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E I N D H O V E N U N I V E R S I T Y O F T E C H N O L O G Y

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TREND PREDICTION AS A BASIS FOR OPTIMAL THERAPY

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CONTENTS

SUMMARY

A survey was conducted to get to know the "state of the art" in trendprediction as a basis for optimal therapy, with emphasis on research being done in the countries of the European Community. Special areas of interest are quantitative prognosis (prognostic indices), the detection and use of trends in the patient's state, the use of models in prediction and their possible use for deciding which therapy is optimal for a specific patient.
An extensive list of centers working in these fields as well as an extensive reference list is included.

TREND PREDICTION AS A BASIS FOR OPTIMAL THERAPY

1. Procedure

A request was put forward to and approved by the ad hoc Working Group Monitoring the Seriously Ill (CMSI) to prepare a survey on "Trend prediction as a basis for optimal therapy" in relation to seriously ill patients. (appendix 1)
The primary goal was to investigate and evaluate different approaches using individually adapted models, trend prediction and automated therapy.
The secondary goal was to investigate and evaluate more pragmatic approaches using relatively simple signal analyses and predictors.

To collect the necessary information an extensive literature study was performed covering both the European and the American journals.

Appendix 2 shows the keywords used for the selection of the publications. Letters were sent to the members of the Ad Hoc Working Group Monitoring the Seriously Ill and to European centres that were known to us or found from the literature study.
Two things were requested: Information about on-going research and clinical studies, and other centres active in the field to be covered by the survey.
Approximately 80 letters were sent and a 50% response was attained.

All information was thoroughly studied and classified. A first rough draft was put together. This draft version was sent to a number of people who are knowledgeable in this field and who agreed to discuss it with at least two of the authors during a planned visit. On that occasion on-going research was also discussed. The comments made and the additional material collected during these visits are incorporated in this final version.

The following persons have been visited:

Dr. J. Bushman	Dept of Anesthetics Royal College of Surgeons, London
Dr. M. de Meester	Free University of Brussels Brussels
Prof. C.J. Dickinson Dr. D. Ingram	Dept of Medicine St. Bartholomeus Hospital, London
Prof. L. Finkelstein Dr. E.R. Carson	Dept of System Sciences City University, London
Dipl.Ing. M. Krämer Dr. H.J. Stahl	Neurochirurgische Universitätsklinik Düsseldorf
Dr. W.W. Mapleson	Welsh National School of Medicine Cardiff
Prof. B.M. Sayers	Imperial College, London
Dr. M.L. Tatnall Dr. P. West	University of Salford Salford
Prof. D.E.M. Taylor	Dept of Physiology Royal College of Surgeons, London

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2. Introduction

This survey will describe methods that utilize information about the patient's past and/or present state in order to predict with a reasonable reliability something about the future course of the patient's state. Since this study deals primarily with methods, no restriction with respect to organ systems or applications is included. It is expected that some " cross fertilization " will be beneficial to all who are professionally interested.

Three hierarchical levels can be distinguished based on different time scales:

- prognosis
- trend
- trend prediction

These notions will be further elucidated here, in general terms. The collected data have been brought together in tables indicating specific aspects of various approaches. A more detailed discussion on prognostic indices, trend, models and trend predictions preceed the tables.

Prognosis is the prediction of the duration, course and outcome of disease in an individual patient. In some studies just one of these topics is considered. Although generally used in a qualitative, descriptive sense, here the term prognosis will only be considered in the sense of quantitative predictions based on measurements of physiological variables. Variables that have prognostic value are called prognostic variables.

Several prognostic variables, each individually giving predictions with a low accuracy, may be combined in some way to obtain one variable with a higher accuracy. Such a variable is called a prognostic index. A prognostic index combines in one number all prognostic information, that is available and deemed relevant.

Prognosis in a quantitative sense is usually expressed in what is called a response variable. This is a measure of the future health or illness of the patient. Its value is usually dependent on several prognostic variables (Armitage and Gehan, 1974), and can be considered a transformation of the prognostic index.

The functional relationship is usually found by some form of discriminant analysis based on data obtained from a large data base.

Thus, while a prognosis may have an average certainty of say 80%, there is no guarantee of the same accuracy for any individual patient. Particularly common response variables include length of survival, length of disease-free interval and death or survival (one or the other). Afifi et al (1971) transforms the response variable, which classifies a patient as a survivor or non-survivor, into a probability of survival.

One of the aims of a prognostic study is to identify the available variables which have substantial prognostic value. This is important, since it provides insight into the mechanism of a disease by revealing which of a number of variables are most significant for the course and outcome of a disease. It is evident, that the prognostic variables are strongly related to the primary cause of the disease. Thus, a variable may have a large prognostic value in one disease, while it may not have any prognostic value in another.

A prognosis, in general, is established on the basis of momentary patient data, because this may be the only information available about the patient in an emergency situation.

The relation between prognostic variables and derived response variables need not be causative.

A trend may be defined as a slow but consistent, unidirectional change. Trends may be observed or calculated for

a) directly measured signals, if they are smooth and noisefree (e.g. temperature)
b) time averages of signals, if they are periodic and/or noisy (e.g. central venous pressure)
c) properties of signals, especially from periodic signals (e.g. heart rate from ECG)
d) relations between signals or properties of signals (e.g. difference between systolic and diastolic arterial pressure).

Various methods to establish whether a trend is present in a signal that shows large periodic or random variations will be discussed in section 4.

For the determination of a trend a series of measurements must be performed. Trend analysis is therefore possible only if patients are under surveillance for some time, either continuously or

intermittently. Slowly developing processes can be monitored at intervals. To establish a trend in signals it is necessary to observe the accuracy and reproducibility of the measurements and the possible influence of different factors on this variable. For this reason, trend analysis of more than one variable is much more meaningful. The coincidence in time of the onset or termination of certain trends may give clues to relations between variables and to underlying common causes. Analysis of sequential cardio-respiratory observations has provided descriptions of the common history of various shock syndromes and some insight into underlying patho-physiological mechanisms. (Shoemaker, 1975)

Trend analysis will in general give more insight into (patho-) physiological phenomena than prognostic indices, which of necessity give a static picture of the patient's state. However, it is also possible to consider trends of a prognostic index.

Trend prediction is extrapolation toward the future of the momentary state of a patient. Reliable predictions, i.e. predictions which are accurate enough to be meaningful, are possible only, if sufficient information is available about the patient's past en present state.
This information is available in two ways:
- much is known about general physiological principles that govern the dynamics of the patient's state
- observations of a particular patient are or will be available to estimate the dynamics of the patient's physiological system.

Thus, for trend prediction there are two necessary conditions:

a) the patient's state must be measured over a period of time; all relevant signals must be measurable. If this condition is fulfilled, trends may be calculated of measured and derived variables.

b) a mechanism (model, transfer function or mathematical rule; see section 5) must exist to extrapolate these trends into the future with sufficient accuracy, including the effects of all possible therapies on the trends.

Both conditions are difficult to fulfill. Some of the relevant signals may only be measurable with discomfort or increased risk, or may not be measurable at all. It may not even be clear what the most relevant signals are. Also, accurate models that give reliable long term predictions may not exist, or even be possible.

Yet the great attraction of trend prediction is, that it could develop into a basis for optimal therapy. Given the possibility of evaluating beforehand the effect of any therapy, it will be possible to calculate the best therapy.

Another attractive side of model-based trend prediction is the possibility to obtain an integrative view of the patho-physiological mechanisms. The importance of this is stressed by Shoemaker (1975). He states that normal values may not be the most desirable goals of therapy, since compensatory protective mechanisms of the body in response to stress also produce departures from the normal values.
The case of the critically ill patient requires indicators for the performance of biological key systems which can be continuously monitored and constitute a reliable and sensitive basis for diagnostic, therapeutic and prognostic decisions, even in conditions of emergency. (Attinger, 1973).
A more detailed treatise of model based trend predictions as applicable to seriously-ill patients will be given in section 6.

3. Prognostic indices *

Introduction

In order to quantify prognosis, it is necessary to define it in terms of one ore more response variables. Response variables exist in three classes. Variables of the first class have a yes-or-no (binary, dichotomous) value (e.g. will the patient survive the next week?). Variables of the second class can have many different values (e.g. what is the expected period of survival for this patient?). Variables of the third class can have one of a limited number of values (e.g. where the survival period must be expressed in one of these answers: less than one week / less than two weeks / less than four weeks / longer).

Similarly, prognostic variables may be fit into the same three classes: dichotomous, continuous and discrete.

The value of the response variable depends on the values of many prognostic variables, some of which may have much more prognostic significance than others. Furthermore, the availability of prognostic variables depends on the circumstances. In a mass screening program invasive measurements are generally not feasible, whereas in an emergency unit measurements entailing some risk may be necessary. Therefore, when searching for relations between response variables and prognostic variables, it should always be mentioned which measurements were available. The selection of prognostic variables for a new class of patients has its own problems. The choise may be based on previous research investigations, either basic research, controlled trials, other forms of prospective studies, or retro-spective studies. In these cases, the variables which were thought to have great prognostic value, may not have been measured, the medical environment may have been different, or the form of disease may have been different.

Alternatively, the prognostic variables may have been determined by an internal analysis of the currently available data. This may exaggerate

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* because of the large number of papers on this subject, the authors have limited themselves almost exclusively to those from EEC countries.

the importance of the selected variables and may lead to overoptimistic estimates of precision (Armitage and Gehan, 1974).
Usually, prognostic studies are based on the availability of a data base containing information about the medical history of a specific group of patients. For the sake of reliability, this group of patients should be large and homogeneous, which is often not the case. If not homogeneous, the group can be split into several smaller groups. However, a group that is too small will not yield statistically significant results. Often, the number of prognostic variables, that may be selected from the data base is too large for a statistician to handle. Somehow the data have to undergo a screening operation, which removes most of the variables from further consideration, leaving a relatively small number which can be studied more intensely. To some extent, the screening may start by inspection, before any formal analysis. For example, if some variables are known to be highly correlated, all but one can be removed with hardly any loss of information. Variables may also be dropped because of doubtful quality of some data, or because there are many missing readings (Armitage and Gehan, 1974).

Methods

Two basic methods for the screening of the data will be described. One approach is used if the prognostic and response variables are all dichotomous. Any variable which is not dichotomous can be made so (with the loss of some information) by choosing an arbitrary critical level, e.g. age less than 55 years or greater than or equal to 55 years. The prognostic variables are then correlated with response variables via tables, constructed by counting occurrences:

		prognostic variable	
		negative	positive
response variable	negative	a	b
	positive	c	d

The aim is to find a high degree of disproportionality in this table, where the percentage of false positives and false negatives is smallest. Checking all prognostic variables this way, the most significant one can be found. The cases are then subdivided by the two levels of the most significant prognostic variable, and within each half a search is made for the next most significant variable. Eventually a "family tree" is produced with, at the finest level subdivision, as wide a spread as possible in the proportions of positive responses.
There are a number of variants of this approach (Armitage and Gehan, 1974).
A second general approach is to put forward a mathematical model relating in some way the average response to the prognostic variables. This will usually take the form of a mathematical equation in which the coefficients are unknown quantities to be determined from the data. An appropriate analysis of the data then provides estimates of the coefficients and enables the investigator to recognize which prospective variables have a substantial effect on response variables.
The best known version of this approach is multiple regression, in which the response variable is regarded as being normally distributed with a mean value which is a linear function of the prognostic variables. If y is the response variable, and x_1, x_2, ..., x_k are prognostic variables, the model postulates that

$$y = a_o + a_1x_1 + a_2x_2 + \ldots + a_kx_k + e$$

where e is an "error term". This error term is often assumed to have a normal distribution with a mean value equal to zero and an unknown variance. It is extremely important to test the normality (or at least the symmetry) of the distribution. If such conditions are not fulfilled it may lead to large errors in the regression coefficients.
The a's are regression coefficients to be estimated, usually by least squares. In one of the a's is zero, this means that the corresponding variable has no effect on the response variable, and can be deleted. Standard methods are available to test whether the estimated a's are significantly different from zero.

Broadly speaking, the more significant the a, the more important is the corresponding variable's contribution to the prediction of y. (Armitage and Gehan, 1974).
Multiple regression in its simplest form is applicable only if all variables are continuous. If the response variable is dichotomous, a trick is necessary. First transform the binary variable into a "probability of success" P, which is a transformation into a continuous variable, having, however, limits of zero and one. Therefore, instead of using this probability variable, a transformation is used into some logarithmic variable(e.g. log (P/(1-P))).
This latter variable may then be called the prognostic index, from which the primary, dichotomous response variable is calculated in a straightforward way.
A dichotomous prognostic variable may be transformed into a "dummy" variable, having a value of either zero or one. Discrete prognostic variables may be used as such, or transformed in some way, e.g. into a set of dummy variables.
Many different techniques and tricks are used (Armitage and Gehan, 1974), but in principle all are based on the earlier described methods.

In case of progressive diseases, the reliability of prognosis may be increased by modelling the course of the disease (Winkel et al, 1972).
The model contains the following suppositions:
- the course of a disease can for any patient be described by a set of "symptoms or signs"
- these symptoms or signs appear in a specific order
- once a symptom or sign appears, it will be permanent

The model therefore attempts to introduce some causal relations in favor of more statistical relations.
Thus, the selection of prognostic variables may be given a sounder medical basis.

Goals of prognostic studies

Prognostic studies are useful in clinical research. They reveal which of a number of variables appear to influence the course and outcome of a disease most, thus providing insight into the mechanism of a disease and isolating the factors that should be closely watched in

the clinical environment, or in mass screening surveys. For instance, when there is a difference between a prognosis and the actual outcome for a certain patient, one should try to find out which information is neglected, that could have improved the prognosis. In this way diagnosis in general will gain tremendously from such a systematic reasoning. (Bushman, personal communication)

They also may be used for the planning of future clinical studies, particularly in the determination of stratifications of patients. (Armitage and Gehan, 1974) They also facilitate the comparison between the outcomes of disease in different groups of patients.

Prognostic studies are also useful in clinical management. They allow comparison of the effectiveness of treatment between different centers treating similar patients through similar therapies. They also allow monitoring the effectiveness of one clinical center over long time periods.

The outcome of prognostic studies, i.e. a reliable prognostic index, is often used in daily clinical practice as a means for assessing the severity of the patient's illness and his response to treatment (Afifi et al, 1974). It may also guide the physician in his discussions with the family. The value of the prognostic index often decides which of several therapies should be used (Schuster et al, 1976). In mass screening, it may isolate high risk patients (W.H.O.E.C.G., 1974). In intensive care units, it may be used to decide upon the moment of discharge from the unit (Serruys et al, 1975).

Applications of quantitative prognosis

In many coronary units prognostic indices are used to asses the severity of a myocardial infarction, to predict a recurrence, an expected period of survival, a probability of survival or some similar measure (Peel et al, 1962 / Gallitz et al, 1974 / Arnould et al, 1975).
Different indices are more or less standard now (De Thomatis and Oddone, 1971).
Emergency therapy may be indicated by the value of a prognostic index (Gallitz et al, 1975).
In a cardiovascular intensive care unit a prognostic index may be used to assess the patient's condition after open heart surgery (Michat et al, 1974).

In other medical fields prognostic indices are used to assess the severity and chances of recovery in cancer (Lê, 1971) neurology (Ramelli, 1970), cirrhoses of the liver (Nakache et al, 1971) and gastro-intestinal bleeding (Christensen et al, 1977).

Discussion

Prognostic indices have severe limitations. A prognostic index is valid only for patients who are members of a particular population and who are treated according to a particular formula; deviation from the therapeutic formula invalidates the index and under these conditions improvement in the index per se cannot properly be used as a therapeutic goal. This is clearly so when symptoms or signs are being treated which also serve as prognostic variables. However, with a well established diagnosis the prognostic index can be useful in assessing therapeutic innovation (Armitage and Gehan, 1974). Prognostic studies are useful for establishing models for the course and outcome of diseases; this is clearly of great value. However, they are models of the "average patient", giving more a prediction of the course of the disease than a prediction of the future condition of a particular patient, and in no way enabling the physician to tune his treatment in a particular case. If the latter is deemed necessary, then the model should allow itself to be modified so, that it can give predictions for any specific patient and indicate the best individual therapy.

When prognosis is applied to a particular patient it only gives a probability of the future condition. As a consequence of these probability figures some important ethical questions can be raised (Jahrmärker, 1978).

Prognostic indices

Institute	number of initial variables	number of prognostic variables	how often measured	organ system or disease	method	goal	results	literature
Katholieke Universiteit Leuven Academische Ziekenhuizen Kapucijnenvoer 35 3000 Leuven Belgium	12	12	once	myocardial infarction	discriminant analysis	hospital survival	prognostic index is clinically used since oct. 1976 and is mainly research oriented	Willems et al, 1978
Service de soins intensifs Service de médicine interne Clinique de St-Pierre B-1340 Ottignies Belgium	7	7	during 48 hours	myocardial infarction	compares three prognostic indices (Norris, Peel and Peel modified by Marx and Yu)	evaluation of three methods	confirmation of the prognostic value of the index of Peel, modified by Marx and Yu	Serruys et al, 1975
Rigshospitalet Medicinisk Afdeling A Blegdamsvej 9 2100 Copenhagen Denmark	30	unknown	once	gastrointestinal bleeding in cirrhotic patients	statistical methods	evaluation of Prednisone therapy	characterization of 5 different groups	Christensen, 1977 (preliminary report)
Clinical Datalogy Laboratory Rigshospitalet Department of medicine B Copenhagen Denmark	16	7	once	aortic valve incompetence	model of the course of a chronic disease	survival period	the first results on a group of 160 patients proved to be clinically meaningful	Winkel et al, 1972
Groupe de Recherche de l'INSERM 53 bd Diderot Paris-12e France	no applications				use of prognostic health care			Lê, 1971

Prognostic indices

Institute	number of initial variables	number of prognostic variables	how often measured	organ system or disease	method	goal	results	literature
Centre de Calcul et de Statistique Pr Grémy C.H.U. Pitié Salpêtrière, Paris France	21	10	once	cirrhosis	discriminant analysis	survival after two years	A prognostic index is derived from a group of 50 patients.	Nakache et al, 1971
Institut National de la Santé et de la Recherche Médicale Groupe de Recherche U88 Service de Chirurgie Cardio-vasculaire Hôpital de la Pitié 91 bld de l'Hôpital F 75634 Paris Cedex 13 France	16	4	pre- and post operative	valve incompetance Starr prosthesis	discriminant analysis	survival 5 months after operation	Two criteria for a good prognosis of a Starr prosthesis are derived.	Michat et al, 1974
Département de Statistiques Faculté de Médicine Marseille France	15	2	once	myocardial infarction	several statistical methods	selection of therapy	The derived prognostic index had 4,5% error in the control group (n=110). The index is used for selection of therapy.	Arnould et al, 1975
Medizinische Klinik Medizinische Hochschule Hannover W-Germany	no applications				use of prognosis in health care			Hartmann, 1974

Prognostic indices

Institute	number of initial variables	number of prognostic variables	how often measured	organ system or disease	method	goal	results	literature
Johannes Gutenberg Universität II Medizinische Klinik und Poliklinik Postfach 3960 6500 Mainz W-Germany	1		3 times uses one	drug poisoning	linear regression	duration of coma	Derivation of a correlation between duration of coma after drug poisoning and blood lactate concentration.	Schuster, personal communication
Medizinische Klinik Innenstadt Ziemssenstrasse 1 8000 München W-Germany	21	7	once	myocardial infarction	discriminant analysis	- survival - duration of stay in intensive care unit	A derivation of a prognostic index.	Gallitz et al, 1975 Jahrmärker et al, 1975 Jahrmärker 1978
I Medizinische Klinik der Universität München und Rechenzentrum Grosshadern München W-Germany	21	8	once	myocardial infarction	discriminant analysis	survival	A derivation of an index for the prognosis of survival.	Gallitz et al, 1974
Clinica della Melattie Nervose e Mentali Dell'Universita di Ferrara Italy	4	2	once	amyotrophic lateral sclerosis	statistical tests	survival period	Two factors affected the course of the disease.	Ramelli, 1970
Ospedale Civile di Imperia Divisione Medicina Imperia Italy	unknown	6/10	once	myocardial infarction	compares two indices; discriminant analysis (Peel & Selvini)	evaluation of two methods	Selvini's index was found more reliable.	De Thomatis and Oddone, 1971

Prognostic indices

Institute	number of initial variables	number of prognostic variables	how often measured	organ system or disease	method	goal	results	literature
Ospedale Maggiore di Milano Sezione Staccata "Citta di Sesto S. Giovanni" Divisione medica D.&G. Campari Milano Italy	19	10	once	myocardial infarction	regression analysis	survival	A derivation of a prognostic index.	Selvini et al, 1967
Erasmus Universiteit Faculteit der Geneeskunde Thoraxcentrum Rotterdam Netherlands	5	3	at admission and after 24 hours	myocardial infarction	discriminant analysis	short-time survival	A derivation of a prognostic index. Its value in guidance of therapy must be further assessed.	Verdouw et al, 1974 Verdouw et al, 1975
Departments of Cardiology and Medicine Royal Infirmary Edinburgh United Kingdom	12	none	once	myocardial infarction	discriminant analysis	short-time prognostic index of infarction	An attempt to derive a prognostic index for myocardial infarction has not succeeded.	Oliver, 1977
Victoria Infirmary Glasgow United Kingdom	-	6	once	myocardial infarction	statistical tests	short-time survival	A derivation of a prognostic index.	Peel et al, 1962
Department of Biomathematics Puseystreet Oxford OX1 2JZ United Kingdom	no applications				description of methods and use of prognostic indices			Armitage and Gehan, 1974

4. Trend

Introduction

"Clinical decisions are made more on the basis of trends in monitored variables than on their absolute values" (Taylor, 1976 a).
"The sequential patterns of haemodynamic parameters for shock patients are important for the evaluation of the patient's condition" (Shoemaker, 1975).
Numerical values give information about the state of a patient. One compares this state with an average of all the preceding patients. By using changes in the values the new state of the patient is compared with preceding states of the same patient. In this way the patient is used as his own reference.
To observe the patient's state the momentary values are sufficient.
For determining the changes in his state much more information must be considered at the same time. A problem arises to make this information easily accessable. Trenddetection is a tool to increase the accessibility.

Methods

The easiest method of trenddetection is the so called "trendrecording". In fact, this is only a manner of presentation of a variable in such a way that either a nurse or a physician has a quick overview over the course of that variable in the past. In this way changes in the variable can be detected easily. For this purpose one can use a "trendrecorder" or, if using a computer aided monitoring system, a graphical display. A trendrecorder plots the value of the variable with fixed time intervals on paper. In a computer aided monitoring system, the variable is sampled with fixed time intervals which are usually shorter than with a trendrecorder; the values are stored in memory. With this information once available one can make trendplots with different timescales and at any desired instant (Krämer and Rohr, 1978 / Grothe et al, 1978 / Brill et al, 1978).
The method, most commonly used for automatic trenddetection, is the time weighted average (Hitchings et al, 1975 a / Hope et al, 1973) with an exponential function as weighting function. The importance of a measured value is decreasing in time for the calculation of the average. In this

way the measurement noise is smoothed to an extent depending upon the chosen time constant in the exponential function. When there is a consistent unidirectional change in the variable the average will follow that change with a short time delay, dependent on the time constant. This process can be compared very well with the human observer, looking at a trendrecorder plot. (Taylor, 1975).
A more general method is an autoregressive model. This model states that at moment k y_k is determined by a number of preceding values.

$$y_k = c + a_1 y_{k-1} + a_2 y_{k-2} + ... + e_k$$

with e_k a noise term with zero mean value.
The coefficients $a_1, .. , a_n$ must be estimated from a number of measured values. When the coefficients a are estimated the next value y_k can be predicted. This means that this method gives the possibility for prediction. Besides that a difference between the estimated y_k and its realisation gives information about the presence of a trend (or a change in trend) of the variable.
Another method is the Mahalanobis distance D (Afifi et al, 1971 / Goldwyn et al, 1972).

$$D^2 = (\underline{Y}_i - \underline{\overline{Y}})^T S^{-1} (\underline{Y}_i - \underline{\overline{Y}})$$

where $\underline{Y}_i$ is the measured state vector at t_1
$\underline{\overline{Y}}$ is the measured state vector at t_2
S is a calculated covariance matrix
(calculated from a control group).

This method has two problems. It is sensitive for noise in the measurements, and it gives no information about the direction of the deviation.

Results

The use of trendrecording in a clinical situation is not new; most anesthesists keep records of blood pressure and heartrate during anesthesia. Trendrecorders are on the market for some time and give records of several variables. The length of the record is, dependent upon the used time intervals,

between three and twenty-four hours. The number of computer systems with possibilities for trendplots is also increasing. The information of the history of the patient's state is now accessable to the medical staff. The physician can detect changes in the patient's state very easily.
The above described method of trendrecording is mostly used for patients in intensive care units or under anesthesia, generally speaking for very well monitored patients. However, there are other examples. For instance, the trend in carcinoembryonic antigen concentration in patients with adenocarcinoma of the gastric and colonic tract after operation gives information for an early diagnosis of recurrence or metastases (Staab et al, 1977).
For the *automatic* detection of trends, trendrecording alone is not sufficient. A further data processing is necessary. This can be either the exponentially weighted time average method or the autoregressive technique. Two further extensions are described in the literature. One can take the difference of two averages, each with a different time constant (Taylor, 1976). By using different time constants the two averages have different delays in following the signal. This means that the difference is unequal to zero as long as a trend in the variable is present.
When the difference exceeds set limits or a certain time, the "trend-detector" can give alarm that the state of the patient is changing.
This type of alarming has been compared with the "normal" type of alarming (the value of the variable is exceeding a set minimum or maximum) for bloodpressure and heartrate (Taylor, 1976 a). There was both a considerable decrease in false positive and false negative alarms.
The other possibility is to use the statistics that are available in the signal. Besides the time weighted average, one calculates an estimator of the variance; as long as new values fall within predetermined tolerances, the situation is considered stable. This method is used to detect arrhythmia's (Boothroyd et al, 1975).
The autoregressive scheme is used by Sayers (personal communication). He uses this scheme, either with constant or with adaptive parameters to generate a tracking signal which serves as a signal predictor and which is compared with the actual data. An error signal is produced, and if this is outside some statistical confidence limits, the occurrence of a trend is reported.

The method described by Afifi (Afifi et al, 1971) is the only method found that uses a multivariate trenddetection. There is a disadvantage to this method. The state of the patient or the change in the state is compared with information from a reference group. This means that an important reason for trendanalysis, viz. the use of the patient as his own reference, is neglected.
From the example that is given (Afifi, 1971) it seems that the presentation of a set of variables by one single value is the main goal of this method.

Trend

Institute	variables	method	goal	results	literature
Medical Computing Centre Department of Physiopathology (C.I.M.H.U.B.) Free University of Brussels Rue de l'Abricotier 7 B-1000 Brussels Belgium	P wave and QRS complex from ECG	time weighted average with variance	automatic arrythmia detection	system in clinical use since 1975	Boothroyd et al, 1975
Institute of Medical Physics TNO Da Costakade 45 Utrecht Netherlands	E.E.G.	zero crossing frequency spectrum	patient monitoring during heart surgery	online presentation clinically in operation	Pronk et al, 1975
Neurochirurgische Universitätsklinik Düsseldorf W-Germany	heart rate respiratory rate temperature auxilliary	data base with graphical display	visualization of trends in neurosurgical patients	clinical tests	Krämer, Rohr, 1978
Friedrich-Miescher-Laboratorium der Max-Planck-Gesellschaft Spemannstrasse 37-39 Postfach 2109 7400 Tübingen W-Germany	Carcinoembryonic antigen	data base with graphical display	early detection of recurrence of cancer after operation	system with data-base and trend plot possibilities is used in further clinical evaluation	Staab et al, 1977 Wehrle, 1977 Staab et al, 1977 or 1978

Trend

Institute	variables	method	goal	results	literature
Department of Tropical Child Health Liverpool school of tropical medicine Liverpool United Kingdom	ECG vector	trendrecording	follow the condition of Kwashiorkor patients	The QRS vector has a relation with the condition of Kwashiorkor patients.	Stephens, 1975
Engineering in medicine laboratory Imperial College London SW7 2BT United Kingdom	intra-arterial blood pressure	autoregressive analysis	to characterise non-stationarity	Has built a trendrecorder for 4 patients, 3 channels each. When a trend is detected it is shown including the confidence level. The device is used for research purposes.	B. McA. Sayers, personal communication
Royal College of Surgeons Lincoln's Inn Fields London WC2A 3PN United Kingdom	heart rate mean arterial- and central venous blood pressure	exponential weighted time average	improvement of automatic alarm system	Two channel trendrecording (heart rate and blood pressure) in clinical use. Especially the alarm system gives good results.	Taylor, 1971 Taylor et al, 1974 Hitchings et al, 1975[a] Hitchings et al, 1975[b] Taylor and Whamond, 1975 Taylor 1976[a], Taylor 1976[b] Taylor 1976[c], Taylor 1977[a] Taylor 1977[b]
Royal College of Surgeons 35-43 Lincoln's Inn Fields London WC2A 3PN United Kingdom	heart rate blood pressure	exponential weighted time average Triggs tracking signal	automatic detection of trends	Comparison of several methods. Plans to implement Taylor's system for clinical use.	Hope et al, 1973 Bushman and Gamble , 1975 Bushman, 1976 Endresen and Hill, 1977 Hill and Endresen, 1978

Trend

Institute	variables	method	goal	results	literature
University of Southern California Medical Centre Coronary Care Unit Los Angeles California 90033 U.S.A.	RR interval from ECG	autoregressive model	arrythmia detection	First order model is sufficient. This technique has been implemented and has proved to be useful.	Haywood et al, 1972
Department of Medicine Mount Zion Hospital and Medical Centre San Francisco California 94120 U.S.A.	different time intervals from ECG	trendrecording	arrythmia detection	Trendrecorder in clinical use proved to be useful.	Uhley, 1976
University of Michigan Ann Arbor Michigan U.S.A.	cephalometric data	exponential smoothing	show the value of the method	unknown	Hirschfeld, 1971
New York State University Department of surgery Buffalo New York 14203 U.S.A.	9 circulation variables	Mahalanobis distance	follow the state of patients with cardiac, respiratory and metabolic imbalances	A quantitative frame of reference has been defined.	Goldwyn et al, 1972

5. Models

A model is a mechanisms (a set of mathematical equations, a computer program, a hardware device) that mimics some other system, i.e. a patient.

For the contruction of a model there are two possible philosophies. According to the first, all available physiological knowledge about unit processes and their interactions are quantified and incorporated into an "isomorphic" model, which is a very detailed copy of the physiological structure of the considered (sub)system. The main advantage of this type of models is the ability to look "inside" physiological processes, that are not observable in a patient (e.g. can the patient's state be explained by a deviation of a certain parameter). The main disadvantage is the necessary detailed knowledge of all unit processes that may interact with the considered system. Very often, some information is lacking, e.g. about the role of central nervous stimuli, which may or may not seriously degrade the model performance.
According to the second philosophy, one can construct a model, that only describes the input-output relations of the system (transfer function). The internal structures of the model and the system are usually quite different. Models of this type are called "isocybernetic", because they mimic the behaviour, not the structure. The main advantage of this type of models is their simpler internal structure, allowing shorter calculation times and, if necessary, easier adjustment. The main disadvantage stems from the dissimilarity in structure: this type of model cannot give answers to questions about effects of changes in the patient's system.

Most models used in clinical practice have characteristics of both. To get a manageable physiological model one has to simplify certain parts, and one needs to make assumptions about unknown parts. To get a workable mathematical transfer function type of model, one needs a priori physiological knowledge, at least about which variables need to be considered and which may be left out.
Multicompartment models combine properties of the isomorphic and isocybernetic models. The parameters represent physiological properties only gross

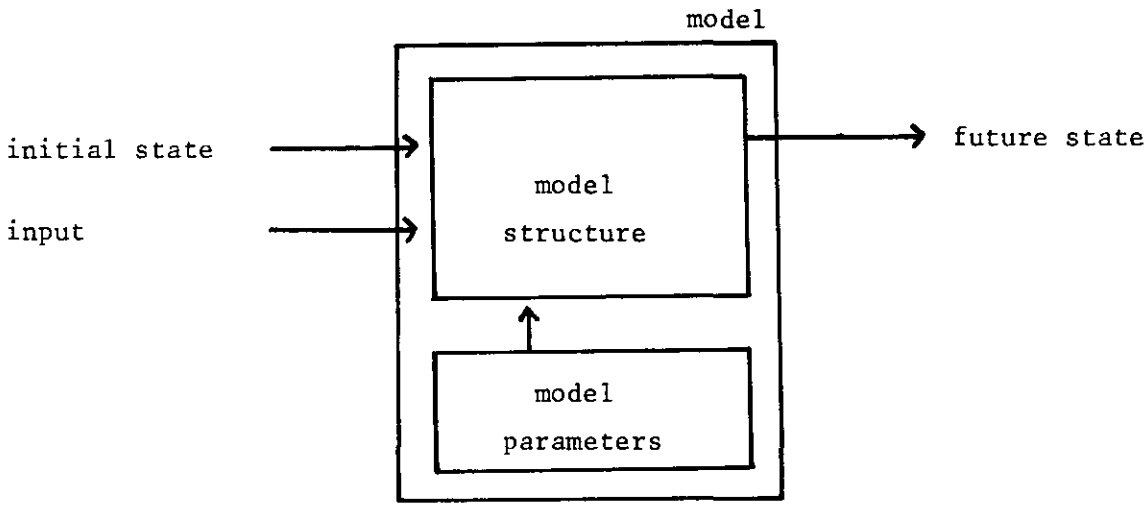
too much detail (too many compartments) makes parameter matching impossible due to observability problems (Cobelli et al, 1975 / Salamonson and Smith, 1976 / Tatnall and Morris, 1972).

Another subdivision of model types, independent from the one made above is based on the changeability of the model parameters:

- models with fixed parameters. The values of the parameters are unchangeably incorporated into the model. The model will in general represent an "average" patient. The fit to any individual patient can only be described in statistical terms.
- models with changeable parameters. The value of some parameters can be introduced into the model beforehand, e.g. age, sex, body weight and length or results from special function tests. Thus a few patient characteristics are incorporated into the model, replacing average values by individual ones, if available.
- models with adaptive parameters. Before running the model, a procedure is carried out to tune the model parameters to those of the patient. This can only be done by comparing an individual patient response to the model response, modifying the appropriate model parameters if a difference is found. Therefore it is necessary to measure input-output relations. It is also necessary, that the obtained input-output relations contain information about the values of the parameters.
- models with tracking parameters. Now the parameters are adapted continuously while the model is running, so that the model will always stay tuned to the patient, even if the patient's characteristics change in time.

Combinations can exist. This subdivision into 4 model types makes clear that more and more information is necessary about the patient going from fixed parameters to tracking parameters. Models with fixed parameters need no extra information; for models with changeable parameters some extra information must be introduced at one time; models with adaptive parameters need a "learning period" during which frequent measurements may be necessary; for models with tracking parameters the "learning period" never ends, and measurements are necessary all the time. The extra information, contained in the measurements, theoretically could be employed to increase the model accuracy. However, a practical complication exists. No efficient methods exist to use the information in the measurements to adapt the parameters of large, complicated (irregular) non-linear models. Therefore it is seen, that in practice physiological models usually have either fixed or changeable parameters, while adaptive or tracking parameters usually are limited to the transfer function

type of models.
The first two types of model may be viewed as a compilation of all knowledge about the physiological processes, that play a part in a certain class of diseases (Dickinson, 1977[a] / Endresen and Hill, 1977). Generally these models are quite complicated descriptions of (parts of) physiological systems and their interactions. The complexity of these models derives from the fact that they should be able to mimic the patient's behaviour in widely different states. Therefore, they usually contain invariant chemical and physical relations. If the goal is more limited, i.e. the predictions of one variable only, the model may be much less complicated (Sheppard et al, 1975).
All types of model may be described by the following block diagram:



The model structure usually is assumed fixed. The model parameters may either be fixed or tracking. The initial state must be obtained from one set of measurements. The input is the actual or considered therapy. The model will predict a future state from the initial state and the input, using the model parameters. Using the future state as the next initial state, predictions can be made over any period of time.

Some practical differences between the different types of models include the following:

- models with adaptive parameters need a "learning period" during which the model parameters are estimated. During this period, predictions may be calculated, but will be less accurate. If the initial model parameters are taken from "average patient" data as a priori knowledge, initial predictions might reach an accuracy comparable with models with fixed parameters. The same applies to models with tracking parameters.
- the accuracy of models with fixed or changeable parameters does not improve after measurements are obtained. Indeed, there is no way to use information from measurements for improvement of parameter values.
- models with adaptive or tracking parameters usually have a simpler structure, often chosen as a set of differential equations, the parameters being estimated with well-known procedures with fast convergence. Because of this simple structure, these models tend to give inaccurate long term predictions; however, short term predictions often suffice.

Application of models

Applications of models are:

- documentation of knowledge, e.g. in respiratory physiology (Dickinson, 1977[a] / Grevisse et al, 1975), of metabolic processes (Cobelli et al, 1975), blood pressure control system (Schade, 1973) and cardio-vascular research (Beneken, 1972). Such models are typical research models. The internal consistency of experimental data can be checked and various hypotheses can be tested with such models.
- providing a patient substitute in the training of medical students. If the model is an accurate physiological replica of an "average patient", it is an excellent educational tool, showing students the effect of their actions on the "patient", up to and including the borders between life and death (Dickinson, 1977[a]).
- prediction of the most probable course and outcome of a disease, e.g. respiratory problems (Dickinson, 1977[a]).
- providing a means to determine an "optimal therapy". This can be done in different ways: "playing" with the model till a good therapy is found (Dickinson, 1977[a]), using an auxiliary program (Cowles et al, 1972 / Siegel et al, 1976), or on-line, processing the most recent measurements immediately (Tatnall and Morris, 1972 / Schade, 1973 / Sheiner et al, 1972 / Sheppard et al, 1975 / Pagurek et al, 1972).

Applications can be found in respiration (Dickinson, 1977[a] / Grevisse et al, 1975), anesthesia (Salamonsen and Smith, 1976 / Alotti et al, 1976 / Weed, 1977 / Tatnall and Morris, 1972 / Cowles et al, 1972), rehabilitation (Hoogendoorn, 1977), shock (Schade, 1973 / Sheppard et al, 1975) and drug dosage regimes (Sheiner et al, 1972 / Sheiner et al, 1974).

Discussion

Accurate general physiological models do not exist. Accurate partial models have been realised (Guyton, 1972), but they are so complex, that adaptation of these models to an individual patient is impractical if not impossible. Dickinson (1977[a]) described a model for respiratory pathophysiology which allows for the incorporation of some individual patient data in order to predict the future course of the patient's state.

Less accurate partial models have been developed (Beneken et al, 1974) that have fast adaptation, but lack any physiological basis. Their prediction accuracy is sufficient over short time intervals, and only if frequent measurements are available. This means that they are practical in intensive care and anesthesia only, because these are environments where monitoring is common.

Integrated patient care, across the borderlines of the classical medical specialisms requires an overall quantitative view of the patient's functioning. The availability of comprehensive and surveyable models is crucial for attaining this integrative view.

In developing such models a balance must be found between simple models that are almost trivial and complex models that require too much a priori knowledge to be practically applicable. This balance is most likely to be found by multidisciplinary teams with mutual understanding of and respect for eachothers abilities.

6. Trend prediction

Introduction

Trend prediction is a step beyond trendanalysis. Different techniques are available (Endresen and Hill, 1977) to extrapolate the momentary state of a patient into the future using already established trends. Every technique uses some kind of model, either based on physiological knowledge or mathematical/statistical methods. Some kinds of trend detection estimate parameters of the measured signal, regarding it as an autoregressive time series (Sayers, personal communication). The estimated parameters may also be used to calculate the expected future continuation of the trend, although the accuracy may be low, especially for long prediction intervals. Slightly modified, the same procedures can in addition produce an estimate of the prediction accuracy.

The goal of trend prediction can be

- prognosis. In section 3, prognosis was shown to be possible without incorporating trends. The availability of more (sets of) measurements over a period of time will generally increase the accuracy of the prognosis (Afifi et al, 1971) even if no explicit model is used, because the influence of momentary random fluctuations is decreased. Prognosis can include warnings about possible complications (Uttamsingh and Carson, 1977).
- optimal therapy. If the future course of the patient's state can be predicted as a function of all possible inputs (therapies) to the patient, the best therapy can be calculated (Beneken et al, 1974 / Blom, 1974 / Blom, 1975).

Prognosis through trend prediction

Prognosis is dependent on the available information about the patient and the development till now of his condition.

Several publications have stated the importance of a rational efficient organization of information in data banks (Weed, 1977 / Hartmann, 1974), using interactive computer programs to make information easily available including not requested relevant information. Here the information is stored in a traditional way, i.e. patient charts, questionaires, abstracts from medical and pharmacological handbooks, etc.

Information can also be stored in model. One might imagine having available a general model, that can be modified in two ways. First, it could be given all signs and symptoms of an individual patient, from the physician's examination and diagnosis. Second, all therapeutical actions on the patient (inputs) and sufficient patient measurements (outputs) of relevant variables should be taken into account by the model. With these two flows of information, the model could adapt to an individual patient in such a way, that it would react to therapy in the same way as the patient would.
Once adapted, the considered therapy could be applied as an input to the model, observing the model output. If the model could be speeded up several orders of magnitude the model would quickly generate the most probable future course of the patient's state, possibly including the outcome of his disease. Quantitative prognosis would be a fact.
A realistic model would also need to give the accuracy of its prediction. Major steps in this direction have already been taken (Dickinson, 1977[a]).

Optimal Therapy through trend prediction

It has not been strictly defined yet what is meant by optimal therapy. Optimal therapy can be defined as that therapy, that is arrived at by using to the full extent all information available about the patient and his disease. Obviously, optimal therapy might not be the "best" therapy, if crucial information is lacking, or not used because it cannot be made available in time. If the above mentioned "ideal" model was available, the optimal therapy could be calculated in a straightforward way, using the individually adapted model in a "reversed" fashion, i.e. specifying the wanted output (patient response) and calculating the inputs necessary.
In practice, the process of "reversing" the model is very difficult and time consuming for complex, non-linear physiological models. The transfer function type of model poses no problems in this respect (Beneken et al, 1974).

Discussion

Trend prediction is possible only through the use of models. Many different types of model exist. Indeed, the philosophy behind the development of models may have little to do with their use in trend prediction. At the moment no models are available that provide accurate long term trend prediction, and it is doubtful whether they can ever be developed except for very homogeneous classes of patients. The main sources of difficulties are the enormous complexity of the human physiology and the broad patient variability, especially in acutely ill patients.

However, doctors have always worked with probabilities, possibilities and trial-and-error. Therefore it may be expected that approximate models will be acceptable tools in medical decision making before too long.

Trend Prediction

Institute	organ system or disease	model	goal	results	literature
Medical Computing Centre Department of Physiopathology Free University of Brussels Rue de l'Abricotier 7 B-1000 Brussels Belgium	Pulmonary function	4 compartment model with combination of fixed and changeable parameters	automatic control of ventilation	The model has been built. Methods to estimate several parameters by perturbating the ventilator setting are developed.	Grevisse et al, 1975 Demeester et al, 1975[a] Demeester et al, 1975[b]
Department of Epidemiology School of Public Health Catholic University of Louvain 1200 Brussels Belgium	leprosy	epidemiometric model with several changeable parameters	find the best control method to decrease the incidence of leprosy	Simulations with different control methods are tested.	Lechat et al, 1977
Delft University of Technology Laboratory for Measurement and Control Department of Mechanical Engineering Mekelweg 2 Delft Netherlands	revalidation of spinal cord injury	mathematical model; parameters are averages from test population	optimal therapy	A model of the effect of therapy has been developed. The use of the model to find an optimal therapy is further investigated.	Hoogendoorn, 1977
Eindhoven University of Technology Department of Electrical Engineering Professional group Measurement and Control Eindhoven, Netherlands in collaboration with Dept of Anesthesiology University of Leiden School of Medicine Leiden, Netherlands	Anaesthesia	mathematical model with tracking parameters	optimal therapy	Satisfactory model simulations. Implementation in clinical situation will start in 1978.	Beneken et al, 1974 Blom, 1974 Blom, 1975

Trend Prediction

Institute	organ system or disease	model	goal	results	literature
Welsh National School of Medicine Department of Anaesthesia Heath Park Cardiff CF4 4XN United Kingdom	anaesthesia	compartment model with fixed and changeable parameters	control of depth of anaesthesia	System is tested with dogs. Development of a "brain halothane tension controller", that needs no or little feedback.	Chilcoat, 1973 Mapleson et al, 1974 Saravia et al, 1975 Allot et al, 1976
Department of Electrical Engineering University of Manchester Oxford Road Manchester United Kingdom	anaesthesia	compartment model with changeable parameters	optimal control of administration of anaesthetics	Model has been evaluated with dog experiments. The investigation is stopped at this moment.	Salamonson and Smith, 1976
St. Bartholomew's Hospital Medical College Department of Medicine West Smith Field London ECIA 7BE United Kingdom	gasexchange and circulation, pharmacokinetics, heart and blood circulation, systemic circulation, kidneys and body fluids	physiological models (MacPuf, MacDope, MacMan, MacPee) with fixed and changeable parameters	teaching try out possible therapies	The models are available for use and further evaluation. Programs are being developed to make MacPuf adaptable to individual patients.	Dickinson, 1976 Dickinson, 1977[a] Dickinson et al, 1977[b] Dickinson et al, 1977[c] Dickinson et al, 1978[a] Block et al, 1978[b]
Department of System Science The City University St. John Street London EClv 4PD United Kingdom	renal dialysis process	physiological model with changeable parameters	improve quality of care	A model has been developed. Some more subsystems will be added.	Uttamsingh and Carson, 1977
	Thyroid disease	mathematical model with adaptive parameters	find better control strategy	Information system has been set up. Selection of clinical and laboratory tests has been made. Control system approach is in early state of development.	Edwards et al, 1977

Trend prediction

Institute	organ system or disease	model	goal	results	literature
University of Salford Department of Aeronautical and Mechanical Engineering Salford M5 4WT United Kingdom	anaesthesia	compartment model with fixed parameters and mathematical model with adaptive parameters	optimal therapy	Development of an "alveolar halothane tension controller", using continuous end-expired halothane concentration measurements.	Tatnall and Morris, 1977
Department of Surgery University of Alabama Birmingham Alabama 35233 U.S.A.	circulation	decision tables and average impulse response	regulation of blood/drug infusion for patients after cardiac surgery	System operates since 1967.	Sheppard et al, 1972 Sheppard et al, 1975 Sheppard and Sayers, 1976
Department of Anaesthesia UCLA School of Medicine Los Angeles California 90024 U.S.A.	anaesthesia	single input - single output	control of depth of anaesthesia	Input/output relations have been investigated.	Bimar and Bellville, 1977
Minneapolis Medical Research Foundation Minneapolis Regional Kidney disease program Minneapolis (Minn.) U.S.A.	end state renal disease	model based on different groups of patients(configuration model)	medical care quality control	A model has been built.	McLaughlin, 1976
Department of Clinical Pathology and Laboratory Medicine University of California San Francisco 94122 U.S.A.	pharmacokinetics	isocybernetic model with tracking parameters	optimal dosage regime for a number of drugs for individiual patients	System has been tested for the drug digoxin with good results.	Sheiner et al, 1972 Sheiner and Rosenberg, 1974

Trend Prediction

Institute	organ system or disease	model	goal	results	literature
City University New York New York U.S.A.	shock	input/output model	optimal therapy	For a good therapy it is necessary to distinguish different types of shock.	Shoemaker, 1975
Department of Pharmacology and Toxicology and of Anaesthesiology University of Rochester School of Medicine and Dentistry Rochester New York 14642 U.S.A.	anaesthesia	compartment model with changeable parameters	prediction of anaesthetic uptake and distribution	Program is verified in experiments with dogs.	Cowles et al, 1972 Cowles et al, 1973
Division of Biomedical Engineering University of Virginia Charlottesville Virginia 22901 U.S.A.	no application yet	isocybernetic model with tracking parameters	optimal therapy	Gives a description of the possible use of such a system for clinical use.	Attinger, 1973
Division of Systems Engineering Carleton University Ottawa Canada	glucose-regulatory system	isocybernetic model with tracking parameters	on-line regulation of blood-glucose metabolism	A first in vivo test on a healthy subject has been succesful.	Pagurek et al, 1972
Electrical Engineering Department University of the Negev Beer-Sheva Israel	no application yet	isocybernetic model with tracking parameters	method for medical diagnosis and prognosis	No results to date.	Cohen, 1973

7. Conclusion

The present report is an attempt to give the state of the art on prognosis, trend and trendprediction. While collecting the material it became apparent that, although the original task was confined to trendprediction, incorporation of an analysis of prognosis and trend would show more clearly the distinctions between the three concepts.
Each of the three subjects covers an extensive field, so that an in depth analysis and a complete coverage is impossible. The extensive list of references in combination with the tables facilitates easy access to the published material.
This report deals with a rapidly developing area of clinical sciences and technology. This is the reason why very few comparative studies have been performed; it is still too early to evaluate the various methods. Another effect of the rapid development becomes apparent in the terminology which is not consistent, but rather confusing.
Prognosis is certainly the oldest technique amongst the three. Yet, relatively few methods are in clinical use. The concept of trend is gaining popularity. Experimental and commercial equipment is becoming available for displaying trends in one signal, or more signals simultaneously. Yet each time-plot represents the development of one single signal and no information is extracted from coincidence of changes or other signal properties.
Much to our surprise, no results have been found of the use of trends in prognostic indices. Yet this seems logical, since the prognostic index is a weighted combination of a number of variables relevant for the patient's condition. The development of such an index must show information about the development of the patient's state.
Trendprediction is a sophisticated method which has not found much clinical application. However it is felt that this is the most promising approach. It opens up the possibility for an integrated view of the patient in which the relative importance of certain patient variables is automatically taken into account. This model based approach forces the user to think in quantitative terms. Compressing all the available information in an patient model is the best way of data reduction. This patient model is the basis for finding the optimal therapy.

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APPENDIX 1

Proposal to:

Committee Monitoring the Seriously Ill.
(CMSI - CRM - European Communities)

Survey

TREND PREDICTION AS A BASIS FOR OPTIMAL THERAPY.

By: Medical Engineering Group
Department of Electrical Engineering
Eindhoven University of Technology
Eindhoven, the Netherlands.

Responsible: Prof.dr.ir. J.E.W. Beneken
Eindhoven, the Netherlands.

March 1977.

INTRODUCTION

Trend prediction

Trend prediction is extrapolation toward the future of the momentary state of a patient. Reliable predictions, i.e. predictions which are accurate enough to be meaningful, are possible only, if sufficient information is available about the patient's past en present state.
This information is available in two ways:
First, much is known about general physiological principles that govern the dynamics of the patient's state.
Second, observations of a particular patient are or will be available to establish initial conditions for the evolving dynamics of the patient's physiological system.
We expect, that these two sources of information will be able to provide us with reliable information about how the patient most probably will react to therapeutic interventions. Hence, if an optimal state is specified it will be able to derive an optimal therapy for any individual patient, optimal meaning that full use is made of all available information and sophisticated equipment to process this information.

Prediction and Models

Prediction is an often used concept in the engineering sciences. Particularly in control engineering it is used as a tool to calculate control sequences for complicated plants. Intimately linked with prediction is the concept of models. A model is a mathematical or physical system, designed to mimick another system.
An adaptive model can be tuned to a particular system. Therefore this model's behaviour can more closely approximate the systems behaviour. Adaptation requires a "learning" period during which certain perturbations and the corresponding responses are being observed.
Purposely perturbing the patient's state will, in general, not be desirable; however, certain therapeutic actions can be considered as such, yielding necessary information for adapting the model. This "updated" model will predict the future state of the patient more accurately.

TERMS OF REFERENCES OF SURVEY

Primary goal

Investigate and evaluate different approaches using individually adapted models, trend prediction and automated therapy in relation with seriously ill patients.

Secondary goal

Investigate and evaluate more pragmatic approaches using relatively simple signal analyses and predictors.

Underlying general goal

Initiate an exchange of ideas, experience, methods and results among investigating teams within the European Community for the benefit of the seriously ill patient.

The following keywords will guide this exchange:

- organ system - respiratory
  - circulatory
  - thermo regulatory
  - nervous
  - other
- situation - surgery, anesthesia
  - post operative care
  - trauma
  - myocardial infarction
  - stroke
  - other
- purpose - monitoring
  - prediction
  - therapy
  - other
- invasive - non invasive data
- conceptual frame work of method
- reproducibility - convergence
- clinical tests
- cost-effectiveness

PROCEDURE AND TIMING

Ir. J.A. Blom and Ir. F.F. Jorritsma, having extensive experience in adaptive control and instrumentation as applied to intensive care monitoring, automated therapy and servoanesthesia, are jointly willing to do the proposed survey.

Phase 1: compilation

- collection of important names and centers through delegates CMSI;
- literature survey, world wide
- requesting information from european centers
  - o research program descriptions
  - o research reports
  - o publications

Phase 2: evaluation

- classify relevant information according to keywords
- select most advanced centers within E.C.
- visit 6-10 of these centers for further information

Phase 3: report writing and submission to CMSI.

Phase 1 is planned for the late summer of 1977; phase 2 and 3 are planned during the fall of 1977.

FOLLOW UP: WORKSHOP

Early in the investigation and certainly in phase 2, sufficient insight will have been gained to constitute a firm basis to propose a workshop on the subject of this survey. The workshop should follow in the summer or fall of 1978.
Participants should be selected on the basis of the survey and further to form a multi disciplinary party consisting of clinicians and control and computer engineers.

COSTS

Estimated costs for secretarial assistance, visits and publication of the survey report are 2.500 - 3.000 A.U.

APPENDIX 2 Literature search

The literature for this survey was searched for in the following three computer files, using combinations of keywords:

1. Inspec-file (since 1971):
   A = parameter estimation OR state estimation OR state space OR adaptive control OR adaptive systems OR closed loop OR optimal control OR predictive control.
   part 1 = A AND medic ....
   part 2 = A AND (biomedic ... OR patient)
   part 3 = (optimization OR multivariable OR digital simulation OR control system analysis) AND (biomedic... OR patient OR medic....)
   part 4 = predictive AND (biomedic... OR patient OR medic....)

2. NTIS-file (since 1970):
   B = medical OR patient OR biomedical OR intensive care OR ill
   C = parameter OR adaptive OR closed loop OR optimal OR estimation OR predictive OR prediction OR multivariable
   part 1 = (control OR systems) AND B AND C
   part 2 = parameter AND estimation AND B
   part 3 = (prediction OR predictive) AND B
   part 4 = (analysis OR detection) AND trend AND B

3. Medline (since 1967):

   Technical

   1. adaptive systems
      predictive control
      adaptive control
      trend prediction
      optimal system
      closed loop systems
      parameter estimation
      state estimation
   2. control system analysis computing
      digital simulation
      optimisation

   Medical

   1. patient monitoring
      patient treatment
      general patient care
      patient diagnosis
   2. medical computing
   3. biomedical techniques

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