DYNAMICS OF THERMOREGULATION IN NEWBORN BABIES

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Summary

This paper presents a simple mathematical model of the thermoregulation system of newborn babies. The parameters of this model are estimated from in vivo measurements with a specially constructed research incubator. The results of fourteen experiments are presented. They can be used in the design and evaluation of commercial incubators.

Introduction

A newborn baby needs his mother to feed him and to care for him. Special care may be necessary if he is born preterm because some vital organs or processes may not have developed sufficiently. For many centuries thermal isolation of the baby has been a major form of protection. Since about 100 years incubators are being used for this purpose. An incubator is a small ($0.5 \times 0.5 \times 1$ m^3) cabinet, with walls which are transparent to light, to easily observe the baby. Inside the incubator an artificial climate is maintained which may differ in temperature, humidity, oxygen concentration etc. from the normal environment. So thermal isolation has been replaced by climate control, and although this does not imply any change in the final aims of medical care, it has some important practical consequences. The mere possibility to control creates a need for clear criteria to evaluate the quality of the control. Since Budin in 1900, many other investigators have tackled this problem. As a result guidelines have been formulated for the practical use of incubators: temperature settings for a particular baby, given its weight, age and gestational age, see for instance Hey [1]. However, criteria for the statical and dynamical accuracy of the control have not yet been formulated. These are important for the evaluation of existing incubators, and for the design and construction of new ones. The criteria must take into account medical objectives, as well as biological characteristics, like for instance the properties of the thermoregulation system of newborn babies. While several authors

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describe the static relation between heat production of the baby and the temperature of the incubator, very little is known about the dynamics of thermoregulation in newborn babies. In this paper a simple model is formulated and results are presented from measurements to validate it.

Physiology

The temperature of the human body is approximately constant, despite variations in temperature, humidity and air velocity of the environment, and despite a varying level of activity. This homeostasis is the result of a thermoregulatory control system which balances heat production and heat loss. Hensel [2] has given an extensive review of the physiology of this system. It can be divided into three subsystems: a sensory, a processing and an effector system. The sensory system consists of a large number of temperature-sensitive neurons, some acting as cold-, others as warm receptors. They are mainly located in the brain (hypothalamus), the spinal cord, the skin and the upper part of the respiratory tract. Although various types exist, in general, the firing rate of a thermoreceptor responds both to a constant temperature level (with respect to a certain threshold) and to a temperature variation with time (proportional plus rate sensitivity). Skin receptors are unevenly distributed over the body-surface, the facial area having a relatively high density. Very little is known about the way in which the central nervous system processes the various signals it receives from the thermoreceptors. A vital role is played by the hypothalamus, but the interaction of central and peripheral signals is not clear yet. Some measurements support the assumption that both signals are added, whereas from other investigations it appears that they are multiplied.

The effector system encompasses shivering and non-shivering thermogenesis, and vasomotor and sudomotor control of heat loss. Shivering is controlled by the spinal and supra-spinal motor system, whereas the other effector mechanisms are mediated by the sympathetic nervous system. Cooling of the spinal cord increases the excitability of motor neurons, and thereby causes shivering. Non-shivering thermogenesis is a very efficient way of producing heat through the oxidation of brown adipose tissues. Normally it occurs in newborn babies as a substitute for shivering, and adults can use it as an additive source of heat production, but babies born small for date usually lack the normal stores of brown fat.

Regional differences exist in the vasomotor control of peripheral blood flow, at least three different zones can be distinguished: extremities (hands, feet, ears, lips, nose), trunk plus proximal limbs, and the head. In the first zone

vasoconstriction is the result of increased sympathetic tone and vasodilation of decreased tone. In the second zone, however, vasodilation is the result of an active process, acting via the sweat glands. The third zone shows a negligible constrictive response to cold but a dilation coupled to sweat secretion when heated. Passive heating of the body produces a bloodflow pattern different from heating by active work, the main increase in bloodflow occurring in zone 1 in the first case, and in zones 2 and 3 in the second situation. Passive heating also causes sweating, first in the lower extremities if the whole body is heated. A rising temperature due to active work causes sweating in zones 2 and 3.

Local heating or cooling of a particular part of the body results in a local response next to the central one. Local control systems are coupled to the central system in a hierarchical structure. Fever raises the conceptual "central set point" and also causes the sensitivity of central warm receptors to decrease, and of cold receptors to increase. Effects on peripheral receptors are unknown. The digestion of a meal causes the production of a certain amount of heat, this phenomenon is called specific dynamic action. The amount of heat seems to be related to the protein content of the food, and it is added to the cold induced heat production. During sleep a lowering of the body temperature occurs after a vasodilation of the extremities, which can be described as caused by a displacement of the setpoint. Newborn babies have a limited capacity for sweating and heat production, which depends upon gestational age and degree of maturation. Considerable variations occur in the ability to stabilize the body temperature, some babies may temporarily loose their thermoregulatory capacity.

Description of the model

A model describing the thermoregulatory system consists of two parts: the body and the controller. Based on anatomy and physiology, several detailed models of the body have been described in the literature. Stolwijk [3] for instance has developed a model of the "standard man", comprised of six different zones, each of which is divided into four layers. The temperatures of the various areas, with respect to a certain setpoint, are taken as inputs to the controller, which is assumed to have a static, piecewise linear relation between input and output. One output variable (like heat production) may be the combined result of several input variables, and a major issue has been whether nature either adds or multiplies different inputs.

A model of the complexity like the one proposed by Stolwijk presents problems of measurement and validation that go beyond our experimental possibilities. We, therefore, grossly simplify the model, and approximate the

body as a core compartment, surrounded by a skin compartment, with thermal capacities C_1 and C_2, respectively. The heat balance of the whole body can be written as:

$$C_1 \frac{dT_c}{dt} + C_2 \frac{dT_{sk}}{dt} = M - W - C_3(T_{sk} - T_a) \tag{1}$$

T_c, T_{sk} and T_a denote the temperature of core, skin and incubator respectively, M denotes metabolic heat production, W evaporative heat loss, and C_3 equals the combined transfer coefficient for radiation and convection, multiplied by the skin surface area. Note that no assumption has been made whether M is produced in the core compartment only or in the skin compartment as well. As a consequence, nothing can be said about the heat transfer from core to skin through conduction and bloodflow.

Various relations have been formulated for the controller. First, inspired by Stolwijk and Hardy [4] a piecewise linear form, with either additive or multiplicative interaction of T_c and T_{sk}:
additive

$$f(T_c, T_k) = g_0 + g_1(T_c - T_{c0}) + g_2(T_{sk} - T_{sk0}); \tag{2}$$

multiplicative

$$f(T_c, T_{sk}) = g_0 + g_1(T_c - T_{c0})(T_{sk} - T_{sk0}). \tag{3}$$

Here T_{c0} and T_{sk0} are setpoints, while g_1 and g_2 represent a static gain. If (2) and (3) are applied to M the values of $(T_c - T_{c0})$ and $(T_{sk} - T_{sk0})$ should be set to zero if they are positive, if applied to W they should be set to zero if they are negative. A serious drawback of (2) and (3) with respect to the estimation of the parameters g_0, g_1, g_2, T_{c0} and T_{sk0} appears to be the nonlinearity in some of the parameters. Therefore, other relations, linear in the parameters, have been used in the model:

$$f(T_c, T_{sk}) = g_0 + g_1 \tilde{T}_c + g_2 \tilde{T}_{sk} + g_3 \tilde{T}_c^2 + g_4 \tilde{T}_{sk}^2 + g_5 \tilde{T}_c \tilde{T}_{sk} \tag{4}$$

Here the tilde $\sim$ means that the mean core or skin temperature has been subtracted from the originally measured value.

Relations (2), (3) and (4) represent a nonlinear feedback controller. Practical experience has shown that linearization is allowed very often:

$$\begin{aligned} \tilde{M} &= g_1 \tilde{T}_c + g_2 \tilde{T}_{sk}; \\ \tilde{W} &= h_1 \tilde{T}_c + h_2 \tilde{T}_{sk}. \end{aligned} \tag{5}$$

Now, to integrate the two parts of the model, that is to combine Eq. (1) and Eq. (5) it is necessary to formulate a relation between T_c and T_{sk}. Since the heat

transfer from the core to the skin compartment cannot be measured, this relation must be based on assumptions concerning the core to skin bloodflow and heat production which cannot be verified. To circumvent this problem we formulate an overall model in state space format:

$$\dot{\tilde{T}}_c = a_{11}\tilde{T}_c + a_{12}\tilde{T}_{sk};$$
$$\dot{\tilde{T}}_{sk} = a_{21}\tilde{T}_c + a_{22}\tilde{T}_{sk} + b\tilde{T}_a. \tag{6}$$

Instrumentation and parameter estimation

The measurements have been done with a closed-circuit calorimeter, see Fig. 1. Water circulates between the double glass walls of the incubator and the temperature of the water is controlled by the thermostat TCl to an accuracy of 0.1 °C. The temperature can be varied at a rate of 40 °C/hr. The air coming from

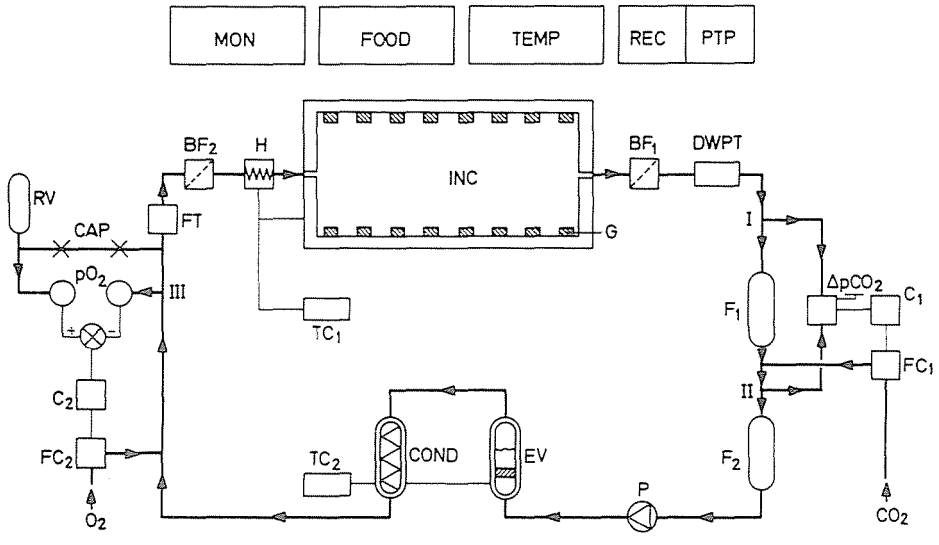

Fig. 1. Schematic diagram of the calorimeter

INC = incubator; G = gradient layer; BF = bacterial filter; DWPT = dewpoint hygrometer; F_1, F_2 = CO_2 absorbers; ΔpCO_{22} = CO_2 partial pressure difference sensor; C = electronical controller; FC_1 = flow controller CO_2; P = main circuit pump; EV = bubble chamber; COND = condensor; TC_2 = temperature controller of condensor and bubble chamber; PO_2 = O_2 partial pressure sensors; RV = reference vessel; CAP = capillary; FT = main circuit flow sensor; H = heat exchanger; TC_1 = temperature controller of incubator and heat exchanger; MON = heart beat and apnoea monitor; FOOD = feeding system; TEMP = thermometer system; REC = recorder; PTP = paper tape puncher

the incubator flows through a bacterial filter and then through a dewpoint hygrometer to measure the evaporative water loss from the baby. Subsequently the carbondioxide production is measured using an infrared analyser and then the CO_2 is absorbed. The air is pumped through a bubble chamber and a condensor to define its dewpoint at 18 °C. The oxygen consumption is measured with two polarographic sensors and a reference vessel. The consumed oxygen is replaced from a bottle through controlled injection. A flow sensor measures the circulating air flow, which is filtered again and preheated before entering into the incubator, where the baby is laying on a specially woven mattress in order to eliminate heat conduction. A gradient layer G consisting of many connected thermocouples can be used to measure radiative and convective heat loss if the temperature of the wall is constant. This measured variable was not used in the experiments reported here. The core temperature of the baby was measured with a small thermocouple in the esophagus and the skin temperature at six sites using one electronic thermometer and a multiplexer. The mean skin temperature was calculated with weighting factors of 0.05, 0.15, 0.25, 0.25, 0.25 and 0.05 for hands, upper arm, head, abdomen, thigh and foot, respectively. All variables were low-pass filtered to avoid aliasing effects, sampled with a period of 16 sec and stored on papertape with 10 bit resolution. Heat production is calculated from O_2 consumption and CO_2 production with an accuracy of ± 0.1 Watt, evaporative heat loss from air flow and dewpoints with an accuracy of ± 0.2 Watt, while the temperatures of the baby are measured with 0.1 C absolute and 0.01 C differential accuracy.

The calorimeter was built in the central research workshop of the Erasmus University in Rotterdam. All measurements have been done in the neonatal unit of the Sophia Childrens Hospital (head: Prof. dr. H. K. A. Visser). Informed consent of both parents was obtained beforehand, healthy newborn babies were selected from the neonatal units' population. The babies were naked except for a small plastic covered napkin. The calorimeter is located in a part of the neonatal unit, where the room temperature was controlled to differ less than 2—3 °C from the incubator temperature in order to assure the thermal balance of the baby during the transfer to the calorimeter. The baby was monitored continuously by an experienced observer, its activity was rated on a 5 points scale and stored on papertape. The data were processed only if the baby remained quiet, otherwise the experiment was not taken into consideration.

The test signal consisted of a sum of sine waves, this was motivated by the application of Van den Bos' identification method [5], which is based on the Fourier transformation of the differential equations. The test signal was

introduced at the setpoint of the incubator thermostat TC1. An a priori choice had to be made of the fundamental period of the test signal, based on an a priori estimate of C_1 and C_2. A length of either 1 or 2 hours was chosen, and the peak-to-peak value was 6 to 10 °C. After some experiments had to be stopped untimely because the baby became restless, the disadvantages of the identification method in this case became clear: an integer number of fundamental periods has to be processed, so if a baby starts crying shortly before another complete period is finished, almost an entire fundamental period is lost. Therefore, time domain estimation with the generalized least squares method was applied in further experiments.

Results

Fourteen experiments have been done, with seven babies. Their body weight was between 0.8 and 2.3 kg, their age between 1 and 70 days and their gestational age between 27 and 34 weeks. The experiments lasted from 3 to 6

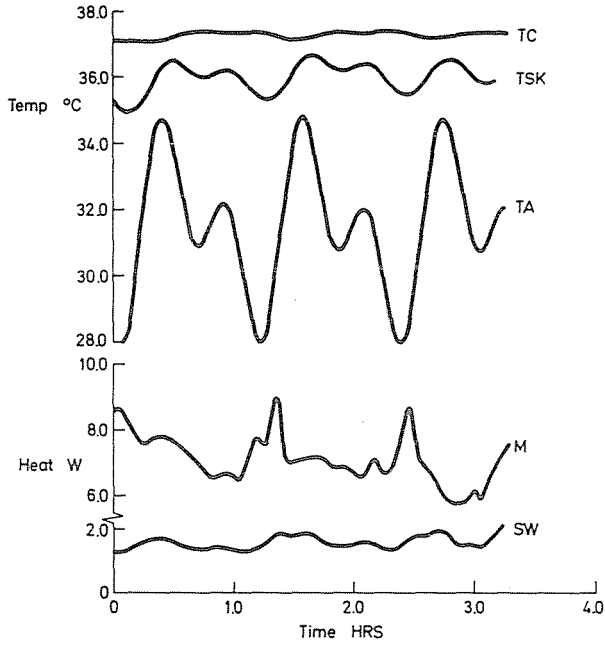

Fig. 2. Sample tracing of a typical experiment (no. 2)
TC = core temperature; TSK = mean skin temperature; TA = incubator temperature; M = metabolic heat production; SW = evaporative heat loss

Table 1

Parameters (mean and standard deviation) of the heat balance equation with two compartments

Exp.	Baby ident	Body weight (kg)	Surface area m^2	C_1 kJ/K	C_2 kJ/K	C_4 W/K
1	OFFE	2.3	0.17	5.1 ± 0.4	1.6 ± 0.1	1.10 ± 0.02
2	OFFE	2.3	0.17	4.6 ± 0.5	2.1 ± 0.1	1.16 ± 0.02
3	OOST	1.5	0.13	2.0 ± 0.5	1.6 ± 0.1	0.84 ± 0.02
4	OOST	1.5	0.13	2.1 ± 0.3	1.9 ± 0.1	0.84 ± 0.01
5	SCHO	1.3	0.12	3.3 ± 0.2	1.5 ± 0.1	0.91 ± 0.01
6	SCHO	1.5	0.13	4.4 ± 0.3	1.1 ± 0.1	0.97 ± 0.01
7	RUIT	2.0	0.16	6.0 ± 0.5	1.2 ± 0.2	1.11 ± 0.03
8	HOOG	0.8	0.09	3.2 ± 0.4	0.6 ± 0.1	0.83 ± 0.03
9	BREV	1.8	0.15	6.0 ± 0.4	1.3 ± 0.2	1.02 ± 0.02
10	BREV	1.8	0.15	4.8 ± 0.3	1.6 ± 0.1	1.00 ± 0.01
11	HOOG	0.9	0.09	2.8 ± 0.3	1.4 ± 0.2	0.70 ± 0.01
12	HOOG	1.0	0.1	2.6 ± 0.2	1.2 ± 0.1	0.73 ± 0.01
13	VERM	0.9	0.09	3.3 ± 0.3	0.9 ± 0.1	0.89 ± 0.01
14	VERM	1.4	0.12	4.3 ± 0.3	1.5 ± 0.1	0.91 ± 0.02

hours, and meanwhile the babies were fed continuously through a nasogastric tube according to their normal clinical treatment. Figure 2 shows a sample tracing of a typical experiment. The estimated thermal capacities C_1 and C_2 of the core and the skin compartment are shown in table 1 along with the estimates of C_3.

The increase of C_1 and C_2 with body weight can be expected on a priori grounds, and illustrated in Fig. 3. Fitting a straight line yields the relations:

$$C_1 = (2.6 \pm 0.2) Wt$$
$$C_2 = (0.6 \pm 0.3) + (0.5 \pm 0.2) Wt \tag{7}$$

We can compute an estimate of the specific heat of human tissue by linear regression of $C_1 + C_2$ against body weight. Fitting a straight line constrained through the origin we find

$$C_1 + C_2 = (3.5 \pm 0.2) Wt\,. \tag{8}$$

This corresponds well to the value of the specific heat used by Stolwijk and Hardy [4]: 3.48 kJ/kgK. Convective and radiative heat transfer is proportional to the surface area SA of the body, which can be estimated from the body weight by Meeh's formula: $SA = 0.1\ Wt^{2/3}$, where SA is in m^2 and Wt in kg. Dividing C_3 by SA we find the combined heat transfer coefficient for convection and radiation to be about 7 W/m^2K, which corresponds well to a

priori estimates of 8 W/m^2K based on measurements with an electrically heated copper manikin.

So we conclude that this part of the model appears to be an acceptable description of the baby. Computational problems emerged due to the non-linearity in the parameters of the assumed piecewise linear structure of the controller. Quite often, the iteration process did not converge at all, or it converged outside a physiologically meaningful region (estimated setpoints higher than the highest temperature that was measured). Therefore the piecewise linear structure was abandoned, in favour of structures linear in the parameters like (4) and (5). In general, the quadratic relation (4) could be found, without, however, the multiplicative term $a_5 \cdot \tilde{T}_c \cdot \tilde{T}_{sk}$. The quadratic relation could be simplified to a linear one with only minor decrease in the goodness of

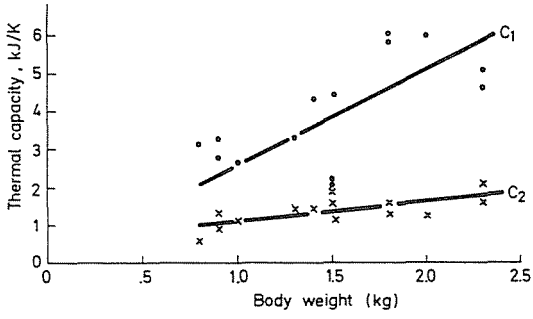

Fig. 3. Estimated thermal capacities of core (C_1) and skin (C_2) compartment as a function of the bodyweight

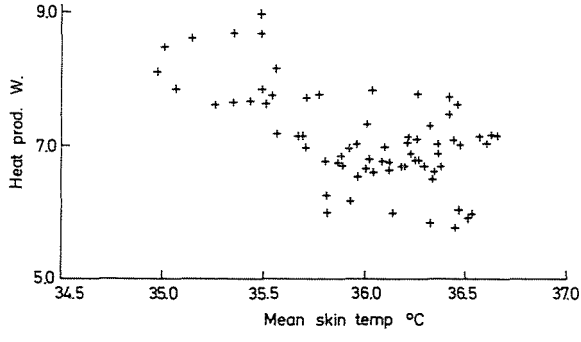

Fig. 4. Metabolic heat production as a function of skin temperature. Each cross represents an average over 160 sec. Experiment no. 2

fit. This is not surprising if one looks at the data. Figure 4 illustrates how the metabolic heat production varies with skin temperature. The interpretation of this picture is not seriously hampered by not considering the core temperature; the variation of heat production is only partly the result of thermoregulation, and the autonomous variation of biological activity has to be modelled as noise. Table 2 shows the estimated coefficients of a linear model of the controller described by Eq. (5). Finally table 3 lists the parameters of the state space description of the integrated thermoregulation system. In fact the parameters of a discrete time state space model have been estimated with the generalized least squares method, (Eykhoff [6]) and these were converted to the continuous time domain.

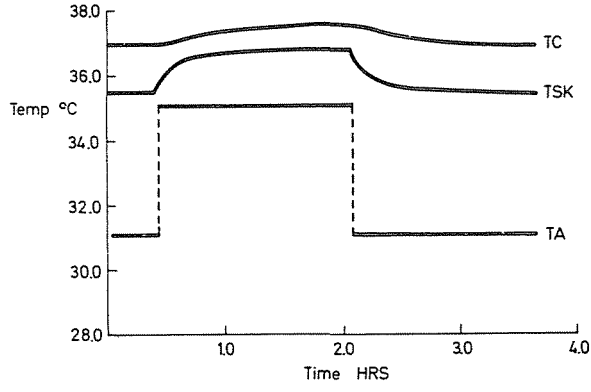

Fig. 5. Simulated response of core and skin temperature TC and Tsk to variations of ambient temperature TA

The parameters of this model appear to be independent of the body weight of the baby. From Table 3 the values for an "average baby" can be computed:

$$a_{11} = -1.0 \quad a_{12} = 0.4 \quad a_{21} = 2.2 \quad a_{22} = -3.9 \quad b = 0.8$$

These five parameters describe the response of the core and skin temperature of an "average baby" to variations of the ambient temperature. As an example this is illustrated in Fig. 5 for an upward followed by a downward step of the incubator's temperature. The eigenvalues of the state matrix are -4.2 and -0.7, with corresponding vectors $(-0.13, 1)$ and $(1, 0.7)$, respectively.

Table 2

Parameters of the linearized model of the controller (all coefficients in W/K, mean plus minus standard deviation)

Exp.	Metabolic heat production		Sweating	
	g_1	g_2	h_1	h_2
1	–	-0.16 ± 0.05	–	$1.0\ \pm0.2$
2	–	$-1.0\ \pm0.1$	-1.3 ± 0.2	$0.2\ \pm0.05$
3	1.8 ± 0.8	$-1.5\ \pm0.2$	-0.9 ± 0.3	$0.3\ \pm0.1$
4	1.7 ± 0.6	$-1.4\ \pm0.2$	-0.5 ± 0.2	$0.3\ \pm0.1$
5	0.5 ± 0.3	$-0.5\ \pm0.1$	-0.6 ± 0.2	–
6	1.5 ± 0.2	$-0.8\ \pm0.1$	0.8 ± 0.2	$-0.2\ \pm0.1$
7	1.8 ± 0.2	$-0.8\ \pm0.1$	1.6 ± 0.3	$-0.2\ \pm0.1$
8	0.7 ± 0.1	$-0.5\ \pm0.05$	-0.2 ± 0.1	0.05 ± 0.02
9	0.4 ± 0.1	$-0.2\ \pm0.1$	-0.6 ± 0.1	$0.5\ \pm0.05$
10	–	$-0.3\ \pm0.1$	-0.6 ± 0.1	$0.3\ \pm0.05$
11	–	$-0.8\ \pm0.1$	-1.6 ± 0.2	$0.7\ \pm0.1$
12	-0.6 ± 0.1	–	-1.0 ± 0.1	$0.6\ \pm0.05$
13	1.2 ± 0.2	$-1.0\ \pm0.2$	0.4 ± 0.1	$-0.2\ \pm0.1$
14	1.4 ± 0.1	$-1.2\ \pm0.1$	-0.2 ± 0.1	–

Table 3

Parameters of the state space model of the integrated thermoregulation system, all expressed in $(10^3\ \text{sec})^{-1}$

Exp.	a_{11}	a_{12}	a_{21}	a_{22}	b
1	−1.0	0.3	3.9	−5.3	1.0
2	−0.5	0.2	0.6	−2.5	0.7
3	−1.6	0.5	2.5	−2.8	0.5
4	−1.1	0.3	1.1	−2.2	0.4
5	−1.2	0.5	1.9	−3.0	0.6
6	−0.9	0.4	0.9	−2.0	0.5
7	−0.9	0.3	1.2	−2.4	0.6
8	−0.7	0.2	4.1	−6.6	1.6
9	−0.9	0.6	3.4	−5.7	0.8
10	−0.8	0.4	1.7	−2.9	0.6
11	−1.8	0.8	1.9	−3.2	0.4
12	−1.9	0.9	2.3	−3.6	0.6
13	−0.4	0.3	3.7	−8.9	2.2
14	−1.0	0.3	2.2	−3.3	0.6

Conclusions

The considerable scatter in the estimated parameters results from biological variations in time and between individual babies, as well as from the fact that the model presented here is a grossly simplified description of the biological reality. Nevertheless, some consistent features can be seen:

— The total thermal capacity of the body estimated from the sum of C_1 and C_2 corresponds to the value that could be expected a priori.
— The ratio of the thermal capacities of core and skin is roughly 3 : 1.
— The linearized controller of the thermoregulation system seems to be driven by the difference $(\tilde{T}_c - \tilde{T}_{sk})$ of core- and skintemperature deviations, the gain ranging between 0.5 and 2 W/K for heat production while the sweating response is about half of this.

The dynamics of core and skin temperature variations can be characterized by time constants of about 1000 and 250 sec. Using the model developed here, it is possible to predict the response of a newborn baby to variations of the temperature inside the incubator. So the reduction of room temperature variations by the thermostat of the incubator can be evaluated, which may lead to an improved and simplified design.

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