Regulation for Medical Treatment by Monitoring and Control of Patient's Physiological Data

Biophysical System Engineering
Graduate School of Health Sciences
Tokyo Medical and Dental University

Prof. Dr. H.Wakamatsu

Overview of Studies

- **Management of Brain Temperature for Hypothermia**
- **Adaptive Control of Respiration**
- **Optimal Control of Intracranial Pressure**
- **Monitoring and Determination of Physiological State**

Development of Automatic Control System of Hypothermia

- Accurate Management of Brain Temperature
- Optimal and Fuzzy Control Processes
- Release from Heavy Loads

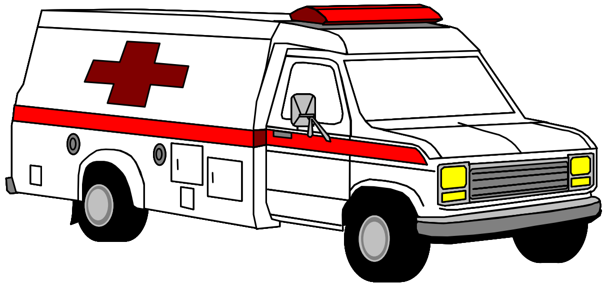
  Physical,Psychological & Economic Burdens
- Improve Medical Condition and Treatment

Based on "System Engineering"

Simulation ⇨ Experiment

Situation

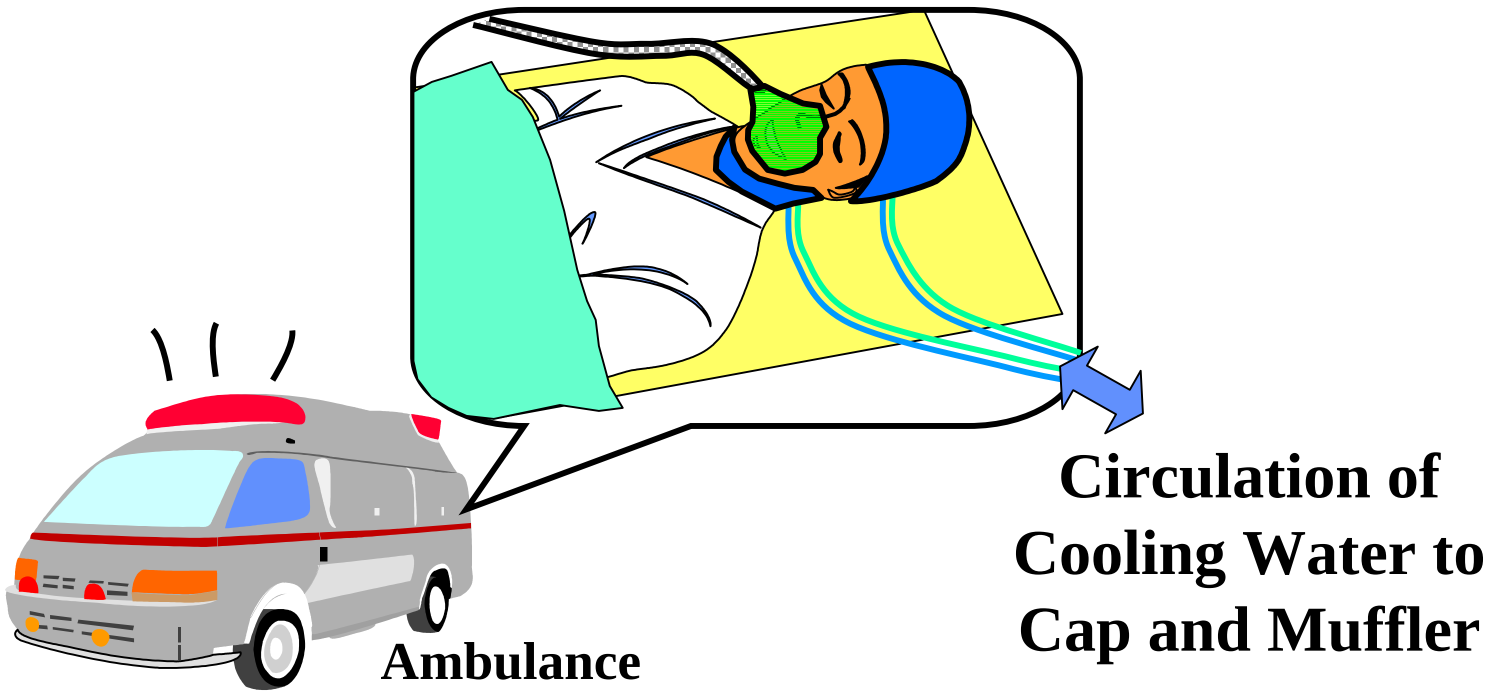
What's matter with him?
It's awful. It's terrible.
Hurry up! Bring him to hospital!



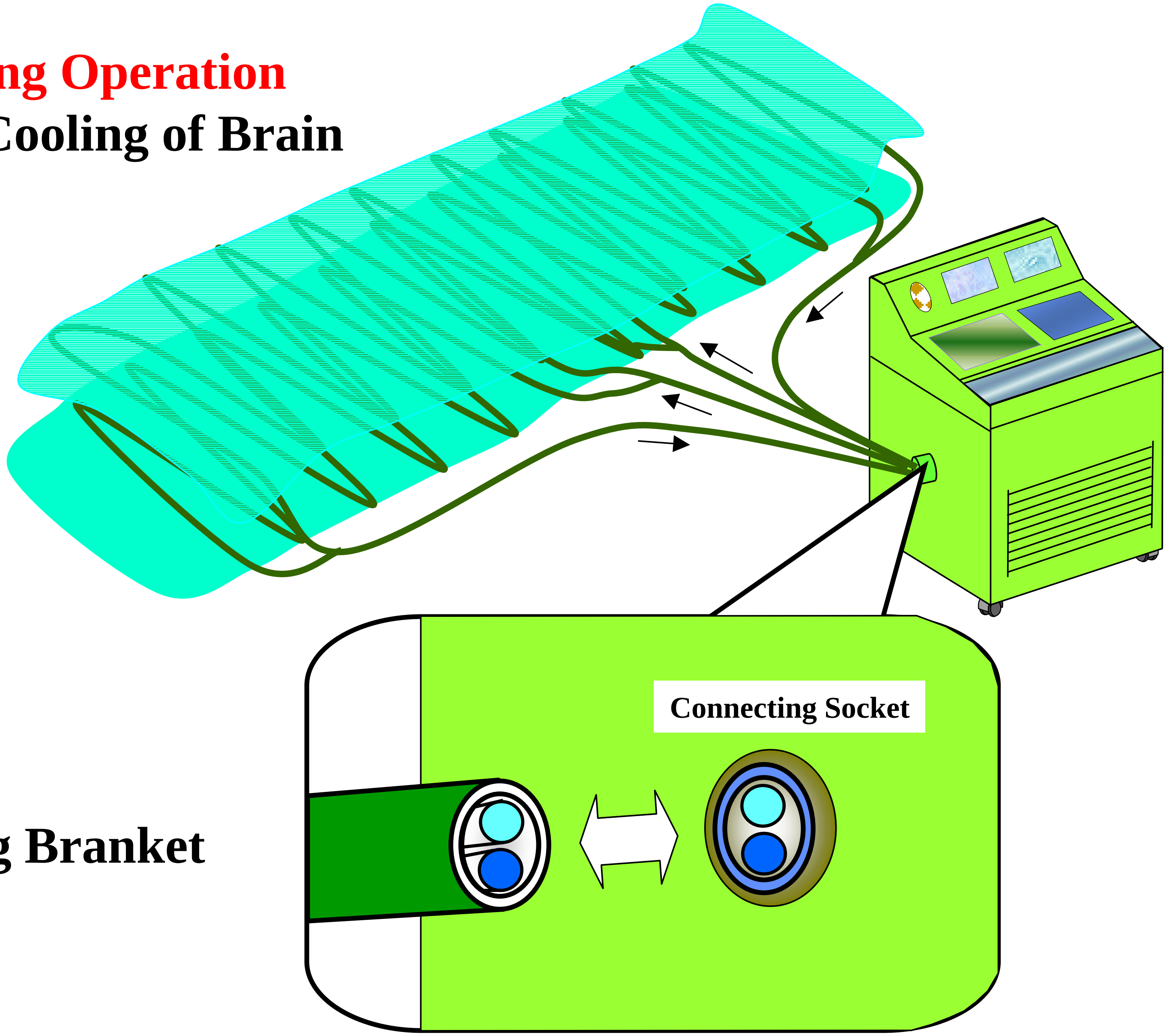
Ambulance

Traffic Accident

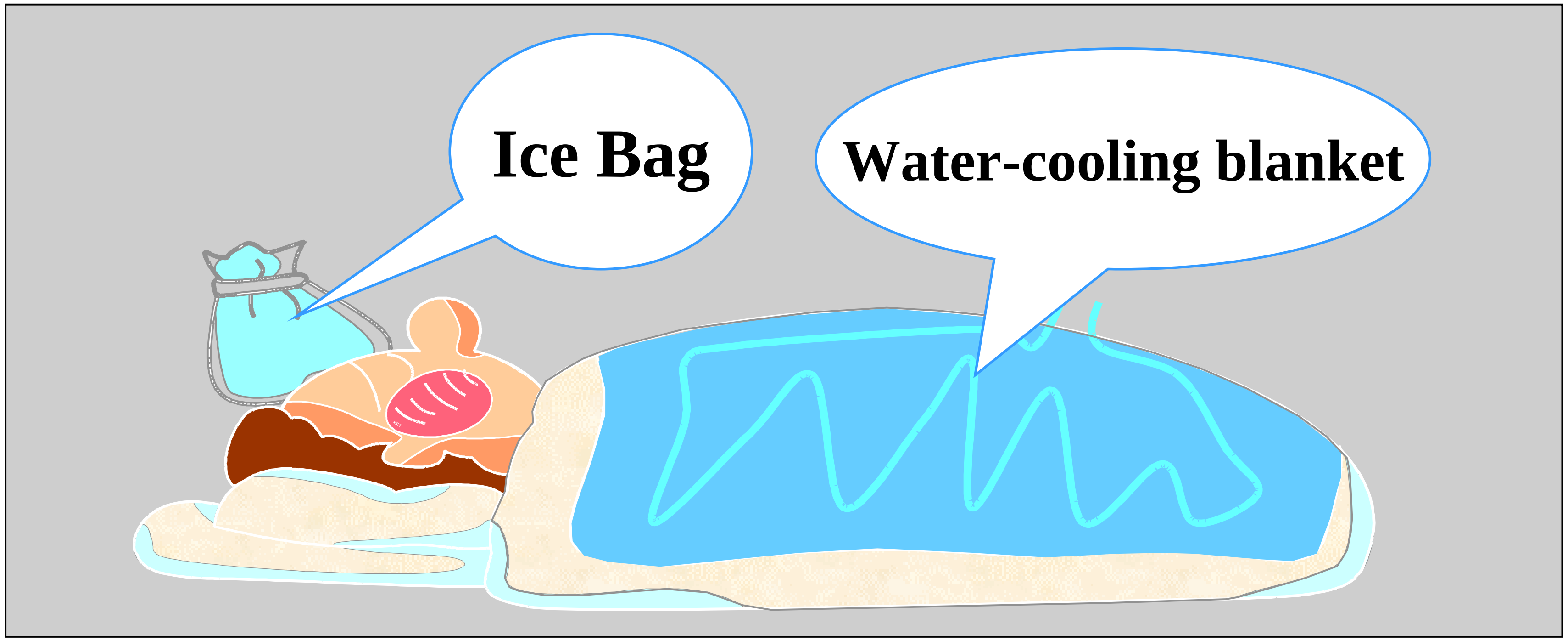
Set Quick Cooling Brain Temperature
By Using Cooling Cap and Muffler



Simple Connecting Operation
Quickly Begins Cooling of Brain

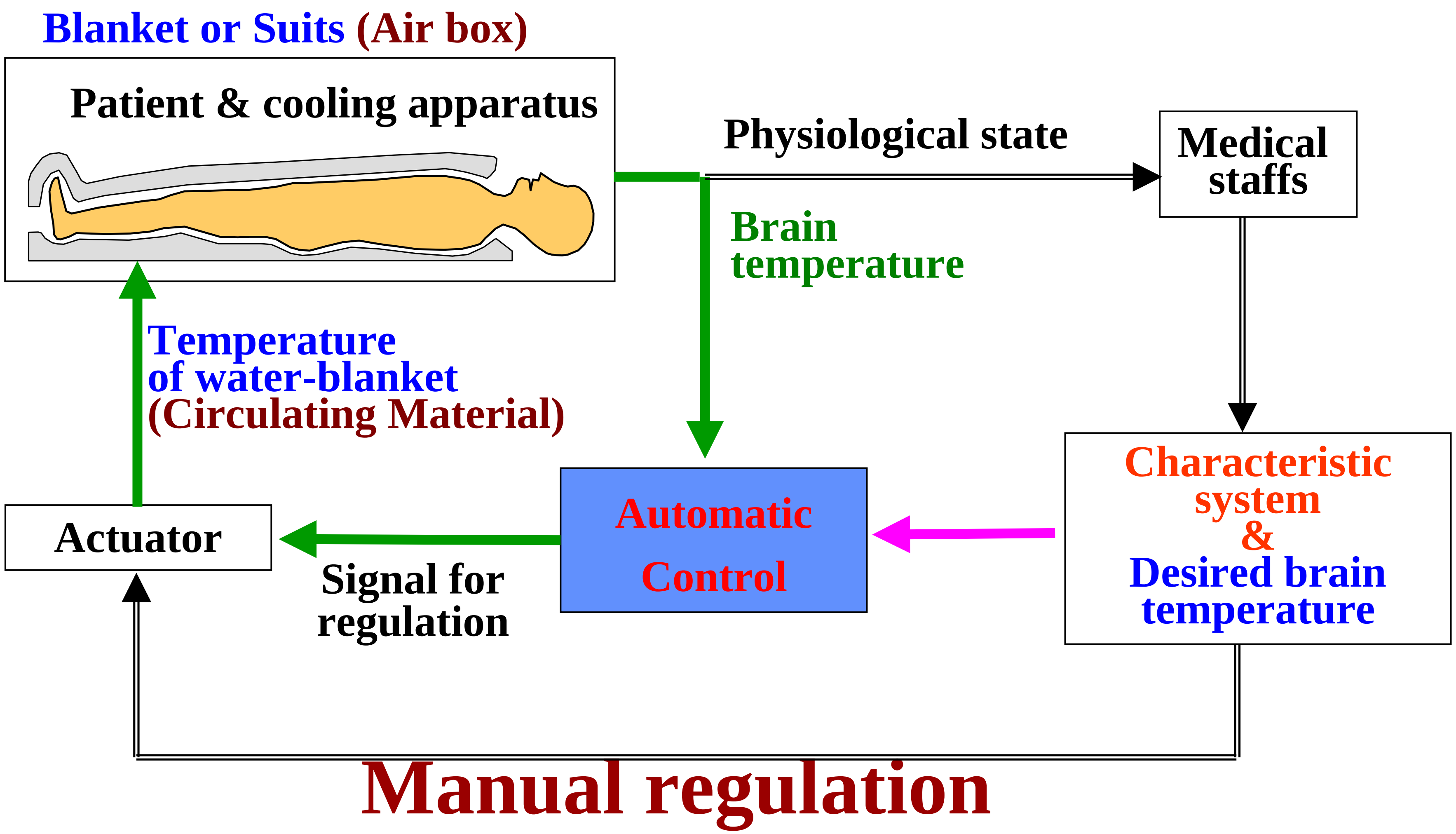


To Cooling Branket

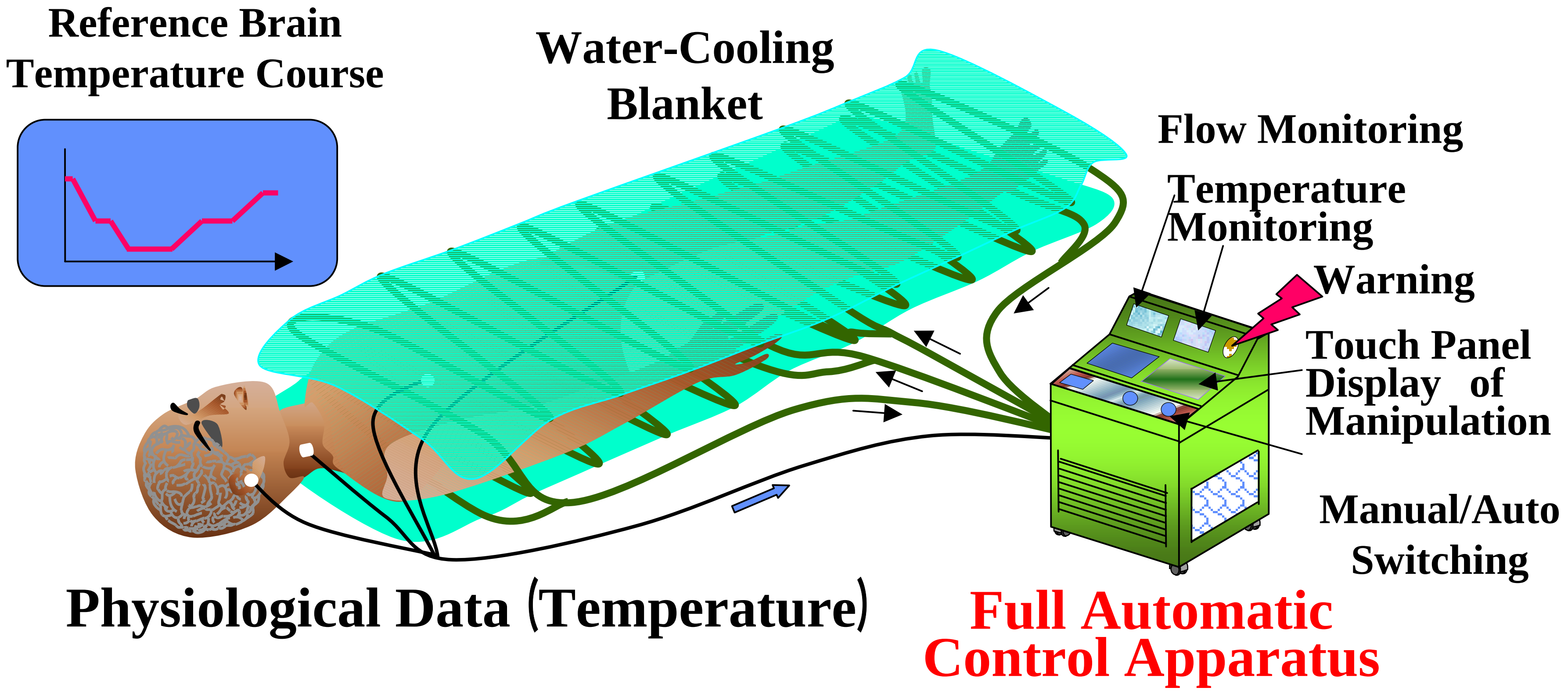


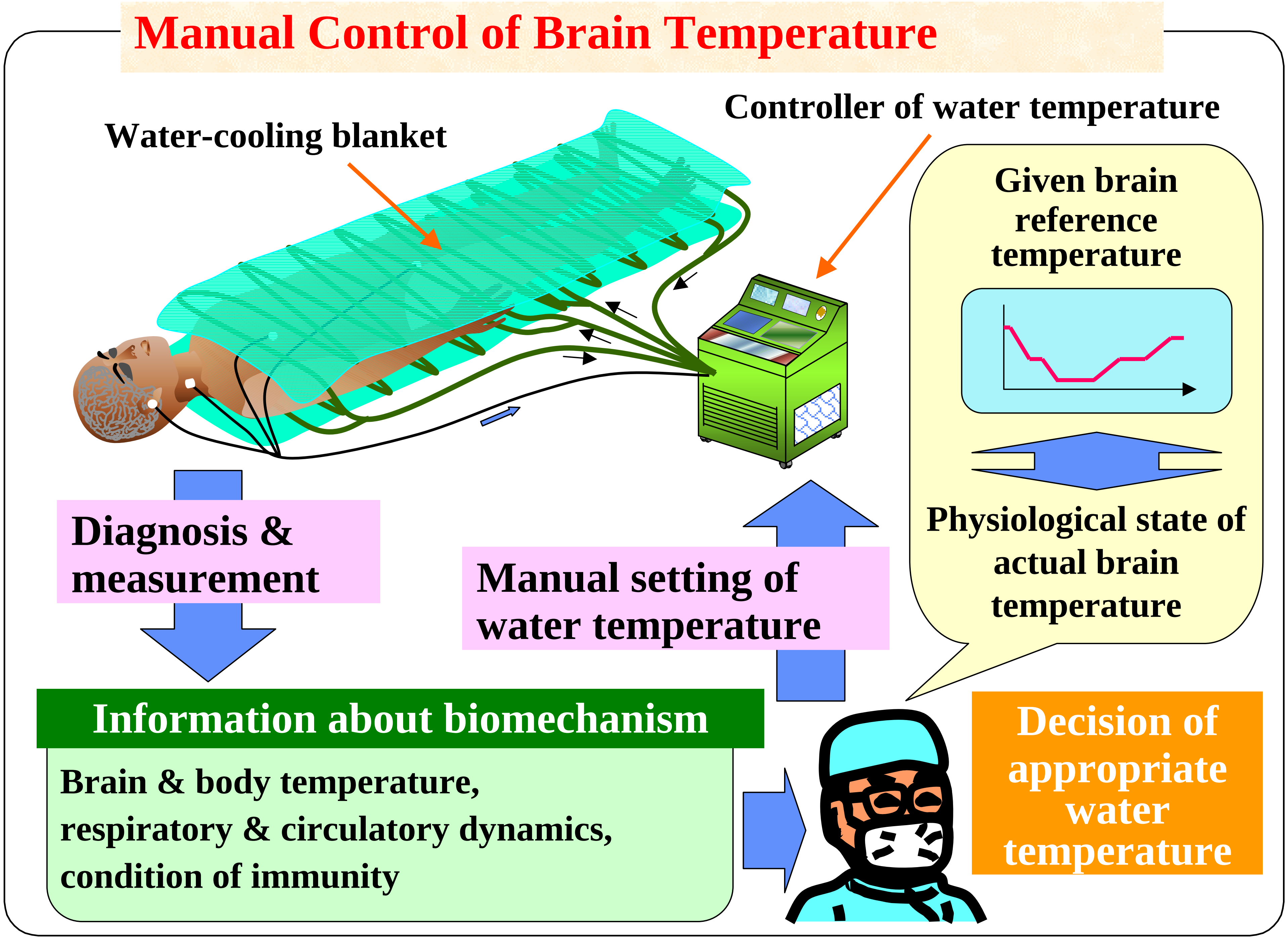
- **Whole Body Cooling is Effective**
- **Head Cooling as Assistance**

Automatic Control of Brain Temperature

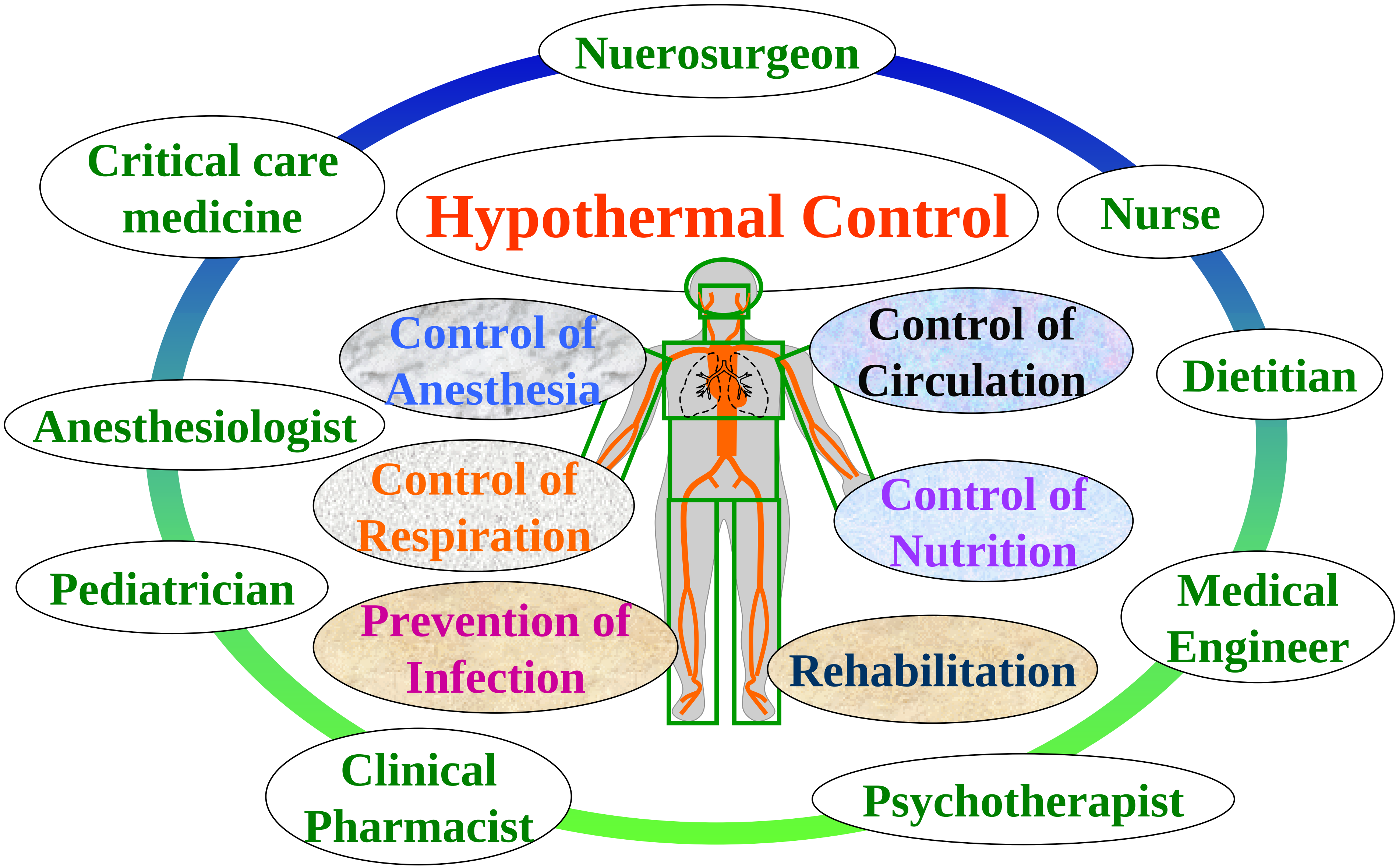


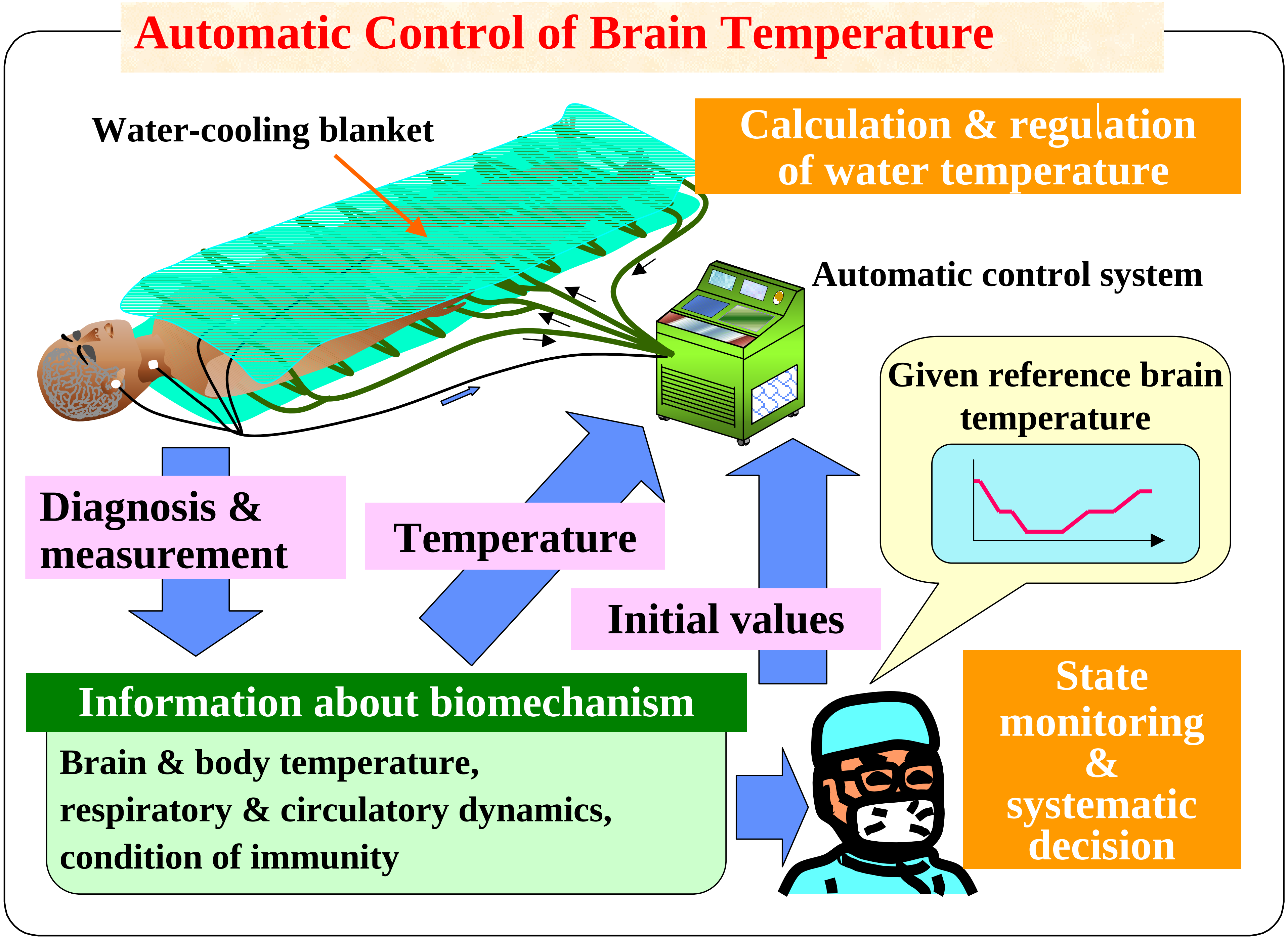
Automatic Control Apparatus of Brain Temperature




Manual Control of Brain Temperature
Water-cooling blanket
Controller of water temperature
Given brain reference temperature
Physiological state of actual brain temperature
Diagnosis & measurement
Manual setting of water temperature
Information about biomechanism
Brain & body temperature, respiratory & circulatory dynamics, condition of immunity
Decision of appropriate water temperature

Hypothermia Treatment in ICU





Automatic Control of Brain Temperature
Water-cooling blanket
Calculation & regulation of water temperature
Automatic control system
Given reference brain temperature
Diagnosis & measurement
Temperature
Initial values
Information about biomechanism
Brain & body temperature,
respiratory & circulatory dynamics,
condition of immunity
State monitoring & systematic decision

Control of Brain Temperature by Water-Cooling System

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Graduate School of Allied Health Sciences
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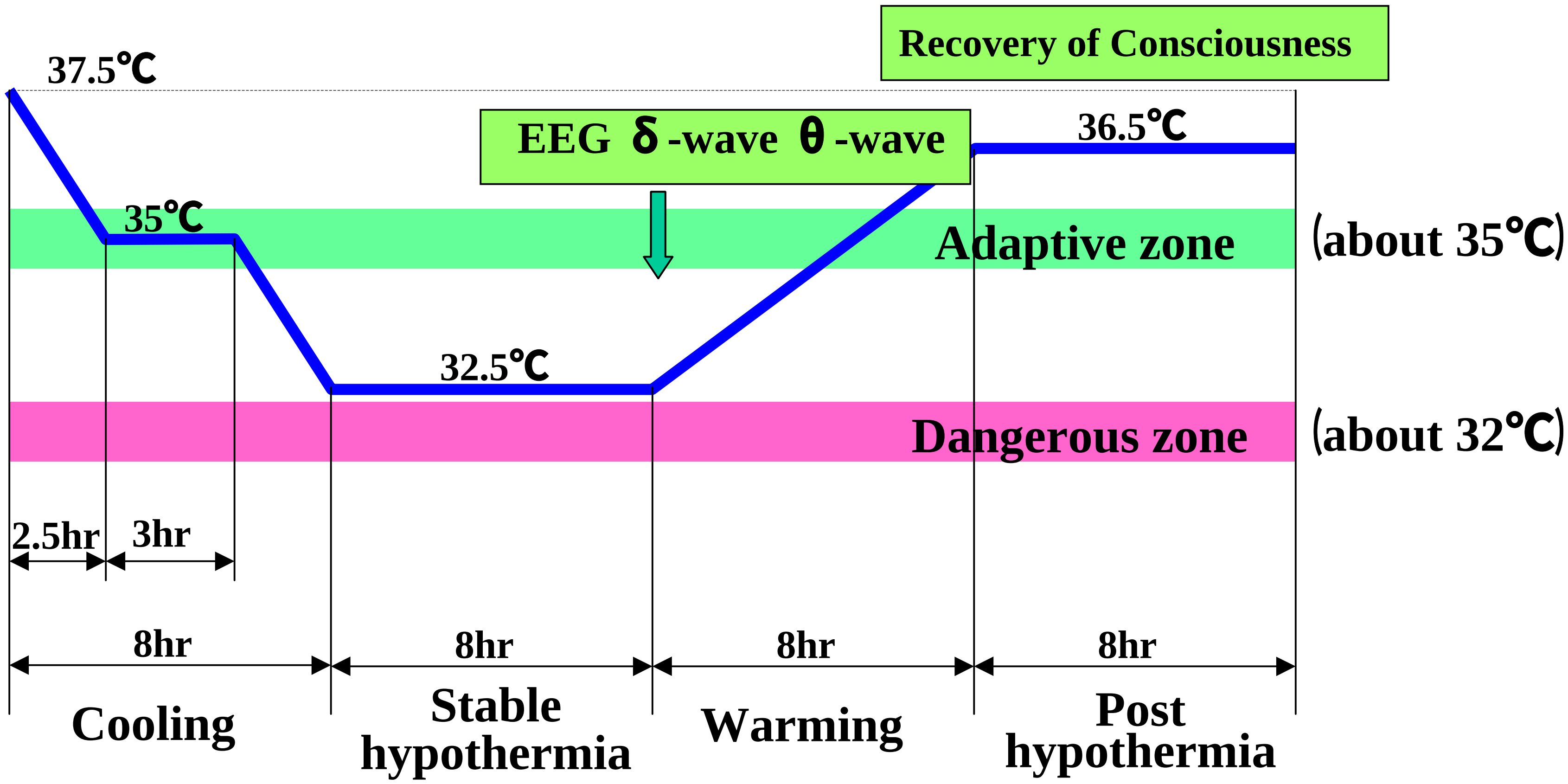
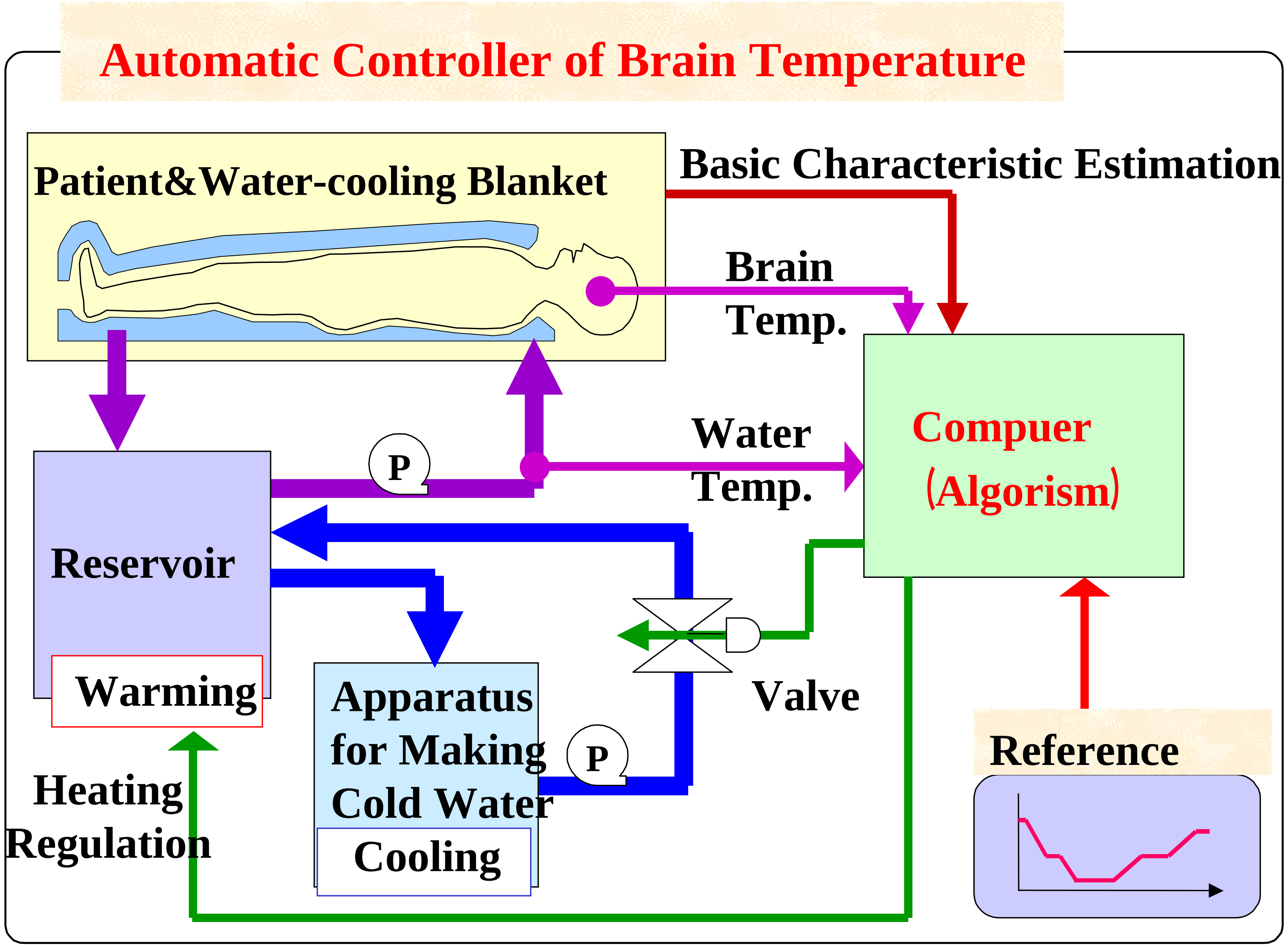
H.Wakamatsu,T.Utsuki, T.Wakatsuki

Schematic Desired Brain Temperature

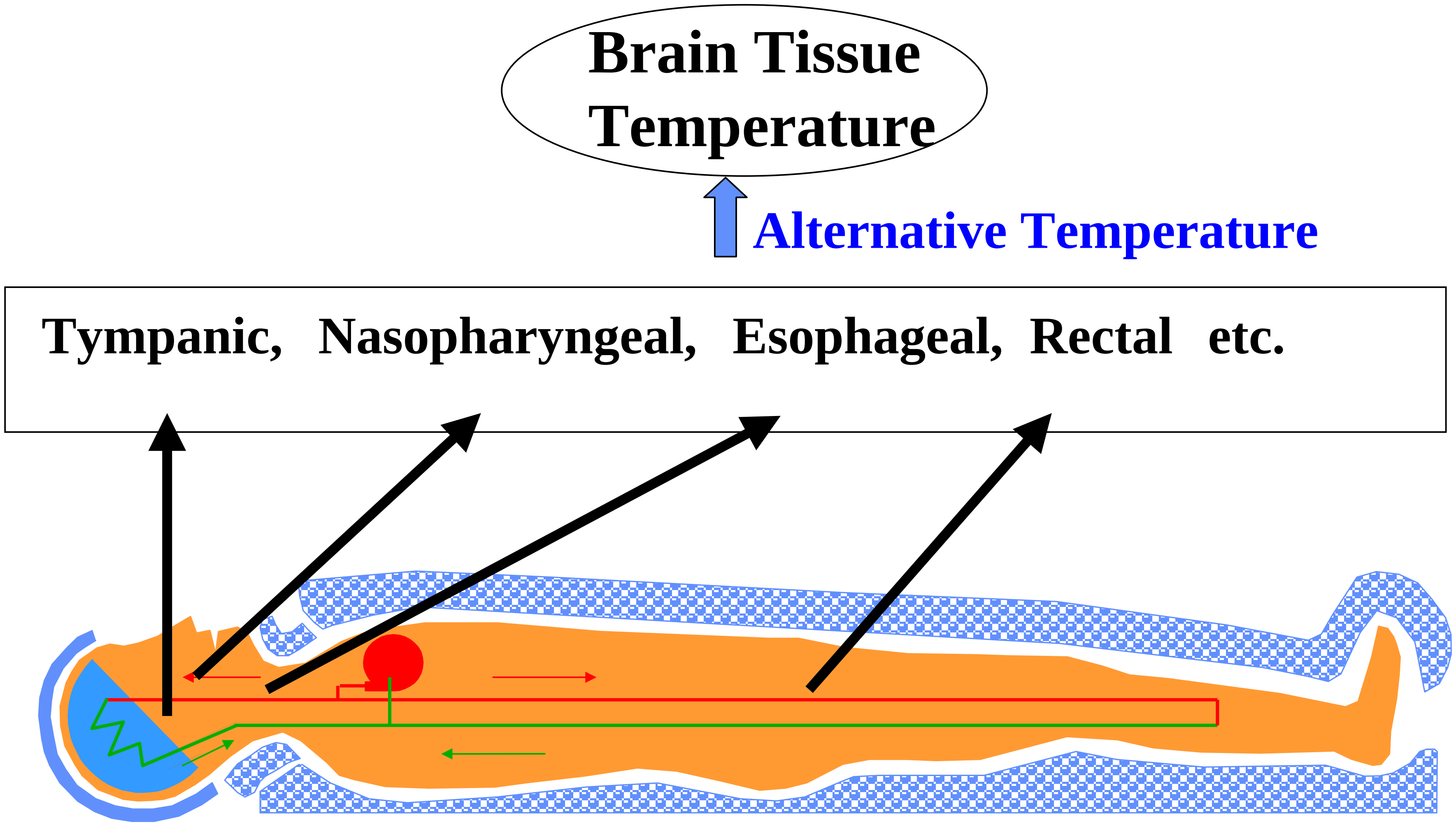


Step-by-step Management of Body Temperature



Automatic Controller of Brain Temperature
Patient&Water-cooling Blanket
Basic Characteristic Estimation
Brain
Temp.
Water
Temp.
Compuer
(Algorism)
Reservoir
P
Warming
Apparatus
for Making
Cold Water
Cooling
P
Valve
Heating
Regulation
Reference

Measurement of Temperature in Hypothermia

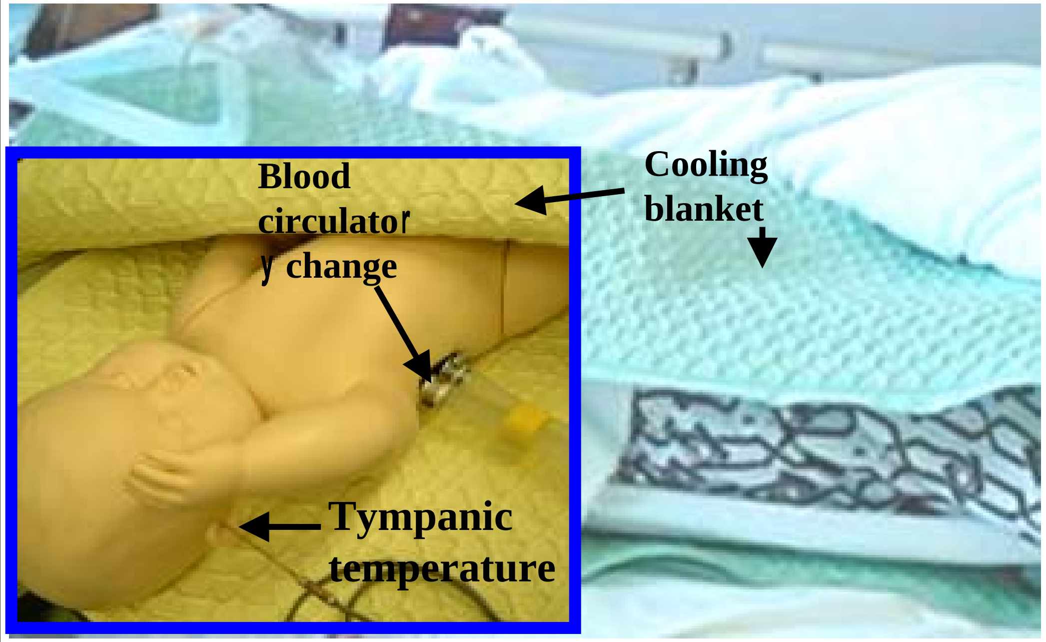


Concept of Adaptive Control Engineering

Different regulation

Various kinds of medical treatment

Change in external environment



Change in internal environment

- Circulatory change
- Metabolic change

etc.

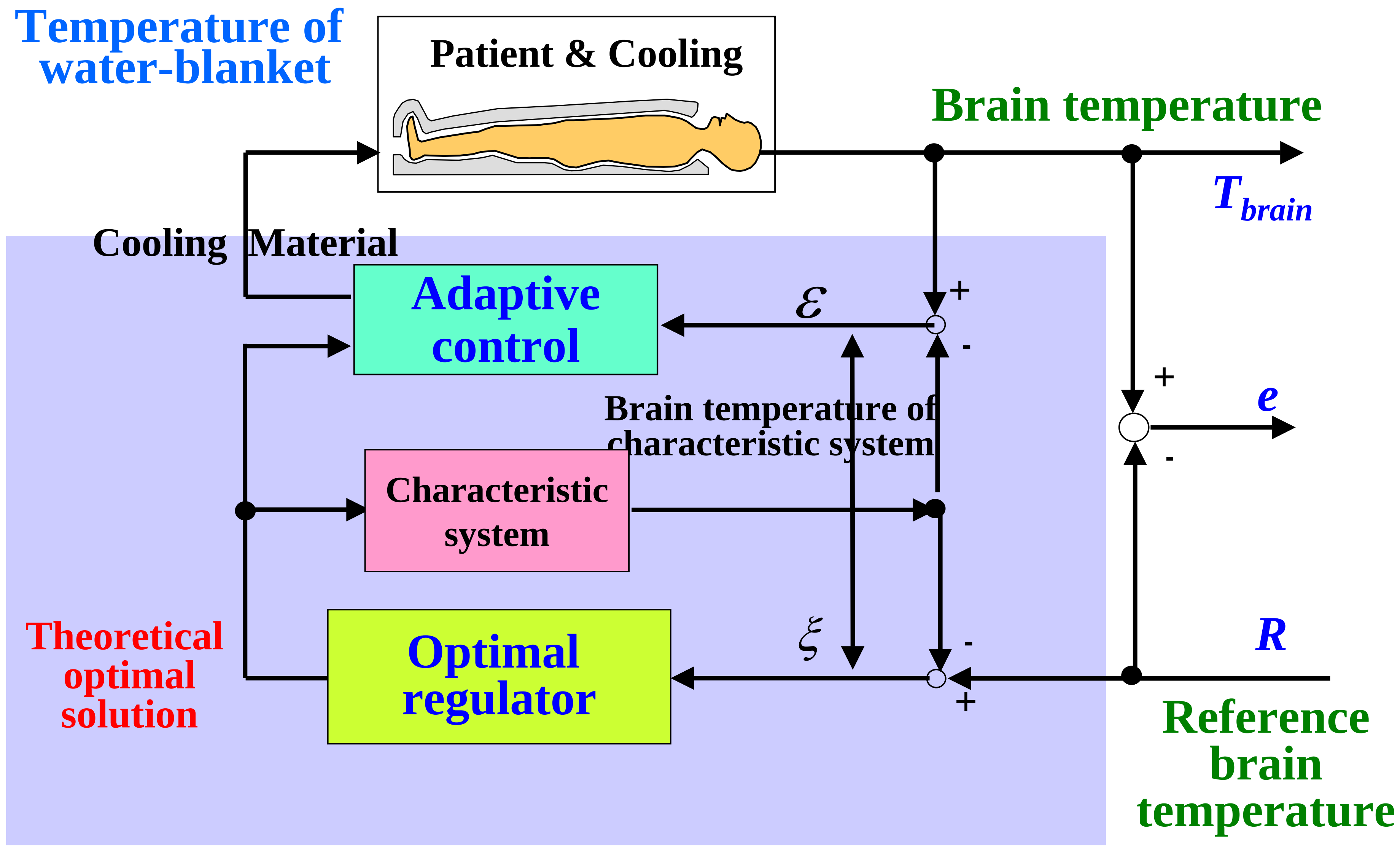
Unknown thermal characteristic

Patient under the brain hypothermia treatment

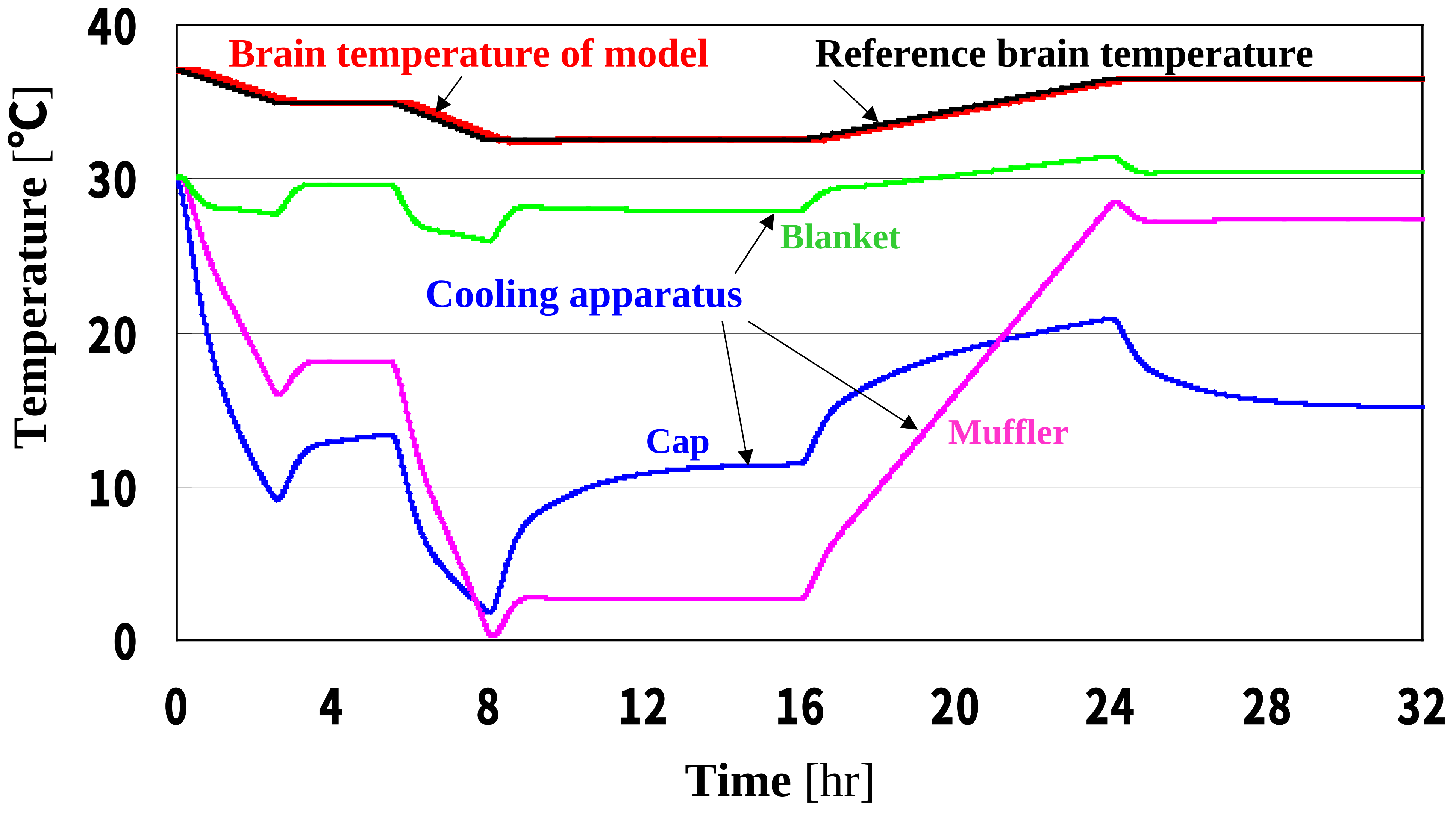
Adaptive control

Realization of desired brain temperature

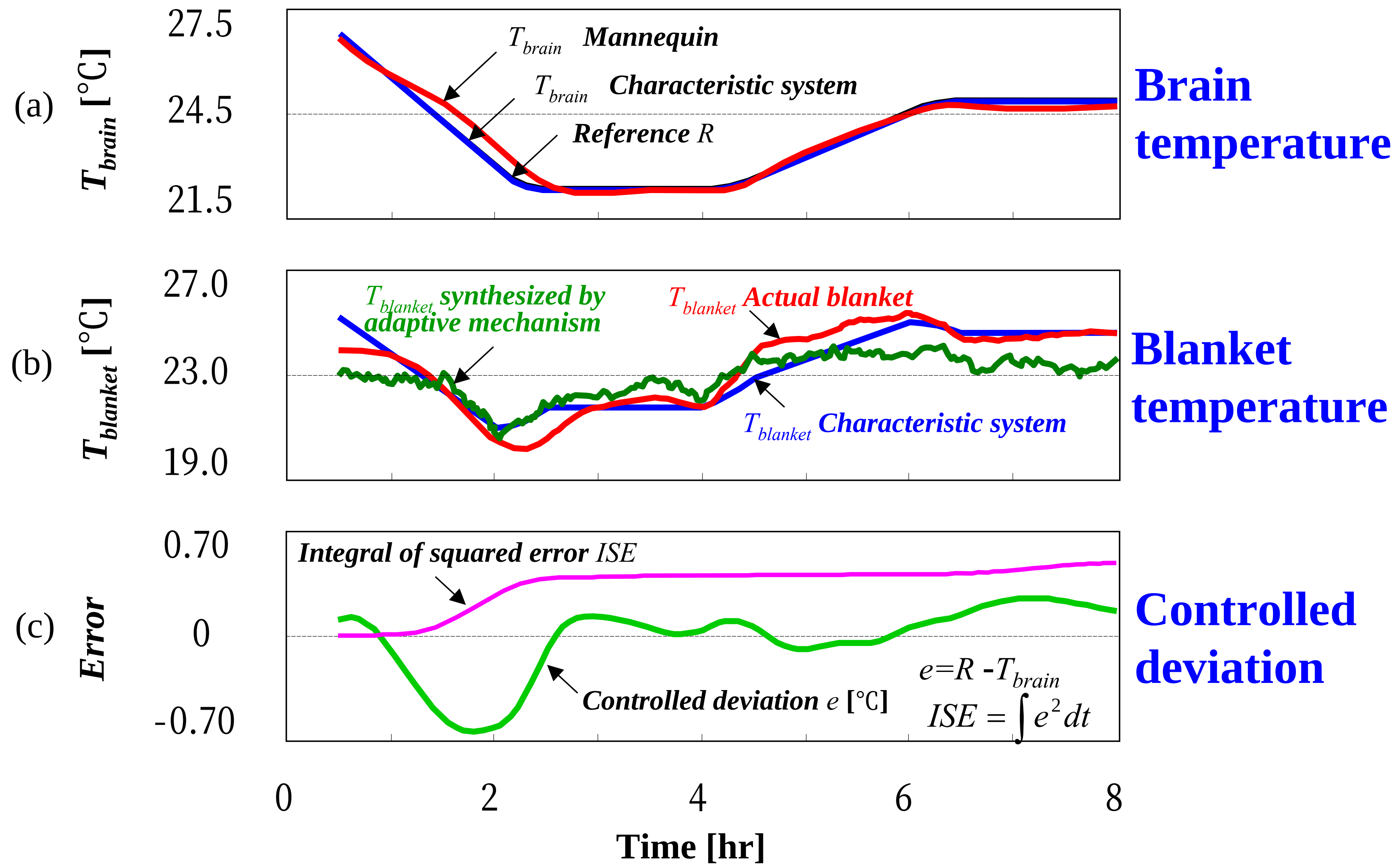
Optimal・Adaptive Control



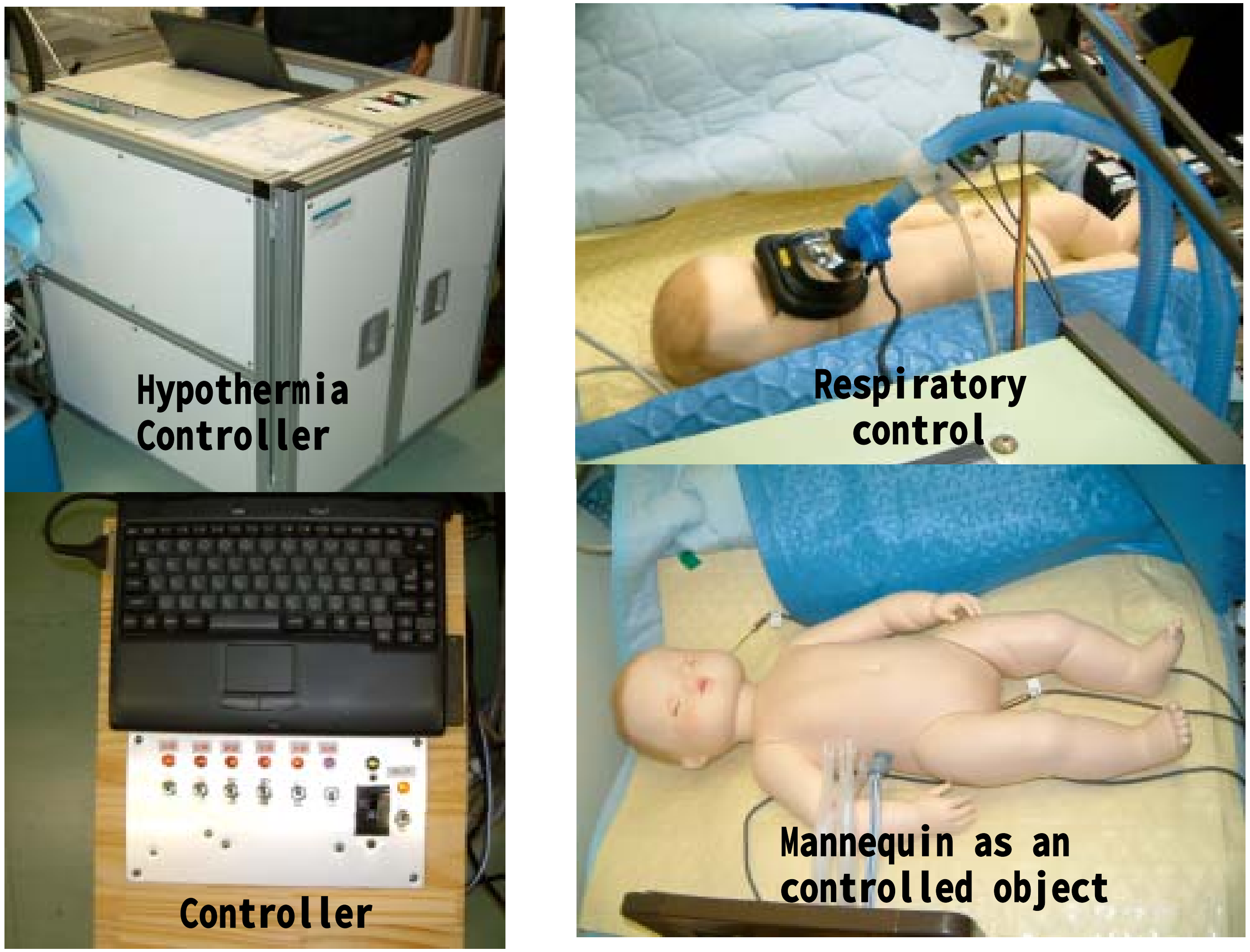
Control using Solution by Optimal Calculation



Experimental Result

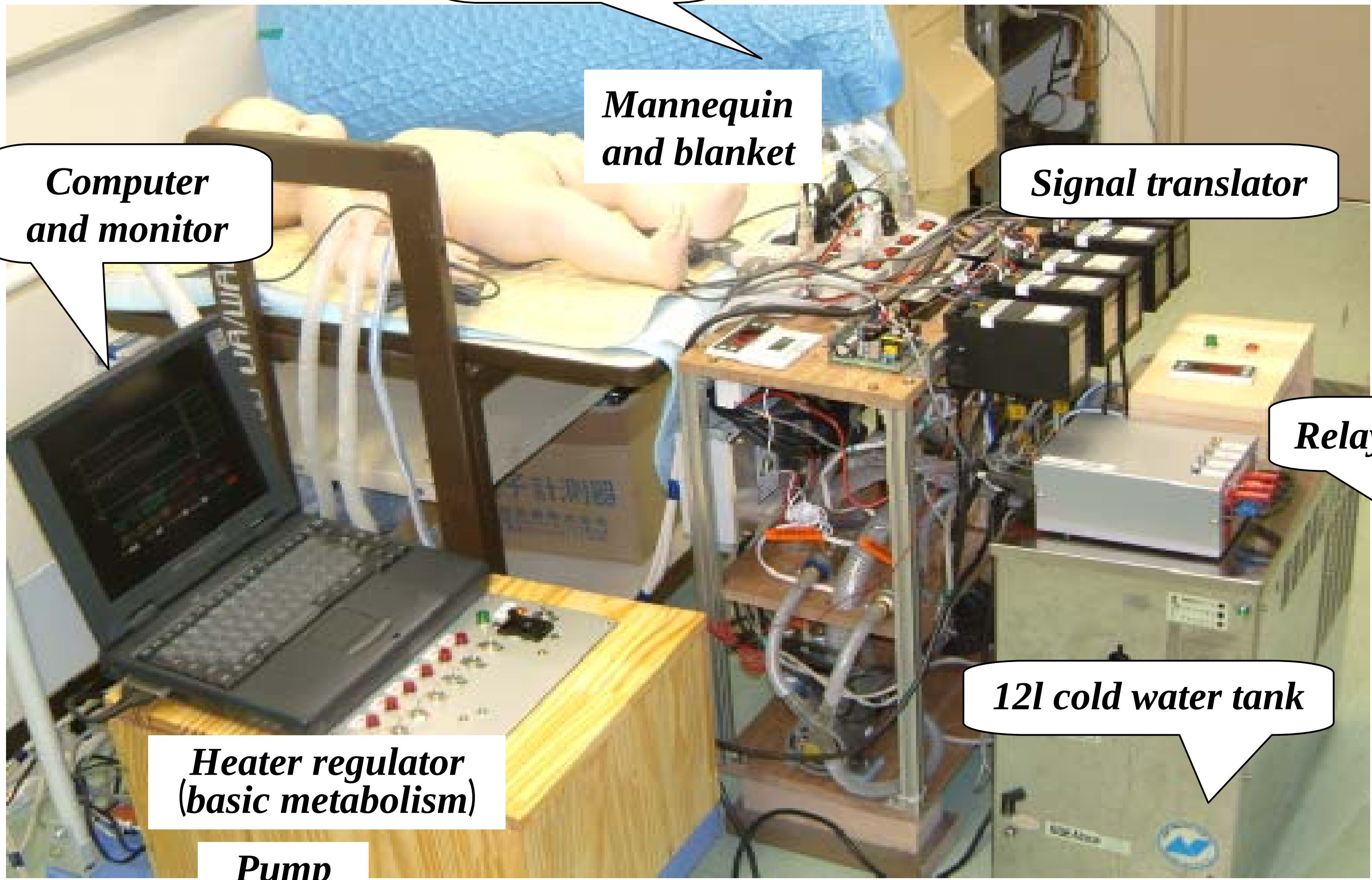


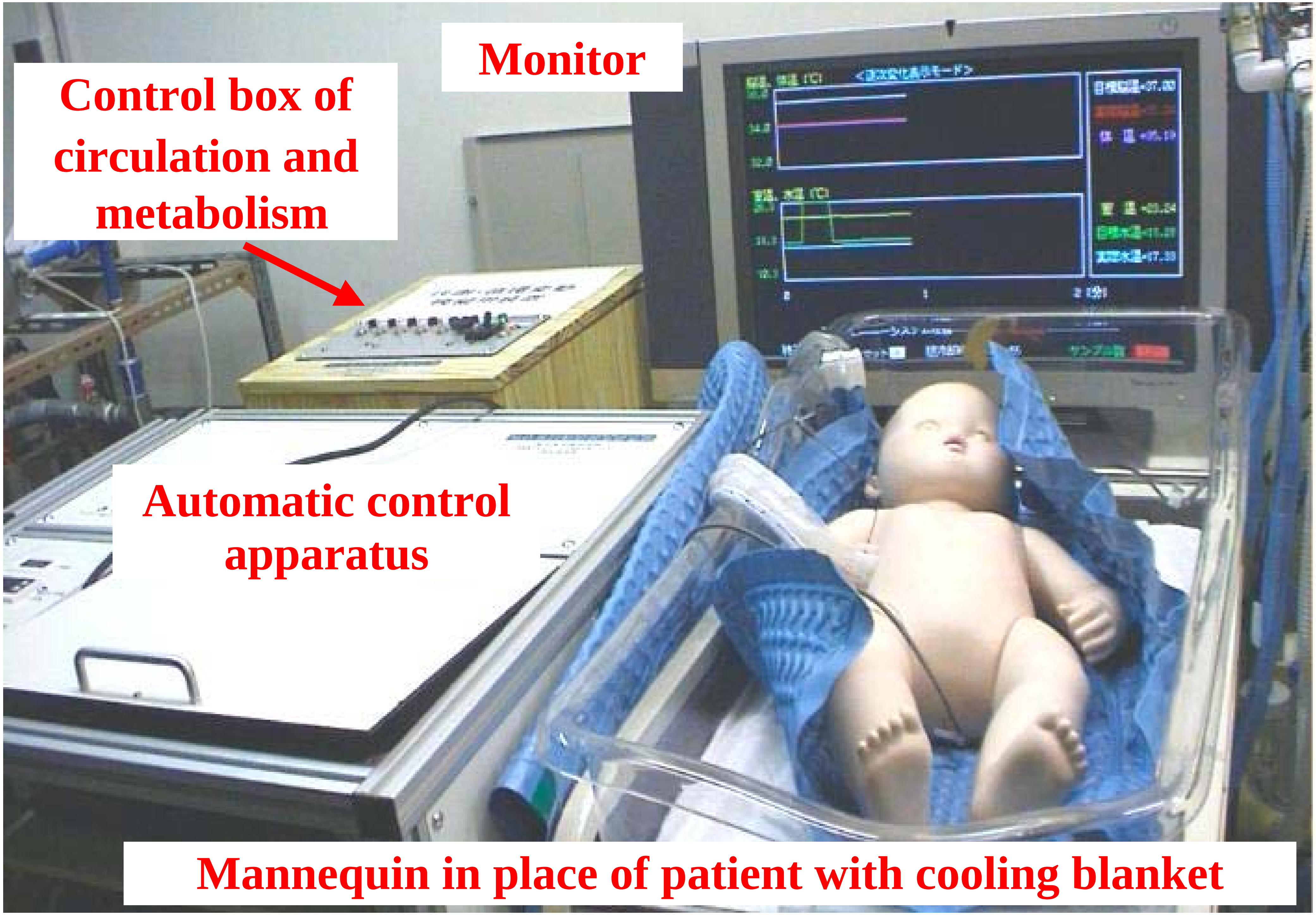
Brain Hypothermia Treatment Using Thermal Mannequin

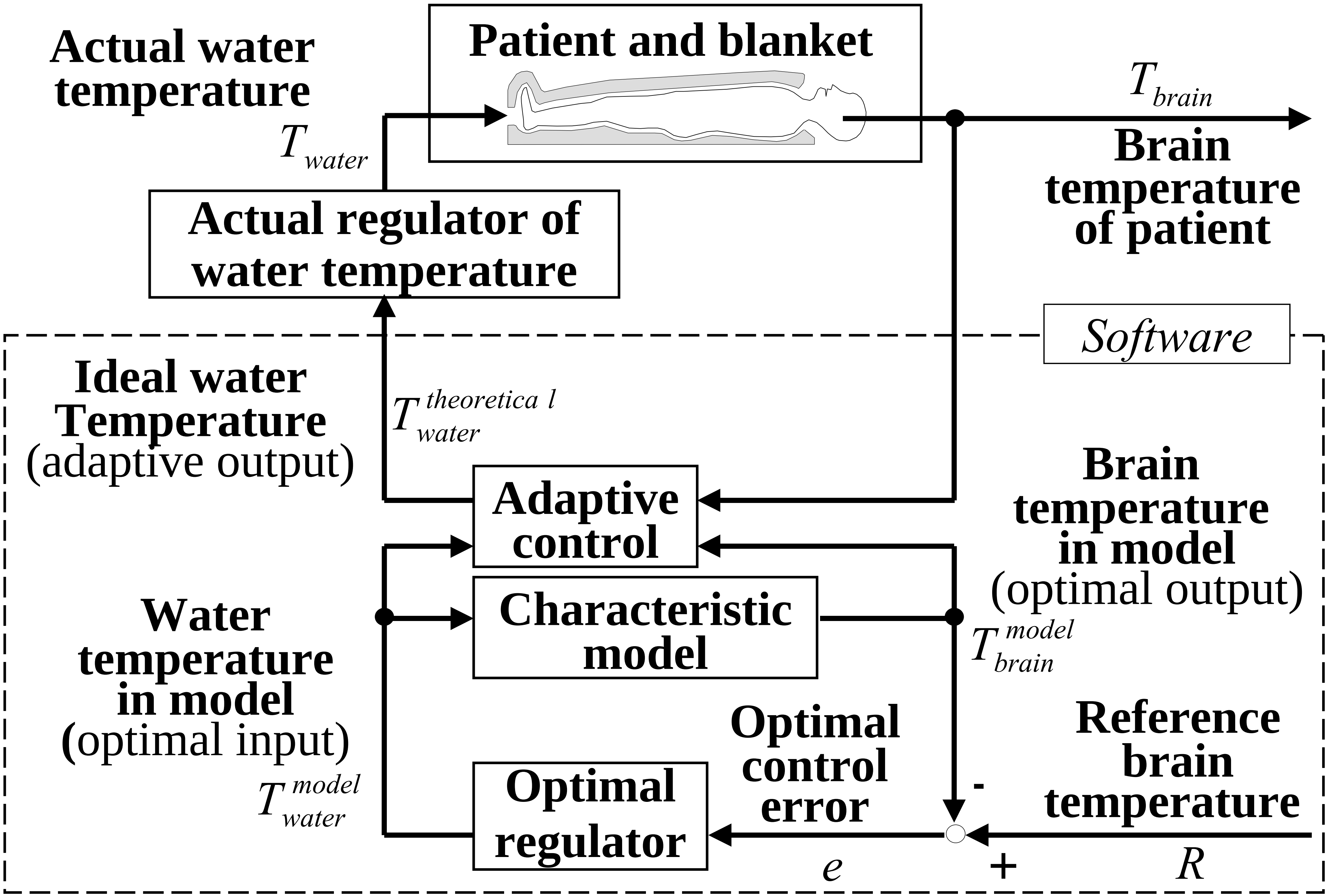


Mannequin controlled by water circulation (blood flow) and heater (metabolic heat)

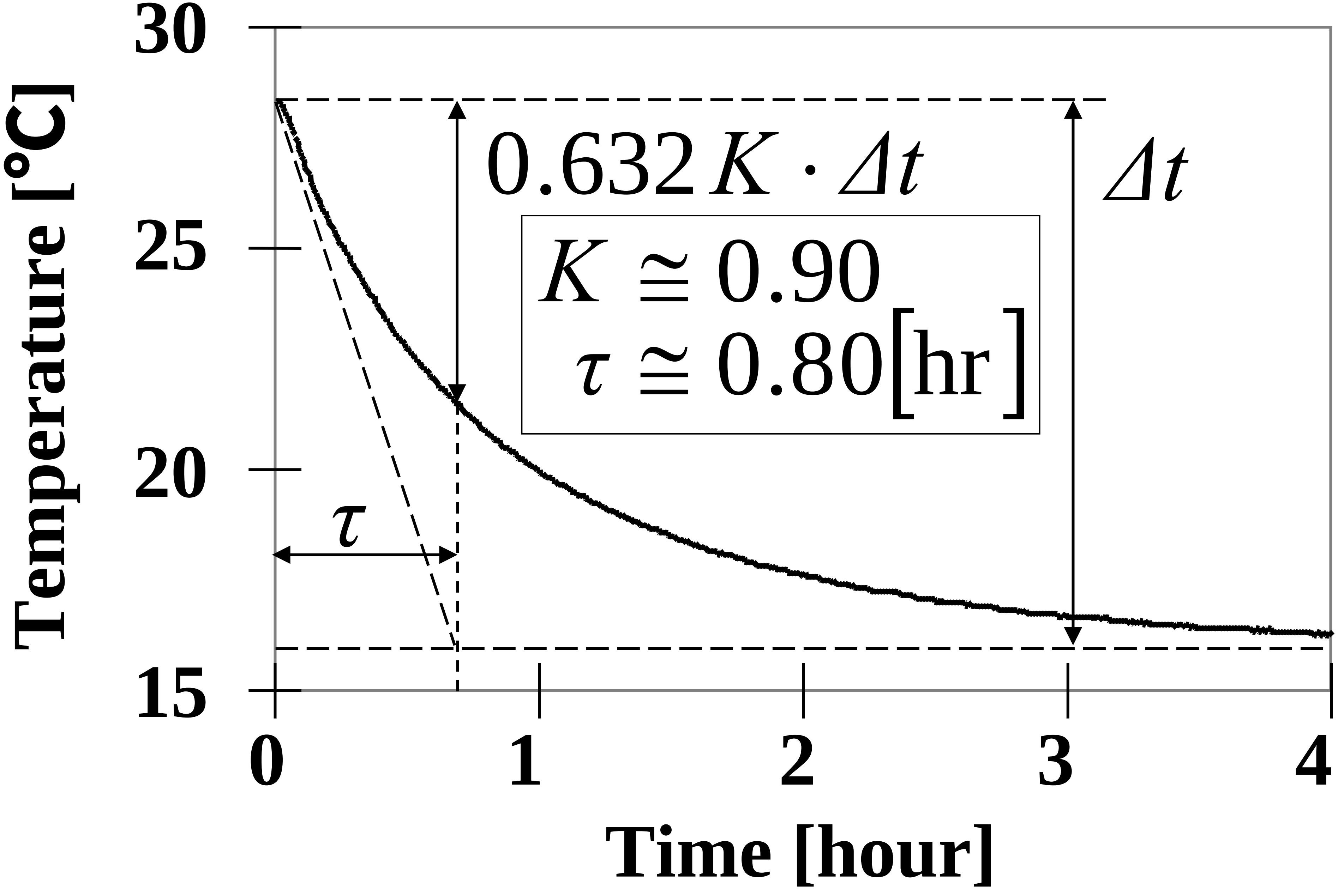
Overview of Experimental Equipment (1)

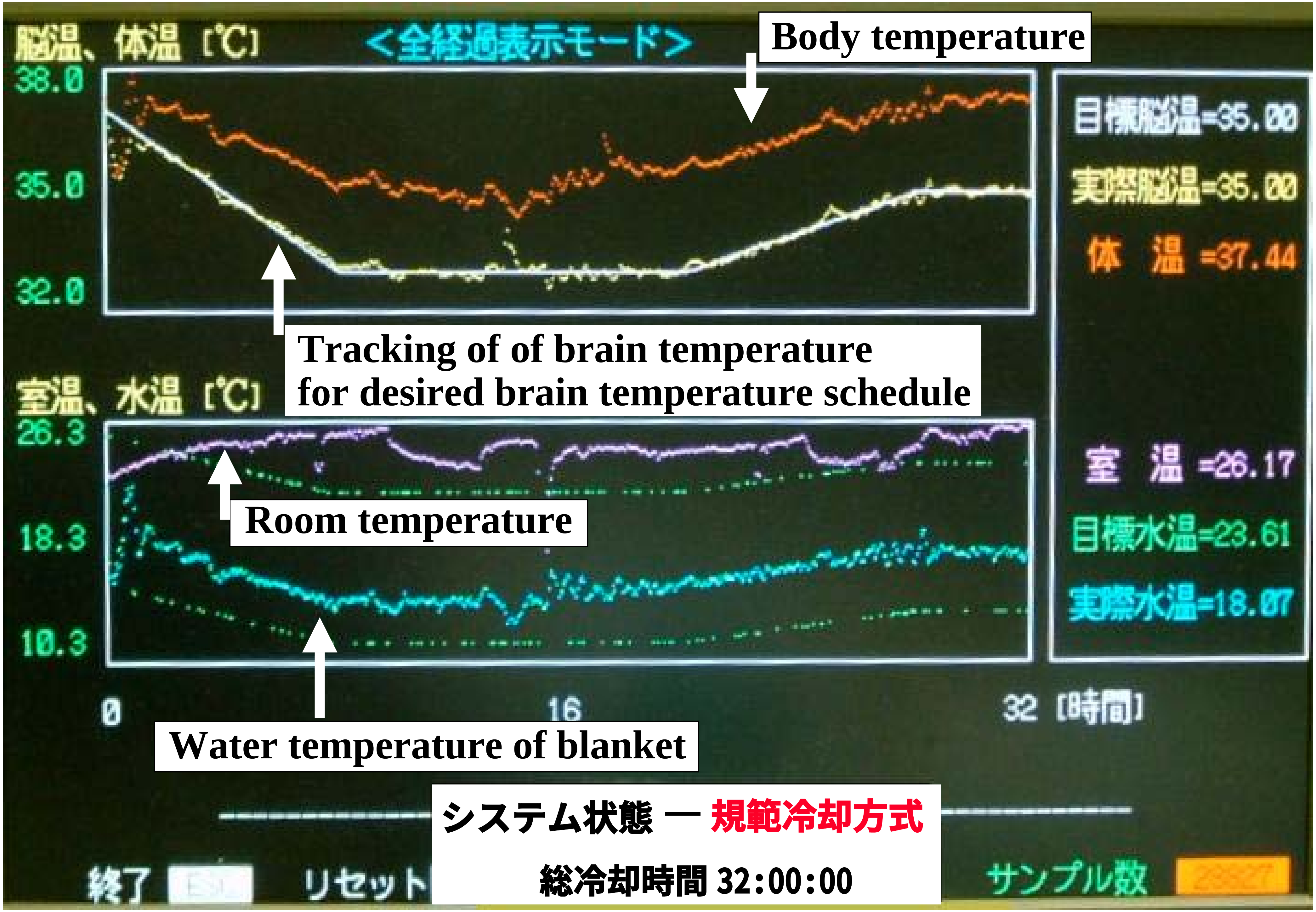



Control box of circulation and metabolism
Monitor
Automatic control apparatus
Mannequin in place of patient with cooling blanket

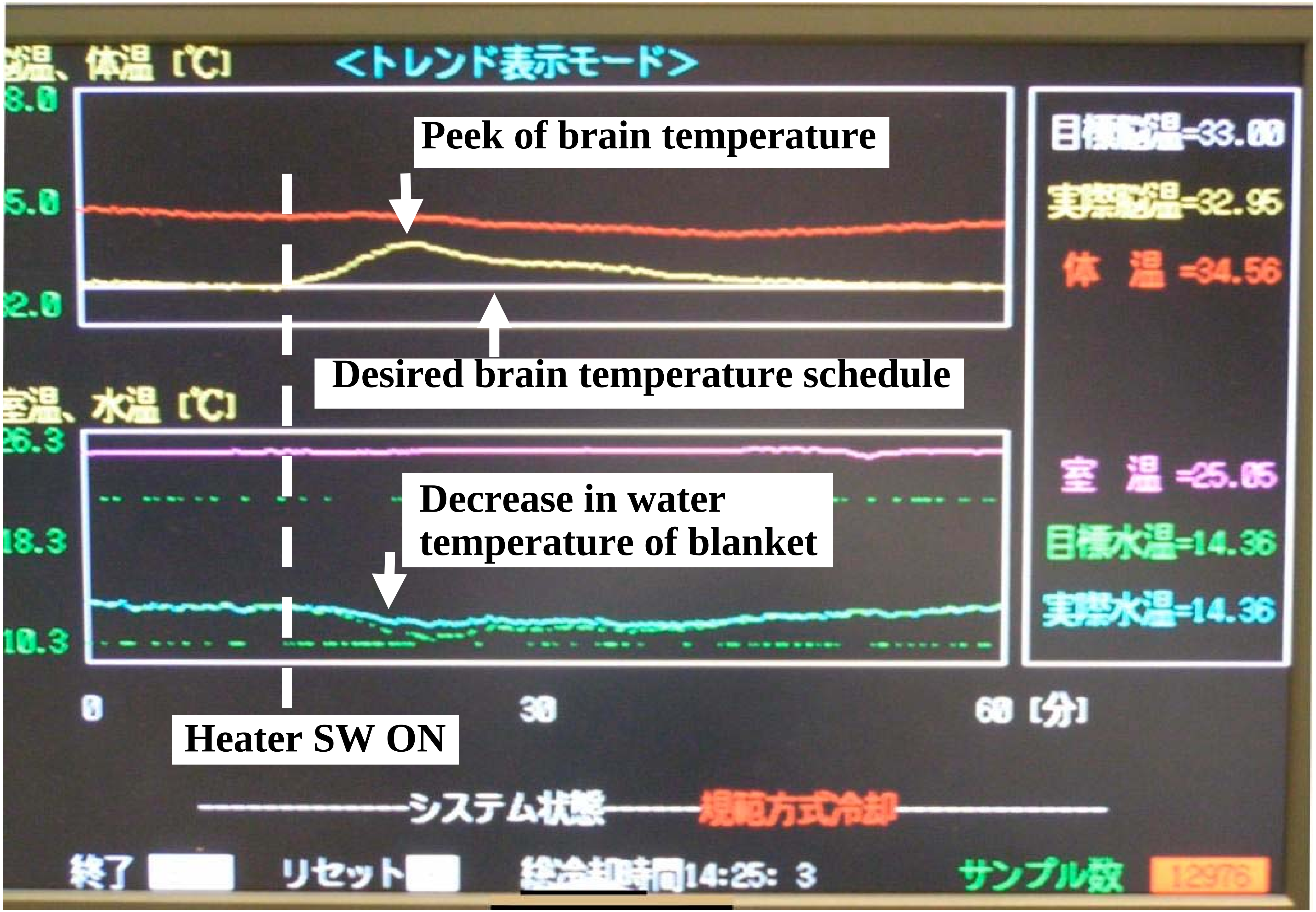

Actual water temperature
T_{water}
Patient and blanket
T_{brain}
Brain temperature of patient
Actual regulator of water temperature
Software
Ideal water Temperature (adaptive output)
$T_{water}^{theoretical}$
Adaptive control
Brain temperature in model (optimal output)
Characteristic model
T_{brain}^{model}
Water temperature in model (optimal input)
T_{water}^{model}
Optimal regulator
Optimal control error
e
-
+
Reference brain temperature
R

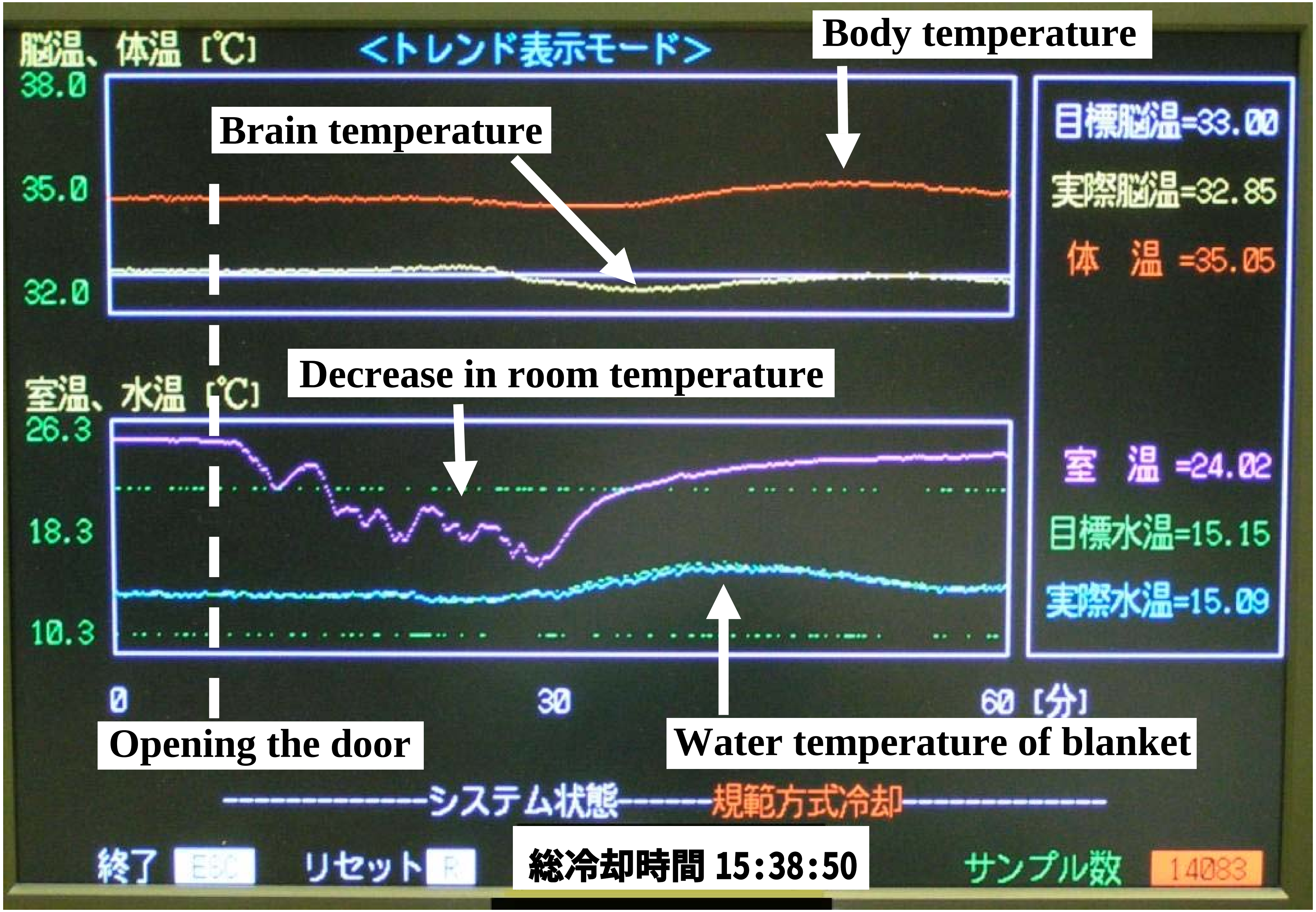
Characteristics of Mannequin to Step change of Temperature





脳温、体温 [℃]
<全経過表示モード>
Body temperature
38.0
35.0
32.0
目標脳温=35.00
実際脳温=35.00
体 温 =37.44
Tracking of of brain temperature
for desired brain temperature schedule
室温、水温 [℃]
26.3
18.3
10.3
Room temperature
室 温 =26.17
目標水温=23.61
実際水温=18.07
0
16
32 [時間]
Water temperature of blanket
システム状態 ― 規範冷却方式
総冷却時間 32:00:00
終了
リセット
サンプル数

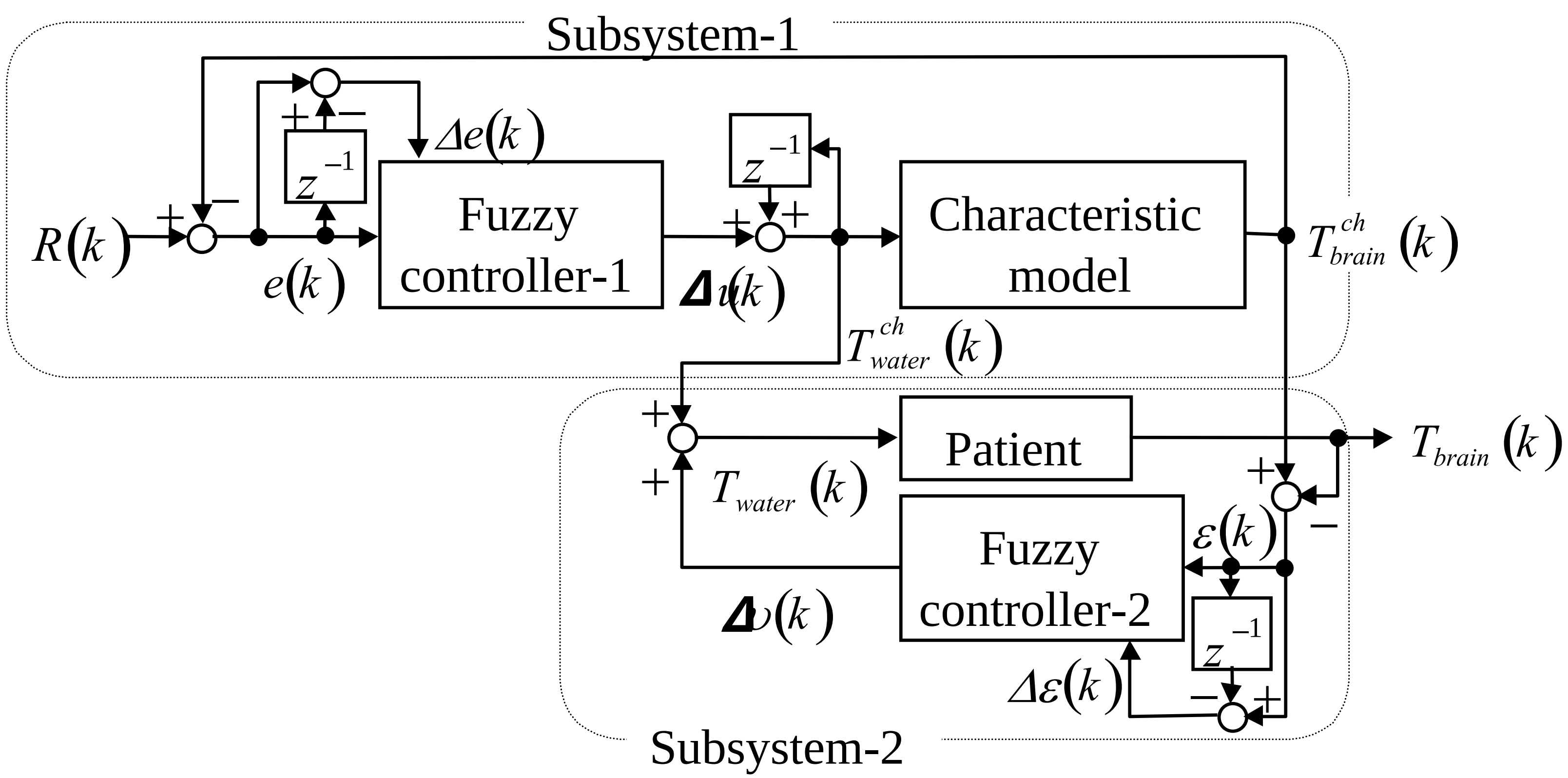

<トレンド表示モード>
Peek of brain temperature
Desired brain temperature schedule
Decrease in water
temperature of blanket
Heater SW ON
体 温 =34.56
目標水温=14.36
実際水温=14.36
0
30
60 [分]
システム状態
サンプル数


脳温、体温 [℃]
<トレンド表示モード>
Body temperature
38.0
Brain temperature
35.0
32.0
目標脳温=33.00
実際脳温=32.85
体 温 =35.05
室温、水温 [℃]
Decrease in room temperature
26.3
18.3
10.3
室 温 =24.02
目標水温=15.15
実際水温=15.09
0
30
60 [分]
Opening the door
Water temperature of blanket
システム状態
規範方式冷却
終了
ESC
リセット
R
総冷却時間 15:38:50
サンプル数
14083

Fuzzy Control of Brain Temperature by Water-Cooling System

Biophysical System Engineering
Graduate School of Allied Health Sciences
Tokyo Medical and Dental University

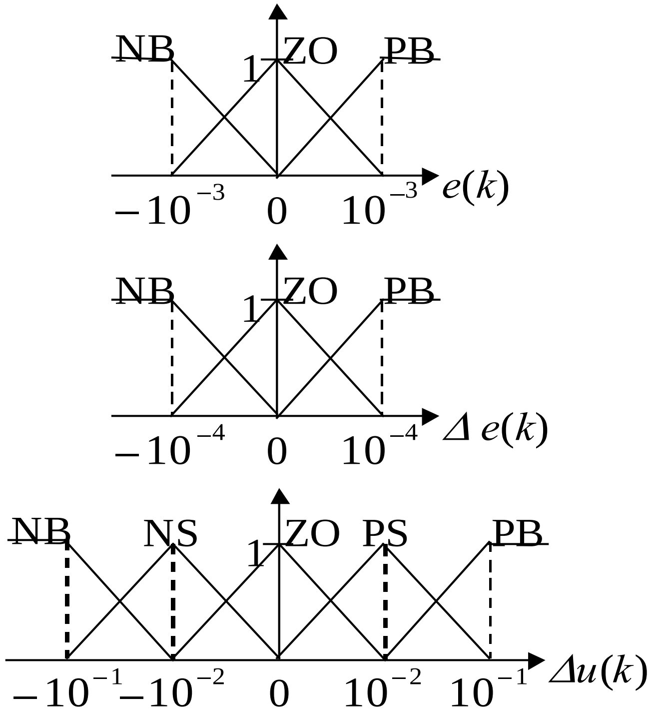
H.Wakamatsu, T.Wakatsuki, T.Utsuki

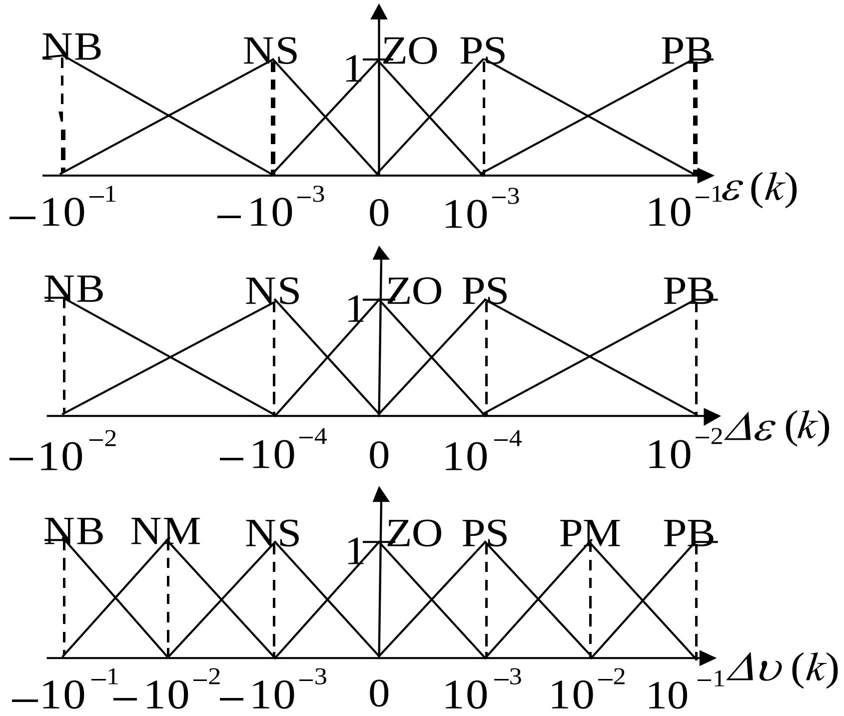


Block Diagram of Fuzzy Control System of Brain Temperature

Membership Function and Inference Rule for the Experiment Using Mathematical Model

Sampling period = 4[sec]



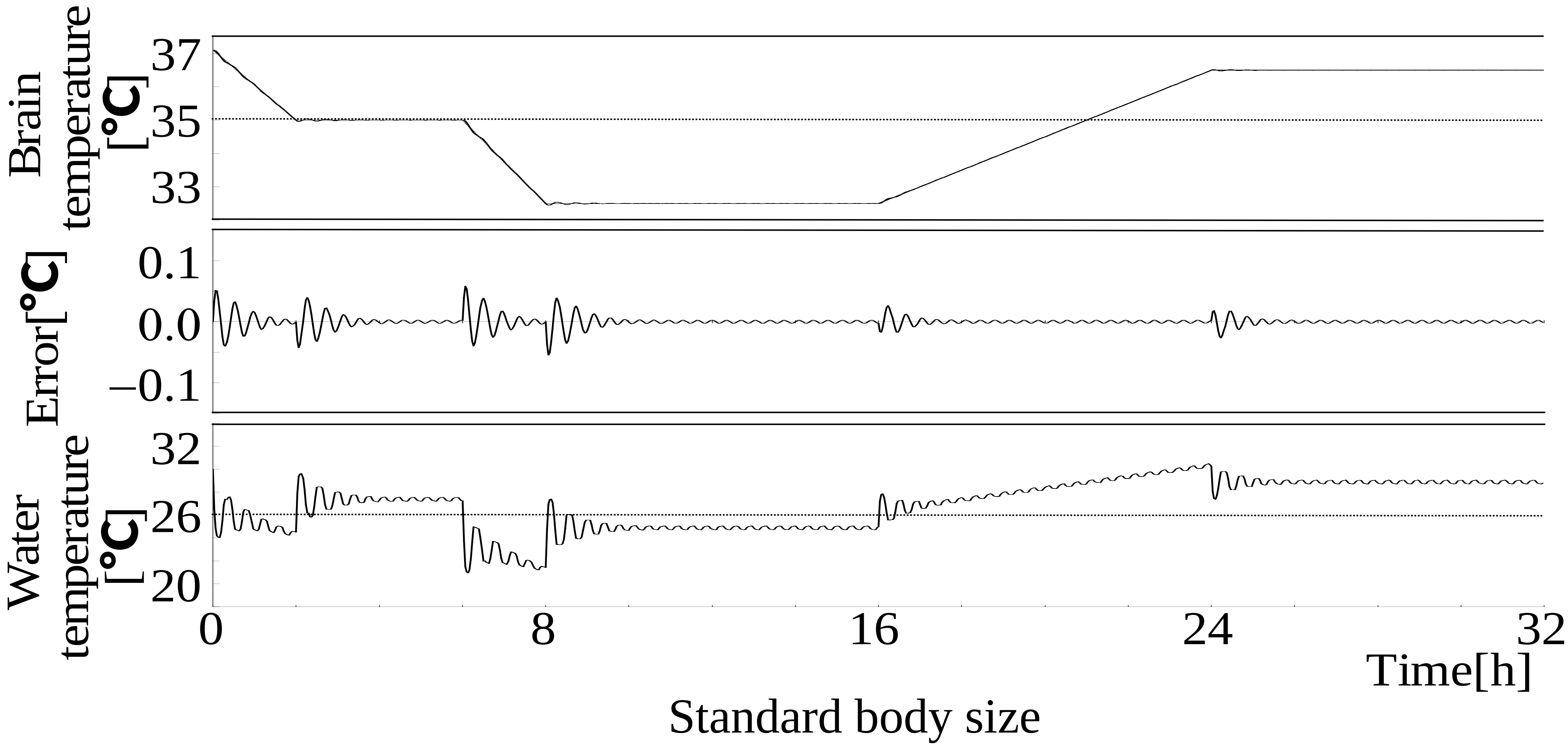


$\Delta u(k)$		$e(k)$ PB	$e(k)$ ZO	$e(k)$ NB
$\Delta e(k)$	PB	PB	PS	ZO
	ZO	PS	ZO	NS
	NB	ZO	NS	NB

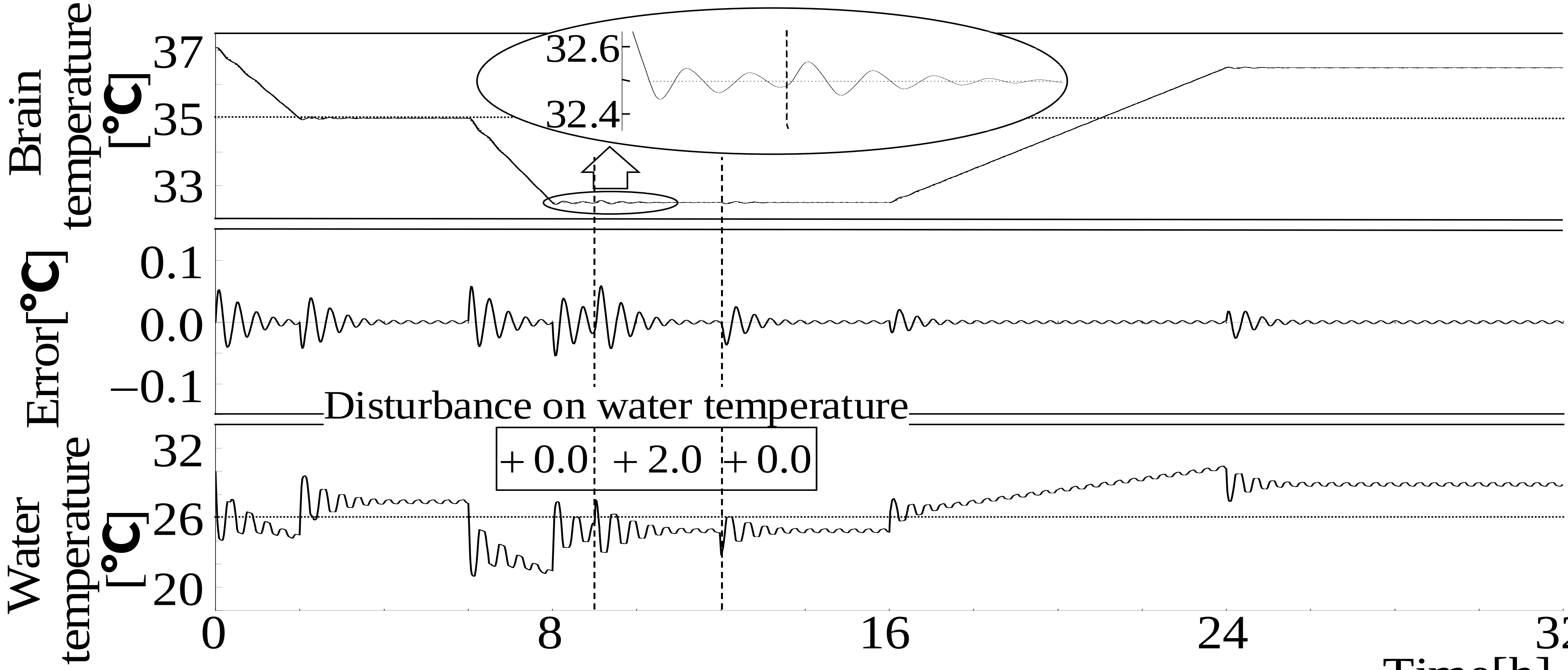
Fuzzy Controller-1

$\Delta\upsilon(k)$		$\varepsilon(k)$ PB	$\varepsilon(k)$ PS	$\varepsilon(k)$ ZO	$\varepsilon(k)$ NS	$\varepsilon(k)$ NB
$\Delta\varepsilon(k)$	PB	PB	PB	PM	PS	ZO
	PS	PB	PM	PS	ZO	NS
	ZO	PM	PS	ZO	NS	NM
	NS	PS	ZO	NS	NM	NB
	NB	ZO	NS	NM	NB	NB

Fuzzy Controller-2

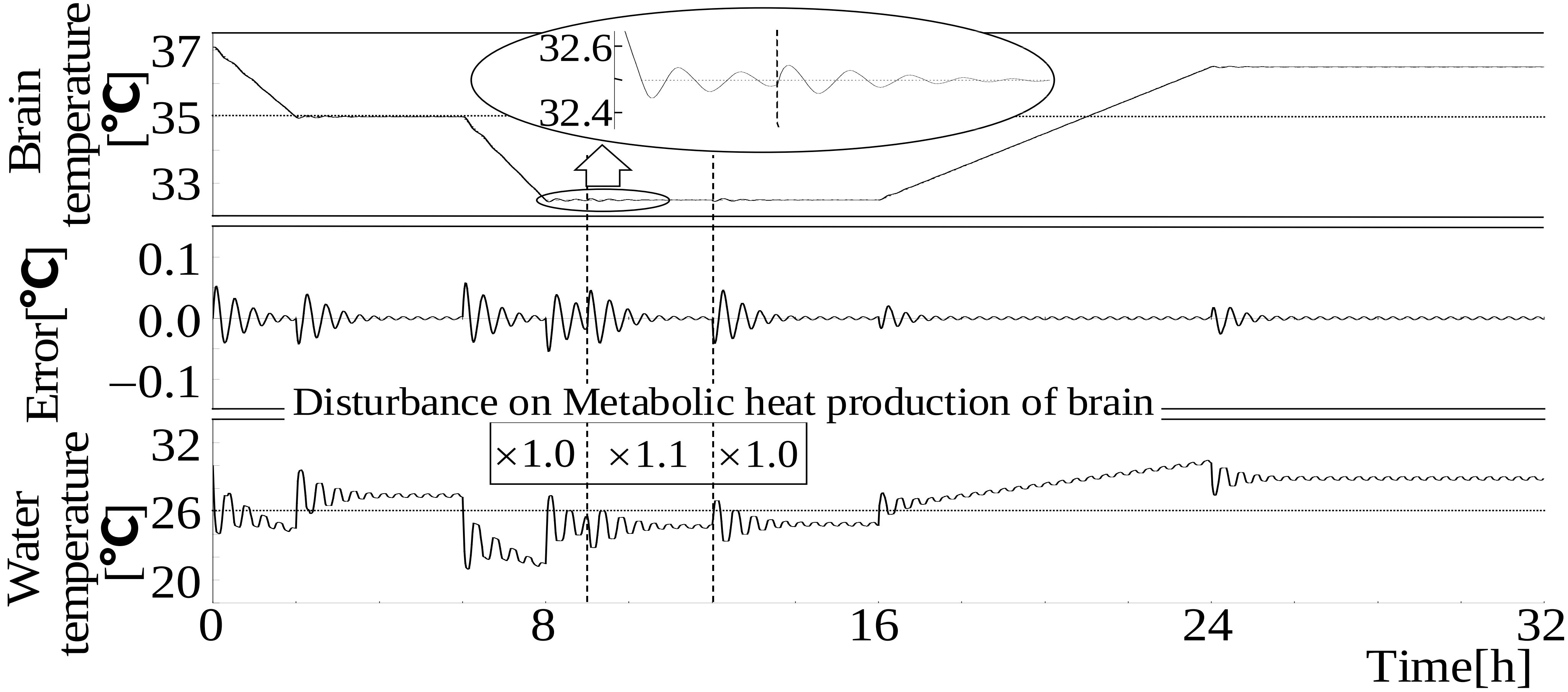


Controlled dynamics of brain and water temperature



On water temperature change during9-12hour from the beginning of experiment.

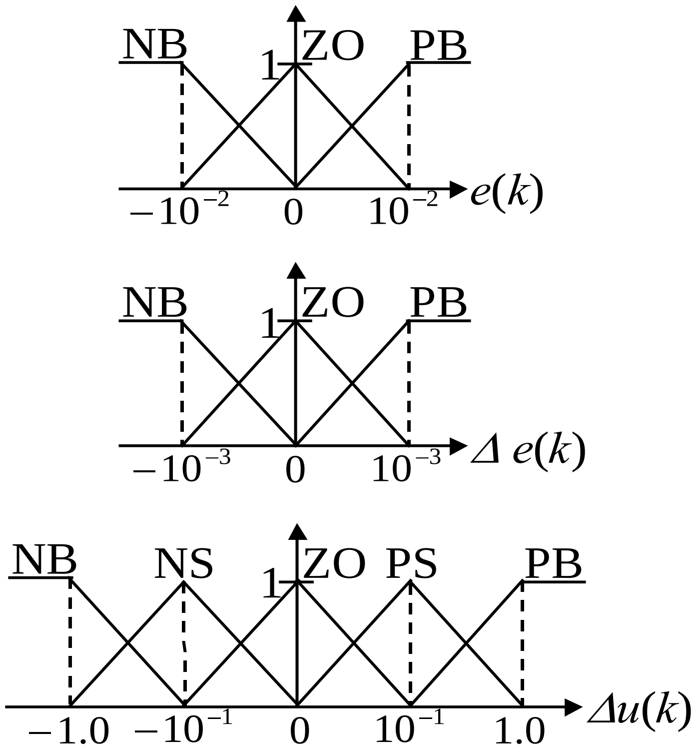
Controlled dynamics of brain and water temperature



On metabolic rate change during9-12hour
from the beginning of experiment.

Controlled dynamics of brain and water temperature

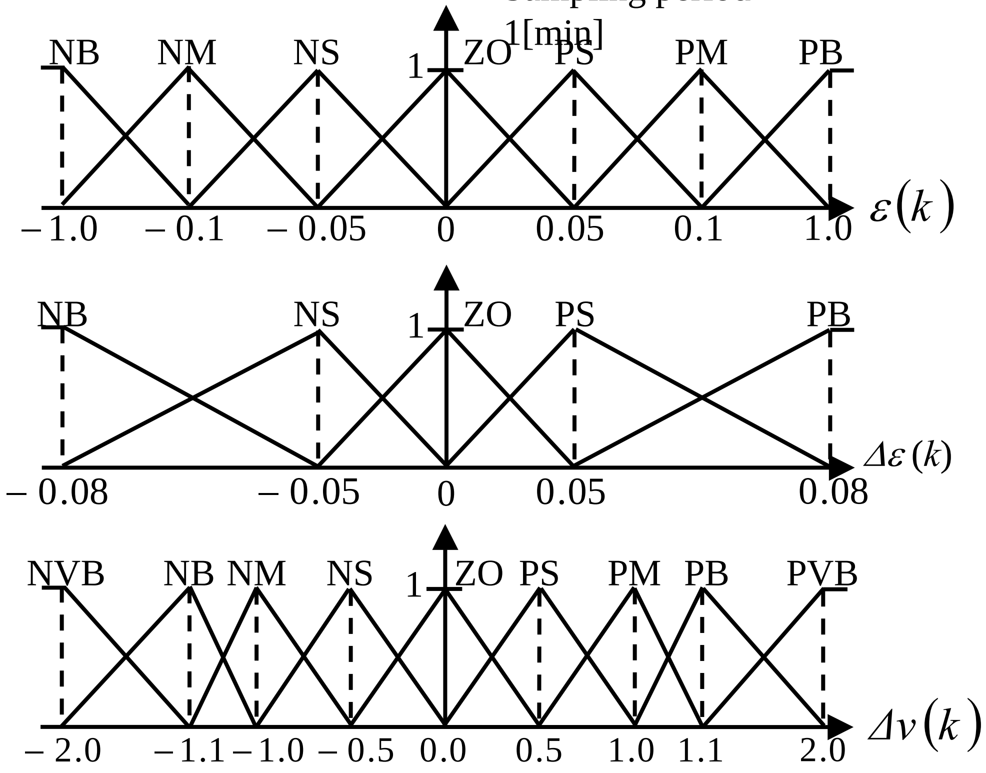
Membership Function and Inference Rule for the Experiment Using Mannequin



$\Delta u(k)$		$e(k)$		
		PB	ZO	NB
$\Delta e(k)$	PB	PB	PS	ZO
	ZO	PS	ZO	NS
	NB	ZO	NS	NB

Fuzzy Controller-1

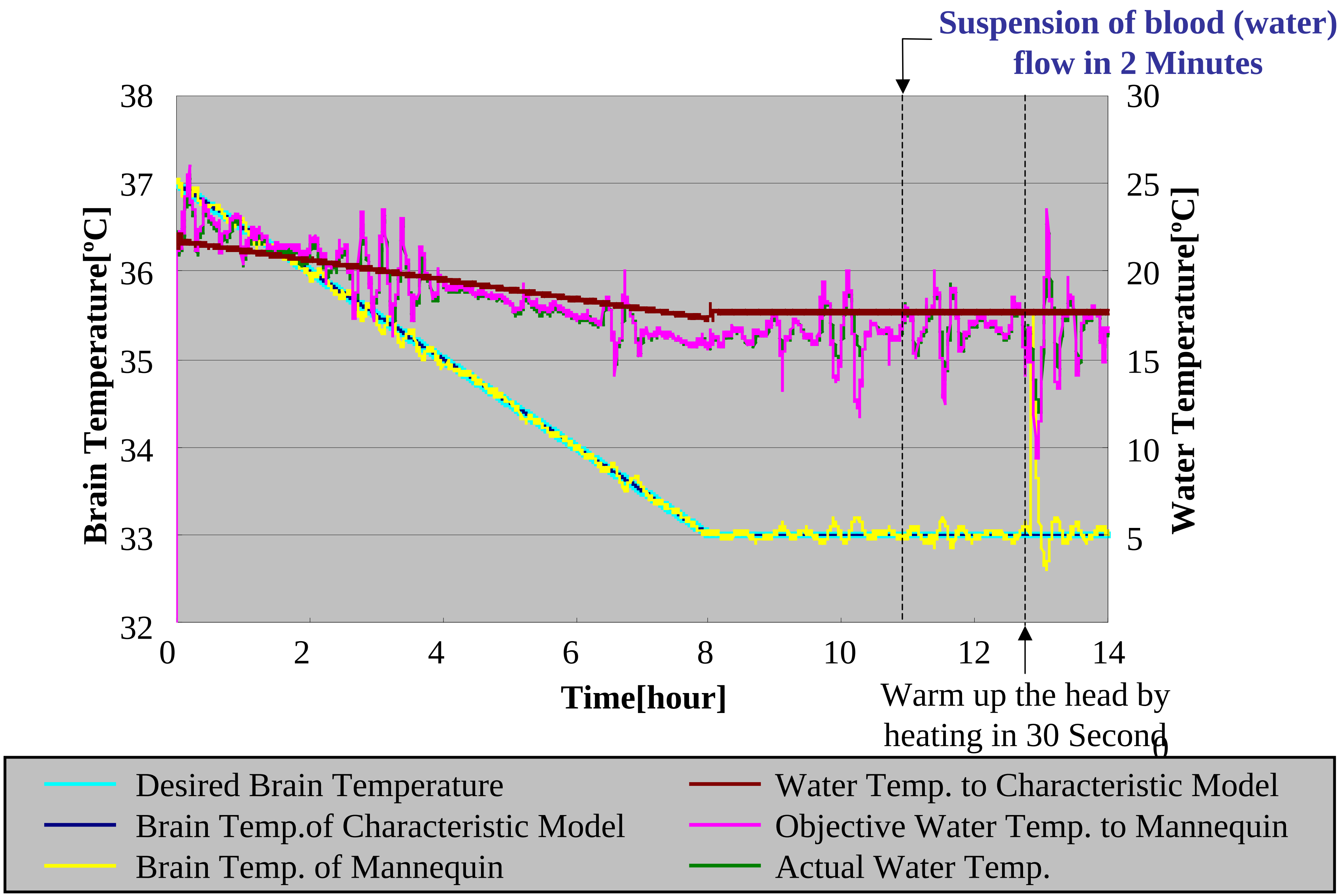
Sampling period = 1[min]



$\Delta \upsilon(k)$		$\varepsilon(k)$						
		PB	PM	PS	ZO	NS	NM	NB
$\Delta\varepsilon(k)$	PB	PVB	PVB	PS	ZO	PVB	PVB	PVB
	PS	PVB	PVB	PS	ZO	PM	PB	PVB
	ZO	PVB	ZO	ZO	ZO	ZO	ZO	NVB
	NS	NVB	NB	NM	ZO	NS	NVB	NVB
	NB	NVB	NVB	NVB	ZO	NS	NVB	NVB

Fuzzy Controller-2

Experimental Result during Cooling and Stable Period

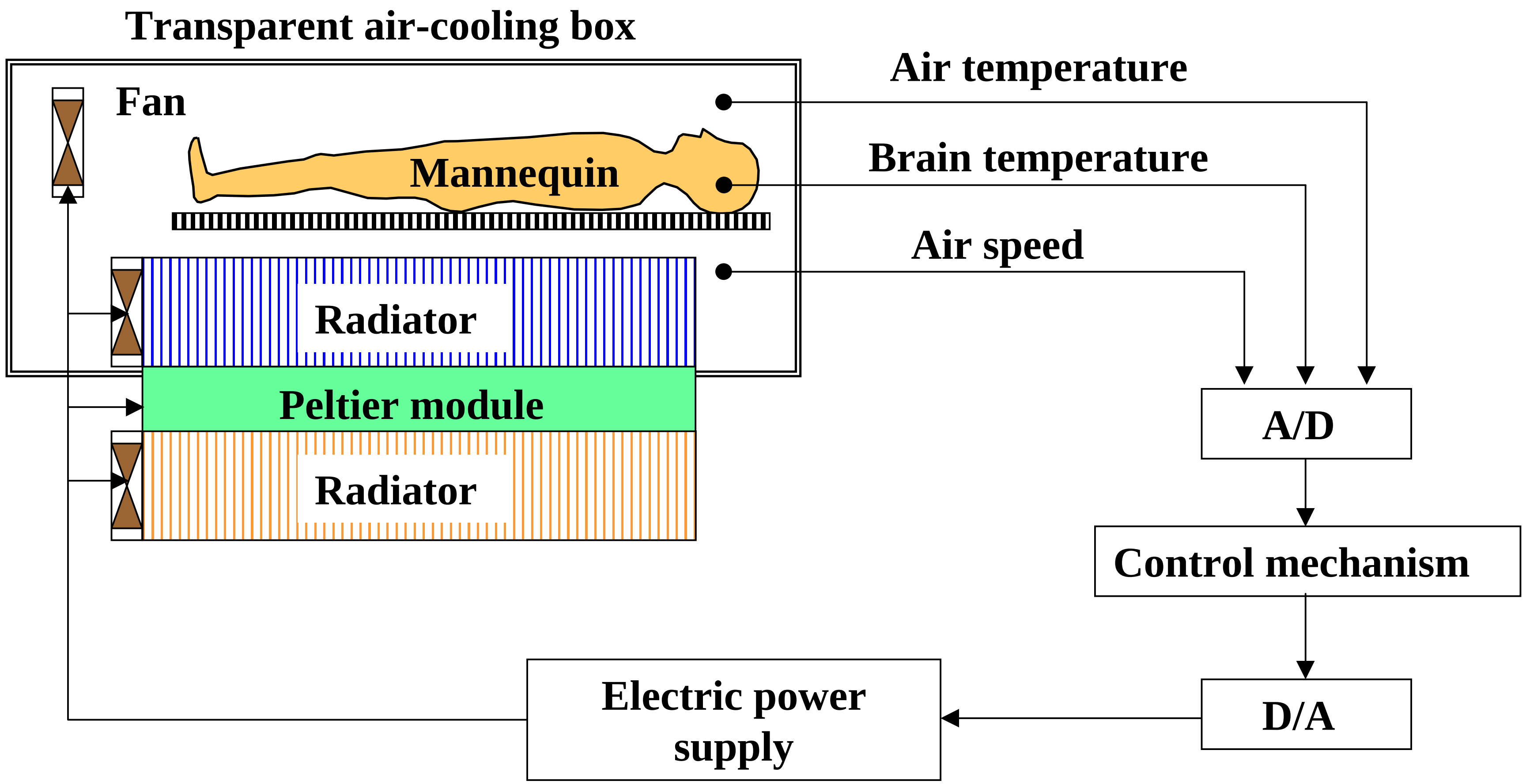


Control of Brain Temperature by Air-Cooling System

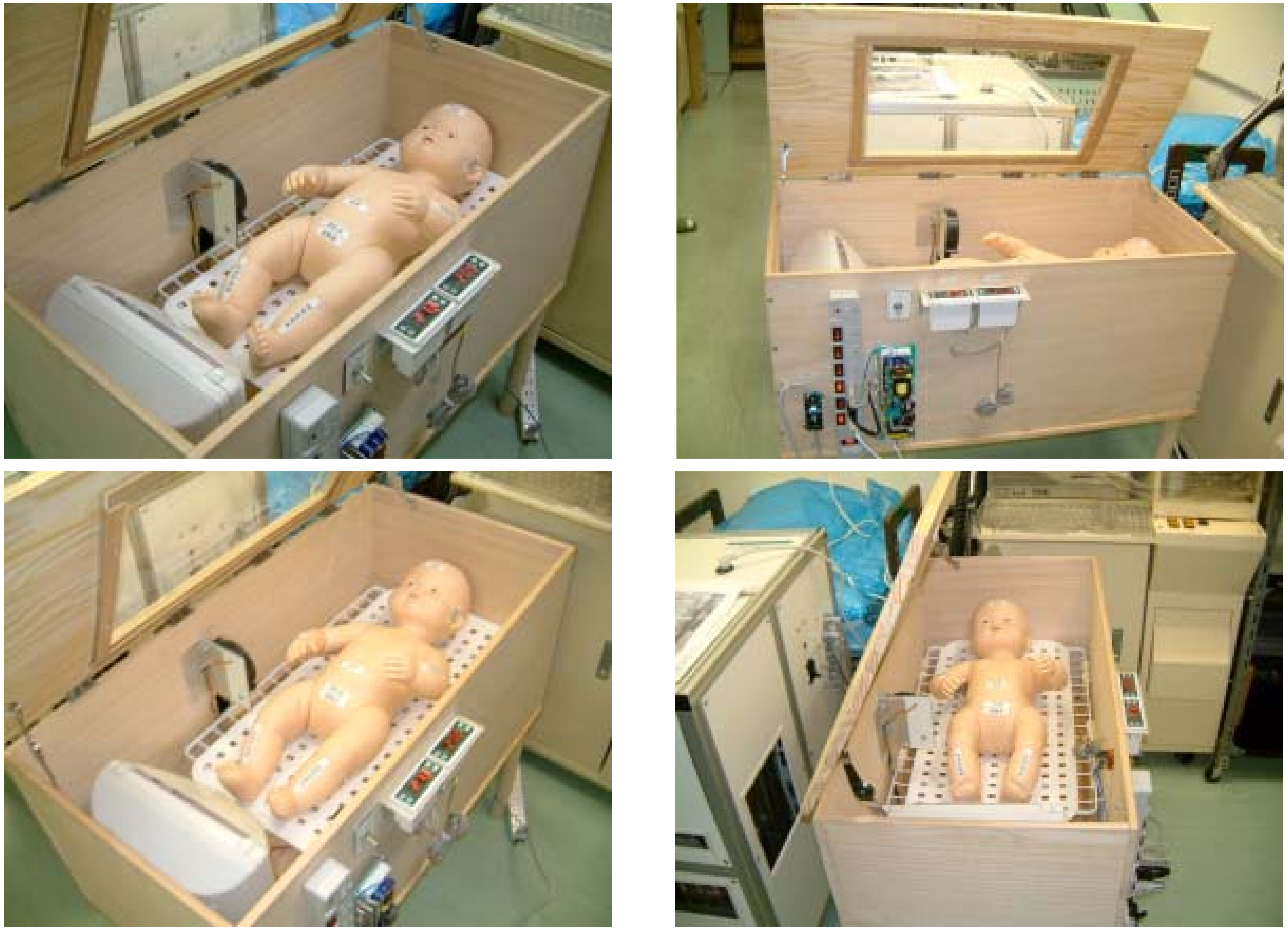
Biophysical System Engineering
Graduate School of Allied Health Sciences
Tokyo Medical and Dental University

H.Wakamatsu,T.Utsuki, T.Wakatsuki

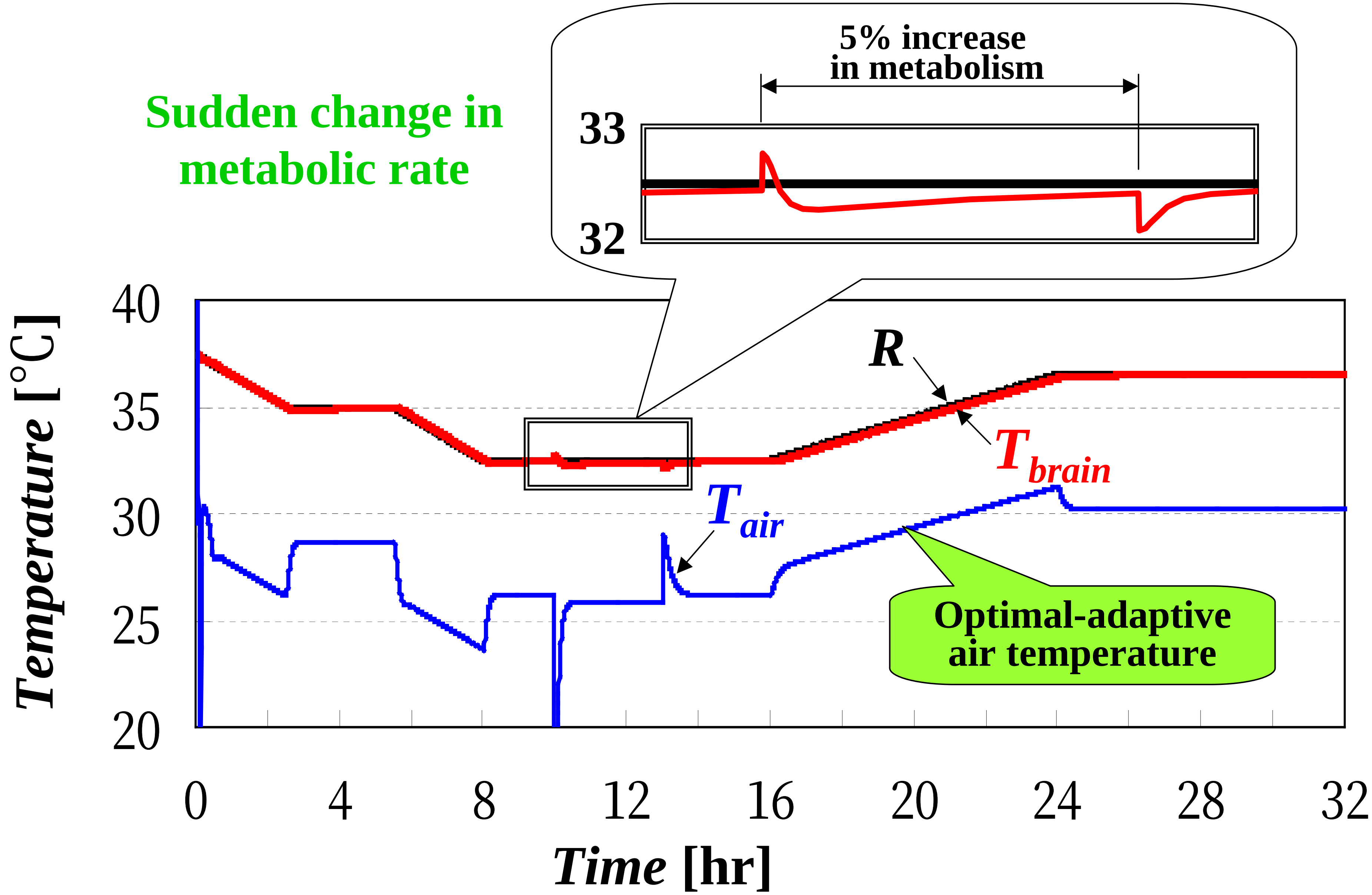
Air-cooling Incubating System



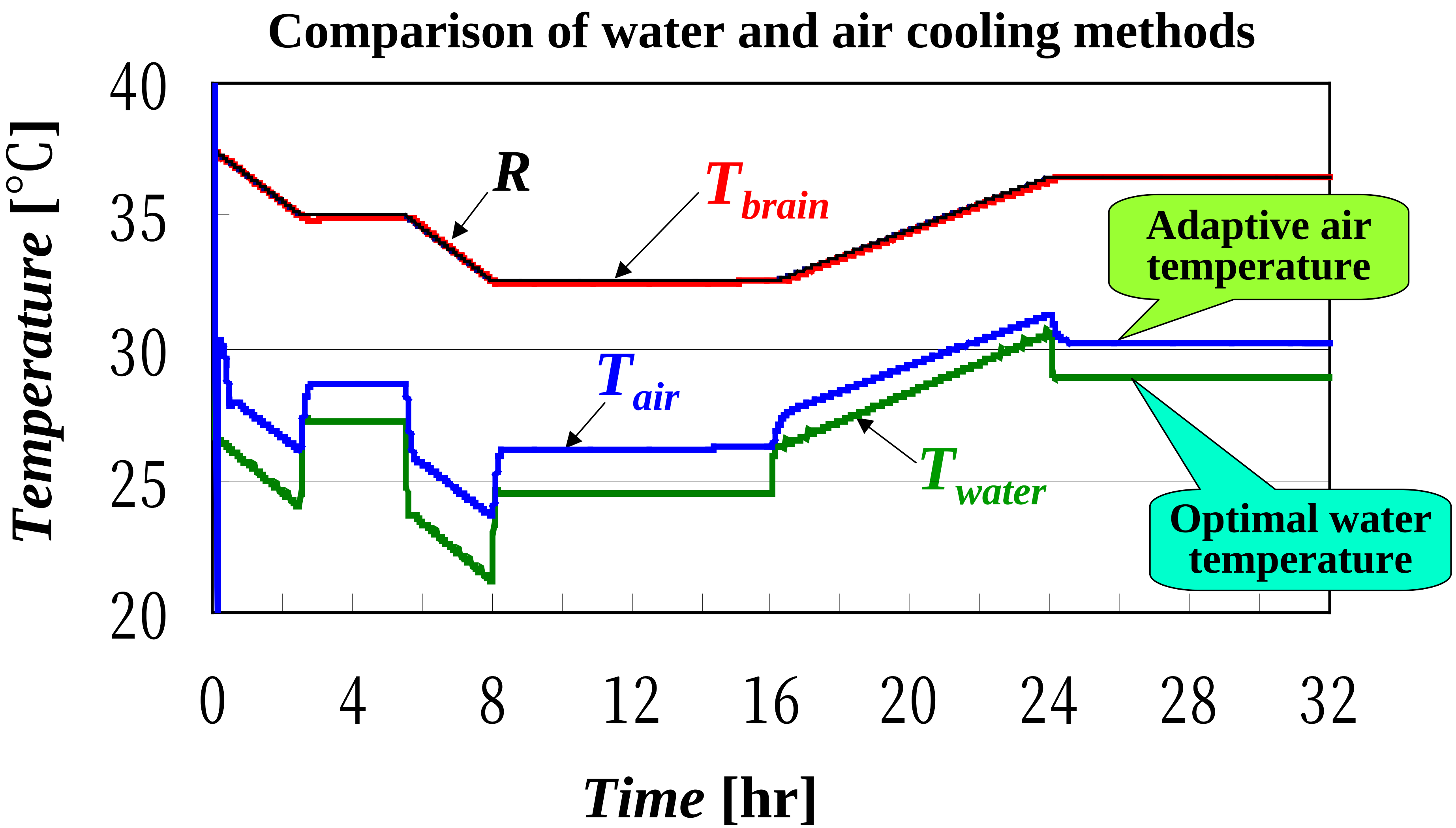
Automatic Air-Cooling Incubating System for Brain Hypothermia Treatment



Air-cooling Simulation Result



Simulation Result



AUTOMATIC CONTROL OF RESPIRATION TO DEAL WITH DIFFERENCE OF INDIVIDUAL CHARACTERISTICS

H. Wakamatsu, K. Takahara
Biophysical System Engineering,
Graduate School of Medicine,
Tokyo Medical and Dental University, Japan

Overview of Talk

- **Development of a Basic Control System for Controlled and Assisted Respiration**
- **Experimental Confirmation on Automatic Control of Alveolar CO_2-concentration**

Background

Automatic Control of Organic Functions

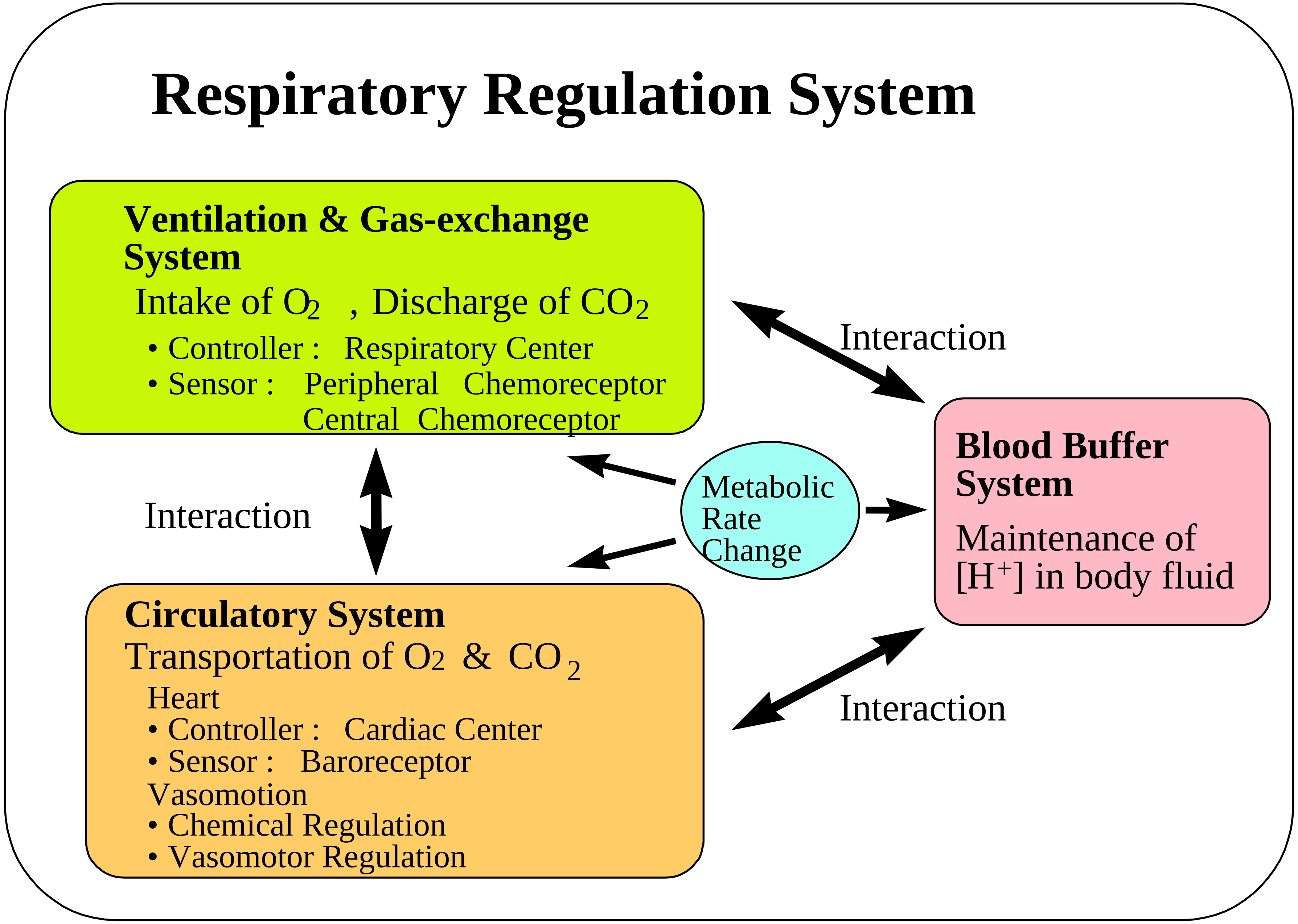
- Organic Function -

- **A Controlled Object with Controllers**
- **Remarkable Characteristics in Organisms**

  Non-linearity, Chronic Change，Individuality

- Respiratory Regulation System -

- **Possibility of Measurement and Control Non-invasively and at Real-Time**


Respiratory Regulation System
Ventilation & Gas-exchange System
Intake of O2 , Discharge of CO2
• Controller : Respiratory Center
• Sensor : Peripheral Chemoreceptor
Central Chemoreceptor
Interaction
Blood Buffer System
Maintenance of [H+] in body fluid
Metabolic Rate Change
Interaction
Circulatory System
Transportation of O2 & CO2
Heart
• Controller : Cardiac Center
• Sensor : Baroreceptor
Vasomotion
• Chemical Regulation
• Vasomotor Regulation
Interaction

Points of Design of the Control System

Respiratory Regulation System

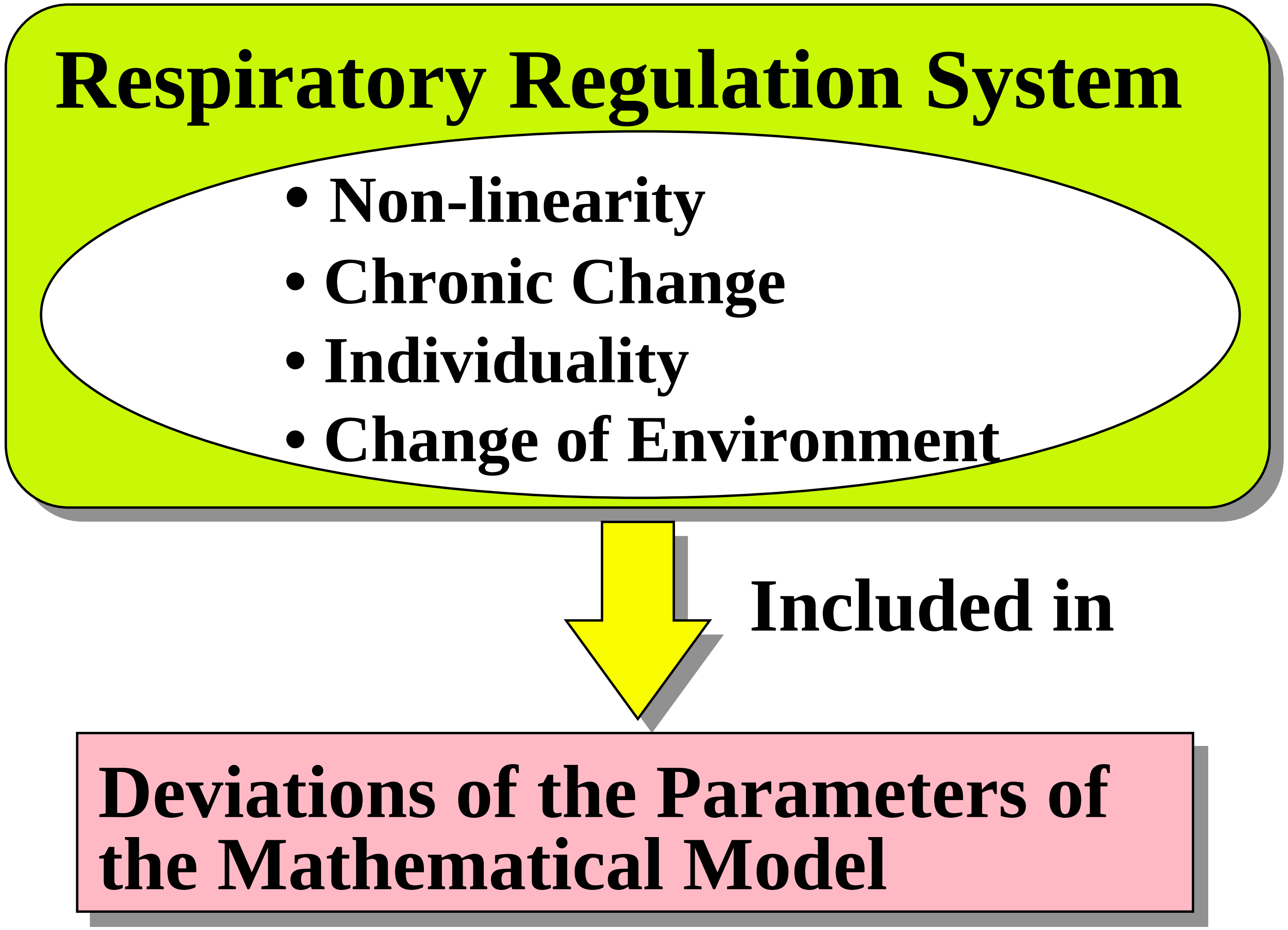
- Non-linearity
- Chronic Change
- Individuality
- Change of Environment

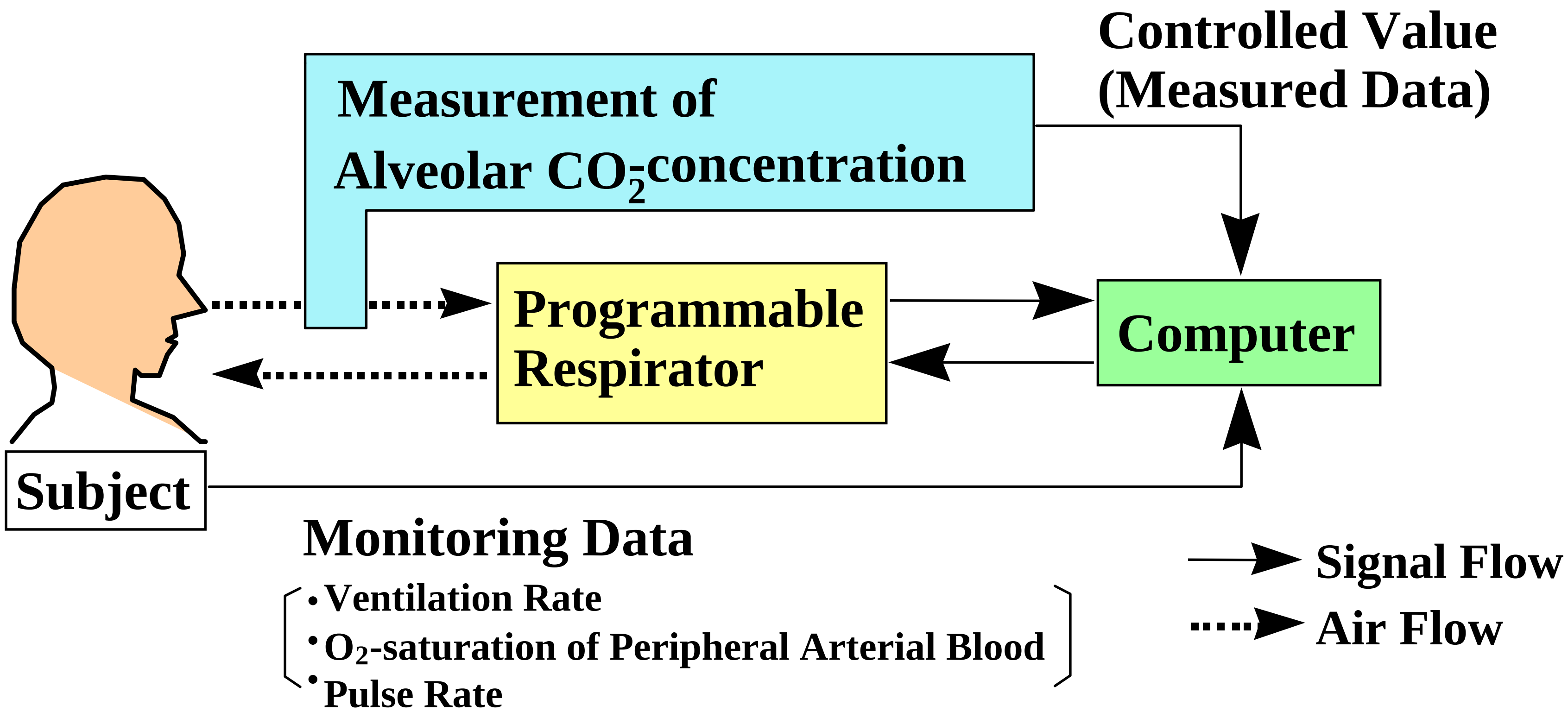
⇩ In order to control

- Understanding by Detection of Its Characteristics
- Design of Control System based on Detected Characteristics

Introduction of an "Adaptive System"

Significance of the Control System Based on Adaptive Method





Concept of the control system of artificial respiration

Technological assumption for the design of control system of respiratory regulation system

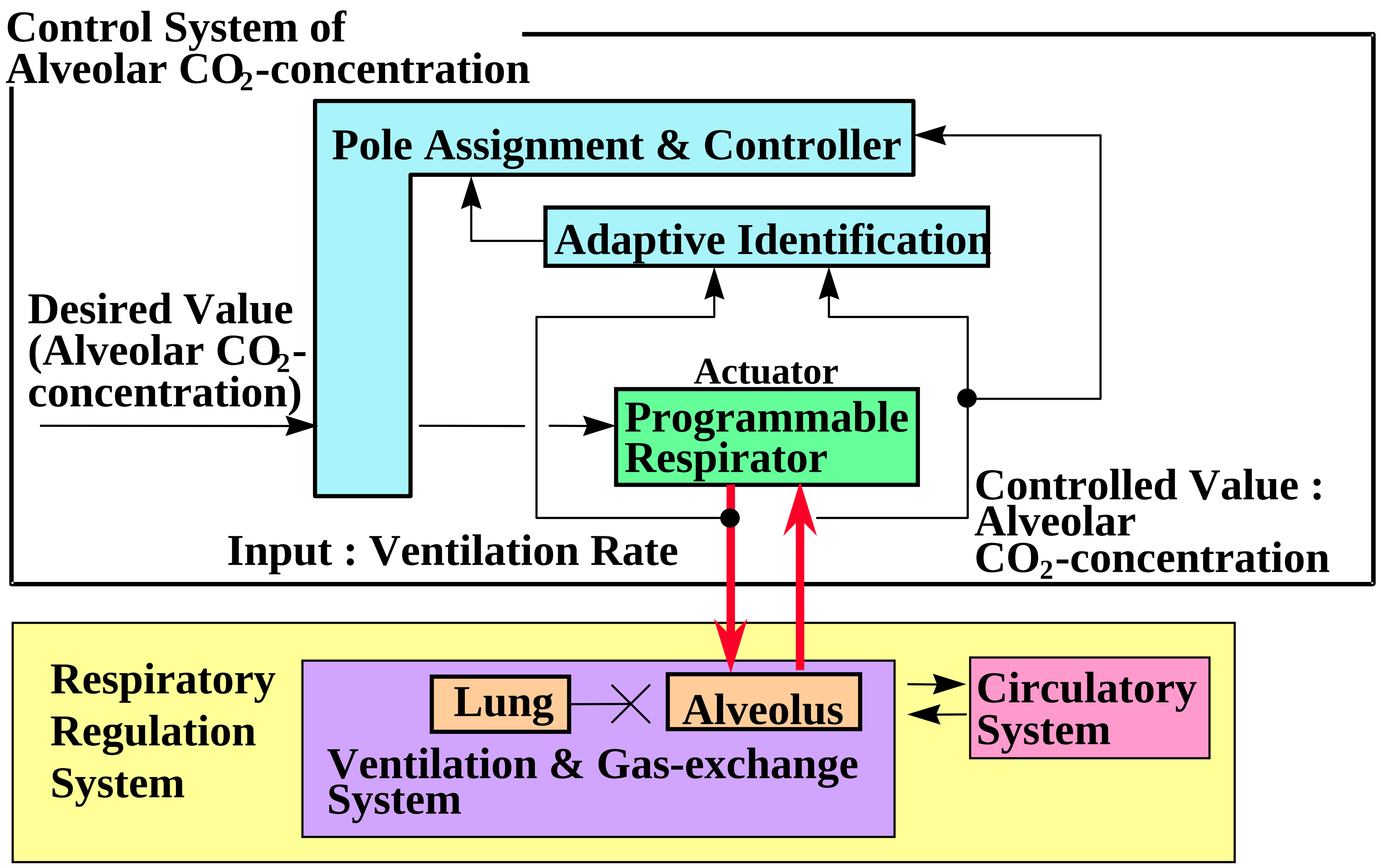
[1] The dynamics of a respiratory system is assumed to be characterized by the relation of input (ventilation rate) and output (alveolar CO_2-concentration).

[2] No consideration of the effect of interaction of ventilation rate with metabolic rate on alveolar CO_2-concentration.

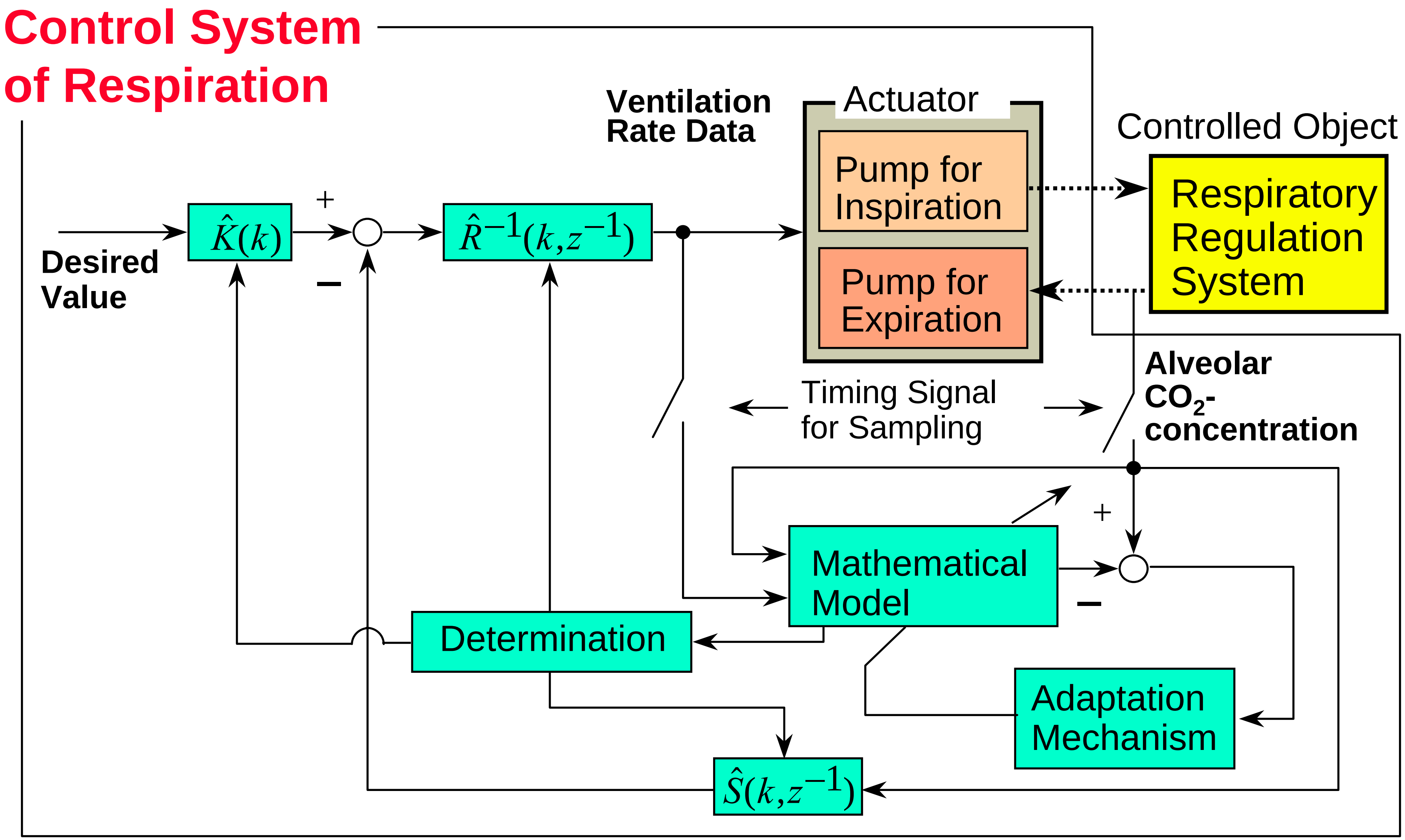
[3] Contribution of metabolic rate change to output is regarded as a characteristic change resulting from parameter deviation.

Design of Control System Coping with Ambiguous Knowledge about Respiratory Regulation System

The control system of a respiration is designed only on the assumption of its description by the appropriate mathematical model that may represent essential characteristics of a respiratory system including characteristics of experimental equipment (Wakamatsu, *et al*., 1990)



Adaptive control system of a respiration using pole assignment method



Block-diagram of control system of alveolar CO_2-concentration

Interior view of the all-built-in-one type respirator

Developed all-built-in-one type respirator

Assisted Respiration and Its Digital Control

Assisted respiration

:Depending on a patient's
Spontaneous respiratory rhythm

Sampling interval

Constant → Disagreement of sampling Time with measuring time of alveolar co_2-concentration

Synchronized with respiratory rhythm → Distorted recognition of the characteristics depending on the sampling interval

Significance of Adaptive System in Assisted Respiration

Respiratory regulation system

- Non-linearity
- Chronic changes
- Individuality
- Change of environment

Distorted recognition of the characteristics depending on sampling interval

↓ **Included in**

Deviations of the parameters of The mathematical model

Controlled Respiration and Its Digital Control

Controlled respiration

: Respiratory rhythm set by medical staff

Sampling interval

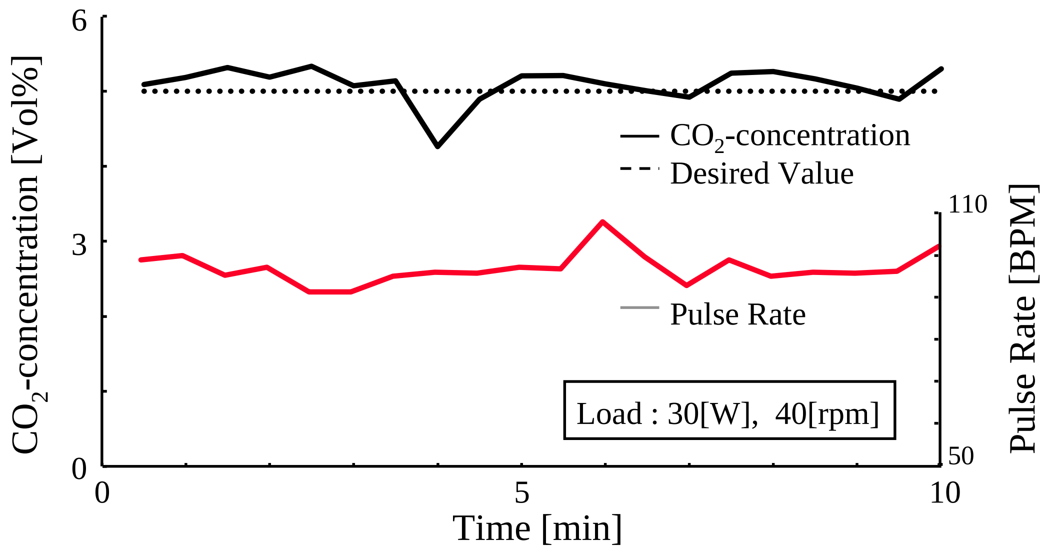
Constant → No difficulty in controlling

Experiment

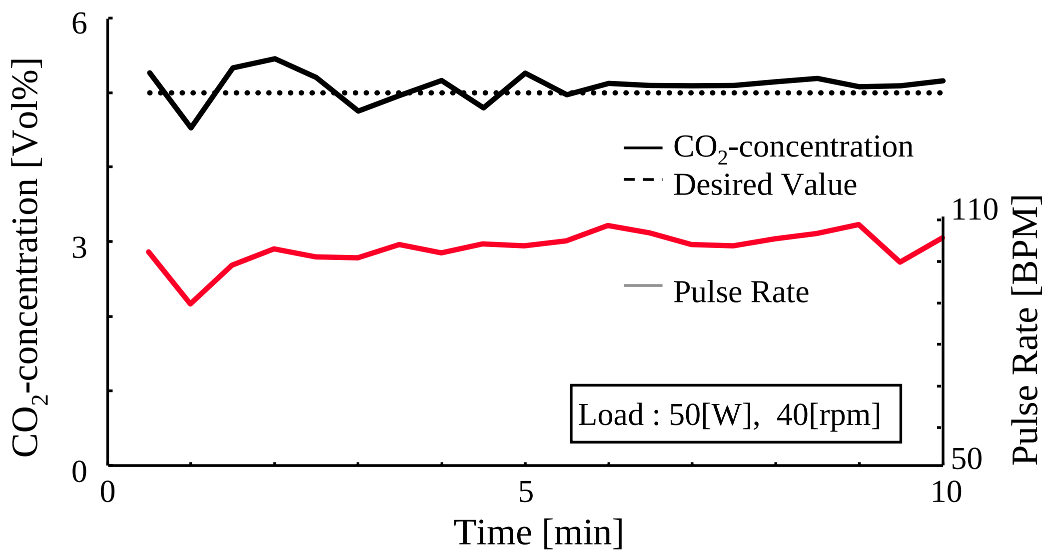
- Subjects : Healthy Persons
  (Male:7, Female:2, Age:27-38)
- Breathing : Lacking Own Respiratory Rhythm and Supported by the Respirator
- Desired Value : Step-like Function Decreased by 1.0[Vol%] after 10[min] from the Start of the Experiment

Controlled Respiration During Light Exercise

(a)



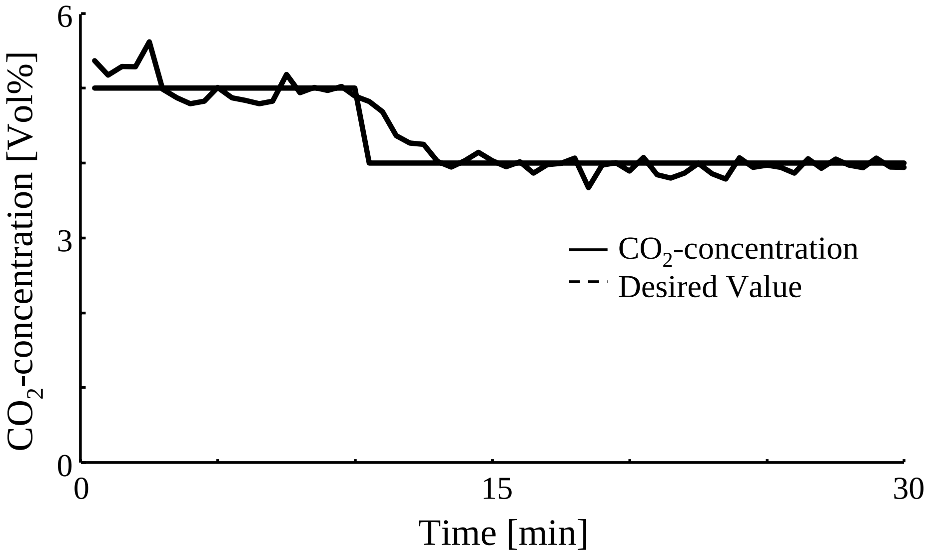
(b)



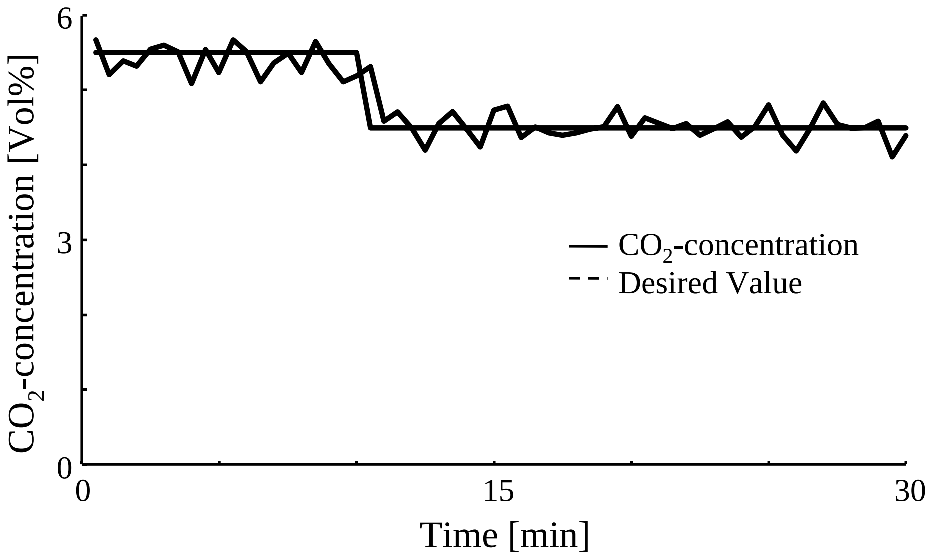
- Sampling Interval : 30 [sec]
- Respiration Rate : 22 [times/min]
- Period of Experiment : 10 [min]

Controlled Respiration at Rest

(a)

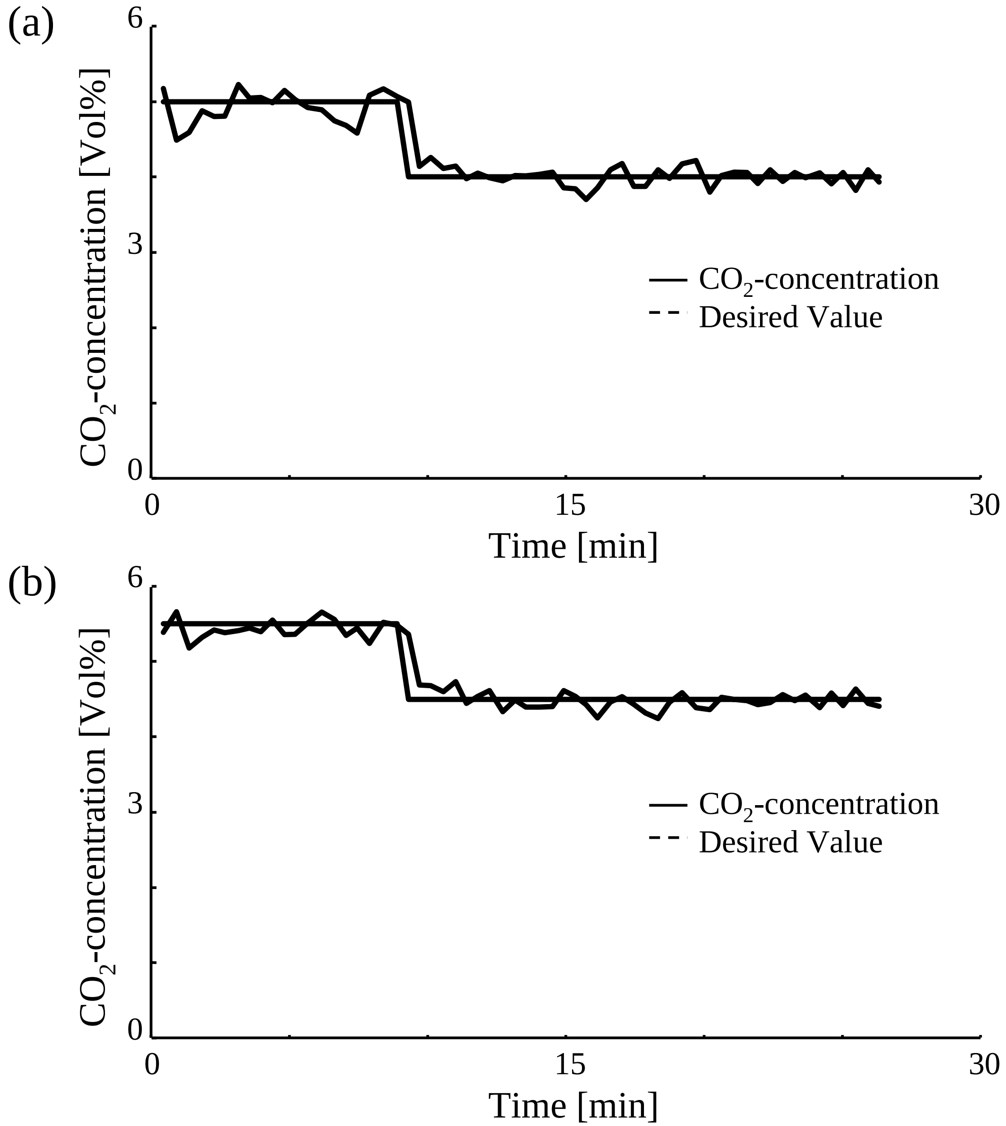


(b)

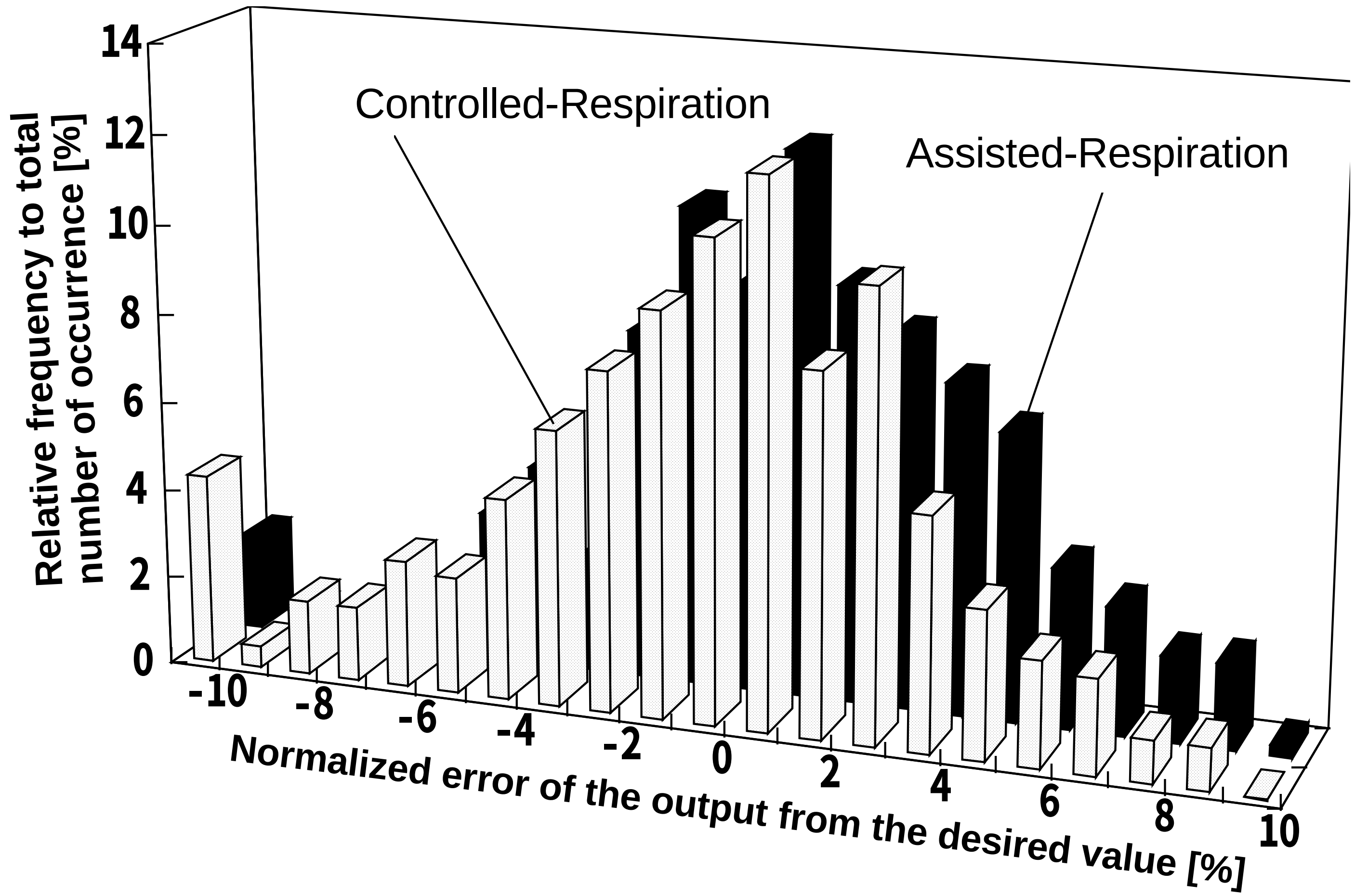


- Sampling Interval : 30 [sec]
- Respiration Rate : 16 [times/min]
- Period of Experiment : 30 [min]

Assisted Respiration



- Variable Sampling Interval :
  Every 7 Ventilatory Periods
  (23.3〜30.0 [sec])
- Respiration Rate :
  Changed at Random from
  14 to 18 [times/min]



Distribution of errors of the outputs from the desired values.

Concluding Remarks

- **Development of a Computer-based Control System of Artificial Respiration by Adaptive Pole-Assignment Method.**
- **Clinical Possibility to Control the Respiratory Regulation System Irrespective of Metabolic Rate Changes in Different Subjects**

Additional Remark

Available to any patient whose dynamic characteristics cannot be completely Known

Generally useful to control of other organic functions

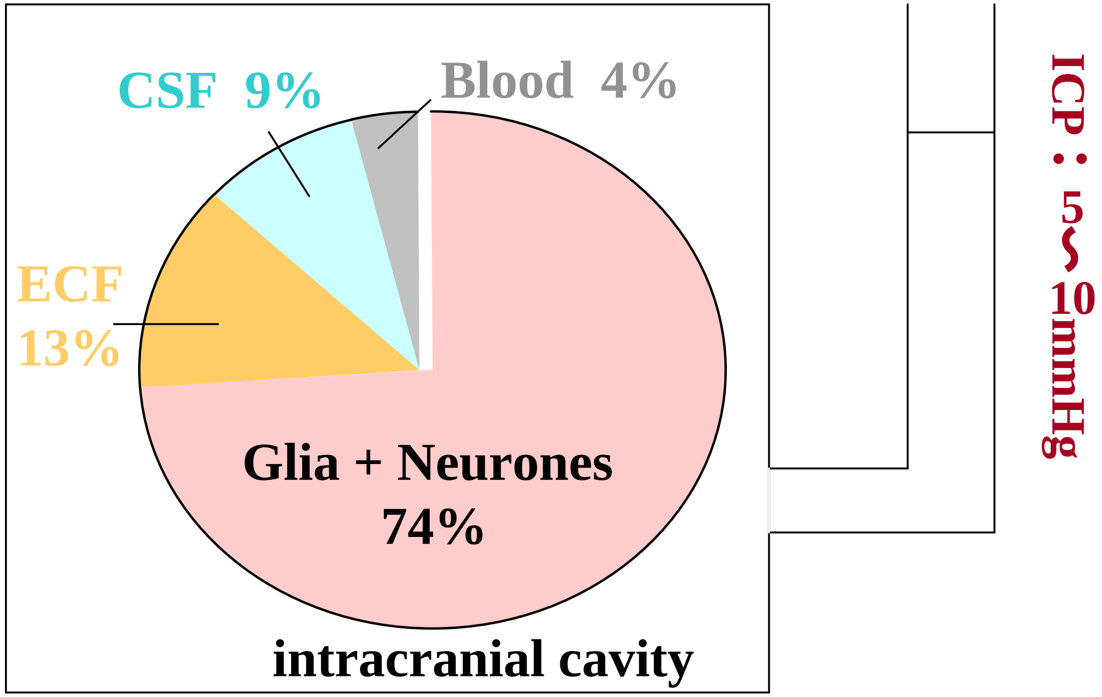
Control of Intracranial Pressure By Administration of Mannitol based on Mathematical Model

Biophysical System Engineering,
Graduate School of Health Sciences,

Tokyo Medical and Dental University

H.Wakamatsu, Ji Nan

Cause of Intracranial Hypertension



- space-occupying lesions （hematoma）
- brain volume ↑（brain edema）
- blood volume ↑（brain swelling）
- CSF volume ↑（hydrocephalus）

⇨ ＞15mmHg

Therapy of Intracranial Hypertension

Ⅰ. Surgical Treatments

① External Decompression
② Internal Decompression
③ Removal of Space-Occupying Mass
④ Drainage of CSF

Ⅱ. Conservative Treatments

① Dehydrators（Osmotherapy）
② Corticosteroids Therapy
③ Oxygen tent
④ Hypothermia
⑤ Barbiturate Therapy

Background and Aim of the Study

（Traumatic brain injuries，brain tumors, etc.）

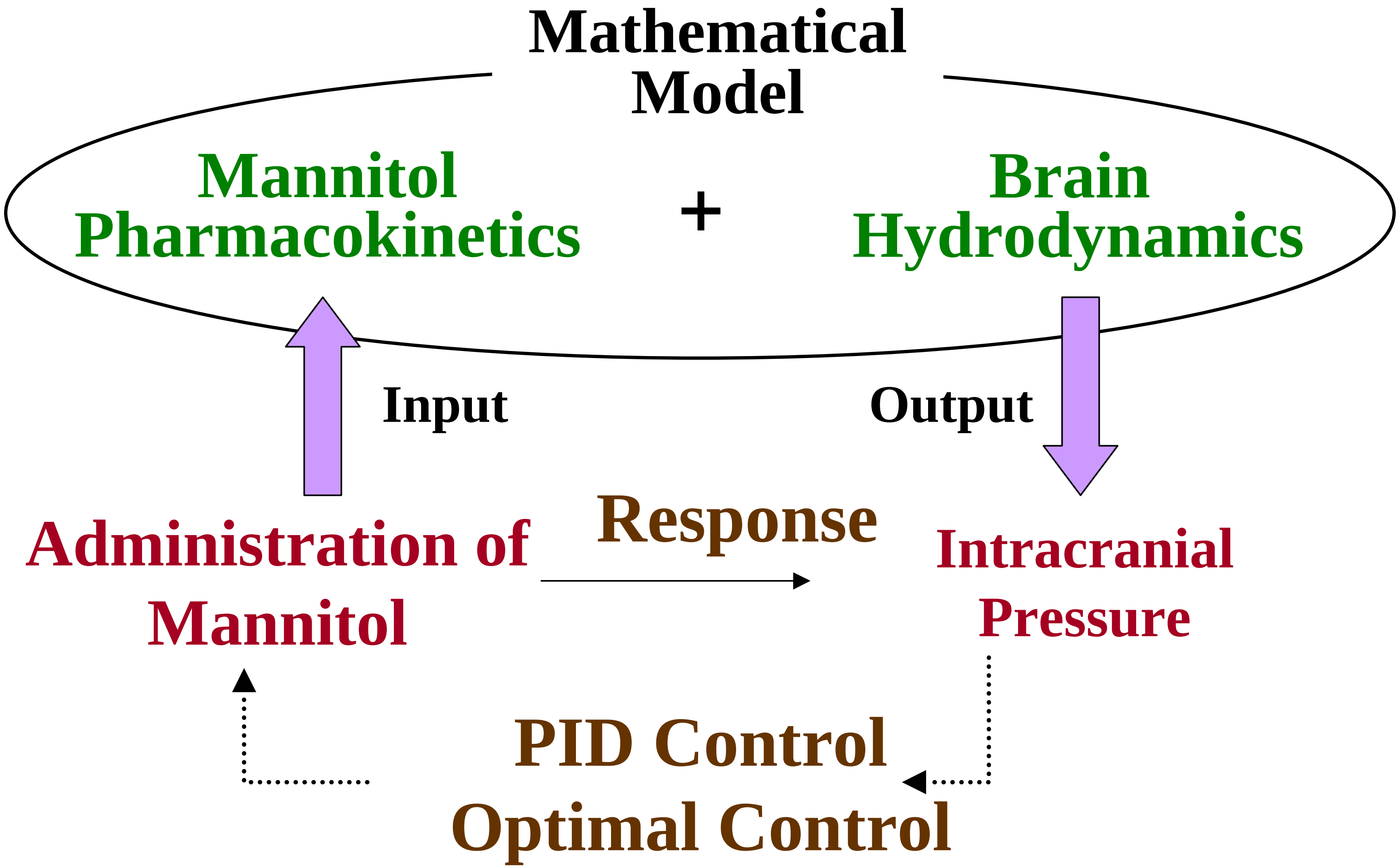
Intracranial hypertension caused by brain edema

Iterative Administration based on experience of Doctors

↓ **TheoreticalA nalysis**

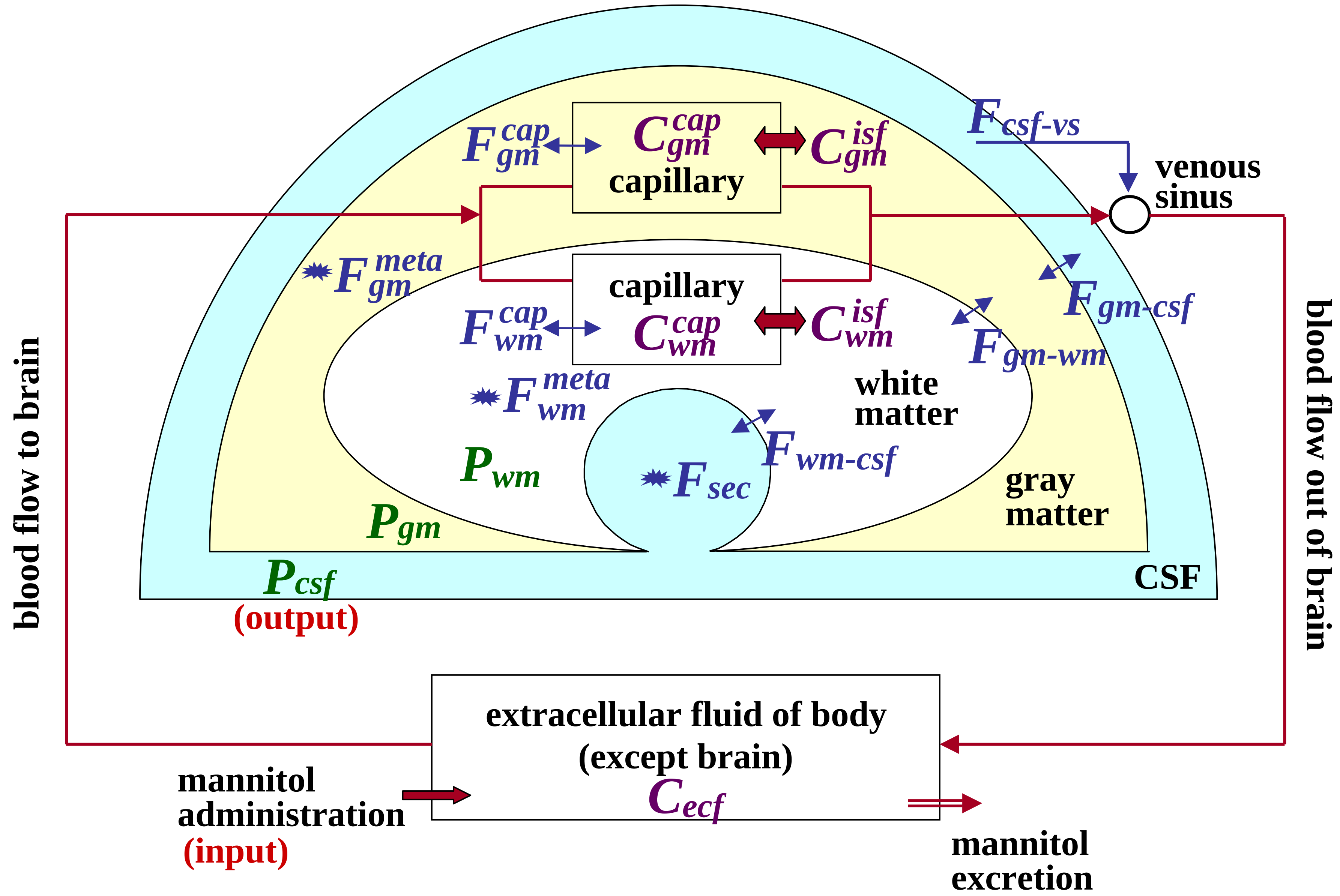
- **Detemination of most effective administration process**
- **Dynamical Prediction of intracranial Pressure**

Method



Mathematical Model
Mannitol Pharmacokinetics
+
Brain Hydrodynamics
Input
Output
Administration of Mannitol
Response
Intracranial Pressure
PID Control
Optimal Control

Schematic Representation of Model



Pharmacokinetic Model of Mannitol

gray matter capillary

$$\frac{dC_{gm}^{cap}}{dt} = \frac{1}{V_{gm}^{cap}}[PS_{gm}(C_{gm}^{isf} - C_{gm}^{cap}) + Q_{gm}(C_{ecf} - C_{gm}^{cap})]$$

permeation **blood flow**

white matter capillary

$$\frac{dC_{wm}^{cap}}{dt} = \frac{1}{V_{wm}^{cap}}[PS_{wm}(C_{wm}^{isf} - C_{wm}^{cap}) + Q_{wm}(C_{ecf} - C_{wm}^{cap})]$$

gray matter stroma

$$\frac{dC_{gm}^{isf}}{dt} = \frac{1}{V_{gm}^{isf}}[PS_{gm}(C_{gm}^{cap} - C_{gm}^{isf})]$$

white matter stroma

$$\frac{dC_{wm}^{isf}}{dt} = \frac{1}{V_{wm}^{isf}}[PS_{wm}(C_{wm}^{cap} - C_{wm}^{isf})]$$

administration

ECF (except brain)

$$\frac{dC_{ecf}}{dt} = \frac{1}{V_{ecf}}(Q_{wm}C_{wm}^{cap} + Q_{gm}C_{gm}^{cap} - Q_{br}C_{ecf} - K_{cle}C_{ecf} + I)$$

excretion

Hydraulic Model of Brain

gray matter

$$\frac{dP_{gm}}{dt} = K_{gm}(F_{gm}^{cap} + F_{gm}^{meta} - F_{gm-wm} - F_{gm-csf})$$

Based on Starling's Hypothesis

$$F_{gm}^{cap} = L_{cap}[(P_{cap} - P_{gm}) - \Sigma\sigma_i(\Pi_{cap}^{i} - \Pi_{gm}^{i}) - \sigma_{ma} RT(C_{gm}^{cap} - C_{gm}^{isf})]$$

CSF

$$\frac{dP_{csf}}{dt} = K_{csf}(F_{sec} + F_{wm-csf} + F_{gm-csf} - F_{csf-vs})$$

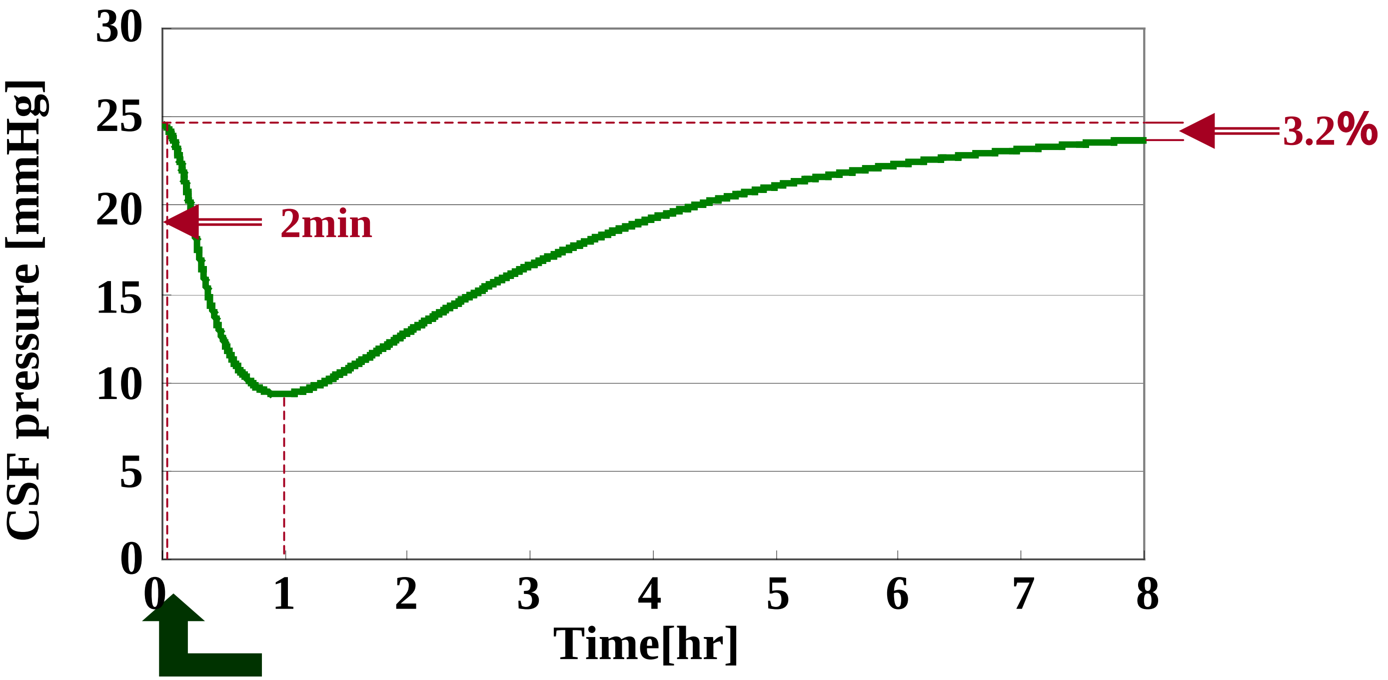
white matter

$$\frac{dP_{wm}}{dt} = K_{wm}(F_{wm}^{cap} + F_{wm}^{meta} + F_{gm-wm} - F_{wm-csf})$$

Due to Difference of Static Hydraulic Pressure

$$F_{gm-wm} = L_{gm-wm}(P_{gm} - P_{wm})$$

Dynamic Pressure in a Bolus Administration



Administration of Mannitol 0.1g/kg/min in the first 15min

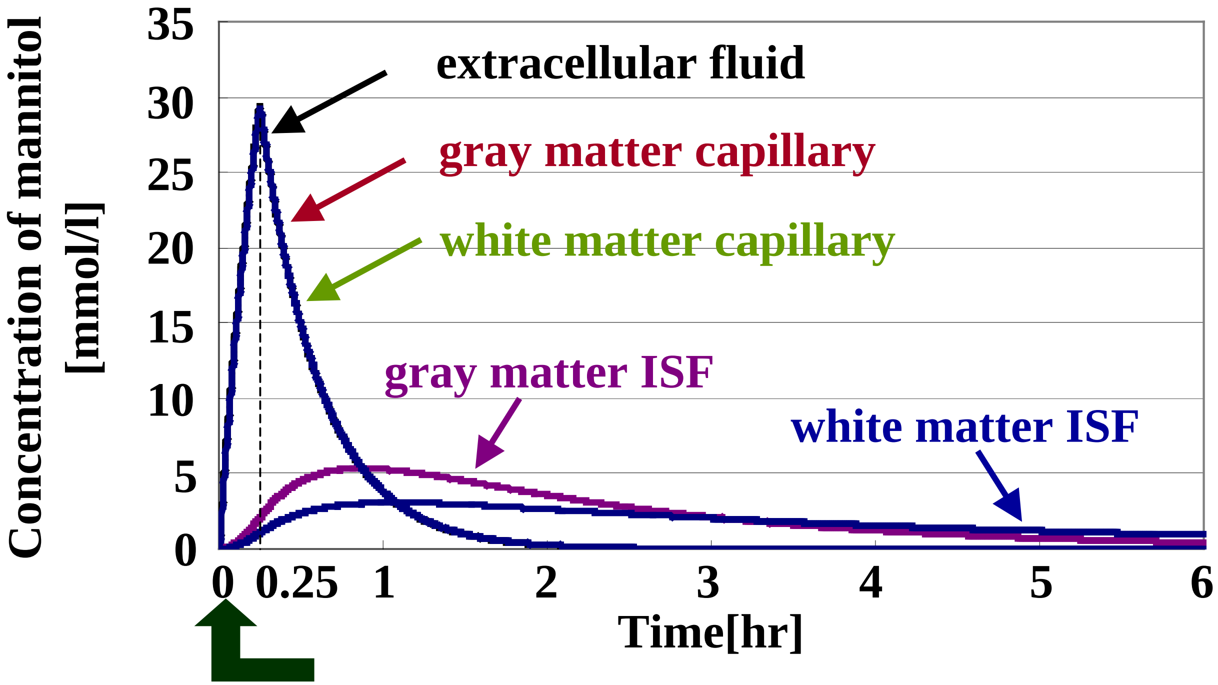
Intracranial pressure quickly decreases in 2min and shows the minimum value in about 1hr after mannitol administration .
Then, it increases slowly and comes back to the 96.8% value of initial one in 8hr.

Consistent

1."Reduction of cerebrospinal fluid pressure occurs within 15 minutes of the start of a mannitol infusion and lasts for 3 to 8 hours after the infusion is discontinued." The extra pharmacopacia. 29th edition, 1989.

2. "By quick infusion to vein ICP decreases in 1-5 min and is expected to reach minimum in 20~60min"
救急医学(Critical Care Medicine) 25:1561-1564,2001.

Dynamics of Mannitol Concentration in a Bolus Administration



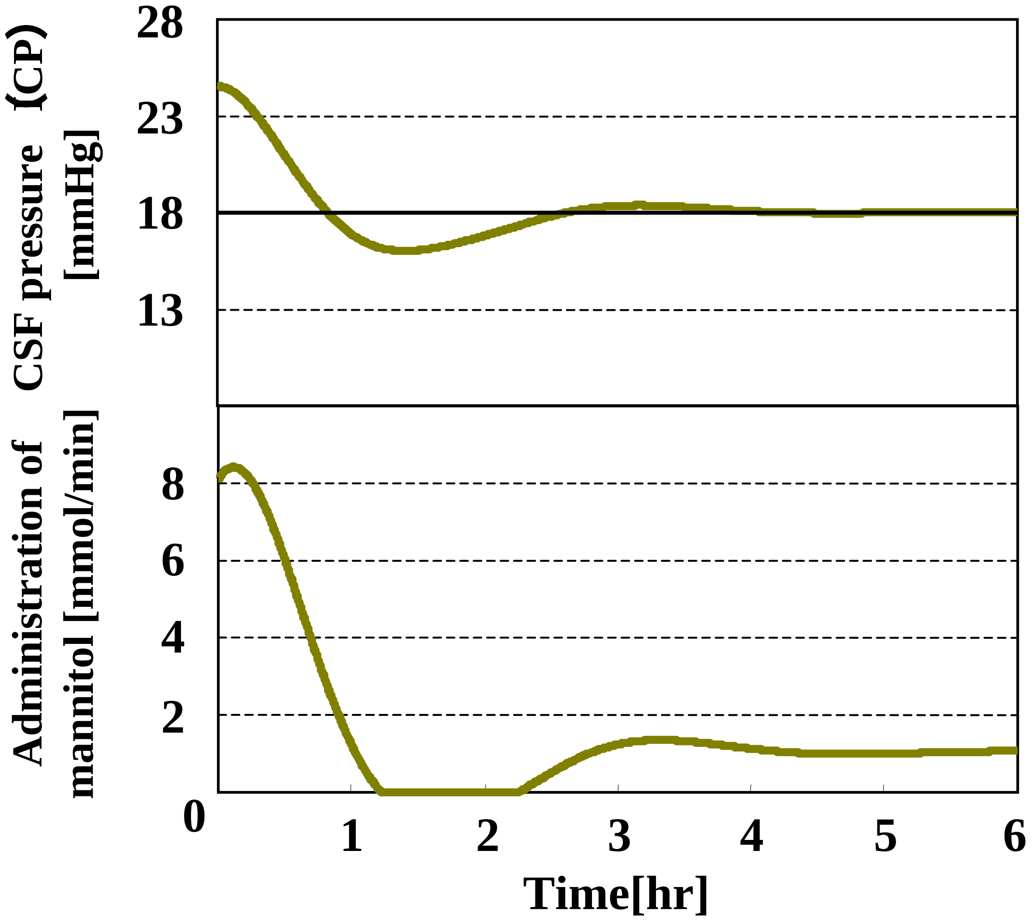
Administration of Mannitol 0.1g/kg/min in the first 15min

Mannitol concentration of extracellular fluid, gray matter capillary and white matter capillary. They decreases exponentially after their peak on the last moment of infusion.

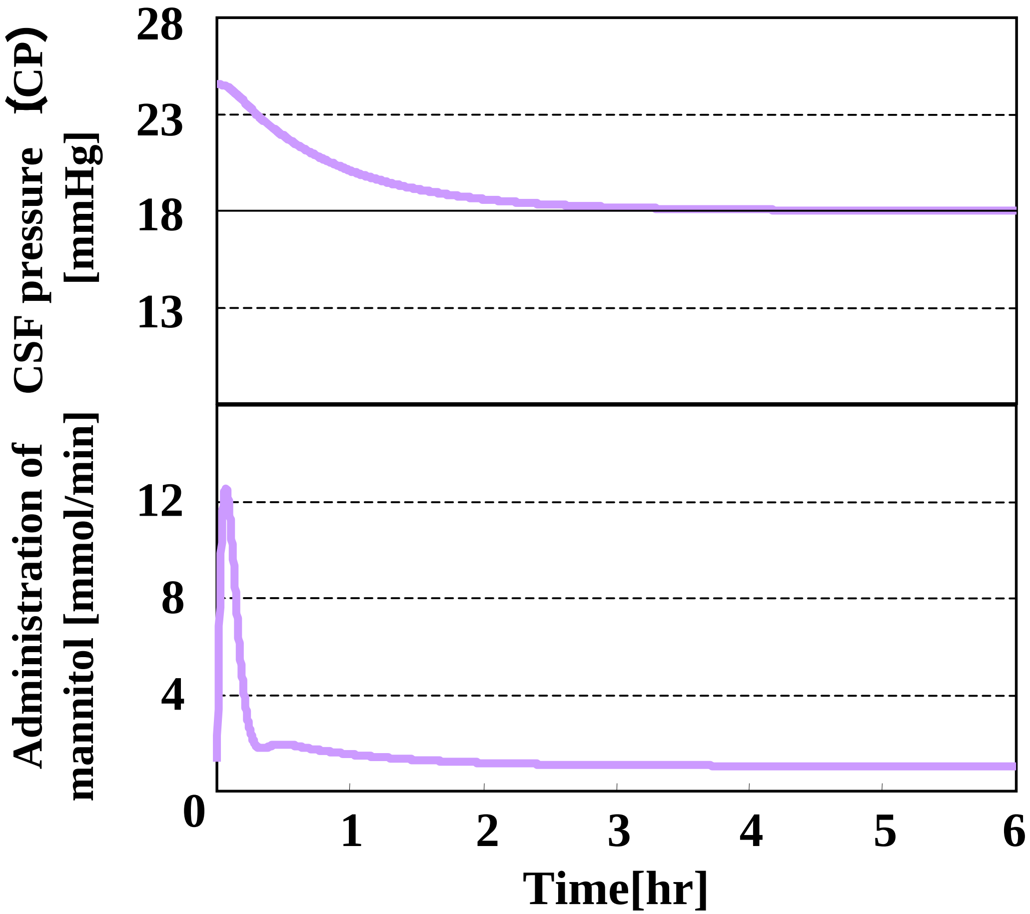
⬍ **Consistent**

> **"Six human subjects received mannitol as an introvenous dip infusion. In each subject, <u>the concentration</u> of mannitol <u>reached the maximun at the end of mannitol administration. Then, it exponentially decreased</u>."**
>
> **Acta neurochir(suppl). 60: 538-540,1994.**

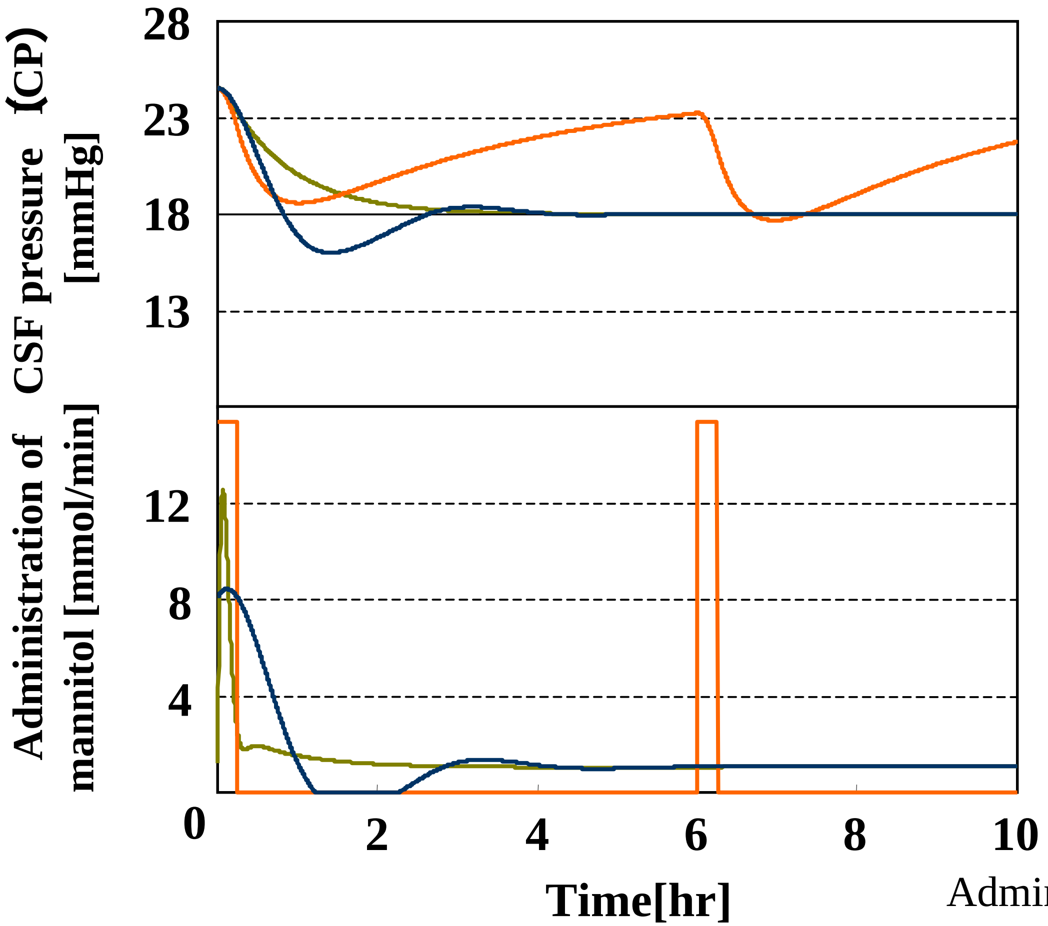
PI-Control of Pressure by Mannitol



Optimal Control of Pressure by Mannitol



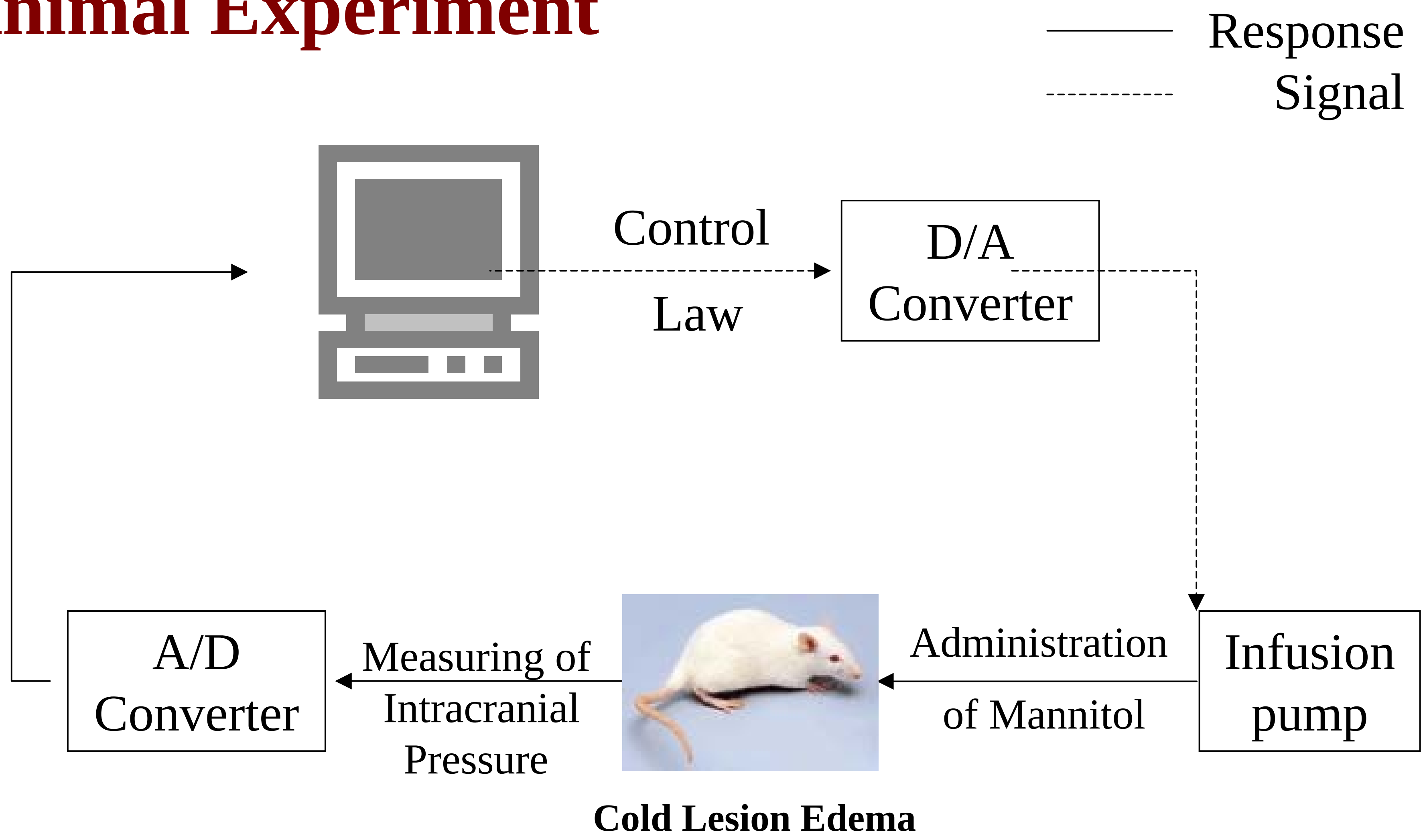
Comparison of Different Methods by Simulation



Administration of Mannitol
By PI-Control
Optimal Control
&Intermittent Control

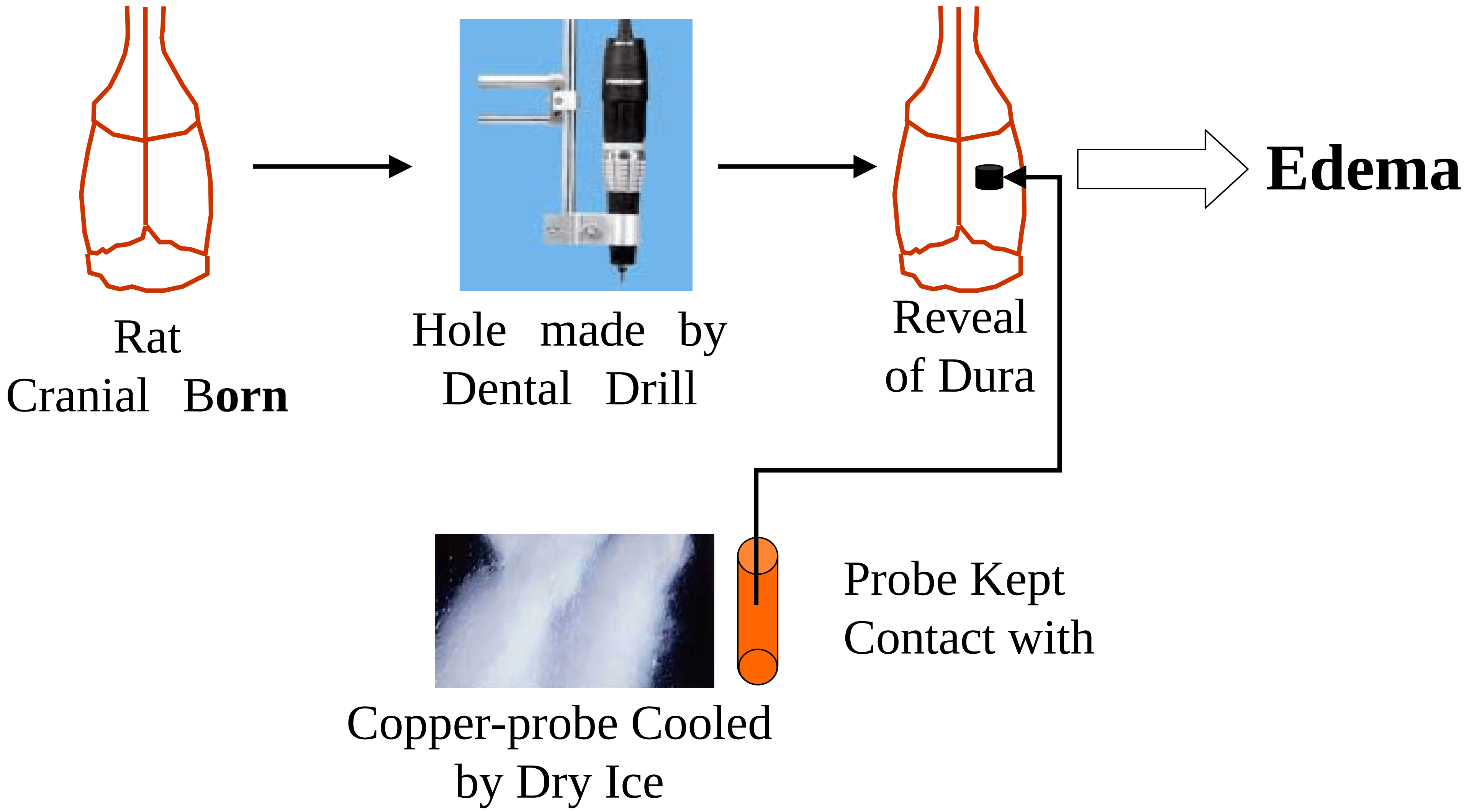
Decrease of ICP by Less Amount of Mannitol in a Optimal Control Process

Animal Experiment



Control of Intracranial Pressure Using Rat

To Make the Cold Lesion Edema



On-line Monitoring of parallel Physiological Data

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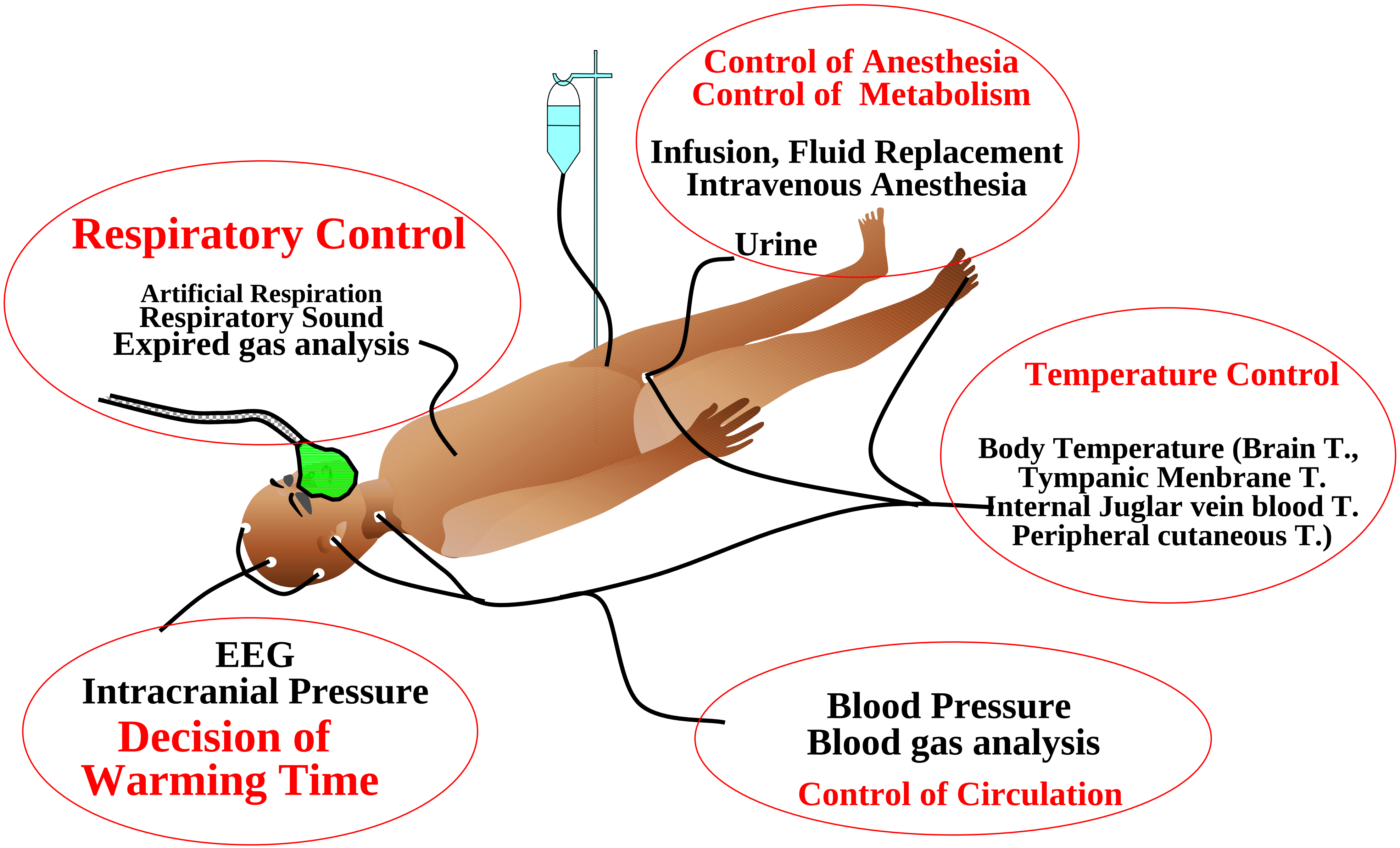
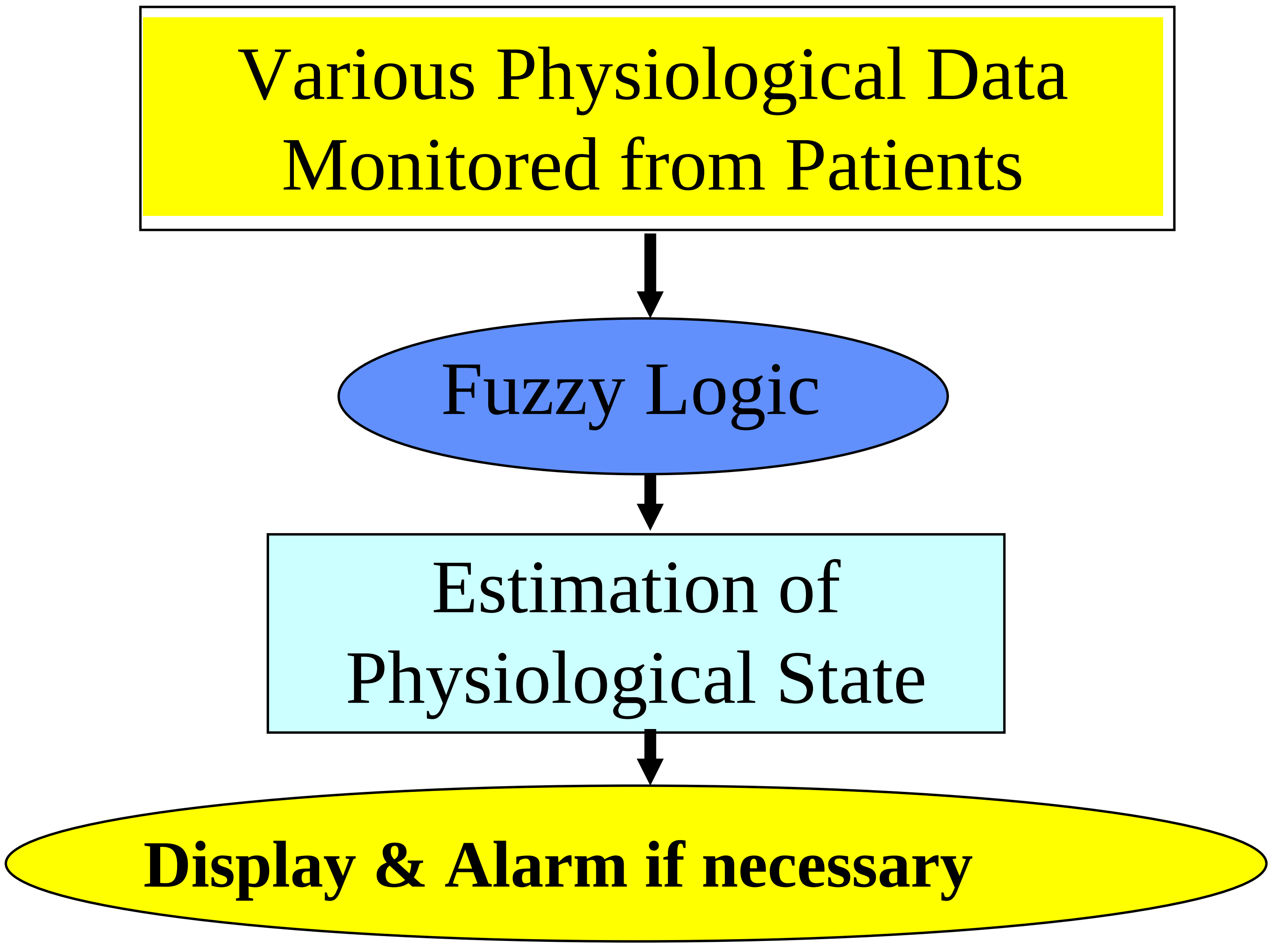
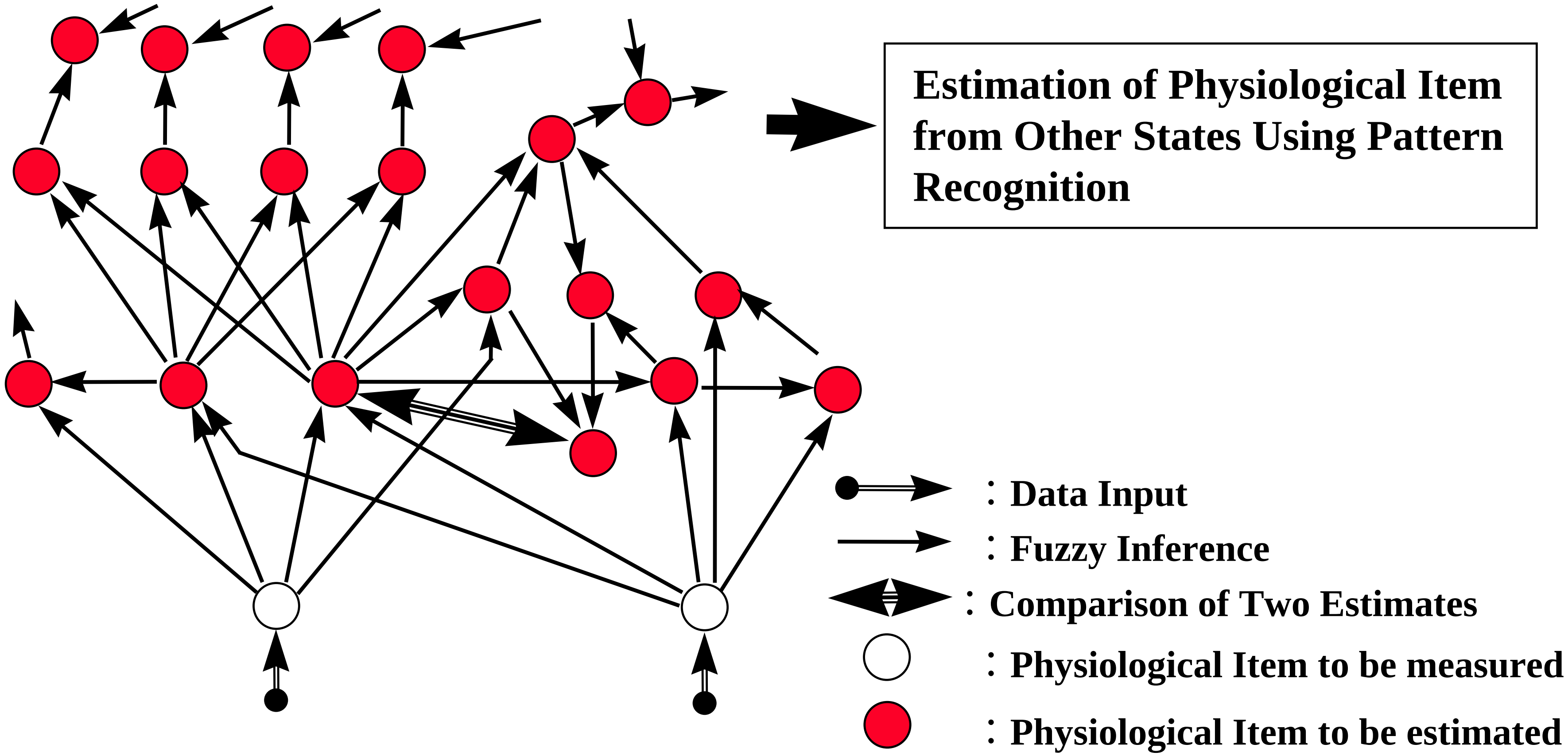
Monitoring System of Parallel Physiological Data

Conventional Monitoring of Physiological State

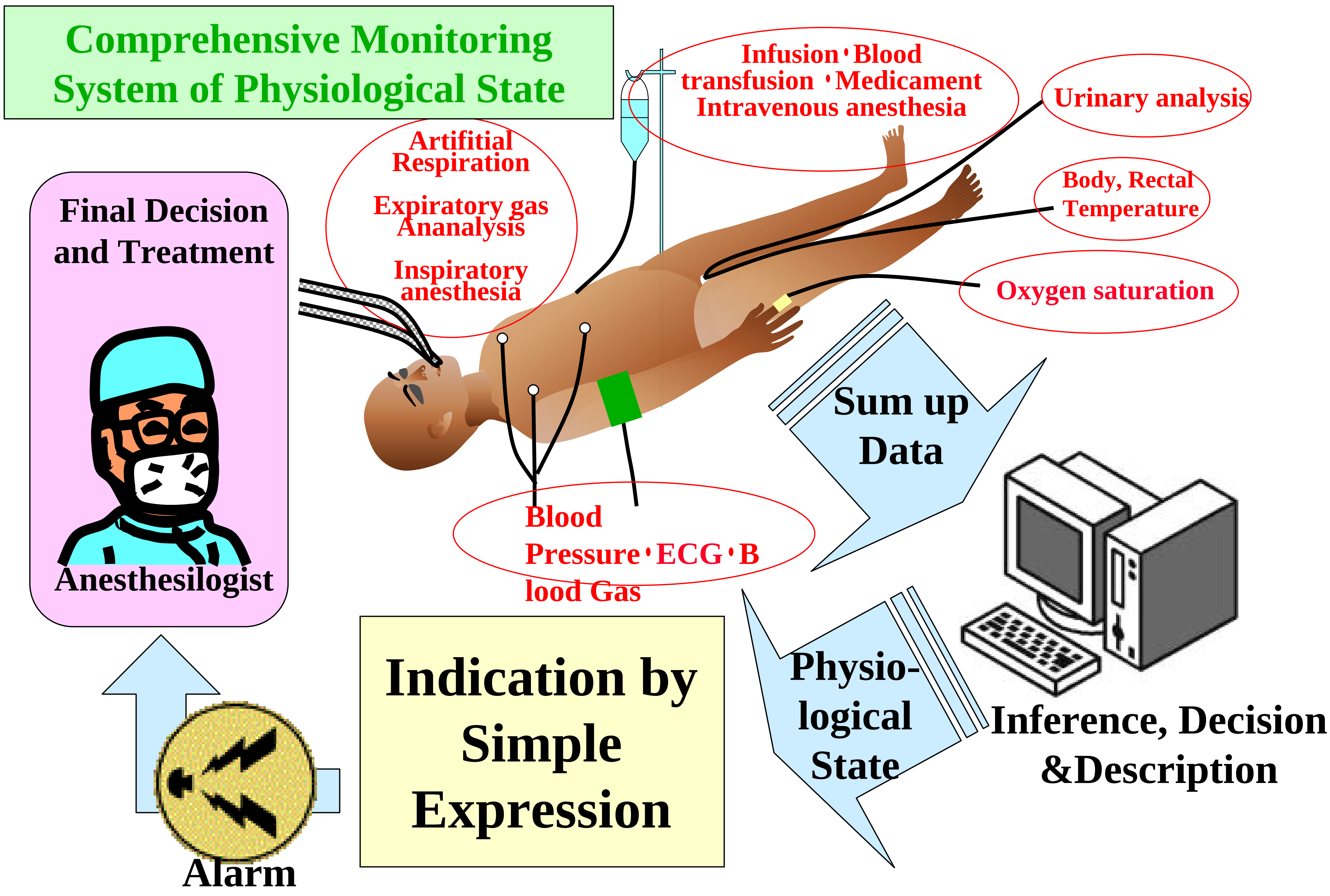




Evaluation and Alarming System



Estimation of Physiological Data by Fuzzy Inference Network


Comprehensive Monitoring System of Physiological State
Final Decision and Treatment
Anesthesilogist
Artifitial Respiration
Expiratory gas Ananalysis
Inspiratory anesthesia
Infusion･Blood transfusion ･Medicament Intravenous anesthesia
Urinary analysis
Body, Rectal Temperature
Oxygen saturation
Blood Pressure･ECG･Blood Gas
Sum up Data
Physio-logical State
Inference, Decision &Description
Indication by Simple Expression
Alarm