

Project Title:**Multi-scale Modeling of Hemodynamics and Bio-thermodynamic in Human Circulatory System****Name:** Xiancheng Zhang, Shigeho Noda, Ryutaro Himeno, Hao Liu**Laboratory at RIKEN:****Computational Engineering Applications Unit Advanced Center for Computing and Communication**

1. Background and purpose of the project
The cardiovascular system (CVS) plays a crucial role in human thermoregulation; heat stress may result in significant cardiovascular adjustments that are necessary to maintain adequate cardiac output and skin blood flow for the heated body [1]. When heating skin temperature rises from 36.5°C up to 40.9°C over a period of 40-53 minutes, it will lead to a 122% increase in cardiac output primarily caused by the increased heart rate, and a 52% decrease in total peripheral resistance [2]. The convective heat transfer via the circulatory system is the most important heat exchange pathway inside the body [3], which is normally responsible for transferring 50-80% heat flow within the human body by blood circulation [4]. Cardiovascular diseases have been a leading cause of death globally. In the studies of 1995 Chicago heat wave [5] and 2003 European heat wave [6], the heat-related morbidity and mortality for people with cardiovascular diseases were reported to increase remarkably. Because of the ethics and legality, experimental investigations on the thermal tolerance of vulnerable population are prohibited or limited to mild heat stress or low-risk patients with cardiovascular diseases. The magnitude of the impact of cardiovascular disease on thermal tolerance is hence usually underestimated [7]. Mathematical modeling of human thermal responses to varying environmental conditions has been widely used in medicine, textile industries and building design because of its advantages in saving time and expense compared with experiments. A large number of mathematical models of human thermoregulation have been developed, from relative simple two-node thermal model to more complex multi-compartment models [8-12]. Very few models, however, have considered the actual human cardiovascular system, not to mention the detailed description of the cardiopulmonary circulation. Therefore, it is highly desirable to develop a mathematical model of human thermoregulation, which is capable to predict human thermal responses under varying environmental conditions, and to assess the effects of various degrees of cardiovascular diseases on thermal tolerance. In this study we aim at developing a dynamic thermoregulation model based on Gagge's two-node thermal model [9] to predict human thermal responses to varying heat stresses.

To predict cardiovascular functions associated with the human thermoregulation, a closed-loop, multi-compartment, lumped-parameter model of the human CVS involving systemic circulation and cardiopulmonary circulation is developed and incorporated into the thermoregulation model based on our previous studies [13, 14]. Furthermore the two key parameters of the CVS during thermoregulation, namely, the heart rate and the vasomotion, are taken into account in the present model. Validation of the CVS and thermoregulation models is extensively discussed and established through a comparison with reliable experimental data. We first give a detailed description of the thermoregulation model and the cardiovascular model. We then give an extended analysis and discussion on the human thermal responses with a combination of various factors involving aging, obesity, and cardiovascular diseases.

2. Method

The Gagge's two-node thermal model is modified to predict human thermal responses during varying environmental conditions (Figure 1a). For simplification, the human body is represented as a cylinder consisting of two layers of core and skin. The skin is the most important heat-exchange organ of the human body, interfacing and exchanging heat with external environment via conduction, convection, evaporation and radiation. Sweating, shivering and cardiovascular adjustments are the primary thermoregulatory control mechanisms that maintain human body internal temperature within a normal physiological range, which may be evaluated with a parameter of the temperature error signal between the instantaneous temperature and the reference temperature.

A closed-loop, multi-compartment, lumped-parameter mathematical model of the entire CVS is developed and incorporated into the thermoregulation model to simulate the blood circulation and to quantitatively evaluate the cardiovascular responses to varying environmental conditions. This cardiovascular model as illustrated in Figure 1b consists of the models for the systemic circulation and the cardiopulmonary circulation.

The energy balance equations for core and skin nodes can then be expressed as:

$$C_{cr} \cdot \frac{dT_{cr}}{dt} = M - W - Q_{res} - Q_{cr_sk} - h_{art} \cdot A_{art} \cdot (T_{cr} - T_{art}) - h_{ve} \cdot A_{ve} \cdot (T_{cr} - T_{ve}) + \dot{m}_{cr} \cdot c_{bl} \cdot (T_{art} - T_{cr}) - \dot{m}_{sk} \cdot c_{bl} \cdot (T_{cr} - T_{sk}) \quad (1)$$

$$C_{sk} \cdot \frac{dT_{sk}}{dt} = Q_{cr_sk} + \dot{m}_{sk} \cdot c_{bl} \cdot (T_{cr} - T_{sk}) - Q_c - Q_r - Q_e \quad (2)$$

where term C_{cr}/C_{sk} denotes the thermal capacitance of core/skin (J K⁻¹), T_{cr}/T_{sk} the temperature of core/skin (°C), t time (s), M the actual metabolic rate (W), W the external work done by body (W), Q_{res} the respiratory heat loss (W), Q_{cr_sk} the heat exchange between core and skin via conduction (W), h_{art}/h_{ve} the convection heat transfer coefficient of artery/vein (W m⁻² K⁻¹), A_{art}/A_{ve} the surface area of artery/vein (m²), T_{art}/T_{ve} the blood temperature in artery/vein (°C), c_{bl} the specific heat of blood (J kg⁻¹ K⁻¹), \dot{m}_{cr} the total blood perfusion rate of core (kg s⁻¹), \dot{m}_{sk} the skin blood perfusion rate (kg s⁻¹), Q_c the convective heat exchange between skin and environment (W), Q_r the radiative heat exchange between skin and environment (W), and Q_e the evaporative heat loss from skin (W). Note that the \dot{m} -related terms used in energy balance equations denote the flow rate through the corresponding compartment multiplied by the density of blood, which is updated based on the cardiovascular model at each time-step.

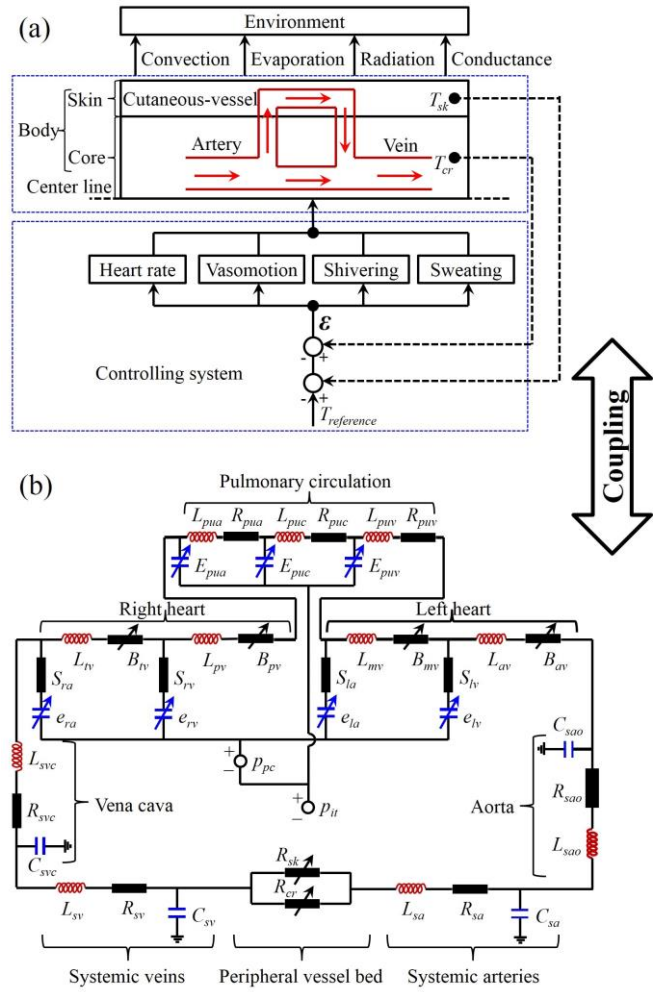


Figure 1. Schematic representations of (a) the integrated bioheat transfer model and its interaction with external environment and (b) multi-compartment lumped-parameter model of the entire cardiovascular system.

The energy balance equations of the thermal model was then solved by using a fully explicit first-order, Euler-Forward integration scheme [12], while the governing equations of the lumped-parameter cardiovascular model was solved with a fourth-order Runge-Kutta method as in our previous studies [13-14]. The time-step used in all simulations was set to be 0.0001s, which was verified to be capable to obtain sufficiently accurate results.

3. Result

The thermoregulation model was then validated through a comparison of the core and skin temperatures between simulation and experimental results [15] as shown in Figure 2, where the model parameters and boundary conditions utilized in the simulations were modified to be identical to those in the experiments. An excellent agreement is observed in both the mean core temperatures and the skin temperatures.

To further investigate the integrated effects of multi-factors on increasing the risk of heat-related morbidity and mortality, we carried out an extensive study on evaluating the impacts of combining factors including the obesity, the aging and the

cardiovascular diseases on human temperature regulation during exposure to passive heat stress. The obese effect was modeled by increasing the thickness of fat from 15.72 to 50 mm. The age-related changes in thermoregulatory ability were assumed to be a 40% reduction in sweating gland output and vasodilation response. The cardiovascular disease was assumed to be the moderate LHF. As shown in Figure 3, the obese adult has a higher core temperature during heat exposure. The mechanism underlying the elevation in core temperature is that the increased thickness of fat causes an increase in thermal resistance between core and skin, and hence a reduction of heat dissipation from core to skin. The aging effects on peripheral vascular resistance are driven by the attenuated vasodilation, which reduces skin blood flow and hence the heat liberated from skin as well. This can result in increasing the core temperature. In addition, the age-related attenuation in sweating can also lead to increasing the core temperature. Obviously our results show a pronounced increase in the body core temperature with the combination of the obesity, the aging, and the cardiovascular diseases.

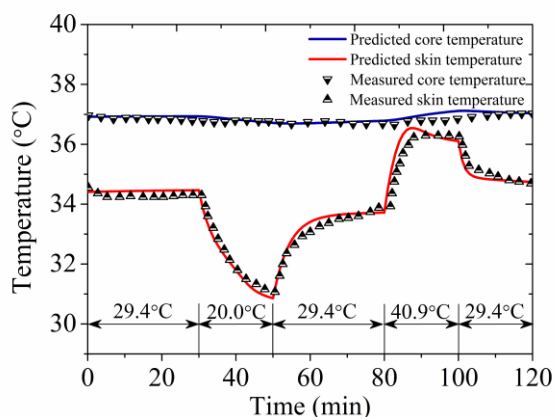


Figure 2. Predicted and measured human transient thermal responses under varying environmental temperatures (mean core and skin temperatures).

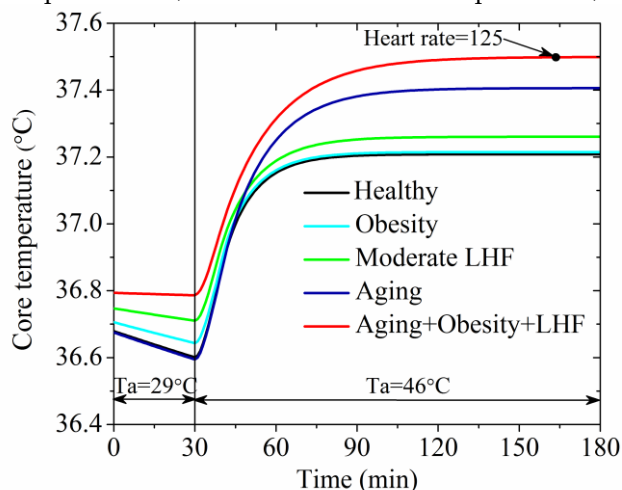


Figure 3. Effects of different factors (aging, obesity, heart diseases) on core temperature and the effects

of combined multi-factors.

3. Conclusion

To the best of our knowledge this study for the first time presents an integrated bioheat transfer model to predict thermal responses of patients with cardiovascular diseases by coupling a two-node thermoregulation model with a closed-loop, multi-compartment, lumped-parameter cardiovascular model. The model is of great potential to predict human thermal responses during varying environmental conditions as well as to quantitatively evaluate the impacts of different types of cardiovascular diseases and effects of obesity and aging on human body core temperature. With this model two hypotheses have been confirmed: 1) the attenuated thermoregulation ability caused by cardiovascular disease can be attributed to the decreased cardiac output and skin blood flow; 2) a combination of obesity, aging and cardiovascular diseases can compound the risk of heat-related morbidity and mortality.

4. Schedule and prospect for the future

Due to the shortage of experimental data, the thermoregulatory control of the resistance, R_{sk} is derived from published skin blood flow models. A more accurate temperature-related resistance model for skin blood flow is urgently in need, which should be derived based on in vivo measurements. Furthermore, because the single compartment human thermal model is adopted to predict human thermal responses, the effects of heat stress-induced redistribution of blood volume, the reduction of cerebral perfusion, the variations in baroreflex control of the CVS on thermoregulation, are not taken into consideration in the present model. In this model, the heart response to heat stress is mainly driven by heart rate. The heat stress-induced increase in cardiac contractility, which is used to maintain stroke volume despite large reductions in ventricular filling pressures, need to be considered in the future study. To model the CVS more accurately, we have recently developed a novel multi-scale model for the closed-loop CVS based on our previous model [13, 14]. This model consists of the one-dimensional representation of large systemic arteries (55 vessels) and veins (72 vessels), and the zero dimensional lumped-parameter representations of cardiopulmonary circulation and peripheral vascular bed. A multi-compartment thermoregulation model by coupling such 0D-1D multi-scale CVS model is now under development, which as an ultimate goal we aim to be able to evaluate human thermal responses for patients undergoing extreme hypothermia surgery.

4. References

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Note: Because I am a new user of the supercomputer, I primarily learnt how to use the supercomputer in the past year of 2015, therefore there are no publications via the supercomputer. But I will use the supercomputer to run my code and present publication of my research in the next year.