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ORIGINAL ARTICLE

Hidetoshi Wakamatsu · Lu Gaohua

Automatic optimal-adaptive air-cooling system for brain hypothermia treatment

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Abstract A new automatic air-cooling system is proposed using a cooling incubator to replace the manual water-cooling blanket which has traditionally been used to lower brain tissue temperature (BTT) in brain hypothermia treatment (BHT). This study concerns its feasibility through a simulation. First, a *biothermal model* is proposed for the adult incubating system based on the geometric structure and parameters of patients. Its dynamics were carefully examined by two simulation experiments testing its step response and feedback control. Then a model reference adaptive control algorithm was introduced for the automatic regulation of BTT, where the newly developed *adult incubating biothermal model*, represented by a state equation, was replaced for the hypothermic patient with a cooling blanket, thus introducing a first-order lag system given as its basic *characteristic model*. Finally, the proposed cooling incubator was controlled by the adaptive control mechanism, which gives a follow-up of BTT to a given reference temperature course, even if a possible environmental change in the therapeutic cooling system exists, including the individual differences of patients and any chronic conditional change. The automatic cooling incubating system based on the air-cooling method was confirmed to be superior to the water-cooling one. Thus, this work supports the possible development of an air-cooling adult incubating system for the automatic regulation of BTT in an intensive care unit (ICU) application.

Key words Brain tissue temperature (BTT) · Biothermal model · Automatic control

H. Wakamatsu (✉) · L. Gaohua
Biophysical System Engineering, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Tel. +81-3-5803-5366; Fax +81-3-5803-0162
e-mail: wakamats.mtec@tmd.ac.jp

Introduction

In brain hypothermia treatment (BHT), the brain tissue temperature (BTT) is kept in a state of moderate hypothermia to protect severely brain-injured patients from secondary brain damage.[1,2] This procedure has been introduced into the clinical treatment of brain-injured adult patients by using water-cooling blankets, where expert nursing staff manually regulate the cooling-water temperature in order to realize the appropriate cooling process prescribed by clinicians. Hypothermia using a water-cooling blanket is a powerful and noninvasive method. However, clinicians are concerned about the following points: (*a*) the cooling effect of the water blanket depends largely on the staff's blanketing technique; (*b*) there may be inadequate peripheral circulation and its resultant decubitus, partially due to the imperfect contact of heavy blankets with the patient's skin; (*c*) the sensitivity of the BTT to the thermal conditions in the intensive care unit (ICU) due to its open surroundings.

As far as water-cooling blankets are concerned, these problems are unavoidable. Thus, clinicians always have to be engaged in an integrated operation of life-support based on the temperature management of BHT in an ICU, together with anesthesia and heart-lung management with possible mechanical respiration.

On the other hand, the nursing staff play an important role in BHT, particularly in checking the BTT of a patient and in regulating the temperature of circulating water. This means that they are continuously forced to measure and control the temperature deviation within to 0.1°C in BTT every 20 min.[1,3] However, this manual control of the water temperature imposes a heavy mental and physical burden on the nurses, which may result in less accurate temperature regulation. Furthermore, there might be no accurate way to realize an optimal cooling process, even if the problematic conditions described above were solved. Thus, the automatic control of BTT is necessary not only for the clinical effectiveness of BHT, but also to release nurses from their laborious work.

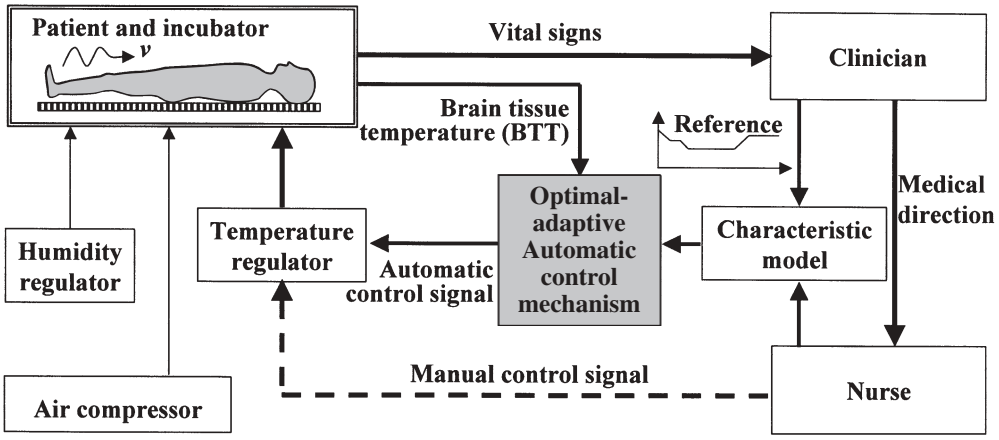

Fig. 1. Concept of the automatic air-cooling incubating system. Clinicians prescribe a characteristic model for the automatic control mechanism. The manual control, loop indicated by a *broken line*, is essential for the safety of the patient in medical treatment. The characteristic model represents the basic characteristics of the patient and the water-cooling blanket used in the intensive care unit (ICU)

This study considered an automatic air-cooling incubating system, including the feasibility of replacing the conventional water blanket system for a new BTT regulation system. First, an *adult incubating biothermal model* was synthesized and its dynamics were examined in two simulation experiments based on its step response and feedback control. Then, an adaptive control mechanism was applied to the automatic regulation of BTT using a *biothermal model*. Finally, the proposed automatic incubating system was tested to find out whether it could realize the controlled temperature course prescribed by clinicians. The present study supports the development of an adult incubator for actual clinical hypothermia applications.

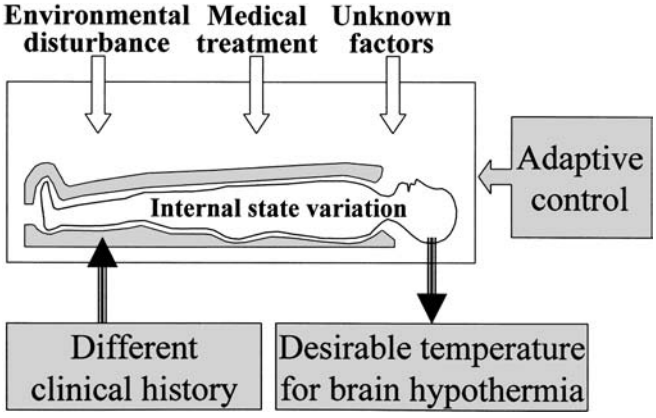

Fig. 2. Principle of the adaptive control of hypothermia

Necessity of an adaptive technique for the control of hypothermia

The conceptual structure of BHT in a clinic is described by the block diagram given in Fig. 1. An incubator is provided for an adult patient lying on a bed on a net or grid support, thus making less mechanical contact with the air-cooling apparatus so that the cooling air circulates in good contact with patient's whole body-surface. The incubator itself consists of a 2-layer transparent thermal insulator which may be necessary in the clinical application.

Therefore, it is necessary to investigate not only how to analyze the biothermal processes in this therapeutic air cooling system consisting of patient and incubator, but also how to synthesize the control system of the present biomedical thermal system.

Thermal regulation is governed by a control law generated by a controller, although it will work according to the physiological control laws generated by the hypothalamus. In general, a thermal system depends on the total volume of body tissue and the blood flow rate, which are different in every individual and are difficult to estimate exactly. In addition, numerous unknown factors exist which affect its dynamics.

Thus, the necessary information for the synthesis of control systems cannot be obtained in advance because the exact physiological function, including some unknown factors, cannot be known for any patient. Therefore, theoretical difficulties can always exist in the modeling and synthesis of a control system by the conventional method because of imperfect recognition. Nevertheless, such problems must be solved by some appropriate method if organic functions are really to be controlled clinically.

To date, no appropriate methods have been proposed which could cope with such difficulties except for fuzzy and adaptive control methods.[4–7] In fact, insufficient recognition of controlled systems, including even the complicated characteristics of experimental equipment, does not have to matter as long as an adaptive control method is applied, which is significant in the present situation without explicit parameter estimates.[8–10] An important concept with the characteristics of an adaptive system is illustrated in Fig. 2. This overcomes internal and external environmental changes as well as the differences between individuals.

The hypothermic patient as a thermal system

The air temperature is automatically regulated to realize the desired cooling process based on the reference cooling

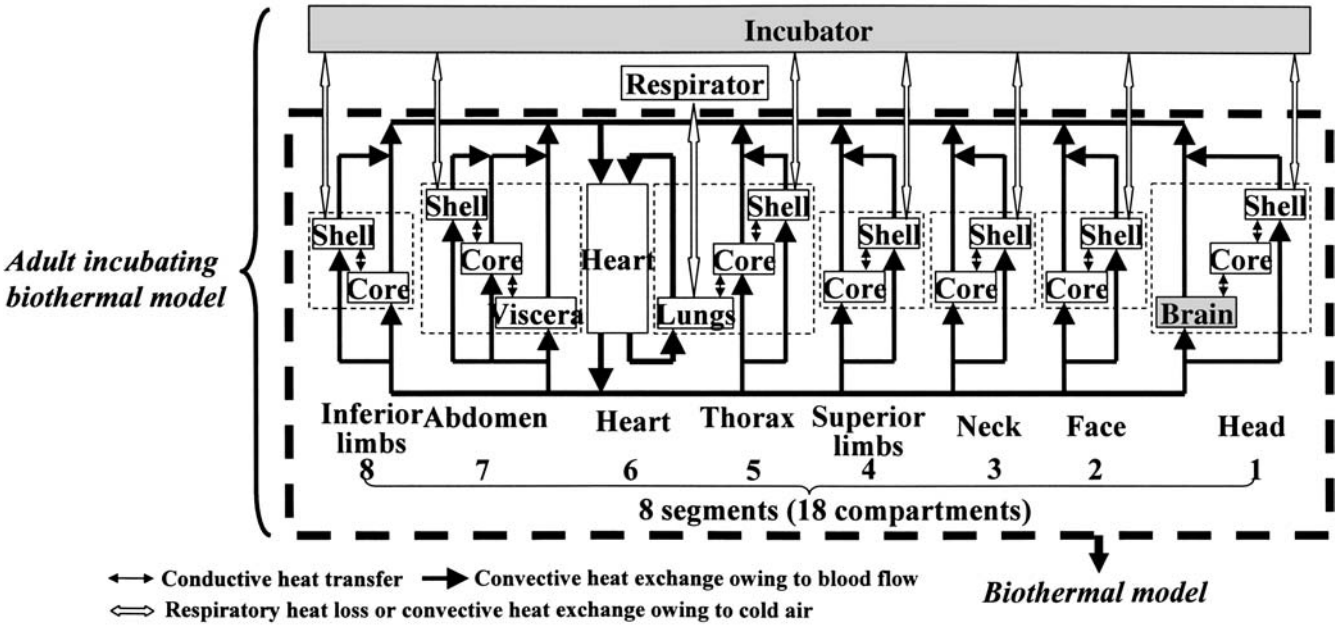

Fig. 3. Adult incubating biothermal model consisting of a biothermal model and an incubator. The biothermal model is represented as an 8-segment, 18-compartment model, with an environmental incubating compartment in which the temperature can be controlled. *Respirator* represents respiratory control in brain hypothermia treatment (BHT). The Blood flow into the lung compartment is equal to the total blood flow into the other compartments. Compartments in the same segment are brought together into the same *dotted-line square*. *The double-headed hollow arrow* represents a direct heat exchange between neighboring compartments. *Solid arrows* represent convective heat exchange due to blood perfusion

process for the BTT given by the clinicians. The air circulation is manipulated efficiently so that its humidity is kept constant to prevent undesirable heat and mass transfer from the skin.

A basic theoretical study is needed before the clinical application of an air-cooling incubating system, although the actual control system will be different because of the various kinds of ambiguity described in the previous section. In order to describe automatic BTT control, a mathematical model of a therapeutic cooling incubating system is described thermophysically, taking into account its geometric structure and parameters. For this purpose, the *adult incubating biothermal model*, consisting of a *biothermal model* and an incubator, is synthesized as shown in Fig. 3 from the viewpoint of thermal system control engineering. Thus, the relation between the BTT T_{brain} and the temperature of the air T_{air} is represented by a state equation with initial conditions according to the anesthetics applied in BHT.

Geometric structure of the biothermal model of a patient

As shown in Fig. 3, the patient's body is described by an 8-segment, 18-compartment model: head (segment number 1), face (2), neck (3), superior limbs (4), thorax (5), heart (6), abdomen (7), and inferior limbs (8). All the segments except for the head and the heart are modeled as two concentric cylinders. The inner part is a core compartment corresponding to bone and muscle, and the outer one is a shell compartment corresponding to skin and subcutis. The head is assumed to consist of a concentric core with shell hemispheres of the cranium and scalp, respectively. The heart is regarded simply as a conceptual compartment representing the physical characteristics without any specified geometric reality. In particular, the brain, lungs, and abdominal viscera are assumed to be in the central location of the head, thorax, and abdomen segments, respectively.

Surrounding air at temperature T_{air} circulates in contact with each shell compartment of the patient, which causes a convective heat transfer through its surface to the inner area. Blood circulates from the heart to the compartments, excluding the core of the head segment because of poor blood perfusion in its corresponding cranium. Owing to the blood circulation, the patient's brain is thermodynamically affected by the condition of the surrounding air. Physical and physiological characteristics are given by combined constants for the compartments in the *adult incubating biothermal model.*

According to the literature relating to the present study, the pertinent parameters of adult patients are summarized in Table 1. Most of the data are revised from the distributed model proposed by Fiala et al.[11] in order to satisfy the present combination model. The heat conductive coefficients of the two neighboring compartments are determined using the method of Lou and Yang,[12] and the air-cooling coefficient is calculated based on the formula proposed by Shitzer and Eberhart.[13]

Table 1. Parameters for the adult incubating biothermal model

Segments	Compartments	L (mm)	R (mm)	λ (W/m/°C)	ρ (kg/m^3)	c (J/kg/°C)	w (×10^{-3} l/s)	q (W/m^3)	$T(0)$[a] (°C)
Head[b]	Brain		86	0.49	1080	3850	10.13	13400	37.10
	Core		101	1.16	1500	1591	0	0	35.47
	Shell		104	0.34	986	3180	3.18	237	35.21
Face	Core	98	68	0.42	1258	2351	0.20	250	36.57
	Shell	98	78	0.34	900	2652	2.36	123	35.53
Neck	Core	84	55	0.42	1118	3464	0.47	601	36.41
	Shell	84	57	0.34	974	3112	3.60	221	34.66
Superior limbs	Core	1609	34	0.42	1139	3278	0.43	549	35.36
	Shell	1609	42	0.34	907	2703	0.27	134	33.36
Thorax	Lungs	306	77	0.28	550	3718	14.32[c]	600[d]	36.65
	Core	306	123	0.42	1143	3247	0.42	539	36.48
	Shell	306	129	0.34	944	2932	0.63	181	33.91
Heart						3550		7.19Watt[e]	36.65
Abdomen	Viscera	552	79	0.53	1000	3697	4.31	4100	37.00
	Core	552	109	0.42	1123	3421	0.46	589	36.29
	Shell	552	126	0.34	874	2472	0.15	89	33.51
Inferior limbs	Core	169	48	0.42	1142	3252	0.42	540	35.92
	Shell	169	55	0.34	918	2770	0.30	147	33.47

L, length of segment (mm); R, outer radius of compartment (mm); λ, thermal conductance (W/m/°C); ρ, multiplication of density (kg/m^3); c, heat capacitance (J/kg/°C); w, blood perfusion rate (m^3 blood/s/m^3 tissue); q, metabolic heat production (W/m^3)
[a] Initial temperature calculated by Eq. 8 with $v = 3.0$ m/s, $\alpha = 1.78$, $T_{air}(0) = 30$°C
[b] Head in a hemispherical form
[c] Blood perfusion rate of lungs, on the assumption that the pulmonary circulation is equivalent to the systemic circulation in value.
[d] Heat loss from the lungs owing to respiratory regulation
[e] Total metabolic heat production in heart
Sources: refs. 11, 14–16

Representation of the model by a state equation

In any compartment, thermal energy is produced as metabolic heat, Q, most of which is washed out as convective heat, W, by the blood circulation. The rest of Q is balanced by the conductive heat, C, transferred from one compartment to the next, and regenerative heat, E, which is stored in the compartment.

Taken together, the thermal energy balance in each compartment is described by Eq. 1.

$$E = Q + W + C \tag{1}$$

where

$$E = \rho c V \frac{dT}{dt} \tag{2}$$

$$Q = qV \tag{3}$$

$$W = \rho_{blood} c_{blood} w V \left(T_{blood} - T\right) \tag{4}$$

$$C = kS\left(T_{adjacent} - T\right) \tag{5}$$

are calculated by using k, conductive heat transfer rate between the adjacent compartments (W/m^2/°C) calculated according to the formula proposed by Lou and Yang[12]; S, outer surface area (m^2); V, volume of the compartment (m^3); t, time (s); T, temperature (°C); T_{blood}, blood temperature (°C); $\rho_{blood} = 1069$ (kg/m^3); $c_{blood} = 3650$ J/kg/°C and $T_{adjacent}$, temperature of adjacent compartment (°C), on reference to the summarized parameters in Table 1.

For the conductive heat C in Eq. 1, there exist two terms for all the shell and core compartments in the head, thorax, and abdomen segments, because any compartment has two neighbors, as shown in Fig. 3. In the heart compartment, W and C do not exist. For the core of a head segment, Q and W are ignored because of the poor blood perfusion in the cranium.

Equation 1 indicates the 18 first-order linear differential equations corresponding to the dynamic temperatures in each of the 18 compartments. The air temperature T_{air} and BTT T_{brain} are regarded as the input and output, respectively, where the representative temperatures of the compartments are the elements of the state variable vector.

The 18 differential equations are summarized as the following state equations:

$$\frac{d\boldsymbol{T}}{dt} = \boldsymbol{A}\boldsymbol{T} + \boldsymbol{b}T_{air} + \boldsymbol{Q} \tag{6}$$

$$T_{brain} = \boldsymbol{c}\boldsymbol{T} \tag{7}$$

where $\boldsymbol{A}$, $\boldsymbol{b}$, and $\boldsymbol{c}$ are an 18×18 system matrix, an 18×1 control matrix, and a 1×18 output vector, respectively. All the elements of vector $\boldsymbol{c}$ are 0 except for its first element, which is 1, since the 18-dimensional state vector $\boldsymbol{T}$ consists of the BTT and the temperatures of the 17 compartments. The column vector $\boldsymbol{Q}$ (18×1) represents the temperature given by the energy source of the biothermal system. As given in the appendix, all elements in $\boldsymbol{A}$, $\boldsymbol{b}$, and $\boldsymbol{Q}$ are determined using the parameters summarized in Table 1.

Equations 6 and 7 interpret the *adult incubating biothermal model* as the stable dynamics, because its coefficient matrix $\boldsymbol{A}$ is a compartmental matrix.[17]

Initial temperature conditions

Heat transfer between the body and the surrounding air is more critical in BHT than in *neutral circumstances*. In general, in healthy adults in a cold environment the metabolic rate increases in order to keep thermal equilibrium.[18] Therefore, it is appropriate to adjust the patient's state in the present study, so that the initial conditions of the state variables correspond to their steady-state temperature.

The initial temperature conditions in each compartment in the *adult incubating biothermal model* are given by Eq. 8, under the condition of nondeviation of temperature in the steady state, i.e., all the derivatives $d\boldsymbol{T}$ of the 18 state variables in Eq. 6 are zero in equilibrium.

$$\boldsymbol{T}(0) = -\boldsymbol{A}^{-1}\left(\boldsymbol{b}T_{\text{air}} + \alpha\boldsymbol{Q}\right) \tag{8}$$

where $\boldsymbol{T}(0)$ represents the initial state variable vector and α is an auxiliary coefficient to compensate for the *enhanced heat loss* in BHT. The coefficient α is implicitly influenced by the air flow speed, and is determined from the initial temperature condition of $\boldsymbol{T}(0)$, the air temperature T_{air}, and the coefficient matrix $\boldsymbol{A}$, $\boldsymbol{b}$. Hereby, α is chosen as 1.78 if the air temperature is 30°C with 3 m/s flow speed. However, this has no effect on the dynamics of the adult incubating biothermal system because its dynamics are determined by matrices $\boldsymbol{A}$, $\boldsymbol{b}$, and $\boldsymbol{c}$.

Validation of the biothermal model

In order to characterize the dynamics of the proposed *adult incubating biothermal model*, two simulation experiments were carried out. One was the step response of BTT, and the other was the realization of a given reference BHT process by proportional integral and derivative (PID) regulation.

Step-response of brain tissue temperature

The air temperature T_{air} is set to decrease by 5°C from the *neutral temperature* of 30°C at the start of the simulation experiment with an air flow of 3 m/s. The BTT of the *biothermal model* is obtained as an exponential declination with respect to the step-like change in environmental temperature T_{air}. Accordingly, the *adult incubating biothermal model* is regarded as a first-order lag system, as shown in Fig. 4. It is thus appropriate to represent the characteristics of adult patients by the transfer function given by Eq. 9.

$$G(s) = \frac{T_{\text{brain}}(s)}{T_{\text{air}}(s)} = e^{-sL}\frac{K}{1+\tau s} \tag{9}$$

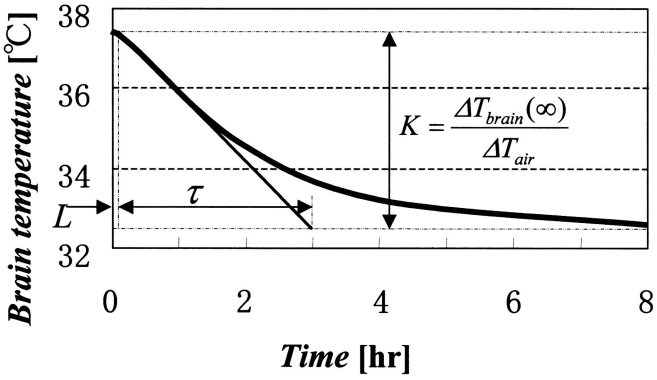

Fig. 4. Brain tissue temperature (BTT) response of the adult incubating biothermal model to the step change in air temperature T_{air}. Parameters L and τ are calculated from the tangential line with the largest gradient of BTT response.

where s is the Laplace operator, and K, L, and τ are the gain, dead time, and time constant, respectively.

Figure 4 shows that the time constant $\tau = 2.7$ h is larger than the dead time $L = 2.3$ min. This means that BTT does not have such a quick response with respect to the change of air temperature. Stone et al.[19] reported a dead time of 1 or 2 min in BTT in their work. The simulation result agrees well with the observed phenomena, since a dead time $L =$ 2 min was determined in the *adult incubating biothermal model*. On the other hand, the model has a time constant of about 3 h, which is consistent with the suggestion given by Iberall and Schindler.[18] A time constant of 2 h was adopted for the core temperature from an electrical circuit model reported by MacDonald and Wyndham.[20] Nevertheless, the body temperature of a patient in an ICU is reported to respond to water temperature regulation in about 4 h when a water blanket is used to warm up the patient from hypothermia to normothermia.[1] The gain K determined from the simulation experiment is almost the same as the one estimated from a clinical examination.[1]

PID regulation of brain tissue temperature

A simulation experiment was carried out to show how BTT follows a reference temperature process when the air temperature T_{air} is regulated by a PID regulator.

The deviation $e = T_{\text{reference}} - T_{\text{brain}}$ between the output T_{brain} of the *adult incubating biothermal model* and the reference temperature $T_{\text{reference}}$ is fed to the PID regulator to determine the controlling input of air temperature T_{air} as follows:

$$T_{\text{air}}(t) = K_P\left(e + \frac{1}{T_I}\int e\,dt + T_D\frac{de}{dt}\right) \tag{10}$$

where the parameters for the PID regulator are determined using the ultimate sensitivity method $K_P = 228$, $T_I = 195$ s, $T_D = 48.75$ s, and the air flow speed is set at 3.0 m/s as previously described.

Figure 5 shows the experimental results inclusive of the time-course of the reference BTT in 32 h. The clinical temperature management is divided into the following four

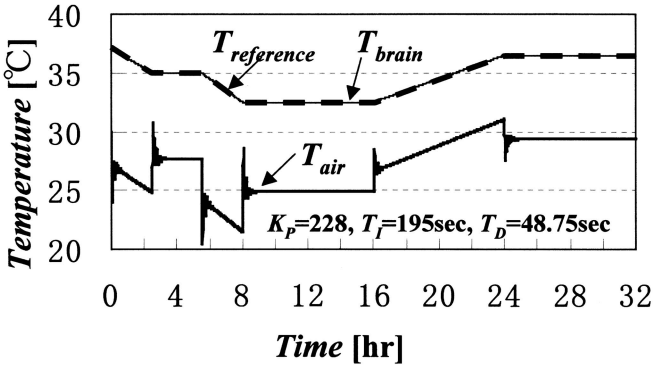

Fig. 5. Proportional integral and derivative (PID) feedback control of BTT using an adult incubating biothermal model. A small violent change occurs in the input T_{air} due to the differential operation of the PID regulator. The temperature course of the brain obtained from the simulation experiment agrees with the reference temperature

phases: (I) a cooling phase of BTT from the basal temperature to moderate hypothermia, during which the accustomed period at 35°C is designated; (II) a stable hypothermia phase, in which BTT is kept at about 32.5°C, i.e., target hypothermia; (III) a warming phase, in which BTT is increased from hypothermia to normothermia at about 36.5°C; (IV) a rehabilitation phase, or post-hypothermia, where BTT is kept at about 36.5°C.

The BTT obtained from PID regulation agrees with the reference temperature, and they overlap along the broken line illustrated in Fig. 5. The input T_{air} produces the appropriate cooling, which is consistent with the clinical information about water-cooling BTT given by Hayashi.[1] There are three important points to note in this simulation experiment. In phase I, the air temperature is controlled to follow the desired process. In phase II, it is desirable to control the air temperature at about 25°C to maintain the hypothermic brain at about 32.5°C. In phase IV, it is suggested that the air temperature should not exceed 30°C to realize a normothermic brain at about 36.5°C.

The airflow speed of 3 m/s is aerodynamically called a light breeze, which is known to be harmless and is normally available to patients in an ICU. The step-response of the incubator to this air flow has been shown to have almost the same cooling effect as a water-cooling blanket, as suggested by Plattner et al.[21] From various simulation experiments, the air-cooling method has been shown to be as suitable as water-cooling in actual clinical therapy.

Automatic control of brain tissue temperature

Characteristic model and therapeutic system

Wakamatsu and Lu Gaohua[22,23] have explained the relation of a patient's BTT to the temperature of a surrounding water blanket in a therapeutic system in which the "actual patient thermal characteristics" is called the *characteristic model.*

If the estimated *characteristic model* is given by a first-order lag transfer function, its discrete-time representation is

$$T_{\text{brain}}^{\text{char}}(i+1) = -a^{\text{char}} T_{\text{brain}}^{\text{char}}(i) + b^{\text{char}} T^{\text{char}}(i);$$
$$a^{\text{char}} = -e^{-\frac{\upsilon}{\tau}}, \qquad b^{\text{char}} = k\left(1 - e^{-\frac{\upsilon}{\tau}}\right) \tag{11}$$

where the suffix "char" indicates its relevant parameters with sampling time υ. The time-constant τ and the gain k are determined according to clinical experience on a "hypothermic patient and water-cooling blanket."

Optimal adaptive control

There is always some ambiguity due to the individual differences of patients, chronic changes in a patient's physiological state, and disturbances caused by the clinical therapy and the operation. In order to deal with these unknown factors, an adaptive mechanism is appropriate to realize an automatic incubating function similar to that of a water-cooling system. Hence, an optimal regulator is introduced to produce an effective input to the *characteristic model* and to the signal synthesis mechanism simultaneously. Then the therapeutic air-cooling incubating system is optimally and adaptively controlled to follow the output $T_{\text{brain}}^{\text{char}}$ of the *characteristic model* by the pertinent input.

Calculation of the optimal input signal

The optimal input T^{char} is calculated using the deviation e of the output BTT of the *characteristic model* from the reference temperature $T_{\text{reference}}$ by introducing the following variables:

$$e(i) = T_{\text{reference}}(i) - T_{\text{brain}}^{\text{char}}(i) \tag{12}$$
$$\Delta e(i) = e(i) - e(i-1) \tag{13}$$
$$\Delta T_{\text{brain}}^{\text{char}}(i) = T_{\text{brain}}^{\text{char}}(i) - T_{\text{brain}}^{\text{char}}(i-1) \tag{14}$$
$$\Delta T^{\text{char}}(i) = T^{\text{char}}(i) - T^{\text{char}}(i-1) \tag{15}$$
$$\Delta T_{\text{reference}}(i) = T_{\text{reference}}(i) - T_{\text{reference}}(i-1) \tag{16}$$

where Δe, $\Delta T_{\text{brain}}^{\text{char}}$, ΔT^{char}, and $\Delta T_{\text{reference}}$ are calculated using the differences in the values of the present and previous sampling times.

Equations 11–16 are summarized in Eq. 17.

$$\boldsymbol{X}(i+1) = \boldsymbol{A}\boldsymbol{X}(i) + \boldsymbol{G}\Delta T^{\text{char}}(i) + \boldsymbol{G}_R \Delta T_{\text{reference}}(i+1) \tag{17}$$

where

$$\boldsymbol{X}(i) = \begin{bmatrix} e(i) \\ \Delta T_{\text{brain}}^{\text{char}}(i) \end{bmatrix}, \qquad \boldsymbol{A} = \begin{bmatrix} 1 & a^{\text{char}} \\ 0 & -a^{\text{char}} \end{bmatrix},$$
$$\boldsymbol{G} = \begin{bmatrix} -b^{\text{char}} \\ b^{\text{char}} \end{bmatrix}, \qquad \boldsymbol{G}_R = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

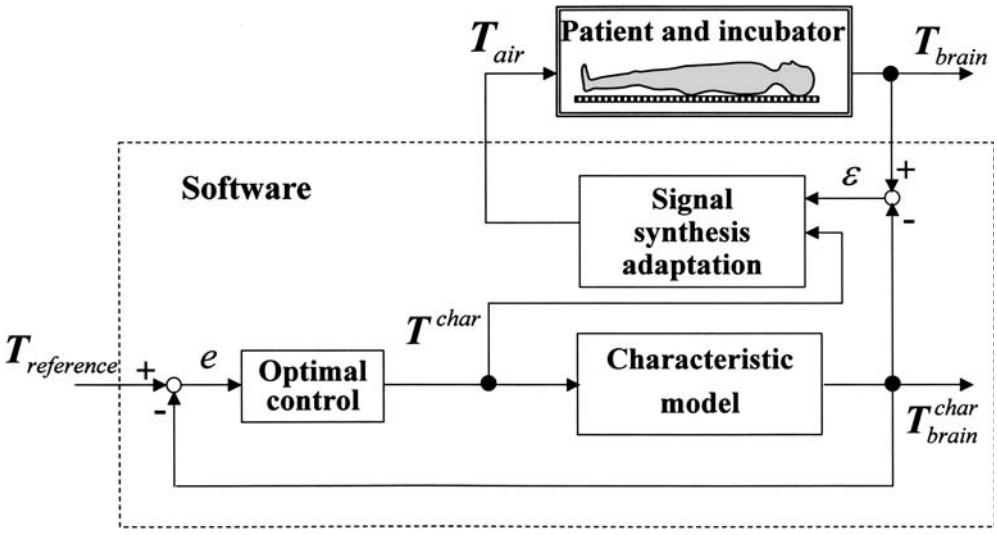

Fig. 6. Diagram of optimal adaptive control. The output BTT of an actual hypothermic patient (here, an adult incubating biothermal model) is adaptively controlled to follow that of the characteristic model using the signal synthesis mechanism, which realizes the desired brain temperature course given by clinicians. The subsystem indicated by the area surrounded by the *dotted-line* corresponds to the control mechanism given in Fig. 1

Then the optimal input to the *characteristic model* is calculated by using Eq. 18, provided that $T^{\text{char}}_{\text{brain}}(0)$ and T^{char} are given as the initial conditions of the brain and air temperatures, respectively, of the estimated *characteristic model.*

$$T^{\text{char}}(i) = h_1 \sum_{k=1}^{i} e(k) + h_2\left(T^{\text{char}}_{\text{brain}}(i) - T^{\text{char}}_{\text{brain}}(0)\right) + T^{\text{char}}(0) \tag{18}$$

The feedback coefficients h_1 and h_2 in Eq. 18 are described according to the optimal algorithm as

$$\boldsymbol{H} = \begin{bmatrix} h_1 & h_2 \end{bmatrix} = -\left[r + \boldsymbol{G}^T \boldsymbol{P} \boldsymbol{G}\right]^{-1} \boldsymbol{G}^T \boldsymbol{P} \boldsymbol{A} \tag{19}$$

$$\boldsymbol{P} = \boldsymbol{Q} + \boldsymbol{A}^T \boldsymbol{P} \boldsymbol{A} - \boldsymbol{A}^T \boldsymbol{P} \boldsymbol{G}\left[r + \boldsymbol{G}^T \boldsymbol{P} \boldsymbol{G}\right]^{-1} \boldsymbol{G}^T \boldsymbol{P} \boldsymbol{A} \tag{20}$$

where $\boldsymbol{Q} = \text{diag}[q_1 \quad q_2]$, $r > 0$.

Mechanism of input signal synthesis

The basic dynamics of adult patients with an incubator could be assumed to be the first-order lag system given by Eq. 21, where $\hat{a}$ and $\hat{b}$ are the estimates during the adaptive process.

$$T_{\text{brain}}(i+1) = -\hat{a}(i) T_{\text{brain}}(i) + \hat{b}(i) T_{\text{air}}(i) \tag{21}$$

Then the input T_{air} to the therapeutic air-cooling incubating system is calculated by

$$T_{\text{air}}(i) = \frac{\left(h - a^{\text{char}}\right) T^{\text{char}} + b^{\text{char}} T^{\text{char}}_{\text{brain}}(i) - \left(h - \hat{a}(i)\right) T_{\text{brain}}(i)}{\hat{b}(i)} \tag{22}$$

where the output BTT $T^{\text{char}}_{\text{brain}}$ and the input blanket temperature T^{char} to the *characteristic model* are given by Eqs. 11 and 18, respectively, and h is parameterized in order that a filter of $(1 + hz^{-1})$ is stable, viz. $|h| < 1$. The parameters of $\hat{a}$ and $\hat{b}$ are estimated from Eq. 23 if the system state vector is $\boldsymbol{\phi}(i) = \begin{bmatrix} T_{\text{air}}(i) \\ T_{\text{brain}}(i) \end{bmatrix}$, and the system parameter vector

$$\hat{\boldsymbol{P}}(i) = \begin{bmatrix} \hat{b}(i) \\ h - \hat{a}(i) \end{bmatrix}.$$

$$\hat{\boldsymbol{P}}(i) = \hat{\boldsymbol{P}}(i-1) + \boldsymbol{F}(i-1)\boldsymbol{\phi}(i-1)e^*(i) \tag{23}$$

where

$$e^*(i) = \frac{T_{\text{brain}}(i) + hT_{\text{brain}}(i-1) - \hat{\boldsymbol{P}}(i-1)\boldsymbol{\phi}(i-1)}{1 + \boldsymbol{\phi}^T(i-1)\boldsymbol{F}(i-1)\boldsymbol{\phi}(i-1)} \tag{24}$$

$$\boldsymbol{F}(i) = \frac{1}{\lambda(i)}\left(\boldsymbol{F}(i-1) - \frac{\boldsymbol{F}(i-1)\boldsymbol{\phi}(i-1)\boldsymbol{\phi}^T(i-1)\boldsymbol{F}(i-1)}{1 + \boldsymbol{\phi}^T(i-1)\boldsymbol{F}(i-1)\boldsymbol{\phi}(i-1)}\right) \tag{25}$$

$$\lambda(i) = 1 - \frac{\left\|\boldsymbol{F}(i-1)\boldsymbol{\phi}(i)\right\|^2}{1 + \boldsymbol{\phi}^T(i)\boldsymbol{F}(i-1)\boldsymbol{\phi}(i)} \cdot \frac{1}{tr\boldsymbol{F}(0)} \tag{26}$$

and $\boldsymbol{F}(0) = \text{diag}[f_1 \quad f_2]$.

Simulation result

The *adult incubating biothermal model* described by Eqs. 6 and 7 was applied to a simulation of the automatic control of BTT instead of the therapeutic air-cooling incubating system shown in Fig. 6.

In the simulation experiment, $f_1 = f_2 = 100$, $h = a^{\text{char}}$ were first set for the adaptive algorithm, and $q_1 = q_2 = 0.01$, $r = 0.001$ for the optimal tracking algorithm. The sampling interval υ was given as 30 s, and k and τ of the *characteristic model* were set at 0.9 and 3.0 h, respectively, according to clinical experience of the water-cooling blanket system.[1,2]

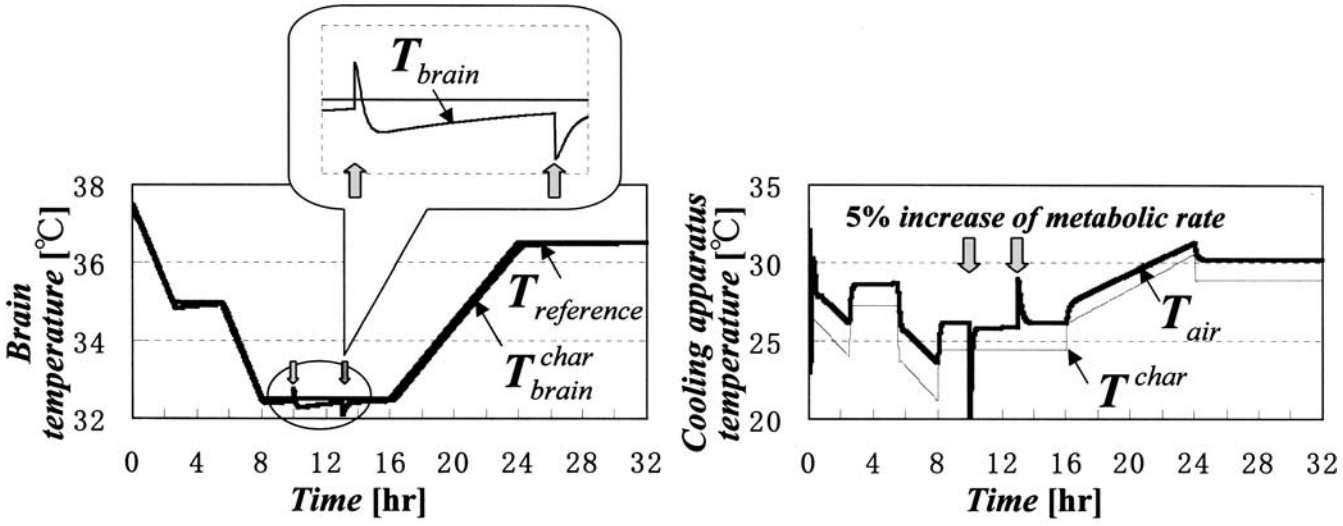

Fig. 7. BTT dynamics of the biothermal model using optimal adaptive control. The temperature courses of the characteristic model and the biothermal model agree with the brain temperature reference given. *Broad vertical arrows* show the brain temperature dynamics due to a 5% metabolic rate increase in the biothermal model

A 5% increase in metabolic rate was reached in 3 h (10 h–13 h from the beginning) in the stable hypothermia phase of BHT in order to simulate any possible undesirable effects during the control process.

In Fig. 7, the BTTs of the *adult incubating biothermal model* and of the *characteristic model* almost overlap with the desired BTT course during the simulation experiment. This means that both the optimal tracking and the adaptive controls work sufficiently well to realize the given reference cooling process.

Note that the temperature of the circulating air of the *adult incubating biothermal model* is actively given by the adaptive mechanism during the 3-h metabolic change in order to follow the reference BTT given by the clinicians. It is obvious that such an increase in metabolic rate is often caused by shivering due to inadequate anesthesia of the integrated life-support in clinical BHT. The adaptive algorithm is effective in dealing with such variations, as illustrated by Fig. 7, even though precise information about patients and their environment is almost never given beforehand.

The estimation of parameters $\hat{a}$ and $\hat{b}$ of the *adult incubating biothermal model* is shown in Fig. 8. Even with violent fluctuations in the values estimated, it is possible to presume that the adaptive system acts efficiently in the first half of the simulation, in contrast to the latter half where the sudden 3-h metabolic change was introduced arbitrarily.

The proposed combinatory control method with optimal mechanism was found to be useful in the automatic regulation of BTT to follow the desired cooling schedule in BHT. Eventually, it is expected to be used in clinical practice if similar adaptive control algorithms are applied to an actual therapeutic air-cooling incubating system.

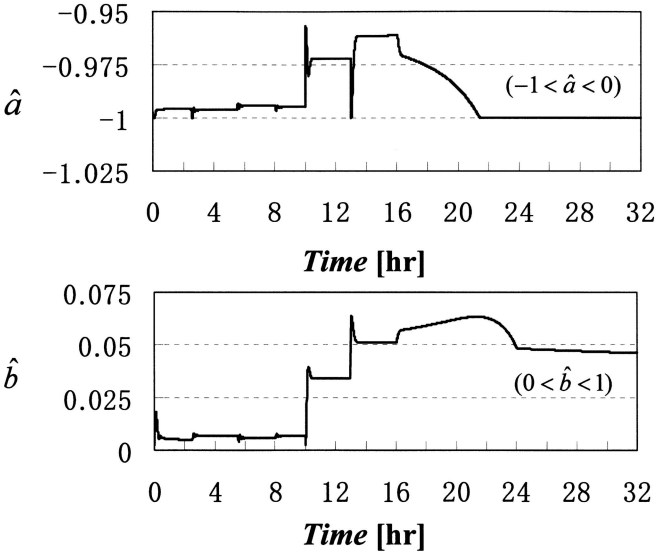

Fig. 8. Estimation of parameters $\hat{a}$ and $\hat{b}$

Discussion

Some biothermal models of healthy people have been proposed, in which neural control has sometimes been partialy considered, although BTT varies very little from the *neutral state* owing to its neural thermoregulation mechanism.[11,14–16,24,25] In BHT, however, the neural thermoregulation mechanism is basically blocked out in the patient by anesthesia, which is an essential life-support measure to prevent reactive shivering and/or to suppress

their immunoreaction. In addition, neural thermoregulation is sometimes damaged by crucial external and internal factors of the mechanical injury and brain hemorrhage.

Thus, a suitable *biothermal model* of an adult patient with a blocked neural regulation mechanism for BHT has been successfully developed and carefully studied to assess its feasibility for clinical applications in the future. Further, the *biothermal model* has been characterized by its environmental temperature,[26] and applied to the development of an optimal control algorithm by examining its step response and feedback control.[22]

In the current system of thermal control, however, conventional PID regulation is not appropriate, because its design requires precise recognition of the biothermal characteristics of the patient. These can vary according to internal and external conditions, including various uncertain factors such as the difference between individuals, and environmental and chronic change.

In order to overcome such unknown factors, model reference adaptive control of BTT have been adopted for the air-cooling incubating system. This has been applied to maintain the body temperature of premature infants,[27,28] but there have been no reports about the treatment of adult patient with severe brain injury.

Brain hypothermia treatment (BHT) has mainly been based on a water-cooling blanket, with manual regulation of the temperature of the circulating water in order to realize the BTT scheduled by the clinicians. In the present study, an automatic air-cooling incubator has been tested to replace not only the manual regulation, but also the automatic water-cooling blanket methods, as they can sometimes have clinically undesirable effects in hypothermia.

To calculate the optimal controlling input, BTT dynamics corresponding to changes in the air temperature have been found by a transfer function with a time constant smaller than 3 h and a gain of about 0.9. These are similar to the dynamics of slender patients with very severe brain injury.[1,2]

In the case of fat patients, a time constant of not less than 3 h is appropriate, and a gain a little smaller than 0.9 is suitable. This is because clinical experience shows that they are difficult to cool down owing to their larger thermal capacity and lower thermal conductivity.[2]

Thus, a combination of optimal tracking control and model reference adaptive control has been shown to be successful in the regulation of BHT, and will be a useful and powerful method. In addition, various problematic phenomena resulting from the water-cooling blanket have been solved by using the air-cooling incubating system. At the same time, some other problems with manual regulation are incidentally overcome by the *optimal adaptive control mechanism* for the regulation of BTT. It can guide clinicians and nurses on the basis of precise and necessary clinical information in advance from an appropriate simulation process of BTT, which they can freely prescribe or change.

In the present air-cooling method, some inevitable problems still remain in its clinical application, for instance, the velocity of the circulating air, by which the temperature of the incubator is automatically controlled. In order to adjust the temperature and humidity of the cooling air efficiently, circulation of the air should be considered. Furthermore, in order to prevent an infection in the skin wound of a patient, it is necessary to clean the circulating air. Even if precise experiments are required before any application, the present method is sure to contribute to the clinical use of BHT in the near future.

Conclusions

The dynamics of an air-cooling system have been clarified in relation to its step response and feedback control, and based on its state equation with a given initial temperature, using a *biothermal model* with a suitable geometric structure and parameters. Thereby, an optimal and adaptive control algorithm has been found to be useful for the realization of effective automatic regulation of BTT in a therapeutic air-cooling incubating system. However, the first-order lag transfer function was first substantially extracted from the basic characteristics of hypothermic patients by a water-cooling blanket system.

From the simulation experiments, the automatic air-cooling incubator was found to be basically superior to a therapeutic water-cooling blanket system in the possible avoidance of decubitus and bedsores during the patient's medical treatment and rehabilitation process. It also had greater cooling efficiency and was less expensive, with an easy manipulation system. It is convenient for keeping patients in sanitary conditions with less environmental disturbance, and releases carers from physical and mental burdens.

We conclude that the optimal-adaptive control mechanism using the proposed air-cooling incubating system ensures that the desired temperature course is followed. In addition, this work has suggested the development of an air-cooled adult incubating system to replace the manual and/or automatic water-cooling blanket system in BHT. At the same time, it has provided a significant medical method which overcomes the individual differences of patients and possible environmental changes in the therapeutic cooling system.

Appendix

Matrix $\boldsymbol{A}$, state vector $\boldsymbol{T}$, vector $\boldsymbol{b}$, and vector $\boldsymbol{Q}$ in Eq. 6 are given as

$$
\boldsymbol{A}_{(18\times 18)} = \left[\begin{array}{ccc:ccc:ccc:ccc:ccc:ccc:ccc:ccc:cc}
a_{1,1} & a_{1,2} & 0 & & & & & & & & & & a_{1,13} & & & & & & & & \\
a_{2,1} & a_{2,2} & a_{2,3} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & 0 & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{2}{c}{\boldsymbol{0}} \\
0 & a_{3,2} & a_{3,3} & & & & & & & & & & a_{3,13} & & & & & & & & \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{4,4} & a_{4,5} & & & & & & & & a_{4,13} & & & & & & & & \\
\multicolumn{3}{c:}{} & a_{5,4} & a_{5,5} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & a_{5,13} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{2}{c}{\boldsymbol{0}} \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{6,6} & a_{6,7} & & & & & a_{6,13} & & & & & & & & \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & a_{7,6} & a_{7,7} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{3}{c:}{\boldsymbol{0}} & a_{7,13} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{2}{c}{\boldsymbol{0}} \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{8,8} & a_{8,9} & & & & a_{8,13} & & & & & & & \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & a_{9,8} & a_{9,9} & \multicolumn{3}{c:}{\boldsymbol{0}} & a_{9,13} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{2}{c}{\boldsymbol{0}} \\
\hdashline
\multicolumn{3}{c:}{\multirow{3}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{3}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{3}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{3}{*}{$\boldsymbol{0}$}} & a_{10,10} & a_{10,11} & 0 & a_{10,13} & & & & & \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & a_{11,10} & a_{11,11} & a_{11,12} & a_{11,13} & \multicolumn{3}{c:}{\boldsymbol{0}} & \multicolumn{2}{c}{\boldsymbol{0}} \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & 0 & a_{12,11} & a_{12,13} & a_{12,13} & & & & & \\
\hdashline
a_{13,1} & 0 & a_{13,3} & a_{13,4} & a_{13,5} & & a_{13,6} & a_{13,7} & & a_{13,8} & a_{13,9} & & a_{13,10} & a_{13,11} & a_{13,12} & a_{13,13} & a_{13,14} & a_{13,15} & a_{13,16} & a_{13,17} & a_{13,18} \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{14,13} & a_{14,14} & a_{14,15} & 0 & & \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & a_{15,13} & a_{15,14} & a_{15,15} & a_{15,16} & \multicolumn{2}{c}{\boldsymbol{0}} \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{16,13} & 0 & a_{16,15} & a_{16,16} & & \\
\hdashline
\multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & \multicolumn{3}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{17,13} & & \multicolumn{2}{c:}{\multirow{2}{*}{$\boldsymbol{0}$}} & a_{17,17} & a_{17,18} \\
\multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & \multicolumn{3}{c:}{} & a_{18,13} & & \multicolumn{2}{c:}{} & a_{18,17} & a_{18,18} \\
\end{array}\right]
$$

$$
\boldsymbol{T}_{(18\times 1)} = \begin{bmatrix} T_{\text{brain}} \\ T_{11} \\ T_{12} \\ T_{21} \\ T_{22} \\ T_{31} \\ T_{32} \\ T_{41} \\ T_{42} \\ T_{50} \\ T_{51} \\ T_{52} \\ T_{60} \\ T_{70} \\ T_{71} \\ T_{72} \\ T_{81} \\ T_{82} \end{bmatrix} \quad \boldsymbol{b}_{(18\times 1)} = \begin{bmatrix} 0 \\ 0 \\ b_3 \\ 0 \\ b_5 \\ 0 \\ b_7 \\ 0 \\ b_9 \\ 0 \\ 0 \\ b_{12} \\ 0 \\ 0 \\ 0 \\ b_{16} \\ 0 \\ b_{18} \end{bmatrix} \quad \boldsymbol{Q}_{(18\times 1)} = \begin{bmatrix} q_1 \\ 0 \\ q_3 \\ q_4 \\ q_5 \\ q_6 \\ q_7 \\ q_8 \\ q_9 \\ q_{10} \\ q_{11} \\ q_{12} \\ q_{13} \\ q_{14} \\ q_{15} \\ q_{16} \\ q_{17} \\ q_{18} \end{bmatrix}
$$

In the symbol $T_{\#\&}$ in state vector $\boldsymbol{T}$, the suffix # represents the segment number (head (segment number 1), face (2), neck (3), superior limbs (4), thorax (5), heart (6), abdomen (7), and inferior limbs (8)) and the suffix & represents the compartment number of the core (compartment number 1) and the shell (2). The brain, lungs, heart, and abdominal viscera have the symbols 10, 50, 60, and 70. Nonzero elements in matrix $\boldsymbol{A}$, vector $\boldsymbol{b}$, and vector $\boldsymbol{Q}$ are calculated as given below.

1. for $\boldsymbol{A}$

row 1 (corresponding to the brain)

$$a_{1,1}=-\frac{k_{101}+\rho_{bl}c_{bl}w_{10}V_{10}}{\rho_{10}c_{10}V_{10}},\qquad a_{1,2}=\frac{k_{101}}{\rho_{10}c_{10}V_{10}},\qquad a_{1,13}=\frac{\rho_{bl}c_{bl}w_{10}V_{10}}{\rho_{10}c_{10}V_{10}}$$

row 2 (corresponding to the cranium)

$$a_{2,1}=\frac{k_{101}}{\rho_{11}c_{11}V_{11}},\qquad a_{2,2}=-\frac{k_{101}+k_{112}}{\rho_{11}c_{11}V_{11}},\qquad a_{2,3}=\frac{k_{112}}{\rho_{11}c_{11}V_{11}}$$

row 3 (corresponding to the scalp)

$$a_{3,2}=\frac{k_{112}}{\rho_{12}c_{12}V_{12}},\qquad a_{3,3}=\frac{k_{112}+\rho_{bl}c_{bl}w_{bl}V_{12}+k_{12a}S_{12}}{\rho_{12}c_{12}V_{12}},\qquad a_{3,13}=\frac{\rho_{bl}c_{bl}w_{12}V_{12}}{\rho_{12}c_{12}V_{12}}$$

row 4 (corresponding to the core compartment of the face)

$$a_{4,4}=-\frac{k_{212}+\rho_{bl}c_{bl}w_{21}V_{21}}{\rho_{21}c_{21}V_{21}},\qquad a_{4,5}=\frac{k_{212}}{\rho_{21}c_{21}V_{21}},\qquad a_{4,13}=\frac{\rho_{bl}c_{bl}w_{21}V_{21}}{\rho_{21}c_{21}V_{21}}$$

row 5 (corresponding to the shell compartment of the face)

$$a_{5,4}=\frac{k_{212}}{\rho_{22}c_{22}V_{22}},\qquad a_{5,5}=-\frac{k_{212}+\rho_{bl}c_{bl}w_{22}V_{22}+k_{22a}S_{22}}{\rho_{22}c_{22}V_{22}},\qquad a_{5,13}=\frac{\rho_{bl}c_{bl}w_{22}V_{22}}{\rho_{22}c_{22}V_{22}}$$

row 6

$$a_{6,6}=-\frac{k_{312}+\rho_{bl}c_{bl}w_{31}V_{31}}{\rho_{31}c_{31}V_{31}},\qquad a_{6,7}=\frac{k_{312}}{\rho_{31}c_{31}V_{31}},\qquad a_{6,13}=\frac{\rho_{bl}c_{bl}w_{31}V_{31}}{\rho_{31}c_{31}V_{31}}$$

row 7

$$a_{7,6}=\frac{k_{312}}{\rho_{32}c_{32}V_{32}},\qquad a_{7,7}=-\frac{k_{312}+\rho_{bl}c_{bl}w_{32}V_{32}+k_{32a}S_{32}}{\rho_{32}c_{32}V_{32}},\qquad a_{7,13}=\frac{\rho_{bl}c_{bl}w_{32}V_{32}}{\rho_{32}c_{32}V_{32}}$$

row 8

$$a_{8,8}=-\frac{k_{412}+\rho_{bl}c_{bl}w_{41}V_{41}}{\rho_{41}c_{41}V_{41}},\qquad a_{8,9}=\frac{k_{412}}{\rho_{41}c_{41}V_{41}},\qquad a_{8,13}=\frac{\rho_{bl}c_{bl}w_{41}V_{41}}{\rho_{41}c_{41}V_{41}}$$

row 9

$$a_{9,8}=\frac{k_{412}}{\rho_{42}c_{42}V_{42}},\qquad a_{9,9}=-\frac{k_{412}+\rho_{bl}c_{bl}w_{42}V_{42}+k_{42a}S_{42}}{\rho_{42}c_{42}V_{42}},\qquad a_{9,13}=\frac{\rho_{bl}c_{bl}w_{42}V_{42}}{\rho_{42}c_{42}V_{42}}$$

row 10 (corresponding to the lungs)

$$a_{10,10}=-\frac{k_{501}+\rho_{bl}c_{bl}w_{50}V_{50}}{\rho_{50}c_{50}V_{50}},\qquad a_{10,11}=\frac{k_{501}}{\rho_{50}c_{50}V_{50}},\qquad a_{10,13}=\frac{\rho_{bl}c_{bl}w_{50}V_{50}}{\rho_{50}c_{50}V_{50}}$$

row 11

$$a_{11,10}=\frac{k_{501}}{\rho_{51}c_{51}V_{51}},\qquad a_{11,11}=-\frac{k_{501}+k_{512}+\rho_{bl}c_{bl}w_{51}V_{51}}{\rho_{51}c_{51}V_{51}},\qquad a_{11,12}=\frac{k_{512}}{\rho_{51}c_{51}V_{51}},\qquad a_{11,13}=\frac{\rho_{bl}c_{bl}w_{51}V_{51}}{\rho_{51}c_{51}V_{51}}$$

row 12

$$a_{12,11}=\frac{k_{512}}{\rho_{52}c_{52}V_{52}},\qquad a_{12,12}=-\frac{k_{512}+\rho_{bl}c_{bl}w_{52}V_{52}+k_{52a}S_{52}}{\rho_{52}c_{52}V_{52}},\qquad a_{12,13}=\frac{\rho_{bl}c_{bl}w_{52}V_{52}}{\rho_{52}c_{52}V_{52}}$$

row 13 (corresponding to the heart)

$$a_{13,1}=\frac{\rho_{bl}c_{bl}w_{10}V_{10}}{c_{60}m_{60}},\quad a_{13,3}=\frac{\rho_{bl}c_{bl}w_{12}V_{12}}{c_{60}m_{60}},\quad a_{13,4}=\frac{\rho_{bl}c_{bl}w_{21}V_{21}}{c_{60}m_{60}},\quad a_{13,5}=\frac{\rho_{bl}c_{bl}w_{22}V_{22}}{c_{60}m_{60}},\quad a_{13,6}=\frac{\rho_{bl}c_{bl}w_{31}V_{31}}{c_{60}m_{60}},$$

$$a_{13,7}=\frac{\rho_{bl}c_{bl}w_{32}V_{32}}{c_{60}m_{60}},\quad a_{13,8}=\frac{\rho_{bl}c_{bl}w_{41}V_{41}}{c_{60}m_{60}},\quad a_{13,9}=\frac{\rho_{bl}c_{bl}w_{42}V_{42}}{c_{60}m_{60}},\quad a_{13,10}=\frac{\rho_{bl}c_{bl}w_{50}V_{50}}{c_{60}m_{60}},\quad a_{13,11}=\frac{\rho_{bl}c_{bl}w_{51}V_{51}}{c_{60}m_{60}},$$

$$a_{13,12}=\frac{\rho_{bl}c_{bl}w_{52}V_{52}}{c_{60}m_{60}},\quad a_{13,13}=-\frac{\rho_{bl}c_{bl}}{c_{60}m_{60}}\big(w_{10}V_{10}+w_{12}V_{12}+w_{21}V_{21}+w_{22}V_{22}+w_{31}V_{31}+w_{32}V_{32}+w_{41}V_{41}+w_{42}V_{42}+w_{50}V_{50}$$

$$+w_{51}V_{51}+w_{52}V_{52}+w_{70}V_{70}+w_{71}V_{71}+w_{72}V_{72}+w_{81}V_{81}+w_{82}V_{82}\big),\quad a_{13,14}=\frac{\rho_{bl}c_{bl}w_{70}V_{70}}{c_{60}m_{60}},\quad a_{13,15}=\frac{\rho_{bl}c_{bl}w_{71}V_{71}}{c_{60}m_{60}},$$

$$a_{13,16}=\frac{\rho_{bl}c_{bl}w_{72}V_{72}}{c_{60}m_{60}},\quad a_{13,17}=\frac{\rho_{bl}c_{bl}w_{81}V_{81}}{c_{60}m_{60}},\quad a_{13,18}=\frac{\rho_{bl}c_{bl}w_{82}V_{82}}{c_{60}m_{60}}$$

row 14 (corresponding to the viscera)

$$a_{14,13}=\frac{\rho_{bl}c_{bl}w_{70}V_{70}}{\rho_{70}c_{70}V_{70}},\qquad a_{14,14}=-\frac{k_{701}+\rho_{bl}c_{bl}w_{70}V_{70}}{\rho_{70}c_{70}V_{70}},\qquad a_{14,15}=-\frac{k_{701}}{\rho_{70}c_{70}V_{70}}$$

row 15

$$a_{15,13}=\frac{\rho_{bl}c_{bl}w_{71}V_{71}}{\rho_{71}c_{71}V_{71}},\qquad a_{15,14}=\frac{k_{701}}{\rho_{71}c_{71}V_{71}},\qquad a_{15,15}=\frac{k_{701}+k_{712}+\rho_{bl}c_{bl}w_{71}V_{71}}{\rho_{71}c_{71}V_{71}},\qquad a_{15,16}=\frac{k_{712}}{\rho_{71}c_{71}V_{71}}$$

row 16

$$a_{16,13}=\frac{\rho_{bl}c_{bl}w_{72}V_{72}}{\rho_{72}c_{72}V_{72}},\qquad a_{16,15}=\frac{k_{712}}{\rho_{72}c_{72}V_{72}},\qquad a_{16,16}=-\frac{k_{712}+\rho_{bl}c_{bl}w_{72}V_{72}+k_{72a}S_{72}}{\rho_{72}c_{72}V_{72}}$$

row 17

$$a_{17,13}=\frac{\rho_{bl}c_{bl}w_{81}V_{81}}{\rho_{81}c_{81}V_{81}},\qquad a_{17,17}=-\frac{k_{812}+\rho_{bl}c_{bl}w_{81}V_{81}}{\rho_{81}c_{81}V_{81}},\qquad a_{17,18}=\frac{k_{812}}{\rho_{81}c_{81}V_{81}}$$

row 18

$$a_{18,13}=\frac{\rho_{bl}c_{bl}w_{82}V_{82}}{\rho_{82}c_{82}V_{82}},\qquad a_{18,17}=\frac{k_{812}}{\rho_{82}c_{82}V_{82}},\qquad a_{18,18}=-\frac{k_{812}+\rho_{bl}c_{bl}w_{82}V_{82}+k_{82a}S_{82}}{\rho_{82}c_{82}V_{82}}$$

2. for $\boldsymbol{b}$

$$b_3=\frac{k_{12a}S_{12}}{\rho_{12}c_{12}V_{12}},\qquad b_5=\frac{k_{22a}S_{22}}{\rho_{22}c_{22}V_{22}},\qquad b_7=\frac{k_{32a}S_{32}}{\rho_{32}c_{32}V_{32}},\qquad b_9=\frac{k_{42a}S_{42}}{\rho_{42}c_{42}V_{42}},\qquad b_{12}=\frac{k_{52a}S_{52}}{\rho_{52}c_{52}V_{52}},\qquad b_{16}=\frac{k_{72a}S_{72}}{\rho_{72}c_{72}V_{72}},$$
$$b_{18}=\frac{k_{82a}S_{82}}{\rho_{82}c_{82}V_{82}}$$

3. for $\boldsymbol{Q}$

$$q_1=\frac{Q_{10}V_{10}}{\rho_{10}c_{10}V_{10}},\qquad q_3=\frac{Q_{12}V_{12}}{\rho_{12}c_{12}V_{12}},\qquad q_4=\frac{Q_{21}V_{21}}{\rho_{21}c_{21}V_{21}},\qquad q_5=\frac{Q_{22}V_{22}}{\rho_{22}c_{22}V_{22}},\qquad q_6=\frac{Q_{31}V_{31}}{\rho_{31}c_{31}V_{31}},\qquad q_7=\frac{Q_{32}V_{32}}{\rho_{32}c_{32}V_{32}},$$
$$q_8=\frac{Q_{41}V_{41}}{\rho_{41}c_{41}V_{41}},\qquad q_9=\frac{Q_{42}V_{42}}{\rho_{42}c_{42}V_{42}},\qquad q_{10}=\frac{Q_{50}V_{50}-Q_{res}}{\rho_{50}c_{50}V_{50}},\qquad q_{11}=\frac{Q_{51}V_{51}}{\rho_{51}c_{51}V_{51}},\qquad q_{12}=\frac{Q_{52}V_{52}}{\rho_{52}c_{52}V_{52}},$$
$$q_{13}=\frac{Q_{heart}}{c_{60}m_{60}},\qquad q_{14}=\frac{Q_{70}V_{70}}{\rho_{70}c_{70}V_{70}},\qquad q_{15}=\frac{Q_{71}V_{71}}{\rho_{71}c_{71}V_{71}},\qquad q_{16}=\frac{Q_{72}V_{72}}{\rho_{72}c_{72}V_{72}},\qquad q_{17}=\frac{Q_{81}V_{81}}{\rho_{81}c_{81}V_{81}},\qquad q_{18}=\frac{Q_{82}V_{82}}{\rho_{82}c_{82}V_{82}}$$

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