

APPLICATION OF AUTOREGRESSIVE MODELLING FOR THE ANALYSIS OF CLINICAL AND OTHER BIOLOGICAL DATA

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(Received April 26, 1988; revised May 26, 1988)

Abstract. This paper deals with the application of autoregressive (AR) modelling for the analysis of biological data including clinical laboratory data. In the first part of the paper, we discuss the necessity of feedback analysis in the field of biochemistry. In order to enable this, relative power contribution analysis was introduced. Next, we utilized the two types of impulse response curves of the open and closed loop systems for elucidating the structure of the metabolic networks under study. Time series data obtained from 31 chronic hemodialysis patients observed for periods of 3 to 7 years were analyzed by these procedures. The results of the analysis were rather uniform among the patients and suggested the consistency of this approach in identifying the dynamical system of individual patients. An example of data set is included in the paper.

Key words and phrases: AR modelling, feedback analysis, clinical data, biological data, homeostasis in the body.

1. Introduction

As early as 1878, Claude Bernard enunciated the general principle of the constancy of the "milieu interieur" (or internal environment), which provides the body cells with an optimal environment for them to live (Bernard (1878)). The basic idea of Bernard was that the maintenance of an internal environment independent of the external environment provides animals with much freedom in choosing a habitat in contrast to the monocellular organisms that are obliged to stay in an environment appropriate to their survival (Houk (1980)).

This idea was extended by Cannon (1932), who coined the term homeostasis. When literally translated, this term means "similar condition", which he believed to be appropriate. Namely, he attached importance to the fact that the state of the body is not actually constant or fixed, but rather is

held within certain narrow range by the actions of autoregulatory mechanisms in the body. Later this term came to be used in broader senses, eventually to be used for expressing anything behaving in dynamical equilibrium. Thus many terms appeared such as "acid-base homeostasis", "divalent cation homeostasis", and even "social homeostasis". Because of the wide use of the term homeostasis, any phenomena in the body tended to be explained with this abstract concept, having most medical scientists give up the trials of developing the true image of dynamical systems in the body. In fact, many scientists were inclined to reject this concept because of its possibility of mystification of the events in the body.

Taken in a narrow sense, the study on homeostasis is almost equivalent to that on the regulatory system, i.e., the control theory. Although the application of traditional control theory helps us to predict the behavior of simple systems in the body, the handling of a complex system such as immunologic network is difficult and sometimes does not lead to satisfactory solutions (Jilek and Prikrylova (1985)).

In 1982, one of the authors, Wada, was studying in collaboration with Aoyagi on the *in vivo* (i.e., "in the body") effects of low molecular weight (LMW) enzyme inhibitors (Aoyagi *et al.* (1983)). Such inhibitors were isolated by Aoyagi, Umezawa and their colleagues from the culture filtrates of actinomycetes and are now widely used for many biochemical studies (Umezawa (1972), Aoyagi and Umezawa (1977), Umezawa and Aoyagi (1977)). In spite of the clear-cut actions of the LMW inhibitors *in vitro* (i.e., "in the test tubes"), hard to understand were the behavior *in vivo* of the enzymes to be suppressed by such inhibitors when the host animals were administered with such agents (Aoyagi *et al.* (1984a, 1984b)).

At the initial stage of the *in vivo* studies utilizing the LMW inhibitors, Wada was convinced that such apparently paradoxical behavior of enzymes could be explained as the dynamic behavior of the enzyme networks in the body but he had no means to prove his hypothesis. Eventually, he found the book by Akaike and Nakagawa (1972) to be useful for this purpose. Analytical results in our serial studies reported so far (Wada *et al.* (1986a, 1986b, 1987, 1988), Matsuo and Wada (1987)) were mainly obtained with the aid of the computer program TIMSAC, which was originally published in the book by Akaike and Nakagawa. The readers are referred to the papers written by Akaike for the principle of AR modelling (Akaike (1967, 1968)).

The purpose of the present paper is to show the practical utility of the AR modelling in the analysis of clinical laboratory data. Below, we will demonstrate that AR modelling may provide a general method for analyzing dynamic phenomena in the body by using the result of clinical time series related to anemia and protein metabolism in a group of patients under chronic hemodialysis. Numerical values of the time series are included in the Appendix to invite the interest of readers to this type of applications.

2. Use of relative power contribution analysis

Spectral analysis is a technique which decomposes a stochastic process into its sinusoidal components. The usefulness of the approach is limited when it is applied to the analysis of data obtained from the feedback system. In order to overcome this problem Akaike introduced multivariate AR modelling approach, and, in collaboration with his colleagues, established a practical method for implementing feedback controls of various systems (Akaike (1968), Akaike and Nakagawa (1972), Otomo *et al.* (1972), Otsu *et al.* (1979), Nakamura and Akaike (1981)).

The k -variate AR model of order M is given by

$$x_i(s) = \sum_{m=1}^M \sum_{j=1}^k a_{ij}(m)x_j(s-m) + n_i(s), \quad (i = 1, 2, \dots, k),$$

where $a_{ij}(m)$ is a weighting coefficient and $n_i(s)$ is a white noise, often called the innovation of x_i . Under the assumption that there is no correlation between the white noises $n_i(s)$ and $n_j(s)$, the power spectrum $p_{ii}(f)$ of $x_i(s)$ can be expressed as a summation of fractions $q_{ij}(f)$ as defined by the following equation:

$$p_{ii}(f) = \sum_{j=1}^k q_{ij}(f) = \sum_{j=1}^k \left| G(f)_{ij}^{-1} \right|^2 s_{jj}^2,$$

where

$$q_{ij}(f) = \left| G(f)_{ij}^{-1} \right|^2 s_{jj}^2 \quad \text{and}$$

$$G(f) = - \left\{ I - \sum_{m=1}^M A(m) \exp(2\pi ifm) \right\},$$

where i denotes $\sqrt{-1}$, $A(m)$ the $k \times k$ matrix of $a_{ij}(m)$, $G(f)_{ij}^{-1}$ the (i, j) -th element of the inverse matrix of $G(f)$, and s_{jj} the variance of $n_j(s)$. $q_{ij}(f)$ represents the portion of $p_{ii}(f)$, the power spectrum of $x_i(s)$, originating in the white noise $n_j(s)$. The relative power contribution of the variable x_j to the variable x_i is defined by

$$r_{ij}(f) = \frac{q_{ij}(f)}{p_{ii}(f)}.$$

At the initial stage of our study on homeostasis, we tried to utilize this concept of relative power contribution (Wada *et al.* (1986a)). We will present here a typical example of this approach for studying the clinical record of a patient on chronic hemodialysis.

Most of the patients undergoing chronic hemodialysis suffer from

various degrees of anemia. Although there are many causes for anemia in such patients, it has been known that nutritional factors play an important role. Since malnutrition often comes from the lack of protein intake, it will be reasonable to assume that the level of total serum protein (TP) is associated with the degree of anemia in the patient.

In order to confirm this hypothesis, we decided to investigate whether or not the changes in the degree of anemia, assessed by the blood hemoglobin level (Hb), can be explained by the changes in TP. Figure 1 shows the time course of the levels of blood hemoglobin and total serum protein (TP) in the patient (Case Y.S.) undergoing chronic hemodialysis. What we did first was to determine, from this set of data, the relative power contribution of TP to Hb in this patient. The length of the time series was 85. Although the two series looked to contain trend-like components, we did not try to eliminate them as this might cause some distortion of the mutual relation between the variables. This point seems in need of further technical analysis.

Figure 2 shows the results of analysis of the bivariate system, composed of Hb and TP. The order of the fitted bivariate AR model was 1. The X -axis shows frequency in terms of cycle/(2 weeks) as the interval for blood examination was 2 weeks. The Y -axis shows the relative power contribution in terms of the ratio ranging between 0 to 1, or 0% to 100% when expressed in percentage. As can be seen in the left panel, relative power contribution of TP to Hb is less than 10% at the frequency of 0.5 cycle/(2 weeks) but is about 40%

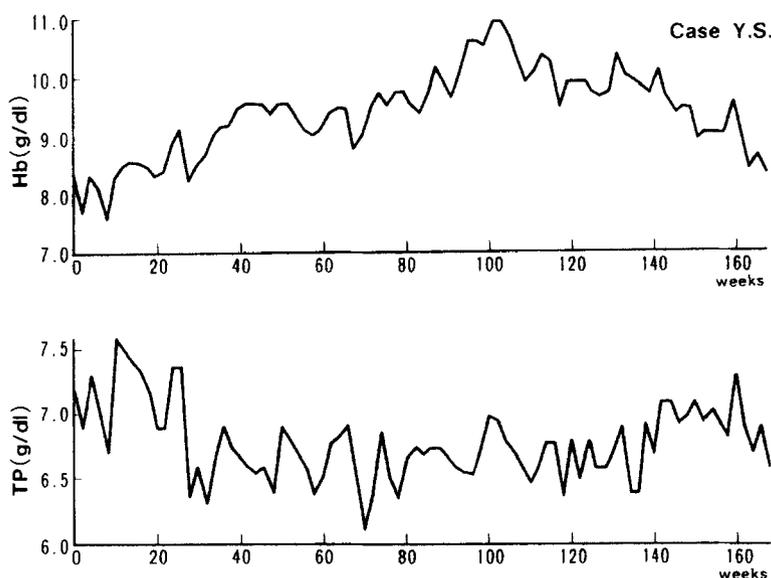


Fig. 1. The time course of the levels of serum total protein (TP) and blood hemoglobin (Hb) in the Case Y.S.

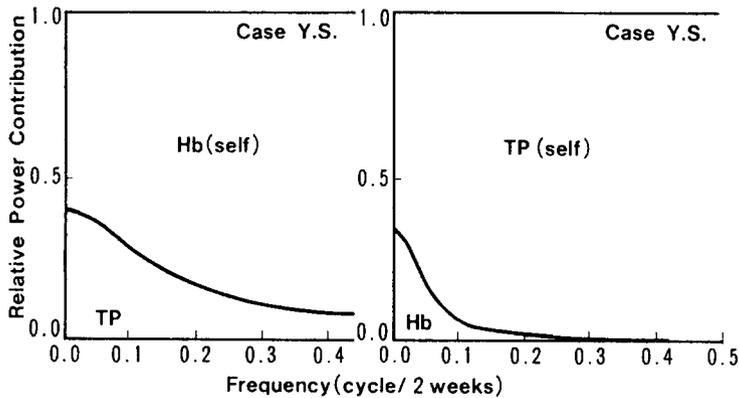


Fig. 2. The map of relative power contribution for the bivariate system in the Case Y.S. See text for explanation.

at the frequency of 0 cycle/(2 weeks). In the right panel, the contribution of Hb to TP is almost 0% at the frequency of 0.5 cycle/(2 weeks) but is about 35% at 0 cycle/(2 weeks). The numerical value of the correlation between the two innovations is 0.46 and is not sufficiently low to justify the present analysis, completely. The value of the correlation shows that about 20% of the variations in terms of the power of the variables are caused by a common source in this particular case. The average of the correlation was around 0.25 within this group of patients. This may suggest the necessity of including some other variables in the analysis. However, to understand the dominant behavior of the two variables we developed the analysis by simply assuming the zero correlation.

The relationship between Hb and TP was re-examined by adding three more variables, the blood urea nitrogen level (BUN), the serum choline esterase level (CHE), and the serum glutamic oxaloacetic acid transaminase level (GOT). The order of the model fitted in this case was 2, and the correlation matrix of the innovation vector is shown in the Appendix along with the raw data of these variables. All of the added variables were considered to be related to the protein metabolism in the body. By doing this, we expected that the relation between Hb and TP might be changed by the effect of the network composed of these variables. However, as can be seen in Fig. 3, the degree of contribution of TP to Hb did not change significantly from the above mentioned 35% at the frequency of 0 cycle/(2 weeks). The contribution of Hb to TP, however, slightly decreased.

It is to be noted here that the contribution from other variables are often maximal at the frequency of 0 cycle/(2 weeks) rather than in the higher frequencies. This might have been caused by the existence of trend like components. However, judging from our experience of analyzing various data, it seems that this is a feature of physiological data in general, in which

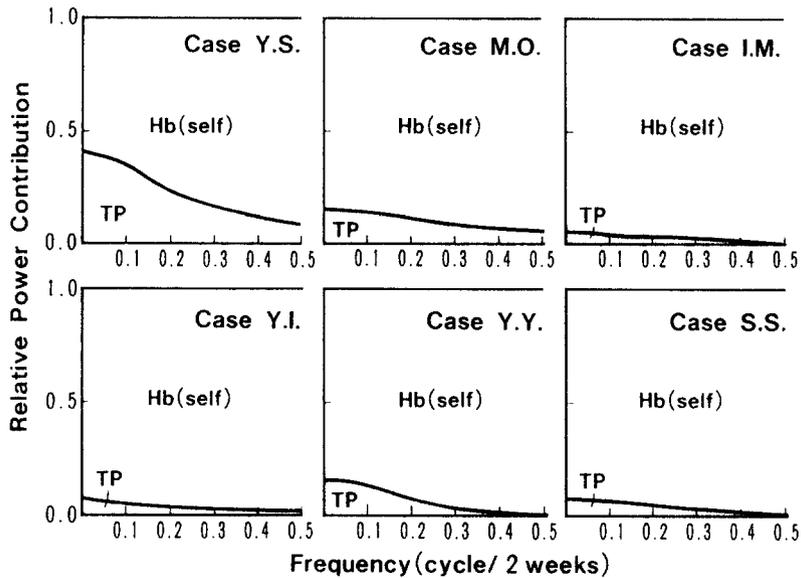


Fig. 3. The map of relative power contribution for the 5-variate system in the Case Y.S.

positive feedbacks, rather than negative ones, probably dominate in the daily regulation.

In order to explain this, let us take an example of the case of compulsive water drinking. The patient's more water drinking on a certain day than usual increases his urine volume on the same day and the next day. This increase in urine volume stimulates the thirst of the patient, increasing his water intake. This temporarily initiates a vicious cycle and, as time proceeds, the patient's urine volume increases up to the point, at which some negative feedback mechanisms come to inhibit the increase in the urine volume. This means that it takes time for the system to exert its stabilizing effects, allowing their signals go repeatedly around the feedback loops of the system. If one should analyze the time sequence data of such patient, he would find the relative power contribution of the quantity of the water drunk to the urine volume not very large at the frequency of one cycle/day. However, as the frequency goes down, the degree of contribution increases, reaching the maximum close to the frequency of 0 cycle/day in this frequency scale.

Figure 4 compares the maps of relative power contribution for the bivariate systems in 6 patients. Although the degree of contribution of TP to Hb varies depending on the patient, ranging between 4% to 40% at the frequency of 0 cycle/(2 weeks), it seems certain that TP plays some significant role in the hemoglobin metabolism.

Clinicians will then ask in which direction Hb influences TP. Namely, does the increase in TP cause an increase, or decrease, in Hb? We cannot answer this question by the relative power contribution analysis. This is why

we decided to utilize the impulse response function analysis in combination with the relative power contribution analysis (Wada *et al.* (1988)).

3. Use of impulse response function analysis

The impulse response function, which will be denoted by $b_{ij}(m)$'s or $\{b_{ij}(m)\}$, represents the response of x_i when an impulse is given to x_j .

Akaike discriminated $b_{ij}(m)$'s from $a_{ij}(m)$'s by the following equations:

$$\begin{aligned} b_{ij}(1) &= a_{ij}(1) , \\ b_{ij}(m) &= a_{ij}(m) + \sum_{k=1}^{m-1} a_{ii}(k)b_{ij}(m-k), \quad (m = 2, 3, \dots, M) , \\ b_{ij}(m) &= \sum_{k=1}^M a_{ii}(k)b_{ij}(m-k), \quad (m = M+1, M+2, \dots) . \end{aligned}$$

The response $b_{ij}(m)$ may be considered to be the response of the open loop system that connects x_j to x_i to an impulse with height equal to 1.0 at time zero.

The response of the closed loop system can conveniently be simulated by using the following equations.

$$\mathbf{Z}(s) = \psi \mathbf{Z}(s-1) + \mathbf{V} ,$$

$$\mathbf{X}(s) = \mathbf{H}\mathbf{Z}(s) ,$$

where

$$\psi = \begin{pmatrix} A(1) & A(2) & \dots & A(M-1) & A(M) \\ \mathbf{1} & \mathbf{0} & \dots & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{1} & \dots & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \dots & \mathbf{0} & \mathbf{0} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ \mathbf{0} & \mathbf{0} & \dots & \mathbf{1} & \mathbf{0} \end{pmatrix}, \quad \mathbf{V} = \begin{pmatrix} U(s) \\ \mathbf{0} \\ \mathbf{0} \\ \vdots \\ \mathbf{0} \end{pmatrix},$$

$$\text{and } \mathbf{H} = [\mathbf{1} \ \mathbf{0} \ \dots \ \mathbf{0}] .$$

On using these equations, one should note that $\mathbf{Z}(s)$ starts from zero vector, $\mathbf{0}$, representing the system at standstill. Putting the i -th component of $\mathbf{V}(0)$ equal to 1.0 and keeping all the other components in $\mathbf{V}(s)$ ($s=0, 1, \dots$) equal to 0, the output $x_j(s)$ ($s=0, 1, \dots$), which appears as the j -th component of the matrix $\mathbf{X}(s)$, gives the impulse response of x_j to x_i .

Figure 5 shows the impulse responses for the bivariate system of case Y.S. whose raw data are given in Fig. 1. One should note that two types of responses are plotted in this figure. The response of the closed loop system is drawn with solid lines, whereas that of the open loop system with dotted lines.

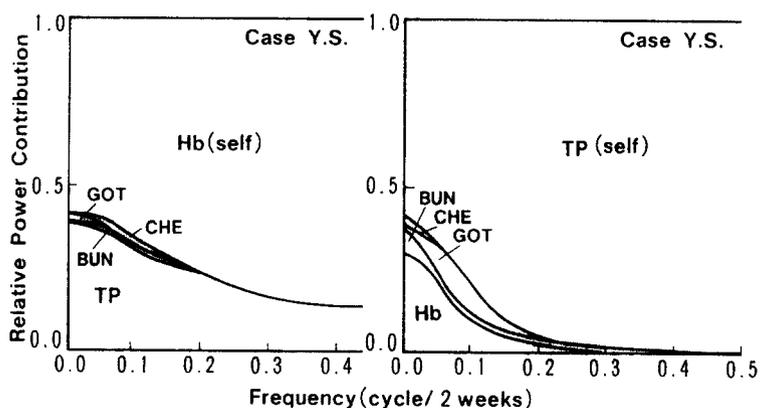


Fig. 4. Comparison of relative power contribution in 6 patients.

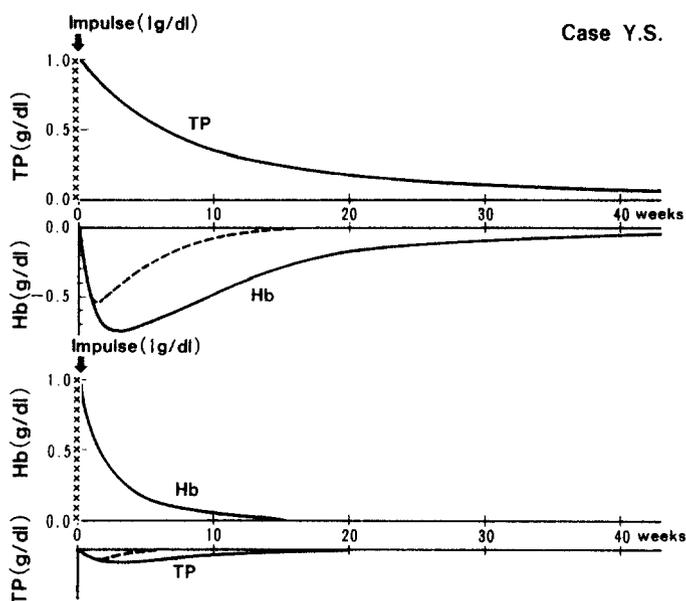


Fig. 5. Impulse response curves for the Case Y.S.

When an impulse equivalent to 1.0 g/dl (or gram/100 ml) was given to TP, the response of TP in the closed loop system rises to 1.0 g/dl and then gradually decreases to zero (the upper panel). In the closed loop system, the maximum decrease in Hb is about 0.75 g/dl. The response of the feedback system is much more pronounced than the response of the open loop and it takes more than 40 weeks for this response to disappear completely.

At this point, one may be concerned with the behavior of TP itself in the

closed loop system which persisted for some time after the input of the impulse. Although this curve is important in the sense that it reflects the usual behavior of TP in this patient, it may cause some inconvenience in understanding the relationship between TP and Hb. In this type of impulse response curves, the response of Hb represents the influence not only of the original impulse of TP but also of the behavior of TP after the impulse. To avoid this, one would like to make TP return to zero immediately after the impulse. The corresponding response is given by the impulse response curves of the open loop system. In the figure, the impulse given to TP is expressed as a hatched bar, which also represents the response of TP itself in the open loop system. The response of Hb in the open loop system, as indicated by a dotted line, was considerably less in amplitude and duration when compared to the response in the closed loop system.

In the lower panel of the figure is shown the response of TP when an impulse, again equivalent to 1.0 g/dl, is given to Hb. Either in the closed or open loop system, the response of TP was very slight, suggesting that the relationship between TP to Hb is practically unidirectional. This is compatible with the observation in the relative power contribution analysis, which showed a lower degree of contribution of Hb to TP, when compared to that of TP to Hb, in higher frequency ranges (Fig. 2).

The negative response of Hb elicited by the impulse given to TP looks paradoxical to most clinicians. Since TP is considered to be an indicator of nutritional state of the body, the increase in TP may well be understood as a sign of an improvement in nutrition of the patient. If so, one naturally would expect that the increase in TP should lead to the amelioration of anemia. But the result of the impulse response function analysis is to the contrary. It rather suggests that the increase in TP causes a decrease in Hb, i.e., anemia. Our first report of this observation in a medical conference drew serious arguments from the side of clinicians. This forced us to repeat the study on many patients as will be described in the next section.

4. Consistency of response patterns among individuals

We tried to compare the impulse response curves of a larger number of patients. Figure 6 shows the response of Hb in 31 patients when an impulse equivalent to 1 g/dl was given to TP. It is apparent that Hb negatively responded in most patients. Only one patient showed an entirely positive response starting immediately after the input of impulse. Two more patients also responded positively but only after the initial negative response. Seeing this consistency of the impulse response, we were convinced of the validity of our numerical results. However, we had to provide an explanation of the paradoxical behavior.

We soon noticed that the end product of the protein metabolism should inhibit the protein synthesis to realize a stabilizing negative feedback

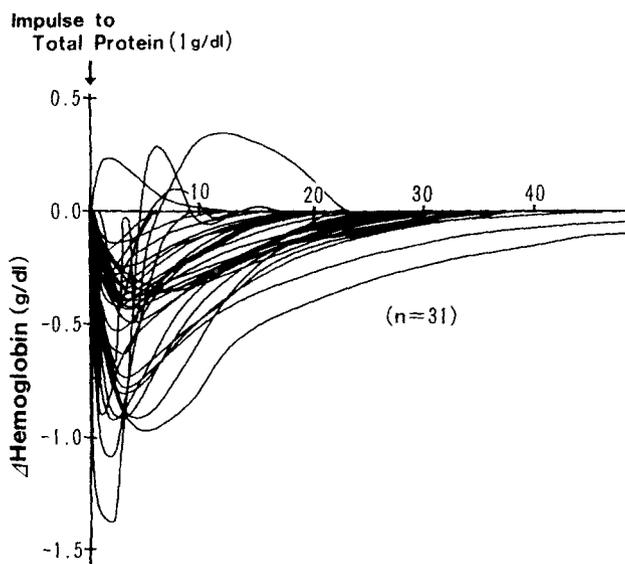


Fig. 6. Comparison of impulse response curves for 31 patients.

mechanism in the body, thus inhibiting the hemoglobin synthesis too. If so, similar results should be obtained by analyzing the relationship between the serum albumin level and Hb.

Figure 7 compares the responses of Hb, when an impulse was given to either TP or to the albumin level. For the impulse with the same magnitude, i.e., 1.0 g/dl, the response of Hb to the albumin level is apparently larger. However, we have to take into account that the serum albumin level occupies only 65%, on an average, of the total protein level, TP. In Fig. 8, the impulse responses were compared by adjusting the size of impulse of albumin to 65%. As can be seen, very similar results are obtained for both TP and albumin.

We also tested the effect of the level of another protein, γ -globulin. It seemed unlikely for this level to be involved in the feedback loop of usual protein synthesis, since the synthesis of this protein is regulated by a completely different system, which is closely related to the immunological defense mechanisms. The lowermost panel of Fig. 8 shows the response of Hb to the impulse given to γ -globulin. In this case, the size of the impulse was made 14% of the case of TP to reflect the actual level of this protein. One can see that essentially no response was elicited by this impulse.

5. Discussion of physiological findings

When one tries to show the applicability of a certain methodology in a new field, he will be confronted with two main problems. One is whether the result obtained by utilizing such a method is correct or not. The other is how

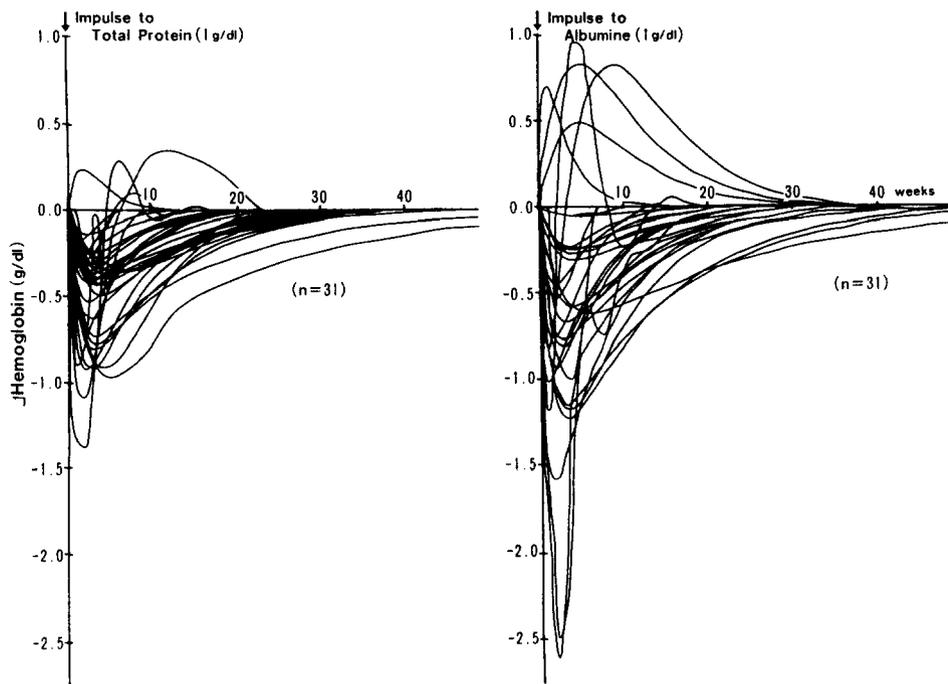


Fig. 7. Comparison of the responses triggered by the impulses given to TP and serum albumin level.

much can the approach give such new information as would not have been obtained by other traditional approaches. These two problems are often contradictory to each other. If one tries to show the correctness of analytical result, the result itself should have already been anticipated by utilizing some traditional approaches. So, at this stage, people will criticize such analytical result for its lack of any novelties. On the contrary, even if one should succeed in disclosing a new finding, they may cast a serious doubt on it only because of its novelty.

In the present study, we have put our weight on proving the reliability of the approach in analyzing the clinical data. The analysis with the relative power contribution helped us to intuitively understand the relationship between the multiple variables chosen for analysis. Usually, we can conveniently use the map of relative power contribution of multivariate analysis for the screening study of finding the most appropriate variables for a particular research subject. In the present study by using the noise contribution map for a 5-variate analysis, we found out that TP is a major regulator of hemoglobin synthesis.

By examining the impulse response curves, we can grasp a concrete image of how a variable is regulating another. Although the impulse response of TP to Hb initially seemed paradoxical, our repetition of the analysis in multiple

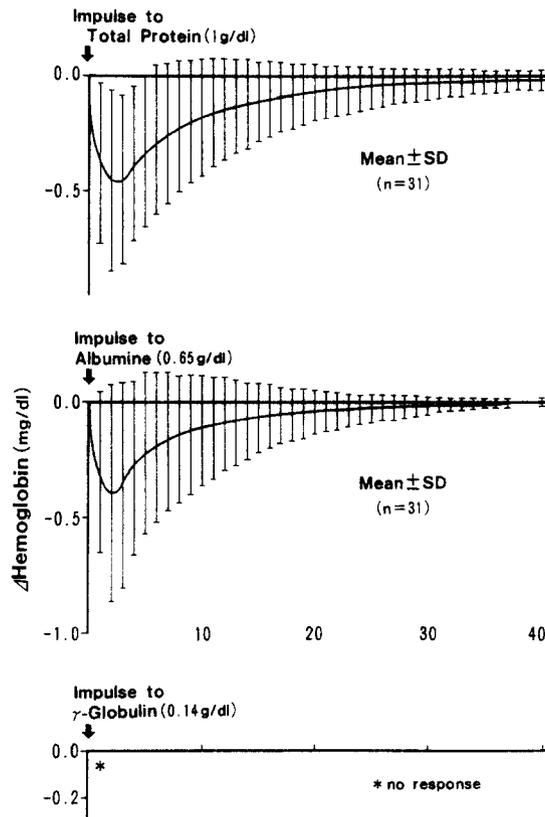


Fig. 8. Comparison of average responses, shown as Mean \pm SD for the above 31 patients, triggered by the impulses given to TP, serum albumin level, and serum γ -globulin level.

patients confirmed the validity of our results. Also, by analyzing the data of albumin and γ -globulin as well, we were convinced of the negative feedback mechanism existing between the protein synthesis in general and the hemoglobin production. Also, we suggested the usefulness of comparing the two kinds of impulse responses, for each closed and open loop systems. Although the usefulness of such comparison was not concretely shown in the present study, it was clearly found useful in detecting the abnormal feedback mechanism in a rheumatic disease (Wada *et al.* (1988)).

6. Concluding remarks

Our application of AR modelling included a wide variety of subjects as follows: the abnormalities in electrolyte balance, the thyroid-pituitary feedback, a case of compulsive water drinking, the syndrome of inappropriate secretion of antidiuretic hormone, diabetes, the rejection phenomenon after kidney transplantation, assessment of the effects of drug administrations,

immunologic networks in normal and collagen disease subjects, acid-base homeostasis, the behavior of renin-angiotensin system, etc. In these applications we encountered with several practical problems, including the minimal required data size for the analysis, the validity of interpolation of missing data, the filtering of the raw data to suppress unnecessary noise, choice of the optimum order of the AR model, etc. The nonlinearity and nonstationarity of the data also have to be taken into account in some cases.

The particularly important problem for us is to evaluate the direct and indirect relationships of the variables separately. This problem was partly solved by comparing the two impulse responses of the open and closed loop systems. Same type of idea has to be extended to the relative power contribution analysis. In fact, such a trial is being done in the field of nuclear power plants, by introducing the concept of "partial power contribution" (Oguma (1983)).

We presented above a relatively simple case taken from the many biological applications we did in the last six years. In spite of the limitations mentioned above, we felt that the multivariate AR modelling and analysis procedure proposed by Akaike would probably be the only practical procedure at present that will find wide application in the analyses of our experimental or clinical data. The reason for this is that generally such data comprise multiple variables, and that feedback relationship between the variables plays an important role in the interpretation of the data. However, we are still continuing the efforts to compare the present approach with others.

Many physiologically active peptides are now being found with the progress of biotechnology. Their roles in the body are explained variously, sometimes even journalistically, with great expectations, but essentially no efforts have been made to reassess their true significance in terms of the "power contributions". The more regulatory factors are found, the more complicated system structure will be required to represent the biological control system, but without proper understanding of such system the progress of the science sometimes will lead to the mystification of events within the body. This even reminds us of the historical fact that medicine originated from the incantation in ancient times. We hope that our studies by the present approach will help to rationalize the way of handling physiological systems.

Acknowledgements

We gratefully acknowledge that Professor H. Akaike permitted us to use the TIMSAC program package for performing the present study. This study was carried out under the ISM Cooperative Research Program (87-ISM-CRP-16) and was partially supported by the New Drug Development Research Project of the Ministry of Health and Welfare, Japan, and a grant from Takahashi Foundation, Tokyo.

Appendix

Numerical values of the time series data of the Case Y.S. are shown below. Sample correlation matrix of the innovation vector is also included.

Original data.

```

TITLE:  HGB
N=      85
FORMAT= (5F10.2)
  8.30    7.70    8.30    8.10    7.60
  8.30    8.46    8.58    8.60    8.50
  8.30    8.43    8.90    9.10    8.20
  8.50    8.70    9.03    9.25    9.25
  9.45    9.55    9.55    9.60    9.40
  9.60    9.60    9.35    9.10    9.00
  9.10    9.40    9.50    9.50    8.80
  9.00    9.50    9.80    9.60    9.75
  9.80    9.55    9.40    9.75    10.25
  9.90    9.70    10.15    10.70    10.70
10.60    11.00    11.05    10.75    10.30
  9.95    10.15    10.37    10.30    9.50
  9.90    9.90    9.90    9.80    9.70
  9.80    10.40    10.00    9.90    9.85
  9.80    10.10    9.70    9.43    9.50
  9.45    8.95    9.00    9.05    9.07
  9.60    9.00    8.40    8.70    8.30

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TITLE:  TP
N=      85
FORMAT= (5F10.2)
  7.20    6.90    7.30    7.10    6.70
  7.60    7.52    7.42    7.34    7.20
  6.90    6.93    7.40    7.40    6.40
  6.60    6.30    6.63    6.90    6.75
  6.65    6.60    6.55    6.60    6.40
  6.90    6.83    6.70    6.60    6.40
  6.50    6.80    6.83    6.90    6.50
  6.10    6.40    6.85    6.50    6.35
  6.65    6.75    6.70    6.75    6.75
  6.65    6.60    6.55    6.55    6.75
  7.00    6.95    6.77    6.72    6.60
  6.45    6.60    6.80    6.80    6.40
  6.80    6.50    6.80    6.60    6.60
  6.70    6.90    6.40    6.40    6.90
  6.70    7.10    7.10    6.97    7.00
  7.10    6.95    7.05    6.95    6.83
  7.30    6.90    6.70    6.90    6.60

```

TITLE: UN

N= 85

FORMAT= (5F10.2)

0.30	0.30	0.30	0.30	0.30
0.40	0.32	0.30	0.30	0.30
0.30	0.30	0.30	0.30	0.40
0.20	0.30	0.37	0.35	0.30
0.35	0.35	0.30	0.33	0.40
0.20	0.27	0.30	0.30	0.35
0.40	0.40	0.40	0.40	0.40
0.40	0.40	0.35	0.30	0.35
0.40	0.35	0.30	0.30	0.30
0.35	0.35	0.25	0.25	0.30
0.35	0.40	0.40	0.40	0.40
0.35	0.30	0.30	0.30	0.20
0.30	0.10	0.20	0.10	0.20
0.30	0.10	0.20	0.20	0.30
0.20	0.20	0.20	0.27	0.30
0.25	0.15	0.15	0.20	0.23
0.30	0.20	0.20	0.20	0.20

TITLE: GOT

N= 85

FORMAT= (5F10.2)

10.00	9.50	9.00	9.00	9.00
9.45	9.90	10.69	11.56	11.00
9.00	7.80	7.40	7.00	6.50
6.00	6.80	7.60	8.00	8.00
8.25	8.75	9.20	9.60	10.00
9.20	8.40	8.00	8.00	9.00
11.00	11.80	11.40	11.00	9.80
8.60	7.50	6.50	6.00	6.00
6.75	8.25	8.75	8.25	8.25
8.75	8.75	8.25	8.75	10.25
11.25	11.75	11.83	11.50	11.17
10.75	10.25	9.20	7.60	6.00
7.00	8.00	8.50	9.00	9.50
10.00	11.50	13.00	13.00	13.00
11.50	10.00	10.00	10.00	9.00
7.00	7.00	9.00	10.00	10.00
10.00	10.50	11.00	9.50	8.00

TITLE: CHE

N= 85

FORMAT= (5F10.2)

6200.00	6349.95	6499.91	5999.90	5499.89
5951.50	6403.11	6740.51	7046.76	6899.87
6299.84	6159.81	6479.79	6799.76	6499.75
6199.73	6319.71	6439.70	6399.67	6199.62
5949.59	5874.59	5859.57	5979.56	6099.54
6188.41	6277.28	6366.14	6455.01	6574.42
6724.37	6779.34	6739.30	6699.27	6379.24
6059.21	6099.19	6499.17	6499.14	6099.11
5949.07	6049.04	6249.00	6548.96	6573.93
6323.90	6248.87	6348.84	6398.82	6398.82
6498.82	6698.81	6765.47	6698.81	6632.14
6573.79	6523.75	6378.72	6138.70	5898.68
5878.17	5857.66	5839.12	5820.58	5598.55
5376.52	4987.47	4598.43	5005.90	5413.38
5561.36	5709.35	5768.52	5827.69	5829.52
5774.02	5829.50	5995.96	6094.18	6124.15

Correlation matrix of the innovation vector.

	1	2	3	4	5
1	1.000	0.451	-0.022	0.139	-0.056
2	0.451	1.000	0.024	0.191	-0.112
3	-0.022	0.024	1.000	0.137	0.238
4	0.139	0.191	0.137	1.000	0.175
5	-0.056	-0.112	0.238	0.175	1.000

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