Do Black-Box Models of Thermoregulation Still Have Any Research Value? Contribution of System-Theoretical Models to the Analysis of Thermoregulation

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The aims and the usefulness of modelling the thermoregulatory system are outlined by demonstrating applications and results of simulation on different levels of complexity. It is shown that both very simple one-loop models and complex models based on spatially distributed parameters have contributed to a better understanding of the system, but that current issues primarily require the latter type. However, mathematical modelling must be performed in conjunction with experimental studies and must be adapted to the amount of basic physiological data. Future fields of modelling are the adaptive mechanisms and the interactions of systems.

INTRODUCTION

Modelling is a very powerful tool in system and control engineering, especially in planning and designing complex industrial processes, nuclear plants, airplanes, and space vehicles. There is no doubt that this technique has turned out to be useful in biology and thermal physiology as well, but in comparison with the engineering sciences it has a limited significance. A basic reason for this fact seems to be that the major task of the engineer is synthesis, whereas that of the physiologist is analysis of systems and processes; i.e., in most cases the engineer models a process he wants to transfer into reality later on, whereas the physiologist is confronted with a complex reality, the subsystems and subprocesses of which must be elucidated. Moreover, there are special reasons which make modelling particularly difficult in physiology, reasons which, as a rule, turn out to be more severe than in technology. Physiological control loops, including thermoregulation, are:

1. Hierarchical multi-level systems
2. Interacting multi-goal systems
3. Spatially distributed parameter systems
4. Non-linear and non-stationary systems

Special difficulties in analysis and simulation arise from

1. Isolation of subsystems
2. Anesthesia
3. Adaptation
4. Spontaneous changes
5. Analysis of representative elements
6. Individual variation

    7. Lack of basic data
    8. Lack of computer capacity

What is a biological model? Generally speaking, a model is an analogous representation of biological phenomena and of their relationships. A black-box model should be suited to solve a special problem by analyzing inputs and outputs; in most cases, it should be suited to clarify the black box itself. Such definitions, however, imply that there is a vast amount of available or designable models. But as each model must serve a definite aim, which should be formulated in advance, structure and complexity can be adapted to this purpose; that is, out of the variety of models there is an optimal type for solving a definite task. From this it should be clear that a model should be judged according to its given purpose.

The possible purposes of modelling may be summarized as follows:

1. Summary or reduction of results and stabilizing the amount of truth
2. Better insight into fundamental mechanisms and formulation and test of hypotheses, together with experimental programs
3. Extrapolation of variables not experimentally attainable and simulation of non-performable experiments

BLACK-BOX SCHEME OF THERMOREGULATION

Figure 1 presents a diagram of the current view of human temperature regulation, from which some essential system characteristics are already evident. A model of the system must thus take into account locally distributed measurement, processing, and effector actuation [1–3]. Historically, starting from the hypothalamus, one additional controller had to be added to another, so that finally Simon [2] speaks of a multiplicity of controllers. Following theoretical control principles, a multiplicity of controllers should be replaced by a distributed parameter control concept, which takes into account all aspects of local distribution, including the control strategy. Nevertheless, according to Table 1, six different levels, a–f [4,3], of model complexity may be distinguished, which have been useful for various purposes and also for the common aim: namely, getting a deeper insight into the functional mechanisms of this biological control system.

ONE-LOOP BLACK-BOX MODELS

Even the very simplest type of model, the one-loop model, although far from reality, has enabled a better understanding of steady-state mechanisms of thermoregulation. The system of temperature regulation may be divided into four subsystems cooperating in a closed control loop, as indicated in Fig. 1 by four large boxes:

1. The receptors which measure temperature and transmit this information to the control centers via afferent fibers and neurons
2. The controlling system which activates the effectors via efferent pathways
3. The effectors which act upon the passive system
4. The passive system itself

Even from this very simple scheme, some essential questions emerge which have been discussed again and again, namely:

1. Which is the regulated variable?
2. How does the regulator get its reference?
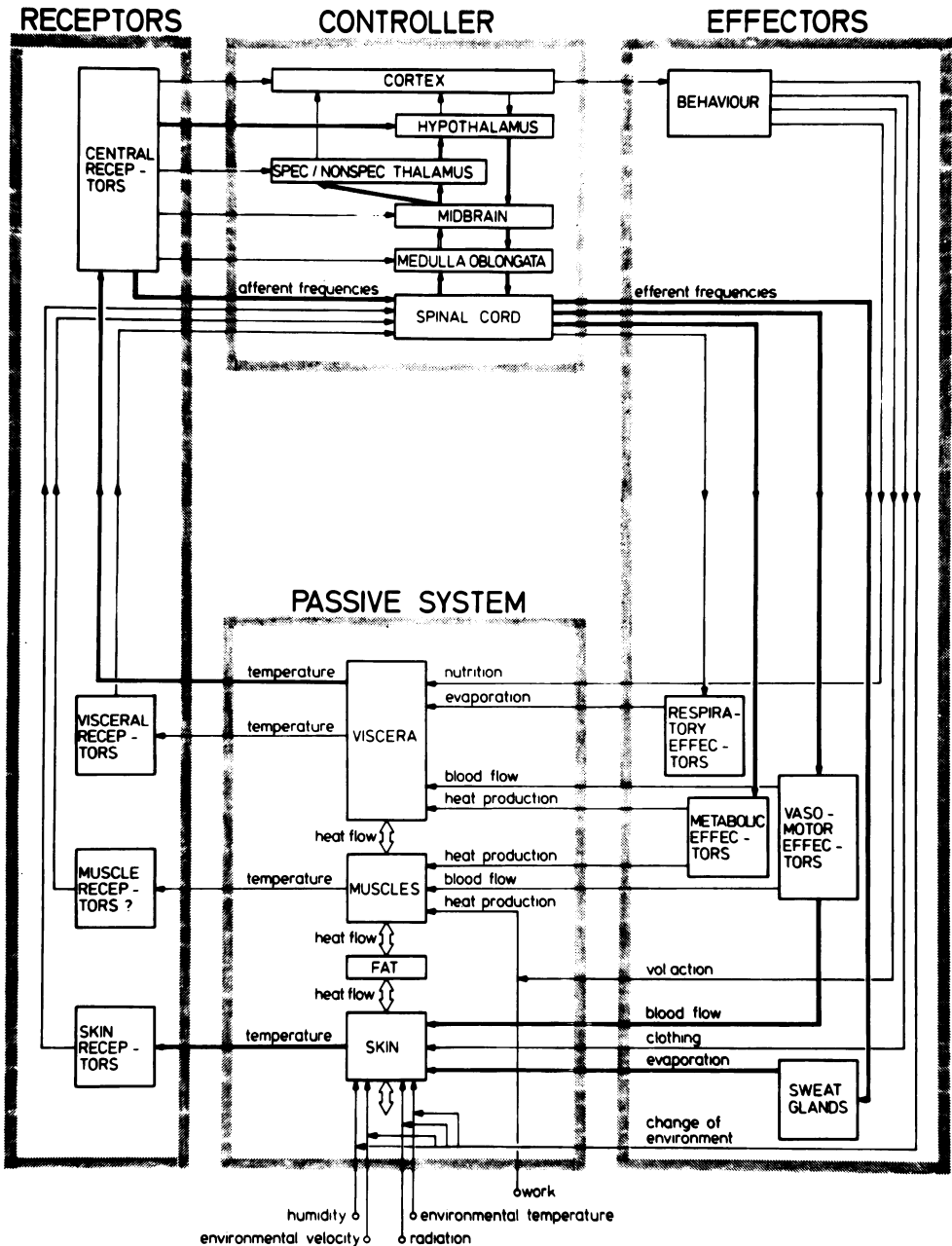3. How does the regulator get the error signal?

RECEPTORS **CONTROLLER** **EFFECTORS**

CORTEX

BEHAVIOUR

CENTRAL RECEP-TORS

HYPOTHALAMUS

SPEC / NONSPEC THALAMUS

MIDBRAIN

MEDULLA OBLONGATA

afferent frequencies

efferent frequencies

SPINAL CORD

PASSIVE SYSTEM

temperature nutrition

evaporation

VISCERAL RECEP-TORS

temperature VISCERA

RESPIRA-TORY EFFEC-TORS

blood flow

heat production

METABOLIC EFFEC-TORS

VASO-MOTOR EFFEC-TORS

heat flow

heat production

MUSCLE RECEP-TORS ?

temperature MUSCLES

blood flow

heat production

heat flow

FAT

vol action

heat flow

blood flow

SKIN RECEP-TORS

temperature SKIN

clothing

evaporation

SWEAT GLANDS

change of environment

work

humidity

environmental temperature

environmental velocity

radiation

FIG. 1. Black-box scheme of the thermoregulatory system.

4. How is negative feedback achieved?

5. What is the nature of temperature change due to fever or circadian rhythm?

In attempting to answer the central question, "What is regulated"? five different control concepts have been under discussion:

1. Control of a locally defined variable

2. Control on the basis of spatial integration of temperatures

TABLE 1
Levels of Modelling the Thermoregulatory System

Type of Model	Realization	Examples of Purpose/Applications/Results
a One-loop	Direct; analog comp.; dig. simul. lang.	Steady state (qual.): Werner, 1975, 1981
b Core-shell	Analog comp.; dig. simul. lang.; direct	Steady state including work: Bleichert et al., 1972; Dynamics of fever (qual.): Werner and Graener, 1983
c Multi-element, lumped parameters	Analog comp.; dig. simul. lang.; digital comp.; (direct)	Dynamics (survey): Stolwijk and Hardy, 1966; Werner, 1974
d One-element, radial dependency	Digital comp.	Dynamics of fever: Graener and Werner, 1985; Dependency on locally distributed parameters: Buse and Werner, 1985
e Multi-element, distributed parameters, radial dependency	Direct; digital comp.	Dynamics of radial profiles: Werner, 1974, 1975, 1981
f Three-dimensional	Vector comp.	Temperature and effector fields; true control strategy; first approaches: Buse and Werner, 1984 ff.

3. Control on the basis of spatial integration of temperature plus local effector actuation
4. Control of local temperature profiles
5. Heat flow regulation

For many years, concept 1 was the accepted control concept for thermoregulation: hypothalamic temperature was considered to be the controlled variable which determined the amount of effector activity. This concept has been replaced by the somewhat vague concept of control on the basis of spatial integration, which essentially means that temperatures measured all over the body contribute, according to definite weighting factors, to the measurement of the overall thermal state, which primarily determines all effector activities. It has turned out that this very reasonable concept must be complemented by the possibility of evaluating local requirements; that is, outstanding thermal load of parts of the body yields intensification of the local effector activity involved (concept 3). This concept seems the one that best fulfills experimentally verified requirements. A great amount of experimental work has still to be done, however, in order to give a more detailed and a really quantitative description of the control strategy, especially of the coupling matrices between local measurement, its central processing, and local effector activity.

Although human thermoregulation turns out to be essentially a distributed parameter control loop, we must deny the existence of the most sophisticated distributed parameter control concept, one which enables regulation of whole local profiles

(concept 4). Even if the skin areas are not taken into account, an analysis of local temperature distribution under various environmental conditions shows that enormous changes in temperature profiles take place, so that a true regulation of temperature profiles is out of the question.

The concept of heat flow regulation (concept 5) of Houdas and co-workers [5] is a very natural principle. According to this concept, however, temperatures are not really regulated; they are rather an open-loop result of a balance of heat production and heat loss (Fig 2d).

The common and necessary element of all control concepts presented is the requirement that steady states are reached on the basis of a balance of two or more variables. Expressed mathematically, a minus sign or sign inversion in the control loop is required.

This may be achieved in the following ways: *(a)* balance of passive and active (of controlled and controlling) processes in the closed control loop [6,7], *(b)* balance of reference and actual value of the controlled variable (basic technical control concept), *(c)* balance of rise and fall feedback elements [8,9], and *(d)* balance of heat production and heat loss (no temperature control) [5].

Figure 2 translates the verbal formulation into block diagrams. They clearly show how a minus sign is obtained in the control loop; in Fig. 2a, there is no explicit subtraction (only sign inversion at an arbitrary point of the closed control loop); in Fig. 2b, there is a reference signal minus a feedback signal; in Fig. 2c, there are positive minus negative feedback signals; in Fig. 2d, there is heat production minus heat loss. Concept *(a)* is based on true proportional temperature control with steady state resulting from a balance of passive and active processes in the control loop. The concept of balance of controlling and controlled processes seems to me the simplest process allowing feedback control. There is only one indispensable requirement for it; namely, the existence of a closed loop with sign inversion at an arbitrary point. It seems that there has never been any doubt that this requirement is fulfilled. But obviously it has not been recognized that this is, indeed, already sufficient for proportional regulation, because additional and special assumptions have been made in other concepts, which can hardly be verified experimentally: namely, temperature-independent reference signals (concept *b*), balance of positive and negative neuronal inputs (concept *c*), and heat flow measurements (concept *d*). So concepts *(b)* and *(c)* are not real contradictions to concept *(a);* rather, they may be characterized as unproven special forms of the more general concept *(a)*. Omitting the second controller inputs, concepts *(b)* and *(c)* are transformed into concept *(a)*, recognizing, according to the considerations above, that negative feedback is already achieved separately for each loop of model *(c)* and not only when both loops cooperate, as implied by the authors. The heat flow regulation concept may also be converted into concept *(a)*, as heat flow measurement can easily be realized by processing differences of temperatures. If we substitute for "transducers" the familiar thermosensitive elements, temperatures are again within the closed control loop and may again be considered the controlled variable.

To summarize, an attempt has been made to give short answers to the five questions by using the simplest type of models:

1. The regulated variable is certainly not a locally defined single temperature; it is probably not heat flow and not mean body temperature, but it seems to be a flexible and adaptable integrative temperature signal according to the so far unknown distributed parameter control strategy.
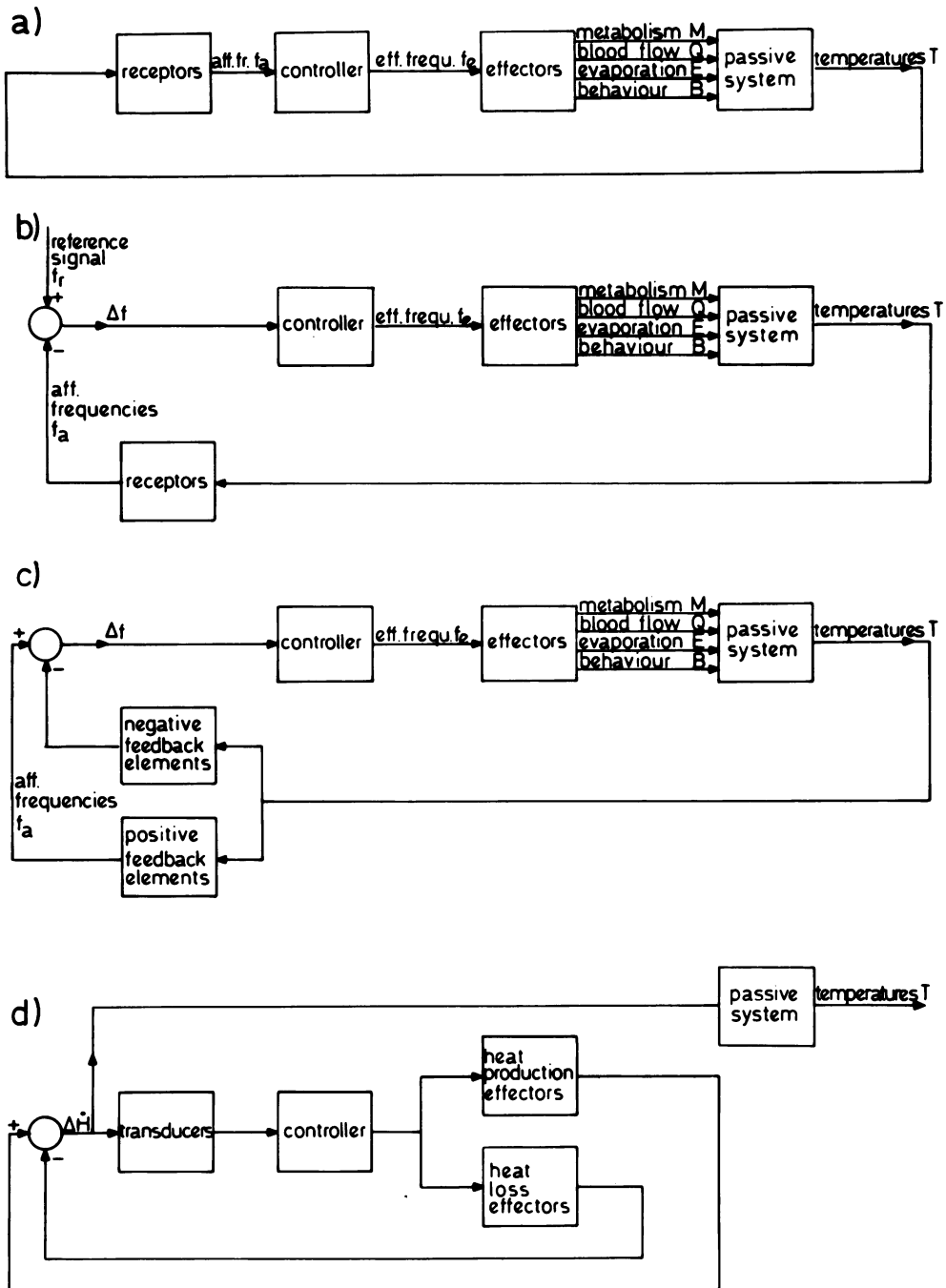
FIG. 2. Block diagrams of control concepts of thermoregulation.   (a) Control without reference and explicit signal subtraction; sign inversion at an arbitrary point of the closed control loop [Werner].   **(b)** Control with reference signal (technical control concept).   (c). Control with positive and negative feedback [Mitchell and co-workers; Bligh].   **(d)** Heat flow regulation [Houdas and co-workers].

2. The regulator does not need any explicit reference, either in the form of a neuronal signal or in the form of the indifferent zone.

3. There is no need for an explicit error signal (subtraction of signals) as input to the controller.

4. Negative feedback is simply achieved by an odd number of negative input/output relations of the subsystems in the closed loop.

5. Fever and circadian rhythm change central neuronal activity and by this means affect the controller characteristics. This result may be achieved by change of gain and/or change of threshold.

MULTI-ELEMENT MODELS: LUMPED PARAMETERS

Using core-shell models (Table 1, level *b*) the passive system is divided into two separate compartments. Well known is the analog computer model of Bleichert and co-workers [10], which delivers a good quantitative survey on steady-state properties of core and skin temperatures and of the effector mechanisms. It particularly demonstrates the influence of work load on temperature regulation. In 1966, Stolwijk and Hardy [1] presented a multi-element model for analog computer treatment. The body is divided into cylinders, which are composed of concentric layers with constant parameters and variables. The single cylinders are coupled to one another by circulation, which is regarded in a highly simplified manner. From a common heart-lung pool the arterial blood is pumped into the body; it spreads via the capillaries within the whole body, is reassembled by the venous vessels, and flows back to the pool. These types of model enabled a first survey of the dynamic behavior of thermoregulation.

ONE-ELEMENT MODEL: DISTRIBUTED PARAMETERS, RADIAL DEPENDENCY

Level *d* of model complexity (Table 1) goes back to the one-element structure but takes into account the radial dependency of temperature. Through this, it was possible to explain the dynamics of fever in the rabbit [12] as well as to determine the dependency of radial temperature profiles on locally distributed parameters [13]. The first problem is outlined in more detail here. In conjunction with an experimental program, a one-cylinder model was developed for the rabbit (Fig. 3). If we neglect temperature variations along and around the axis of the cylinder, temperature distribution within the body is described by Fourier's differential equation:

$$\rho c \frac{\partial T}{\partial t} = \lambda \left\{ \frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} \right\} + q \qquad [1]$$

with T = temperature
 t = time
 ρ = density
 c = specific heat
 λ = heat conductivity of tissue
 r = radius of the body
 q = heat sources/sinks within the body.

As the boundary condition of this equation, we get at the body surface:

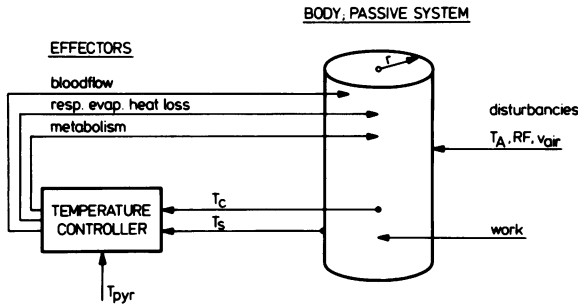$$\lambda \, dT/dn|_{r_{max}} = h(T - T_a) \qquad [2]$$

FIG. 3. One-cylinder model of the rabbit's thermal system.

with h = effective heat transfer coefficient of skin
     n = outward-drawn normal at skin surface
     T_a = air temperature.

Because thermoregulatory blood flow changes take place almost exclusively in the ear of the rabbit, the total vasomotor action can be simplified by describing ear blood flow via a heat-exchanger differential equation. Warm central blood at core temperature loses, when passing the ear tissue, the following amount of heat:

$$HLB = c_B \, \rho_B \, B(T_c - T_e) \qquad [3]$$

with c_B = specific heat of the blood
        ρ_B = specific density of the blood
         B = ear blood flow
        T_e = mean ear temperature
       HLB = heat loss of blood when passing ear tissue.

On the other hand, this heat gain in the ear is transferred to the environment via ear skin and also used to change the temperature of the ear tissue. Thus we get:

$$m_e \, c_e \, dT_e/dt - h_e \, A_e \, (T_e - T_a) = HLB \qquad [4]$$

with A_e = surface area of ear skin
     m_e = mass of ear tissue
     c_e = specific heat of ear tissue
     h_e = effective heat transfer coefficient of ear skin.

As HLB is removed from the body, we can now replace q in equation 1:

$$q = (M - REHL - HLB)/V \qquad [5]$$

with V = body volume
        M = metabolic heat production
     $REHL$ = respiratory evaporative heat loss.

The model was tested with different types of controller equations, seeking for the best conformity with the results of experiments on *nonfebrile* animals in steady-state conditions as well as during temperature transients. Under these conditions, the

following controller descriptions showed the best results with respect to the least-squares criterion [14]:

$$T_c = T(r = 0) \quad \text{and} \quad T_s = T(r = r_{max})$$

$$M = k_{mc}(K - T_c) - k_{ms}T_s + M_{rest}$$

$$k_{mc} = 5.0 \text{ W/kg°C}; \quad k_{ms} = 0.3 \text{ W/kg°C}; \quad K = 45.4°C \qquad [6a]$$

$$M_{rest} < M < 12 \text{ W/kg}$$

The constant K does not mean that we assume an explicit subtraction in the CNS (see above!) and, clearly, K, although expressed in °C here, is not a reference temperature.

$$B = k_{bc}(T_c - K) + k_{bs}T_s$$

$$k_{bc} = 1{,}600 \text{ ml/min°C}; k_{bs} = 300 \text{ ml/min°C} \qquad [6b]$$

$$0.5 \text{ ml/min} < B < 60 \text{ ml/min}$$

$$REHL = k_{rc}(T_c - K) + k_{rs}T_s$$

$$k_{rc} = 1.5 \text{ W/kg°C}; \quad k_{rs} = 0.09 \text{ W/kg°C} \qquad [6c]$$

$$0.25 \text{ W/kg} < REHL < 2 \text{ W/kg}$$

The time course of pyrogen influence is imitated by a non-stationary shift, also expressed analogously in °C, and by solving equation 6a for $SHIFT(t)$, in order to get a quantitative dynamic description for the pyrogenic effect on the controller.

$$SHIFT(t) = -(K - T_c) + (k_{ms}/k_{mc})T_a - (M_{rest} - M)/k_{mc} \qquad [7]$$

Because all values on the right side are known from experiments or from equation 6a, and assuming the values do not change during fever, we can calculate the time course of $SHIFT$ for any experiment at low ambient temperature. Additionally, we assume that $SHIFT(t)$ describes the pyrogen influence of any other experiment with the same pyrogen dose.

This hypothesis is confirmed by the results of the simulation, demonstrated by some examples in Fig. 4, A–D (dashed lines), in which the calculated core temperatures and the active effectors are compared with experimental results. The model is able to predict the characteristics of the experimental time courses at *any* ambient temperature by making use of only one time course of *SHIFT*.

From the model, together with the experiments, it is concluded:

1. Dynamic properties must be taken into account when describing the febrile process.

2. The febrile temperature increase essentially results from a non-stationary shift of the controller characteristics. Changes of thermal sensitivity as reported from neurophysiological experiments seem to be of little or no importance in the febrile process.

3. The proposed controller is a proportional controller operating in an additive manner [14,15], whereas experiments with local hypothalamic cooling suggest a multiplicative model [16,17]. Jessen [18], too, found an almost linear controller structure for control in the goat, when he varied not only the hypothalamic temperature but also the whole central body temperature over a wide range. The contrast, additive and multiplicative characteristics, might result from the Q_{10}-behavior of
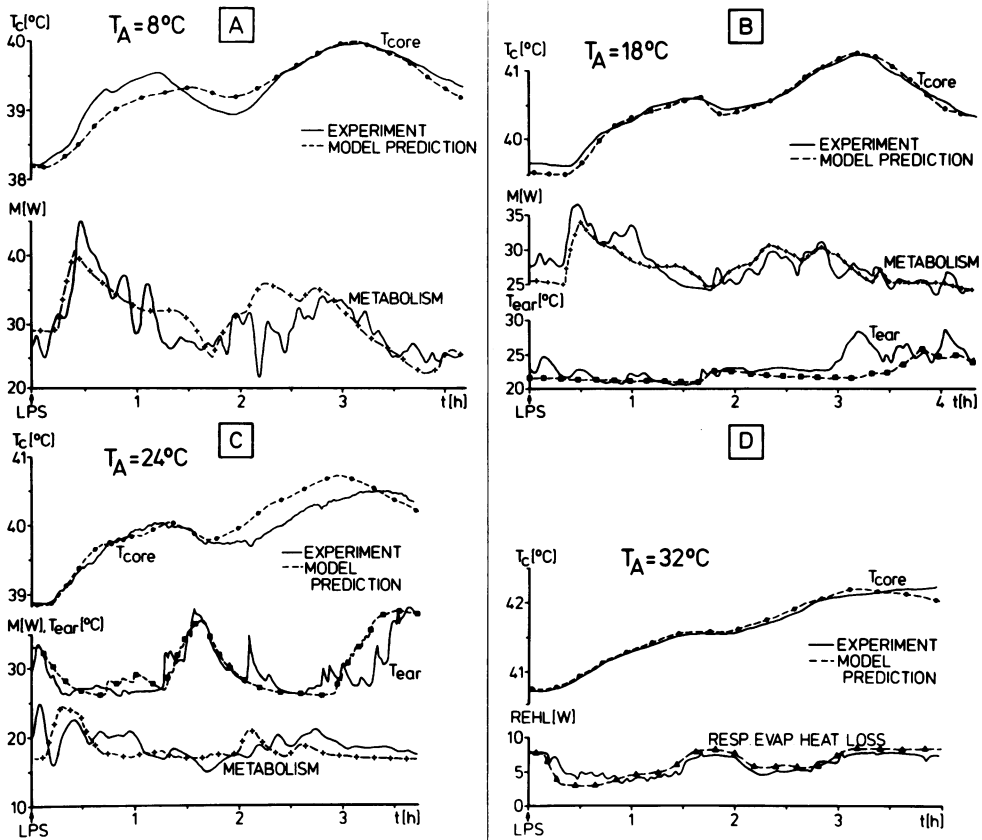
FIG. 4. Comparison of experimental (*solid line*) with calculated (*dashed line*) core temperatures and effectors at different ambient temperatures T_a (A, B, C, D). In experiments, 0.1 μg/kg LPS was injected at $t = 0$.

hypothalamic integrating structures which evokes non-linear responses [19], when hypothalamic temperature is varied over a wide range. However, the question of additive or multiplicative operation is of minor importance within the normal operating range of control.

4. The pyrogen may be imagined to act on the controller via a non-stationary shift, which is biphasic too, but increases more steeply than core temperature does [12].

5. The pyrogen influence on each of the three subcontrollers, metabolism, ear blood flow, and *REHL*, is apparently related to the *same* time course of *SHIFT*. Thus, we may exclude the possibility that pyrogen acts on the efferent pathways. The experimental differences observed at different ambient temperatures are not caused by a different pyrogen action on the subcontrollers, but by the different effector capacities and gains of the subcontrollers.

6. It should be possible to explain the time course of *SHIFT* by a pharmacokinetic process which takes into account the dynamics of the different pyrogenic substances (LPS, EP, PGEs, . . .). The question of whether one or two or more agents cause LPS fever [20,21] could perhaps be answered by such an analysis.

AIR - TEMPERATURE   30 °C ⌐ 48 °C
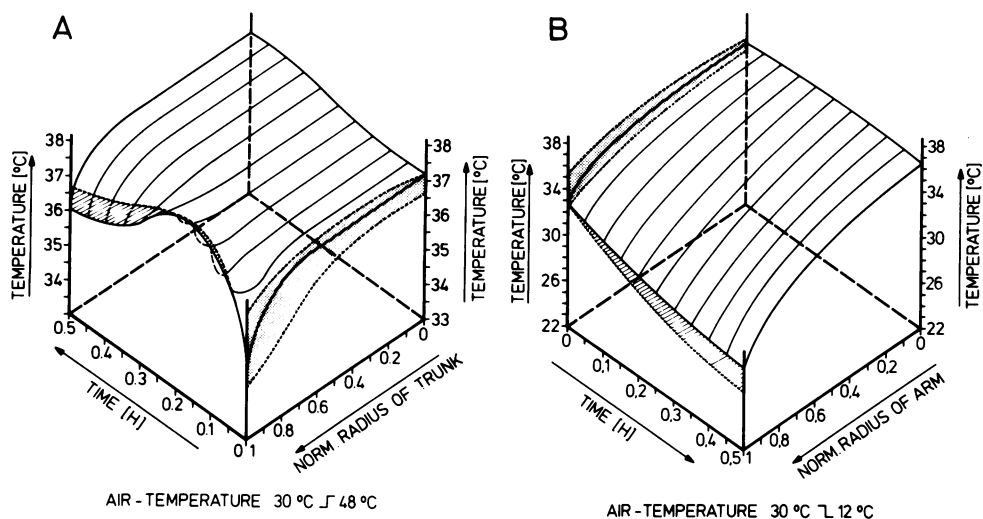
AIR - TEMPERATURE   30 °C ⌐ 12 °C

FIG. 5. Dynamics of radial temperature profiles in man obtained by mathematical simulation. *Dashed lines:* Experimental values.   (A) Trunk, heat load.   (B) Arm, cold load.

MULTI-ELEMENT MODELS: DISTRIBUTED PARAMETERS, RADIAL AND THREE-DIMENSIONAL DEPENDENCIES

If we return to a multi-element structure (Table 1, level *e*), but take explicitly into account radial dependencies, we get a set of partial differential equations, which may be solved by numerical methods or after linearization by direct methods [22,23,24,25]. Using this model, for the first time dynamics of radial temperature profiles within the body were computed.

As an example, Fig. 5 (A and B) shows the dynamics of the radial profiles after a stepwise change of environmental temperature for a naked man at rest (30 percent relative humidity, 0.1 ms^{-1} air velocity). The step response to heat load (Fig. 5A) is characterized by an overshoot in certain areas. In the direct centers (radial coordinate $r = 0$) we observe small overshoots only in the hands and the feet. The increase of temperature in the new steady state is greater in the peripheral parts of the body, so that, on the whole, we obtain the effect of a local temperature equalization. In the head and the trunk (Fig. 5A), we recognize a strong oscillation, as relatively low stationary skin temperatures are finally reached. In these parts there is a strong radial gradient of temperature only in the peripheral areas, while temperature at $r = 0$ increases gradually. A comparison between the final temperatures of the different parts of the body at the same radius yields only very small differences: at $r = 0$ about 0.5°C and at $r = 1$ about 2°C. The maximum value at temperature difference in the final profiles is smaller than 2.5°C.

The dotted and shaded areas show the range of experimental results as far as these can be obtained in man. The dotted areas reproduce radial profiles measured by Reader and Whyte [26]. The results were taken from different parts of the trunk (Fig. 5A) and arm (Fig. 5B) and reveal that, beside the radial coordinate, which is the only one taken into account here, the axial coordinate in particular and in part also the angular coordinate around the axes are of importance. The upper dashed boundary

lines refer to the upper parts of trunk and arm, the lower lines to the more distal parts. Remaining aware that apart from this there are differences between individuals and also certain variations in a single subject from experiment to experiment, the simulation results seem to fit reality quite well. This statement holds also for the dynamics, where the dashed lines show our own experimental results [27], indicating that the final decrease of peripheral temperatures after heat load (Fig. 5A) seems to be slower than extrapolated by the simulation, whereas after cold load it seems to be a bit faster (Fig. 5B).

In order to get the complete temperature and effector fields and to analyze the true distributed parameter control strategy, it is necessary that the following requirements be fulfilled by a model:

1. All variables (e.g., temperature, heat flow, and so on) must be regarded as functions of time and of three-dimensional local coordinates within the human body.

2. All parameters (e.g., density, conductivity index, and the like) must be considered as locally distributed parameters.

3. Geometry and anatomy of the body must be adequately represented. This has been achieved by photogrammatic analysis of anatomic models [28].

4. All heat transport mechanisms, conduction, convection, and radiation, must be separately taken into account.

5. All locally dependent effector mechanisms, heat production by metabolism, vasomotor control, and heat loss via sweat production and respiration, must be considered.

6. All disturbances to the control process, environmental temperature, humidity, air velocity, and eventually radiation and work load must be incorporated.

7. The local definition of the really controlled variable (i.e., the temperature to be held as constant as possible) has to be adaptable to future results. Control of a single discrete temperature is as improbable as control of complete temperature profiles.

There is sufficient experimental evidence that an adequate system treatment of human temperature regulation must take into account the non-linear distributed parameter properties of this biological control loop. The results can be verified experimentally only to a certain extent, because it is impossible to measure at all important sites within the human body. However, it is one of the purposes of a mathematical model to extrapolate states which cannot be performed experimentally and to give approximations for those variables which cannot be measured by the experimenter.

Furthermore, it must be realized that the exact simulation requires the use of a comprehensive data bank, which we have built up [28,13]. As to the necessary computing time, we had realized in the preceding years that the power of a big vector computer is needed to solve the problem. As a CYBER 205 has been installed at Ruhr University since 1982, we hope to present our final results within the next year. First results are reported in [13].

CONCLUSIONS

1. Mathematical modelling on the system-theoretical level is a useful tool in thermoregulation.

2. Model structure and complexity depend on the purpose of the model. Current

issues in thermal physiology primarily require models with spatially distributed parameters and variables.

     3. The limited significance of modelling of thermoregulation is primarily due to lack of basic experimental data and to the complexity of the real system.

     4. Mathematical simulation has to be used in conjunction with an experimental program. As an isolated technique, it is as insufficient as any physiological technique.

     5. Mathematical equations have to be formulated using the underlying physical laws. Parameters should be associated with realistic values and dimensions. Pure black-box models, analogies, or curve fittings will be of minor or no importance in the future.

     6. Relevant fields of future modelling are: *(a)* Interaction with other control loops, such as circulation, respiration, metabolism, osmoregulation; and *(b)* higher levels of thermoregulatory control, such as adaptive mechanisms.

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