M. J. Warmus

Mathematical Modelling in Medicine

1. I deeply appreciate your invitation and I am really very glad to have the possibility of speaking in your Department. First of all, I'd like to introduce myself. I am a mathematician specialized in applications of mathematics. I have been cooperating with physicians for over 30 years. I came from Poland one year ago to spend here the rest of my life, which, I hope, will be a long one.

In my work I have never constrainted myself to any particular mathematical method but always tried to fit a proper method to a problem, in order to solve it as well as possible. On that way I have checked many of mathematical tools and techniques. Although I had been successful in various fields, medicine was the most stubborn. I constructed hundreds of ineffectual medical models because of their insufficient accuracy. After more than 20 years of such unsuccessful trials I was near to think that medical problems are too complicated for being solved by mathematical means. I might continue my cooperation with doctors only because they enjoyed toys I was constructing for them in the form of coloured nomograms or three-dimensional geometrical models. But all the time I was aware of the fact that I hadn't solved the main problem: how to construct adequate mathematical models of medical problems. Here I'd like to explain that I consider logical methods and models as a particular case of mathematical ones.

It was only about 8 years ago I succeeded, above all my expectations, in constructing new medical models, even dynamical ones. I started to be able to construct models of surprisingly high accuracy. It was not the result of discovering of a new wonderful method. No! It was rather the result of joint action of many elaborated and appropriate tricks. I will describe some of them to-day.

2. Not long ago many physicians considered mathematical inference in medicine as a misconception. As time goes on, they are now afraid of saying this openly, but most of them still prefered not to deal with mathematics. Some young doctors try to do it, but in order to take a scientific degree in an easier way.

Nevertheless, slowly but constantly, more and more examples appear in which mathematics contributes to discover new possibilities in medical research and new tools in everyday medical practise. And more and more medical institutions start to use mathematical means in their everyday activities.

Therefore it seems perhaps moth-eaten to ask today why to construct mathematical models in medicine, but I am now using this disused question in order to look once more at the advantages of such models from a special point of view.

First, let us take into consideration that modelling is the only way of our cognition. We come to know the surrounding world exclusively by models. For instance, we don't see the real world immediately. We see only its model, its image in our eyes. We don't know any person immediately. We know only his or her model constructed in our mind. The person may be the same and his models by different people may be quite different, especially when we add to objective observations some subjective opinions. In the same way a disease or a patient may be the same but his image by different doctors may be different. We see that it doesn't matter whether a doctor is aware of it or not, whether he wants it or not, in his acting he is always compelled to use models: models of diseases, models of patients, models of medical treatment and medical strategy, although sometimes deficient and vague.

Therefore the question: why to construct mathematical models in medicine, ought rather to be reduced to the following one: to what extend may mathematical methods improve intuitive and subjective models created spontaneously in the mind of a medical practitioner on the basis of his knowledge, experience and actual observations.

Advantage 1. Mathematics compels a practitioner to state precisely and to define accurately his model, to find out its gaps and failures, to clear up all obscurities and to make it consistent.

Advantage 2. Mathematics compels a practitioner to manage observations, measurements and data in an economical way: not to gather unnecessary, not to omit necessary and to minimize their number without decrease of model accuracy, which means reduction of costs.

Advantage 3. Human brain is not able to comprehend interaction of many factors. I have investigated this experimentally for many years. It makes no difference whether we watch physicians, economists, commanders, politicians or other decision-makers. All of them are taking decisions by virtue of two, maximum three, premisses, often subjective. This is not my subjective opinion, this is an empiric fact I have observed. This doesn't bring discredit upon these decision-makers, because, I repeat it, it is only scantiness of our human brain. Therefore mathematical models, especially supported by computers, introduce here large possibilities of taking decisions by virtue of many and best factors, after a deep analysis of their interaction. There is no need to discuss whether decisions made on basis of two factors are better. It is because of wonderful intuition of our practitioners that we have only about 50 % wrong decisions in medical practise. Let us not speak about economy or politics.

Advantage 4. Decisions of a medical practitioner (economist, commander, politician too) are not consistent and can not be, because of our psychical constitution. It is surprising how people can change their opinions and their decisions in a short time. Mathematical models help practitioners to be consistent.

Advantage 5. Mathematical models often enable practitioners to take decisions in a shorter time without decrease of accuracy and time is sometimes vital for a patient, for example, in the case of acute poisonings.

I could mention more advantages issuing from application of mathematical models in medicine but I have confined myself to lay stress on above five ones.

3. Mathematical modelling is rather an art, a skill than a science. It is rather like dancing. Try, please, to start dancing only on the base of knowing its principles. The result will be miserable. There are, of course, exceptional cases of wonderful talents, but generally you need much experience as for nice dancing so for proper and effective mathematical modelling. However, it may happen that an inexperienced newcomer obtains a nice mathematical model at the first blow. I know such a case. But this is an accident. Such a person is not able to repeat his success, is not even able to appreciate such a result and to deduce all possible conclusions from it.

Especially in mathematical statistical modelling we must be very careful, having not sufficient experience. Perhaps in no other field you can find so many misuses of mathematical methods as in applications of mathematical statistics. May be because of paradoxes obtainable. Only in mathematical statistics we have such a situation that big books were written about difficulties in applying of its methods.

Let us consider some examples. I am taking them not from academic literature but from my own living experience.

One of Polish young statisticians, with Doctor's degree in mathematics, came to me for help, because he had been solving a medical problem, I am sorry but I don't remember now, which one, and willing to analyse it thorougthly, he had applied ten different statistical tests in parallel. He had been totally surprised when obtained ten different results, some of them contradictory. He was not aware that each of his statistical tests needed different assumptions to be satisfied. But even after removing tests with non-satisfied assumptions, there remained six or seven tests with different assumptions and quite different results and we were not able to determine which assumptions were more adequate to the problem. Of course, sometimes it is sufficient to get a solution in the form „if, ..., if" but generally such a conditioned answer has no practical meaning. The investigated statistics was not robust and the only way out was to look for another statistics which would be robust. Since many statisticians met similar troubles, many papers about robust statistics appeared last time. But a great number of papers means only that the problem is important, is being attacked but not yet solved.

Another example. In many regression models coefficients have sometimes unexpected signs, which fact causes troubles for practical interpretation. This fact was sufficiently explained in some books on statistical modelling. I have a more sophisticated example of the same kind. Everybody knows that in the case of diabetes mellitus the level of sugar in blood can be regulated by an appropriate dosage of insulin. Nevertheless if you took corresponding data from a clinic or hospital you would see that the correlation coefficient between sugar in blood and insulin is practically zero. I asked many statisticians for an explanation but never received a satisfactory answer. Most of them suggested that my data are wrong. Other started with doubt whether insulin really regulates sugar in blood. I was never so defeated as in the above problem, because I had given a young doctorant the theme for his thesis: automation of insulin dosing in the case of diabetes mellitus. This thesis totally failed, because of the above paradox. What was worse, there were personal changes in the clinic we cooperated with and there was no possibility for obtaining additional data. Later I solved the puzzle and the solution is rather simple. As usual: a puzzle is difficult only before getting its solution. But after it everybody says that there was no trouble at all. That's just the point that nobody could solve it before. I am telling you this story because it is rather typical. The solution is as follows. All our data had been taken from patients with sugar in blood already balanced by insulin. So all patients had sugar in blood near norm. But for some of them it costed minimal doses of insulin and for other very big doses for a long time until they reached the above balanced state. And here you are: pretty much the same level of sugar in blood and very different doses of insulin. Of course the real situation was not so clear, because of dispersion as of sugar in blood so of insulin.

I have mentioned the above examples in order to illustrate the following statement: it is quite not sufficient to know methods of mathematical modelling. The core of the matter lies in the ability of proper interpreting of models. This is the art of modelling, the skill needed. This is the most difficult element of mathematical modelling. Here intelligence and experience are needed. Here a close cooperation of physicians and mathematicians is a necessary condition.

A proper interpretation of results means proper planning of further investigation, collection of proper data and, what is of major importance, enables to take proper decisions.

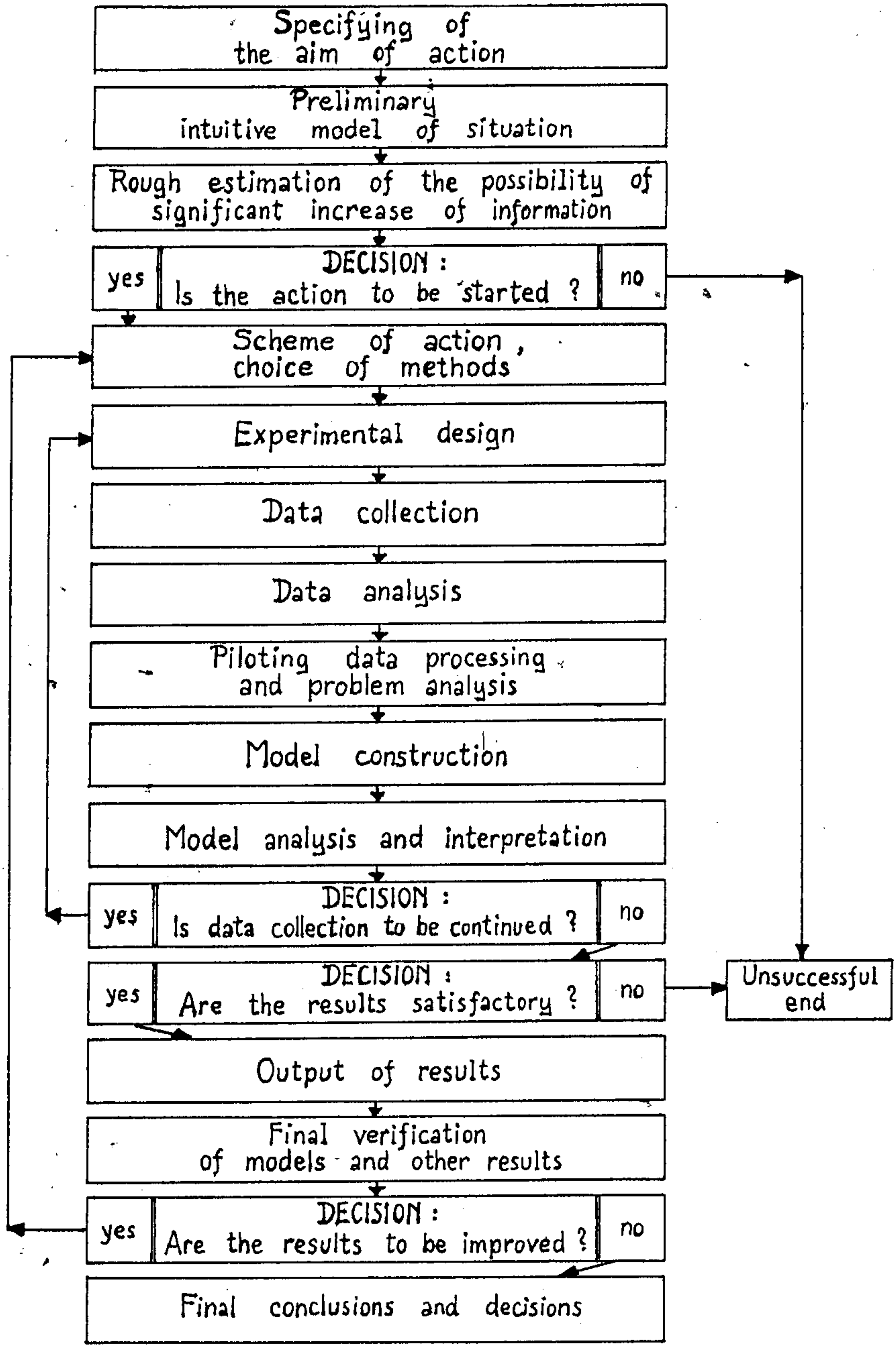
4. Every decision is based on information. Modelling, especially mathematical modelling, is one of the main elements in circulation of information. Hence the role of modelling in taking decisions, for example decision of a treatment of a patient taken by his doctor.

Simplifying in great part the problem, we can imagine elementary circulation of information in the following way:

⟵ here the scheme ⟶

The above scheme needs some explanation. Because of having loops the scheme includes the possibility of progressive collection of data and iterative improving of models. I have observed many times an enormous waste of effort, money and time in consequence of using big sets of data from the very beginning of research. I learned to start the problem with a tiny collection of data, to extract maximum of information from it, including piloting model construction,

Elementary
CIRCULATION OF INFORMATION
(Simplified)



and then to collect more and more data in parallel with constructing of better and better models. This is the most economical way, by leaps and bounds, to get a successful solution. It is surprising how funds of data and corresponding models change during such a recurrent process. It follows that collection of data must be flexible. And flexibility of tiny collections of data is cheap, contrary to flexibility of large collections which can be very expensive in money, effort and time.

5. The above remarks already form one of principles of modelling. Let us now consider principles of modelling in a more systematic manner.

Principle 1. There is no sense in speaking about modelling of an object, process or situation, without exact determination of its aim. Models of the same object, but with respect to different aims, may be quite different.

Principle 2. Every model is a result of an abstraction. Keeping the aim of the whole action in our mind, we abstract from our consideration all marginal, superfluous attributes, selecting from the rest those, which, we hope, will be the most important for our investigation. Thus modelling does not mean copying. Its essence lies in abstraction, in maximal simplification by abstracting all, what is superfluous, not needed.

Principle 3. Sets of attributes, used for model construction in consequence of an abstraction, are never unique. So we can distinguish equivalent sets of attributes. Sets equivalent with respect to logical structure of the problem may be not equivalent with respect to costs or other premises.

Principle 4. A very important element of modelling processes is a proper selection of objects, for example patients from a clinic. General tendency is to choose objects homogeneous to a maximum. More homogeneous are the objects, higher is the model accuracy. But here we meet a competition: the stronger is our selection of objects, the smaller is the group of selected patients, which fact causes a decrease in accuracy from another reason. In such a situation we are looking for an optimum : to choose objects as homogeneous as possible, keeping their number above a fixed limit. Such an optimization belongs to the art of modelling. It is one of the most important elements to be manipulated in order to obtain a high accuracy of our models. Let us not forget that objects homogeneous with respect to one attribute may be not homogeneous with respect to another. This means that in each case homogeneity must be determined with respect to the set of chosen attributes.

Principle 5. Selection of attributes connected with abstraction of others depends not only on the aim of modelling. It depends also on the chosen type of model, on the method of modelling. For example, statical models need less parameters than dynamical ones. The number of observations needed depends also on the method of modelling.

Let us constrain ourselves to the above principles, although there is a possibility of developing of a consistent theory of modelling. I will try to do it in connection with a lecture course I am to have at the University of Wollongong during the next session. Now, let us not to forget dancing: not too many principles but more and more experience.

6. For the same reason I will constrain myself in classification of modelling mathods to the most important differentiation. We have statical models or dynamical ones, according to negligence or taking into account the variability in course of time. On the other hand we have deterministic or stochastic models, according to negligence or taking into account the random variability of observed variables. Thus we have 4 fundamental types of models: deterministic statical, deterministic dynamical, stochastic statical and stochastic dynamical. Some authors distinguish also one- and multi-dimensional models. I have never met a one-dimensional modelling in medicine, except academic examples. Fundamental medical problems are multidimensional, stochastic and dynamical.

Modelling of dynamical problems is the modelling of processes, which is to be called simulation of processes iff the model is dynamical too. We don't call it a simulation when we model dynamical problems by means of statical methods. I succeeded in such an approach to medical dynamical problems. I have treated, namely, values of an attribute measured in different days as values of different variables. For instance, heart rate measured two days ago and actual heart rate are treated as two distinct variables. In such a way we are able to construct statical models for dynamical problems and these statical models very often have a nice dynamical interpretation. For example, if dosage of digitalis depends positively on the actual heart rate and negatively on the heart rate two days ago, we are able to conclude that dosage of digitalis depends positively on the increase of heart rate, which is already a dynamical interpretation.

Simulation of processes is a very difficult task because of enormous amount of information needed. In medical problems generally we are not able to collect such many data, because most often billions of measurements would be not yet sufficient for an adequate simulation of a medical process. We have a much better situation when modelling dynamical problems by statical methods. I we observe, for each patient from a selected group, 100 attributes measured 5 times during hospitalization, we obtain a regression-matrix of degree 500, which can be handled by a computer. If we have 200 patients, then we need to do 100 000 measurements, which is difficult but possible.

We see that such amounts of data can be processed only by computers. Hence the role of computers in mathematical modelling. But their role is not constrained to such a numerical help. By means of analog devices we are often able to get a geometrical model on a screen immediately, without any numerical intervention. Moreover, we have now special medical equipments, which give us similar geometrical models of specialized kind, for example, coloured thermographs or ultrasonic apparatus. Some of them have already partial converters into numerical data. Here I see the next progress in mathematical modelling in medicine: geometrical models obtained automatically by means of special devices, with all facilities for numerical conversion, on line with a computer, supplied of printers, plotters and cameras. Let us take notice that a simple geometrical model can sometimes give us millions of numerical data. I see here the future of mathematical simulation in medicine.

The possibility of an adequate mathematical simulation opens quite new possibilities of mathematical prediction, because such a simulation can get ahead of the real process and show its future.

Let us emphasize that accurate prediction is the main base of correct control of a process. And we must agree that main problems in medicine lie in correct controlling of processes. Hence the role of prediction methods in medicine.

Medical processes are generally stochastic. The theory of stochastic control is one of most difficult mathematical theories. Moreover, there exists a big gap between theory and practise of stochastic control. Therefore nowadays the theory of stochastic control is not an adequate way for medical stochastic control, the more so as we observe permanent lack of data.

Mathematicians must concentrate themselves on discovering of quite new methods of taking optimal decisions and of practical stochastic control under unfavourable conditions of striking lack of information. Many important medical and nonmedical problems are waiting for such new mathematical methods.

7. I could speak a long time about problems of model accuracy but I can not do it during such a short seminar. Therefore I'd like to outline some of them only.

First of all I'd like to emphasize that in medical modelling we don't need to check accuracy after each step, except cases when we are interested in intermediate results. Generally it is sufficient to estimate the accuracy of a model from results obtained during its experimental usage. For example, we may construct a statistical model algebraically and analyse statistically only errors resulting from its use. These errors include all partial ones and are the only interesting for a practitioner. We meet such a situation when we construct manydimensional models and are not able to get joint distributions of, for example, 500 random variables, but we are able to analyse statistically errors of estimation of one or two resulting variables.

There are various ways of defining the accuracy of statistical models. Generally we measure it by means of correlation coefficient between approximated and approximating variables or by relative error of approximation. It is my proposal to use instead of them the angle of approximation, cosinus of which is the above correlation coefficient and sinus of which is the relative error. The smaller angle of approximation the higher accuracy. Such an angle, which can be often interpreted as an angle between two vectors, is easier for our imagination than the previous two measures.

8. Let us now discuss specific difficulties in mathematical modelling we meet in medicine. Some of them have been already mentioned above. In my opinion the main difficulty lies in the already mentioned lack of information. A practitioner struggling for life of a heavily poisoned patient often has no time to collect necessary information but he must take a quick decision. A practitioner dealing with a patient on the verge of death can not perform necessary measurements because they are too dangerous for the patient, but he must take a dramatic decision. A researching physician is restricted in his experiments, because we may experiment on living patients on a very limited scale. In such a situation physicians experiment on animals. But transferring of results from animals to human beings is a break-neck job. Such a transferring is sometimes more difficult than the problem itself. In some European countries most of cows suffer from leukaemia. Although we know already that drinking of milk is one of the main risk-factors for human leukaemia, this one remains to be a rather rare disease. We may not transfer conclusions concerning cow-leukaemia to human leukaemia The analogy with hen-leukaemia is better.

On the second place I'd like to mention great big dispersion in values of most biological parameters. Therefore it is much easier to construct epidemiological models than models of treatment for single patients. A proper selection of homogeneous patients decreases dispersions.

A further difficulty is the high responsibility of a practitioner with respect to false decisions. We must respect this element when constructing mathematical medical models.

The last difficulty I will mention to-day lies in the fact that most of practitioners having to take a decision concerning a patient and being aware that they don't have sufficient information, as from actual observation so from their knowledge and experience, are acting on the base of their intuition and don't want to be controlled by any outsider in that sphere.

9. So let us now discuss such a medical intuition of a practitioner. I mean here pure intuition uncorrupted by intellectual slipperiness, like securing himself against responsibility for his decisions. I have investigated the problem of intuition by mathematical means. Contrary to other fields as geography or economy, I ascertained an essential role of intuition in decisions taken by practitioners, especially when we consider the mean of intuitive opinions of several independent doctors. For instance, doctors were able to predict death of a patient two weeks before in a situation when not any symptom changed.

I must say that I appreciate in a high degree the intuition of practitioners and I have introduced subjective intuitive opinions of doctors into my mathematical models. It was possible and useful in medicine but not in other fields. May be, because we have here to deal with interaction of two living beings.

Of course, sometimes there is some subconscious experience in our intuition, but I know also cases when intuition of a practitioner was contradictory to his knowledge and experience and was right.

We must, however, be aware that use of a false intuition may be very dangerous. Therefore, we mathematicians, we must try to model mathematically the intuition of best practitioners as far as possible. I started it in Poland with prediction of death in some heart-failures but I had no time to develope it. Moreover I had only few cases to my disposal and I could not ask doctors for more deaths in their clinic.

Nevertheless I am able to construct such prediction models and I hope to find a possibility in this country to cooperate here with interested physicians.

10. I have no time today to speak about bounds to mathematical inference in medicine, but I'd like to emphasize that mathematical results form only a most objective suggestion and may never be treated as an oracle, because they never cover the whole of the problem. Final decisions belongs always to the practitioner.

11. Last of all I'd like to show you 3 examples of medical models from my own practise.

The first is the model of blood protein patterns in liver diseases. It is interesting as a 4-dimensional model, where each vector represents one patient, the fractions albumin and α_1 define the coordinates of the initial point of the vector and the fractions γ and α_2 the coordinates of the end point but measured not from the origin as albumin and α_1 but from the initial point of each vector because of graphical reasons. Let us take notice of good geometrical differentiation of liver diseases.

The second is the model of leukaemia-risk. From about 500 risk-factors 10 best were selected in order to estimate the risk of leukaemia. The selection was automatic. I don't give coefficients in the formula because they depend on the number of first risk-factors we want to consider. Let us take notice that in order not to risk leukaemia we must eat many vegetables and fruits, not eat poultry and not drink milk, especially from one cow. Moreover we must drink hard water, reach in minerals. The risk in a rural environment is greater than in town. I'd like to emphasize that the above 2 models were not the only ones, constructed by us. But in all of them the above-mentioned risk-factors happened again and again

It is a pity that I hadn't these results before. I lost many packets I sent from Poland, perhaps confiscated, and I got the above models last time. Therefore I was not able to take part in the International Congress of Haematology in Sydney, one month ago.

Although the mentioned models are simply they are a result of my many years' cooperation with the Institute of Haematology in Cracow. and persistant many years' work.

Much more time and effort costed the third model, this is a dynamical model for dosing of digitalis in the case of chronic congestive heart failure, in the form of a convenient nomogram.

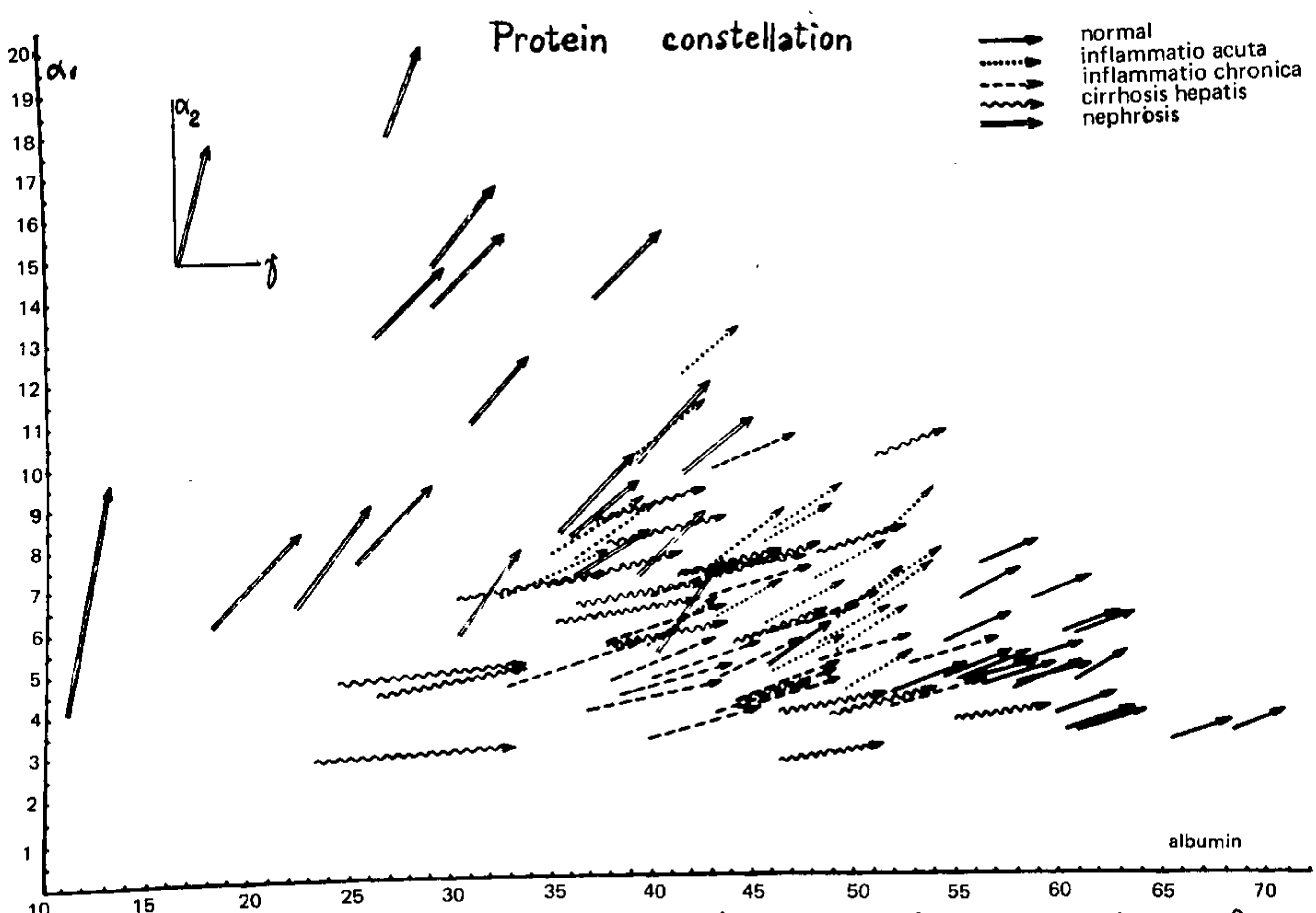


Fig. 1.

T. Bogdanik, B. Bogdanikowa and M. Warmus. The Application of Computer Methods to the Differentiation of Immunoelectrophoretic and Electrophoretic Blood Protein Patterns in Liver Diseases.
10^{th} International Congress of Gastroenterology. Budapest 1976.

LEUKAEMIA RISK-FACTORS

Number of risk factors investigated : about 500.
Number of people investigated : for each model: 40 with leukaemia and 160 healthy.

Method : step-wise linear „normal" regression with automatic selection of 2 best factors at each step:

$$y = c_1(x_1 - a_1) + \dots + c_{10}(x_{10} - a_{10})$$

where y is an index of leukaemia risk (0 no risk, 1 full risk) and a_i is the „normal" value of the attribute x_i, $i = 1, \dots, 10$.

Cooperation: Dr. A. Kwiatkowski, Institute of Haematology, Medical Academy in Cracow, Poland.

Remark: Not yet published.

I. ACUTE LYMPH-BLASTIC LEUKAEMIA

	Risk factors	Sign of c_i		Joint „normal" correlation coeff.
x_1	virus infections (last 5 years)	+	1st step	0.819
x_2	amount of vegetables eaten weekly	−		
x_3	amount of food eaten weekly	+	2nd step	0.886
x_4	wall-fungus at home	+		
x_5	neoplastic diseases in the family	−	3rd step	0.923
x_6	hardness of water	−		
x_7	vaccination against smallpox (how long ago)	−	4th step	0.940
x_8	standard of life (wealth level)	+		
x_9	rural (+) or urban (−) environment	+	5th step	0.948
x_{10}	social conflicts	−		

II. ACUTE NON-LYMPH-BLASTIC (MEDULLARY) LEUKAEMIA

	Risk factors	Sign of c_i		Joint „normal" correlation coeff.
x_1	amount of poultry eaten weekly	+	1st step	0.706
x_2	amount of vegetables eaten weekly	−		
x_3	size of poultry-farming	−	2nd step	0.843
x_4	number of chicken-cholera cases	+		
x_5	amount of milk being drunk weekly	+	3rd step	0.882
x_6	working time (not at home)	−		
x_7	milk from one (+) or many (−) cows	+	4th step	0.904
x_8	amount of fruits eaten weekly	−		
x_9	hardness of water	−	5th step	0.913
x_{10}	neoplastic diseases among neighbours	−		

THE SPECIFYING OF DIGOXIN (DG) AND LANATOSID C (LA) DOSAGE BASING ON THE PREDICTION OF TOTAL BODY CONCENTRATION OF DIGITALIS

„Normal" correlation coefficient: 0.952
Central correlation coefficient: 0.705