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Integrated Physiological Interaction Modeling and Simulation for Aerobic Circulation with Beat-by-Beat Hemodynamics

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1. Introduction

This chapter describes a simulation system for modeling and testing aerobic circulatory physiology on the virtual environment. There have been many models of the biological system at various scales and from various viewpoints, intended to simulate physiological changes and pathological conditions (McLeod, 1966). However, these models are designed primarily for medical education, and are unsuitable as practical tools for clinical diagnosis. The reason for this unsuitability is their insufficiently accurate quantitative representation of the physiological system compared to clinical data or the results of animal experiments (Ackerman, 1991). A further problem in developing practically useful models of biological systems is the need for expert physiologists to engage in computer programming in order to create the mathematical models. The useful modeling and simulation tool for an integrated circulatory system is important for physiological diagnosis and evaluation.

The development of a simulation tool that uses a basic exercise model of circulatory system enables to facilitate model testing, formulation, and refinement for solving the above problems. Another purpose is to provide a basic model that combines macro and micro models for the aerobic circulation with the heart function. The macro model includes the comprehensive physiological functions, and the micro model analyzes the pulsatile behavior of the hemodynamics in adaptive fitness support. By combining the macro and micro models of the circulatory system, it becomes possible to simulate subtle changes of the blood flow in response to various factors, such as body temperature, body weight, and basic metabolism, which is impossible using a single-purpose model.

In this simulation system, the macro model includes multiple organs and physiological functions, and calculates the physiological variables with time steps of a second or longer. The macro model is designed to allow the calculation of long-term biological phenomena over periods ranging from several hours to several months. In the heart activity, on the other hand, time steps of the order of milliseconds or microseconds are required in order to analyze the contraction and expansion cycle of the heart, which takes place in a cardiac period of less than a second. Consequently, the micro model is designed to calculate variables with a time step of less than a second, focusing on a single physiological function.

The integrated physiological simulation would be proposed, here a basic model that combines the macro and micro models of the aerobic circulatory system is provided. In addition, a modeling support function is proposed in which sensitivity analysis is used to assist the user in modifying the basic model. In an experiment using the combined macro and micro model, realistic simulation results were obtained for the blood flow, lactic mass, and O_2 consumption when the parameters representing the exercise intensity was varied.

2. Circulatory system model

The macro model of the circulatory system comprehensively describes multiple organs and physiological functions. The circulatory system model (Coleman, 1979; Randall, 1987) includes 25 physiological modules, including 321 variables and 70 parameters. The 25 modules are as follows: *HEART* (cardiac output and blood flow to major organs), *CARDFUNC* (strength levels of left and right heart), *CIRC* (pulmonary circulation), *REFLEX-1* and *REFLEX-2* (the activities of sympathetic nerve and vagus nerve, and heart rate), *TEMP* (heat generation and consumption in body temperature), *EXER* (control of exercise), *DRUGS* (prescription of drugs), O_2 (oxygen balance), CO_2 (carbon dioxide balance), *VENT* (control of ventilation), *GAS* (gas exchange), *HORMONES* (hormone adjustment), *KIDNEY* (kidney function and status), *RENEX* (excretion from kidneys), *HEMOD* (hemodialysis), *FLUIDS* (injection and loss of systemic fluids), *WATER* (water balance), *NA* (sodium balance), *ACID/BASE* (acid-base balance), *UREA* (urine balance), *K* (potassium balance), *PROTEIN* (protein balance), *VOLUMES* (blood distribution), and *BLOOD* (hematocrit control), which are connected with input and output variables shown in Fig. 1.

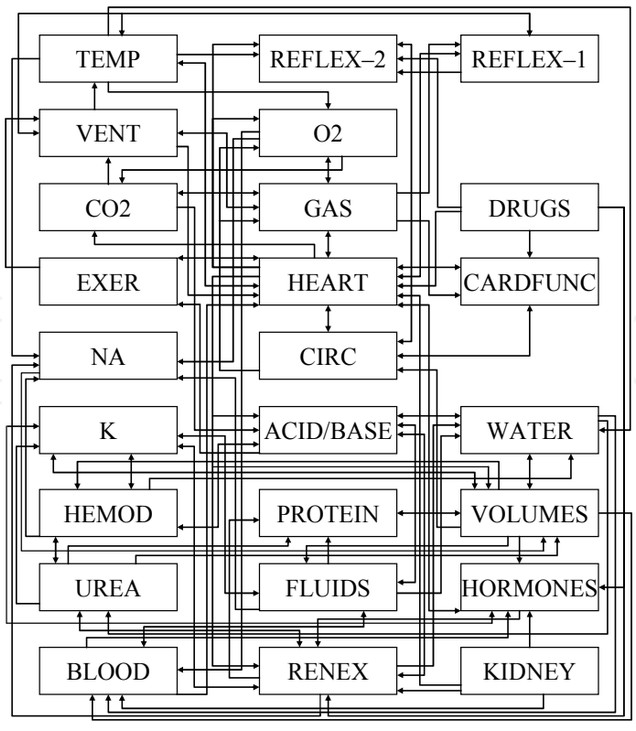
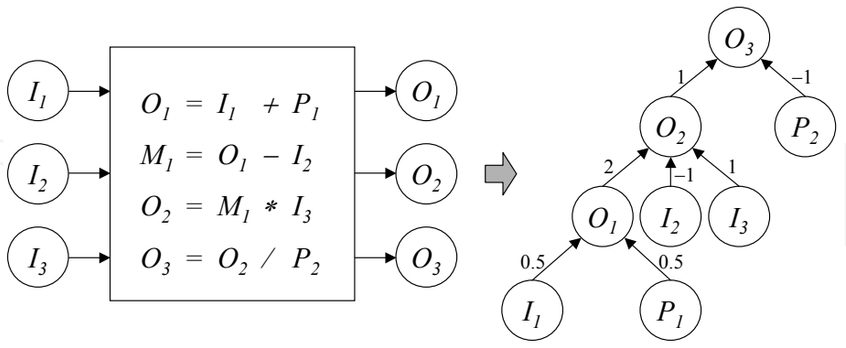


Fig. 1. Modules connected with input and output variables

2.1 Sensitivity analysis

The proposed simulation system provides the user with the ability to modify the basic macro model. The user could wish to examine the quantitative behavior of the output variables by simulation, and to correct the time course of the output variables. It is necessary in such cases to trace the input variable and the parameters that strongly affect the output variables under consideration. The modeling support is a function that helps such tracing of variables. It can be utilized effectively to view the structure of the mathematical expressions in the module. The modeling support function applies sensitivity analysis to the module. The sensitivities among the variables are represented by a directed graph that visualizes the causal relations among variables. The directed graph has a hierarchical structure, indicating the extent to which output variables are affected by individual input variables or parameters. By using this function, the user can determine which parameters should be adjusted and by how much in order to move the output variable toward the target value.

Fig. 2 outlines the sensitivity analysis of a simple module. *I* denotes an input variable, *O* an output variable, *M* an intermediate variable used for convenience in computation, and *P* a parameter. In this study, sensitivity is defined as the ratio of the rate of change of the output variable to the rate of change of the input variable in the module. In sensitivity analysis, the value of the input variable is temporarily increased by 10%, and the percentage in output variable changes is determined. A simple example is presented below. Consider the computation formula $A = B + 2*C$. From this formula, the two causal relations $B \rightarrow A$ (sensitivity 0.333) and $C \rightarrow A$ (sensitivity 0.666) are derived as paths in the directed graph. The sensitivities are calculated by setting the initial values of both *B* and *C* to 100. The sensitivity to parameters is similarly determined. When the directed graph contains an intermediate variable, the sensitivities are calculated for the two paths passing through the intermediate variable. Then the paths are replaced by a path corresponding to the product, and the intermediate variable is eliminated. However, it may happen that an output variable is also used as an intermediate variable. The output variable has the role of describing the



A simple module A directed graph

I: input *O*: output *P*: parameter *M*: medium variable

Definition:

$$Sensitivity = \frac{\Delta Rate\ of\ Output}{\Delta Rate\ of\ Input}$$

Calculation:

$$Sensitivity = \frac{O'-O}{O} \Big/ \frac{I'-I}{I}$$

Fig. 2. Outline of sensitivity analysis

behavior of the module and is not eliminated, since it must be referred to by other modules. In the directed graph shown in Fig. 2, there are seven causal relations ($I_1 \rightarrow O_1$, $P_1 \rightarrow O_1$, $I_2 \rightarrow O_2$, $O_1 \rightarrow O_2$, $I_3 \rightarrow O_2$, $O_2 \rightarrow O_3$, $P_2 \rightarrow O_3$) among the variables. In this case, the sensitivity is calculated by setting the initial values of all the input variables and parameter values to 100. The modeling support is a function that helps the user to understand the causal relations among the variables. It traces the parameters, starting from the output variable, and finally identifies the parameter that most strongly affects the output variable of accompanying with the sensitivity. Suppose that the user wishes to modify the value of output variable O_3. The user then traces the path among the variables, $P_1 \rightarrow O_1 \rightarrow O_2 \rightarrow O_3$, in the editorial interface and ascertains the sensitivity of parameter P_1 for the output variable O_3. The user can then correct the behavior of the output variable by adjusting the parameter value.

2.2 Structural analysis

The structure of equations, variables, and parameters of module is visualized to the hierarchy by the ISM (Interpretive Structural Modeling). Because the directed graph consisting of extracted linkages does not explain the whole systematic order of cause-effect relationships, a user would not be able to grasp how to calculate an output variable from other input variables and parameters. The structural analysis by ISM classifies variables and parameters in accordance with the hierarchical levels, which are obtained by finding a set of nodes that cannot reach any other nodes except the set itself. The hierarchized directed graph guarantees that only the linkages from the lower level to the upper level are included in the whole graph, but there is no reverse directional one. Nodes in the same level means to be either irrelevant to each other or related mutually. The structure of causal relationships among variables and parameters enables the simulation system to solve effectively a diagnostic problem, which is defined as follows: An output variable whose value is out of its normal range is given, all input variables which can reach to the output are found into the hierarchical graph, and an input variable whose path to the output has the maximum total gain is proposed as a causative one for adjusting the unusual output's value. Otherwise parameter is considered as causative factor in the abnormal variation of the output. The total gain helps to decide major causative inputs and parameters because the maximum gain says that they can be the most noteworthy factors about the change of the output.

Fig.3 shows the hierarchy of the module *ACID/BASE*, where acidity in blood is determined. Here variables figured by square and parameters by ellipse are classified to 6 levels. There are two final output variables *PH* (blood pH) in the top level and *BICARB* (plasma bicarbonate) in the 3rd level. They clearly depend on other variables and parameters in the lower levels. The module *ACID/BASE* contains input variables PCO_2 (venous CO_2 tension) from module CO_2, *BICRT* (added bicarbonate) from module *FLUIDS*, *EXBIC* (excretion of bicarbonate) from module *RENEX*, *DYBIC* (dialyzed bicarbonate), BH_2OL (body water in litters) from module *WATER*, and DMO_2C (delta muscle O_2) from module *HEART*, and has one parameter *BACID* (basic acid production), which are terminal nodes of this module. It is visualized that there are well-ordered connections of variables, such as *BICRT* → *DBIM* → *BIMASS* → *BICARB*, from input to output in the module. Fig.4 describes the hierarchy classified in 6 levels of module *BLOOD*, where blood volume and red cell mass are calculated. The outputs are *HCT* (hematocrit), *BV* (blood volume), and *WGHT* (body weight). *WGHT* is calculated from parameter *OBM* (other body mass), input BH_2OL (body

water in litters) from module *WATER*, and variable *RCM* (red cell mass). The hierarchical directed graphs not only help to understand the calculation structure of the module, but also enable to track paths between input and output variables that are connected with recursive links in the large circulatory system model. Exploring large structure of cause and effect relationships becomes effective with respect to diagnosis time by ignoring irrelevant paths among input and output variables.

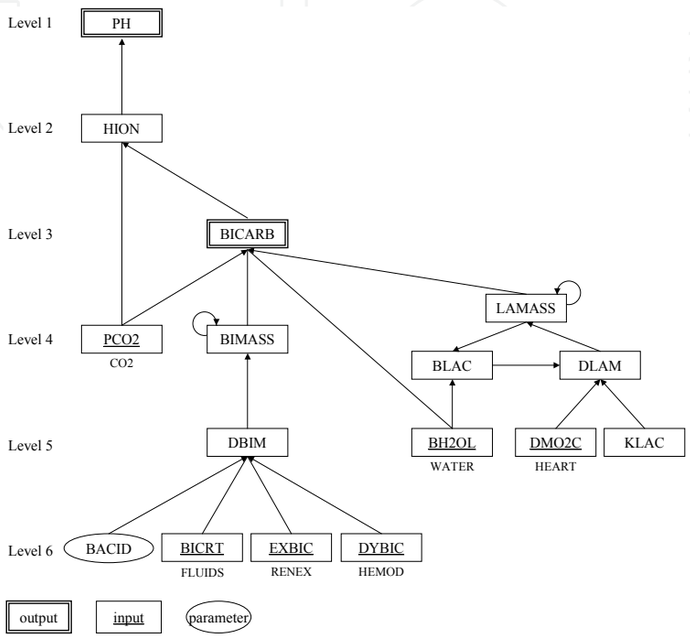


Fig. 3. Hierarchical directed graph of module *ACID/BASE*

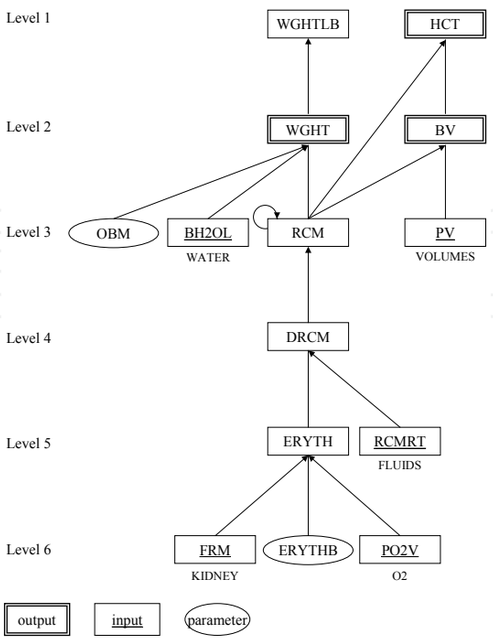
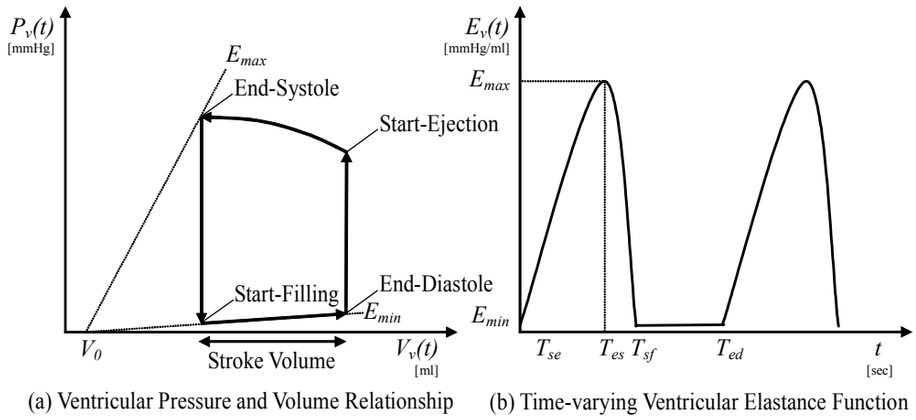


Fig. 4. Hierarchical directed graph of module *BLOOD*

3. Beat-by-beat model

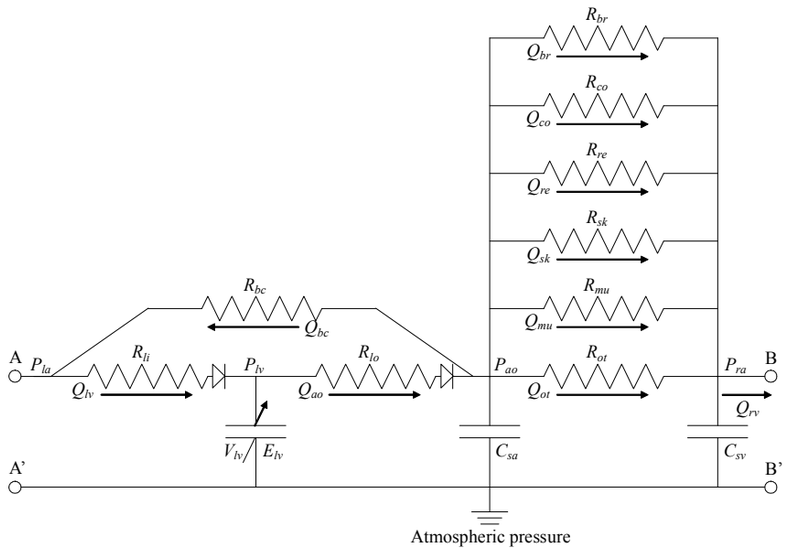
The hemodynamics of the heart as a pump could be described as a micro model based on time-varying elasticity from the Frank-Starling law, which defines the ventricular mechanical properties in a cardiac cycle. The *HEART* module simulates hemodynamics in the macro model with the aortic pressure, the cardiac output, and the blood flow to the major organs. However, it is a macroscopic model, and the pulsations cannot be represented even if the time step of temporal changes is shortened to millisecond order. Therefore, a micro model of the circulatory system is constructed so that hemodynamics with periodic pulsations due to heart activity can be simulated. The definition of ventricular elastance as the ratio of ventricular pressure to volume indicates, $E_v(t) = P_v(t)/(V_v(t)-V_0)$ where the inferior v refers to the ventricle and V_0 represents the unstressed volume of ventricles. Fig. 5 shows the function of the time-varying elastance, which repeats systole and diastole for ejecting blood from the chamber. During the systolic phase of the ventricle, elastance rises rapidly, and the rise ceases at ejection. During the diastolic phase of the ventricle, elastance falls rapidly in isovolumetric relaxation, and is almost constant in passive filling.



(a) Ventricular Pressure and Volume Relationship (b) Time-varying Ventricular Elastance Function

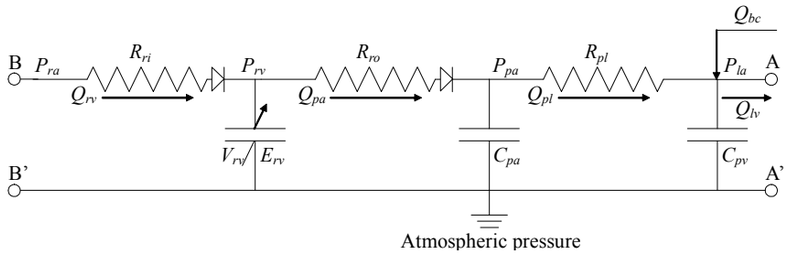
Fig. 5. The ventricular elastance function

In the micro model of the circulatory system, the elastics of the left and right ventricles correspond to variable capacitors. In the cardiovascular system model, the blood flow is represented by the electrical current, the blood pressure is represented by the voltage, and the vessel resistance is represented by the electrical resistance. The ventricular valve is represented by a diode, so that backflow of the blood does not occur. The compliance simulates the softness of the vessels and the blood pool in the vessels, and corresponds to the capacitor in the electrical circuit. Fig. 6 shows the electrical circuit model of systemic circulation, and Fig. 7 pulmonary circulation. The systemic and pulmonary circulation is closed in series by connecting points A and B. The aortic flow output from the left ventricle (Q_{ao}) branches into the brain vessel blood flow (Q_{br}), the coronary vessel blood flow (Q_{co}), the renal vessel blood flow (Q_{re}), the skin vessel blood flow (Q_{sk}), the muscle vessel blood flow (Q_{mu}), the bronchial vessel flow (Q_{bc}), and the other vessel blood flow (Q_{ot}). On their return, the blood flows are combined in the vena cava and the right atrium to form the right ventricular blood flow (Q_{rv}). The outlet valve is the aortic valve and the inlet valve is the mitral valve. Compliances are provided with the systemic artery compliance C_{sa} and the systemic vein and right atrium compliance C_{sv}. Three differential equations are derived from



P_{lv} : Pressure in left ventricle [mmHg]	E_{lv} : Elastance of left ventricle [mmHg/ml]
P_{la} : Pressure in left atrium [mmHg]	V_{lv} : Volume of left ventricle [ml]
P_{ao} : Pressure in aorta [mmHg]	C_{sa} : Compliance of systemic artery [ml/mmHg]
	C_{sv} : Compliance of systemic vein and right atrium [ml/mmHg]
Q_{lv} : Quantity to left ventricle [ml/sec]	R_{li} : Resistance of left ventricular inflow valve [mmHg/ml/sec]
Q_{ao} : Quantity to aorta [ml/sec]	R_{lo} : Resistance of left ventricular outflow valve [mmHg/ml/sec]
Q_{br} : Quantity to brain blood vessel [ml/sec]	R_{br} : Resistance of brain blood vessel [mmHg/ml/sec]
Q_{bc} : Quantity to bronchial blood vessel [ml/sec]	R_{bc} : Resistance of bronchial blood vessel [mmHg/ml/sec]
Q_{co} : Quantity to coronary blood vessel [ml/sec]	R_{co} : Resistance of coronary blood vessel [mmHg/ml/sec]
Q_{re} : Quantity to renal blood vessel [ml/sec]	R_{re} : Resistance of renal blood vessel [mmHg/ml/sec]
Q_{sk} : Quantity to skin blood vessel [ml/sec]	R_{sk} : Resistance of skin blood vessel [mmHg/ml/sec]
Q_{mu}: Quantity to muscle blood vessel [ml/sec]	R_{mu}: Resistance of muscle blood vessel [mmHg/ml/sec]
Q_{ot} : Quantity to other blood vessel [ml/sec]	R_{ot} : Resistance of other blood vessel [mmHg/ml/sec]

Fig. 6. The systemic circulation model



P_{rv} : Pressure in right ventricle [mmHg]	E_{rv} : Elastance of right ventricle [mmHg/ml]
P_{ra} : Pressure in right atrium [mmHg]	V_{rv} : Volume of right ventricle [ml]
P_{pa} : Pressure in pulmonary artery [mmHg]	C_{pa} : Compliance of pulmonary artery [ml/mmHg]
	C_{pv} : Compliance of pulmonary vein and left atrium [ml/mmHg]
Q_{rv} : Quantity to right ventricle [ml/sec]	R_{ri} : Resistance of right ventricular inflow valve [mmHg/ml/sec]
Q_{pa} : Quantity to pulmonary artery [ml/sec]	R_{ro} : Resistance of right ventricular outflow valve [mmHg/ml/sec]
Q_{pl} : Quantity to pulmonary blood vessel[ml/sec]	R_{pl} : Resistance of pulmonary blood vessel [mmHg/ml/sec]

Fig. 7. The pulmonary circulation model

the electrical circuit model of the systemic circulation, based on the relations among the changes in blood flows. Equations (1), (2), and (3) are concerned with the changes of the blood flow in the left ventricle, the aorta, and the vena cava, respectively. Three variables, namely, the left ventricular volume V_{lv}, the aortic pressure P_{ao}, and the right atrium pressure P_{ra}, are described by the differential equations:

$$\frac{dV_{lv}}{dt} = Q_{lv} - Q_{ao} \tag{1}$$

$$\frac{dP_{ao}}{dt} = \frac{Q_{ao} - Q_{br} - Q_{co} - Q_{re} - Q_{sk} - Q_{mu} - Q_{ot} - Q_{bc}}{C_{sa}} \tag{2}$$

$$\frac{dP_{ra}}{dt} = \frac{Q_{br} + Q_{co} + Q_{re} + Q_{sk} + Q_{mu} + Q_{ot} - Q_{rv}}{C_{sv}} \tag{3}$$

The left ventricular pressure P_{lv} can be determined based on the relation among the pressure, the volume, and the elastance of the left ventricle. Here E_{lv} is the elastance, V_{lv} is the volume, and V_{lv0} is the unloaded volume, respectively, of the left ventricle:

$$P_{lv} = E_{lv} \times (V_{lv} - V_{lv0}) \tag{4}$$

The blood flow into the left ventricle (Q_{lv}) and the blood flow from the left ventricle (Q_{ao}) can be determined by Ohm's law from the change in the blood pressure and the vessel resistance. Since a valve is present, no backflow occurs in the inlet and outlet blood flows of the left ventricle:

$$Q_{lv} = \begin{cases} \dfrac{P_{la} - P_{lv}}{R_{li}} & if \quad P_{la} > P_{lv} \\ 0 & if \quad P_{la} \le P_{lv} \end{cases} \tag{5}$$

$$Q_{ao} = \begin{cases} \dfrac{P_{lv} - P_{ao}}{R_{lo}} & if \quad P_{lv} > P_{ao} \\ 0 & if \quad P_{lv} \le P_{ao} \end{cases} \tag{6}$$

The blood flow to each vessel in the systemic circulation system can be similarly determined from the change in the blood pressure and the vessel resistance. For example, the blood flow in the brain vessel is calculated as follows:

$$Q_{br} = \frac{P_{ao} - P_{ra}}{R_{br}} \tag{7}$$

The pulmonary arterial flow (Q_{pa}) output from the right ventricle flows in the pulmonary vessel (Q_{pl}) to the pulmonary vein and left atrium, and then into the left ventricle (Q_{lv}). The outlet valve is the pulmonary valve, and the inlet valve is the tricuspid valve. Compliances are provided with the pulmonary artery compliance C_{pa} and the pulmonary vein and left atrium compliance C_{pv}. The following three differential equations are derived from the change in blood flow in the electrical circuit model of the pulmonary circulation. Equations (8), (9), and (10) are concerned with the blood flows in the right ventricle, the pulmonary artery, and the pulmonary vein, respectively. Three variables, the right ventricular volume V_{rv}, the pulmonary artery pressure P_{pa}, and the left atrium pressure P_{la}, are described by the differential equations:

$$\frac{dV_{rv}}{dt} = Q_{rv} - Q_{pa} \tag{8}$$

$$\frac{dP_{pa}}{dt} = \frac{Q_{pa} - Q_{pl}}{C_{pa}} \tag{9}$$

$$\frac{dP_{la}}{dt} = \frac{Q_{pl} + Q_{bc} - Q_{lv}}{C_{pv}} \tag{10}$$

The right ventricular pressure P_{rv} can be determined similarly. Here E_{rv} is the elastance, V_{rv} is the volume, and V_{rv0} is the unloaded volume, respectively, of the right ventricle:

$$P_{rv} = E_{rv} \times (V_{rv} - V_{rv0}) \tag{11}$$

The blood flow into the right ventricle (Q_{rv}) and the blood flow from the right ventricle (Q_{pa}) can be determined from the change in the blood pressure and the vessel resistance:

$$Q_{rv} = \begin{cases} \dfrac{P_{ra} - P_{rv}}{R_{ri}} & if \quad P_{ra} > P_{rv} \\ 0 & if \quad P_{ra} \le P_{rv} \end{cases} \tag{12}$$

$$Q_{pa} = \begin{cases} \dfrac{P_{rv} - P_{pa}}{R_{ro}} & if \quad P_{rv} > P_{pa} \\ 0 & if \quad P_{rv} \le P_{pa} \end{cases} \tag{13}$$

The blood flow in the pulmonary vessel (Q_{pl}) is calculated similarly:

$$Q_{pl} = \frac{P_{pa} - P_{la}}{R_{pl}} \tag{14}$$

The cardiovascular system model consisting of systemic and pulmonary circulations is connected to the basic macro model with common variables of vascular resistance, heart rate, and body weight. Moreover, the cardiovascular system model products beat-by-beat blood flow and pressure as output. Numerical analysis using the Runge-Kutta-Gill method aiming at high speed calculation is applied to the differential equations (1) to (14). The micro model of the circulatory system is written in C programming language to take priority on the computation speed in the simulation.

4. Exercise control model

A suitable exercise level is presented and controlled according to the individual hemodynamic conditions. The responses of respiration, venous contraction, and muscle metabolism for exercise are presented in the circulatory system model. The exercise is defined as the addition of oxygen in blood from 0 to 10,000 ml/min for normal oxygen use 250 ml/min. Fig. 8 shows basic relationships between physiological variables in the exercise

control model. If the exercise is given, respiration rate, sympathetic activity, venous pressure, and muscular metabolism increase according to the exercise levels. Consequently, cardiac output and venous return rise in the circulatory system. In addition to the above functions, the exercise control model is constructed by introducing personal parameters of body weight, height, age, and sex and evaluation variables of maximum oxygen uptake, basal metabolic rate, and body fat percentage, related to fitness training. By giving personal parameters, the simulation system could calculate adequate exercise levels. In the exercise control model, actual exercise intensity, ventilation in exercise, and venous multiplier in exercise are calculated. Here, the exercise is terminated if blood pH becomes 7 or less acidity, consciousness is lost, oxygen debt exceeds 10 l/min, or coronary ischemia happens.

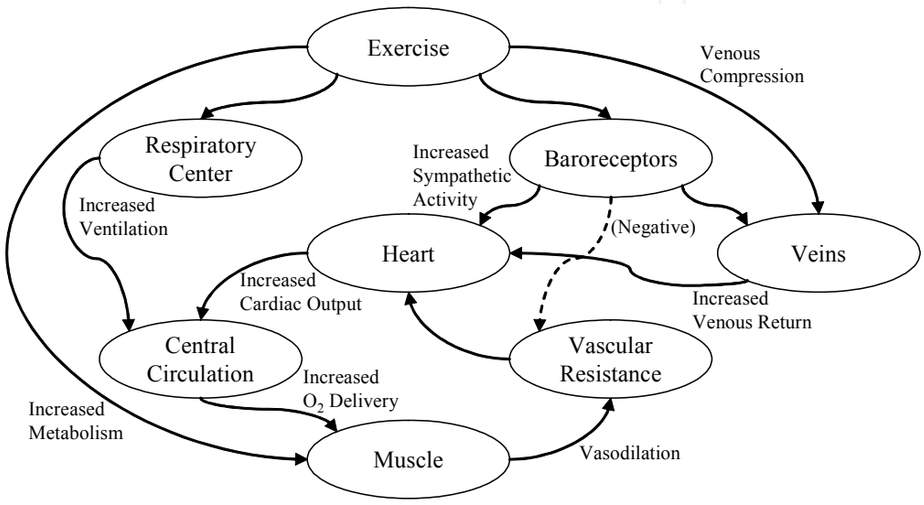


Fig. 8. The relationship among variables in exercise control model

VO_2max as exercise intensity promotes individual endurance and performance. Understanding personal VO_2max in ml/kg/min or aerobic power is the key for enhancing personal maximum uptake of oxygen, because it indicates the maximum amount of oxygen the person can take in and utilize. The exercise control model uses VO_2max for deciding when the fitness training should be terminated, although the amount of oxygen debt does not reach to 10,000 ml/min. VO_2max is described as the following equation by Wolthuis depending on the age, gender, and fitness habits, where the first coefficient is set to 50.6 for the active level, 45.8 for the moderate level and 43.2 for the sedentary level. For women, the value becomes 75% regardless of age. Thus the maximum oxygen uptake is determined by multiplying VO_2max by body weight.

$$VO_2max = 50.6 - 0.17 \times AGE \tag{15}$$

Basal metabolic rate (*BMR*) is an estimate of how many calories the body would burn if the person was to do nothing but rest for 24 hours. It represents the minimal amount of caloric requirement needed to sustain life including heart beating, lungs breathing, and body temperature normal in a resting individual. The purposes of the fitness training would be health and weight management in many cases. Therefore, *BMR* is an essential index in the exercise control model, and influences to calorie production presented to the user. *BMR* is

calculated by the Harris-Benedict equation from weight in kilograms, height in centimeters, and age in years, where the upper one is used for men and the lower for women.

$$\begin{cases} BMR = 66 + (13.75 \times WEIGHT) + (5.0 \times HEIGHT) - (6.76 \times AGE) \\ BMR = 655 + (9.56 \times WEIGHT) + (1.85 \times HEIGHT) - (4.68 \times AGE) \end{cases} \quad (16)$$

Body composition and health are affected by the amount of body fat because muscle tissue is more compact than fat. Measuring changes in body fat percentage, rather than just measuring changes in weight, can be very motivational for dieting. Body fat percentage is measured by several methods, such as bioelectrical impedance, skin fold measurement, hydrostatic weighing, and infrared interactance. In the exercise control model, body fat percentage as input influences to muscle mobilizing rate in the fitness training.

5. Simulation results

The macro and micro models of the circulatory system are combined through the common variables. It is important to synthesize the macro model with comprehensive parameters and the micro model with beat-by-beat hemodynamics for evaluating fitness support. The inputs from the macro model to the micro model are the vessel resistance, the heart rate, and the body weight. The outputs from the micro model are the blood pressure and the blood flow for the major vascular parts. By combining the macro and micro models, it becomes possible to simulate microscopics in hemodynamics that are affected by the parameters of the whole body. After a step (default 15 seconds) is performed in the macro model, the values of the vessel resistance in each subsystem are passed to the micro model. Then, the micro model runs for 15 seconds (with a default step of 0.01 second), and the 15-second average values of the blood flow in each component and of the aortic flow (Q_{ao}) and aortic pressure (P_{ao}) are passed to the macro model.

5.1 Simulation for body weight

Using the integrated macro and micro models, we confirmed whether a quantitatively adequate result could be obtained by the simulation when the body weight parameter was varied. Three values of the body weight parameter were input, namely, 50, 65, and 80 kg. Fig. 9 shows the simulation results of the aortic flow for various body weight parameters. The waveform is shown for 5 seconds after the steady state is reached. The micro mode required approximately 10 seconds until steady state for the blood flow was reached. The average aortic flow for a pulsation cycle is 4997 ml/min for a body weight of 50 kg, 6384 ml/min for 65 kg, and 7719 ml/min for 80 kg. We see that the aortic flow increases roughly in proportion to the body weight and that the average as a function of the body weight changes as approximately 100 ml/kg/min. The average aortic pressure is 99 mmHg for a body weight of 50 kg, 97 mmHg for 65 kg, and 96 mmHg for 80 kg. Thus, the aortic pressure is approximately 100 mmHg and remains almost constant independently of the body weight. The result for the blood flow is similar for vessels other than the aorta. Thus, the adequate pulsatile hemodynamics can be observed, which is impossible if only the macro model is used. The hemodynamic results obtained by the micro model are quantitatively reasonable as the body weight parameter is varied.

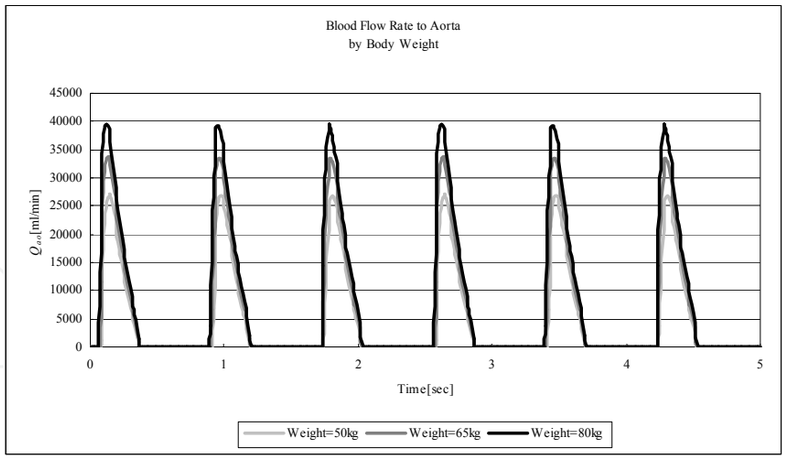


Fig. 9. Micro changes in aortic blood flow by body weight

5.2 Simulation for ambient temperature

We investigated whether a quantitatively adequate result could be obtained by the simulation when the ambient temperature parameter was varied. Because it is impossible to evaluate physical condition under considerable bad environment by subjects, the simulation system contributes to find the hemodynamic behavior for experimental approach in fitness support. The ambient temperature parameter (*TEMAB*) was raised by 10 °C and 20 °C from the initial value of 27 °C. In the macro model, the body temperature (*TEMP*) is described by an integral function of heat generation and loss. Heat generation depends on metabolism, exercise, and shivering. Heat loss depends on skin blood flow, perspiration, ambient temperature, and moisture. Fig. 10 shows the simulation result for microscopic changes of the skin blood flow for various ambient temperatures. The figure shows the time course of the change in the period from 5 seconds to 1 hour after the start of the simulation, when the skin blood flow reaches a steady state. The average skin blood flow for a pulsation is 377 ml/min for an ambient temperature of 27 °C, 640 ml/min for 37 °C, and 802 ml/min for 47 °C. The heart rate is 72 for an ambient temperature of 27 °C, 79 for 37 °C, and 83 for 47 °C.

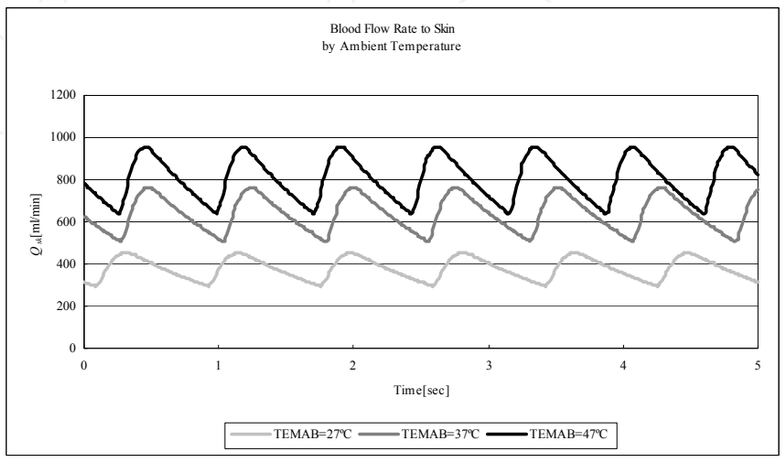


Fig. 10. Micro changes in skin blood flow by ambient temperature

Thus, the heart rate increases with the ambient temperature. By coupling the macro and micro models, it becomes possible to observe both the macro and micro aspects of changes. When the ambient temperature parameter is changed, the blood flow in the skin and in other vessels is obtained as a realistic value. Using this simulation system, the hemodynamics can be examined when the ambient temperature is raised to 47 °C, which is not easy to determine in real subjects.

5.3 Simulation for exercise load intensity

The parameter of gradual exercise load intensity of 100W, 200W, and 300W was introduced to the integrated circulatory system model. The parameter of exercise intensity was introduced to the macro model of the circulatory system, in which hemodynamic, respiratory, metabolismic, and sympathetic activities would increase. It was confirmed that evaluation of exercise for setting up an optimum load could be expressed by the model. Personal parameters with body weight of 60kg, height of 175cm, age of 40 years old, the male sex, body fat percentage of 20%, and fitness habit of the moderate level were set in this exercise evaluation. 2 hours of a continuous exercise and subsequent 1 hour of a steady state were given to the model.

Fig. 11 and 12 show the simulation results for physiological variables related to the exercise evaluation. Lactic acid is produced by anaerobic metabolism mainly from muscles, and it can be used as an index of the intensity of exercise training. Moreover, lactic acid production is proportional to oxygen debt. In Fig. 11, lactate mass rapidly went up to 250 mmol when the exercise intensity was set to 300W. Generally, produced lactic acid is used as energy to a certain amount of exercise intensity. In Fig. 12, Muscle O_2 use was almost proportional to the exercise intensity, where the marginal exercise intensity could be determined by being kept muscle O_2 use less than VO_2max.

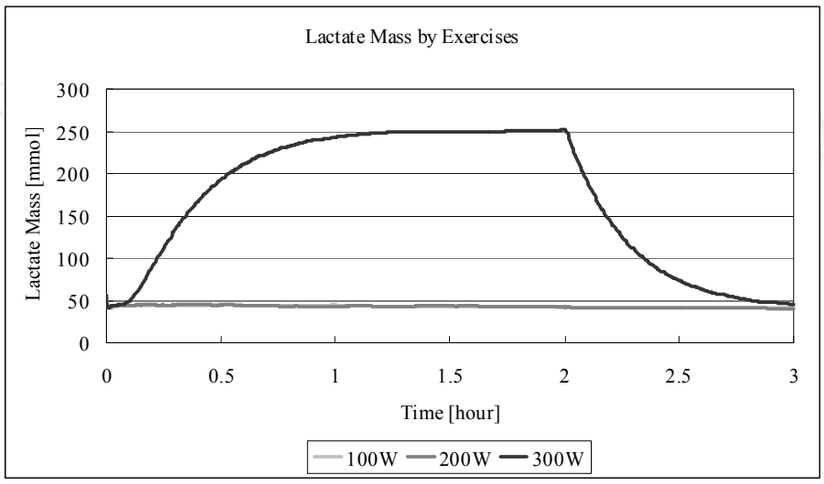


Fig. 11. Macro changes in lactate mass by exercise load intensity

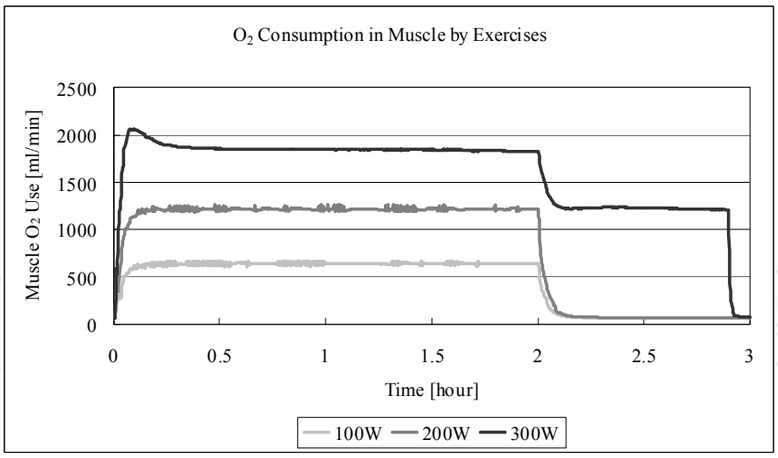


Fig. 12. Macro changes in O_2 consumption in muscle by exercise load intensity

Fig. 13 and 14 show the simulation results for blood flow to muscle and skin in an aerobic state of 5 seconds by the cardiovascular system model according to exercise intensities of 100W, 200W, and 300W. The muscle blood flow (Q_{mu}) was 5649 ml/min for 100W, 9648 ml/min for 200W, and 12520 ml/min for 300W. The skin blood flow (Q_{sk}) was 849 ml/min for 100W, 1063 ml/min for 200W, and 1509 ml/min for 300W. Moreover, the cardiac output (Q_{ao}) was 10435 ml/min for 100W, 14295 ml/min for 200W, and 17146 ml/min for 300W. The heart rate rose 87 for 100W, 102 for 200W, and 121 for 300W. In a resting condition, about 25% of cardiac output flows to muscle and skin. In an exercising condition, about 85% of cardiac output flows to muscle and skin. In Fig. 13 and 14, 62% of cardiac output for 100W, 74% of cardiac output for 200W, and 82% for cardiac output for 300W flowed to muscle and skin in the cardiovascular system model. By this exercise evaluation, the macro and micro behavior of blood flow control were adequate in the duration of 2 hours that the respective exercise load intensity was given and on the post exercise condition of 1 hour. Basically, the ratio of blood vessel resistances for muscle and skin decreased by the exercise control and the temperature regulation functions, and the heart rate increased by the sympathetic nerve activity and the cardiac output control functions. Consequently, the micro hemodynamics was quantitatively reasonable on the exercise conditions.

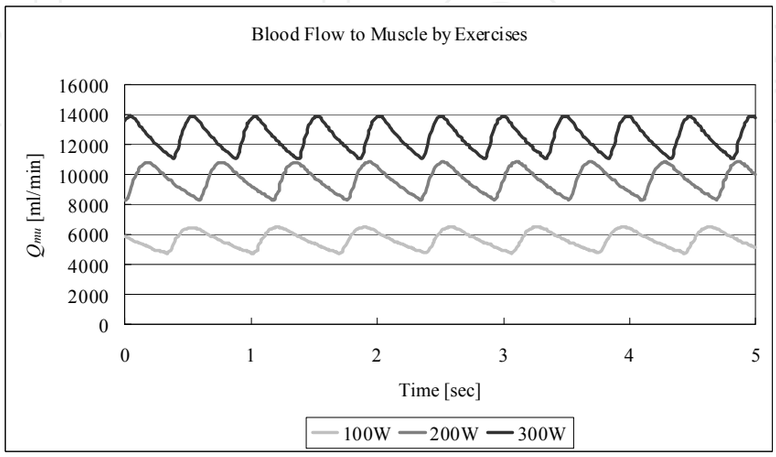


Fig. 13. Micro changes in muscle blood flow by exercise load intensity

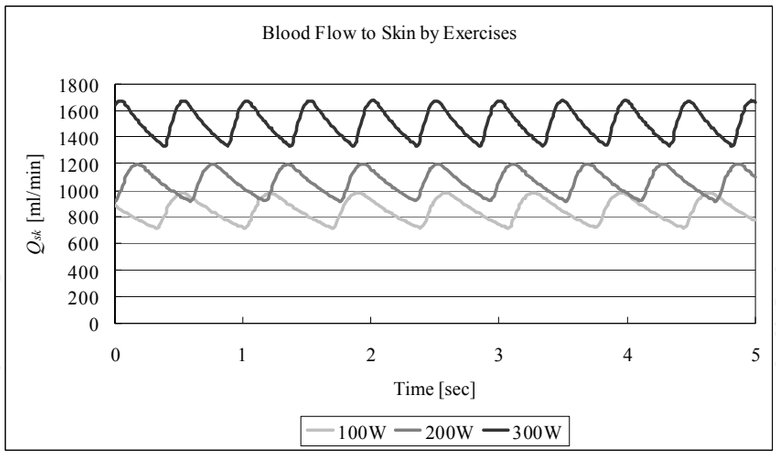


Fig. 14. Micro changes in skin blood flow by exercise load intensity

6. Conclusion

This chapter described a simulation system which combines macro and micro models of the circulatory system for exercise evaluation. In the simulation system, a macro model which includes multiple organs and functions and a micro model which describes a single physiological function are connected to provide the basic model. It is expected that the simulation system using integrated macro and micro models would be useful for comprehensive understanding of the physiological interactions for fitness support.

The proposed modeling support function can trace the sensitivities among the variables and parameters in the physiological modules. When part of a large-scale physiological model is modified, it may happen that the temporal behavior of the output variable changes greatly. In order to handle such situations, the user can examine the sensitivities of the output variables to each parameter, rather than performing many repeated simulations, and the adjustment of parameter values and the modification of the mathematical formulas can be systematically achieved.

Remaining problems include spatial refinement of the micro model in the cardiovascular system model. In the present micro model, only the blood flow branching into major vessels has been constructed. The compliance, which represents the elasticity of the vessels and the blood reservoir in the vessels, is taken into account at only four points. It is planned to refine the vessel system down to parts other than the capillaries by using anatomical data in order to allow simulations for the evaluation of detailed O_2 consumption in muscle. In order to apply the fitness support for practical use, the technological development to measure more precise physiological data would be need. Detailed dynamic data for O_2/CO_2 and lactic acid concentration in blood are essential to the extension of the exercise control model. The sensitivities and the hierarchized directed graph of the exercise control model need to be sophisticated so that the diagnosis and evaluation of aerobic hemodynamics could help efficiently fitness activity under various situations.

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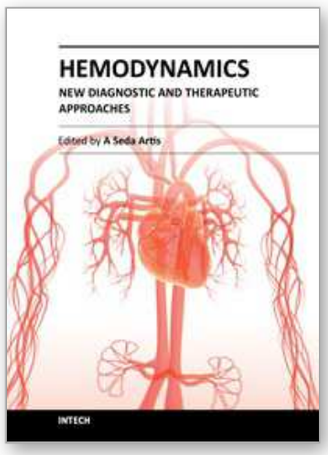

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Hemodynamics is study of the mechanical and physiologic properties controlling blood pressure and flow through the body. The factors influencing hemodynamics are complex and extensive. In addition to systemic hemodynamic alterations, microvascular alterations are frequently observed in critically ill patients. The book "Hemodynamics: New Diagnostic and Therapeuric Approaches" is formed to present the up-to-date research under the scope of hemodynamics by scientists from different backgrounds.

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