Lecture Notes in Control and Information Sciences

Edited by A.V. Balakrishnan and M. Thoma

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18

Modelling and Optimization of Complex System

Proceedings of the
IFIP-TC 7 Working Conference
Novosibirsk, USSR, 3–9 July, 1978

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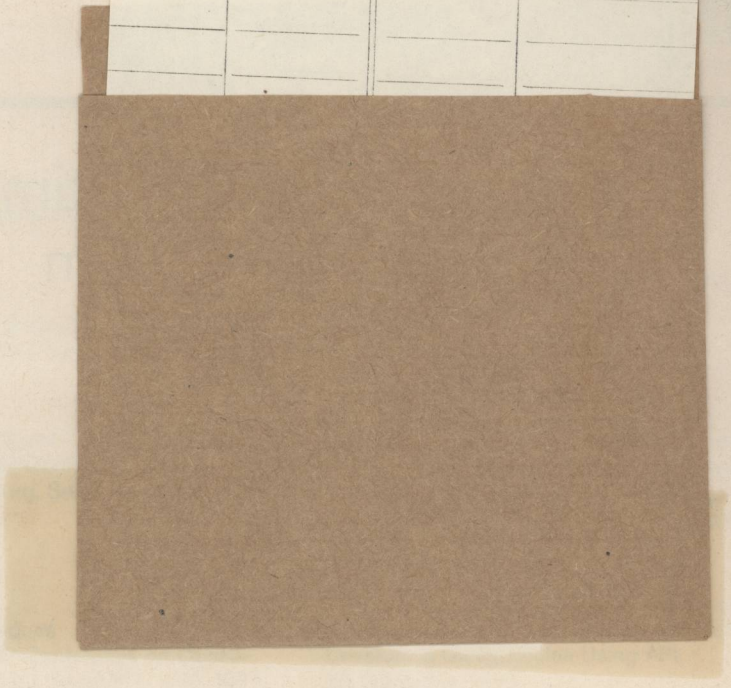

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PREFACE

These Proceedings contain most of the papers presented at the IFIP TC-7 Working Conference on Modelling and Optimization of Complex Systems held in Novosibirsk on 3-9 July, 1978.

The Conference was organized by the IFIP Technical Committee on Optimization with the Computing Center of the Siberian Branch of the USSR Academy of Sciences and sponsored by the USSR Academy of Sciences.

The Conference was attended by 70 scientists from 10 countries. The program offered a broad view of optimization techniques currently in use and under investigation. Major emphasis was on recent advances in optimal control and mathematical programming and their application to modelling, identification and control of large systems, in particular, recent applications in areas such as biological, environmental and socio-economic systems.

The International Programme Committee of the Conference consisted of:

A.V.Balakrishnan (Chairman, USA), C.Bruni (Italy), J.L.Lions (France), K.Malanowski (Poland), G.I.Marchuk (USSR), R.R.Mohler (USA), L.S.Pontryagin (USSR), J.Stoer (FRG).

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Invited Speakers

MATHEMATICAL MODELS IN IMMUNOLOGY

MAXIMUM LIKELIHOOD IDENTIFICATION OF AN IMMUNE RESPONSE MODEL (*)

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1. INTRODUCTION

In a previous work a model for the humoral immune response was established, based on the clonal selection theory (Bruni et al.1974, 1975). This model was tested against available data in the literature (Eisen and Siskind, 1964; Siskind et al.,1968;Werblin et al., 1973) giving the parameters some reasonable values, with rather satisfactory results. In order to achieve a more thorough validation of the model, it appeared necessary to a) obtain a more complete and homogeneous set of experimental data, b) achieve a better knowledge of the values of the model parameters.

As far as the first point is concerned, an *ad hoc* experimental program was carried out, in which the population of antibodies generated in the primary and secondary immune response triggered by inoculation of a suitable antigen was tested at different times (Oratore, 1977). Inbred Guinea pigs (strain 13) were inoculated by doses of 0.1 mg and 1 mg of DNP-RNAase in Freund's complete adjuvant. Bleedings were performed weekly and the adopted titration procedure was the Farr technique.Also, some experiments were made to get information about the time evolution of the free antigen concentration in the blood during the maturation of the immune response (Oratore, unpublished results).

The aim of this paper is to deal with the second point, namely to identify the unknown parameters of the model.

(*) This work was partially supported by C.N.R.. The experiments which are referred to in this paper were conducted at Oregon Regional Primate Research Center, under a joint scientific program between the Centro di Studio dei Sistemi di Controllo e Calcolo Automatici and the Oregon State University, supported by Italian National Research Council and the U.S. National Science Foundation (Grant n. ENG-74-15330 AOI).

2. AN IDENTIFICATION ORIENTED MODEL

A first problem was to revise the previously proposed model in order to get an identification oriented version of it. This primarily led to assume as input and output variables the free antigen concentration and respectively the antibody concentration density, i.e. those quantities which were experimentally observed. With reference to the original model, this means to consider only the phenomena of stimulation, differentiation and duplication of lymphocytes, and of antibody production and removal, while the feedback phenomena of antigen removal by the antibodies was cut off (see Fig. 1). In addition, the term which in the original model described a burst of antibody synthesis by immunocompetent cells immediately after their duplication was disregarded, since it was found to be not quantitatively relevant. By this way we arrived at the following simplified model equations:

$$\frac{\partial C(K,t)}{\partial t} = \alpha_c \frac{1}{1+KH(t)} p_s(KH(t))C(K,t) - \alpha_c \frac{KH(t)}{1+KH(t)} p_s(KH(t))C(K,t) + \\ - \frac{1}{\tau_c} C(K,t) + \beta p_c(K) \tag{2.1}$$

$$\frac{\partial C_p(K,t)}{\partial t} = 2\alpha_c \frac{KH(t)}{1+KH(t)} p_s(KH(t))C(K,t) - \frac{1}{\tau_p} C_p(K,t) \tag{2.2}$$

$$\frac{\partial S_T(K,t)}{\partial t} = \alpha_s C_p(K,t) + \alpha_s' C(K,t) - \frac{1}{\tau_B} \frac{KH(t)}{1+KH(t)} S_T(K,t) - \frac{1}{\tau_s} \frac{1}{1+KH(t)} S_T(K,t) \tag{2.3}$$

where:

K is the *association constant* between antigen and antibody sites ranging in the interval $[0,\infty)$ (antigen is considered functionally univalent)

$H(t)$ is the *free antigen concentration* in the circulating fluids

$C(K,t)$ is the *concentration density*, with respect to K, *of immunocompetent cells*

$C_p(K,t)$ is the *concentration density of plasmacells*

$S_T(K,t)$ is the *total* (free and bound) *antibody sites concentration density*

$p_s(KH(t))$ is the probability that a cell of affinity K is stimulated; in (Bruni et al., 1975) it is shown that this is a smooth window function, which takes value very close to 1 if $\frac{\sigma_1}{1-\sigma_1} \leq KH(t) \leq \frac{\sigma_2}{1-\sigma_2}$ and very close to zero otherwise

$p_c(K)$ is the original distribution of immunocompetent cells and it is assumed to be lognormal and known.

The parameters which appear in the model, are:

α_c proliferation rate constant of stimulated immunocompetent cells

β rate of production of new immunocompetent cells from stem cells

τ_c mean lifetime of immunocompetent cells

τ_p mean lifetime of plasmacells

τ_B mean lifetime of the immune complex

τ_s mean lifetime of free antibody sites

α_s rate constant of antibody production by plasmacells

α_s' rate constant of antibody production by immunocompetent cells

σ_1, σ_2 endpoints of the interval of occupied receptor site ratio causing stimulation.

To these parameters we must add suitable initial conditions for equations (2.1)-(2.3).

While the input H is directly measured at different times, the total antibody sites concentration density is indirectly measured through the concentration Y(X,t) of bound antibody sites in the titration assay made on the circulating fluids at different times and for fixed free hapten concentration X:

$$Y(X,t) = \int_0^\infty \frac{KX}{1+KX} \frac{S_T(K,t)}{1+KH(t)} \, dK \qquad (2.4)$$

Noting that the free antibody site concentration density in the circulating fluids is given by the term $\frac{S_T(K,t)}{1+KH(t)}$, the previous relation provides under mild assumptions (Bruni et al., 1976) a one to one correspondence between the free antibody site concentration density itself at time t and the behaviour of Y(X,t) as a function of X. Thus Y(X,t) plays the role of actual model output (Fig. 1).

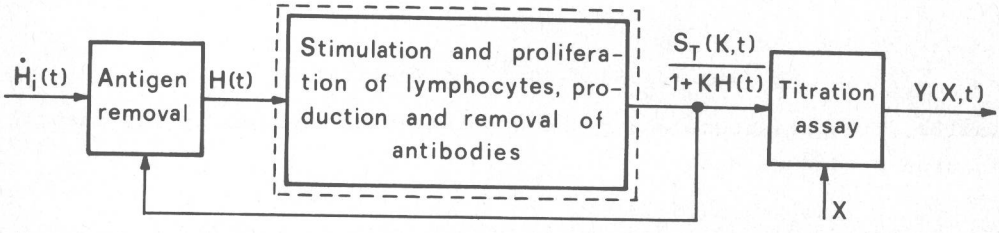

Fig. 1 - Block diagram showing connection among quantities relevant for identification purpose. The dashed square includes the identification oriented immune response model; $\dot{H}_i(t)$ denotes the rate of injection of antigen in the organism.

Now the second problem is to choose those parameters in the model which are to be identified. Indeed, if all parameters and initial conditions appearing in the model were assumed to be unknown in the identification procedure, then we would face: a) difficulties in meeting possible a priori (or experimental) information about relationships among some of them, b) possible non identifiability problems due to low sensitivity of the output with respect to some parameters and/or equivalent effect on the output itself, c) an excessive comp tional burden. With the purpose of overcoming these difficulties, only the primary response was considered, so that the initial conditions reduce to:

$$C(K,0) = C_o p_c(K) = \tau_c \beta p_c(K)$$

$$C_p(K,0) = 0 \qquad (2.5)$$

$$S_T(K,0) = \tau_s \alpha'_s C(K,0)$$

In the first equation (2.5), C_o denotes the initial total number per unit volume of immunocompetent cells which turns out to be equal to $\tau_c \beta$, since $C(K,0)$ must be a stationary solution of (2.1) in absence of stimulation.By simulation of the model it appeared that variations in C_o may be (output) compensated by suitable variations of α_s , α'_s. Therefore C_o was fixed to the biologically reasonable value:

$$C_o = 8 \cdot 10^{-16} \text{ moles/liter}$$

Information reported in the literature (Weigle, 1961; Gowans, 1970; Mattioli and Tomasi, 1973) further suggest to assume the following values:

$$\tau_p = 6 \text{ days} = 144 \text{ h}$$

$$\tau_c = 300 \text{ days} = 7200 \text{ h}$$

$$\tau_s = 2\ \tau_B$$

$$\beta = C_o/\tau_c = 1.1 \cdot 10^{-19} \text{ moles/liter} \cdot \text{h}$$

Finally, the parameters which are considered as unknown in the identification procedure are :

$$\sigma_1, \sigma_2, \alpha_c, \alpha_s, \alpha'_s, \tau_B$$

This selection seems to meet some remarks (Mohler, 1978) about the sensitivity of the model with respect to various parameters.

As a matter of fact, in order to take the positivity constraint for all six parameters into account, the unknown parameter vector was defined as:

$$\gamma \triangleq \left[\ln \sigma_1 \quad \ln \sigma_2 \quad \ln \alpha_c \quad \ln \alpha_s \quad \ln \alpha'_s \quad \ln \tau_B \right]^T \tag{2.6}$$

3. PROBLEM FORMULATION

We first note that the experimental data presently available for [illegible] are constituted by its value at a very limited number of times, so that an interpolation procedure is required to simulate the model. Simple interpolating functions were chosen constituted by the sum of two exponentials which for the two doses of 1 mg and 0.1 mg are respectively (Fig. 2, solid lines) - H moles/liter, t hours:

$$H(t) = 8.16 \cdot 10^{-7} \left[e^{-t/85} - e^{-t/11} \right] \tag{3.1}$$

$$H(t) = 10^{-7} \left[e^{-t/100} - e^{-t/14} \right] \tag{3.2}$$

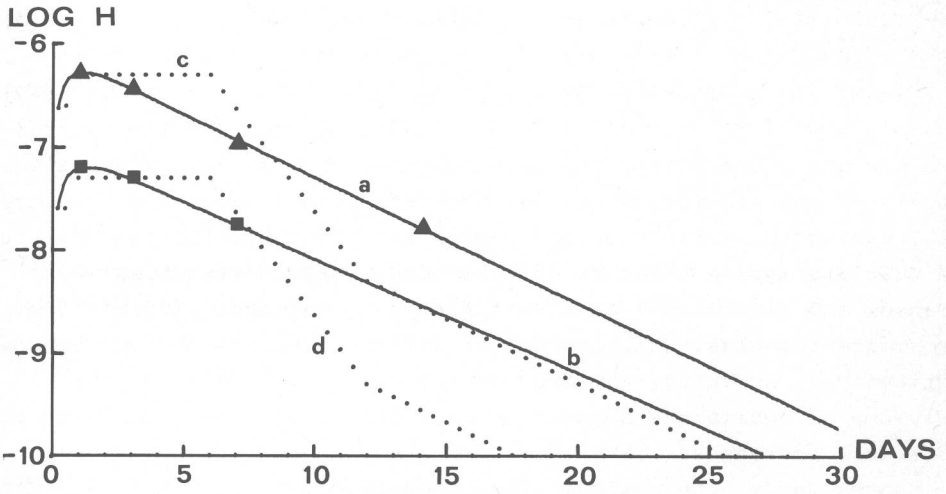

Fig. 2 - Time evolution of free antigen: experimental points (▲, ■), exponential interpolation (solid lines), piecewise exponential behaviour (dotted lines) for 1 mg dose (lines a-c) and 0.1 mg dose (lines b-d).

As a matter of fact, equations (3.1),(3.2) differ from the real behaviour of free antigen not only because of interpolation errors but also because of random measurement errors which affect the data. These errors influence the output function (2.4) both directly and indirectly

through the dependence of S_T on H itself (taking the dynamics of the model into account). However, if one linearizes the functional dependence of Y(X,t) on H for fixed X and t, as described by (2.4) and the model equations, one finds that the first order approximation of the influence on Y(X,t) of the random errors of H is negligible with respect to those experimental errors which affect Y(X,t) itself in the titration assays. As far as interpolation errors on H,it is not possible to evaluate their magnitude with such a low number of data. For sake of simplicity their effect on Y(X,t) was also neglected, while some considerations about possible consequences of this fact are reported in the concluding section.

Let now $t_1,t_2,\ldots,t_N$ be the bleeding times and $X_j(t_i)$, $j = 1,2,\ldots,n_i$, $i = 1,\ldots,N$,be the j-th hapten concentration in the i-th titration assay. Let $Y(X_j(t_i),t_i;\gamma)$ be the corresponding bound antibody site concentration given by (2.4) in which the dependence of the model output on γ is evidentiated. Denoted by x and $y(x,\gamma)$ the vectors of all $X_j(t_i)$ and $Y(X_j(t_i),t_i;\gamma)$, respectively, and by z_x,z_y the vectors of the measured values for the same quantities, the measurement equations may be written as:

$$z_x = x + u \tag{3.3}$$

$$z_y = y(x,\gamma) + v \tag{3.4}$$

where u,v are respectively the measurement errors on x,y. A detailed analysis of the statistics of u,v was carried out (Koch and Oratore, 1978), taking the various error sources into account. The conclusions were that u,v may be taken to be zero mean gaussian variables whose variances and covariances at each titration point are deducible from approximate formulas, while errors at different points are incorrelated. Quantitatively speaking, the mean square error on X data is approximately 2 - 3%, while the same error on Y data increases from 2% up to 20-30% as X increases.

Consequently, the maximum likelihood functional for x,γ is given by:

$$J(x,\gamma) = \begin{bmatrix} z_x - x \\ z_y - y(x,\gamma) \end{bmatrix}^T \Psi^{-1} \begin{bmatrix} z_x - x \\ z_y - y(x,\gamma) \end{bmatrix} \tag{3.5}$$

where:

$$\Psi = E\left\{ \begin{bmatrix} u \\ v \end{bmatrix} \begin{bmatrix} u^T & v^T \end{bmatrix} \right\} = \begin{bmatrix} \Psi_u & \Psi_{uv} \\ \Psi_{uv} & \Psi_v \end{bmatrix} \tag{3.6}$$

is a known block-diagonal non singular matrix. Due to small values of Ψ_u entries, we may linearize $y(x,\gamma)$ around z_x. Then minimizing $J(x,\gamma)$ with respect to x and substituting back the obtained value for x leads to the reduced functional:

$$J_1(\gamma)=\left[z_y-y(z_x,\gamma)\right]^T \Psi_e^{-1}(z_x,\gamma)\left[z_y-y(z_x,\gamma)\right] \tag{3.7}$$

where:

$$\Psi_e(z_x,\gamma)=\Psi_v-2\frac{\partial y(z_x,\gamma)}{\partial z_x}\Psi_{uv}+\left[\frac{\partial y(z_x,\gamma)}{\partial z_x}\right]^2\Psi_u \tag{3.8}$$

It can be proved (see Bruni and Germani, to appear) that Ψ_e is always nonsingular, since the absolute value of the correlation coefficient between u and v values is always less than one.

4. IDENTIFIABILITY

The problem now arises of identifiability of γ, namely of the existence and uniqueness of an optimal estimate $\hat{\gamma}$ of γ with respect to the loss functional (3.7). Of course, local identifiability of γ is equivalent to the existence of an isolated minimum of (3.7) within a suitable neighbourhood $D(\gamma^o,\delta) \subset \mathbb{R}^6$ of the initial guess γ^o.

Since our functional $J_1(\gamma)$ is continuously differentiable with respect to γ, this problem may be regarded as the problem of local existence and uniqueness of a solution of the equation:

$$P(\gamma) = \frac{dJ_1(\gamma)}{d\gamma} = 0 \tag{4.1}$$

and therefore studied by adapting well-known Kantorovich theorems (Kantorovich and Akilov, 1964). Specifically, let $\gamma^o, \delta_R, \delta_I, B_o, \eta_o$ be such that:

(i) $|P'(\gamma^o)| \neq 0$

(ii) $\|[P'(\gamma^o)]^{-1}\| \leq B_o$

(iii) $\|[P'(\gamma^o)]^{-1}P(\gamma^o)\| \leq \eta_o$

(iv) $\Omega = D(\gamma^o,\delta_R) \times D(0,\delta_I)$ is contained in the complex region of $\mathbb{C}^6$ in which $P(s)=P(\gamma+j\omega)$ is holomorphic.

Then the following theorem may be proved (Bruni and Germani, to appear):

*Thm.*1. Let $M_{\partial\Omega} = \sup_{s \in \partial\Omega} \|P(s)\|$.

a) If: $h_o = \dfrac{\eta_o B_o M_{\partial\Omega}}{\delta_I^2} \leq 1/4$

$$r_o \leq \delta_R < r_1 \quad , \quad \text{with} \quad r_o = \frac{1-\sqrt{1-4h_o}}{2h_o}\,\eta_o \quad , \quad r_1 = \frac{1+\sqrt{1-4h_o}}{2h_o}\,\eta_o$$

or

b) if: $h_o = 1/4$

$$r_o \leq \delta_R \leq r_1$$

then a unique optimal estimate $\hat{\gamma}$ exists in $D(\gamma^o, \delta_R)$.

The estimate $\hat{\gamma}$ may be looked for through a suitable minimization algorithm. If one adopts the Newton method, the following result turns out to be useful:

Thm. 2. Under the same assumptions of Thm.1, the Newton method for the solution of (4.1), starting from γ^o, yields a sequence quadratically convergent to $\hat{\gamma}$.

Remark 1. It is possible to prove that if the function P is that defined by our problem, for each $\delta_R > 0$, and γ^o satisfying (i) above, a $\delta_I > 0$ exists such that (iv) is satisfied.

Remark 2. The results of Thm.1,2 allow to set in a rigorous framework the identification problem under both aspects of identifiability and of numerical determination of the optimal estimate. However, we must say that checking conditions of Thm.1, and specifically computing $M_{\partial\Omega}$, is not at all an easy task. Furthermore in our case, due to the high degree of nonlinearities and to the dimensionality of the problem, the Newton method implementation requires heavy computational effort.

Therefore to obtain the results reported in the following section, a simpler direct search method (Hooke and Jeeves) was adopted.

5. IDENTIFICATION AND VALIDATION OF THE MODEL

In the minimization of functional $J_1(\gamma)$, as initial guess γ^o we assumed those parameter values which in a previous work (Bruni et al., 1975) were selected according to information available directly or indirectly from the literature. In particular we assumed:

$$\sigma_1^o = 0.01 \; ; \quad \sigma_2^o = 0.9 \; ; \quad \alpha_c^o = 0.06 \; h^{-1} \qquad (5.1)$$