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A Control-Theoretical Approach to Model-Based Medicine

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Abstract: This paper discusses the notion of model-based medicine which is expected to give a solution to various difficulties in clinical medical systems based upon the familiar methodology of control science. The model-based medicine relies essentially on an integrated model of the visceral system of human body that includes various functional subsystems such as respiration, circulation, thermal, digestion, urinary, endocrine/neuronal systems as its component. We introduce an example of such integrated models of human body developed in our laboratory. Some novel results which enhance the effect of therapy are presented concerning brain hypothermia treatments based on the model. In the latter half of the paper, we propose a new hypothesis on the cause of diabetes based on the integrated model, as well as clinical evidence. We think the real cause of elevation of blood glucose is the homeostasis of glucose concentrations in the brain. In other words, the elevation of blood sugar itself is not as harm as people think, because it is an outcome of control of the brain sugar. Long-term effect of psychological stress is shown to cause diabetes based on our model.

1. INTRODUCTION

In spite of the far-reaching progress of medical science, the clinical practices are still very much labor-intensive, based crucially on the repeated face-to-face interlocution of the patient and doctor. A patient with multiple diseases must sometimes consult with several doctors with different specialties. On the other hand, many doctors and medical stuffs with different disciplines and skills are required to attend the treatment of one patient in the intensive care unit (ICU). As the aged society comes, it becomes impossible to afford such labor-intensive ways of clinical treatments to patients. Some drastic changes of clinical science and methodology must take place in future to resolve this bottleneck. Model-based medicine based on control scientific strategy which we propose in this paper seems to be able to lessen the burden of medical stuffs and is expected to provide a way to solve the problem.

Medical treatments are essentially some sort of controls with human body as plant. However, control science which has been developed for man-made systems for years cannot be applied to clinical applications. This is simply because human body dynamics is very much different from dynamics of man-made systems in many aspects. First, human body is a complex integration of many subsystems which makes very difficult to identify the transductions of signals and commands. Second, its characteristics are always changing through its behaviors. The plasticity is indeed one of the most salient features of human body that makes modelling extremely difficult. Third, human body dynamics are very much different from one individual to another. Specificity of the subject is the most important factor of clinical practice. Forth, human body is equipped with the innate regulatory systems to maintain homeostasis of the body which are very complex and difficult to identify the effects of add-on control systems.

In addition to the above differences of dynamics, there are many other reasons that prevent the application of control science to clinical practices. For example, it is very difficult to make experimental study of control strategy to evaluate the effectiveness of control systems, because such an experiment might be fatal or toxic to human body.

In spite of the obvious difficulties stated above, there are many possibilities to significantly improve the current labor-intensive clinical practices, based on the proper construction and use of models of human body. The term *model-based medicine* is coined to represent the clinical treatments deduced rationally from the model. The proposal of this methodology is based essentially on our belief that the modelling is already enough matured in control science on the one hand, and the powerful medical sensors and detectors are well developed to provide enough information to build a model of individual human body, on the other hand.

The total model of human body, of course, plays a crucial role in model-based medicine. It is essentially a tool for providing the detailed information about the state of human body during the medical treatments, instead of the real diagnosis of human body. Based on the model, we can derive effective control/medical strategies for treatment (input to human body) from an integrative point of views. It includes the possibility to automatize various administrations of medical actions which lead to saving of labors. We present in this paper some crucial benefits brought by integrative model of human dynamics which is related to hypothermic intracranial decompression.

It even goes further. The model may represent the state of various diseases, through which we may be able to identify

the cause of the diseases, or at least hypothesize the cause of diseases, through the extensive analysis of the model. This is another fundamental advantage of model-based medicine. In the latter part of this paper, we propose a hypothesis about the cause of diabetes which is drastically different from the conventional one. This conclusion has been naturally drawn from our study of glucose-insulin-glucagon dynamics using our total model.

The paper is organized as follows: The notion of model-based medicine is discussed in Section 2. Section 3 describes the integrative model of human body which is mainly developed for ICU use and Section 4 shows applications of the model to acute diseases. Section 5 addresses modelling of the glucose-insulin-glucagon (GIG) regulatory system, which is used to validate our hypothesis on the cause of diabetes discussed in Section 6.

2. MODEL-BASED MEDICINE

Actually, all diagnosis and treatments are essentially model-based in the sense that they are done based on some sort of models of diseases and/or dynamics of human body that are included in the medical knowledge of doctors. The problem is that these models are not explicitly represented in unified or common ways that can be shared by people and rather the outcome of accumulated clinical experiences of individual medical doctors. These models are just quantitative and may differ from one doctor to another even for the identical medical targets. The model-based medicine is an attempt to construct explicit *quantitative* models of human dynamics and diseases exploiting their common features as much as possible, and use them for efficient clinical treatments.

One of the fundamental issues concerning the model-based medicine lies in the distinction between the healthy and the unhealthy. If we regard the disease as a deviation of body characteristics, the model describing the healthy body and the one describing unhealthy body might be different. On the other hand, if we regard the disease as a deviation of the *state*, then we can construct a unified model of the human body that can describe the healthy state and the disease in using the common model. We take this point of view to emphasize the common feature of control of artifacts and human body. All the therapeutic actions are regarded as controls of human body dynamics to bring the state of the human body from ill states to healthy one.

In control engineering, the model is primarily used for designing control systems. In model-based medicine, it is used for designing therapeutic strategies which correspond to the controllers in control engineering. The primal design objective is to make smooth state transition from the current body state to some desirable states which are good towards cure in some optimal way. In this paper, we show some design examples of this therapeutic strategies concerning the brain hypothermia treatment.

Some design methodologies of control systems use models more explicitly in the controller architecture. The *internal model control* (IMC) is a typical example of such controller schemes and it fits the model-based medicine, particularly for

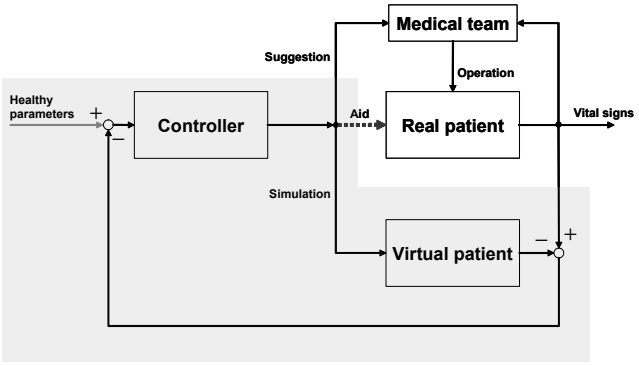


Fig. 1. Concept of model-based medicine

continuous medical processes that require intensive care. In these processes, the model can be used as a monitoring tool of body state to survey and predict the impact of medical maneuvers on the body. Sometimes, it can give useful advice to medical stuffs to choose best strategies among possible alternatives. Figure 1 illustrates the concept of model-based medicine in terms of IMC. This scheme is not well-elaborated in this paper, though it offers great potential for future *systems medicine* that integrates multiple medical disciplines in order to treat patients suffering from multiple diseases.

The most salient advantage of model-based medicine is to its ability to analyze diseases dynamics and identify their causes. The most effective clinical strategy must be based on the identification of the major cause of the disease. Also, in order to find the best maneuver for disease elimination must be based on the quantitative knowledge on the disease dynamics. The total body dynamics, if it is properly constructed, can provide the quantitative information to attack diseases. We will give such an example concerning diabetes based upon the total model of body dynamics.

3. DEVELOPMENT OF INTEGRATIVE PHYSIOLOGICAL MODEL FOR INTENSIVE CARE

3.1 Model description

An integrative model of biothermal regulatory, circulatory, respiratory and pharmacokinetic systems is presented here, together with its application to control of brain temperature, intracranial pressure, minute ventilation and anaesthesia, in order to support the clinical medicine in the ICU.

3.1.1 Model structure

The modelling is based on some assumptions, since the detail of various physiological functions and their interaction is still partially understood. Main assumptions include compartmental structure of the body, lumped approximation values of physiological and/or physical parameters, absence of inherent neuronal and hormonal regulation and so on (Gaohua and Kimura, 2006; Gaohua et al., 2006).

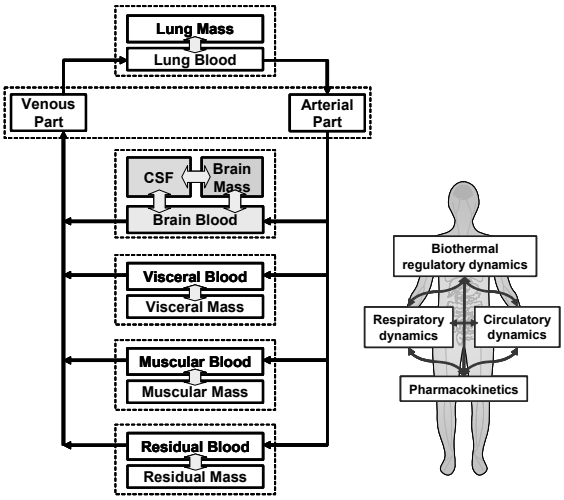


Fig. 2. Model structure

Model consists of 6 parallel segments, that is, the cranial, the cardiocirculatory, the pulmonary, the visceral, the muscular and the residual segment (Fig. 2). Each of the latter 4 segments is divided into 2 elements, the parenchyma (mass) compartment and the vessel (capillary blood) compartment. Apart from the brain mass and the cerebral capillary blood compartments, a compartment of cerebral spinal fluid (CSF) is especially introduced into the cranial segment. The cardiocirculatory segment comprises no mass compartment, but 2 blood compartments of the arterial and venous parts. All blood compartments are correlated together via blood flow. Taken together, the body is modelled by 13 compartments.

The physiological and physical parameters are constant within each compartment, based on the concept that each compartment is homogeneous and well stirred.

According to the clinical practice in the ICU, the human body could be considered as a passive system without the inherent neuronal regulation, as the patient is generally deeply sedated. Alternatively, it is considered that an extracorporeal feedback loop is formed via medical diagnosis and treatment.

Various therapeutic devices applied to the human body are considered as ambient input of the integrative model. For example, the artificial ventilator sets minute ventilation to the lung mass compartment, while various drugs such as diuretics and anaesthetics are infused into the venous part of the cardiocirculatory segment. Therapeutic cooling could be modelled by introducing temperature-adjustable surroundings to the muscular segment.

In the same model structure, the biothermal regulatory system, the respiratory system, the circulatory system, the pharmacokinetics of diuretic and anaesthetic in the human body are described simultaneously.

3.1.2 Governing equation

Analogy of temperature, hydrostatic pressure, respiratory gases (O_2 and CO_2) and drugs (diuretic and anaesthetic) concentration occurs in each compartment. Therefore, a unified form of governing equations is possible to describe simultaneously the dynamics of temperature, hydrostatic pressure and concentration of respiratory gas or drug.

$$d(CX)/dt = q_{in} - q_{out} \quad (1)$$

where C denotes thermal capacity in the biothermal regulatory system, compliance in the circulatory system, distribution volume in the respiratory system and the pharmacokinetic system. X is temperature, hydrostatic pressure and concentration of respiratory gas or drug in the targeted compartment. The left hand side means the storage rate of energy or substance (water, gas, diuretic or anaesthetic). q_{in} and q_{out} on the right hand side are the rate of energy or substance in and out, respectively.

Again, various physiological functions of the biothermal regulatory system, the respiratory system, the circulatory system, the pharmacokinetics of diuretic and anaesthetic in the human body are described simultaneously in the same governing equation.

3.1.3 Interaction mechanism

Besides the interaction via blood flow, which transports heat, respiratory gases and various drugs throughout the body, special mechanisms are included in the integrative model to combine the target subsystems together. These are the temperature dependency of metabolism, permeability at the interface of capillary bed, hemoglobin-oxygen dissociation, diuretic and anaesthetic clearance. At the same time, the thermoregulatory threshold is dependent on the arterial concentration of anaesthetic.

3.1.4 Parameter setting

Hundreds of kinetics constants would be needed to simulate this integrative system. These are thermal capacity, distribution volume, compliance, permeability coefficient, blood or lymph flow, metabolic generation or consumption, drug clearance, as well as the initial value of temperature, hydrostatic pressure and concentration of respiratory gases.

For simulation, some data are given on the base of literature while some data are given on the base of extrapolation. However, several data have to be assumed at first and then revised through the model verification and model improvement.

Data of the biothermal regulatory system, the respiratory system, the circulatory system, the pharmacokinetics of diuretic and anaesthetic are available in the previous reports (Gaohua and Kimura, 2006; Gaohua et al., 2006; Gaohua and Kimura, 2007; Gaohua and Kimura, 2008).

3.2 Model verification

Taken together, the body and its physiology are described by a compartmental structure, a set of nonlinear differential equations, various physiological parameters together with some interaction mechanisms. Various medical treatments are considered as adjustable input to the model.

The model is verified by comparing its simulation results with the existing data reported clinically. For example, partial model of the biothermal regulatory system, the hemodynamic system and the pharmacokinetics of diuretic or anaesthetic are tested separately, according to the similarity in characteristics in brain temperature response to step cooling and the similarity in the time course of intracranial pressure, as well as the intracranial concentration of diuretic or anaesthetic, in response to the bolus injection and to periodic infusion of diuretic or anaesthetic. Various properties of the respiratory part of the integrative model are also compared qualitatively with the general knowledge or quantitatively with the experimental data published in literature.

4. MODEL APPLICATONS TO ACUTE DISEASE

As an example of model applications, we target on the simultaneous management of various physiological functions in brain hypothermia treatment, which is a representative of systems medicine of acute disease enrolled in the ICU. Various simulations are carried out in the integrative model in order to find optimal strategy, (i) for the decoupling control of intracranial temperature and pressure, (ii) for the feed forward control of minute ventilation and (iii) for the feedback control of sedative infusion for hypothermic intracranial decompression (Gaohua et al., 2006; Gaohua and Kimura, 2007; Gaohua and Kimura, 2008).

4.1 Introduction of brain hypothermia treatment

Brain hypothermia treatment is an intensive care carried out to protect the secondary neuron death by therapeutic hypothermia (Poldermann et al., 2002; Hayashi and Dietrich, 2003; Polderman, 2004). Although the mechanism by which hypothermia can prevent brain damage has not yet been fully elucidated, more than one mechanism has been proved to play a role. These may include decreased brain swelling and lowering of the intracranial pressure and a decrease in the metabolic rate and oxygen demand in the brain (Poldermann et al., 2002). Other potential mechanisms for hypothermia's neuroprotective effects are related to Ca^{2+} homeostasis in the neuron, immune response and inflammation, free radical production, cerebral thermo-pooling and so on (Polderman, 2004).

Because of these aforementioned neuroprotective effects, the clinical use of therapeutic brain hypothermia is therefore likely to increase in the future. The doctors and medical staffs working in the ICU should have a systemic knowledge regarding the mechanisms supporting its clinical application, as well as the physiological consequences and side effects that may develop when a patient is treated with hypothermia.

However, the clinical practice is full of difficulties and it mostly relies on empirical knowledge. One of the difficulties encountered is the lack of basic quantitative information on the interactions among various physiological functions. The clinician, for example, uses diuresis to control high intracranial pressure generally based on the clinical knowledge of pharmacokinetics of diuretic, but seldom or never takes account of the possible effect of hypothermic intracranial decompression.

4.2 Decoupling control of intracranial temperature and pressure

In clinical brain hypothermia treatment, the reference brain temperature is about 34 ^{o}C and the reference intracranial pressure is less than 20mmHg (Hayashi and Dietrich, 2003). The complex interactions among the biothermal regulatory system, the circulatory system and the pharmacokinetics of diuretic have not been actively considered and the management of ambient cooling and diuresis are carried out separately in clinical practice. Although such clinical management is useful, it is difficult to realize the full usage of hypothermic intracranial decompression and optimal diuresis in the simultaneous management of intracranial temperature and pressure.

Based on responses of the integrative model to various stimuli of cooling and diuresis, a transfer function matrix is identified to linearly approximate the characteristic interrelationships between medical treatments (ambient cooling and diuresis) and the vital signs (intracranial

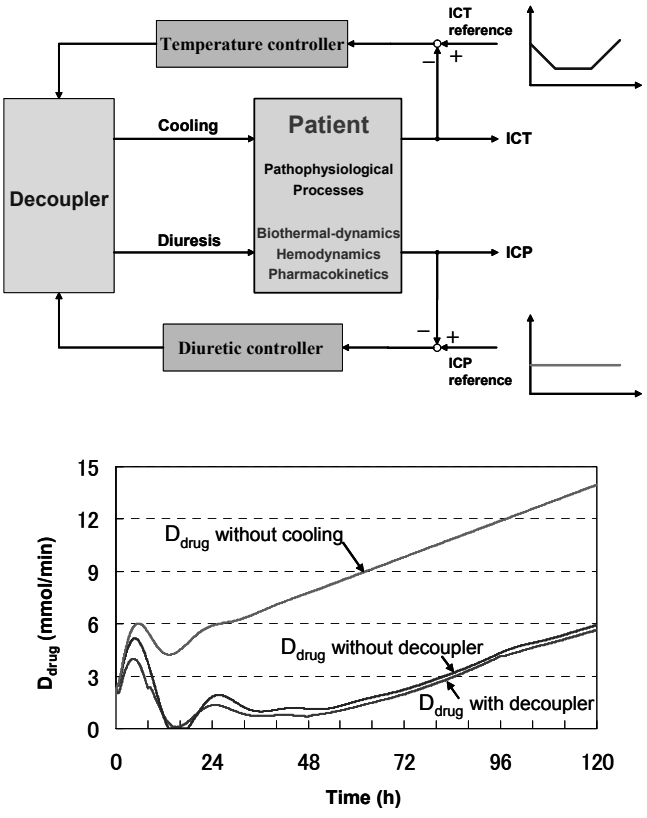


Fig. 3. Block diagram and simulation result of decoupling control of intracranial temperature and pressure

temperature and pressure). Then a controller that decouples ambient cooling and diuresis is proposed for efficient management of the intracranial temperature and pressure, enhancement of hypothermic decompression and reduction of diuretic dosage (Fig. 3).

Decoupling control simulation indicates that the intracranial temperature and pressure of the integrated model, representing a clinical patient under brain hypothermia treatment, can be simultaneously regulated by a single PID controller for ambient cooling and another for diuresis. The proposed decoupler effectively establishes hypothermic decompression, reduces the dosage of diuretic and improves the management of intracranial pressure. For example, with the decoupler, the dose of the diuretic can be reduced by about 12% for the simulated period (Gaohua et al., 2006).

4.3 Feedforward control of minute ventilation

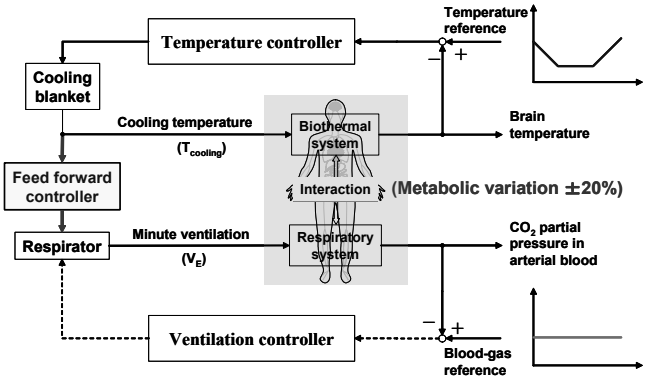
Although some recent studies recommended using low minute ventilation in brain hypothermia treatment in order to maintain the arterial CO_2 partial pressure within the normal range, it is still difficult for the clinicians to adjust the ventilator settings in the clinical practice, mainly due to the lack of quantitative guideline.

Indeed, the minute ventilation is often unchanged in operative setting and the development of respiratory alkalosis is facilitated by the hypothermia-induced decrease in the metabolic CO_2 production. Such respiratory management would affect the neuroprotection of therapeutic hypothermia, as systemic hypocapnia also results in alkalosis in CSF, which decreases cerebral blood flow and O_2 delivery and then induces brain ischemia and hypoxia.

Model-based simulation of the current respiratory management in brain hypothermia treatment suggests a reduction of minute ventilation in reference to cooled brain temperature in order to stabilize the states of blood and brain oxygenation. Therefore, the relationship between cooling temperature and minute ventilation is approximated by a linear first-order transfer function (Gaohua and Kimura, 2008). Therefore, it is possible to develop a feedforward control to tune the mechanical ventilator in concert with temperature regulation of the cooling blanket (Fig. 4). Discussion of the regulation of minute ventilation in the integrative model encourages further studies that provide direct evidence from clinical experiments.

4.4 Feedback control of anaesthesia for hypothermic intracranial decompression

Propofol is commonly used for general anaesthesia of normothermic patients in clinical practice of ICU. However, little information is available in the literature regarding the use of propofol anaesthesia for intracranial decompression



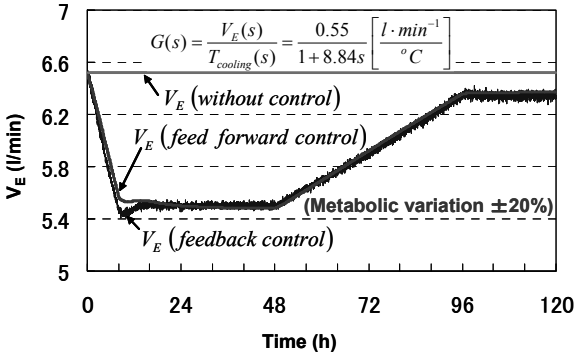
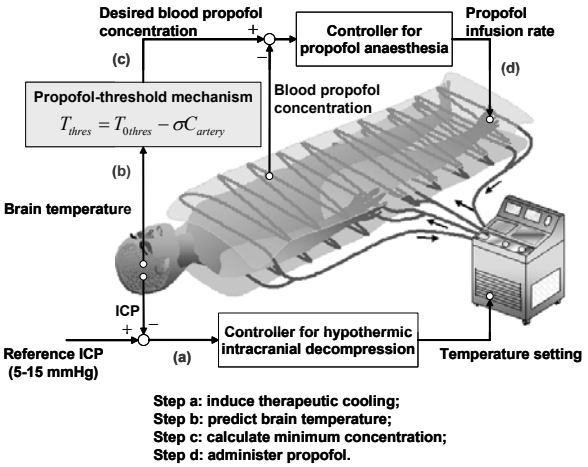


Fig. 4. Block diagram and simulation result of feedforward control of minute ventilation



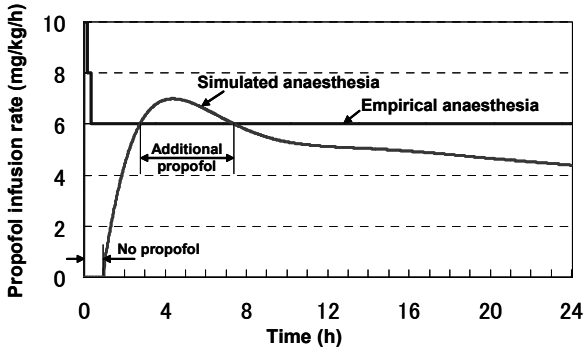


Fig. 5. Block diagram and simulation result of propofol anaesthesia for hypothermic intracranial decompression

using brain hypothermia treatment. A novel propofol anaesthesia scheme is proposed that should promote such clinical application and improve understanding of the principles of using propofol anaesthesia for hypothermic intracranial decompression (Fig. 5).

Theoretical analysis was carried out using the developed integrative model of the thermoregulatory, hemodynamic and pharmacokinetic subsystems. In particular, the propofol kinetics is combined with the thermoregulation subsystem through a pharmacodynamic relationship between the arterial propofol concentration and the thermoregulatory threshold which is termed as *propofol-threshold mechanism* in the model (Fig. 5). A propofol anaesthesia scheme for hypothermic intracranial decompression was simulated using the integrative model. Compared to the empirical anaesthesia scheme, the proposed anaesthesia scheme can reduce the required propofol dosage by more than 18% (Gaohua and Kimura, 2007).

Altogether, the integrative model of the thermoregulatory, hemodynamic and pharmacokinetic subsystems is effective in analyzing the use of propofol anaesthesia for hypothermic intracranial decompression. This propofol infusion scheme appears to be more appropriate for clinical application than the empirical one.

4.5 Remarks on integrative model

As the human body consists of multiple physiological functions at multiple levels, modelling physiological functions at various levels has been a major target of the computational physiology. However, the currently existing models of each physiological function are ineffective to theoretical discussion of systems medicine, as they seldom consider the interactions among various physiological functions.

To the best of our knowledge, the developed integrative model provides the first framework of modelling various physiological functions simultaneously at the organ level in the human body. Actually, the biothermal regulatory system, the respiratory system, the circulatory system, the pharmacokinetics of diuretic and anaesthetic are modelled in the same compartmental structure and the same governing equations. In particular, these systems are integrated through the circulating blood flow, together with the temperature-dependency mechanisms of various physiological functions.

As exemplified in the simulations using the integrative model, the present model succeeds in providing a holistic perspective of various physiological functions, while the developed controllers inspire the clinical medicine to a systems approach to the acute diseases.

The same framework is appropriate to model other physiological functions, such as ion concentration, blood pH and nutrient availability. Especially, the integrative model is extended to model the dynamics of blood glucose and its regulating hormones, namely, insulin and glucagon, in order to validate our hypothesis concerning the cause of diabetes.

5. MODEL OF GLUCOSE-INSULIN-GLUCAGON REGULATORY SYSTEM FOR DIABETES CONTROL

5.1 Hypothesis of brain glucose homeostasis

Because of the importance of providing a continuous source of fuel to the brain, the body has developed an elaborate glucose-insulin-glucagon (GIG) regulatory system to maintain the glucose homeostasis in the blood and the glucose delivery to the brain when blood glucose levels fall or raise out the euglycemic boundaries.

It is observed in rats that an increase of 50 mg/dl in the blood glucose level from its baseline only causes 10 mg/dl increase in the brain glucose level (Silver and Erecinska, 1998). It means the variation occurring in the blood glucose is damped down significantly in the brain glucose. One of its mechanisms may be the facilitated diffusion for glucose in the blood-brain barrier (BBB). Since the brain glucose concentration is of smaller range of variation than that of the blood glucose concentration, it is reasonable to hypothesize that the ultimate goal of GIG regulatory system is not the blood glucose homeostasis, but the brain glucose homeostasis.

Physiologically, such brain glucose homeostasis could be realized by an inherent feedback control of brain glucose through the brain-endocrine interaction. Anatomically, glucosensing neurons in the hypothalamus are capable of responding to physiological changes in the extracellular glucose (directly and via presynaptic input) (Routh, 2002). Also, the hypothalamus sends signals to the peripheral organs, including the liver and the pancreas, to keep homeostasis, after receiving information from afferent nerves (Uyama et al., 2004).

To our knowledge, brain glucose homeostasis has not been studied to date, although the neuronal and hormonal regulation of blood glucose homeostasis has been a target of some qualitative studies (Schwartz et al., 2000; Marty et al., 2007; Sandoval et al., 2008). Several mathematical models of the GIG regulatory system are used for theoretical and clinical applications to diabetes control (Makroglou et al., 2006; Boutayeb and Chetouani, 2006), but, no theoretical model has been developed to discuss the role of the brain in the brain glucose homeostasis within the healthy or the diabetes, both of which are generally under varying stresses. Also, neither the effect of brain nor that of stress is included in any currently existing quantitative models of GIG regulatory system.

5.2 Model description

A brain-centered compartmental model of GIG regulatory system is developed by extending the integrative model of physiological functions previously developed for the acute disease, while taking the feedback control loop of brain glucose and the effects of long-term stress encountered in the chronic disease into account.

5.2.1 Model structure

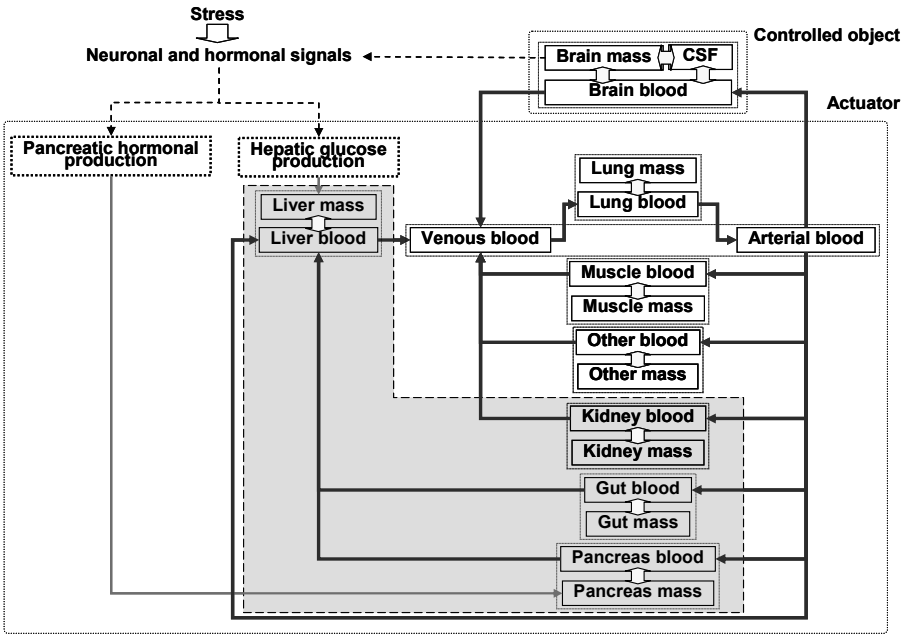


Fig. 6. Compartment model of glucose-insulin-glucagon regulatory system (The visceral segment consisting of liver, kidney, gut and pancreas is within the long dash line)

The previously developed integrative model is composed of 6 segments or 13 compartments (Fig. 2). The visceral segment represents a set of the liver, kidney, gut and pancreas. In order to model the GIG regulatory system, it is necessary to describe this visceral segment in detail.

As shown in Fig. 6, the extended model consists of 9 segments or 19 compartments. It is assumed that, hepatic endogenous glucose is produced in the liver mass, while exogenous glucose is given to the gut mass or the venous blood. Insulin is produced in the pancreas mass or infused into the venous blood or the muscle mass. Glucagon is generated in the pancreas mass.

Based on the anatomy of hepatic portal vein, blood flow from the pancreas segment and that from the gut segment enter the liver segment, together with the hepatic arterial blood flow, and then join the systemic circulation.

One of the main differences between the extended model and its original version is that the extended model considers the cranial segment as the controlled object, the body consisting of the extracranial segments as the actuator, and the arterial blood glucose as the actuating signal. It is consistent with the hypothesis that the brain glucose homeostasis is the ultimate target of GIG regulatory system.

Another difference is that an inherent feedback loop is introduced in the extended model. Exactly, the feedback loop is due to the neuronal and hormonal signals from various central and peripheral glucosensors and central insulin sensors. The reference would be the euglycemic value of brain glucose. Through such feedback loop, homeostasis of brain glucose is hypothetically realized.

For simplification, modelling is limited within the GIG regulatory system. That is, the interactions among the glucose dynamics, insulin dynamics and glucagon dynamics are modelled, while the interactions of the GIG regulatory system with the biothermal regulatory, circulatory and respiratory systems are ignored.

5.2.2 General governing equation

Applying the mass conservation law, similar to the approach previously used in developing the integrative model for acute disease, the dynamics of glucose, insulin and glucagon is described mathematically as follows:

$$d(VY)/dt = g_{in} - g_{out} \tag{2}$$

where V denotes distribution volume, Y substance (glucose, insulin or glucagon) concentration in the targeted compartment. The left hand side means the storage rate of substance. g_{in} on the right hand side is the rate of substance production or exogenous infusion, and g_{out} is the rate of substance utilization or clearance.

Equation (2) represents the common feature of three dynamics, namely, glucose dynamics, insulin dynamics and glucagon dynamics within the human body. It is the same as the equation (1), because both equations are based on the same conservation law of mass.

5.3 Detailed explanations g_{in} and g_{out}

In case of glucose dynamics, g_{in} is mainly the hepatic glucose generation, which is dependent on the concentration of

glucose, insulin and glucagon in the liver mass. It is also dependent on the stress and the central neuronal and hormonal signals. Exogenous glucose given to the gut mass or the venous blood is also included in the term g_{in}. The term of g_{out} consists of two parts, namely, insulin-independent utilization and insulin-dependent utilization. The former is mainly the metabolism in the brain mass and the red cells and the glucose discard through the urine if hyperglycemia, while the latter is mostly due to the muscular mass and various visceral masses.

In case of insulin dynamics, g_{in} is insulin production mainly from the beta-cells in the pancreas mass or insulin infusion into the venous blood or the muscle mass. The concentrations of glucose and glucagon in the pancreas determine the endogenous insulin production. As insulin is cleared by all insulin sensitive tissues, g_{out} depends on the local concentrations of glucose and insulin in the each extracranial mass compartment.

In case of glucagon dynamics, the term g_{in} corresponds to glucagon production from the alpha-cells in the pancreas mass. It depends on the concentrations of glucose and insulin in the pancreas mass. Glucagon is degraded in all extracranial mass compartments, mainly by the kidney and the liver. The term g_{out} is a function of the local concentration of glucagon.

5.4 Model of neuronal and hormonal control

Hypothalamus-centered neuronal circuits in the central nervous system play a critical role in orchestrating the control of glucose homeostasis. It is known that various glucosensing neurons are organized in an interconnected distributed network throughout the brain, which also receives afferent neural input from glucosensors in the liver, carotid body, and small intestines (Levin et al., 2006). However, the glucose concentration in the brain mass would be the major signal to the hypothalamus for the regulation of glucose homeostasis.

On the other hand, central insulin is another hormonal signal that provides negative feedback to the brain for the regulation of glucose homeostasis, as an increased insulin signal in the hypothalamus elicits responses that limit food intake and reduce hepatic glucose secretion.

After receiving information (central and peripheral glucose, central insulin) from afferent nerves, the hypothalamus sends signals, by stimulating the autonomic nerves or by releasing hormones from the pituitary gland, to the peripheral organs, including the liver and pancreas, to keep homeostasis (Uyama et al., 2004).

All of the current knowledge concerning the neuronal and hormonal signals to the hepatic glucose production and the pancreatic hormonal production are qualitative. For simplification, it is hypothesized that a proportional feedback control of brain glucose occurs in the GIG regulatory system, which is mainly based on the difference of brain glucose concentration from its baseline. The peripheral glucose and central insulin are considered as auxiliary input to the hypothalamus.

5.5 Model of stress

In order to take the effect of psychological stress into consideration, it is necessary to quantify it. To the best of our knowledge, a quantitative measure of stress has not been established. Therefore, a rather abstract variable of value varying between 0 and 1 is introduced to describe the degree of stress from the very slight to the very heavy. Various duration of stress, namely, short-term, repeated, long-term, are also used to describe the stress encountered in the daily life.

It is well documented that stress causes a direct increase in the pancreatic glucagon production through the hypothalamus-pituitary-adrenal axis. Stress responses also include increasing hepatic glucose production and decreasing pancreatic insulin secretion. After assuming that the stress affects the signals sent from the hypothalamus to the liver and pancreas, it is possible to introduce various coefficients into the hepatic glucose and pancreatic hormonal production to modify the stress responses quantitatively.

Taken together, the dynamics of GIG regulatory system is given as follows:

$$\begin{aligned} V\,dG/dt = {} & (1+s)\gamma g_{hgp}(G,I,E) \\ & - g_{brain}(G) - g_{red\ cell}(G) - g_{urine}(G) \\ & - g_{periph}(G,I) \end{aligned} \tag{3}$$

$$V\,dI/dt = (1-s)\beta i_{beta}(G,I,E) - i_{periph}(G,I) \tag{4}$$

$$V\,dE/dt = (1+s)\alpha e_{alpha}(G,I,E) - e_{periph}(E) \tag{5}$$

where G, I and E denote the concentrations of glucose, insulin and glucagon, respectively, and s a parameter representing stress. γ, β and α are the parameters describing neuronal and hormonal signals. They are functions of the controlled error (the difference of the controlled brain glucose concentration from its baseline). $g_{hgp}(G, I, E)$ means hepatic glucose production, which are dependent on concentrations of glucose, insulin and glucagon in the liver mass. Similarly, i_{beta} and e_{alpha} describe pancreatic hormonal secretions, each of which is function of the concentrations of glucose, insulin and glucagon in the pancreas mass. g_{periph}, i_{periph} and e_{periph} denote glucose utilization and hormonal clearance by the extracranial mass compartments. It should be pointed out that, not all terms occur in all compartments. For example, g_{brain} only occurs in case of the brain mass compartment.

5.6 Model of blood-brain-barrier adaptation

Blood-brain-barrier (BBB) is the interface between the brain blood and the brain mass. Physiologically, BBB maintains brain homeostasis, regulates transport of glucose by the facilitated transport process, and blocks harmful compounds from reaching the brain mass by its semi-impermeability.

The glucose transport at the BBB is described by the Michaelis-Menten equation with two parameters, namely, the

maximal transport rate (T) and Michaelis constant (K), as follows (Rapoport, 1976):

$$f_{blood\_brain} = \frac{TG_{blood}}{K + G_{blood}} \quad (6)$$

However, the maximal transport rate, T, is glucose-dependent. It was shown in rats that, following 12-14 days of hypoglycemia, brain glucose content was significantly increased about 50%, which was consistent with a similar increase in the maximal glucose transport rate T (58%) compared with the sham-treated animals (Lei and Gruetter, 2006). In contrast, the maximum glucose transport capacity of the blood-brain barrier decreased from 400 to 290 mM/100g/min in rats with chronic hyperglycemia. When plasma glucose was lowered to normal values, the glucose transport rate into brain was 20% below normal (Gjedde and Crone, 1981). It is suggested that repressive changes of the glucose transport mechanism occur in brain endothelial cells in response to increased plasma glucose.

As pointed by Gjedde and Crone (1981), diabetic patients with increased blood glucose concentrations may develop cerebral symptoms of hypoglycemia when their blood glucose is rapidly lowered to normal concentrations. The symptoms do indicate insufficient transport of glucose from blood to brain in the diabetes. Meaningfully, it was observed in the clinical practice that chronic hyperglycemia in diabetic patients does not alter brain glucose concentrations, compared with the healthy volunteers (Seaquist et al., 2005).

Clinical observations suggest the dynamics of the glucose transport from the brain blood to the brain mass is influenced by an adaptive nature of the BBB. Its underlying mechanism is not clear to date, although an increase in the expression of glucose transporter-1 (GLUT-1) and a redistribution of GLUT-1 at the BBB were observed in rats made chronically hypoglycemic (Simpson et al., 1999).

This mechanism is termed as *BBB adaptation* in this model. Such *BBB adaptation* should be a dynamical process characterized by long time constant, as it is observed that brain glucose transport is not altered following short episodes of recurrent hypoglycemia in the healthy human volunteers (Criego et al., 2005). Furthermore, the adaptation should be inactive within the euglycemic range, on account of the physiological fact that frequent variations, known as ultradian rhythm, occur in the blood glucose level in the healthy human.

Therefore, a first-order dynamics of two parameters, that is to say, gain and time constant, is introduced to modify the maximal glucose transport rate T as follows:

$$T = \begin{cases} T_0 & (G_{blood}\ within\ euglycemic\ range) \\ T_0 - \Delta T & (G_{blood}\ without\ euglycemic\ range) \end{cases} \quad (7)$$

$$\frac{\Delta T(s)}{\Delta G(s)} = \frac{k}{1 + \tau s} \quad (8)$$

where ΔT is the response of maximal glucose transport rate T with respect to hyperglycemia (ΔG>0) or hypoglycemia (ΔG<0). k and τ are gain and time constant, respectively. s is LapLace operator. Particularly, the time constant τ should be some days in case of rats, are some years in case of human. Both gain and time constant are individual dependent.

A similar BBB adaptation mechanism is assumed to the BBB insulin transport in the model, as insulin transport from the brain blood to the brain mass is also described by the Michaelis-Menten equation.

5.7 Model verification

Since the current model is an extension of the original model, some parameters such as the distribution volume, blood flow and metabolic allocation are common. The original data are applicable. Some data are available from literature.

On the other hand, several data have to be assumed at first and then revised through the model verification and model improvement. This is mainly because the hepatic glucose production, the pancreatic hormonal production, glucose utilization and hormonal clearance are assumed to depend on local concentrations of glucose, insulin and glucagon in the mass compartments in the current model. By contrast, these production and utilization are evaluated as functions of the blood concentrations in the existing glucose-insulin-glucagon models. Therefore, the reported values are inapplicable in the present model.

After tuning the values of physiological and physical parameters, mainly by trail and error, the simulation profiles obtained from the compartmental model are compared well with the clinical data (data not shown). In particular, the current model is appropriate in describing the GIG regulatory system responses to bolus, durational or continuous glucose infusion, qualitatively and partially quantitatively, even though the model consists of some parameters assumed arbitrarily by the modeller.

6. PRELIMINARY SIMULATION RESULTS

As a result of intensive simulations, it is shown that some unique features of the GIG regulatory system are well embodied in our model. Preliminary simulation results are summarized to reveal the role of long-term and heavy stress in the hyperglycemia and the role of BBB adaptation in the diabetes.

6.1 Role of stress

The response of the GIG regulatory system to small or short-term stress is essential to the survival of an individual. As shown in Fig. 7, all stresses, of varying degree and duration, cause hyperglycemia transiently or persistently.

A slight stress, corresponding to s=0.01 in equation (3)-(5), resulted in a steady-state of the GIG regulatory system, which is characteristic of an ultradian rhythm. By contrast, the ultradian oscillation disappeared in case of a heavy stress (s=0.2).

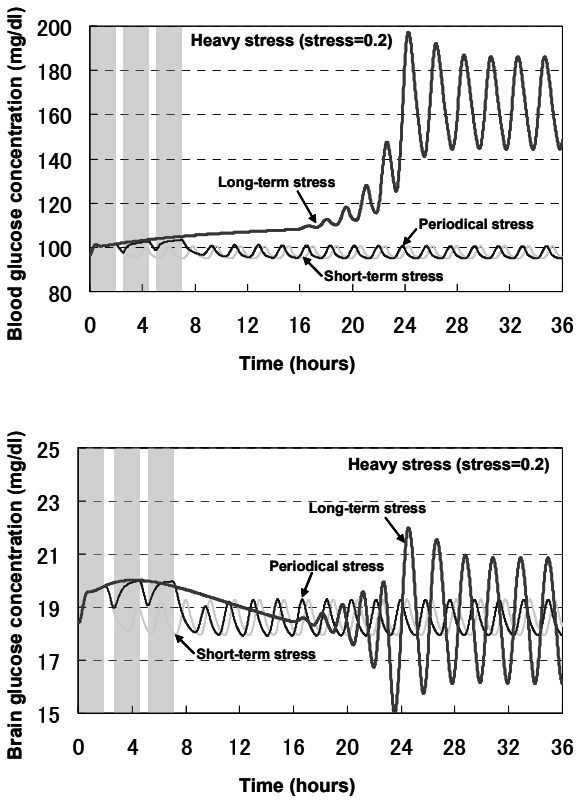


Fig. 7. simulation results of brain glucose homeostasis (repeated stresses are shown by shaded area)

Short-term stress (s=0.2) given from 0 to 2 hour transiently caused an increase in the blood glucose, as shown in Fig. 7, and a decrease in the blood insulin and the blood glucagon (data not shown). These transient responses disappeared after the stress ended. However, a steady-state, characteristic of an ultradian rhythm, was resulted.

To simulate the adaptation of the GIG regulatory system, recursive stress of 2.5-hour period (2 hour active and then 0.5 hour inactive) was applied, as shown by the shaded areas in Fig. 7. The simulation results showed a continuous increase in maximum blood glucose after every stress. Such an increase should be due to the inertia of the GIG regulatory system. Similar to the short-term stress, responses of blood glucose to repeated stress also converged to the steady-state when the stress ended.

If stress (s=0.2) was applied continuously, the blood glucose would never return to its original state. A new steady, but hyperglycemic state of GIG regulatory system would be resulted (data not shown). The resulted hyperglycemia depended on the degree of stress, that is to say, the heavier the stress, the higher the blood glucose level resulted. However, in the simulated case of heavy stress (s=0.2), the resulted blood glucose level was still within the euglycemic range (data not shown). Taken together, quantification of heavy stress using s=0.2 seems reasonable.

6.2 Role of blood-brain-barrier (BBB) adaptation

In order to simulate the role of BBB adaptation in hyperglycemia and diabetes, the gain k and the time constant τ in formula (8) were given hypothetically, for example, k=0.3 for glucose, k=0.01 for insulin, τ=4 hour for both glucose and insulin. Generally, the time constant τ may be some years for the adapting BBB in human. Such an assumption of short time constant is due to the time limitation of computer simulation. Therefore, the simulation results hereafter should be considered as fast-forward of the responses.

As shown in Fig. 7, in case of long-term stress, a hyperglycemic steady-state of blood glucose was generated by the current model, while the brain glucose was maintained within the euglycemic range. At the same time, it was observed that both concentration of blood insulin and that of blood glucagon were higher than their basal, and the ratio of glucagon to insulin was elevated (data not shown). Therefore, the current model of GIG regulatory system developed an abnormal state, which is characterized by hyperglycemia, hyperinsulimia and hyperglucagonemia.

The simulation results are consistent with clinical facts, that is, as cited by Jiang and Zhang (2003), the absolute levels of glucagon or the ratios of glucagon to insulin are often elevated in various forms of diabetes in both animal and human subjects. The same authors also pointed out that, chronic hyperglucagonemia was correlated with and was partially responsible for increased hepatic glucose production and hyperglycemia in type 2 diabetes.

As shown in Fig. 7, in any simulations including that of hyperglycemia, brain glucose homeostasis was realized after considering BBB adaptation. It meant that brain glucose concentration was maintained within euglycemia range even in case of blood hyperglycemia. This simulation result is consistent with the clinical observations that chronic hyperglycemia in diabetic patients does not alter brain glucose concentrations, compared with the healthy volunteers (Seaquist et al., 2005).

In order to simulate the effect of gain k on the resulted hyperglycemia, k was varied from 0 to 0.5. Simulation results showed that the resulted blood hyperglycemia was dependent on k, that is, the larger the gain k, the higher the resulted blood hyperglycemia (data not shown). If k=0, which corresponds to the case of inadaptive BBB, a state of elevated brain glucose would be resulted, together with the elevated blood glucose within the euglycemic range. However, the elevated brain glucose would never return to its basal. Although this simulation result had not support from any clinical observation, it revealed the role of BBB adaptation in the brain glucose homeostasis.

6.3 Remarks

6.3.1 Concerning stress

Stress has long been shown to have major effects on metabolic activity as energy mobilization is a primary result

of the fight or flight response. Stress stimulates the release of various hormones, which can result in elevated blood glucose levels. Due to the same mechanism, stress may be a potential contributor to chronic hyperglycemia in diabetes. Although human studies on the role of stress in the onset and course of type 2 diabetes are few, a large body of animal study supports the notion that stress reliably produces hyperglycemia in this form of the disease (Surwit, et al., 1992).

Obviously, the simulation results are compared well with the clinical knowledge. Various simulations on the degree and duration of stress reveal the roles played by the stress in hyperglycemia, not only qualitatively but also partially quantitative. To the best of our knowledge, a quantitative measure of stress has not been established for theoretical discussion. Our approach should be a meaningful trial.

6.3.2 Concerning blood-brain-barrier (BBB)adaptation

To maintain the brain's high rate of metabolism and the neuronal homeostasis, glucose transport from the blood to the brain should be regulated closely, according to short-term and long-term levels of the blood glucose. Actually, BBB helps govern the brain glucose homeostasis through temporary and permanent mechanisms. The former is through the neuronal and hormonal regulation, where the body except of the brain acts as an actuator, while the latter would be the BBB adaptation, which is a physical change with respect to chronic hypoglycemia or hyperglycemia.

As shown by the simulation results, BBB adaptation for brain glucose homeostasis, together with the long-term heavy stress, contributes to the blood hyperglycemia. Particularly, both blood insulin and glucagon are elevated, as observed in some type 2 diabetes. Therefore, it is considered that a theoretical model of diabetes could be developed in the current model by introducing BBB adaptation.

Long-term and heavy stress results in hyperglycemia both in blood and in brain, but seldom causes diabetes, if without BBB adaptation. This simulation result suggest a novel hypothesis, namely, hyperglycemia observed in the diabetes would be one of the controlled results for brain glucose homeostasis through the permanent adaptation mechanism. Based on this hypothesis, brain may be a new potential target for the therapeutic treatment of diabetes.

7. CONCLUSIONS

In this paper, we proposed the notion of model-based medicine, which is expected to give a solution to various difficulties in clinical medical systems, based upon the familiar methodology of control science. The model-based medicine relies on integrated modelling of the various physiological functions of human body. It is considered that the clinical practice following this paradigm will be distinctly different from the status quo, particularly for complex acute or chronic diseases. The bottleneck is how to build an exact model applicable in the clinical practice.

For this purpose, a mathematical model of patient under brain hypothermia treatment was developed. On the base of the integrative model, various controllers were introduced to simulate the decoupling control of intracranial temperature and pressure, the feedforward control of minute ventilation and the feedback control of anaesthetic infusion. Theoretical discussion would benefit the integration of various medical apparatus and the collaboration among various medical specialists in the current ICU.

The integrative model was then extended to describe the glucose-insulin-glucagon (GIG) regulatory system for diabetes control. Some unique features of the GIG regulatory system were revealed by various simulations. Particularly, the role of long-term and heavy stress in the hyperglycemia and the role of BBB adaptation in diabetes were discussed. According to the simulation results, it is concluded that, (i) both long-term heavy stress and BBB adaptation contribute to hyperglycemia and diabetes; (ii) blood hyperglycemia may be an outcome of control of brain glucose homeostasis.

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