymph nodes. This is based on data given in Hammond [17]. Therefore,

$$a_{1SB} = 10a_{1LB}$$

a_{1BS} is calculated from the steady state equation for the spleen, so

$$a_{1BS} = a_{1SB}\frac{x_{1B}}{x_{1S}} - a_{10S}$$

The lifetime of plasma cells is given by Yoffey and Courtice [27, p. 576]. Therefore (plasma cell lifetime in hours)$^{-1}$ is the fractional transfer coefficient for plasma cells entering the environment, a_{20S} and a_{20L}.

Eisen [31, p. 483] indicates that the flux of antibody (IgG) out of the blood $a_{3LB}x_{3B}$ is equal to the flux into the blood via the thoracic duct $a_{3BL}x_{3L}$. Since the "natural" level of antibody to environmental factors is the same in the blood and lymph, $a_{3LB} = a_{3BL}$.

The half life of mouse gamma globulin is given by Sell and Fahey [20, p. 83]. The inverse of the half life gives, a_{30B}, a_{30S} and a_{30L}.

The mechanism by which protein leaves the spleen is discussed in detail by Guyton [33, p. 244], in which he indicates that all antibody above the spleen's "normal" value due to environmental factors is expelled. Therefore,

$$a_{3LS} + a_{30S} = 1$$

The viability of SRBC as an antigen is shown in plaque studies [51]. Therefore the inverse of the lifetime will be a_{40S} and a_{40L}.

The value of the fractions transfer coefficients are shown in Table 2.

The birth rate constant of stimulated B cells, α, is given by Yoffey and Courtice [27, p. 472]. β, the number of antibody molecules produced per plasma cell per hour, is given by Hiramoto et al. [39, p. 961]. The value given is for IgM molecules, but Voss [40] indicates that the value is the same for IgG. Bell and Delisi [13, p. 417] gives the association constant for a multivalent antigen. Bigley [22, p. 16] indicates that there are about 10 antigenic determinants which are recognized. These values are given in Table 3.

Experiments by Lees and Sinclair [41] show that an antigen dose of 1×10^5 SRBC results in low zone tolerance. Amounts above this level result in antibody production.

A high zone tolerance level could not be found reported in the literature. However, doses above 1×10^9 SRBC are seldom used. Therefore

$p_{ss} = 1$ (1×10^5)(% in spleen)(# of determinants) $< x_{4S}$

$= 0$ Otherwise

$p_{sl} = 1$ (1×10^5)(% in lymph nodes)(# of determinants) $< x_{4L}$

$= 0$ Otherwise

The probabilities that a B cell will differentiate is derived from Bruni, et al., to be

$$p_{dl} = \frac{kx_{4S}}{1 + kx_{4S}}$$

$$p_{dl} = \frac{kx_{4L}}{1 + kx_{4L}}$$

TABLE 2

Value of Fractional Transfer Coefficients

Coefficient	Value (hr^{-1})	Reference
a_{1SB}	$10a_{1LB}$	17
a_{1BS}	$a_{1SB}\frac{x_{1B}}{x_{1S}} - a_{10S}$	follows from compartmentation
a_{1LB}	$(a_{1BL}+a_{10L})\frac{x_{1L}}{x_{1B}}$	follows from compartmentation
a_{1BL}	$7.0\times10^{5}/x_{1L}$	26, 33, 34
$a_{10B}, a_{10S}, a_{10L}$	1/96	26
a_{20S}, a_{20L}	0.1	26
a_{3LB}	0.01	29
a_{3LS}	128.6/129.6	follows from compartmentation
a_{3BL}	0.01	29
$a_{30B}, a_{30S}, a_{30L}$	1/129.6	20
a_{40S}, a_{40L}	1/120	50

TABLE 3

Value of Constants

Constant	Value	Reference
α	$1/40\ hr^{-1}$	2
β	$2.5 \times 10^{6}\ \frac{\text{Ab molecules}}{\text{cell hr}}$	39, 40
k	1×10^{7}	13
D	10 determinants/cell	22

IV. SIMULATION

Computer Program

Simulation is defined by Calligan [1, p. 19] to be the utilization of a computer to study the behavior of the model and by inference the behavior of the system. The simulation described here is written in GASP IV and run on a CDC 3300 digital computer. GASP IV is a combined continuous-discrete FORTRAN based simulation language. A GASP IV program consists of a set of subroutines, some written by the user and some automatically supplied by the GASP IV library.

> The user part contains subprograms for initialization (the main program and subroutine INTLC); equations for state variables and conditions defining state-events (subroutines STATE and SCOND); event code definitions (subroutine EVNTS); event processing (subroutines called by EVNTS); and special data collection and reporting procedures (subroutines SSAVE, OTPUT, and UERR). The GASP IV part contains subprograms that provide for the following functions: the executive or mode controller (subroutine GASP), data and event initialization (subroutine DATIN), data storage and retrieval, data collection, statistics computation and reporting, monitoring and error reporting, random deviate generation, and miscellaneous support [42, p. 21].

The user supplied code in this simulation is:

1. THESIS, the main program in which constants are defined and which calls the subroutines,
2. INTLC, a subroutine for initializing the state

variables,

3. STATE, the subroutine containing the state variables,
4. SSAVE, the data collection and reporting subroutine.

A fourth order Runge-Kutta integration routine is supplied by the GASP IV library. A truncation error of 10% is allowed in the Runge-Kutta integration, above 10% the model becomes unstable. All state variables are designated as SS(•) and their derivatives as DD(•). A complete listing of the simulation program and sample output are given in Appendix 1, as well as Table 4 which lists the model symbols and the corresponding GASP IV notation.

Simulation Results

Antibody levels are reported in the literature by titer, an approximation of the antibody content in the serum. In this method, a constant amount of antigen is added to dilutions of serum. The lowest dilution which results in a precipitate, the antigen-antibody complex, may be considered to contain one arbitrary unit of antibody [22, p. 84]. This arbitrary antibody unit cannot be compared to the antibody unit used in the model. However, the relative time responses of antibody production reported in the literature and observed in the simulated model can be compared by normalizing their units to the highest

response.

The antibody produced against SRBC in the mouse is first IgM and later switches to lgG [37]. This phenomenon is illustrated by Figure 12.

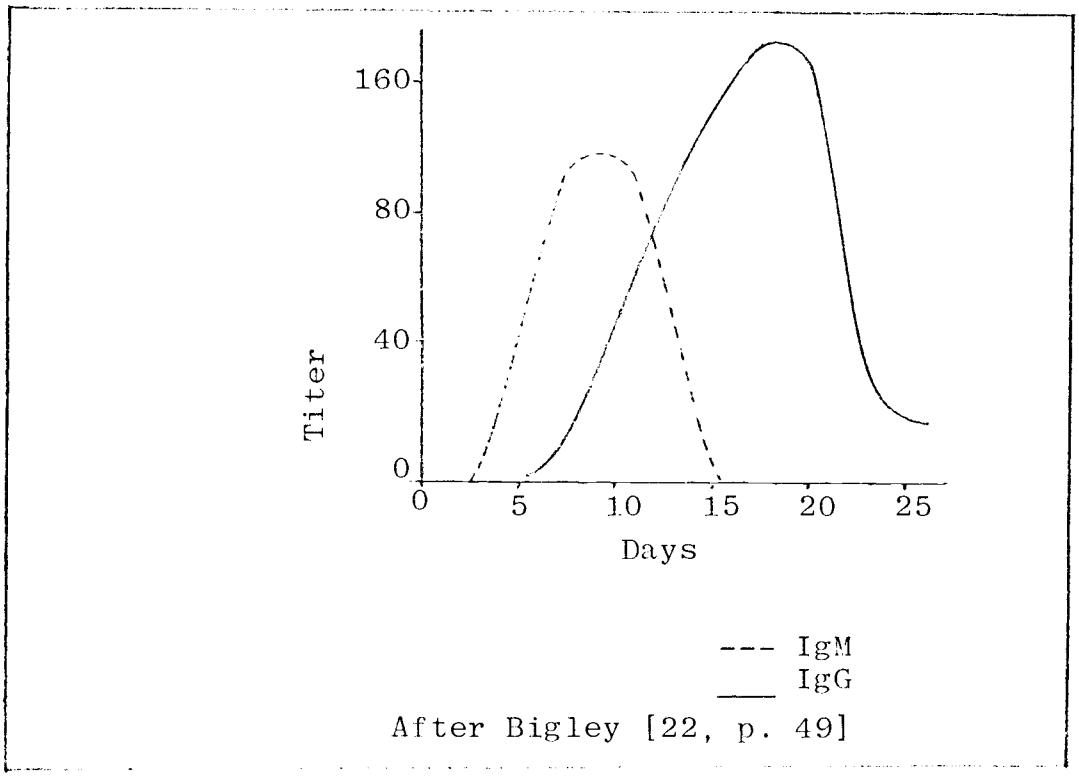

Figure 12. Hypothetical primary response

This model only considers the production of IgG antibody but does not include the time delay in its production. Therefore, the model's antibody time response behaves like a sum of the IgG and the IgM responses. Because of this simplification, the model does not reproduce the decrease in antibody production observed experimentally during the IgM to IgG switch.

The response of this model is dependent upon the antigen dose as shown in Figure 13. The probabilities, p_{ds} and p_{dl}, that B cells will become antibody secreting cells have been assumed to be directly proportional to the antigen dose, and the antibody retained in the organs has been assumed to be a small fixed percentage of the total dose. These assumptions are probably the major reasons for the model dependence on dose. The results are not very sensitive to the percentage of antigen retained in the lymph and lymph node compartment, but they are significantly altered by changing the percentage of antigen retained in the spleen compartment as shown in Figure 14. These are reasonable findings because most antibody production is known to occur in the spleen [37].

The dependence of the antibody response upon the antigen dose is not in agreement with the experimental results of Alder [37] who reports only small variations in antibody responses over a wide range of antigen doses. For the choice of parameters given in Table 3, an antigen dose of 1×10^8 SRBC most closely matches Alder's data as shown in Figure 15 and has been used throughout this study. Comparisons have been made with experimental data resulting from other dose amounts since the experimental results are roughly dose independent.

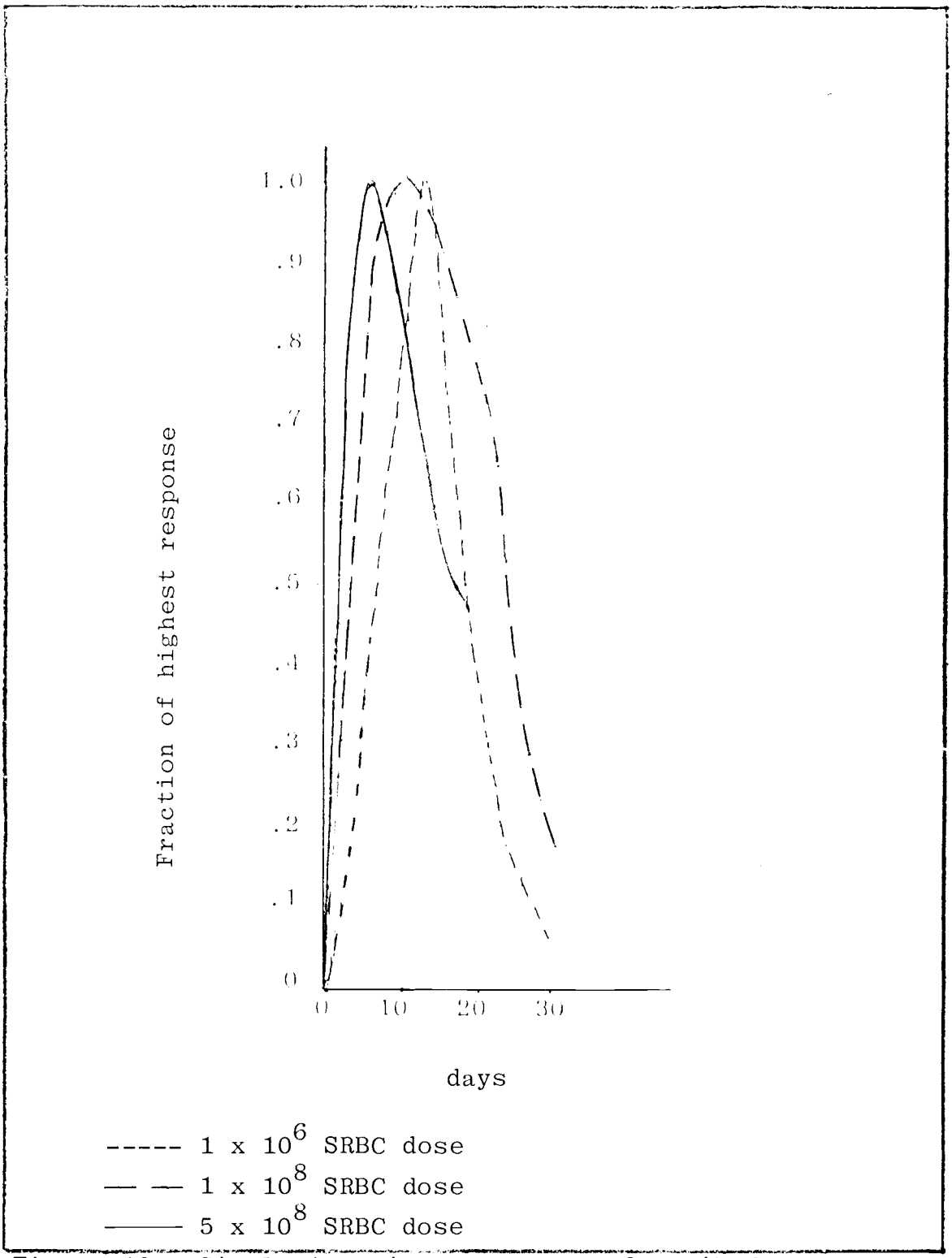

Figure 13. Simulation time responses of antibody in the blood for varying antigen doses

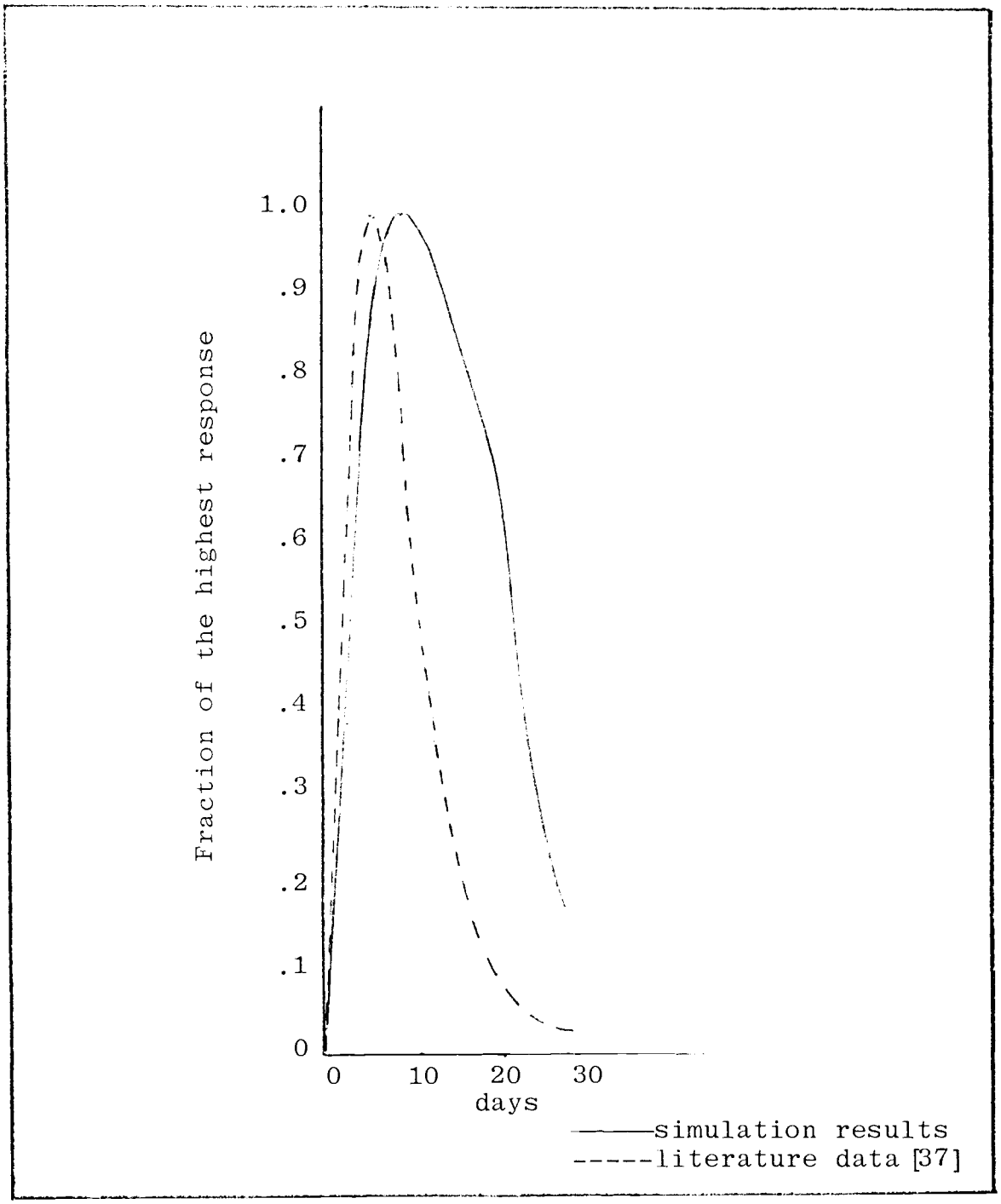

Figure 14. Simulation time response of antibody in the blood for two values of the percentage of antigen retained in the spleen

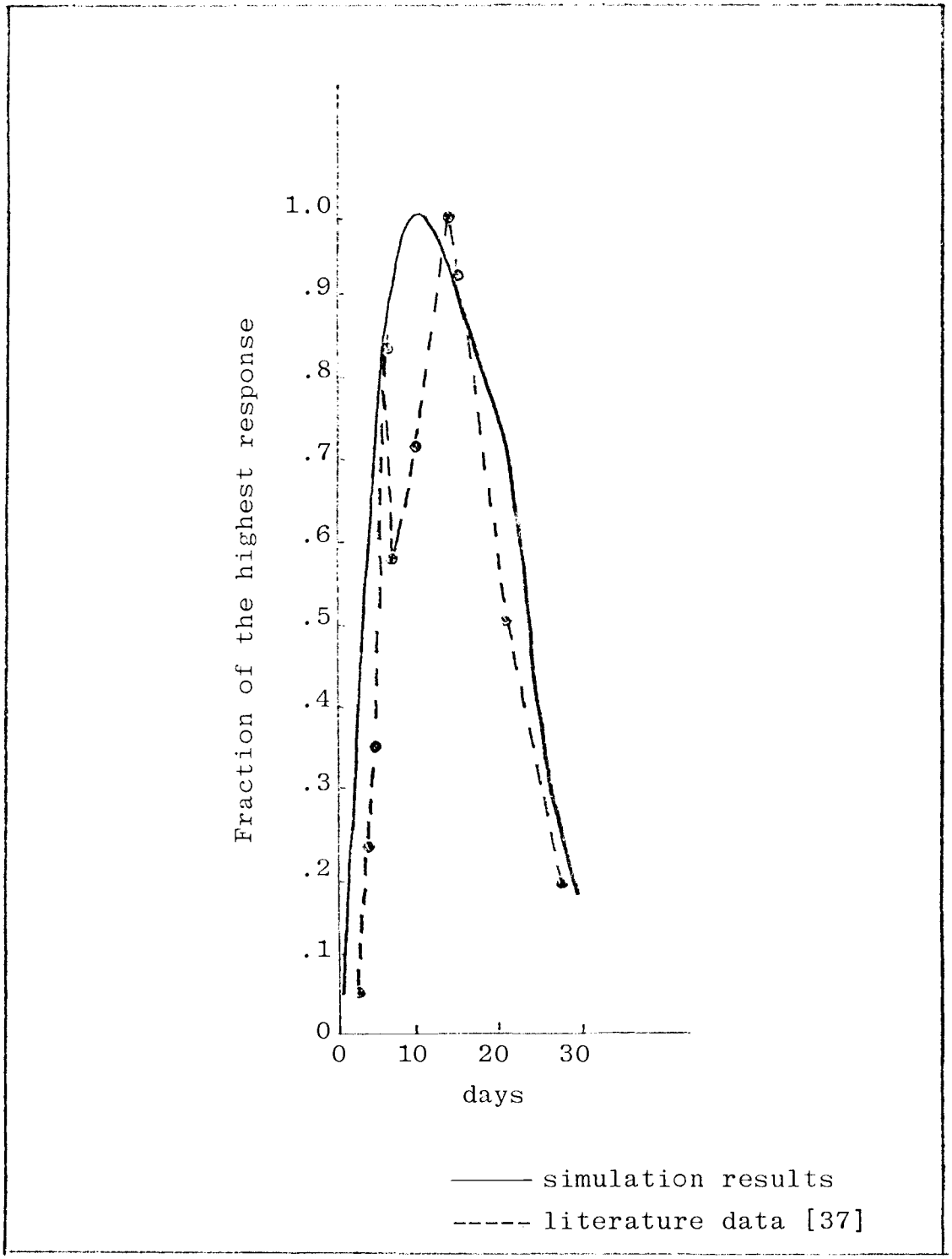

Figure 15. Comparison of literature and simulation time responses of antibody in the blood

The assumption of a fixed percentage of trapped antigen in the organs follows from the experimental results of Perkins [32], which indicate that the same percentage of the given SRBC dose is trapped in the spleen over a wide range of dose values. Since this assumption apparently causes the simulation response to be dose dependent, it seems inconsistent with Alder's [37] findings which indicate that the response is dose independent between the low and high zone tolerance thresholds. The model's results would be independent of the antigen dose if a fixed amount rather than a percentage of the antigen dose were retained in the organs and if the probability terms were proportional to this fixed amount. It is possible that there is an unknown controlling mechanism not included in this model which could reconcile these apparently conflicting conclusions.

The antibody produced by the spleen can be determined by performing identical experiments on whole and splenectomized mice. The model can be used to simulate a splenectomized mouse by setting all initial spleen compartment populations and all fluxes into or out of the spleen compartment to zero. The literature antibody response in a splenectomized mouse and the simulation response are shown in Figure 16. The experimental findings indicate that about 2/3 of the antibody in the blood is produced by the spleen.

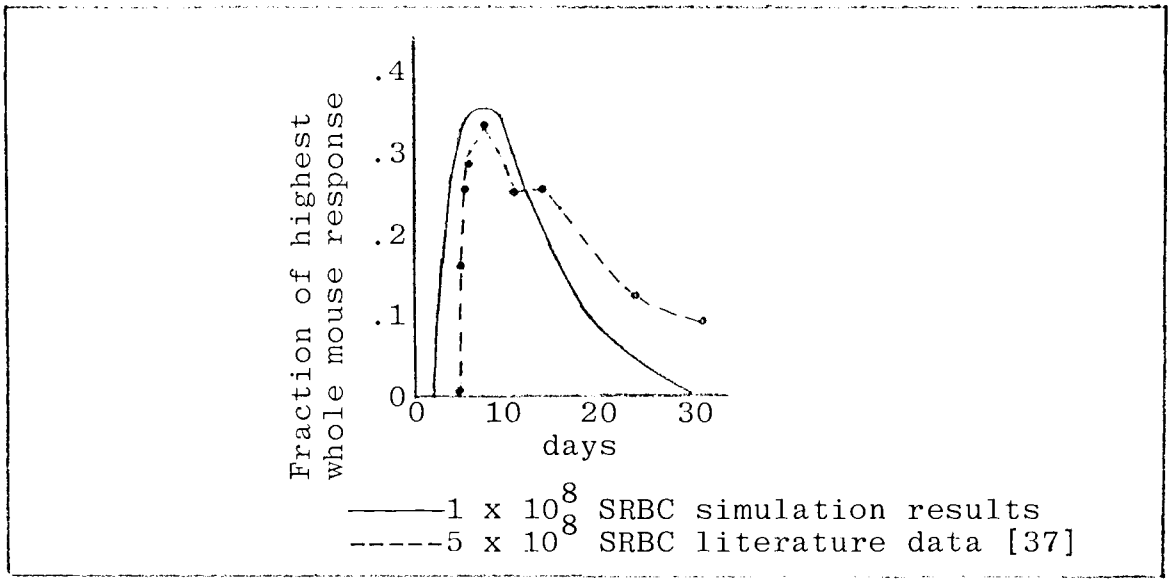

Figure 16. Comparison of literature and simulation time responses of antibody in the blood in a splenectomized mouse

The simulation results for all of the compartments are shown in Figure 17. The model response is similar to the results of Mohler et al. [8]. Their model does not consider compartmentation, and hence, provides only information on the sum of responses for the B cell compartments, the plasma cell compartments, the antigen compartments, and the antibody compartments. These sums are shown in Figure 18.

The simulation results are credible since they are consistant with the observed experimental data. The compartments representing the small B cell populations in the blood, the spleen, and the lymph and lymph nodes increase by a factor of 100 during the simulated immune

KEY for Figure 17

notation	compartment
x_{1B}	B cells in the blood
x_{1S}	B cells in the spleen
x_{1L}	B cells in the lymph and lymph nodes
x_{2S}	plasma cells in the spleen
x_{2L}	plasma cells in the lymph and lymph nodes
x_{3B}	antibody in the blood
x_{3S}	antibody in the spleen
x_{3L}	antibody in the lymph and lymph nodes
x_{4S}	antigen in the spleen
x_{4L}	antigen in the lymph and lymph nodes

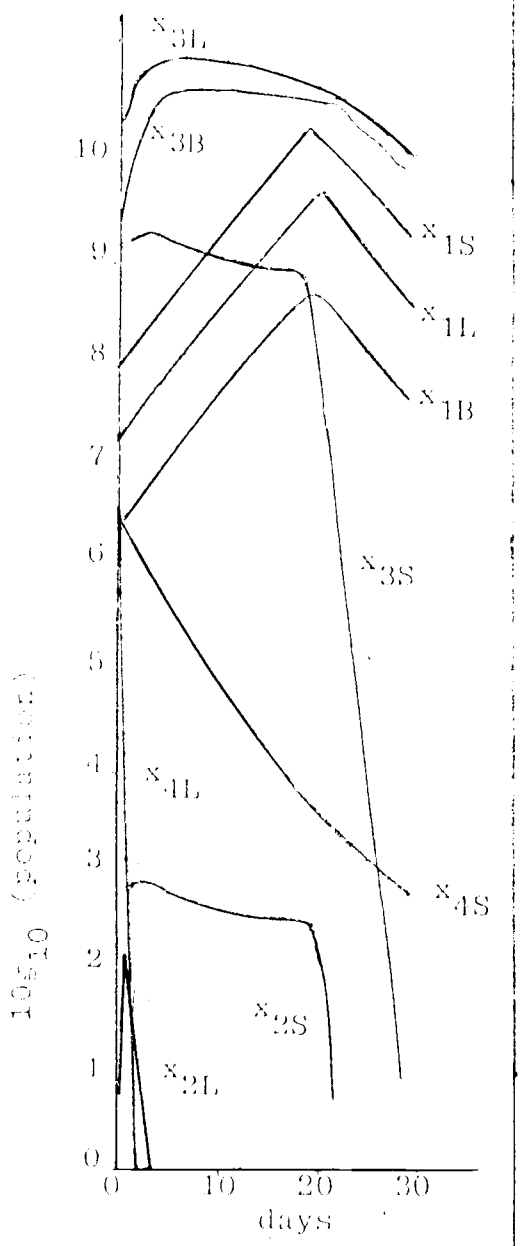

Figure 17. Simulation results for all the compartments

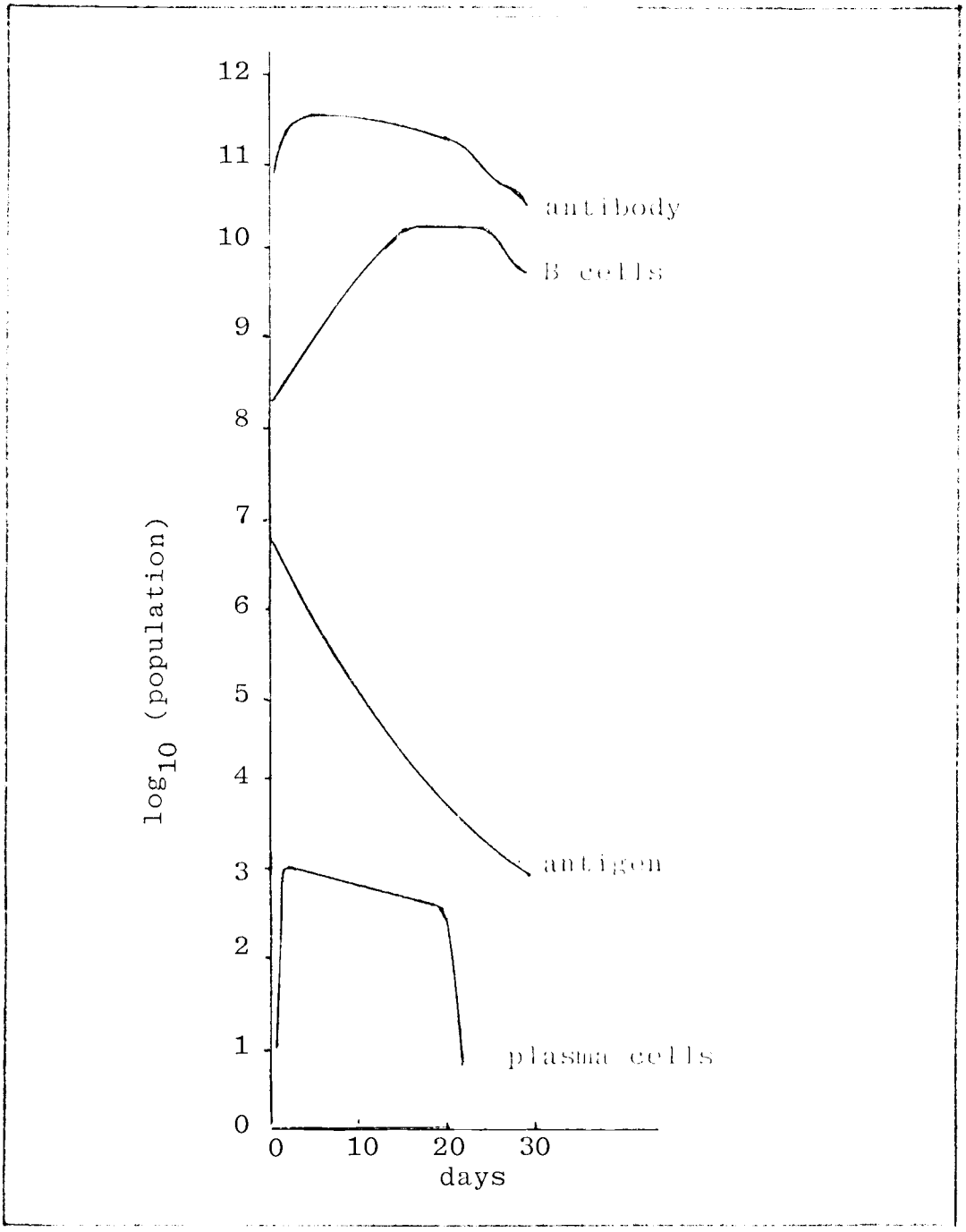

Figure 18. Simulation results for major cell and molecule classes following from the sumation of the compartmental results shown in Figure 17

response. This is somewhat smaller than the thousand fold increase in the small B cell population experimentally observed by Makinodan and Albright [43]. It may be that B cells differentiate more rapidly than assumed due to the probability terms p_{ds} and p_{dl}. For example Roitt [54, p. 15] discusses a "bonus" effect which would increase the probability values.

The birth of plasma cells is dependent upon the antigen population. As explained later, the antigen in the lymph and lymph node compartment is removed rapidly, and, as a consequence, the plasma cell population in this compartment increases up to day one and then rapidly decreases. The model suggests that there is an immediate increase in the plasma cell population in the spleen which slowly decreases until the B cell population starts to decline, triggering an immediate plasma cell population drop. Bell [9] reports that a similar phenomenon occurs in his simulation of the immune response. Since the plasma cell response has not been directly observed experimentally, there is no way to estimate the credibility of the simulated plasma cell responses. However, since all other compartments in the model behave in a plausible manner, it is possible to hypothesize that the simulated plasma cell response is equally plausible.

The simulation time response of the antibody levels closely follow experimental data as discussed earlier.

Data on the absolute levels are not readily available. In the simulation, the highest antibody level is about 5×10^{-5} mg. This is calculated from the largest number of antibody molecules using a molecular weight of 150,000 for gamma globulin. Such an amount is insignificant when compared to the normal gamma globulin level of 11.3 mg in the mouse [20]. This amount of antibody is not unreasonably large since in all such experiments the ratio of antibody produced in an immune reaction is very small in comparison to "natural" antibody amounts.

The lymph and lymph node compartment antigen time response looks like an impulse function. This occurs because a large amount of the antibody produced during the immune response comes into contact with the antigen in this compartment as a result of splenic antibody emptying into the lymph and lymph node compartment. Therefore, the antigen is rapidly removed by the formation of the antigen-antibody complex. Results of experiments with splenectomized mice indicate that the majority of antibody is produced in the spleen. Therefore, the fast removal of antigen from the lymph and lymph node compartment does not appear to distort the model's response. Splenic antigen continually decreases as it should.

Model Sensitivity

A model is "sensitive" to a given parameter if a "slight" change in that parameter value causes a "large" change in the simulation results. If a model is sensitive, the system is probably sensitive. Therefore, parameters, initial conditions, or flux paths to which the model seems to be quite sensitive should have first priority for further experimental study. A partial sensitivity analysis for this model has been performed. Parameter values, state variable initial conditions, and flux paths for which there seems to be general agreement in the literature have not been considered.

Those areas which were selected for sensitivity analysis are:

1. the value of k, the association constant for SRBC,
2. the initial population of B cells in the lymph and lymph node compartment,
3. the plasma cell lifetime,
4. the path of the antibody flux leaving the blood, and
5. the initial populations of the antigen compartments.

In the sensitivity analyses, all model parameters are those given in Tables 1, 2, and 3 except the one being varied.

Sensitivity to k

The association constant, k, controls the probabilities, p_{ds} and p_{dl}, that antigen will bind to antibody. k can vary from 1×10^4 to 1×10^{12}; however, values in the range of 1×10^6 to 1×10^8 are usually cited for multivalent antigens [9, 22, 52, 54]. When $k = 1 \times 10^6$ is used in the simulation, with a SRBC dose of 1×10^8, the antibody population in the blood peaks too late. For $k = 1 \times 10^8$, the antibody population in the blood peaks too soon. A value of $k = 1 \times 10^7$ results in a curve which most closely matches the experimental data. These results are shown in Figure 19. High values of k result in a short period of antibody production because antigen, which induces antibody formation, is rapidly destroyed by the antigen-antibody complex. Likewise, low values of k result in a long antibody production period due to less antigen-antibody complex formation. The optimal value of k varies with the antigen dose.

Sensitivity to Initial B Cell Population

It is difficult to locate all of the lymph nodes in a mouse, so the initial B cell population for the lymph and lymph node compartment determined from the literature could be somewhat low. Increasing the B cell population in the lymph and lymph node compartment by 10% results in an almost

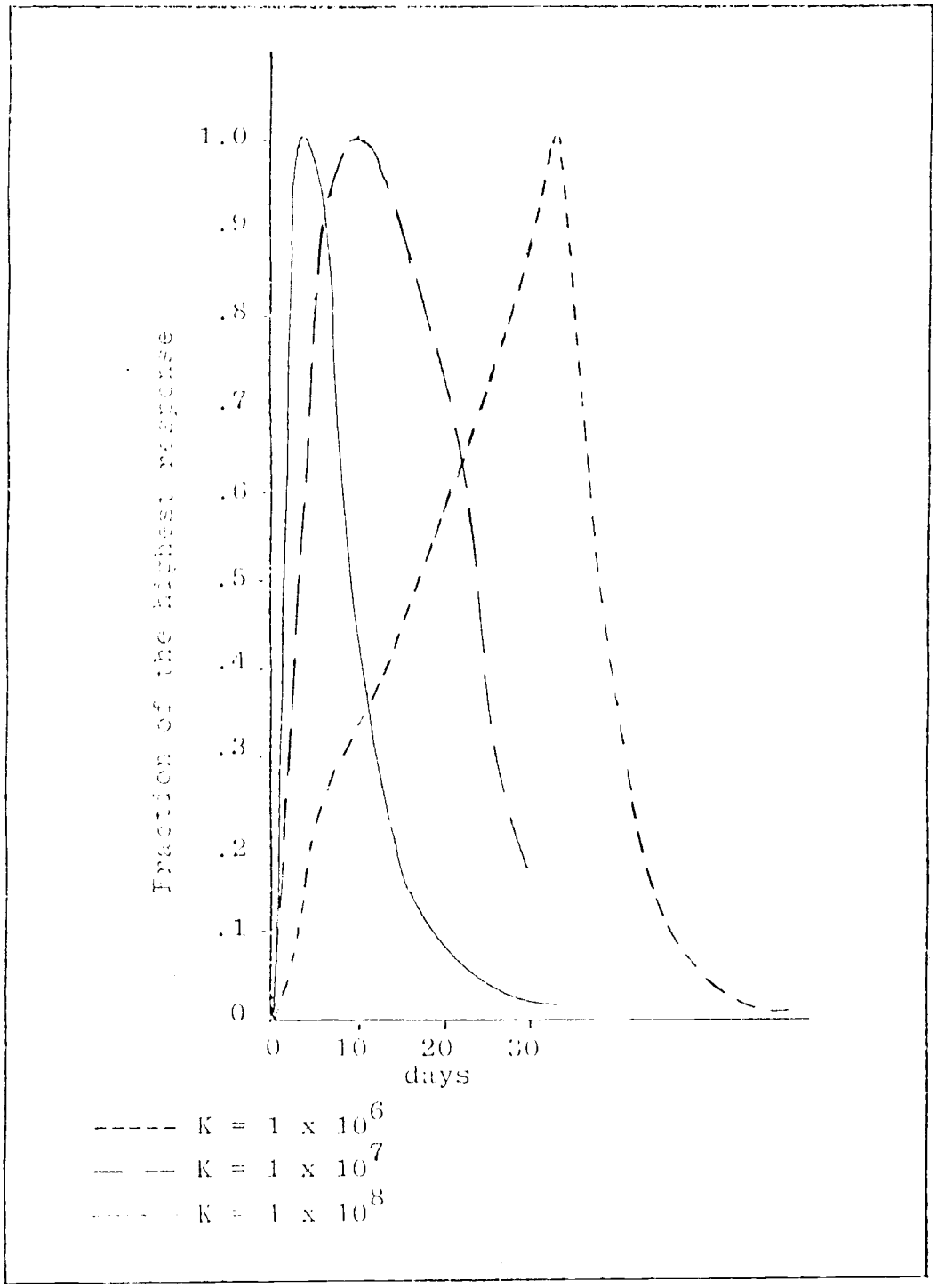

Figure 19. Simulation time responses of antibody in the blood when the association constant is varied

identical time response as when the original population is used.

Sensitivity to Plasma Cell Lifetime

Mohler et al. [8] use a plasma cell lifetime of 40 hours which is four times larger than the value used in the simulations discussed in this study. When this larger value is substituted, the plasma cell population becomes larger resulting in higher antibody production. This causes the antigen-antibody complex formation to increase resulting in the antigen being removed more quickly. Therefore, the immune response time is shorter which causes the time response of the antibody in the blood to peak too soon. Plasma cell lifetimes of 40 and 100 hours result in almost identical antibody time responses. The response for a two hour lifetime peaked later than experimental data. These responses are shown in Figure 20.

Dependence on Flux Path

Simulation results show that it is reasonable to assume that the leakage of antibody from the blood into the extravascular fluid can be approximated as a flux from the blood compartment to the lymph and lymph node compartment as discussed in Chapter II. However, it is known that antibody also leaks out of the capillaries into the splenic pulp as discussed in Chapter III. Thus, it could be proposed that

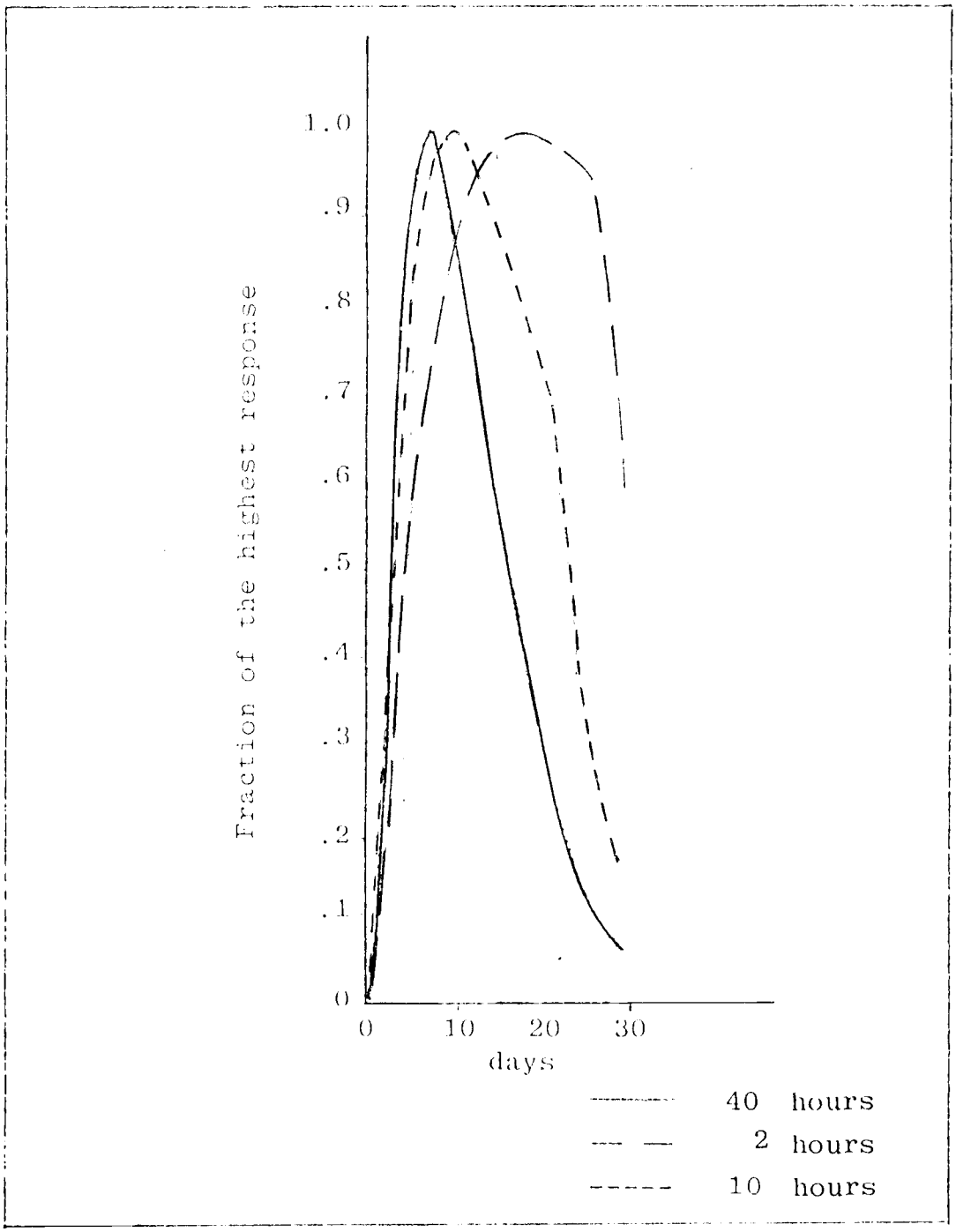

Figure 20. Simulation time response of antibody in the blood for varying plasma cell lifetimes

that most of the antibody which leaves the blood enters the spleen rather than the lymph nodes because a higher volume of blood passes through the spleen than the lymph nodes. This assumption was temporarily incorporated in the model by routing all of the antibody leaving the blood compartment through the spleen compartment as shown in Figure 21. When simulated, this new model acceptably matched experimental data for the whole mouse immune response, but was inaccurate for the splenectomized mouse immune response as shown in Figures 22 and 23. These results tend to confirm the hypothesis that antibody probably enters both the spleen and lymph nodes from the blood. This could be incorporated into the model as a future refinement, but further experimentation would be needed to determine the fractional transfer coefficient values.

Dependence on Antigen Initial Conditions

Sensitivity to antigen dose and to trapping by the spleen and lymph nodes are considered earlier in this chapter. Another factor affecting the initial conditions of the antigen compartments is the number of antigenic determinants per SRBC, a parameter, which is not well known. Increasing or decreasing this factor has the same effect as increasing or decreasing the initial antigen dose.

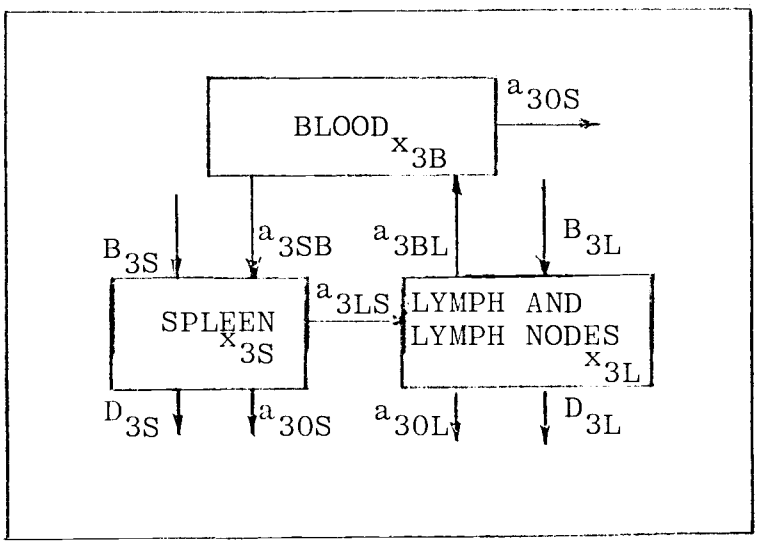

Figure 21. Alternate circulation of antibody among the antibody compartments contained in the tissues and fluids

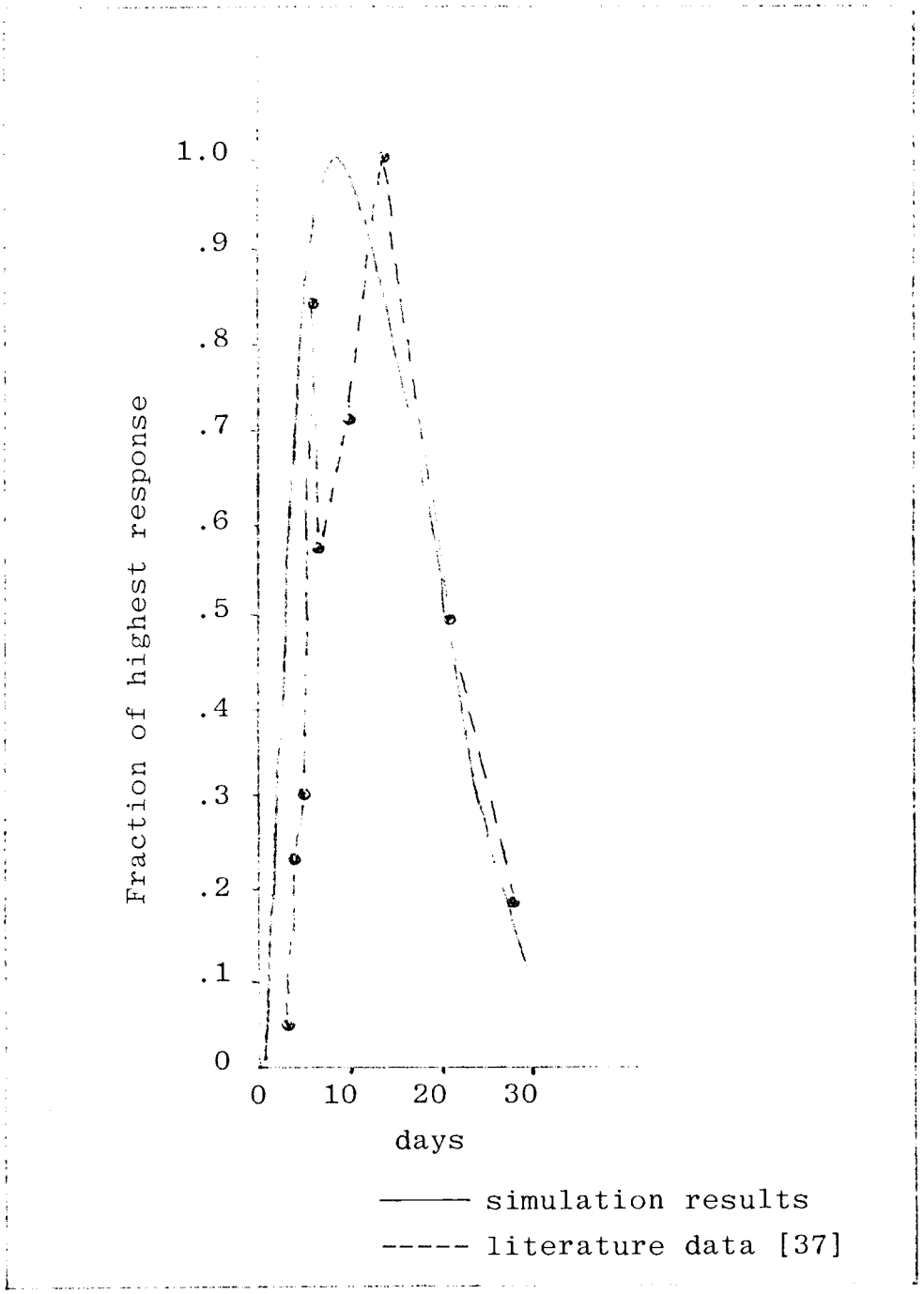

Figure 22. Comparison of literature and simulation time responses of antibody in the blood for the alternate antibody circulation route shown in Figure 21

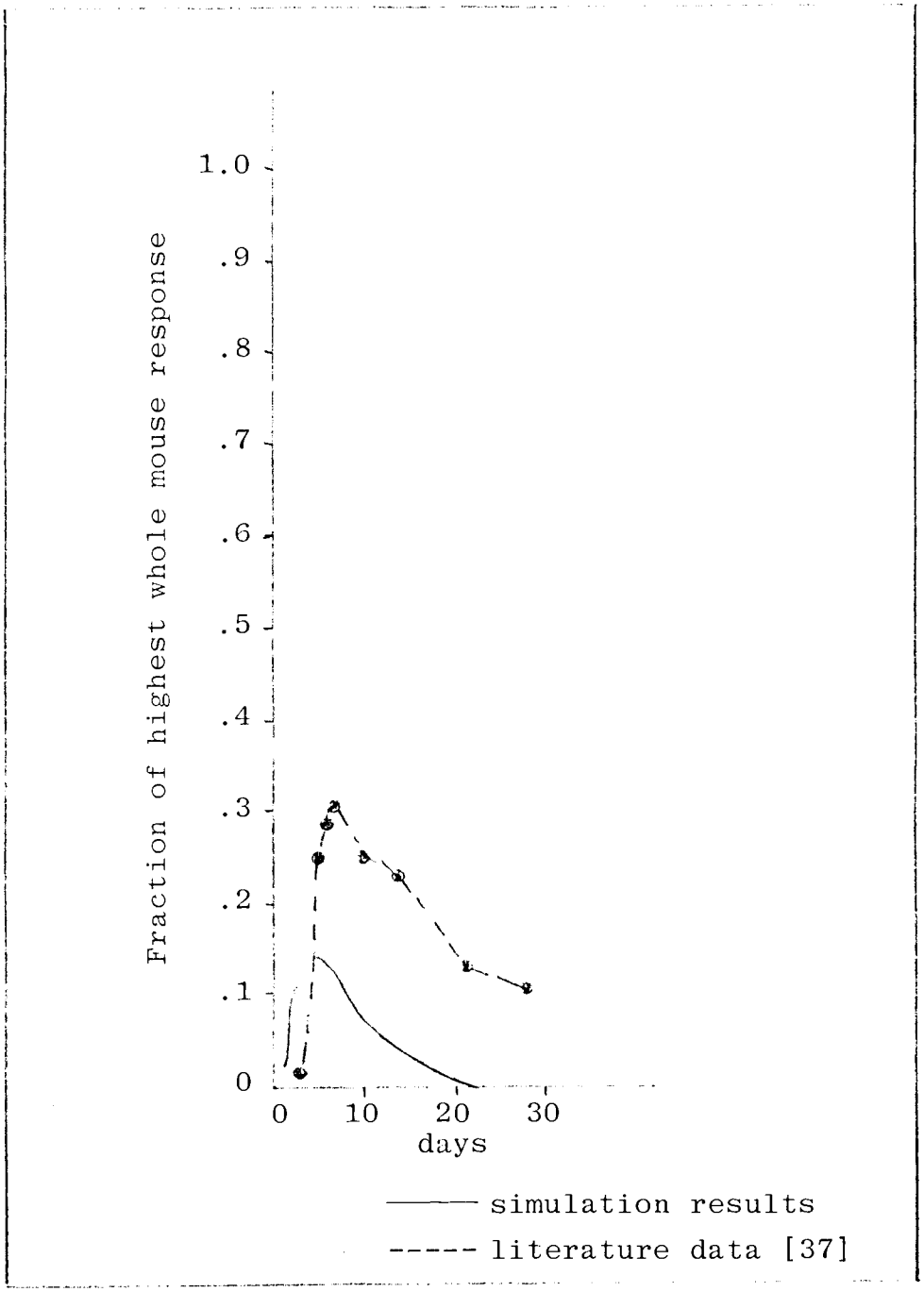

Figure 23. Comparison of literature and simulation time responses in the blood for the alternate antibody circulation route in a splenectomized mouse

The model's sensitivity to the antigen kinetics is best illustrated by the causal loop diagram showing the positive and negative feedback loops in Figure 24. The dashed lines represent causal links where a plus indicates that an increase (decrease) in the population in the compartment of origin causes an increase (decrease) in the terminal compartment population, while a minus means that an increase (decrease) results in a decrease (increase) [1, p. 121]. The feedback loops are represented by the solid lines with plus and minus representing positive and negative feedback respectively. The causal loop diagram shows that the major negative feedback loops are dominated by the antigen populations, x_{4S} and x_{4L}. In this model, the negative feedback loops appear to control population growth. This control results from the formation of the antigen-antibody complex which removes antigen from the system.

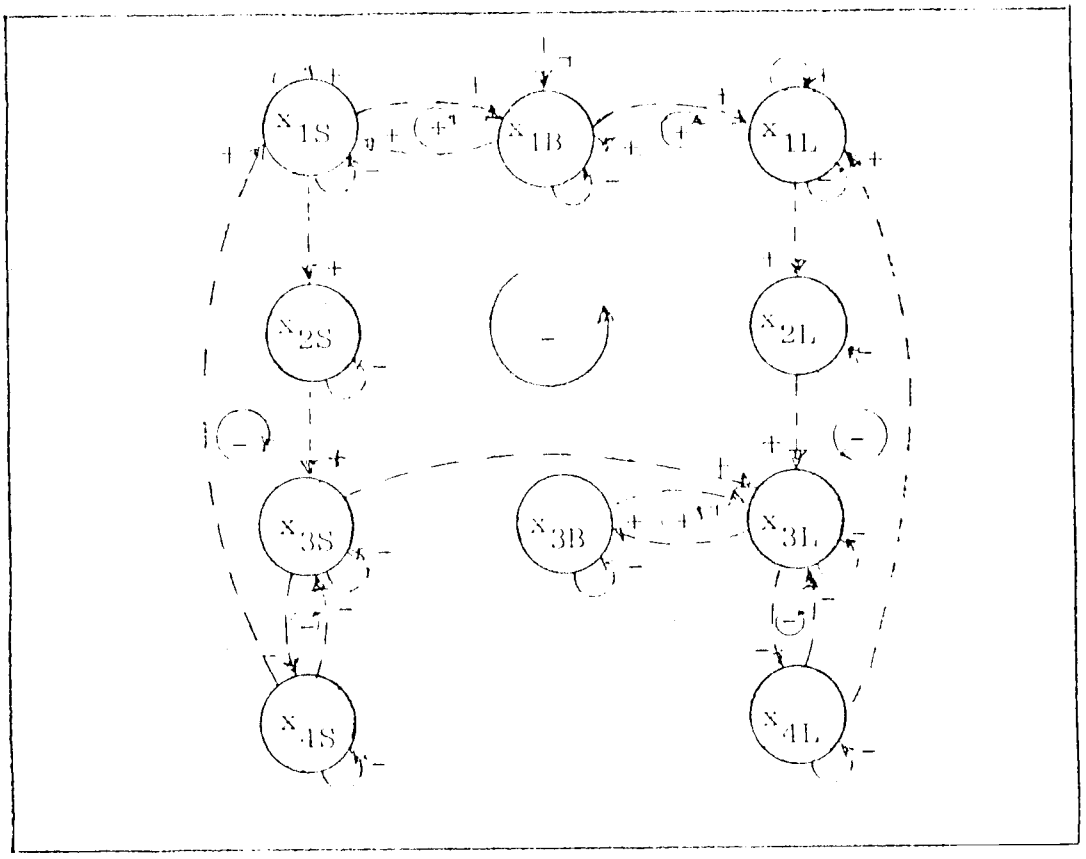

Figure 24. Causal loop diagram of the simplified model

Conclusion

The simplified compartmental model of the immune system simulated here appears to have face validity. Face validity is defined by Hermann to be the subjective estimates of experimenters, observers, or human participants as to the correspondence between the model's operation and their perception of the actual phenomena which the game or simulation represents [45]. The antibody levels for whole and splenectomized mice after SRBC injection found by Alder [37], are closely matched by the simulation output. The other compartments also follow reported levels.

The dependence of the model's response on the antigen dose is, however, a defect of the model. The hypotheses which result in the dose dependence and which indicate that the model should be somewhat dose independent appear to be equally valid. Further experimentation to determine the mechanism by which antigen triggers the immune response is needed to resolve this problem.

The model's credibility could be enhanced by determining more accurately the values of the association constant to which the model is quite sensitive and the plasma cell life time to which the model is somewhat less sensitive.

The model presented here is an improvement over previous models but is still a very simple representation of the immune system. A more sophisticated model could be

used as an aid in immunotherapy, in the planning of immunological experiments, and in testing conflicting hypotheses. Such a model would encompass a more complete immunological theory including, for example, the contributions of T cells and macrophages, the population dependence of birth and death parameters, and the multiple values of k. A more complicated model would also include more compartments. However, most of the fractional transfer coefficients for these additional compartments have unknown values. Tracer experiments are the only way to determine some of these values. Compartmental analysis and tracer analysis are complimentary because a compartmental model suggests tracers experiments, and the interpretation of tracer data suggests a compartmental model. Smith and Mohler [46] discuss important theoretical concepts which relate to tracer studies of the immune system.

This model demonstrates the feasibility and usefulness of the compartmental approach in the study of the immune system. Simulation of this model successfully mimics the immune response as well as locating areas needing further experimental study. Compartmental analysis theory appears to provide a significant conceptual framework for studying the immune system.

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APPENDIX

TABLE 4

Model Notation	GASP IV Notation
x_{1B}	SS(1)
x_{1S}	SS(2)
x_{1L}	SS(3)
x_{2S}	SS(4)
x_{2L}	SS(5)
x_{3B}	SS(6)
x_{3S}	SS(7)
x_{3L}	SS(8)
x_{4S}	SS(9)
x_{4L}	SS(10)
a_{1SB}	A1
a_{1BS}	A2
a_{1LB}	A3
a_{1BL}	A4
a_{10B}, a_{10S}, a_{10L}	A5
a_{20S}, a_{20L}	A6
a_{3LB}	A7
a_{3LS}	A8
a_{3BL}	A9
a_{30B}, a_{30S}, a_{30L}	A10
a_{40S}, a_{40L}	A11
I	SI
k	RK
α	ALPHA
β	BETA
p_{ss}	PSS
p_{sl}	PSL
p_{ds}	PDS
p_{dl}	PDL

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EQUIP,2=FILE
EQUIP,3=FILE
FORTRAN,L,X
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0*002          COMMON /GGOM1/ ATSIG(25),JEVNT,MEA,MEE(100),MLS(100),MSTOP,MOSOR,M
0*003         1MAXO,MNAPT,NMATS,NMFIL,NNO(100),NNTSY,NPRNT,PPASM(50,4),TMOW,TTREG
0*004         2,TTCLS,TTFIN,TTRIP(25),TTSET
0*005          COMMON /GGOM2/ OO(100),DDL(100),DTOUL,DINOW,ISETS,LFLAG(50),NFLAG,
0*006         1NNEOO,NNEOS,NNEOT,SS(100),SSL(100),TTNEX
0*007          COMMON /GGOM3/ AAARE,DTMAX,DTMIN,DTSAV,IITES,LLERR,LLSAV,LLSEV,RRE
0*00F         1SR,TTLAG,TTSAV
0*009          COMMON /GGOM4/ DTPLT(10),HHLOW(25),HHWID(25),IICRO,IITAB(10),JJCEL
0*010         1(25),LLARG(25,2),LLA3H(25,3),LLARR(11,3),LLART(25,2),LLFHI(10),LL
0*011         2SL(11),LLPLT,LLSUP(15),LLSYM(10),MMPTS,NNCEL(25),NNCLT,NNHTS,NNPL
0*012         3T,NNPTS(10),NNSTA,NNVAR(10),RPHI(10),PPLO(10)
0*013          COMMON /GGOM5/ IIEVT,IISEO(6),JJREG,JJCLR,MMNIT,MMON,NNAME(3),NNCF
0*014         1I,NNOAY,NNPT,NNSET,NNPRJ,NNRSM,NNENS,NNRUN,NNSIM,NNYR,SSEED(6)
0*015          COMMON /GGOM6/ EPNO(100),IINN(100),KKPNK(100),MMAXO(100),OOTIM(100
0*016         1),SSORV(25,5),SSTRV(25,6),VVNO(100)
0*017          END
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0►021          END
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*GASPCOM *         2,TTCLS,TTFIN,TTRIB(25),TTSET
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*GASPCOM *         1(500),LLA3C(25,2),LLA3H(25,2),LLAPP(11,2),LLAPT(25,2),LLPHI(10),LL
*GASPCOM *         2FLO(10),LLPLT,LLSUP(15),LLSYM(10),MMPTS,NNCEL(25),NNCLT,NNHIS,NNFL
*GASPCOM *         3T,NNPTS(10),NNSTA,NNVAR(10),PPHI(10),PPLO(10)
*GASPCOM *          COMMON /GCOM5/ IISET,IISE(5),JJREG,JJCLR,MXNIT,MMON,NNAME(3),NNCF
*GASPCOM *         1I,NNDAY,NNPT,NNSET,NNPRJ,NNPRM,NNPNG,NNRUN,NNSTR,NNYR,SSEED(6)
*GASPCOM *          COMMON /GCOM6/ EENQ(100),IINN(100),KKRNK(100),MMAXQ(100),QQTIM(100
*GASPCOM *         1),SSQAV(25,5),SSTDV(25,6),VVNQ(100)
     0+024          INCLUDE USERCOM
*USERCOM *          COMMON/UCOM1/ A1,A2,A3,A4,A5,A6,A7,A8,A9,A10,A11,PN,PI,XAG,
*USERCOM *         1                ALPHA,BETA,PK,Q,QS,QL,VS,VL,XB,XS,XL
     0+025          DIMENSION NSET(1200)
     0+026          COMMON QSET(1200)
     0+027          EQUIVALENCE(NSET(1),QSET(1))
     0+028          NQJOB=50
     0+029          NPRNT=61
     0+030          XB = 1.60E6
     0+031          XS = 6.30E7
     0+032          XL = 1.32E7
     0+033          PN = 5.023E23
     0+034          A5 = 1.0/25.0
     0+035          A6 = 0.1
     0+036          A7 = 6.91
     0+037          A3 = 128.6/129.6
     0+038          A9 = 0.01
     0+039          A10= 1.0/129.0
     0+040          A11= 1.0/120.0
     0+041          A4 = 7.0E5/XL
     0+042          A3 = (A4+A5)*XL/XB
     0+043          A1 = 10.0*A3
     0+044          A2 = A1*XB/XS - A5
     0+045          PI = (A1+A3+A5)*XB - A2*XS - A4*XL
     0+046          ALPHA = 0.225
     0+047          BETA = 2.5E6
     0+048          VS = 2.0E-4
     0+049          VL = 1.0E-4
     0+050          XAG=1.45A
     0+051          CALL GASP
     0+052          STOP
     0+053          END

 NO ERRORS FOR THESIS
LENGTH OF SUBPROGRAM        00166
LENGTH OF COMMON UCOM1      00062
LENGTH OF COMMON GCOM6      02652
LENGTH OF COMMON GCOM5      00044
LENGTH OF COMMON GCOM4      01653
LENGTH OF COMMON GCOM3      00022
LENGTH OF COMMON GCOM2      01836
LENGTH OF COMMON GCOM1      01464
LENGTH OF COMMON            04540
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            083 FORTRAN  VERSION 3.13                09/23/77  1409

                      SUBROUTINE INTLC
                      INCLUDE GASPCOM
*GASPCOM *            COMMON /GCOM1/ ATRIB(25),JEVNT,MFA,MFE(100),MLE(100),MSTOP,NCRDR,N
*GASPCOM *           1NAPO,NNAPT,NNATR,NNFIL,NNQ(100),NNTRY,NPRNT,PPARM(50,4),TNOW,TTBEG
*GASPCOM *           2,TTCLR,TTFIN,TTRIB(25),TTSET
*GASPCOM *            COMMON /GCOM2/ DD(100),DDL(100),DTFUL,DTNOW,ISEES,LFLAG(50),NFLAG,
*GASPCOM *           1NNEQD,NNEQS,NNEQT,SS(100),SSL(100),TTNEX
*GASPCOM *            COMMON /GCOM3/ AAERR,DTMAX,DTMIN,DTSAV,IITES,LLERR,LLSAV,LLSEV,RRE
*GASPCOM *           1RR,TTLAS,TTSAV
*GASPCOM *            COMMON /GCOM4/ DTPLT(10),HHLOW(25),HHWID(25),IICRD,ITTAP(10),JJCEL
*GASPCOM *           1(500),LLABC(25,2),LLABH(25,2),LLABP(11,2),LLABT(25,2),LLFMI(10),LL
*GASPCOM *           2PLO(10),LLPLT,LLSUP(15),LLSYM(10),MMPTS,NNCEL(25),NNCLT,NNHIS,NNPL
*GASPCOM *           3T,NNPTS(10),NNSTA,NNVAR(10),PPHI(10),PPLO(10)
*GASPCOM *            COMMON /GCOM5/ IIEVT,IISEO(6),JJBEG,JJCLR,MMNIT,MMON,NNAME(3),NNCF
*GASPCOM *           1I,NNDAY,NNPT,NNSET,NNPRJ,NNPRM,NNRNS,NNRUN,NNSTR,NNYR,SSEED(6)
*GASPCOM *            COMMON /GCOM6/ FENQ(100),IINN(100),KKRNK(100),MMAXO(100),QQTIM(10
*GASPCOM *           1),SSOBV(25,5),SSTPV(25,6),VVNQ(100)
                      INCLUDE USERCOM
*USERCOM *            COMMON/UCOM1/ A1,A2,A3,A4,A5,A6,A7,A8,A9,A10,A11,EN,RI,XAG,
*USERCOM *           1              ALPHA,BETA,RK,D,GS,GL,VS,VL,XI,XS,XL
                      READ(60,10)RK,D
                   10 FORMAT(2E10.0)
                      GS = .0043*1.0E5*D
                      GL = .0457*1.0E5*D
                      SS(1) = XR
                      SS(2) = XS
                      SS(3) = XL
                      SS(4) = 0.
                      SS(5) = 0.
                      SS(6) = 0.
                      SS(7) = 0.
                      SS(8) = 0.
                      SS(9) = XAG*.0043*D
                      SS(10)= XAG*.0067*D
                      SS(11)= SS(1)+SS(2)+SS(3)
                      SS(12)= SS(4)+SS(5)
                      SS(13)= SS(6)+SS(7)+SS(8)
                      SS(14)= SS(9)+SS(10)
                      RETURN
                      END

   NO ERRORS FOR INTLC
  LENGTH OF SUBPROGRAM       00110
  LENGTH OF COMMON UCOM1     00262
  LENGTH OF COMMON GCOM6     02652
  LENGTH OF COMMON GCOM5     00044
  LENGTH OF COMMON GCOM4     01653
  LENGTH OF COMMON GCOM3     00022
  LENGTH OF COMMON GCOM2     01535
  LENGTH OF COMMON GCOM1     01464
```

OO3 FORTRAN VERSION 3.13 08/23/77 1400

```
          SUBROUTINE STATE
          INCLUDE GASPCOM
*GASPCOM *  COMMON /GCOM1/ ATRIB(25),JEVNT,MFA,MFE(100),MLE(100),MSTOP,NCRDR,N
*GASPCOM * 1NAPO,NNAPT,NNATR,NNFIL,NNQ(100),NNTRY,NPRNT,PPARM(50,4),TNOW,TTBEG
*GASPCOM * 2,TTCLR,TTFIN,TTRIB(25),TTSET
*GASPCOM *  COMMON /GCOM2/ DD(100),DDL(100),DTFUL,DTNOW,ISEES,LFLAG(50),NFLAG,
*GASPCOM * 1NNFQD,NNEQS,NNEQT,SS(100),SSL(100),TTNEX
*GASPCOM *  COMMON /GCOM3/ AAERR,DTMAX,DTMIN,DTSAV,IITSO,LLERR,LLSAV,LLSEV,PRE
*GASPCOM * 1RR,TTLAS,TTSAV
*GASPCOM *  COMMON /GCOM4/ DTPLT(10),HHLOW(25),HHWID(25),IICRD,IITAP(10),JJCEL
*GASPCOM * 1(500),LLABC(25,2),LLABH(25,2),LLABP(11,2),LLAPT(25,2),LLPHI(10),LL
*GASPCOM * 2PLO(10),LLPLT,LLSUP(15),LLSYM(10),MMPTS,NNCEL(25),NNCLT,NNHIS,NNPL
*GASPCOM * 3T,NNPTS(10),NNSTA,NNVAR(10),PPHI(10),PPLO(10)
*GASPCOM *  COMMON /GCOM5/ IIEVT,IISED(6),JJBEG,JJCLR,MMNIT,MMON,NNAME(3),NNCF
*GASPCOM * 1I,NNDAY,NNPT,NNSET,NNPRJ,NNPRM,NNRNS,NNRUN,NNSTR,NNYR,SSEED(6)
*GASPCOM *  COMMON /GCOM6/ EENQ(100),IINN(100),KKRNK(100),MMAXQ(100),QQTIM(100
*GASPCOM * 1),SSOBV(25,5),SSTPV(25,6),VVNQ(100)
          INCLUDE USERCOM
*USERCOM *  COMMON/UCOM1/ A1,A2,A3,A4,A5,A6,A7,A8,A9,A10,A11,RN,PI,XAG,
*USERCOM * 1                   ALPHA,BETA,RK,D,GS,GL,VS,VL,XB,XS,XL
          PSS=0.
          IF(SS(9).GT.GS) PSS=1.0
          PSL=0.
          IF(SS(10).GT.GL) PSL=1.0
          QS = 60.*RK*SS(9)/(VS*RN)
          QL = 60.*RK*SS(10)/(VL*RN)
          POS =      QS/(1.+QS)
          POL =      QL/(1.+QL)
          DD(1) = PI + A2*SS(2) + A4*SS(3) - (A1+A3+A5)*SS(1)
          DD(2) = ALPHA*PSS*(1.-2.*POS)*SS(2) + A1*SS(1) - (A2+A5)*SS(2)
          DD(3) = ALPHA*PSL*(1.-2.*POL)*SS(3) + A3*SS(1) - (A4+A5)*SS(3)
          DD(4) = 2.*ALPHA*PSS*POS*SS(2) - A6*SS(4)
          DD(5) = 2.*ALPHA*PSL*POL*SS(3) - A6*SS(5)
          DD(6) = A9*SS(8) - (A7+A10)*SS(6)
          DD(7) = BETA*SS(4) - (A8+A10+QS)*SS(7)
          DD(8) = BETA*SS(5) + A7*SS(6) + A8*SS(7) - (A9+A10+QL)*SS(8)
          DD(9) = -A11*SS(9) - QS*SS(7)
          DD(10)= -A11*SS(10) - QL*SS(8)
          DD(11)= DD(1)+DD(2)+DD(3)
          DD(12)= DD(4)+DD(5)
          DD(13)= DD(6)+DD(7)+DD(8)
          DD(14)= DD(9)+DD(10)
          RETURN
          END
```

```
 NO ERRORS FOR STATE
LENGTH OF SUBPROGRAM      00332
LENGTH OF COMMON UCOM1    00062
LENGTH OF COMMON GCOM6    02552
LENGTH OF COMMON GCOM5    00044
LENGTH OF COMMON GCOM4    01653
LENGTH OF COMMON GCOM3    00022
LENGTH OF COMMON GCOM2    01535
LENGTH OF COMMON GCOM1    01464
```

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073 FORTRAN  VERSION 3.13              09/23/77  1409

    0+104          SUBROUTINE SSAVE
    0+105          INCLUDE GASPCOM
*GASPCOM *         COMMON /GCOM1/ ATRIB(25),JEVNT,MFA,MFE(100),MLE(100),MSTOP,NCRDR,N
*GASPCOM *        1NAPO,NNAPT,NNATR,NNFIL,NNQ(100),NNTRY,NPRNT,PPARM(50,4),TNOW,TTBEG
*GASPCOM *        2,TTCLR,TTFIN,TTRIB(25),TTSET
*GASPCOM *         COMMON /GCOM2/ DD(100),DDL(100),DTFUL,DTNOW,ISEES,LFLAG(50),NFLAG,
*GASPCOM *        1NNEQD,NNEQS,NNEQT,SS(100),SSL(100),TTNEX
*GASPCOM *         COMMON /GCOM3/ AAERR,DTMAX,DTMIN,DTSAV,IITES,LLERR,LLSAV,LLSEV,RRE
*GASPCOM *        1RR,TTLAS,TTSAV
*GASPCOM *         COMMON /GCOM4/ DTPLT(10),HHLOW(25),HHWID(25),IICRD,IITAP(10),JJCEL
*GASPCOM *        1(500),LLABC(25,2),LLABH(25,2),LLABP(11,2),LLABT(25,2),LLPHI(10),LL
*GASPCOM *        2PLO(10),LLPLT,LLTUP(15),LLSYM(10),MMPTS,NNCEL(25),NNCLT,NNHIS,NNPL
*GASPCOM *        3T,NNPTS(10),NNSTA,NNVAR(10),PPHI(10),PPLO(10)
*GASPCOM *         COMMON /GCOM5/ IIEVT,IISEE(6),JJBEG,JJCLR,MMNIT,MMON,NNAME(3),NNCF
*GASPCOM *        1I,NNDAY,NNPT,NNSET,NNPRJ,NNPRM,NNRNS,NNRUN,NNSTR,NNYR,SSEED(6)
*GASPCOM *         COMMON /GCOM6/ EEMQ(100),IINN(100),KKRNK(100),MMAXQ(100),QQTIM(100
*GASPCOM *        1),SSOBV(25,5),SSTPV(25,6),VVNQ(100)
    0+106          INCLUDE USERCOM
*USERCOM *         COMMON/UCOM1/ A1,A2,A3,A4,A5,A6,A7,A8,A9,A10,A11,RN,PI,XAG,
*USERCOM *        1                   ALPHA,BETA,RK,C,GG,GL,VS,VL,XB,XS,XL
    0+107          DIMENSION R1(5),R2(5),R3(4)
    0+108          DO 100 I=1,5
    0+109          R1(I)=SS(I)
    0+110      100 CONTINUE
    0+111          CALL GPLOT(R1,TNOW,1)
    0+112          DO 200 I=1,5
    0+113          J=I+5
    0+114          R2(I)=SS(J)
    0+115      200 CONTINUE
    0+116          CALL GPLOT(R2,TNOW,2)
    0+117          DO 300 I=1,4
    0+118          J=I+10
    0+119          R3(I)=SS(J)
    0+120      300 CONTINUE
    0+121          CALL GPLOT(R3,TNOW,3)
    0+122          RETURN
    0+123          END

 NO ERRORS FOR SSAVE
LENGTH OF SUBPROGRAM        00157
LENGTH OF COMMON UCOM1      00062
LENGTH OF COMMON GCOM6      02652
LENGTH OF COMMON GCOM5      00044
LENGTH OF COMMON GCOM4      01653
LENGTH OF COMMON GCOM3      00022
LENGTH OF COMMON GCOM2      01535
LENGTH OF COMMON GCOM1      01464
LOAD,F6,L=*GASFLIB
    RUN
RUN
```

```
                              SIMULATION PROJECT NUMBER    4   BY  LAWRENCE

                              DATE 08/23/77.   2:09 PM   RUN NUMBER    1 OF     1
                              LLSUP=0000000000000000   GASP IV VERSION 13APR75

NNCLT=      0     NNSTA=      0     NNHIS=      0     NNPRM=      0     NNPLT=      3     NNSTR=      1     NNTRY=     10
NNATR=      0     NNFIL=      0     NNSET=   6000     NNEQD=     14     NNEQS=      0     NFLAG=      0

GPLOT NO.   1     LLABR= HOURS      IITAP=      1     NNVAR=      5     LLPLT=      2                   DTPLT=     2.4000E 01
  VAR NO.   1         1=  X1S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     2.5000E 10
  VAR NO.   2         2=  X1S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     2.5000E 10
  VAR NO.   3         3=  X1L       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     2.5000E 10
  VAR NO.   4         4=  X2S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     2.5000E 10
  VAR NO.   5         5=  X2L       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     2.5000E 10
GPLOT NO.   2     LLABR= HOURS      IITAP=      2     NNVAR=      5     LLPLT=      2                   DTPLT=     2.4000E 01
  VAR NO.   1         6=  X3S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.2500E 11
  VAR NO.   2         7=  X3S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.2500E 11
  VAR NO.   3         8=  X3L       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.2500E 11
  VAR NO.   4         9=  X4S       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.2500E 11
  VAR NO.   5         0=  X4L       LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.2500E 11
GPLOT NO.   3     LLABR= HOURS      IITAP=      3     NNVAR=      4     LLPLT=      2                   DTPLT=     2.4000E 01
  VAR NO.   1         B= B CELLS    LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.7500E 11
  VAR NO.   2         P= PLASMA     LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.7500E 11
  VAR NO.   3         A=ANTIBODY    LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.7500E 11
  VAR NO.   4         G= ANTIGEN    LLPLO=      1     LLPHI=      1     PPLO =           0E 00        PPHI =     1.7500E 11

IIEVT=      0     LLERR=      1     AAERR=     1.0000E 02               RRERR=     1.0000E-01
DTMIN=     1.0000E-04               DTMAX=     1.0000E 00               DTSAV=     2.4000E 01

MSTOP=      1     JJCLR=      1     JJBEG=      1     IICRD=     13     IIBEG=           0E 00        IIFIN=     7.2000E 02
JJFIL=      1
IISEQ=      0
```

GASP STATE STORAGE AREA DUMP AT TIME 0E 00

(I)	SS(I)	DD(I)
1	1.60000E 06	-2.44148E-04
2	6.35000E 07	1.57435E 06
3	1.30000E 07	3.29966E 05
4	0E 00	6.74655E 01
5	0E 00	4.40438E 01
6	0E 00	0E 00
7	0E 00	0E 00
8	0E 00	0E 00
9	4.30000E 06	-3.58335E 04
10	5.70000E 06	-5.58335E 04
11	7.78000E 07	1.90042E 06
12	0E 00	1.11151E 02
13	0E 00	0E 00
14	1.10000E 07	-9.16675E 04

INTERMEDIATE RESULTS

GASP SUMMARY REPORT

SIMULATION PROJECT NUMBER 4 BY LAWRENCE

DATE 09/23/77, 2:09 PM RUN NUMBER 1 OF 1

CURRENT TIME = 7.200E 02

GASP STATE STORAGE AREA DUMP AT TIME 7.200CE 02

(I)	SS(I)	DD(I)
1	5.2172E 07	-2.4499E 05
2	2.2291E 07	-2.0803E 07
3	5.1343E 08	-5.0375E 05
4	2.4711E-08	-2.4712E-08
5	1.0091E-28	-1.0090E-28
6	9.6819E 03	-7.4460E 07
7	5.9634E-32	-6.9637E-03
8	9.7412E 03	-7.6106E 07
9	5.0129E 02	-5.0106E 05
10	2.1578E-201	-2.2940E-202
11	2.7977E 09	-2.8209E 07
12	2.9216E-08	-2.4712E-08
13	1.0423E 11	-1.0057E 09
14	6.0129E 02	-5.0106E 05

TABLE NUMBER 1
RUN NUMBER 1

HOURS	X1S	X1C	X1L	X2S	X2L
0.0	1.000000E 00	6.330000E 07	1.320000E 07	0.000000E 00	0.000000E 00
0.4	1.000000E 00	6.330000E 07	1.320000E 07	0.000000E 00	0.000000E 00
0.4	1.000000E 00	1.266000E 08	2.640000E 07	7.196800E 02	1.632000E 02
0.8	1.000000E 00	1.899000E 08	3.960000E 07	8.142400E 02	1.537300E 01
0.8	1.000000E 00	2.531999E 08	5.280000E 07	7.696000E 02	1.304800E 00
1.2	1.000000E 00	3.165000E 08	6.600000E 07	8.099776E 02	1.265520E-01
1.2	1.000000E 00	3.798000E 08	7.919999E 07	8.134400E 02	1.147700E-02
1.6	1.000000E 00	4.431000E 08	9.240000E 07	8.133000E 02	1.041200E-03
1.6	1.000000E 00	5.063999E 08	1.056000E 08	8.129600E 02	9.644560E-05
2.0	1.000000E 00	5.697000E 08	1.188000E 08	8.129600E 02	8.556800E-06
2.0	1.000000E 00	6.330000E 08	1.319999E 08	8.129600E 02	7.727760E-07
2.4	1.000000E 00	6.963000E 08	1.452000E 08	8.129600E 02	7.052800E-08
2.4	1.000000E 00	7.596000E 08	1.584000E 08	8.129600E 02	6.497440E-09
2.8	1.000000E 00	8.229000E 08	1.716000E 08	8.129600E 02	6.038768E-10
2.8	1.000000E 00	8.862000E 08	1.847999E 08	8.129600E 02	5.660160E-11
3.2	1.000000E 00	9.495000E 08	1.980000E 08	8.129600E 02	5.329600E-12
3.2	1.000000E 00	1.012800E 09	2.112000E 08	8.129600E 02	5.037760E-13
3.6	1.000000E 00	1.076100E 09	2.244000E 08	8.129600E 02	4.777632E-14
3.6	1.000000E 00	1.139400E 09	2.376000E 08	8.129600E 02	4.544160E-15
4.0	1.000000E 00	1.202700E 09	2.508000E 08	8.129600E 02	4.333280E-16
4.0	1.000000E 00	1.266000E 09	2.640000E 08	8.129600E 02	4.141520E-17
4.4	1.000000E 00	1.329300E 09	2.772000E 08	8.129600E 02	3.966240E-18
4.4	1.000000E 00	1.392600E 09	2.904000E 08	8.129600E 02	3.805520E-19
4.8	1.000000E 00	1.455900E 09	3.036000E 08	8.129600E 02	3.658160E-20
4.8	1.000000E 00	1.519200E 09	3.168000E 08	8.129600E 02	3.523120E-21
5.2	1.000000E 00	1.582500E 09	3.300000E 08	8.129600E 02	3.398560E-22
5.2	1.000000E 00	1.645800E 09	3.432000E 08	8.129600E 02	3.283760E-23
5.6	1.000000E 00	1.709100E 09	3.564000E 08	8.129600E 02	3.177120E-24
5.6	1.000000E 00	1.772400E 09	3.696000E 08	8.129600E 02	3.078160E-25
6.0	1.000000E 00	1.835700E 09	3.828000E 08	8.129600E 02	2.986480E-26
6.0	1.000000E 00	1.899000E 09	3.960000E 08	8.129600E 02	2.900800E-27
7.0	1.000000E 00	2.215500E 09	4.620000E 08	8.129600E 02	2.533600E-28
7.2	1.000000E 00	2.278800E 09	4.752000E 08	8.129600E 02	2.473600E-29
MINIMUM	1.000000E 00	6.330000E 07	1.320000E 07	0.000000E 00	0.000000E 00
MAXIMUM	1.000000E 00	2.278800E 09	4.752000E 08	8.142400E 02	1.632000E 02

OUTPUT CONSISTS OF 33 POINT SETS (165 POINTS)

TABLE NUMBER 2
RUN NUMBER 1

HOURS	X33	X35	X3L	X45	X4L
0E 00	0E 00	0E 00	0E 00	4.3000E 06	6.7000E 06
0E 00	0E 00	0E 00	0E 00	4.3000E 06	6.7000E 06
2.4000E 01	2.9250E 09	1.7639E 09	3.3202E 10	3.0898E 06	2.0393E 05
4.8000E 01	1.1944E 10	2.0355E 09	6.4117E 10	2.0622E 06	1.1730E 00
7.2000E 01	2.2513E 10	1.9308E 09	8.4200E 10	1.2913E 06	1.6694E-08
9.6000E 01	3.2521E 10	1.7566E 09	9.6131E 10	8.4799E 05	5.1353E-18
1.2000E 02	4.0759E 10	1.5914E 09	1.0235E 11	5.6848E 05	1.9595E-28
1.4400E 02	4.5922E 10	1.4485E 09	1.0433E 11	3.8819E 05	2.8472E-39
1.6800E 02	5.1169E 10	1.3283E 09	1.0491E 11	2.6927E 05	3.0755E-50
1.9200E 02	5.3798E 10	1.2257E 09	1.0349E 11	1.9927E 05	3.9444E-61
2.1600E 02	5.5119E 10	1.1407E 09	1.0113E 11	1.3453E 05	7.9367E-72
2.4000E 02	5.5461E 10	1.0674E 09	9.8207E 10	9.6538E 04	3.0364E-82
2.6400E 02	5.5078E 10	1.0047E 09	9.4978E 10	6.9839E 04	2.4963E-92
2.8800E 02	5.4191E 10	9.5361E 08	9.1613E 10	5.0876E 04	4.1757-102
3.1200E 02	5.2134E 10	9.0373E 08	8.8230E 10	3.7296E 04	1.6197-111
3.3600E 02	5.1463E 10	8.6287E 08	8.4907E 10	2.7470E 04	1.3959-120
3.6000E 02	4.9365E 10	8.2705E 08	8.1696E 10	2.0330E 04	2.6190-129
3.8400E 02	4.8204E 10	7.9551E 08	7.8539E 10	1.5107E 04	1.5378-137
4.0800E 02	4.6544E 10	7.6761E 08	7.5730E 10	1.1266E 04	8.3673-146
4.3200E 02	4.4909E 10	7.4240E 08	7.3095E 10	8.4277E 03	1.3195-153
4.5600E 02	4.3327E 10	7.2071E 08	7.0459E 10	6.3223E 03	3.8991-161
4.8000E 02	4.1315E 10	7.0091E 08	6.8090E 10	4.7547E 03	2.0711-168
5.0400E 02	4.0166E 10	1.6494E 08	5.1595E 10	3.6675E 03	2.3956-175
5.2800E 02	3.6371E 10	1.4363E 07	4.8950E 10	2.8804E 03	3.5332-181
5.5200E 02	3.2793E 10	1.3574E 06	3.8841E 10	2.4395E 03	8.7449-186
5.7600E 02	2.8041E 10	1.2314E 05	3.1265E 10	1.9963E 03	1.7124-189
6.0000E 02	2.3791E 10	1.1171E 04	2.5449E 10	1.6344E 03	1.6407-192
6.2400E 02	2.0314E 10	1.0134E 03	2.0866E 10	1.3392E 03	5.4046-195
6.4800E 02	1.6751E 10	9.1935E 01	1.7183E 10	1.0956E 03	4.7537-197
6.7200E 02	1.3977E 10	9.3402E 00	1.4202E 10	8.3700E 02	9.2417-199
6.9600E 02	1.1640E 10	7.5661E-01	1.1755E 10	7.3440E 02	3.4315-200
7.2000E 02	9.5319E 09	6.3638E-02	9.7412E 09	6.0129E 02	2.1676-201
7.2000E 02	9.5819E 09	6.9634E-02	9.7412E 09	6.0128E 02	2.1676-201
MINIMUM	0E 00	0E 00	0E 00	6.0128E 02	2.1676-201
MAXIMUM	5.5461E 10	2.0355E 09	1.0491E 11	4.3000E 06	6.7000E 06

OUTPUT CONSISTS OF 33 POINT SETS (165 POINTS)

TABLE NUMBER 7
RUN NUMBER 1

HOURS	B CELLS	PLASMA	ANTIBODY	ANTIGEN
0E 00	7.7800E 07	0E 00	0E 00	1.1000E 07
0E 00	7.7800E 07	0E 00	0E 00	1.1000E 07
2.4000E 01	1.3222E 08	8.9189E 02	5.7830E 10	3.2927E 06
4.8000E 01	1.9394E 08	8.2961E 02	7.7997E 10	2.0622E 06
7.2000E 01	2.7277E 08	7.7104E 02	1.0865E 11	1.2913E 06
9.6000E 01	3.7519E 08	6.9399E 02	1.3041E 11	8.4799E 05
1.2000E 02	5.0775E 08	6.3401E 02	1.4469E 11	5.6843E 05
1.4400E 02	6.7024E 08	5.7736E 02	1.5320E 11	3.8819E 05
1.6800E 02	9.0107E 08	5.2950E 02	1.5741E 11	2.6927E 05
1.9200E 02	1.1388E 09	4.8914E 02	1.5851E 11	1.8927E 05
2.1600E 02	1.5591E 09	4.5496E 02	1.5739E 11	1.3453E 05
2.4000E 02	2.0392E 09	4.2585E 02	1.5474E 11	9.6578E 04
2.6400E 02	2.5501E 09	4.0092E 02	1.5106E 11	6.9838E 04
2.8800E 02	3.4637E 09	3.7942E 02	1.4674E 11	5.0875E 04
3.1200E 02	4.5021E 09	3.6078E 02	1.4207E 11	3.7786E 04
3.3600E 02	5.3459E 09	3.4452E 02	1.3723E 11	2.7475E 04
3.6000E 02	7.3864E 09	3.3027E 02	1.3239E 11	2.0330E 04
3.8400E 02	9.8322E 09	3.1772E 02	1.2763E 11	1.5107E 04
4.0800E 02	1.2740E 10	3.0663E 02	1.2304E 11	1.1266E 04
4.3200E 02	1.6502E 10	2.9675E 02	1.1866E 11	8.4277E 03
4.5600E 02	2.1367E 10	2.8794E 02	1.1451E 11	6.3223E 03
4.8000E 02	2.7660E 10	2.8006E 02	1.1061E 11	4.7547E 03
5.0400E 02	2.5345E 10	5.9380E 01	1.0203E 11	3.6675E 03
5.2800E 02	2.2145E 10	5.3868E 00	8.5396E 10	2.9924E 03
5.5200E 02	1.9707E 10	4.3869E-01	7.1422E 10	2.4385E 03
5.7600E 02	1.7249E 10	4.4332E-02	5.9307E 10	1.9963E 03
6.0000E 02	9.5571E 09	4.0218E-03	4.9239E 10	1.6344E 03
6.2400E 02	7.4603E 09	3.6490E-04	4.0890E 10	1.3382E 03
6.4800E 02	5.8273E 09	3.3172E-05	3.3949E 10	1.0956E 03
6.7200E 02	4.5555E 09	3.0771E-06	2.8173E 10	8.9700E 02
6.9600E 02	3.5550E 09	3.4699E-07	2.3395E 10	7.3449E 02
7.2000E 02	2.7337E 09	9.9216E-08	1.9423E 10	6.0129E 02
7.2000E 02	2.7337E 09	9.9216E-08	1.9423E 10	6.0129E 02
MINIMUM	7.7800E 07	0E 00	0E 00	6.0129E 02
MAXIMUM	2.7660E 10	8.9189E 02	1.5851E 11	1.1000E 07

OUTPUT CONSISTS OF 33 POINT SETS (132 POINTS)

```
END OF FORTRAN EXECUTION
LOGOFF
    COST $5.14
    CPU TIME SEC.     56.4
    MEMBLKS             31
    WC TIME MIN.       2.5
    LP RECORDS         935
    CARDS READ         156
```