### Developing Biomedical Simulations for Next-generation Healthcare

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Supercomputers today are applied in ways that go beyond academic research and into diverse fields such as manufacturing and climate/meteorological predictions. Meanwhile, the use of information and communications technology (ICT) in medicine goes only as far as the latest medical equipment such as medical imaging diagnostic systems, or administrative support such as electronic medical record systems. Supercomputers, computer simulation in particular, have developed few practical applications in medical and surgical therapy and healthcare. We believe there is great potential for using computer simulations in this domain, and therefore we are pursuing research and development of several biomedical simulation systems. In this paper, we describe one of our projects, a biomedical simulation system using the heart simulator which has been under development since 2007 in joint collaboration with Specially Appointed Profs. Toshiaki Hisada and Seiryo Sugiura from the Graduate School of the University of Tokyo and their research team. We present an overview of the heart simulator, followed by descriptions of pre-processing and visualization in simulation with accounts of a case of application. Finally, we conclude with issues and future developments in order to realize practical application.

### 1. Introduction

Supercomputers have made rapid progress in recent years. The performance capacity has improved by 1000 fold over the last 11 years. This is a result of many computer manufacturers throughout the world, Fujitsu being one, pursuing developments in the fiercely competitive market. This advance is also backed by fast-growing demand for high-speed computers with increased capacity. Supercomputers are mainly deployed for computer simulations, thereby enabling virtual computational experiments to make predictions about problems that cannot be conducted in principle or that experiments would require too much time and cost to be conducted otherwise. Thus, they are often deployed in astronomical studies such as investigations into the births of stars and in predictions of the state of global warming in 100 years' time, as well as for meteorological forecasting and other uses. Similarly, they are increasingly employed in manufacturing. In the automobile industry, for example, computer simulation is used in collision analyses for improving safety design,

and aerodynamic analysis for enhancing fuel efficiency.

Meanwhile, information and communications technology (ICT) is applied in medicine, significantly improving the handling of healthcare information through medical support applications such as an electronic medical record system. ICT-enhanced medical equipment and techniques, such as a medical imaging diagnostic system and catheter-based surgical procedures, are more widely used in clinical practices today. Further contributions to medical progress are anticipated by leveraging supercomputers if biomedical simulation can make it possible to predict treatment outcomes. In reality, such a simulation system is rarely used, and instead, most hospitals rely on procedural guidelines and physicians' knowledge and experience. We have been pursuing research and development with a conviction that the biomedical simulation assisted by a supercomputer will make a significant contribution to the development of clinical medicine.

This paper describes a biomedical simulation system, one of our projects that using "the development of

a heart simulator." This is a joint research project with Specially Appointed Profs. Toshiaki Hisada and Seiryo Sugiura from the Graduate School of the University of Tokyo and their research team, and it commenced in 2007.

### 2. Heart simulation

The heart movement in brief is as follows: The sinoatrial node (pacemaker cells), located in the right atrium of the heart, generates regular electrical impulses that determine the sinus rhythm. The impulses are propagated to the rest of the heart via the electrical conduction system in the ventricle. Upon receiving an electrical stimulation, the cardiac muscle cells increase the calcium ion  $(Ca^{2+})$  concentration, causing a structural change in contractile proteins. As a result, the excited muscle fibers generate power to cause the muscle contraction. Conversely, when the impulse passes at the end of the stimulation, the muscles relax. By repeating this cycle of contraction and relaxation, all the cardiac muscle cells coordinate the heart's pumping action. Thus, the heart is an extremely complex organ whose macroscopic movement as a whole relies on microscopic phenomena of a biochemical, electrical and mechanical nature that occur in the cardiac muscle cells (Figure 1).

### 2.1 Development of the heart simulator

Reproducing the heart's pulsation and resulting blood flow in a computer simulation requires mathematical models that express a wide range of physical phenomena as described above. For the heart simulator that is to be jointly developed with the Graduate School of the University of Tokyo, we have created a mathematical model to reconstruct these phenomena with physiological validity, using clinical data to verify it. The model is capable of coupling and solving equations based on the finite element method (FEM).<sup>1)</sup> This mathematical model used in the heart simulator is described in the following.

In the domain of the electrical phenomena, the bidomain equation is used for computing the electric potential distribution inside/outside of the cardiac muscle cells, and the thorax area.<sup>2)</sup> The bidomain equation has an embedded electrophysiological model,<sup>3)</sup> with descriptions of the ion channels, exchange mechanism, and pumping mechanism on cardiac muscle cells, and the Ca<sup>2+</sup> pumping motion of the sarcoplasmic reticulum within the cells. Finding solutions to these equations makes it possible to analyze the behaviors of various ion currents that pass through the cardiac muscles. Furthermore, Ca<sup>2+</sup> concentrations in various parts of the cardiac muscles can be obtained, and these then serve as the input values for the excitation-contraction



Figure 1 Cardiovascular system from the perspectives of multi-scale and multi-physics problems.

coupling (ECC) model in the mechanical analysis, as we will describe below. For the macro-mechanical domain, the Navier-Stokes equation is used for the blood, while the cardiac muscles are provided with a motion equation based on the constitutive law with non-linear material properties. In the analysis, these are coupled together using the Arbitrary Lagrangian and Eulerian (ALE) Method, an interface-tracking method that takes into account the stress equilibrium, and geometric matching conditions on the respective boundary planes. For the coupled analysis of the heart valves, in particular, the interface-capturing method was developed by applying the Lagrange multiplier, in order to counter the disappearance of finite elements due to a major deformation or collision.

The heart simulator is also able to run a micromacro correlation simulation between the motion of contractile proteins and general contraction power. Actin and myosin, the contraction coupling proteins inside the cardiac muscle cells, are expressed for structural changes in a state transition model, in a three-state and six-state format respectively, and computed using the Monte Carlo method for each motion to generate sliding motions of two different filaments. The transition mode has been embedded with a transition rate that is determined by a combination of the conditions in the surroundings and the elasticity of the cardiac muscles, thus making it possible to reproduce congruity as well as unique relationships between Ca<sup>2+</sup> concentrations and contraction power in a natural fashion. In addition, a motion equation is formulated to match the mechanical work of filaments' sliding

motion with that of finite element continuum in the cardiac muscle cells through the coupling computation, thereby facilitating a stable, energy-coordinated analysis.

A precise and comprehensive simulation of a human heart by means of a multi-scale simulation model such as this would need to solve equations with degrees of freedom at a 100 million level. To conduct such a simulation, it is essential to have a supercomputer. In addition to the above-stated development of the mathematical model, we are pursuing research and development on ways to achieve stable and efficient solutions using supercomputers.<sup>4</sup>

## 2.2 Development of pre-processing technology

For the heart simulation, mesh-based models are generated for the heart and thorax. These are digital representations of shapes and internal structures of the organ, described with tetrahedrons and hexahedrons as elements, a method used in the FEM. For the purpose of providing treatment procedures individually tailored to patients, these mesh models are generated from the three-dimensional image data obtained via computed tomography (CT) and/or magnetic resonance imaging (MRI) (**Figure 2**). There are two issues to be addressed in the process of generating the mesh models:

1) Construction of the heart profile

Medical imageries such as CT and MRI tend to be affected by noise and distortion due to uneven distributions of contrast agents, which are ingested to enhance the visibility of vascular territories, as well



Figure 2 Input data for the heart simulator.

as by surrounding organs and the heart's pulsation. These make it difficult to accurately extract the shape of the heart. Therefore, it is sometimes necessary to consult physicians and speculate the form, particularly for lesions, using their anatomical knowledge and diagnostic data. Thus, we need to develop a technology that makes it easier to construct a flexible profile in collaboration with physicians.

2) Reconfiguration of mesh models

In order to execute simulations, each mesh element is assigned with component part data such as "atrium," "ventricle" or "great vessel." The meshes are developed by component units while keeping contact information between adjacent parts intact. However, it is difficult to generate meshes for parts with multiple areas conjoined, like mitral annulus (a ring that is attached to the mitral valve in the heart), without undermining the quality. In many cases, the profile and contact information are adjusted through the development process. Because the quality of meshes affects the simulation results, all corrections are manually executed. A problem to solve is find a way to minimize the number of meshes that require post-adjustments.

As explained above, generating a mesh-based model from a patient's medical images and diagnostic data involves tremendous work. We therefore are aiming to develop technology to establish an efficient input data generation flow.

### 2.3 Development of visualization system

The heart simulation generates a multitude of data relevant to the heart's mechanical and electrochemical phenomena. We are developing a system that allows users (physicians) to visualize such data, and then easily select and display the information they need.

CT, MRI and ultrasonography (US) are often used in diagnoses at hospitals to monitor the cardiac muscle movements and blood circulation velocity. However, these methods do not allow for a quantitative observation of the internal structure of heart to be made. The heart simulator is equipped with functionality to generate quantitative data, such as cardiac muscular force generated for pulsation and its load, as well as the blood flow inside the cardiac muscles.

The visualization system that we have developed utilizes computer graphics to depict the values of these

data three-dimensionally. The volume of data processed for one palpitation cycle is several gigabytes. The data are distributed to several servers with the graphics processing units (GPU) for fast processing (in several seconds) to generate motion images. The simulation, when completed, will display the results immediately for the physicians to view.

This fast processing enables them to make a detailed observation of the heart's conditions, with features such as a cross-section view and graph generation of physical quantities. For example, quantitative values regarding the force and load of cardiac muscles in pulsation, and blood flow within the muscles, are subject to position and time variations. The system can extract these pieces of data and generate graphs instantly, which proves useful for quantitative diagnostics. Figure 3 depicts the visualization results. The system is also equipped with the same feature that measures the thickness of the cardiac muscles over time using ultrasonography. The guantified data obtained from the system and ultrasonography, make quantitative comparison between them possible. Therefore, the system is employed in evaluating the heart simulator's validity.

Regarding the display unit, the system is compatible not only with ordinary display devices, but also with tablet and 3D displays, which are useful in patient consultations and procedure conferences.

This visualization system was installed at the University of Tokyo Hospital in 2012, as a pilot case through the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST) of the Cabinet Office of the Japanese Government. The system has been well received by physicians, for advancing clinical research. Technological development is being continued in order to enhance the system's functionalities with the aim of fulfilling the needs of clinicians.

### 3. Applicability of heart simulation

The heart simulation technology can be leveraged in determining treatment procedures in clinical contexts, as well as in the development of medical equipment.

# 3.1 Optimization of CRT-D electrode positioning<sup>5)</sup>

Malfunctions of the electrical conduction system,



Figure 3 Example of post-visualization.

myocardial infarction and other conditions may disturb the propagation of excitation signals and cause a discrepancy in the excitation-contraction cycles between the two ventricles of the heart. For example, if the septum of the left ventricle contracts first, followed by a contraction of its free wall with a delay, then the heart cannot produce sufficient circulation pressure into the aorta. Patients suffering from such a condition may be treated with a special implantable device, with three electrodes placed in coronary veins of the right atrium and ventricles, and the left ventricle, respectively, to synchronize the pulsation pacing. This therapy is called cardiac resynchronization therapy (CRT), and the pacemaker is called a CRT-D. The therapy has been known to improve the patient survival rate and quality of life (QOL) significantly, but it is also the case that this invasive and very expensive treatment is ineffective in about 30% of the patients treated.

In view of this fact, we are developing a method to predict the CRT-D effect and optimal electrode positions with the heart simulation based on the medical images of a patient's heart and thorax, electrocardiogram, sonogram and information on the infarct lesion. The device's parameter is adjusted before implantation, so that the virtual heart's pulsation pattern (thick line) is assimilated to the patient's actual heartbeat (narrow line) shown in the electrocardiogram data [**Figure 4 (a)**]. It has been confirmed that, after this procedure, the electrocardiogram of the virtual heart with the electrode positions input (thick line), yields a wave pattern very close to that of the patient after the CRT-D implantation (narrow line) [**Figure 4 (b)**]. This suggests the great potential of a pre/post-operative pulsation simulation through the reconstruction of electrical phenomena in the patients' hearts using the virtual heart. In the clinical context, the heart simulation before a CRT-D implantation procedure will make it possible to predict the effect of the operation.

As of November 2014, clinical research had been conducted on 18 patients with approval from the committee on research ethics of the University of Tokyo School of Medicine.

### 3.2 Application to planning of treatment for hereditary cardiac disorders

Surgical operations on patients with hereditary cardiac disorders can be difficult, for the profile of their hearts may be very different from ordinary hearts. Therefore, there are high expectations for a technology that makes it possible to predict post-operative conditions.

Prof. Hisada's laboratory at the Graduate School, the University of Tokyo, conducted joint research with the cardiovascular surgery of Okayama University Hospital. In this project, they simulated pediatric surgery on patients with a hereditary cardiac disorder. They confirmed in three cases that the operational procedures selected on the basis of the simulation Y. Kadooka et al.: Developing Biomedical Simulations for Next-generation Healthcare



(b) CRT-D implanted in August 2009. The virtual heart's electrode locations were adjusted according to the patient's actual electrodes to compare the ECG charts.

Figure 4 Optimization of the electrode positions of CRT-D.

had better results in terms of blood circulation and blood pressure than the alternative procedures. The heart simulator can also predict oxygen saturation and adenosine triphosphate (ATP) consumption, which make the system a potentially effective method for carrying out a multidimensional evaluation of surgical procedures.

### 4. Structure of service provision

It is essential to have a large supercomputer for the heart simulation. Some engineers technically highly skilled in computer simulations are also needed. Major hospitals may have a capacity to install supercomputers, but other hospitals may not be able to afford it. Therefore, the system may be more widely available if a dedicated center is developed and operated on a cloud-computing basis, as shown in **Figure 5**. Each hospital submits patient data to the simulation center via a network, and the center returns the simulation results to the hospital. The plan is to provide a visualization system either at the center or each hospital, for viewing the simulation results.

## 5. Challenges in practical applications and future development

We believe that the heart simulator has many potential applications. To leverage the simulation system's unique features and realize such potential in practical usage, there are many challenges to overcome.



Figure 5 Structure of the heart simulation service.

### 5.1 Early legal sanctions in terms of the Pharmaceutical and Medical Device Act and the health insurance coverage

As stated above, the heart simulator is undergoing a series of evaluations to verify its technological effect in clinical research. For clinical applications in the future, it needs to obtain legal approval in relation to the Pharmaceutical and Medical Device Act (amended Pharmaceutical Affairs Act). Unlike CT and MRI, which are employed in visualizing the patients' internal conditions, the heart simulator aims to serve as a tool for comprehensive diagnostic processes through predicting surgical procedure outcomes as well as visualizing areas which conventional methods have hitherto been unable to depict. However, states of patients' illnesses being variable, it will be necessary to employ some statistical method to objectively evaluate the system's effectiveness. We hope to be able to incorporate past patient data (data with results already attained) to conduct evaluations, so that the effectiveness can be ascertained sooner.

## 5.2 Reimbursement of medical cost in cases of rare disease simulation

Application of the heart simulation to a case of hereditary cardiac disorder, for example, would incur additional cost instead of simplifying the existing clinical trial protocol. The same applies to the case of CRT-D implant operations, which may employ a simulation optimizing electrode positions. Therefore, it is necessary to define how this cost is distributed in order to spread the system for safer, more effective treatment procedures. We hope to proceed with the development of business models with the assistance of the relevant governmental institutions.

## 5.3 Development of a system for medical research

This is the only simulator in the world that renders the image of a human heart from the perspectives of mechanical, biochemical and electrical phenomena, and also can conduct multi-scale simulation. There are high expectations among physicians specializing in circulatory disorders and cardiovascular surgeons that the heart simulator may be potentially applied not only to personalized medicine, but also in etiological investigations and development of new treatments. It may also possibly influence medical advancement worldwide. However, the endeavor is too profound for a single private company to conduct. Thus, further government support is indispensable. We will explore some paths to propose to the government the establishment of a collaborative project between industry, academia and government.

Research and development into biomedical simulations is advancing in the USA and Europe for practical applications. We will also strive to succeed amid this global competition so that Fujitsu can offer practical technologies and services that contribute to advancements in medicine. We will do this by strengthening the R&D structure and our collaborative relationships with medical research institutions.

### 6. Conclusion

In this paper, we described our project on biomedical simulation, centered on the heart simulator that we developed. Computer simulation is a useful tool not only in this heart simulation, but also in other areas such as highly sophisticated medical device development and radiotherapy treatment procedure planning processes. We hope to make contributions to advancements in these fields through Fujitsu's technologies.

This study has been partly funded by the Japan



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