SYSTEM THEORETIC CONTROL IN IMMUNOLOGY[†]

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ABSTRACT

A systematic overview is presented of body immune response from which a primitive mathematical model is derived as a base for more extensive research. The model provides a basic description of one basic class of cells (B-cells) with extensions for antibody switch-over and secondary response.

Introduction

The purpose of this paper is to present a kinetic model of cellular and antibody secretion changes during the immune response. The immune system can be defined as that which distinguishes between "self" and "non-self" and rejects foreign agents. This definition will be taken as a starting point for developing a mathematical model of the immune system which is comprised of:

- (1) a group of cells, the lymphocytes, of which each human body possesses about 10^{12} and,
- (2) a group of molecules, the antibodies, of which each human possesses about 10^{20}

When an organism is invaded by an antigen (i.e. a foreign agent which could be a virus or a bacterial product), lymphocytes and antibodies are mobilized toward a common objective - the final elimination of the antigen invader. Some subgroups of the lymphocytes will get larger (the B-cells); other subgroups of lymphocytes (the T-cells) will modify their function during the immune response by first enhancing the antibody production, and then eventually by decreasing this production rate. After elimination of the antigen the system will go back to a state of equilibrium where the immunocompetent cells will gradually cease to differentiate and produce the antibodies.

The immune response appears as a highly complex and finely controlled variable structure system [1] with each type of immunocompetent cell and response modulating the others. A systematic understanding of immunology should provide valuable clues to the solution of relevant problems in such areas as: (1) immunotherapy, where the immune response is activated and/or inactivated artificially, (2) transplant rejection, (3) viral diseases, and (4) cancer, where because of the presence of blocking factors, immunocompetent cells lose their inhibiting effect on the tumor. Further,

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a mathematical model of the immune response should help to extract the few most essential variables from the more complex real situation. It could therefore be valuable in correlation and interpretation of the findings of the vast number of experimental projects becoming available, and could help avoid the need for certain experiments which may be impossible to perform on human beings. Several different models are being developed - each one with the objective of interpreting a specific function of the immune system. Even the mathematical models taken together will, of course, remain an oversimplification of the real system.

Present Overview of the Immune System⁺

Lymphocytes are produced in the bone marrow at an approximate rate of 10^7 cells/minute. Whereupon they reach, by means of circulating antibody molecules in the blood stream, most tissues of the body. They are collected and concentrated in some parts of the immune system such as the lymph nodes, the thymus and the spleen, and in the bone marrow. When antigen enters the body, two different types of immunological reaction may occur:

- (1) The synthesis and release of free antibody into the blood and other fluids (humoral immune response). The antibody reacts with antigen to form complexes which are subsequently eliminated.
- (2) The production of "sensitized" lymphocytes which have antibody-like molecules on the surface. These are the effects of cell-mediated immunity.

At the rest state, the lymphocytes secrete small amounts of antibody which coats the cells and constitutes the antibody-combining sites or receptors. The antigen is formed of a large protein molecule that displays on its surface some antigenic determinant called epitopes susceptible to recognition by the cell receptors. The epitope-receptor recognition is the stimulating signal for the lymphocyte, identified then as a B-cell, to undergo proliferation and differentiation. The offspring cells form family lines called clones. Some cells, termed plasma cells, will secrete the antibody at a rate of about 10^8 molecules/cell·h. Other cells, called memory cells, return to rest and represent the "memory" of the antigen exposure. According to the clonal selection theory, all those clones generated by the stimulation of the lymphocytes are committed either to produce or to carry the memory of the same antibody which originally stimulated the lymphocyte cell. [22]

The stimulation of the lymphocytes depends on several factors:

- (i) the concentration on the lymphocyte surface of recognized epitopes,
- (ii) the degree of fit for epitope-combining sites,
- (iii) the way epitopes are presented, either on the surface of a molecule or on the surface of a cell,
- (iv) and in most humoral reactions, but not in all, on the presence of another type of lymphocyte, the T-cells.

⁺ For a detailed discussion the reader is referred to the excellent texts by Roitt [2] and by Abramoff and LaVia [3].

The T-cells constitute approximately 70 percent of the total lymphocyte population. They are experimentally distinguished from the B-cells, about 25 percent of the lymphocytes, rather by their function than by morphological differences. (The remaining cells not included in both counts are sometimes termed "null cells.") T-cells are processed by or in some way dependent on the thymus. They are responsible for cell-mediated immunity, and although they do not seem to secrete antibody themselves, they do play a key role in the humoral immune primary response and in the secondary response (immune response to second exposure to antigen).

Antibody and antigen react together to form an antibody-antigen complex. The chemical reaction is characterized by an intrinsic equilibrium constant or antibody affinity (k in $l/mole$) which refers to the energy of interaction between one site of antibody and one antigen-determinant [4]. This intrinsic affinity is not measurable experimentally since it is not possible to isolate one single site and one determinant. One rather measures a functional affinity which represents an average of all interactions of antigen combining sites in one antibody molecule with corresponding copies of specific determinants.

The final elimination of antigen follows essentially two patterns.

- (1) Opsonic adherence: the antibody reacting with antigen develops an increase binding affinity for specific sites on the surface of scavenger cells such as polymorphonuclear leucocytes and macrophages. The bacteria coated with antibody become easier to be engulfed and digested.
- (2) Lysis of cell by complement cascades. Complement operation requires the presence of antigen-antibody complex on the surface of bacteria and of the first complement which is a protein. The complement cascade is activated by the Ab-Ag complex whereupon several molecules of the next component in the complement sequence (at least 9 basic complements altogether) are generated. At their turn, each of these molecules generate several molecules of the next complement for an amplified cascade effect. The last molecule formed in the chain has the ability to punch "a functional hole" through the cell membrane on which they are fixed, leading to the death of the cell or lysis. Similar cascade chains and the effect of enzyme concentration to increase membrane permeability as demonstrated by lysis is discussed by Mohler [5] and Banks [6].

Kinetics of Cell Population and Antibody Production - Model I

The first mathematical analysis of the immune process was of a preliminary nature by Hege and Cole [7]. Jilek [8,9] derives a probability model of different cell types to undergo repeated contacts with specific antigens. He assumes a Poisson form of process and considers a Monte Carlo simulation. Bell [10,11,12] derives a model, which was a significant advance, for the binding of antigen to antibodies of different affinity constants. The research discussed here is most closely related to

recent research conducted at the University of Rome through our joint US-Italy research program [13,14].

Basic assumptions usually made in past research include:

- (a) clonal selection theory as discussed above;
- (b) antigen is monovalent, but the model could be easily extended to a multi-valent antigen;
- (c) T-B cell cooperation is not considered;
- (d) the model describes the humoral immune response, and cell-mediated immunity is not considered;
- (e) existence of the numerous different types of antibodies and of different types of cells secreting them is not considered;
- (f) any mutual interaction between cell receptors is neglected;
- (g) system parameters are assumed to be independent of total cell population;
- (h) immunological tolerance is neglected or poorly explained,
- (i) switch-over phenomenon is neglected;
- (j) difference between primary and secondary response is neglected.

Model I may be derived with assumption (a) to (j) as listed above. It should be noted that this model is only intended to be a base for further work and by no means a complete model of the immune system.

Consider the following classification according to state and control:

$x_1(k,t)$: population density of B-cells, which are stimulated lymphocyte cells with particular surface receptors for antigen according to the antibody affinity constant k . They may divide to produce plasma cells and/or memory cells. The latter which may further divide and enter the original pool of immunocompetent cells or stimulated lymphocytes.

$x_2(k,t)$: population density of plasma cells of given k which are non-reproducing offspring of B-cells.

$x_3(k,t)$: population density of antibody sites of given k .

$x_4(k,t)$: population density of antibody-antigen complexes.

$h(t)$: antigen concentration which triggers the response mechanism (assumed to stimulate the response according to an average specific affinity in the initial model).

This derivation assumes that antibody reacts with antigen to form the antibody-antigen complex following the law of mass action, with an antibody affinity constant k . There is a population distribution of B-cells with continuous values of the affinity constant k over a range k_1, k_2 which in Model I has an average value $\bar{k}$. A second model considers a distributed population of B-cells with respect to k .

The following parameters are used in the model:

- α = birth rate constant of stimulated B-cells
- p_s = probability that an antigen stimulates cell (h, k dependent)
- p_d = probability that a B-cell differentiates into a plasma cell (h, k dependent)
- β = rate of generation of new B-cells (from bone marrow, k dependent)

- τ_1 = mean life time of B-cells
 τ_2 = mean life time of plasma cells
 τ_3 = mean life time of antibody cells
 τ_4 = mean life time of antibody-antigen complex
 τ_h = mean life time of antigen
 α' = plasma cell antibody production rate
 $u_1(\bar{k}, h) = p_s(1 - 2p_d)$
 $u_2(\bar{k}, h) = p_s p_d$
 $c_{\bar{k}}$ = dissociation rate of antibody-antigen complex
 $\bar{k}c_{\bar{k}}$ = association rate of antibody-antigen complex
 $\dot{h}_i$ = inoculation rate of antigen.

The dynamics of the population density of B-cells depends on three phenomena:

- B-cells stimulated at a rate $\alpha p_s x_1$, disappear and differentiate into plasma cells at a rate $2\alpha p_s p_d x_1$, and into memory cells at a rate $2\alpha p_s(1-p_d)x_1$ which enter the pool of immunocompetent B-cells.
- New B-cells are generated in the bone marrow at a rate β .
- Immunocompetent cells have mean death rate of $\frac{x_1}{\tau_1}$.

Consequently, the sum of these three terms leads to the rate of change of immunocompetent cells:

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

Similarly, plasma cells, antibody sites and antibody-antigen complex for an average affinity constant $\bar{k}$ may be approximated by birth rate minus death rate equations as follows:

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

$$\frac{dx_3}{dt} = -c_{\bar{k}} \bar{k} h x_3 - \frac{x_3}{\tau_3} + \alpha' x_2 + c_{\bar{k}} x_4, \quad (3)$$

$$\frac{dx_4}{dt} = c_{\bar{k}} \bar{k} h x_3 - (c_{\bar{k}} + \frac{1}{\tau_4}) x_4. \quad (4)$$

The generation of a particular free antigen of given antibody affinity $\bar{k}$ may be approximated by inoculation rate - rate of catabolism - net complex association rate, or

$$\frac{dh}{dt} = \dot{h}_i - \frac{h}{\tau_h} - \bar{k} c_{\bar{k}} h x_3 + c_{\bar{k}} x_4 \quad (5)$$

Bruni, et al. [13] derive the following probability approximation:

for a given concentration of antigen with an antibody affinity constant k

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

and

$$p_s \approx \begin{cases} 1, & \text{for some sensitive interval, } \gamma_1 < kh < \gamma_2 \\ 0, & \text{for other } kh. \end{cases}$$

Model I was simulated on a digital computer (OS3-system) with a program based on a RUNGE-KUTTA fourth-order method of integration. The parameters used in the simulation are listed in Table I. They all represent observed values except for the antibody-antigen complex dissociation rate c_k which was estimated; to simulate the injection of antigen in Freund's adjuvant the antigen inoculation rate was represented by the sum of two functions - a step function accounting for two-thirds of the total amount of antigen injected and an exponential function accounting for the remaining one-third.

The results of the simulation are shown in Figure 1. The kinetics of the cell and antibody molecule populations are consistent with known immunological phenomena. It is worth noting that the model is very sensitive to the dissociation rate c_k , and that experimental data for the conditions presented here were not yet available at the writing of this paper.

$$\dot{h}_1(t) = \frac{Q}{3\tau_u V} e^{-\frac{t}{\tau_u}} + \frac{2}{3} \frac{Q}{T_u V} \delta_{-1}(T_u - t)$$

TABLE I

α	5.780×10^{-2}	hr^{-1}
β	1.627×10^{-9}	mole/hr
τ_1	7140	hr
τ_2	71	hr
k	10^6	mole^{-1}
c_k	10^6	hr^{-1}
α'	2×10^{-8}	hr^{-1}
τ_3	200	hr
τ_4	100	hr
τ_h	50	hr
Q	3.33×10^{-8}	mole
V	0.2	liter
T_u	1000	hr
τ_u	100	hr

Distribution Effect of k , Secondary Response and Switch-over - Model II

Model II as represented below is a refinement of Model I to take account of these three important phenomena in the immune response whereby cell clones, and antibodies are generated according to a distribution of affinities. The second response to a

Figure 1. Simulation of Model I

given antigen is more pronounced than the first, and there is a rapid cut-off of one antibody (IgM) as another (IgG) is produced.

Similar to the immune population density (Model I) derivation above, Model II is derived as follows:

$$\frac{dx_1}{dt} = \alpha p_s (1 - 2p_d - 2p_m) x_1 - \frac{x_1}{\tau_2} + \beta p_c(k) , \quad (6)$$

$$\frac{dx_2}{dt} = 2\alpha p_s p_d x_1 + 2\alpha_m p_{dm} x_5 - \frac{x_2}{\tau_2} , \quad (7)$$

$$\frac{dx_{3M}}{dt} = -c'_k k' h x_{3M} - \frac{x_{3M}}{\tau_{3M}} + \alpha' x_2 + c'_k x_{4M} , \quad (8)$$

$$\frac{dx_{3G}}{dt} = -c''_k k'' h x_{3G} - \frac{x_{3G}}{\tau_{3G}} + \alpha'' x_2 [t - t_s(h)] + c''_k x_{4G} , \quad (9)$$

$$\frac{dx_{4M}}{dt} = c'_k k' h x_{3M} - (c'_k + \frac{1}{\tau_{4M}}) x_{4M} , \quad (10)$$

$$\frac{dx_{4G}}{dt} = c''_k k'' h x_{3G} - (c''_k + \frac{1}{\tau_{4G}}) x_{4G} , \quad (11)$$

$$\frac{dx_5}{dt} = 2\alpha p_s p_m x_1 - 2\alpha_m p_{dm} x_5 - \frac{x_5}{\tau_5} , \quad (12)$$

$$\begin{aligned} \frac{dh}{dt} = & \dot{h}_i - \frac{h}{\tau_h} - h \int_{k'_1}^{k'_2} k' c'_k x_{3M}(k', t) dk' - h \int_{k''_1}^{k''_2} k'' c''_k x_{3G}(k'', t) dk'' \\ & + \int_{k'_1}^{k'_2} c'_k x_{4M}(k', t) dk' + \int_{k''_1}^{k''_2} c''_k x_{4G}(k'', t) dk'' , \end{aligned} \quad (13)$$

Notation used here, and not previously defined in Model I, is as follows:

- p_m = probability that a B-cell differentiates into a memory cell
- p_{dm} = probability that a memory cell differentiates into a plasma cell
- x_{3M} = population density of antibody sites IgM,
- x_{3G} = population density of antibody sites IgG,
- x_{4M} = molecule density of complex antigen - IgM immunoglobulin (Ag-IgM),
- x_{4G} = molecule density of complex antigen - IgG immunoglobulin (Ag-IgG),
- x_5 = population density of memory cells,

- c'_k = dissociation rate of Ag-IgM,
 c''_k = dissociation rate of Ag-IgG,
 $c'_k k'$ = association rate of Ag-IgM,
 $c''_k k''$ = association rate of Ag-IgG,
 τ_{3M} = mean lifetime of IgM,
 τ_{3G} = mean lifetime of IgG,
 τ_{4G} = mean lifetime of complex Ag-IgG,
 τ_{4M} = mean lifetime of complex Ag-IgM,
 τ_5 = mean lifetime of memory cells,
 α_m = production rate of plasma cell by memory cell,
 $\alpha' \neq \alpha''$ = the immunoglobulin production rates of plasma cells are different for IgM and IgG,
 $t_s(h)$ = delay time associated with the switch-over mechanism,
 k'_1, k'_2 = antibody affinity limits associated with IgM,
 k''_1, k''_2 = antibody affinity limits associated with IgG.

- 1) The average affinity constant of the antibody generated during the immune response increased with respect to time as a consequence of the distributed effect of B-cells which can differentiate into antibody producing cells (plasma cells) with a large number of k (assumed continuous here) over some allowable interval k_1, k_2 . Whereas in Model I, the population densities and k dependent parameters were computed for an average value of $\bar{k}$, in Model II they are determined for each particular k . Equation (1) becomes equation (6) where the production rate of B-cells β is modulated by a probability of generation $p_c(k)$.

The amount of antigen binding with antibodies and the amount of antigen liberated by dissociation of the complexes are respectively obtained by integrating over the interval k_1, k_2 or k'_1, k'_2 and k''_1, k''_2 as explained in the next section. The model assumes that antibody is entirely generated by the plasma cells (amount of antibody generated by memory cells is neglected).

- 2) The secondary response is characterized by three facts observed experimentally:
- i) The interval time between antigen challenge and proliferation is smaller in the secondary response than for the primary.
 - ii) The serum antibody level is higher in secondary response, there is an expanded pool of antigen-sensitive memory cells.
 - iii) Higher-affinity antibodies are produced.

Model II considers stimulated B-cells and memory cells as two distinct populations. (Note change in first term of equation (6) and the introduction of equation (12) for memory cells). It is assumed that the time interval between the antigen injection is short compared to the lifetime of a memory cell but long compared to the lifetime of a plasma cell and antibody. Also,

the memory cells are not included in the population of immunocompetent cells in order to follow recent experimental findings which indicate that memory and immunocompetent cells present different affinity distributions. As stated earlier, the immunocompetent cells show at the end of the primary response a shift toward higher antibody affinity. The same phenomenon is not seen for the memory cells which present a greater heterogeneity in their affinity and therefore a larger selectivity. This provides the organism to react more adequately against a wide range of antigen doses upon secondary exposure [4]. Memory cells are stimulated and differentiate into plasma cells; this is represented by the term $2 \alpha_m p_{dm} x_5$ in equation (7).

- 3) The B-cell switch-over phenomenon is characterized by the secretion of various antibodies after contact with antigen. The synthesis of these antibodies proceeds at different rates. Usually there is an early IgM response (generated from a μ -protein chain) which tends to fall off rapidly. And apparently, the same plasma-cells start secreting IgG (from a γ -protein chain) which builds up to its maximum over a longer time period.

The same phenomenon, this time amplified, is observed in the secondary exposure to the same antigen. The time trajectory of the IgM responses resembles that seen in the primary though the peak may be higher. By contrast the synthesis of IgG antibodies accelerates to a much higher peak, and there is a relatively slow fall-off in serum antibody levels [2]: Equation (3) of Model I has been replaced by equations (8) and (9) of Model II for the generation of IgM and IgG antibodies. IgG is produced after a time delay t_s which according to some experimental evidence depends on h . The gradual decrease in IgM production should be reflected in the model by appropriate production rates α' and α'' . Until demonstrated otherwise by more precise correlation of experiment and simulation, any introduction in equation (8) for a step function to shut off the IgM production is neglected. Here it is assumed $c'_k \approx c''_k$ and $k' \approx k''$ for a given h for the antibody-antigen complexes.

The initial conditions are:

- a) At start of primary response

$$x_1 \neq 0$$

$$x_2 = x_{3M} = x_{3G} = x_{4M} = x_{4G} = x_5 = 0$$

- b) At start of secondary response

$$x_1 \neq 0$$

$$x_2 \approx x_{3M} \approx x_{3G} \approx x_{4M} \approx x_{4G} \approx 0$$

$$x_5 = \text{value at the end of primary response}$$

Discussion

At the present time Model II is simulated and biological experiments specifically designed to validate the model are performed. It seems appropriate now to review and assess the above assumptions made prior to Model II. In regards to assumption (b), Bell [15] and Bell and Delisi [16] derive simple mathematical models for specific binding of multivalent antigen to immune cell receptors when competition exists with non specific bindings of antigen to all surfaces and with binding of haptens to receptors. Effectively this competition decreases the antigen-receptor association constant. In most cases of humoral immune response the antigen is not T-cell independent and therefore assumption (c) fails. Several subpopulations of T-cells have been "identified" mainly by their distinct function in process regulation by antigenic stimulation of B-cells to be more effective, or by suppressing it. Several non-mathematical models have been proposed for the cooperation between T and B cells [17-21] - most of them assume that a stimulation signal is sent directly by the T-cells or, indirectly through the macrophages, another type of cell, to the B-cells. Several types of stimuli coming from specific T-cells or allogenic T-cells might be present in the T- and B-cells cooperation - T-B cooperation should be incorporated into the mathematical model with at least one new state variable for the T-cells. The "helper" and "suppressor" functions of T-cells may be expressed in the probability of B-cell stimulation being function of the T-cell population. The T-B interaction changes the rate of all proliferation; therefore it should be influential in the secondary response and in the switch-over phenomena for which the time-delay parameter t_s is expected to change.

Immunological tolerance and one of its counterparts graft rejection are other aspects of the immune system which could be analyzed in the T-B cell model. Experiments on thymectomized animals have shown that T-cells are involved in the rejection of grafts [2]. Assumption (g) is not always valid either since cellular proliferation and death rates depend to some extent on population density.

These assumptions are being investigated in more detail with new model refinements. Indeed, model development must proceed in an iterative manner, integrated with extensive immunological experiments such as are being conducted at the Oregon Regional Primate Research Center in conjunction with this project and that at the University of Rome.

In the long range, research of this nature is intended to bring focus to a somewhat disjointed world-wide experimental program, and eventually lead to a systematic understanding of disease control, cancer and transplant rejection.

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