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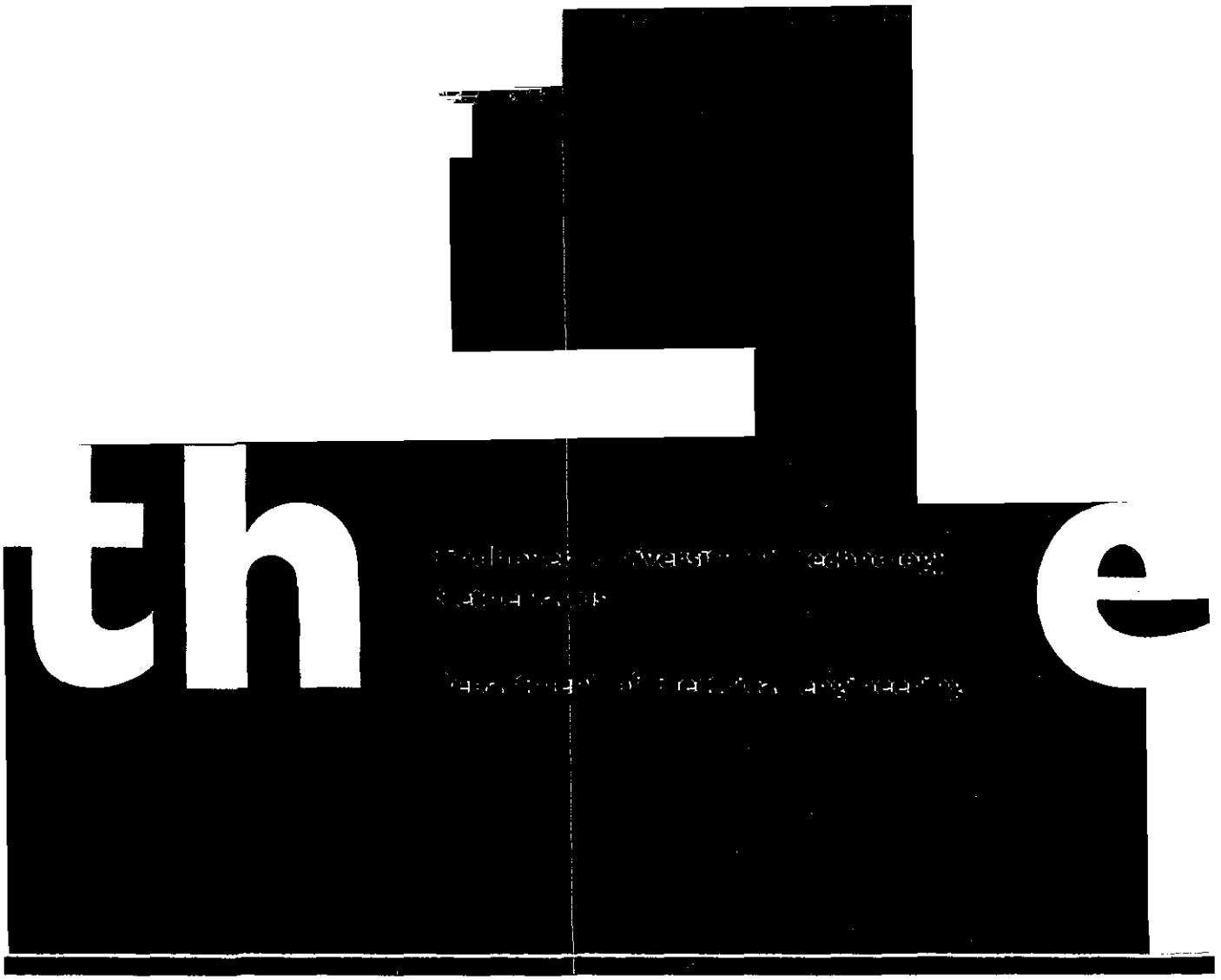
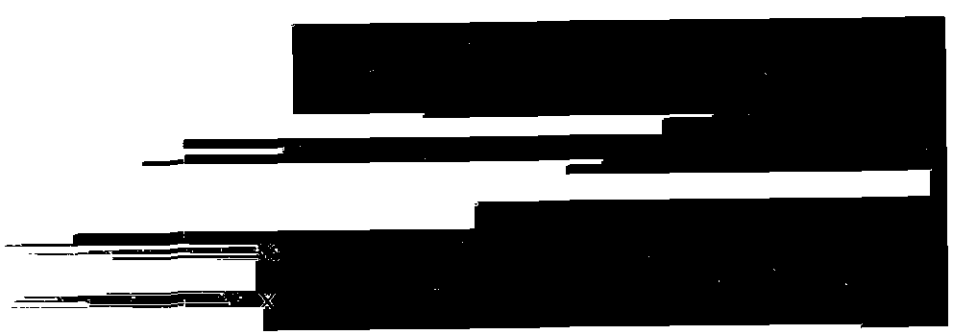


ANALYSIS OF PHYSIOLOGICAL SYSTEMS BY PARAMETER ESTIMATION TECHNIQUES

by

Ir. J.A. Blom



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Abstract

Physiological systems belong to the class of "difficult systems", about which little a priori information exists. If information is available, it may often be difficult to express mathematically. First some basic notions are formalized, like state and optimal state. Using these notions we progress to develop some models of the patient's system and we will indicate when they can be useful. The ultimate goal is to predict the patient's reaction to drug administration quantitatively in order to apply a therapy that is in some way optimal.

Goal of the analysis

This report is an initial account of some ideas that have evolved and some studies that have been done in an attempt to help the physician provide better care for his patients. It will be a starting point for further research.
The ultimate goal is to help find the best possible therapy for a particular patient. This goal may be reached in two steps.
First, acquire as much knowledge as possible about the patient's condition and extract from it the symptoms that indicate what parts of his basic mechanism are malfunctioning and how; decide which control forces (drugs, infusion, radiation, etc.) should be considered in an attempt to influence the functioning of the patient's mechanism.
Second, we have to adapt this knowledge to this patient's therapy: decide upon the doses of drugs etc. to be used at any time. An indication of the "goodness" of the therapy can only be obtained by permanently observing the patient's condition, i.e. his symptoms.

In this study we will be mainly concerned with this second step, and of course we will lean heavily upon the physician's knowledge. In addition, several times we will point to methods which may be of value in physiological and pharmacological research.

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Introduction:

When an engineer starts to work on medical problems, he is often perplexed by the huge amount of information he is supposed to have, and by the enormous complexity of the system "man". It seems at first glance, that ordinary engineering knowledge could never provide means to establish flow diagrams of material and information exchange patterns inside the human body, or even to provide input-output relationships.
Although we certainly do not want to belittle the results of physiological research, we feel that we are far from understanding the functioning of the human organism, and that for the moment we may rather want to distinguish between important and unimportant features than try to understand all.
This will tend to be our point of view: try to find the essential relationships and forget the remaining influences. This reasoning may prove to be sound enough, if it gives us a good therapy.
The functioning of many parts of the human body, and of many physiological control systems is reasonably well understood; their interactions to a lesser degree. The functioning of the entire human body is an almost untouched field of research.
A start could be made if only "important" features were taken into account, but a distinction between important and unimportant can hardly be based on a priori knowledge.
The method proposed in this study may help to distinguish between these two categories from the point of view of relevance with respect to the delivering of an optimal therapy.
This study may also indicate an optimal strategy in therapeutics.

The state of the patient.

When a physician speaks of "the state" of his patient, he has in mind a general idea about the patient's condition. He may think of the mental impression the patient gave him, his facial expressions, the color of his skin, whether the patient was fat or not, but he will also think of facts, which may be formulated more precisely. He has a record giving a medical history of the patient, from which he may know periods of illness, dates of surgical operation and figures giving blood pressure, blood gas analysis data etc. When the physician examines the patient, his idea of the patient's state may include also his momentary heart rate, rate of inspiration, systole, diastole and mean arterial pressure, or more complex quantities like ECG and EEG.

Two aspects are obvious:

1) the more information is available, the more valuable the physician's knowledge.
2) the more recently the information was obtained, the more reliable it is.

But why is the patient's state so important to the physician? Actually, the only reason is the physician's wish to look ahead, to predict what the patient's state will be in the future, or rather, what the patient's state would be without therapy, or after some therapy he has in mind. More or less, the physician looks at the patient as some system, which behaves according to certain fundamental laws he is aware of, the state of which he can influence by applying some kind of therapy. The physician has in mind a more or less simplified, abstract model on which he may experiment mentally and from which he may deduce a therapy.

The definition of "state".

In order to be able to formalize information about the patient we have to define the notion "state" in a more precise way. Therefore we first introduce the notion "state variable":

A state variable is a variable, having a numerical value and giving information about the patient. It may be given an obvious name, and may have an obvious dimension.

Examples of state variables are:

length	, value e.g.	185 (cm)
weight	,	76,3 (kg)
heart rate,		98 (beats/min.)
systolic pressure,		142 (mm Hg).

It seems that complex information about a patient, like an EEG, cannot be a state variable. This is true; saying "the EEG = 6" would mean nothing. However, the physician interprets the EEG by observing some special features of it, like the amplitude of the alpha waves, the dominant frequency and so on. We can do the same: break up the information of the EEG into several components, each of which will be a state variable.
This breaking up of complex information into units, the state variables, can be done with all types of information, which at first glance cannot be quantized.

Now we may endeavor to define the state of the patient. We keep in mind, that the only thing we are interested in, is in making predictions. Let us state the definition, as is in use in systems engineering:

> The state of a patient is the minimum set of state variables, which contain sufficient information about the past history of the patient to permit us - provided we know the ways, the state variables interact and the control forces that we will apply in the future - to compute all future states of the patient.

It must be stressed, that we do not have to know the exact interactions between state variables in order to define the state. Still, it is clear, that if several state variables interact, the state should include all of them.

This definition seems of no value to us. We would have to include so many state variables (and be able to measure them) that we would never be able to describe the state of a patient. The only thing to do is to narrow down the state concept. We know that, whatever the illness, not all state variables of the body are affected by it, at least not significantly. And if these state variables are not changed during the illness, there is no need to predict them. So we can narrow down the state concept, if we relate it to the patient's illness. Let us try another definition:

> By the state of a patient we mean the minimum set of state variables, which contain sufficient information about the past history of the patient to permit us to uniquely describe his illness and - provided we know the ways the state variables interact and the control forces that we will apply in the future - to compute this state of the patient at any time in the future.

This is the definition we are going to work with. We note certain features:

1) - The minimum set of state variables -
   In some cases an erratic behavior of only one state variable is the cause of a general deviation of many other state variables from their normal values. Still the illness may be described in terms of this one state variable, of which the other state variables are dependent.
   If, by some external control, we could restore this one state variable to its normal value, all other state variables would follow.

2) - Sufficient information -
   Sometimes one value at one time of one state variable could be enough information to describe the illness. Sometimes we need a series of values of one variable. Or we could need several values of several variables to give us enough information about the illness and the ability to predict.

3) - Uniquely describe his illness -
If it is not possible to uniquely describe the illness, it is certainly impossible to predict. We need a sufficient set of state variables.

4) - To compute the state -
It is only possible to compute any future state, if we know the exact relationships between state variables. A priori, we usually know very little of these relationships, but it will be one of our main goals to estimate them from our measurements. In practice, therefore, we will not be able to compute, we will merely estimate the future states, and the estimate will be the more unreliable the more we want to look ahead.

The definition does not contain a statement, that we should be able to measure the state variables directly. We will however demand, that the state can be derived from the outputs (i.e. measurements). The system must be observable.

Neither contains the definition a suggestion, which minimum set of state variables we should choose. Clinical experience, together with physiological insight, might suggest one particular choice, mathematical insight another.

The definition of optimal state.

The definition of optimal state is as difficult to formulate as definitions of health or illness. Intuitively we feel that the patient is in a good state if he is healthy, if the physician does not feel the necessity to apply drugs or perform an operation to improve the state of the patient. Therefore we rely on the physician and formulate:

> The optimal state of the patient is the state the physician tells us the patient should be in.

It will be clear, that we rely heavily on the experience and judgment of the doctor. He has to lay down upper and lower bounds for the state variables, and thus define a region, in which his team should try to keep this patient's state.
Later on too, it will become clear, that we cannot do anything without a priori knowledge. Here we start with the doctor's best guess, which of course can be improved later on, for instance if we notice that the patient's system has a different definition of what is optimal than the doctor. It will tend to be our philosophy to start with the best guess, and to use all new information to improve on it.

Control of the state.

If the patient's state is far from the optimal state, we would like to do something about it. Here again, we rely on the doctor. He had at least a fair guess about the nature of the illness, he told us which state variables to watch, now he should tell us which drugs can be or are to be used.

Now let us conduct an experiment. Observe the patient's state for some time. Then apply a (small) drug dose and observe the influence on the state. If the state gets nearer to the optimal state, compute the optimal drug dose, i.e. that dose which takes the state as close as possible to the optimal state. Now try another drug, and do the same. Some drugs would have a negative effect, and hence are not used. Some have the right effect; of those the optimal dose can be computed.

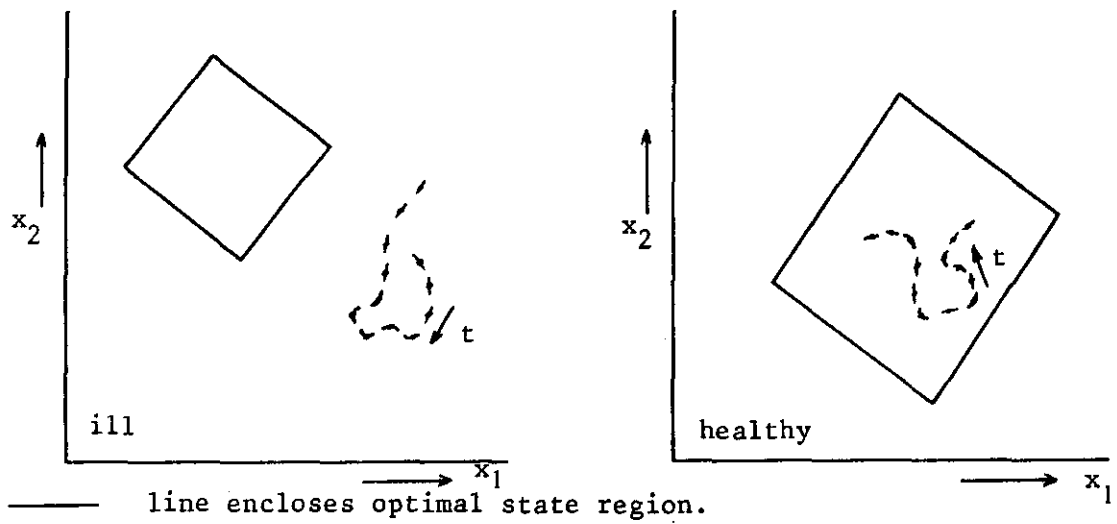
It should not be taken too literally that we can control the state. First, the state is usually subject to random fluctuations (noise) which we cannot keep under control. Second, our range of drugs usually cannot be chosen large enough to really force the state to go where we would like it to go. What we can do, however, is to choose the doses of drugs in such a way, that the state is forced toward the optimal state and stays "close" to it, thereby avoiding doses that are too small and thus ineffective, or too large and thus maybe causing side-effects.

Some modelling fundamentals.

From now we will on look at the state as a vector, the state vector. Suppose the patient's state can be described by n state variables. Those n variables are ordered in some way: choose one and call it x_1, choose a second and call it x_2 and so on. Now we have

$$\underline{x} = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ x_n \end{bmatrix}$$, where $\underline{x}$ is the state vector.

Now choose a coordinate system.
Suppose we align x_1 along the x-axis, x_2 along the y-axis, and so on. Then the state vector represents a point in n-dimensional space. By observing $\underline{x}$ for some time, plotting it in this n-dimensional state space, we have a means to follow movements of the patient's state.
In the same way we may represent the previously defined optimal state as a point or an area in state space. It is obvious that the distance between the (average) state and the optimal state in some way corresponds with the seriousness of the illness. If the patient's state moves close to the optimal state, his condition is good. If the distance is large, therapy is indicated.



——— line encloses optimal state region.

-•-•-•- patient's state evolving during some time

In the same way we introduce a drug vector $\underline{u}$, having components u_1, u_2.... u_m, each of which corresponds to one particular drug (or rather: external influence, because we will want to include other kinds of therapy like artificial respiration, blood infusion, radiation etc.). It will be clear, that each drug exerts some influence on the state, i.e. moves the state vector into a certain direction.

Now we have defined the fundamental notions, that we will use in our models: the state, at any time a point in n-dimensional space; the optimal state, likewise a point or a region in n-dimensional space; and the m-dimensional drug vector, which will be our tool to force the state into the direction of the optimal state.

Modelling the patient.

Instead of starting with a fundamental theory of models of complex systems, we will derive some models intuitively.
Suppose that we observe the patient's state for some time. Each state variable is to be measured directly, or to be derived from measurements. We notice, that during this time the state fluctuates around some equilibrium value.
A model of this will be:

$$\underline{x}\ (t) = \underline{x}_o + \underline{w}\ (t) \qquad (1)$$

where $\underline{x}\ (t)$ is the state at time t, $\underline{x}_o$ is the average state (equilibrium state), and $\underline{w}\ (t)$ is the vector that accounts for the perturbations of the state around the equilibrium state. We will call $\underline{w}\ (t)$ the noise vector or vector of uncertainties.
Now we may observe several features of this model, which will apply to more elaborate models too:

1) the only thing we seem to be interested in, is the equilibrium state. The measurements are needed only to determine $\underline{x}_o$.
2) since we assumed, that the average value of $\underline{w}\ (t)$ is zero, the model says , that the expected value of the state at any time is $\underline{x}_o$. Note, that this implies a prediction.
3) the noise vector $\underline{w}\ (t)$ not only stands for uncertainties, but also for that behavior of the system, that we do not want to include in the model, because it may be considered unimportant. Surely, if we expected other interesting features of the system, we would like to include those and come up with a more detailed model.
4) if we know the variance of the noise, we can construct a region in n-dimensional space in which the state will almost certainly be observed at any time in the future. We can indicate the accuracy of predictions.
5) the smaller the noise, the better the model fits the patient's system. If the noise is zero, we may say that we have identified the system. In that case our predictions will be infinitely accurate.
6) In order to determine $\underline{x}_o$ and the variance of the noise exactly we need an infinite number of measurements. If we have fewer measurements it is impossible to be exact, and we have to be satisfied with more or less accurate, estimated values.

7) if $\underline{x}_o$ changes in time, even an infinite number of measurements would not be enough to determine the ever changing value of $\underline{x}_o$ exactly. If we want to estimate $\underline{x}_o$ with some degree of accuracy, we need to have at least a number of measurements during a time in which $\underline{x}_o$ hardly changes. Now and in the future we will only consider systems with slowly varying parameters (slow compared to the frequency of measurements).

8) before the first measurement we may have a priori information about $\underline{x}_o$. After the first measurement we have gained some information, which we may use to improve our estimate. After many measurements we will have adapted our a priori knowledge to this particular patient. In this way, by using new information to improve our estimate, we will be able to track slowly changing parameters, too.

We have introduced the notion "parameter". Parameters are those quantities, that we want to extract from the measurements. In this case we have a parametervector $\underline{x}_o$, whose value we would like to know.
For the moment we will assume, that we have some means to acquire reasonally accurate estimates of the parameter values. At a later time we will digress to some parameter estimation procedures.

The previously derived model, though it revealed several fundamental features of models in general, hardly seems of any value. This may be different if we incorporate the influence of drugs on the state:

$$\underline{x}(t) = \underline{x}_o + B\,\underline{u}\,(t-T) + \underline{w}(t) \qquad (2)$$

This extended model formulates, that the state at time t will depend on the doses of drugs given T seconds before. The relation between change of state and drugvector is given by the parameter matrix B.
This model does not take into account any long term influence of the drugs on the state, so it will be useful primarily for fast acting drugs.
If our a priori information includes knowledge about the length of time the drugs exert their influence, the model may be adapted in the following way:

$$x(t) = \underline{x}_o + B_1\,\underline{u}\,(t-T) + B_2\,\underline{u}\,(t-2T)+\ldots+ B_k\,\underline{u}\,(t-kT)+ \underline{w}\,(t) \qquad (3)$$

where we take into account the drug influence during kT seconds, where T is the time between measurements and k is to be chosen according to the available a priori information.
It is to be understood, that the drug matrices B_1, B_2, ...B_k may be time dependent. This is easy to understand, because during a serious illness to organism may welcome a drug, which the recovered organism would fight. We therefore expect that during a proces of illness and recovery all parameters may change. This is especially true about $\underline{x}_o$, because, if the patient is ill, $\underline{x}_o$ will by definition be outside the optimal state region, while treatment is only stopped, if $\underline{x}_o$ is optimal again.
This leads us to the rather philosophical problem, whether to consider the system and the model as linear, vari-linear (linear with time-varying parameters) or non-linear. Undoubtedly the system is non-linear, because in general we may expect all kinds of non-linear relationships between the states. The same goes for the model: in general the B-matrices will depend on $\underline{u}$ and $\underline{x}_o$, and $\underline{x}_o$ may depend on the previous values of $\underline{u}$. Still, these dependencies will be so difficult to describe, that we would rather say, that the model is vari-linear, i.e. the parameter values only change because time changes. In general this would not be allowed, but in our case this assumption seems to be allowed because:

1) most non-linear systems, and possibly all physiological systems that we will consider, can be linearized about some state. As it is our goal to stabilize the patient's state around some state (the optimal state), linearization will probably induce small errors.

2) while no saturation effects appear to be present because of too heavy drug doses, a large drug dose will cause a larger change of the state.

Only in these cases, where we have small excursions of the state around some average state, where we apply only small drug doses, the model may be thought to be vari-linear. Moreover, if we assume slow parameter changes the model may be considered linear during a limited observation time.

It appears, that there are so many limitations, that we may be happy to have some model at all. Actually, in practice we will have a very good indication whether a particular model can be used: the noise term. If the noise is too large, the model is worthless because predictions will be

very inaccurate. But if the noise is small enough, we will accept the model, although we will be aware of its limited value.

Models (2) and (3) may be very valuable. They permit us, if we know all parameter values and the noise variance, to predict the next state after application of a certain drug dose, and the accuracy of the prediction. This implies, that we can calculate such doses as will take the state as close as possible to the optimal state, and to keep it there.
These models give a method to apply an optimal therapy: by optimal we mean: using to the best all a priori information and all information that became available by measurements.

Of course, the models may be used for other purposes, e.g. in pharmacological research, for determination of the effect of a certain drug, possibly in combination with other drugs on the patient's state during the process of recovery.

Finally, we want to stress that the usefulness of these models does not only depend on their structure (and the magnitude of the noise variance), but also on the accuracy with which all parameter values can be determined.

Dynamic models.

If we observe that the movement of the state around the equilibrium state is not all random, we may expect that (some) state variable values depend on the values they had during the previous measurement.
We may incorporate this expectation in a new model:

$$\underline{x}\ (t) = \underline{a}_o + A\ \underline{x}\ (t-1) + \underline{w}\ (t) \qquad (4)$$

which states, that the momentary state has, except for the noise, not only a constant part, but depends on its previous value, too.
The equilibrium state $\underline{x}_{eq}$ may be computed from (4) by observing that the equilibrium state is that state, the system will be in ultimately, if no noise were present. Then we have, if an equilibrium state exists,

$$\underline{x}_{eq} = \underline{a}_o + A\ \underline{x}_{eq} \quad , \quad (I - A)\ \underline{x}_{eq} = \underline{a}_o \ ,$$

$$\underline{x}_{eq} = (I - A)^{-1}\ \underline{a}_o \qquad (5)$$

Now we may rewrite (4):

$$\underline{x}\ (t) - \underline{x}_{eq} = A\ \{\underline{x}\ (t-1) - \underline{x}_{eq}\} + \underline{w}\ (t) \qquad (6)$$

which states, that excursions of the state from the equilibrium state will in general have time constants, i.e. a large excursion may only after some time be corrected.

If we want to incorporate the effect of drugs, we extend (4) to:

$$\underline{x}\ (t) = \underline{a}_o + A\ \underline{x}\ (t-1) + B\ \underline{u}\ (t-1) + \underline{w}\ (t) \qquad (7)$$

Now we want to know what the new state will be if we apply a certain, constant drug dose. Therefore, we take expected values of both sides of (7):

$$E\ \{\underline{x}\ (t)\} = \underline{a}_o + A\ E\ \{\underline{x}\ (t-1)\} + B\ \underline{u} + E\{\ \underline{w}\ (t)\}$$

The last term is zero by definition; after some time we have

$E\{\underline{x}(t)\} = E\{\underline{x}(t-1)\} = E\{\underline{x}\}$, and $\underline{u}(t-1) = \underline{u}(t-2) = \ldots = \underline{u}$

Therefore

$$E\{\underline{x}\} = \underline{a}_o + A\,E\{\underline{x}\} + B\,\underline{u}\ ,$$

$$(I-A)\,E\{\underline{x}\} = \underline{a}_o + B\,\underline{u}\ ,$$

$$E\{\underline{x}\} = (I-A)^{-1}\,\underline{a}_o + (I-A)^{-1}\,B\,\underline{u} = \underline{x}_{eq} + (I-A)^{-1}\,B\,\underline{u} \qquad (8)$$

Now (8) shows, that the drug effect depends on B and A.

Models (4) and (7) are more suitable for analysis of complex systems then more simple models like (1) and (2). They offer a way to separate large complex systems into subsystems. If we are able to establish relationships between these mathematically independent subsystems and physiological subsystems, we have a powerful tool for basic physiological research.

Let us introduce:

$$\underline{y}(t) = \underline{x}(t) - \underline{x}_{eq} \qquad (9)$$

Now y (t) represents the excursion of the state from the equilibrium state. From (7) follows:

$$\underline{y}(t) = A\,\underline{y}(t-1) + B\,\underline{u}(t-1) + \underline{w}(t) \qquad (10)$$

Now we will try to find such a coordinate system, that (10) may be more simplified. Our original choice of coordinate system depended on the actual state variables we choseas basic units. Mathematically a different coordinate system could be more appropriate.
Therefore we introduce a transformed state $\underline{z}(t)$ such that

$$\underline{y}(t) = Q\,\underline{z}(t) \qquad (11)$$

where the square matrix Q remains to be chosen. Now (10) transforms into:

$$Q\,\underline{z}\,(t) = AQ\,\underline{z}\,(t-1) + B\,\underline{u}\,(t-1) + \underline{w}\,(t),$$

$$\underline{z}\,(t) = Q^{-1}\,AQ\,\underline{z}\,(t-1) + Q^{-1}\,B\,\underline{u}\,(t-1) + Q^{-1}\,\underline{w}\,(t) \qquad (12)$$

Now Q can be chosen such that $Q^{-1}\,AQ = D$, where D is a diagonal matrix. The diagonal elements of D represent the eigenvalues of A, and Q is the eigenvectormatrix of A.
Now (12) becomes

$$\underline{z}\,(t) = D\,\underline{z}\,(t-1) + Q^{-1}\,B\,\underline{u}\,(t-1) + Q^{-1}\,\underline{w}\,(t), \text{ or}$$

$$\underline{z}\,(t) = D\,\underline{z}\,(t-1) + B^{*}\,\underline{u}\,(t-1) + \underline{w}^{*}\,(t) \qquad (13)$$

Now, if $\underline{x}\,(t)$ and $\underline{z}\,(t)$ are n-vectors, (13) indicates that we have obtained n independent subsystems, each with its own time constant. If one or more timeconstants appear to be zero, this simply means, that one or more of the new, transformed state variables $\underline{z}$ is completely determined by all other transformed state variables; the same is true for the original state variables $\underline{x}$. In this case A is singular.

It remains to be established, whether we will be able to find relations between the mathematically independent subsystems, that we can calculate from a patient's data, and some physiological processes.This will all depend on our assumptions: that the model is a reasonable picture of the real system. If so, we can not only find the system's simplified structure, its time constants and its uncertainties, but we also have found the influence of the applied drugs on all subsystems. This again may present a powerful tool in pharmacological research.

Non-linear models.

The immediate purpose of a model is, of course, to have a picture of a real system. This picture should not be so simple, that it shows nothing, nor should it be so complicated that it is useless to work with.
We started with some simple models, because we assumed that practically no a priori information was available. A small degree of non-linearity was allowed: it did not make the model useless, only enlarged uncertainties. On the other hand, if we do have sufficient a priori information about certain non-linearities in the system, it would be advantageous to include those in a model. Sometimes it is absolutely necessary to have a non-linear model, because the system cannot be linearized. This is especially the case with memory-type non-linearities like hysteresis, which fortunately seem not to be important in most physiological control systems.

We will not go into non-linear modelling deeply. Two points should be clear, though.
First, if we have sufficient information about the type of non-linearities which play an important role in the system, we can easily include those in the model.
Second, if we start without much a priori knowledge, and with a simple , linear model, we may in time start noting, that we can extract information from that, which at first we called noise. This information, possibly about non-linearities,may then be the source of a new, better model. Whether this new model is really better, will be shown by a smaller noise term .

Parameter estimation - general.

Having chosen an appropriate model, describing qualitatively the relationships of the system, our next task is to obtain the parameter values.

Consider a system without noise, and a model with exactly the same structure. Suppose the model has q parameters. To solve for q unknowns we need q knowns. Suppose that we measure periodically r values (state variable values, drug doses). Generally we have $r < q$. Therefore we need $\frac{q}{r}$ measurement periods to obtain q knowns. If now during this time parameter values change, it is impossible to obtain their values, because we simply do not receive sufficient information. All we can hope to calculate is average parameter values. This sets an upper limit to the speed of parameter variations we can estimate, or alternatively, it indicates a lower limit to the measurement frequency.

Now consider a system with constant parameter values, but with noise. Depending upon the magnitude of the noise term, we now need more than q knowns to establish reasonably accurate parameter values. The more measurements we can obtain, the better we can "average out" the noise and arrive at better estimates.

If we have both noise and parameter variations, we need some compromise. On the one side we want to calculate parameter values after only a few measurements so we can track changing values fast. On the other side we would like to first have done many measurements so we can present accurate values. In general the compromise can only be resolved after we have obtained information about the speed of parameter variations.

One problem will remain untouched in this report: the effect of state-dependent, "coloured" noise, which may lead to incorrect parameter estimates. An attack of this problem will lead to schemes for estimation of the noise parameters.

Parameter estimation - linear models.

Every linear (linearized) model can be represented by:

$$\underline{x}\ (t) = R\ \underline{y}\ (t-1) + \underline{w}\ (t) \tag{14}$$

where $\underline{x}\ (t)$ represents the state at time t; $y\ (t-1)$ is a set of quantities, which are known at time t; $\underline{w}\ (t)$ is the noise term; and R is a matrix including all parameters.

If, for example, we consider equation (7), it may be rewritten as:

$$\underline{x}\ (t) = \left[\underline{a}_o\ A\ B\right] \begin{bmatrix} 1 \\ \underline{x}\ (t-1) \\ \underline{u}\ (t-1) \end{bmatrix} + \underline{w}\ (t).$$

By defining $R = \left[\underline{a}_o\ A\ B\right]$ and $\underline{y}\ (t) = \begin{bmatrix} 1 \\ \underline{x}\ (t) \\ \underline{u}\ (t) \end{bmatrix}$

we obtain equation (14).

Now suppose we want to estimate R from the last p measurements.

Define $X\ (t) = \left[\underline{x}\ (t)\ \ \underline{x}\ (t-1) \ldots\ \underline{x}\ (t-p+1)\right]$

$$Y\ (t-1) = \left[\underline{y}\ (t-1)\ \underline{y}\ (t-2) \ldots\ \underline{y}\ (t-p)\right] \tag{15}$$

$$W\ (t) = \left[\underline{w}\ (t)\ \ \underline{w}\ (t-1) \ldots\ \underline{w}\ (t-p+1)\right]$$

If R is constant during these last p measurements, we have

$$X\ (t) = R\ Y\ (t-1) + W\ (t) \tag{16}$$

the least squares solution of which is:

$$\hat{R} = X\ (t)\ Y^{+}\ (t-1) \tag{17}$$

where Y^{+} is the pseudo-inverse (Moore-Penrose inverse) of Y.

Alternatively, suppose we have at time t an initial estimate $\hat{R}\ (t-1)$ of R which should be updated. Using $\hat{R}\ (t-1)$ we can predict $\underline{x}\ (t)$:

$$\hat{\underline{x}}\ (t) = \hat{R}\ (t-1)\ \underline{y}\ (t-1) \tag{18}$$

where the reliability of this prediction is limited by our information concerning the reliability of $\hat{R}$ (t-1) and the noise variance.
Similarly:

$$\hat{X}\ (t) = \hat{R}\ (t-1)\ Y\ (t-1) \tag{19}$$

Having measured $\underline{x}$ (t) we can calculate the prediction error

$$F(t) = \hat{X}\ (t) - X(t) = \{R - \hat{R}\ (t-1)\}\ Y\ (t-1) + W\ (t) \tag{20}$$

Now we want to update $\hat{R}$ (t-1) in such a way, that $L = \frac{1}{2}||F(t)||^2$ is minimized. Therefore we have to change $\hat{R}$ (t-1) into the direction

$$-\frac{\partial L}{\partial \hat{R}(t-1)} = F\ (t)\ Y^T\ (t-1) \tag{21}$$

Thus we can take

$$\hat{R}\ (t) = \hat{R}\ (t-1) + F\ (t)\ K\ Y^T\ (t-1) \tag{22}$$

where K remains to be determined. We want a K such that $\hat{R}$ (t) = R, or such that

$$X\ (t) = \hat{R}\ (t)\ Y\ (t-1) \tag{23}$$

Combining (22) and (23) we have

$$X\ (t) = \hat{R}\ (t-1)\ Y\ (t-1) + F\ (t)\ K\ Y^T\ (t-1)\ Y\ (t-1)$$

$$= \hat{X}\ (t) + F\ (t)\ K\ Y^T\ (t-1)\ Y\ (t-1)$$

$$F\ (t) = F\ (t)\ K\ Y^T\ (t-1)\ Y\ (t-1),$$

hence

$$K = \{Y^T\ (t-1)\ Y\ (t-1)\}^{-1} \tag{24}$$

Combining (24) with (22) we have

$$\hat{R}(t) = \hat{R}(t-1) + F(t)\{Y^T(t-1)\,Y(t-1)\}^{-1}\,Y^T(t-1)$$

$$= \hat{R}(t-1) + F(t)\,Y^+(t-1) \qquad (25)$$

Now we have a way to continuously update our previous parameter estimates in such a way, that the relations between the last p measurements are best described.

Parameter estimation - nonlinear models.

Nonlinear models, too, can be represented by equation (14) by choosing y (t) accordingly, including nonlinear terms. The same methods of solution, equations (17) and (25) apply here.

A warning should be issued here, however. If the model is a very good replica of the real system there are no problems. In this case we have actually changed the nonlinear model into a linear one by a suitable choice of new variables. Problems do arise, if the structure of the real system is unknown, so non-linearities cannot be modelled properly. Now model parameters are less meaningful, and may have fast changing values, if the state changes much. As an example, let us take the following:

$$\text{system:} \quad x = y^2$$
$$\text{model :} \quad x = x_o + ay$$

The model has two parameters, so two measurements of x and y suffice to determine x_o and a. Suppose we measure y = 0.9, x = 0.81, and y = 1.1, x = 1.21. We have a complete fit if $x_o = -0.99$ and a = 2.0. As long as y remains about 1, the model gives a reasonably accurate fit. But if y moves to about 2, we may for instance measure y = 1.9, x = 3.61 and y = 2.1, x = 4.41. Now we will estimate $x_o = -3.99$ and a = 4.0 and have the impression that parameter values have changed in time. This latter is exactly our philosophy: if y moves slowly from 1 to 2, and if we measure frequently enough, we will keep track of changing parameter values, and do not bother about possible nonlinearities. In this case short term predictions will be very well possible, though maybe physiological insight may be hampered: We have not identified the system in the real sense. After working with this simplified model for some time, we will probably notice, that another, more detailed model gives a better understanding of the system, though for many practical purposes an improved model would hardly be necessary, e.g. in control applications.

Dual Control.

Since in recent years control theory was applied to ever more complex systems, the phrase "dual control" was coined to indicate that type of control, in which the control laws itself could only be calculated after performing measurements.
Control can be optimal only, if all system parameters are known; if system parameters themselves change in an unknown way, we can only hope to reach a certain optimality if we keep track of those parameter values. Dual control is only possible on-line.
We differentiate between three steps:
1) measurement of state and drug vectors,
2) estimation (updating) of parameter values,
3) calculation and application of optimal drug doses.

The first step is self-explanatory. The second step has been treated. The third step will be explained here.

We have available estimates of all model parameter values. We assume, that all estimated parameters are sufficiently accurate. Now we have the freedom to choose drug doses. If at time t we apply a dose $\underline{u}$ (t), we can predict the state vector at time t+1. Now choose $\underline{u}$ (t) such that the predicted next state $\hat{\underline{x}}$ (t+1) is optimal (is in the optimal region or as close to it as is possible).

Let us take model (2) for example. We have an estimate $\hat{\underline{x}}_o$ of $\underline{x}_o$ and an estimate $\hat{B}$ of B. The predicted next state is

$$\hat{\underline{x}}\ (t+1) = \hat{\underline{x}}_o + \hat{B}\ \underline{u}\ (t) \qquad (26)$$

where $\underline{u}$ (t) remains to be chosen.
Suppose that we have defined the optimal state as a point $\underline{x}_{opt}$, the distance to which should be minimized.

Our task is to minimize

$$L = ||\underline{x}_{opt} - \hat{\underline{x}}\ (t+1)||^2 = ||\underline{x}_{opt} - \hat{\underline{x}}_o - \hat{B}\ \underline{u}\ (t)||^2 \qquad (27)$$

with solution

$$\hat{\underline{u}}\ (t) = \hat{B}^{+}\ (\underline{x}_{opt} - \hat{\underline{x}}_{o}) \tag{28}$$

The only thing left is to compare the calculated optimal dose $\hat{\underline{u}}$ (t) with our a priori knowledge about maximum doses. If some calculated doses are too large, their value should be diminished, and possibly a warning should be issued that either the parameter estimation process is not working correctly, possibly due to measurement errors, or that this particular drug is not effective any more. Is the solution within bounds, then drug administration can be performed automatically, and the next cycle can start with new measurements.

Automated intensive care.

The purpose of intensive care treatment is to optimize the patient's state, watching closely whether all measurable state variables remain within previously set bounds, and if not, applying such a therapy as to force the patient's state within those bounds. This therapy may be applied by a doctor or a nurse, in routine cases it can be done automatically, too, with the aid of a small computer.

We will describe a feasible set-up of such a system.

The first requirement is that of safety. The system should in any case work at least as well as previously, without automation. This means, that in case of a computer failure an immediate warning should be issued, and care must be taken over by the doctor or the nurse; all information that is available to the computer should be presented to the doctor, too.

This is best accomplished by a set of preprocessing units as is in general use already, each adapted to its own (group of) state variables, and presenting some kind of display of state variable values. These units now should be equipped with digital outputs, transmitting the state variable values to the computer.

Because the basic estimation and control algorithms are very compact, information processing can be done with a small computer. Such a computer usually has a high speed, so many measurements can be done every minute, allowing very early warning in case of emergencies; or the computer may care for several patients.

Output signals of the computer now should be able to control valves, roller pumps etc. for drug administration. This requires modifications and new apparatus.

Human communication with the computer system is realizable with a cathode ray tube display with keyboard, allowing alphanumeric and graphical data to be displayed and new data to be entered manually. Compared to a teletype, a tube display is noiseless and at least ten times faster.

Error detection is partly done in each preprocessing unit, which gives a warning if the measured state variable value is outside previously set limits. This allows for very early warning of bad electrode contacts, clogged catheters, etc.

A more subtle type of error check is done in the computer; our a priori information includes knowledge of relationships between certain state variable values. It is, for instance, hard to imagine a diastolic pressure

higher than the corresponding systolic pressure, even though both values may be within the limits of the preprocessing units. Thus the consistency of the data can be checked. In case of an error, a warning should be given, and incorrect data should not be used in calculations.

When the described computer system is fully realized, we may expect something like the following practical situation:

1) the doctor starts therapy or observation,
2) technician or nurse connects all equipment; a priori information is typed in on the keyboard; the computer system starts measurements, which are displayed; information processing starts,
3) the doctor defines this patient's optimal state,
4) the computer starts to give suggestions about drug doses; after a "learning period" the computer gives correct results, which the doctor will accept,
5) change to automatic control,
6) in case of emergencies: the computer gives a warning signal; change to human control; search for cause of alarm and correction of defaults.

Besides intensive care the computer system can be assigned to other tasks, e.g. graphical presentation of state and drug doses during the last number of hours, analysis of the trend of the state, and presentation of statistical data.

It is possible at any time to redefine the optimal state, so the system is not only to be used when the patient's state should be stabilized around a certain steady state, it is also useful if the patient's state has to follow a certain trajectory like in anaesthesia during surgery. This widens the field of application considerably.

The total cost of a complete computer system depends on the number and kind of state variables to be watched, the number and kind of drugs or other therapeutical means to be applied, and the number of patients. The central part, a small computer of $ 4000.- and a cathode ray tube terminal of $ 5000.- will probably, depending upon the application take care of up to ten patients. Benefits include earlier warning in case of emergencies, a better, smoother regulation of the patient's state, better detection of errors, trend detection, minimal quantities of applied drugs, hence probably a shortening of the re-

convalescence period, and last but not least an ease of the burden of the nurse by automatically taking care of part of their routine tasks.

Simulation Results.

Several simulation experiments have been done on systems modelled according to (2) and (7), both with constant and with time varying parameters. Results depended, as expected, on the available a priori information. Estimation of the parameters of systems having constant parameters proved to be succesful, the noise variance approaching zero in the long run, if the a priori information included the knowledge of constancy of the parameters; if not, the noise variance did not approach zero, but tended to a constant value, depending upon the time window (i.e. the period in which parameter values were assumed to be constant).
If system parameters varied in time, but the assumption was that they were constant, no convergence was possible. Estimated parameter values tended to be averages of the real, time varying parameters.
If in this case the a priori information included time variation of the parameters, estimates depended on the time window, both in correctness and accuracy. First, parameter estimates proved to be the average of the real values during the applied time window; if parameter values changed fast, we tended to estimate the real values of half the time window ago, indicating that the time window should be short. Second, the noise variance was large if the time window was extremely short, and large if the time window was too long, indicating that there exists an optimum time window; generally it will be impossible to reach this optimum, because we do not know a priori how parameter values will change in time.
Maybe in the future schemes will be conceived which will find the right compromise between accuracy and fast tracking of changing parameter values.
For the time being we will assume slow parameter variations, i.e. measurements at a sufficiently high frequency.

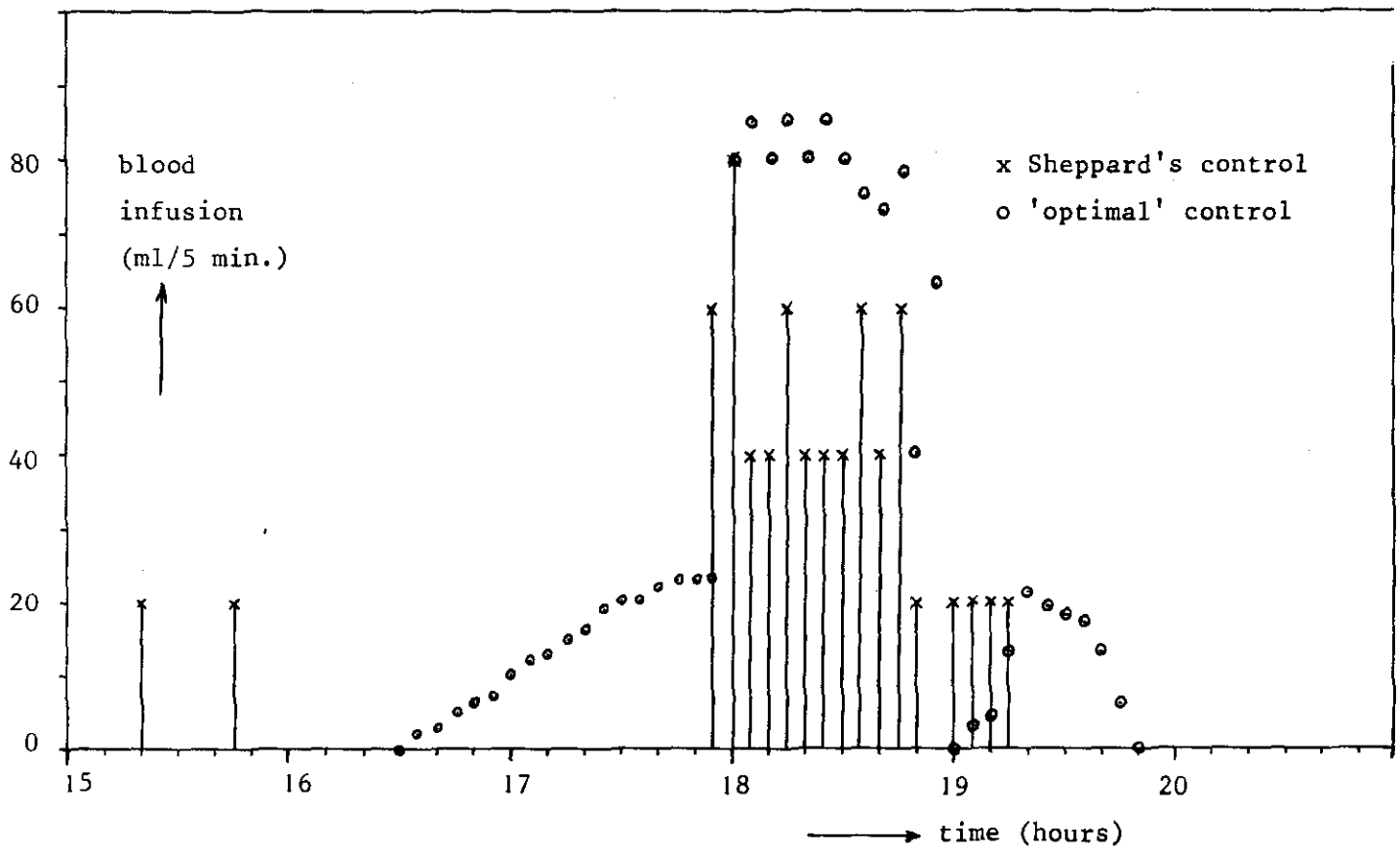
Louis C. Sheppard, University of Alabama in Birmingham Medical Center, works with a partly automated intensive care unit for patients who have had open heart surgery, and uses a similar computer system as the one we described. After installation of the computer system their results improved markedly: the number of deaths, which was already at a low 15 % was halved to about 8 %, while the average period patients spent in the intensive care unit was brought down from two or three days to less than 24 hours.
Sheppard states that he has "programmed his surgeon", thus implementing all available a priori information on the computer, without making use of an

adaptive algorithm. He was so friendly to send us data of two patients, who spent about 20 hours in the unit.
There are several reasons why we cannot fully compare his results with our simulation results. First, our estimation takes place on-line, learning from its previous mistakes. Now this possibility is partly excluded. Second, our model is a linearization about a certain state and a certain drug dose. Sheppard's algorithm leads to an on-off type of control; if certain conditions are fulfilled, a constant drug dose is given. If saturation effects are present with large doses, this makes linearization questionable. Third, our model assumes measurements at regular intervals. The data that were made available to us, were alternately taken after four and six minutes. Fourth, our model assumes that state variables are available rather accurately. This was not true with all state variables, especially the most important ones.
For all these reasons it is very difficult to draw any conclusions. Very carefully we dare state the following observations:

1) system identification according to the dynamic model (7) was impossible: we did not obtain consistent estimates during most of the time. Prediction of the next state usually was correct though not very accurate; however, sometimes large errors occurred. Calculated optimal drug doses still agreed qualitatively with doses actually given.
2) system identification according to the static model(2) agreed very well with the data. Predictions were reasonably good, large errors did not occur. Calculated optimal drug doses agreed qualitatively with doses actually given.
3) in our system, drugs would be applied more evenly. Large doses seemed to be less effective than expected, indicating a saturation effect. Moreover, sometimes the applied drug seemed to have an adverse effect, especially at the end of the patient's stay in the unit, possibly indicating that therapy could have been stopped earlier.
4) the optimal state had to be redefined at least once, indicating that at the start of therapy a safety margin was incorporated.

Conclusive results of adaptive intensive care will only become available after working on-line, which should be the next stage of this research.

The difference between Sheppard's control strategy and our proposed control strategy is shown in the next figure. There is a good qualitative agreement between the two strategies: both would infuse comparable quantities of blood at the same times, blood infusion being the only control force.



We choose the following state variables: systolic, diastolic and mean arterial pressure, heart rate and left and right atrial pressure. Sheppard observes also rectal temperature, chest drainage and urine output (catheter), and if considered necessary, blood analysis data.

In this case the optimal state was defined as:

systolic pressure	120	mm Hg	weight	0,2
diastolic pressure	80	mm Hg	"	0,2
mean arterial pressure	100	mm Hg	"	0,5
heart rate	80	/ min.	"	0,1
right atrial pressure	8,5	mm Hg	"	1,0
left atrial pressure	8,5	mm Hg	"	1,0

The weight factors indicate the relative importance, that we attached to keeping a particular state variable "optimal".

The main difference between the two control strategies is, that with our proposed control strategy a downward trend of the state variables, which might lead to a state of shock, is detected (and would be corrected) earlier.

Conclusions.

It seems feasible to construct a mathematical basis for the description and analysis of (parts of) physiological systems. Basic are notions like state vector, drug vector and optimal state region. They allow us to consider the patient's state at any time as a vector moving in n-dimensional space, which can be forced in certain directions. Drug doses can be calculated, such that the state is forced toward the optimal state.
Under certain conditions, none of which seems unrealistic, the patient's system can be approximated by a more or less simple, linear model with time varying parameters, which can be estimated. This model may allow a better understanding of the structure and main characteristics of the real system, or it may serve as a tool to control the system in such a way that its state is optimized.

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