Integrated Physiological Interaction Simulation for a Large-scale Circulatory System with Beat-by-beat Model

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Abstract: This paper presents integrated physiological interaction simulation for a large-scale circulatory system which combines macro and micro models concerning with heart functions. The macro model is composed of physiological modules such as neural activity, hormonal adjustment, and body temperature control, and provides a mathematical representation of comprehensive knowledge of circulation physiology. The micro model, on the other hand, uses differential equations to describe hemodynamics with the heart as a pump, and calculates the heart pulsations in millisecond time steps. An electrical circuit model is constructed for the systemic and pulmonary circulatory systems, in which the time-varying elasticity of the ventricular muscle corresponds to a variable capacitor. By connecting the macro and micro models through common variables, a simulation which combines macroscopic and microscopic hemodynamics is produced. Namely the investigation of the response of the pulsatile blood flow under various parameter conditions in the human body becomes possible.

Keywords Circulatory System, Beat-by-beat Model, Integrated Model, Physiological Interaction, Sensitivity Analysis

1. Introduction

This paper describes a simulation system for the efficient editing, sharing, and testing of 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 [1], [4]. 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 [7]. 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.

In this study, the development of a simulation tool that uses a basic model of circulatory system enables to facilitate model testing, formulation, and refinement for solving the above problems. Another purpose of this study is to provide a basic model that combines macro and micro models for the blood circulation with the heart function. The macro model includes the comprehensive physiological functions, and the micro model analyzes the pulsatile behavior of the hemodynamics. 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, neural activity, and hormonal adjustment, 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 observation 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.

This paper discusses the integrated physiological simulation, where a basic model that combines the macro and micro models of the biological 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 when the parameters representing the body weight and the ambient temperature were varied.

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2. Macro Model of Circulatory System

The macro model of the circulatory system comprehensively describes multiple organs and physiological functions. The Human model [1] was constructed in the 1980s by Coleman in order to support physiology education. It is an early effort, intended to identify useful approaches to quantitative calculation in a circulatory system model. In this study, the source code of the BASIC version by Randall [2] for Coleman's Human model was rewritten in the platform-independent expressions. The arithmetic parser in the simulation system is able to execute and edit the computation formulas for the macro model.

The Human model includes 25 physiological function modules, including 321 variables and 70 parameters. The program consists of 707 lines of mathematical expressions. The model as a whole consists of a system of differential equations, for which solutions can be derived numerically by Euler's method with 38 variables. Thus, The Human model is a large-scale model of the circulatory system. The typical functions in this model are as follows:

(1) Prescription: Nine different prescriptions can be provided according to the situation, namely, digitalis (cardiotonic), furosemide (diuretic), chlorothiazide (diuretic), hydralazine (hypotensive), phenoxymethylamine (vasodilator), norepinephrine (hypertensive), nitroglycerin (coronary dilator), atropine (antispasmin), and transfusion antagonists (angiotensin transferase antagonist).

(2) Exercise: The intensity of exercise is specified by 10 steps. For each one-step increase, the blood oxygen is increased by 1 liter/min, which increases gas exchange, produces venous contraction, and activates the sympathetic nerve. Consequently, the venous return, the cardiac output, and metabolism are increased. When muscle oxygen demand exceeds 10 liters or the blood becomes acid with a pH below 7, the exercise is automatically terminated.

(3) Artificial heart: It is possible to switch the circulation from the natural heart to an artificial heart. The artificial heart is a servo-controlled blood pump in which the right-heart output is kept constant. The operation of the artificial heart is limited so that the right-heart output does not exceed the maximum venous return. The left-heart output is controlled in the same way. The heart rate is fixed at all times.

(4) Hemodialysis: Wastes and toxins are filtered from the body by a dialyzer. Water, sodium, urine, bicarbonate, and potassium are deleted in order to maintain a constant concentration in the blood.

(5) Transfusion and instillation: The levels of water, protein, sodium, bicarbonates, and potassium in the plasma, and the hematocrit, are kept constant by transfusion. Red blood cells are not supplemented by instillation.

The 25 modules in the Human model 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), O2 (oxygen balance), CO2 (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).

The above 25 modules are connected by means of input and output variables. The AP variable (arterial pressure), for example, is calculated in the HEART module as its output variable. The CARDFUNC, CIRC, REFLEX-1, and REFLEX-2 modules, on the other hand, refer to the value of the variable AP as an input variable. The values of the variables change with the time-passing in the system simulation.

Some modules include parameters, and the user can set the values. The NITRO parameter (dose of nitroglycerin), for example, is contained in the DRUGS module, and the TEMAB parameter (ambient temperature) is contained in the TEMP module. The parameters have the time-independent values in the system.

2.1 Sensitivity Analysis

The proposed simulation system provides the user with the ability to modify the basic macro model. The user may 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 to choose 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 [5]. 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. 1 outlines the sensitivity analysis of a simple module. This module is composed of four computation formulas and includes six input/output variables and two parameters. I denotes an input variable, O an out-
put variable, \( M \) an intermediate variable used for convenience in computation, and \( P \) a parameter.

\[
\begin{align*}
I_1 &\rightarrow O_1 - I_1 + P_1 \\
I_2 &\rightarrow O_2 - I_2 + P_2 \\
I_3 &\rightarrow O_3 - I_3 + P_3 \\
I_4 &\rightarrow O_4 - I_4 + P_4
\end{align*}
\]

A simple module

\[
\begin{align*}
A &\rightarrow B + 2C \\
B &\rightarrow A \\
C &\rightarrow A
\end{align*}
\]

A directed graph

\[
\text{Definition:} \\
\text{Sensitivity} = \frac{\Delta \text{Rate of Output}}{\Delta \text{Rate of Input}}
\]

\[
\text{Calculation:} \\
\text{Sensitivity} = \frac{O^2 - O}{O} / \frac{I^2 - I}{I}
\]

Fig. 1 Outline of sensitivity analysis.

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 \( A = B + 2C \).

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 behavior of the module and is not eliminated, since it must be referred to by other modules.

In the directed graph shown in Fig. 1, there are seven causal relations \( I_1 \rightarrow O_1, P_1 \rightarrow O_1, I_2 \rightarrow O_2, O_1 \rightarrow O_2, I_3 \rightarrow O_3, O_2 \rightarrow O_3, P_3 \rightarrow O_3 \) among the variables. In this case, the sensitivity is calculated by setting the initial values of all the input variables and all the 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 \( O_2 \). 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 \( O_2 \). The user can then correct the behavior of the output variable by adjusting the parameter value.

3. Micro Model of Circulatory System

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 [3]. 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.

3.1 Beat-by-beat Model

In the micro model of the circulatory system, the elastics of the left and right ventricles correspond to variable capacitors. The blood flow is represented by the 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. 2 shows the electrical circuit model of the systemic circulation. The aortic flow output from the left ventricle (\( Q_{oa} \)) branches into the brain vessel blood flow (\( Q_{ob} \)), the coronary vessel blood flow (\( Q_{oc} \)), the renal vessel blood flow (\( Q_{os} \)), the skin vessel blood flow (\( Q_{os} \)), the muscle vessel blood flow (\( Q_{om} \)), the bronchial vessel flow (\( Q_{ob} \)), and the other vessel blood flow (\( Q_{oa} \)). On their return, the blood flows are combined in the vena cava and the right atrium to form the right ventricular blood flow (\( Q_{oa} \)). 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 \( C_{rv} \).

Three differential equations are derived from 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 \( V_{lm} \), the aortic pressure \( P_{am} \), and the right atrium pressure \( P_{rm} \), are described by the differential equations:

\[
\begin{align*}
\frac{dV_{lm}}{dt} &= Q_{oa} - Q_{oc} \\
\frac{dP_{am}}{dt} &= \frac{Q_{oa} - Q_{os} - Q_{co} - Q_{os} - Q_{oa} + Q_{oc} - Q_{oa}}{C_{sa}} \\
\frac{dP_{rm}}{dt} &= \frac{Q_{oa} + Q_{oa} + Q_{oa} + Q_{oa} + Q_{oa} - Q_{oa}}{C_{rv}}
\end{align*}
\]
the change in the blood pressure and the vessel resistance. For example, the blood flow in the brain vessel is calculated as follows:

$$Q_{br} = \frac{P_{a0} - P_{br}}{R_{br}}$$  \hspace{1cm} (7)$$

Fig. 3 shows the electrical circuit model of the pulmonary circulation. The pulmonary circulation is closed in series to the systemic circulation system at points A and B. The pulmonary arterial flow ($Q_{pa}$) output from the right ventricle flows in the pulmonary vessel ($Q_{pv}$) 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:

$$\frac{dV_{rv}}{dt} = Q_{pv} - Q_{pv}$$  \hspace{1cm} (8)$$

$$\frac{dP_{pa}}{dt} = \frac{Q_{pv} - Q_{pa}}{C_{pa}}$$  \hspace{1cm} (9)$$

$$\frac{dP_{la}}{dt} = \frac{Q_{pv} + Q_{pv} - Q_{la}}{C_{pv}}$$  \hspace{1cm} (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:

$$P_{rv} = E_{rv} \times (V_{rv} - V_{rv0})$$  \hspace{1cm} (11)$$

The blood flow into the right ventricle ($Q_{rv}$) and the blood flow from the right ventricle ($Q_{rv}$) 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:

$$Q_{rv} = \begin{cases} \frac{P_{rv} - P_{rv}}{R_{rv}} & \text{if } P_{rv} > P_{rv} \\ 0 & \text{if } P_{rv} \leq P_{rv} \end{cases}$$  \hspace{1cm} (12)$$

$$Q_{rv} = \begin{cases} \frac{P_{rv} - P_{rv}}{R_{rv}} & \text{if } P_{rv} > P_{rv} \\ 0 & \text{if } P_{rv} \leq P_{rv} \end{cases}$$  \hspace{1cm} (13)$$

The blood flow to each vessel in the systemic circulation system can be similarly determined from...
Numerical analysis using the Runge-Kutta-Gill method 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. Simulation Results

The macro and micro models of the circulatory system are combined through the common variables. 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. 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 vessel pressure 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.

4.1 Result for Body Weight Parameter

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. 4 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.

4.2 Result for Ambient Temperature Parameter

Using the macro and micro models, we investigated whether a quantitatively adequate result could be obtained by the simulation when the ambient temperature parameter was varied. 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. 5 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 pulse is $377 \text{ ml/min}$ for an ambient temperature of 27 °C, $640 \text{ ml/min}$ for 37 °C, and $802 \text{ ml/min}$ for 47 °C. The heart rate is 72 for an ambient temperature of 27 °C, 79 for 37 °C, and 83 for 47 °C. 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.

![Fig. 4 Micro changes in aortic blood flow by body weight.](image1)

![Fig. 5 Micro changes in skin blood flow by ambient temperature.](image2)
5. Conclusions

This paper has described a simulation system which combines macro and micro models of the circulatory system. In the simulating system, a macro model which contains multiple organs and functions with a long time scale, and a micro model which describes a single physiological function with a minute time scale, are connected to provide the basic model. It is expected that the simulating system using integrated macro and micro models will be useful for comprehensive understanding of the physiological interactions into the human body.

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 and the addition of a disease diagnosis 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 [8], [9] in order to allow simulations for the diagnosis of arteriosclerosis from the resistance and compliance of each vessel.

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References


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