

# ***WORKING PAPER***

## **A SYSTEMS OVERVIEW OF IMMUNOLOGY, DISEASE AND RELATED DATA PROCESSING**

*A.L. Asachenkov*  
*R.R. Mohler*

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INTERNATIONAL INSTITUTE FOR APPLIED SYSTEMS ANALYSIS  
A-2361 Laxenburg, Austria

## Preface

This paper gives a brief but systematic overview of topics in “mathematical immunology” and may be considered as an introduction to a new IIASA activity on these topics. Theoretical and experimental research in this area is aimed at an understanding of the precise manner by which the immune system controls (or attempts to control) infectious diseases and diseases such as AIDS and cancer.

Available mathematical methods, the difficulties arising in the respective problems, and some possibilities to overcome them are discussed.

Alexander B. Kurzanski  
Chairman  
System and Decision Sciences Program

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# A Systems Overview of Immunology, Disease and Related Data Processing

*A.L. Asachenkov and R.R. Mohler*

## 1. Introduction

### 1.1 Objective

This paper is intended to provide a systematic overview of immunology and disease control. The emphasis is on mathematical synthesis within the individual rather than a society of individuals as characterized in epidemiology.

It is intended that system theory should directly affect the planning of experiments so that such programs may proceed in a coherent fashion towards a better understanding of immune functions and disease control. Similarly, experimentation must impact systems analysis to formulate a multidisciplinary integrated research program to achieve this goal. In the long run, hopefully, systems theory will directly affect disease diagnosis and treatment.

The research is intended to focus theoretical research and experimental research in systems mathematics and immunology to experimental planning and prediction for the purpose of relevant disease applications. IIASA already has sponsored two workshops in this area: (1) The Working Conference on "Theoretical Immunology", Mogilany, Poland, 1985, and (2) the Workshop on "Selected Topics in Biomathematics", Laxenburg, Austria, 1987. The proceedings of the first are published by Springer Verlag in the series on *Biomathematics*, [1] and the second volume is in preparation [2].

Here, a summary of past immunological systems analysis is presented along with a brief mathematical synthesis of the major components of the immune process. This is followed by a study of recently developed methodologies for clinical data analysis with respect to cancer patients and for immune model identification.

### 1.2 Past Research

A mathematical approach was exploited for the analyses of immunological experiments even before the birth of modern system theory. This included the hemolysis by compliment and the antigen-antibody precipitation reaction and is discussed in a nice his-

torical review by Bell and Perelson [3], [4]. More recently, mathematics was applied to the analysis of the formation of hemolytic plaques in the Jerne essay and the determination of the antibody affinity distribution for an antiserum. For the first point, a mathematical theory of plaque growth, initiated in 1974 [5], [6] was successively developed to a large extent in [7], [8]. This theory allows the determination of the secretion rate as well as of the affinity of antibodies generated by a cell. With regard to the second point the antibody affinity distribution has been analyzed from experimental binding data both considering a discrete-value distribution [9] and a continuous one [10].

As for the impact of the systems approach to the dynamics of the immune response, an early preliminary model was presented in [11]. The concept of activation and suppressive signals was introduced to describe the triggering and the paralysis of the immune process [12]. In the meantime, Jilek, Ursioya, and Sterzl [13], [14], developing the hypothesis of Sicarz and Coons [15] on the lymphocyte differentiation, proposed a probability model of different cell types undergoing repeated contact with specific antigens.

A more complete description of the immune process was presented in the past decade by Bell [16] who gives a mathematical formulation of the clonal selection theory introducing heterogeneity of antibodies with respect to the affinity for the antigen.

This concept was successively developed by Bruni et al. [17] in which, remaining in the context of the clonal selection theory, a continuous affinity description was proposed to derive a distributed dynamical model. This model was studied in the context of variable-structure systems.

A simple mathematical model of infectious disease was investigated by Marchuk [18], Belykh and Asachenkov [19].

Similarly, single-valued antibody-affinity models were studied in [20]-[22], introducing a switch over in the class of the produced antibodies (from IgM to IgG) and analyzing some mathematical properties. Furthermore, Mohler and his associates studied the spatial inhomogeneity of the immune system introducing a compartmentation in the model [21] and T-B cellular cooperation [22]. This work also shows the role of bilinear systems in immunology.

Contributions to T-B cellular cooperation also was given by Marchuk [18], Comincioli et al. [23].

Starting from 1974, other contributions to the mathematical description of the immune process were also given by Richter [24], Hoffmann [25], Adam and Weiler [26], and Hiernaux [27], on the basis of the immune network theory proposed by Jerne [28] which arises from the antigenic properties of each antibody molecule. Richter gives a general

modeling approach to activation and suppression of antibody production of different idiotypic classes, with each class suppressing the class from which it was activated and stimulating production of the following class. While this model lacks precise experimental verification, it does simulate the essence of low zone and high zone tolerance, along with primary and secondary responses. Hoffmann suggests a symmetric model which includes antigen-binding "positive" and antiidiotypic "negative" B and T cells and T-cell factors.

Parallel to these efforts on the mathematical modeling of the overall immune process, other results are also available on the modeling of specific aspects of the same process. In particular, the mechanism of binding a multivalent antigen to lymphocyte receptors has been deeply analyzed due to its fundamental role in the triggering of the immune response. From 1974, this phenomenon has been studied either under the hypothesis of irreversible binding with particular emphasis on the time description of lattice formation [29] or under the hypothesis of reversible binding, to analyze the equilibrium and stability properties of the related model [30].

A second phenomenon, related to the one of cell cooperation, which more recently has been considered by Bell with the aim of deducing a mathematical description, was that of the formation of molecular bridges between cells [31].

A systems overview of immune processes is given by Mohler, Bruni and Gandolfi [32] but the most comprehensive mathematical analysis of disease control is presented by Marchuk [33]. Mathematical models of disease and related data processing was investigated by Zuev, Belykh, Asachenkov, Pogochev, Nisevich, Zubikova, Sobolev, Smolianinov [34]-[36], Romanycha, Bocharov, Janenko [65]-[66], [61].

Conferences devoted primarily to these topics include: 1978 Working Conference on System Theory and Immunology in Rome, 1978 Working Conference on Modeling of Complex Systems (with immune emphasis) in Novosibirsk, 1982 IFIP Conference on Mathematics in Immunology and Disease in Moscow, 1985 IASA Working Conference on Mathematical Models in Immunology in Mogilany, Poland, 1987 IASA Workshop on Biomathematics (with immune emphasis) in Laxenburg, and 1987 DOE Workshop on Theoretical Immunology in Santa Fe. These are indicative of the increasing role of mathematics in immunology.

## 2. Mathematical Synthesis

### 2.1 Components of Cells and Molecules

Obviously, the immune process is extremely complex, and it would be impossible to develop an encompassing mathematical model to address all questions. However, immunological theory and experimentation has developed to the point that mathematical models and system studies can be useful for specific applications and as a basis for a general mathematical structure for future research. This joint analytical-experimental approach may lead eventually to a systematic understanding of body immune defense and its stimulation for effective health care.

Experimentation shows that decay rate of bacteria is proportional to the product of its concentration with that of antibody and that of complement (prior to saturation), i.e., parametric control. If the effect of antibody and complement were linearly additive, as for conventional linear systems, the bacterial decay would not be so rapid since superposition would apply. Such multiplicative effects (rather than superposition) seem very prevalent throughout immunology.

Roughly, the immune system is a communication command and control system to defend the body from alien intrusion and infection. Various immune subsystems, including complement, humoral system, and cell-mediated systems, are activated and deactivated according to antigen level and chemical structure in concert with other substances, such as antibody, suppressors, helpers, lymphokines, etc.

Cellular and molecular kinetics are the basis of the entire immune process. These processes are quite well defined from conservation equations and chemical mass-action principles. In general, the *cellular population* (or concentration),  $x_i$ , of  $i$ th class may be described by [40]-[42]

$$\frac{dx_i}{dt} = \text{source rate} - \text{death rate} + \text{division rate} +$$

$$+ \text{rate differentiation to } - \text{rate differentiation from ,}$$

or

$$\frac{dx_i}{dt} = v_i(t) - \frac{x_i}{\tau_i} + p_i(\cdot)x_i + \sum_{j \neq i} 2p_j(\cdot)p_{ji}(\cdot)x_j - \sum_{k \neq i} 2p_i(\cdot)p_{ik}(\cdot)x_i, \quad (2.1)$$

where  $v_i(t)$  is the source term (from bone marrow via blood);  $\tau_i$  is death time constant;  $p_i(\cdot)$ ,  $p_{ji}(\cdot)$ , and  $p_{ik}(\cdot)$  are appropriate growth coefficients (including probabilities of



stimulation and differentiation from one class to the other). These coefficients or probabilities represent parametric feedback control in the immune system of a very complex nature. Indeed, it is these terms upon which much of immunological research is currently focused, i.e., what manner is cell production activated and controlled by mainly molecular substances. Consequently,  $p_i(\cdot)$ ,  $p_{ji}(\cdot)$ , and  $p_{ik}(\cdot)$  are functions of primarily molecular concentrations. They may be deterministic functions or random processes depending on the approximation used.

Here  $i$  refers to different cell types; e.g., this might refer to  $B, T$ , and macrophage cell lineages, such as resting cells, excited cells, cytotoxic cells, suppressors, helpers, memory cells, and plasma cells (which generate antibody). Also, other killer cells and mast cells could be included.

An  $m$ th class of molecular concentrations,  $y_m$ , may be described by

$$\frac{dy_m}{dt} = \text{molecular source rate} + \text{generation rate} + \text{dissociation rate of appropriate complexes} - \text{association rate of appropriate complexes} - \text{death rate.}$$

This is usually approximated by

$$\frac{dy_m}{dt} = w_m(t) + \sum_i \beta_{im} x_i + \sum_{n \neq m} c_{mn} y_n - \sum_{\ell \neq m} c_{\ell m} y_\ell y_m - y_m / \tau_m, \quad (2.2)$$

or more accurately described by

$$\frac{dy_m}{dt} = w_m(t) + \sum_i \beta_{im}(\cdot) x_i + \sum_{n \neq m} c_{mn}(\cdot) y_n - \sum_{\ell \neq m} c_{\ell m}(\cdot) y_\ell y_m - y_m / \tau_m. \quad (2.3)$$

Here,  $w_m(t)$  is an external source rate;  $\tau_m$  is a lifetime;  $\beta_{im}$  is an  $i$ th-cell source rate for generating  $y_m$ ; and  $c_{mn}$ ,  $c_{\ell m}$  are appropriate coefficients of dissociation and association, respectively. In eq. (2.3), these coefficients would be functions of the appropriate  $y_\ell(t)$ .  $y_n$  refers to immune complexes of bound molecules which may dissociate. They may be assumed to be deterministic or stochastic, depending again on the approximation desired or the information available.  $m$  refers to the  $m$ th class of molecules, such as antibody, antigen, appropriate cell receptor, appropriate lymphokine, IFN (interferon), or other molecular substance. Here, the alien substance (such as a virus) is represented by the molecular chemical structure called antigen, Ag.

If  $x_i^s$ ,  $y_m^s$  refer to a particular *compartment*,  $s$ , or organ with migration between compartments, then eqs. (2.1) - (2.3) must include a net migration term such that

$$\begin{aligned} \frac{dx_i^s}{dt} = & v_i^s(t) - \frac{x_i^s}{\tau_i^s} + p_i^s(\cdot)x_i^s + \sum_{j \neq i} 2p_j^s(\cdot)p_{ji}^s(\cdot)x_j^s - \sum_{k \neq i} 2p_i^s(\cdot)p_{ik}^s(\cdot)x_i^s + \\ & + \sum_{u \neq s} \delta_{i,s,u}(\cdot)x_i^s - \sum_{r \neq s} \delta_{i,r,s}(\cdot)x_i^r. \end{aligned} \quad (2.4)$$

Here, superscript  $s$  shows possible dependence on the compartment or organ. (For example, an inflamed spleen should cause more stimulation of appropriate cells.) In general, the migration coefficients,  $\delta_{i,s,u}(\cdot)$  and  $\delta_{i,r,s}(\cdot)$ , could be deterministic or stochastic functions of appropriate  $y_m(t)$  since certain lymphokines (e.g., macrophage migration inhibition factor, MIF) manipulate migration coefficients. A similar molecular version of eq. (2.3) may be developed.

A simple building block synthesis of the immune system is presented here. It is shown that, mathematically, this complex system consists of numerous cascades of bilinear processes [42], [43] which are themselves coupled together by nonlinear gain elements. These coupling elements include stimulation and inhibition terms which are a focus of much immunological research. The mathematical structure is further divided for convenience into cellular and molecular components with mainly molecular terms affecting nonlinear coupling. If the appropriate measurements are made, the system can be shown to take the, sometimes analytically convenient, form of a conditionally-linear system [44].

## 2.2 The Humoral Process

For the humoral immune system which leads to the generation of antibodies, cellular state variables may consist of immunocompetent cell concentration (ICC)  $x_1(t)$  and plasma-cell concentration  $x_2(t)$  (with memory cells neglected or combined with ICC). The molecular states,  $x_3(t)$ ,  $x_4(t)$ ,  $x_5(t)$ , include concentrations of free antibody, bound antibody-antigen complexes and free antigen respectively. Here,  $p_1(\cdot)$  and  $p_{12}(\cdot)$  terms include  $x_3$  and  $x_5$  state feedback control if the molecular lymphokines and interferon of the cell-mediated immune (CMI) response are neglected. Subsequently, the humoral control of antigen may be modeled approximately from (1) and (2) by

$$\begin{aligned} \frac{dx_1}{dt} = & \alpha u_1 x_1 - \frac{x_1}{\tau_1} + v_1, \\ \frac{dx_2}{dt} = & 2\alpha u_2 x_1 - \frac{x_2}{\tau_2}. \end{aligned} \quad (2.5)$$

The molecular (mass-action binding) behavior is nearly described by the following for

concentrations of free antibody  $x_3(t)$ , bound antibody-antigen complexes  $x_4(t)$  and free antigen  $x_5(t)$ :

$$\begin{aligned}\frac{dx_3}{dt} &= -cu_3x_3 - \frac{x_3}{\tau_3} + \alpha'x_2 + cx_4 \\ \frac{dx_4}{dt} &= cu_3x_3 - \left(c + \frac{1}{\tau_4}\right)x_4, \\ \frac{dx_5}{dt} &= v_2 - \frac{x_5}{\tau_5} - Nc(u_3x_3 - x_4).\end{aligned}\tag{2.6}$$

The immune parameters are defined as follows:  $\alpha$  is the birth-rate constant;  $\alpha'$  is plasma-cell antibody production rate;  $\tau_1$  is the mean lifetime of immuno-competent cells; and  $\tau_2, \tau_3, \tau_4, \tau_5$  are the appropriate lifetimes.  $c$  and  $N$  are appropriate dissociation and weighting constants.

The additive control  $v_1$  is independent of the multiplicative feedback control variables ( $u_1, u_2, u_3$ ) and is significant in immunotherapy.  $u_1$  and  $u_2$  both are functions of  $x_3$  and  $x_5$ , and  $u_3 = kx_5$  is the classical binding term.

The other additive control, rate of inoculation of antigen  $v_2$ , is independent of the other control variables and has significance in disease prevention (or more correctly, disease control) by vaccination as well as in simulation of experiments whereby certain animal strains may be inoculated with antigens of particular characteristics. The multiplicative controls may be manipulated by the synthesis of interferon, interleukins, etc. -- naturally by  $T$  and macrophage mediation or artificially when the first fails.

### 2.3 Disease Models and AIDS

Consider the deterioration of organ tissue from a virus of concentration  $V$  by

$$\frac{dm}{dt} = \sigma V - H_m m, \tag{2.7}$$

where  $m$  is a relative damage characteristic of the tissue;  $\sigma$  is a virus damage coefficient, and  $H_m$  is a tissue recovery coefficient. In this model, which follows [18],  $V$  is described similar to  $x_5$  in (2.6) but with an added virus (antigen) destruction term by cytotoxic  $T$  cells. Model state variables include equivalent concentrations of virus (antigen), antibody, ICC, plasma cells, and  $m$  (above). The Marchuk model assumes the generation of antibody concentration  $x_3$  in response to  $v_1, v_2$  according to (2.6) where  $\alpha'(m)$  is now an appropriate monotone decreasing function. An analysis of the time response for this

model is presented in [33]. Similar equations were developed for various  $T$  cells and macrophages which in turn affect feedback controls.

Further investigations show the relation of stationary solutions to healthy organ state and chronic disease. The latter may also result in periodic solutions. It is shown by simulation, that sufficiently increasing the initial virus dose results in more effective control of the chronic disease by the immune system.

Acquired Immune Deficiency Syndrome, AIDS, has been targetted as the most life-threatening disease of the future. During the 1980's, the number of cases seems to be increasing almost as an uncontrolled exponential function. The intent of this paper is to describe the progressive nature of the disease and the resulting loss of immunocompetence. Hopefully, such a model may be useful to control AIDS.

Again, AIDS is linked with a virus which is called HIV, Human Immunodeficiency virus. HIV has a particular affinity for a certain class of  $T$  cell lymphocytes,  $T_4$  ( $T$  helper lineage). It is reasonable to expect that the eventual death of the  $T_4$  lymphocytes from the viral infection may be a principal inducement of immunocompetence. While the HIV does infect macrophages, experimental evidence indicates that their death rate from this virus is not drastic enough to cause a detrimental loss of immunocompetence.

AIDS dynamics may be approximated by (2.1) and (2.2) with a few equations provided here. First, the antibody generation might be approximated by the humoral model (2.5)-(2.7) with a more complex  $u_1(\cdot) = u_1(x_5, x_T, x_\phi)$ ,  $u_2 = u_2(x_5, x_T, x_\phi)$ , where  $x_T, x_\phi$  refer to concentrations of free helper- $T$  cells,  $T_h$ , and free macrophages,  $M_\phi$ .  $x_5$ , antigen concentration here refers to HIV. Although appropriate molecular interactions are responsible for the HIV control it is assumed proportional to the primary molecular source  $x_T$  for simplicity. Any HIV control effects from  $x_\phi, x_3$  are neglected, despite their increases, which is consistent with present experimental data. Such data suggests that  $T_h$ -generated CD4 molecules do have some detrimental effect on HIV.

If the humoral antibody and macrophage components are neglected, and HIV is represented through its infected  $T$ -cell component (with the infected macrophages neglected), then the dynamical structure may be approximated as follows:

$$\dot{x}_5 = v_3 + (\alpha_5 - 1/r_5)x_5 + \beta_{T_5}x_T' - c_{T_5}'x_5x_T - u_4x_5, \quad (2.8)$$

where again  $v_3$  is the source rate of HIV infection from the environment; the second is a net birth rate term;  $\beta_{T_5}x_T'$  is the generation rate from infected  $T_h$  cells of concentration  $x_T'$ ; the last two terms are the rate of HIV infections binding with free  $T_h$  cells and  $T_h$ -cell control term respectively. The latter may be approximated by  $u = c_{T_5}x_T$ , where  $c_{T_5}$  is

an effective positive association constant (via CD4 molecules).

Consequently,  $T_h$  cell dynamics may be approximated by

$$\dot{x}_T = u_5 x_T - x_T/\tau_T - u_4 x_5 + v_4, \quad (2.9)$$

where  $u_5$  is a stimulation coefficient function of antigen concentration and possibly other molecular controls.  $v_4$  is the source rate of free helper cells which in reality would involve several stages of precursors. Similarly, the infected- $T_H$  dynamics become

$$\dot{x}'_T = u_6 x'_T - x'_T/\tau'_T + c'_{T5} x_5 x_T + v_5, \quad (2.10)$$

where  $u_6, v_5, \tau'_5, c'_{T5}$  are appropriately defined similar to the corresponding term in (2.9) above.

A study of a simpler two-dimensional AIDS model, but which assumes  $x_T(t)$  to be a random process, is studied by Merrill [45]. A simple deterministic AIDS model also is studied by Cooper [46]. The two models were compared with the deterministic model projecting the most rapid deterioration of immune response.

As noted above, it is commonly believed that the pathogenesis of AIDS involves an attack on  $T_H$  cells by the AIDS virus HIV. In a recent paper [47] it is suggested that the HIV mimics a genetically recognizable antigen, and causes the disease by inducing autoimmunity to self for this class together with an anti-idiotypic response against  $CD_4$  bearing cells. On this basis a network model is developed by Hoffmann in [48] which involves network interactions and leads to additional testable predictions. The model includes immune responses to HIV and to anti-host receptors on foreign cells.

Two complementary immune responses are considered in this model. The first is the response to HIV which binds to the  $CD_4$  molecule on helper  $T$  cells. It is shown that certain antibodies can potentially destabilize the network. The second response is an anti-anti-self response, which occurs when lymphocytes are transferred from one person to another [48]. Anti-anti-self response is against the receptors of the foreign lymphocytes that recognize the host. Homosexuals can receive allogeneic lymphocytes together with sperm in ejaculates, and this could result in anti-anti-self responses. Other high risk groups (intravenous drug users, recipients of blood transfusions) also typically receive cells when infected.

Since the immune system and AIDS models in particular have a conditionally-linear structure if appropriate measurements (of "nonlinearly appearing" states) are made, the optimal filter and theory developed in [44] forms a good base for observer design and parameter identification. Also, Walsh functions have been applied successfully to a simple humoral im-

immune model for estimation of parameters from simulation data [32], [48], [49].

#### *2.4 The Role of Models in Experimental Analysis*

A few of the primary purposes of mathematical models are to systematically plan experiments, to mimic experimental results, to reduce the number of experiments (and thereby laboratory animals and time), to better understand immunology and to assist in the methodical treatment of disease. In order to accomplish these objectives, it is necessary that analysis, experimentation and computer simulation proceed hand in hand. The methods of analysis include parameter estimation and optimization, from which evolve appropriate software developments. Fig. 1 depicts this procedure.

The development of the model may involve various levels of detail which depend on the questions addressed for a particular immune reaction along with its respective experimental approach.

Indeed, the success of the systems approach to immunology depends on the ability to bridge the gap between mathematics, experimental programs and clinical practice. Some details of such interactions are studied in [32], [53]-[54].

While such issues relative to questions addressed, include state controllability, state observability, stability and model sensitivity are very significant and addressed to some extent in past research, parameter estimation and optimization methodologies are the main concern of this paper. In this manner a quantitative characterization might be made of patient health and the effectiveness of various therapeutic policies such as drug effect on certain immunological parameters in the model, the experimental animal and the patient. More details of these questions are studied in [33], [54].

In the selection of a cost function, for optimal parameter estimation relative to the data received and the model utilized, consideration should be given to immunologically relevant standards as well as mathematical convenience. Such questions are addressed below with more details given in [54]-[57]. The subsequently developed software should be available to theoreticians, experimentalists and clinicians.

A new methodology, which has been applied successfully to clinical practice in Moscow, is presented next.

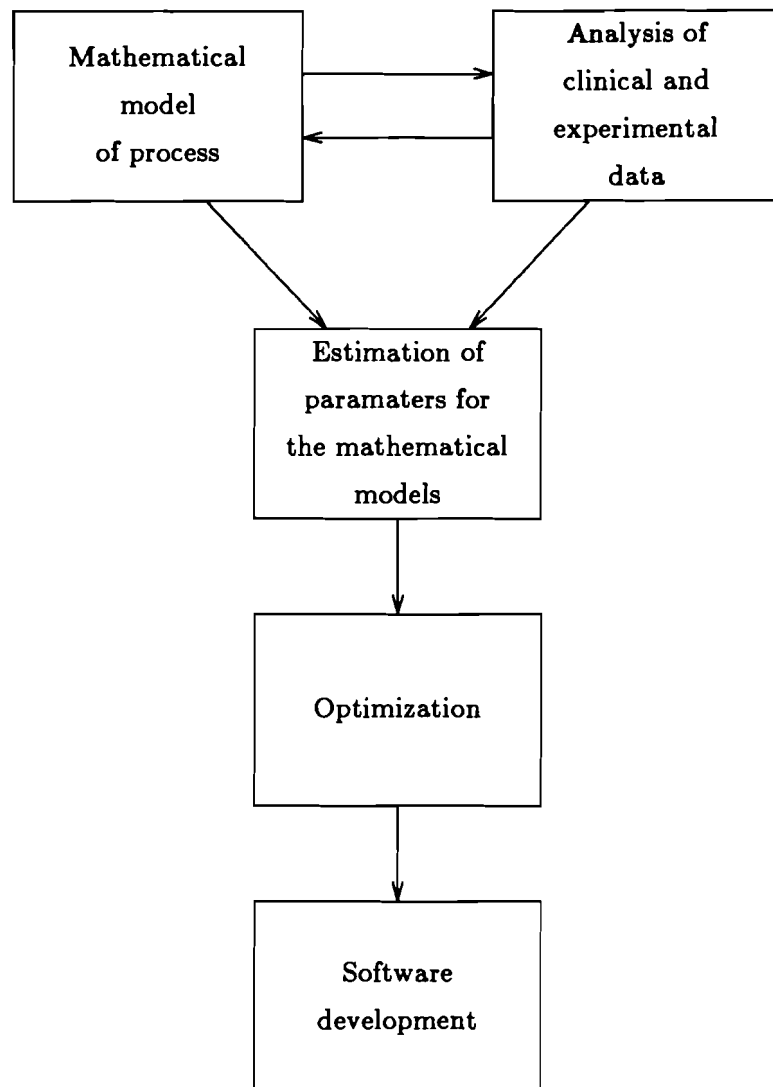


Fig. 1. A methodology of application to immunological experiments and clinical practice.

### 3. Data Processing and Disease Treatment

There are many medical and mathematical publications dealing with methods of processing medical data for the diagnosis of diseases. We take for granted here that the diagnosis has been made correctly and that the problem consists in evaluating the degree of seriousness of the disease or of evaluating the state of the organism.

Let  $X = (x_1, \dots, x_n)$  be a vector of clinical data which characterizes the state of the organism. Functional destruction of homeostasis of the organism by the given illness may be reduced to deviations of these variables from levels which correspond to the healthy state of the organism. State control of the organism which is based on an objective analysis of available information, is a useful concept for choosing the method of treatment.

Special functions for analysis of the clinical data for infectious diseases such as viral hepatitis and pneumonia, which are called disease gravity indices were proposed by G. Marchuk in 1975. Experience using these functions in the clinic showed that, with the help of such indices, one can successfully solve various practical problems such as estimating the degree of seriousness of the disease, estimating the state of the organism, investigating the process dynamics and comparing the effectiveness of different treatments. A more or less general framework of mathematical analysis of medical information is formulated by G.I. Marchuk, S.M. Zuev [33], [34], [38]. The numerical index of the gravity of an illness and the appropriate treatment are developed there. Clinical experience with such analyses are discussed by I.B. Pogochev, N.I. Nisevich, G.I. Marchuk, I.I. Zubikova [34], [53], [54].

Consider briefly available mathematical methods for processing clinical data, the difficulties arising and some possibilities to overcome them.

#### 3.1 Clinical Data

As a consequence of clinical observations or experiments with animals we have a set of the instants of time

$$\Theta = \{t_0, t_1, \dots, t_n \mid 0 \leq t_0 < t_1 < \dots < t_N \leq T\} \quad (3.1)$$

at which the state variables of the model are measured to define the set

$$X = \{x_{t_0}, x_{t_1}, \dots, x_{t_N}\} \equiv \{x_t, t \in \Theta\} . \quad (3.2)$$

Let here  $x \in R^n$  be a vector of the state variables of the mathematical model. It is an ideal case from the mathematical point of view.



If the experiment is carried out with a group of  $M$  animals, there is a group of trajectories

$$X_M = \{x_t^j, j = 1, \dots, M, t \in \Theta\} \quad (3.3)$$

for which the trajectory

$$X^j = \{x_t^j, t \in \Theta, x_t^j \in R^n\} \quad (3.4)$$

corresponds to the observation of the  $j$ -th animal. The experiments are carried out, of course, with animals of a single strain, and therefore assume the set of trajectories as the result of repeated experiments with one organism.

The actual experiment, however, results is not a set of trajectories but a set of presumably independent values of variables for  $t \in \Theta$  so that we define

$$X = \{x_t^j, j = 1, \dots, m_t, t \in \Theta, x_t^j \in R^n\} \quad (3.5)$$

This case occurs while performing the experiment in the following way. At the time  $t = 0$  a group of  $M = \sum_{t \in \Theta} m_t$  animals receive the same quantity of antigen. At the instant  $t = t_0 > 0$  the model state variables are measured to define a set of values

$$\{x_{t_0}^j, j = 1, \dots, m_{t_0}, x_{t_0}^j \in R^n\} .$$

As far as the existing measurements, the variables, which are of interest to medical specialists, are those, as a rule, for which the animals are killed, a consequence of the measurement of a group of  $M - m_0$  survivors. Then the measurements are repeated at the instants of time  $t_1, t_2, \dots, t_N$  on another group of animals. Consequently we have the sets

$$\{x_{t_k}^j, j = 1, \dots, m_{t_k}, x_{t_k}^j \in R^n\}$$

$$\{x_{t_\ell}^j, j = 1, \dots, m_{t_\ell}, x_{t_\ell}^j \in R^n\}$$

and for  $k \neq \ell$  these sets are assumed independent.

One of the problems connected with clinical data is the following. *The measurement variables are not the state variables of the model.* These data can be considered only as observations connected with state variables of the model  $x \in R^n$  by means of some functions

$$Z = \Psi(x, \beta), \quad (3.6)$$

where

$Z = (z_1, \dots, z_m)$  is a vector of the laboratory measured variables;

$\beta \in R^q$  is a vector of coefficients or parameters, and

$\Psi(x, \beta)$  is a known function relating observable and state variables.

Consider the following problem as an example of the simplest model of a disease which is proposed by G. Marchuk. Given the system of nonlinear ordinary differential equations [34]

$$\frac{dx_1}{dt} = (\alpha_1 - \alpha_2 x_3) x_1,$$

$$\frac{dx_2}{dt} = \xi(x_4) \alpha_3 x_1(t - \tau) x_3(t - \tau) - \alpha_4(x_2 - \alpha_5),$$

$$\frac{dx_3}{dt} = \alpha_6 x_2 - (\alpha_7 + \alpha_8 x_1) x_3,$$

$$\frac{dx_4}{dt} = \alpha_9 x_1 - \alpha_{10} x_4,$$

with the initial data for  $t = t_0$

$$x_i(t_0) = x_i^0, \quad i = 1, \dots, 4$$

$$x_1(t)x_3(t) = \phi(t) \text{ for } t < t_0;$$

where

$x_1(t)$  is a concentration of multiplying pathogenic antigens,

$x_2(t)$  is a concentration of plasma cells,

$x_3(t)$  is a concentration of antibodies,

$x_4(t)$  is a relative characteristic of a damaged organ

$\xi(x_4), \phi(t)$  are known functions

$\alpha_j = \text{const}, j = 1, \dots, 10.$

There are four state variables in this model ( $x_1, x_2, x_3, x_4$ ). We can easily measure common levels of antibodies  $x_3$  and plasma cells  $x_2$  but specific antibodies and plasma cells are only an unknown part from these levels. The measurement of antigen is more difficult, and we do not know how to measure a relative characteristic of a damaged organ  $x_4$ , or degree of seriousness of the disease.

How can we use the information from clinical measured variables? By using these data, specialists can attempt the diagnosis of diseases, evaluate the state of the organism, choose the method of treatment and investigate the process of rehabilitation of the afflicted organs.

One of the ways to solve this problem is to construct a gravity index of a disease.

### 3.2 The Gravity Index of Infectious Disease

Let  $z \in R^m$  be a measurement vector of clinical variables. We shall consider  $z$  as an  $m$ -dimensional random variable.

Introduce the expert estimation of the gravity of the disease by the  $r = 0, 1, \dots, R$ . Based on clinical practice, the following scale is suggested:

- $r = 0$  for healthy individuals;
- $r = 1$  for patients with a mild form of affliction;
- $r = 2$  with the average form;
- $r = 3$  with the serious form and
- $r = 4$  with the serious form and unpredictable outcome.

Denote

$$E[z_j | r] = g_j(r) \quad (3.8)$$

as the regression  $z_j$  with respect to  $r$ .

Here

$E$  is a mathematical expectation operator,

$g_j(r)$ ,  $j = 1, \dots, m$  are known functions.

Construct the scalar function  $\varphi(z)$  of the vector of observed variables by minimization of

$$E[\varphi(z) - r]^2. \quad (3.9)$$

The function  $\varphi(z)$  is called the gravity index of a particular disease. If

$$g_j(r) = r, \quad j = 1, \dots, m \quad (3.10)$$

the function  $\varphi(z)$  can be chosen in the form of a linear combination

$$\varphi(z) = \sum_{j=1}^m \alpha_j z_j, \quad \sum_{j=1}^m \alpha_j = 1, \quad (3.11)$$

where  $\alpha_j$ ,  $j = 1, \dots, m$  are unknown, non-negative constants.

If  $g_j(r)$ ,  $j = 1, \dots, m$  are nonlinear functions, we can try to transform them by means of some functions  $f_j(z_j)$  so that

$$E[f_j(z_j) | r] = r. \quad (3.12)$$

In this case, a polynomial transformation is used.

To simplify the data analysis it is convenient to transform the state vector characterization to a scalar one. Now, we can study the dynamics of the process by calculating values of the index in time

$$\varphi(z, t_1), \varphi(z, t_2), \dots, \varphi(z, t_N).$$

Introduce a normalized index of gravity

$$y(t) = \frac{\varphi(z, t)}{\varphi(z, t_0)}, t \in \Theta, \quad (3.13)$$

where  $\varphi(z, t_0)$  is the initial index value corresponding to the arrival of a patient at the clinic.

Referring to the example from Section 3.1, we can consider the function  $y(t)$  as the observed variable for a relative characteristic of a damaged organ.

Since, if  $x_1 = 0$  for  $t = \tilde{t} > t_0$  then

$$\frac{dx_4}{dt} = -\alpha_{10} x_4, \quad x_4(\tilde{t}) = \tilde{x}_4. \quad (3.14)$$

Using statistical analysis of the simple case clinical data, we have a linear differential equation describing  $y(t)$ :

$$\frac{dy}{dt} = -\lambda y, y(0) = 1, \quad (3.15)$$

where  $\lambda$  is a rate of restoration functions of damaged organ.

Equation (3.15) is the basis for constructing mathematical models of functional rehabilitation processes, for methods of estimating parameters of such models and methods for comparison of effectiveness of the different variants of treatment [34], [53], [54], [38].

### 3.9 Analysis of Data for Oncological Patients

In Section 3.2, we introduced the expert estimation for degree of seriousness of disease. This is hardly practical when we deal with oncological patients. There is only one objective estimation for degree of seriousness of disease in this case, that is patient-termination time data.

Since the tumor process, as a rule, eventually leads to patient termination, we can use mathematical methods traditionally applied to mortality dynamics for the analysis of observed variables of oncological patients [35]-[37], [62], [63].

Let  $T > 0$  denote the instant of patient death such that  $T$  is a random variable with continuous distribution function  $F(t) = P\{T \leq t\}$ . Mortality dynamics of a group is described by the survivor function

$$S(t) = \int_t^{\infty} f(u) du, \quad S(0) = 1, \quad (3.16)$$

where  $f(t)$  is a probability density function.

The hazard or risk function  $\lambda(t)$  plays a highly important role in the statistical analysis of failure time data so that

$$\lambda(t) dt = P\{t < T \leq t + dt \mid T > t\} \quad (3.17)$$

Therefore

$$\lambda(t) = - \frac{1}{S(t)} \frac{d}{dt} S(t) = - \frac{d}{dt} \ln S(t), \quad (3.18)$$

$$S(t) = \exp \left\{ - \int_0^t \lambda(u) du \right\}. \quad (3.19)$$

Unfortunately, available experimental data, as a rule, are data from a heterogeneous group of patients. Heterogeneity is manifested in individual dynamic of measured variables.

Let  $\mathbf{Z}(t, \omega) \equiv \mathbf{Z}_t(\omega) \in R^m$  be a vector of physiological parameters of a patient with index  $\omega \in \Omega$  at the instant of time  $t$ , where  $\Omega$  is a set of indices.  $\omega$  is an index which characterizes a homogeneous group of patients. For example, we can consider a homogeneous group of individuals with respect to lifetime after the beginning of treatment. The individual evolution in time  $\{\mathbf{Z}_t(\omega)\}$  can be considered as a realization of some stochastic process  $\{\mathbf{Z}_t(\omega), t \in [0, T], \omega \in \Omega\}$ . In this case we can study the conditional survivor function

$$S(t, \omega) = P\{T > t | (\mathbf{Z}_u(\omega), u \leq t)\}, \quad (3.20)$$

where  $\mathbf{Z}_t(\omega)$  are individual trajectories of the physiological parameters of the patients with index  $\omega$ .

If the conditional survivor functions have the convenient reasonable form (see 3.19)

$$S(t, \omega) = \exp\left\{-\int_0^t \mu_u(\omega) du\right\} \quad (3.21)$$

then the individual hazard function can be defined as

$$\mu_t(\omega) = -\frac{d}{dt} S(t, \omega) = P\{t < T \leq t+dt | T \geq t, (\mathbf{Z}_u(\omega), u \in (0, t))\} dt. \quad (3.22)$$

Consequently, group mortality dynamics in terms of observations could be written in the form of

$$P\{T > t\} = E\left\{\exp\left[-\int_0^t \mu(Z_u(\omega)) du\right]\right\}, \quad (3.23)$$

where  $\mu(Z_t(\omega))$  is an unknown function.

In this case [62], [63], [37] the observable hazard function for a group of patients has the form

$$\lambda(t) = -\frac{d}{dt} \ln S(t) = E\{\mu(Z_t(\omega) | T > t)\}. \quad (3.24)$$

To study mortality dynamics as a function of clinically measured variables we must parameterize the hazard function.

In practice, various forms of parameterization are used, for example,

$$\mu(Z_t(\omega)) = Z_t^T Q(t) Z_t + \lambda_0(t), \quad (3.25)$$

where  $Z_t \in R^m$ ,  $Q(t)$  is an unknown symmetric positive definite matrix of appropriate dimension, and  $\lambda_0(t)$  is a hazard function which is not connected with the disease but which may be considered as a function of age, sex, etc.

Elements of the matrix  $Q$  and  $\lambda_0(t)$  can be estimated from observed data  $Z_t \in R^m$  and  $S(t) = E[S(t, \omega)]$ .

Consequently we can use (3.25) or  $\int_0^t [Z_u^T Q(u) Z_u + \lambda_0(u)] du$  for studying individual dynamics and for choosing the individual method of treatment [37].

#### 4. Estimation of Immune Model Parameters

Assume that the model consists of a system of ordinary differential equations

$$\frac{d}{dt} x_t = f(x_t, \alpha), \quad t \in [0, T], \quad x_0 = q, \quad (4.1)$$

where

$x_t \in R^n$  is a vector of state variables,

$\alpha \in R^\ell$  is a vector of coefficients.

Furthermore, assume a linear parameter structure such that

$$f(x_t, \alpha) = F(x_t)\alpha,$$

where  $F(x)$  is an appropriately smooth  $n \times \ell$  function.

Let  $x_t(\alpha)$  denote the solution of equation (3.1) for  $t \in [0, T]$ . It was assumed previously that the experimental data have the following form:

$$\hat{X}_m = \{\hat{x}_t^j, t \in \Theta, j = 1, \dots, M, \hat{x}_t^j \in R^n\}$$

or

$$\hat{X}_o = \{\hat{x}_t^j, j = 1, \dots, m_t, t \in \Theta, \hat{x}_t^j \in R^n\}$$

*However the real trajectories of the state variables presumably have a stochastic character and can not be described within the framework of a deterministic model.*

The stochastic character of the trajectories depends not only on errors of measurements but also various internal and external factors which influence process dynamics.

##### 4.1. Maximum Likelihood Estimation

The stochastic character of trajectories can be described by the introduction of a small random perturbation for the model parameters. For each trajectory  $x_t^j \in X_m$  assume that there exists a piecewise continuous function  $\alpha_t^j$  such that  $x_t(\alpha_t^j) = \hat{x}_t^j, t \in \Theta$ . A set of these functions can be considered as a set of realizations of some stochastic process

$$\{\alpha_t(\omega), \omega \in \Omega, t \in [0, T]\}.$$

Moreover

$$E\alpha_t = \int_{\Omega} \alpha_t(\omega) dP(\omega) = \bar{\alpha}, \quad \forall t \in [0, T].$$

In this case a set  $X_m$  can be considered as a contraction on  $\Theta$  of the set of realizations of the stochastic process

$$\{x_t(\omega), \omega \in \Omega, t \in [0, T]\},$$

which satisfies the stochastic equation

$$\frac{d}{dt} x_t = f(x_t, \alpha_t), \quad t \in [0, T]. \quad (4.3)$$

Then the solution to the problem of model coefficient estimation reduces to maximizing the likelihood function

$$\max_{\alpha} \Phi(\hat{X}_m, \alpha). \quad (4.4)$$

This problem is discussed in detail in [38], [64].

#### 4.2. Adjoint Estimation of Model Parameters

In the previous section the problem of stochastic estimation of model parameters is discussed. It is a difficult problem, because the likelihood function depends on parameters of the model in the implicit form.

Fortunately an effective numerical algorithm can be constructed which uses the adjoint equations. As an example, consider the simple deterministic task [50]-[52].

Let the model be represented by (4.1). For the sake of simplicity, we assume that the initial values  $x(0, \alpha) = q \in R_+^n$ ,  $R_+^n = \{x \in R^n \mid x \geq 0\}$  are known. Denote  $x^0 \equiv x(t, \alpha_0)$  the solution of equation (4.1) satisfying the initial condition  $x(0, \alpha_0) = q$ . This solution is said to be a non-perturbed or a reference one.

Assume that

- (a) statistical errors in the measurements are eliminated by appropriate preprocessing of the data,
- (b) within the given accuracy  $\hat{x}(\theta) \approx x(\theta, \alpha_0 + \epsilon \delta \alpha)$ ,  $\theta \in \Theta$  where  $x(t, \alpha_0 + \epsilon \delta \alpha)$  is the true or perturbed solution of equation (4.1) satisfying the initial condition  $x(0, \alpha_0 + \epsilon \delta \alpha)$ ,  $\alpha_0$  is a known vector,  $\epsilon > 0$  is a small parameter.

The problem of evaluating the coefficients of the model using the available data reduces to that of determining the variation of the coefficients of the model  $\delta \alpha_j$ ,  $j = 1, \dots, \ell$ , which have been chosen, for example, from the condition

$$\|\hat{x}(\theta) - x(\theta, \alpha_0 + \epsilon \delta \alpha)\|^2 \rightarrow \min.$$



Alternatively, a sequence

$$\alpha_j^{u+1} = \alpha_j^u + \delta \alpha_j^u, \quad j = 1, \dots, \ell$$

has to be defined such that

$$\| \hat{x}(\theta) - x(\theta, \alpha^u + \delta \alpha^u) \|^2 \rightarrow \min .$$

as  $u \rightarrow \infty$  where  $\alpha_0 \in R^\ell$  is a given vector.

Let us write the perturbed solutions of equation (4.1)  $x(t, \alpha_0 + \epsilon \delta \alpha)$  as a series in powers of a small parameter  $\epsilon$  such that  $0 < \epsilon \leq \epsilon_0$  ( $\epsilon_0 > 0$  is a fixed number)

$$x(t, \alpha_0 + \epsilon \delta \alpha) = x_t^{(0)} + \epsilon x_t^{(1)} + \epsilon^2 x_t^{(2)} + \dots . \quad (4.5)$$

Substitute (4.5) into (4.1); expand the right-hand side of the above equality in powers of the small parameter  $\epsilon > 0$  up to terms of the order of  $O(\epsilon^N)$ , and equate the terms with the same powers of  $\epsilon > 0$  to obtain a recursive system

$$\frac{d}{dt} x_t^{(0)} = f(x_t^0, \alpha_0), \quad x(0, \alpha_0) = q, \quad (7.6)$$

$$\frac{d}{dt} x_t^{(1)} = \frac{\partial}{\partial x} f(x_t^0, \alpha_0) x_t^{(1)} + \frac{\partial}{\partial \alpha} f(x_t^0, \alpha_0) \delta \alpha, \quad x^{(1)}(0, \alpha_0) = 0 .$$

Neglecting terms of the order of  $\epsilon^2$  or higher, for  $\delta x_t \approx x_t(\alpha_0 + \delta \alpha) - x_t(\alpha_0)$ , we have

$$\frac{d}{dt} \delta x_t = A(t) \delta x_t + B(t) \delta \alpha, \quad (4.7)$$

$$\delta x_0 = 0, \quad t \in [0, T],$$

where

$$A(t) \equiv \frac{\partial}{\partial x} f(x_t^0, \alpha_0), \quad B(t) \equiv \frac{\partial}{\partial \alpha} f(x_t^0, \alpha_0),$$

For system (4.7) write the adjoint system

$$\frac{d}{dt} y_t = -A^T(t) y_t + p(t), \quad (4.8)$$

$$y(T) = 0, \quad t \in [0, T],$$

where  $p(t)$  is an appropriate function which will be defined below.

Taking the scalar product of (4.7) by  $y_t$  and (4.8) by  $\delta x_t$ , integrating from 0 to  $T$ , adding together and using the relation

$$\langle A(t) \delta x, y_t \rangle - \langle A^T(t) y_t, \delta x_t \rangle = 0,$$

we obtain

$$\begin{aligned} & \int_0^T \left[ \langle y_t, \frac{d}{dt} \delta x_t \rangle + \langle \delta x_t, \frac{d}{dt} y_t \rangle \right] dt \\ &= \int_0^T \frac{d}{dt} \langle y_t, \delta x_t \rangle = \\ &= \int_0^T \langle B(t) \delta \alpha, y_t \rangle dt + \int_0^T \langle p(t), \delta x_t \rangle dt, \end{aligned} \quad (4.9)$$

or

$$\int_0^T \langle B(t) \delta \alpha, y_t \rangle dt + \int_0^T \langle p(t), \delta x_t \rangle dt = 0, \quad (4.10)$$

If we choose the function  $p(t)$  as follows:

$$p_i(t) = \begin{cases} 0 & \text{for } i \neq k, \quad i = 1, \dots, n, \\ \delta(t-\theta) & \text{for } i = k, \end{cases} \quad (4.11)$$

where  $\delta(t - \theta)$  is the Dirac delta function,  $1 \leq k \leq n$ , then (4.10) can be rewritten in the form

$$\delta x_k(\theta, \alpha_0) = - \int_0^T \sum_{j=1}^{\ell} \delta \alpha_j \sum_{i=1}^n b_{ij} y_j^k dt = \langle \delta \alpha, \psi \rangle, \quad (4.12)$$

where

$$\Psi_j^k = \int_0^T \sum_{i=1}^n b_{ij} y_j^k dt, \quad j = 1, \dots, \ell,$$

and  $y^k(t)$  satisfies equation (4.8) for  $k = 1, \dots, n$ .

Let  $\delta \alpha_0$  be the solution of system (4.12) for  $t \in \Theta$ .  $\alpha^* = \alpha + \delta \alpha$  is an unknown vector. As a result of our computation we have  $\delta \alpha_0$ . Therefore  $\alpha_1 = \alpha_0 + \delta \alpha_0$  is a first approximation for the unknown vector  $\alpha^*$ . Now we can write an iterative process for estimating  $\alpha^*$ .

$$\alpha^{u+1} = \alpha^u + \delta \alpha^u, \quad u = 0, 1, \dots \quad \alpha^u \in R^\ell \quad (4.13)$$

Actually this is the Newton process with the convergence rate [38]

$$| \alpha^u - \alpha^* | \leq c^{-1} (c | \alpha_0 - \alpha^* | )^{2^u}, \quad c = \text{const} . \quad (4.14)$$

#### 4.3. Simple Example

Let us consider the following zero system [52]

$$\frac{dx}{dt} = f(x, \alpha), \quad t \in [0, t_k], \quad (4.15)$$

$$x(0, \alpha) = x^0,$$

where

$$x(t, \alpha) = (x_1(t, \alpha), x_2(t, \alpha))^T,$$

$$x(0, \alpha) = (1, x_2^0)^T \in R_+^\ell$$

$$\alpha = \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{bmatrix},$$

$$f(x, \alpha) = \begin{bmatrix} -\alpha_1 x_1 & 0 \\ \alpha_2 x_1 x_2 & -\alpha_3 x_2 \end{bmatrix}.$$

This system of equations in a simplified form describes the change in the number  $x_2$  of T-lymphocytes ( $x_2$ ) which occur during the immune response to non-reproductive antigens, e.g. sheep red blood cells in CBA mice. The data on the number of T-cells (helpers) were obtained by R.N. Stepanenko.

$$X = \{ \hat{x}_2(\theta_\ell), \theta_\ell \in [0, t_k], \ell = 1, \dots, 5, 0 < \theta_1 < \dots < \theta_5 < t_k \}$$

Here,  $\hat{x}_2(\theta_\ell)$  is an average number of T-cells at the instant of time  $t = \theta_\ell$ ,  $\ell = 1, \dots, 5$ .

The non-perturbed solutions of equation (4.15) has the form

$$x_1(t, \bar{\alpha}) = e^{-\bar{\alpha}_1 t} \quad (4.16)$$

$$x_2(t, \bar{\alpha}) = x_2^0 \exp \left\{ \frac{\bar{\alpha}_2}{\bar{\alpha}_1} (1 - e^{-\bar{\alpha}_1 t}) - \bar{\alpha}_3 t \right\}$$

Let us write the equation for the linear part of the variation,

$$\frac{d}{dt} \delta x = \frac{\partial f(\bar{x}, \bar{\alpha})}{\partial x} + \frac{\partial f(\bar{x}, \bar{\alpha})}{\partial \alpha} \delta \alpha, t \in [0, t_k] \quad (4.17)$$

$$\delta x(0, \bar{\alpha}) = 0.$$

$$\frac{\partial f(\bar{x}, \bar{\alpha})}{\partial x} = \begin{bmatrix} -\bar{\alpha}_1 & 0 \\ \bar{\alpha}_2 x_2(t, \bar{\alpha}) & \bar{\alpha}_2 x_1(t, \bar{\alpha}) - \bar{\alpha}_3 \end{bmatrix},$$

$$\frac{\partial f(\bar{x}_1, \bar{\alpha})}{\partial \alpha} = \begin{bmatrix} -x_1(t, \bar{\alpha}) & 0 & 0 \\ 0 & x_1(t, \bar{\alpha}) x_2(t, \bar{\alpha}) & -x_2(t, \bar{\alpha}) \end{bmatrix},$$

and the corresponding adjoint equation

$$-\begin{bmatrix} \frac{d}{dt} y_1 \\ \frac{d}{dt} y_2 \end{bmatrix} = \begin{bmatrix} -\bar{\alpha}_1 & -\bar{\alpha}_2 x_2(t, \bar{\alpha}) \\ 0 & \bar{\alpha}_2 x_1(t, \bar{\alpha}) - \bar{\alpha}_3 \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} + \begin{bmatrix} 0 \\ \delta(t - \theta) \end{bmatrix}, \quad (4.18)$$

where

$$y_i(t_k) = 0, \quad i = 1, 2, t \in [0, t_k], \theta \in (0, t_k).$$

The solution of problem (4.18) has the form

$$y_1(t) = \begin{cases} \frac{\bar{\alpha}_2}{\bar{\alpha}_1} x_2^0 \exp \left[ \frac{\bar{\alpha}_2}{\bar{\alpha}_1} (1 - e^{-\bar{\alpha}_1 \theta}) - \bar{\alpha}_3 \theta \right] (1 - e^{-\bar{\alpha}_1 (\theta - t)}), & \text{for } t < \theta \\ 0, & \text{for } t \geq \theta \end{cases}, \quad (4.19)$$

$$y_2(t) = \begin{cases} \exp \left[ \frac{\bar{\alpha}_2}{\bar{\alpha}_1} (e^{-\bar{\alpha}_1 t} - e^{-\bar{\alpha}_1 \theta}) + \bar{\alpha}_3 (t - \theta) \right], & \text{for } t < \theta \\ 0, & \text{for } t \geq \theta \end{cases}$$

The estimate of the variation  $\delta \alpha$  of the coefficients of the model can be found from the condition

$$\| J - D \delta \alpha \|^2 \rightarrow \min, \quad (4.20)$$

where

$$J = \begin{bmatrix} \hat{x}_2(\theta_1) - x_2(\theta_1, \bar{\alpha}) \\ \dots\dots\dots \\ \hat{x}_2(\theta_5) - x_2(\theta_5, \bar{\alpha}) \end{bmatrix},$$

and  $D$  is a  $5 \times 3$  matrix whose entries are

$$\begin{aligned} d_{l1} &= -\frac{\bar{\alpha}_2}{\bar{\alpha}_1} x_2(\theta_l, \bar{\alpha}) \left[ \frac{1}{\bar{\alpha}_1} \left( 1 - e^{-\bar{\alpha}_1 \theta_l} \right) - \theta_l e^{-\bar{\alpha}_1 \theta_l} \right], \\ d_{l2} &= x_2(\theta_l, \bar{\alpha}) \left[ \frac{1}{\bar{\alpha}_1} \left( 1 - e^{-\bar{\alpha}_1 \theta_l} \right) \right], \\ d_{l3} &= -x_2(\theta_l, \bar{\alpha}), \quad l = 1, \dots, 5. \end{aligned}$$

#### 4.4 Stochastic Case

In this case  $\alpha(t) = \alpha_0 + \epsilon \xi(t)$ ,  $\{\xi_t, t \in [0, T]\}$  is a stochastic process with  $E\xi_t = 0$  and  $\epsilon > 0$  is a small parameter. A vector of deviations  $\delta x_t(\alpha)$  has random character so that

$$\delta x_{t_k}^i(\alpha) = -\langle \delta \alpha, \psi_k^i(\alpha) \rangle + \int_0^T \langle B y_k^i, dw_s \rangle \quad (4.21)$$

which has approximately a Gaussian probability density function. If the perturbations are independent, the mathematical expectation and dispersion have forms of

$$E \delta x_{t_k}^i(\alpha) = -\langle \delta \alpha, \psi_k^i(\alpha) \rangle, \quad (4.22)$$

$$D \delta x_{t_k}^i(\alpha) = \langle \Gamma, \int_0^T [B y_k^i]^2 ds \rangle$$

where  $\Gamma$  is a vector of intensity of perturbation. Estimation of the coefficients of this model can be obtained from the likelihood function

$$\phi(\alpha, \delta \alpha, \Gamma) = \sum_{t \in \theta} \sum_i \left\{ \ell n \langle \Gamma, b^i(\alpha) \rangle + \frac{[\delta x_t(\alpha) + \langle \delta \alpha, \psi_t^i(\alpha) \rangle]^2}{\langle \Gamma, b^i(\alpha) \rangle} \right\}.$$

In [38] it is proven that the iterative process

$$(\delta \alpha^u, \Gamma^u) = \arg \min_{\delta \alpha, \Gamma} \phi(\alpha, \delta \alpha, \Gamma)$$

$$\alpha^{u+1} = \alpha^u + \delta \alpha^u,$$

$$\Gamma^{u+1} = \Gamma^u, \quad u = 0, 1, 2, \dots$$

is a quasi-Newton process with first-order convergence rate. The estimators, computed by this method, converge to the true values  $\alpha^*$ ,  $\Gamma^*$ , with probability one.

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