Proceedings of the 2005 IEEE
Engineering in Medicine and Biology 27th Annual Conference
Shanghai, China, September 1-4, 2005

Strong Coupling System for the LV Motion Simulation in a Distributed Simulation Environment

Akira Amano*, Toshifumi Nishi*, Jianyin Lu§, Natalie Schneider§,
Tetsuya Matsuda*, Hidetoshi Kotera†, Akinori Noma‡
*Graduate School of Informatics, †Graduate School of Engineering,
‡Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, Japan 606-8501
§Leading Project for Biosimulation, Kyoto University, Shimogyo-ku, Kyoto, Japan 600-8815
Email: {amano, to-nishi, tetsu}@sys.i.kyoto-u.ac.jp, {lu, nati}@biosim.med.kyoto-u.ac.jp,
kotera_hide@mech.kyoto-u.ac.jp, noma@med.kyoto-u.ac.jp

***Abstract*— A system where model parts can be easily exchanged and modified is of great advantage, especially in a combination of models such as an electrophysiological cell model and a mechanical model to a more complex left ventricular (LV) motion model. The use of a distributed simulation environment is straightforward because each simulation model is calculated by an existing user-friendly simulator. However, the weak coupling calculation usually used in a distributed environment reduces the accuracy of the simulation and results in an unstable simulation of the LV motion. To overcome this problem, we have developed a strong coupling simulation system for the distributed simulation environment. Simulation results for a myocardial tissue and a simple LV shape model are presented to elucidate the effectiveness of our system.**

I. Introduction

To improve our knowledge of biological mechanisms, a quantitative and integrated study of each biological element is necessary. Despite the rapid advancement in the accumulation of quantitative data from biological elements, the integrated systems are still not well analyzed. The simulation of complex biological models is of great importance, because biosimulation has been proved to be a powerful tool

for the analysis of complex biological functions[1]. Since the heart is an essential organ, it is a major target for biological simulation[2][3][4][5]. Hunter and his coworkers have modeled the whole heart geometry, tissue properties, cell and torso geometry. Other research groups have incorporated fluid dynamics, distribution of different cell models etc.

For an accurate heart motion simulation model a good myocardial cell model is essential. In general a myocardial cell model consists of an electrophysiological model and a mechanical model. The contraction force generated by a myocardial cell is related to the cell length and the shortening velocity. Therefore, it is necessary to execute the electrophysiological and mechanical model simultaneously using a coupling mechanism for the interaction of both models. Due to the fact that these models are constructed by researchers in different fields and especially the cell models are constantly being improved, these models are generally evaluated in an isolated environment. However, the evaluation results may differ after two or more models have been combined to a more complex model. Therefore, it is very important to construct a simulation environment, which is suitable for an easy exchange of single models within a complex model. To date, it is hard to modify single models in a multifaceted model environment. Here we introduce a strong coupling simulation system for the LV motion simulation in which the electrophysiological or mechanical model can easily be changed or modified.

II. Electrophysiological model for a myocardial cell and left ventricle motion simulation

A. Electrophysiological model for a myocardial cell

Generally, an electrophysiological model consists of two parts: a membrane excitation model and a contraction model.

Many models for membrane excitation have been published. The model from Noble et al.[6] is based on the Hodgkin-Huxley[7] model and incorporates intracellular ion concentration, ion transporters and the sarcoplasmic reticulum. The Luo-Rudy model[8] includes an intracellular Ca2+ buffering system. The "Kyoto model" from Matsuoka et al.[9] is a precise model which can reproduce the membrane potential and various ion concentrations with high accuracy.

A great number of cardiac contraction models are available. Many models are pure biochemical models and consist of proteins such as troponin and tropomyosin necessary for the Ca filament activation and acto-myosin important for force development. Only a few models also include crossbridge mechanics. However, this is an important part because the contraction force is known to be affected by external force and the shortening velocity. The majority of available mechanical models is based on the crossbridge structure model proposed by Huxley[10] which is composed of thick and thin filaments, the crossbridge spring and a parallel elastic component. In order to reproduce experimental results of quick release force recovery, most contraction models use similar mechanical models whose contraction force is monotonously related to the cell length[11][12][13].

In the contraction model from Negroni and Lascano (NL model)[11], the biochemical Ca kinetics model consists of four troponin states (T, TCa, TCa*, T*). The contraction force F_b[mN/mm^2] is represented as follows:

$$F_b = a(L - X)([TCa^*] + [T^*]). \quad (1)$$

Note that, a is a constant which represents the stiffness of the crossbridge spring, L is the half sarcomere length, and $h = L - X$ is the crossbridge length. [TCa*], [T*] give the number of crossbridge. For the parallel elastic component, the force is represented as follows:

$$F_p = K_p(L_0 - L)^5. \quad (2)$$

K_p is the passive stiffness of the myocardial cell and L_0 is the resting half sarcomere length. When the myocardial cell is loaded with an external force F_{ext}, the half sarcomere length is calculated by the following equation.

$$F_b = F_p + F_{ext} \quad (3)$$

B. Simulation of LV tissue deformation

Previous LV deformation simulation models were developed as a single matrix equation. However, it is time consuming to construct and modify these models. Nevertheless, many efficient simulators are available such as the E-cell simulator[15], suitable for metabolic model simulation, and the simBio[16] simulator for electrophysiological models. These simulators have their own model description languages, and new simulation models can simply be constructed. For mechanical deformation models commercial software for the finite element method are accessible. Using this software, mechanical models can easily be composed and modified.

For a rapid construction of complex simulation models, we have developed the simulation platform "DynaBioS"[17] which utilizes existing simulators as subsimulators. In a distributed simulation environment the calculation algorithm usually ends in a weak coupling. Weak coupling causes instability in the calculation of the LV deformation. Therefore, we propose a strong coupling simulation system for a distributed simulation environment.

III. Distributed Coupling Simulation System

A. Overview of the system

Our system has been constructed for a distributed environment, where each model is simulated by a specific simulator on a different computer. We used simBio as electrophysiology simulator and Marc (MSC inc.) as FEM solver. Each simulator is handled as a component by the central controller called the DynaBioS core. Both simulators have their own model description format allowing a simple and fast construction and modification of simulation models.

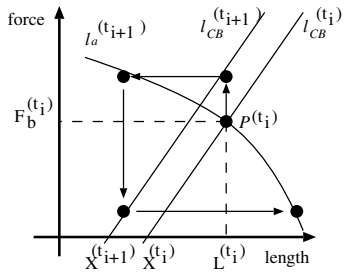


Fig. 1. A weak coupling calculation of a cell contraction model and a mechanical model, results in an unstable cell length calculation if the slope of the line l_a is less than that of the line l_{CB}.

B. Strong Coupling Algorithm

1) Stability of the model: The electrophysiological model employs the NL model for the calculation of the contraction force (equation (1)), passive force (equation (2)) and for solving (equation (3)).

Consider that the contraction force $F_b^{(t_i)}$ and the cell length $L^{(t_i)}$ are given results of equation (1), equation (2) and equation (3) at time $t = t_i$. Then let the relation between the cell length and the contraction force be represented by a line $l_{CB}^{(t_i)}$ whose tangent is $f_{CB}^{(t_i)} = a([TCa^*]^{(t_i)} + [T^*]^{(t_i)})$, and its crossing point on the L axis is $X^{(t_i)}$. In addition, let the relation between the cell length and the passive force be represented by a curve $l_a^{(t_i)}$. $l_{CB}^{(t_i)}$ and $l_a^{(t_i)}$ share the crossing point $P^{(t_i)}$ which has the coordinates $(L^{(t_i)}, F_b^{(t_i)})$.

At time $t = t_{i+1}$, the tangent of the line $l_{CB}^{(t_i)}$ becomes $f_{CB}^{(t_{i+1})} = a([TCa^*]^{(t_{i+1})} + [T^*]^{(t_{i+1})})$, with $X^{(t_{i+1})}$ as L axis crossing point. Now it is necessary to calculate the crossing point of $l_{CB}^{(t_i)}$ with $l_a^{(t_{i+1})}$.

In a distributed simulation environment, this calculation is usually performed by weak coupling. In a weak coupling calculation first the contraction force $F_b^{(t_{i+1})}$ is calculated by equation (1). Then the cell length $L^{(t_{i+1})}$ is calculated by the FEM solver via the passive force using equation (2). If the tangent of l_{CB} is larger than l_a, the calculation results are as shown in Fig.1. If the calculation is continued in this way, the resulting cell length gets oscillating and divergent. For this reason previous simulation systems for LV motion utilize the single matrix calculation method where such a problem does not occur.

2) Coupling Algorithm: Here we propose a strong coupling system for the distributed simulation environment. Using strong coupling it is necessary to calculate the force at different cell lengths, and the cell length at different contraction forces. It is possible to calculate such kind of cycle in a distributed environment. However, the communication overhead becomes very large.

The mechanics part of several contraction models relates the contraction force monotonously to the cell length. Therefore, this calculation can be moved to the FE calculation without the loss of generality. From this consideration, we developed a simulation system with a contraction model that is divided into a biochemical state transition part and a mechanical part. The mechanical part is implemented in

the FE model. The interacting variables, i.e. the coefficient of the force-length relation f_{CB} and the crossbridge motion variable X, are transferred. Using this caculation way, the FE solver can obtain the

correct crossing point $P^{(t_{i+1})}$ of l_{CB} with l_a which was not possible using weak coupling.

IV. Experiments

A. Exchange of contraction modes

To show the efficiency of our system, we have evaluated the cost of modifying the contraction part of the electrophysiological cell model. The NL model has been changed to the HM2 model (unpublished) which is a hybrid model consisting of the mechanics part from the NL model and a biochemical part composed of a 2 state troponin activation by Ca, a 2 state system for tropomyosin to account for conformational changes and a 4 state myosin crossbridge formation. In contrast to the NL model, HM2 shows cooperativity in filament activation introduced through rate constant changes similar to the Sachse model[13]. Cooperativity is an important mechanism in muscle characterized by the steepness of the sigmoidal force-Ca relationship. Given that the mechanical part in both models is identical, the NL model can be exchanged by only replacing the biochemical part and the equation of the contraction force.

The cell model in the simBio system is composed of several java programs and one corresponding XML file. For the replacement of the contraction model only the XML file needs to be modified. Since the equation for the contraction force is different, it is necessary to change the interacting variables between the cell and the mechanical model. The variable names are written in the simulation scenario file of the DynaBioS system, therefore only the variable names in the scenario file need to be changed.

To validate these modifications, simulation results of the half sarcomere length time course of the NL and the HM2 model are shown in Fig.2. This example reveals that using this system simulation results of models which have new combinations of elementary models can easily be generated.

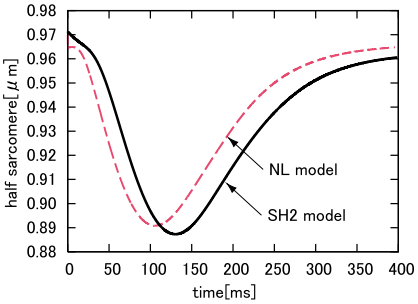
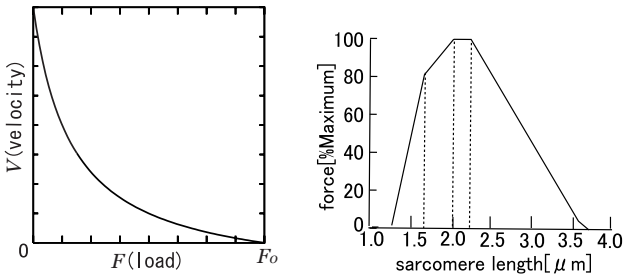


Fig. 2. Simulation results of the half sarcomere length time course from the NL and HM2 model.

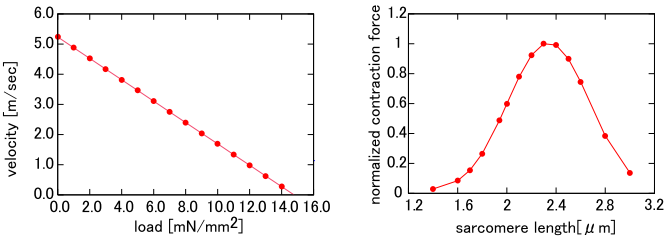
B. Simulation using a one element model

To show the accuracy of the system, we have conducted two simulation experiments according to physiological experiments. The relationship between the shortening velocity and



(a) Force-Velocity relation (b) Force-Length relation

Fig. 3. Shown are experimental data of two peculiar myocardial tissue characteristics: (a) Force-velocity relationship which results from isotonic contractions and (b) force-length relationship derived from isometric contraction experiments.



(a) force-velocity relation (b) force-length relation

Fig. 4. Simulation results of (a) the force-velocity and (b) the force-length relationships.

an applied load called force-velocity relation can be determined using isotonic contraction experiments (Fig.3(a)). The relationship between peak contraction force and sarcomere length called the force-length relation results from isometric contraction experiments (Fig.3.3(b)). The maximum peak force of a myocardial cell is measured at around $2.2\mu m$ sarcomere length.

We used a one cube element as a myocardial tissue model with a linear elastic material property due to the limitation of the FEM solver. The resulting force-velocity relation is shown in Fig.4(a). In this simulation, the shortening velocity gets small with increasing load as found in real experiments. However, the relation is linear and not parabolic due to the fact that a linear elastic material property was used. It is known that the relationship gets linear if the material property is linear elastic[18]. This shows the importance to incorporate nonlinear material properties to reproduce a more realistic force-velocity relationship.

The resulting force-length relation is shown in Fig.4(b). Peak force has been normalized to maximum peak force. In this simulation, the peak contraction force shows a maximum if the sarcomere length is $2.3\mu m$ coming close to experimental data.

C. Experiments using a Ring Shape Model

A shape deformation simulation of a simple LV ring shape model whose inner radius is $20mm$ and represents a short axis slice of the LV has been carried out. The model consists of 16 elements in the circumferential direction, 5 elements

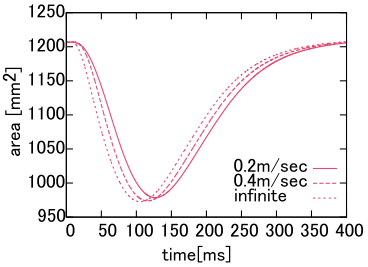


Fig. 5. Simulation results for the ring model: Shown is the area change at different conduction velocities.

in the transmural direction and 1 element in the long axis direction. The five layers in the transmural direction are called endo, sub-endo, mid, sub-epi and epi from endocardium to epicardium. The length in the transmural direction is $10mm$, and the height is $2mm$. All myocardial cells are aligned in the circumferential direction. In this simulation, we have incorporated the excitation delay from the endocardium to the epicardium. We used 0.2, 0.4 and ∞ [m/sec] for the conduction velocity. The results are evaluated by the inner area change for each velocity and the amount of the contraction length (%) of each cell type (contraction ratio). The resulting area change is shown in Fig.5. The maximum area change and the maximum contraction ratio of each cell type are shown in Tab.I. From these results, we can conclude that the area change decreases with decreasing conduction velocity. Furthermore, the contraction ratio of each cell type decreases with decreasing conduction velocity. Nevertheless, the contraction ratio of cells in the endocardium is always larger than that of the cells in the epicardium regardless of the velocity.

Due to the missing inner pressure and a not physiological cell direction the simulation model is not realistic. The simulation results may not be comparable to the real heart. However, it is obvious that our system can be used as an analyzing tool of the complex LV model, and the cell and mechanical models can easily be modified.

V. Conclusion

We have developed a strong coupling simulation system for the combination of an electrophysiological and a mechanical model as used in the simulation of the LV motion which is suitable for a distributed simulation environment. For the evaluation of various biological models a distributed simulation environment is of advantage. However, a weak coupling as generally applied results in a low simulation accuracy. With our proposed strong coupling system, we can obtain accurate simulation results for the LV motion model in a distributed simulation environment. The efficiency of our system was shown by an exchange of the contraction model employed in the electrophysiological model. Furthermore, the accuracy of our system has been shown with simulations of physiological experiments.

TABLE I

The inner area change ratio and the contraction ratio of each layer of the ring model.

conduction vecocity [m/sec]	area change [%]	contraction ratio[%]				
		endo	sub-endo	mid	sub-epi	epi
0.2	18.89	9.25	8.11	7.17	6.40	5.75
0.4	19.34	9.48	8.31	7.36	6.57	5.90
∞	19.47	9.55	8.37	7.41	6.62	5.95

References

[1] McCulloch A, Bassingthwaighte JB, Hunter P, and Noble D. Editorial: "Computational biology of the heart: from structure to function", Prog. Biophys. Mol. Biol., 69, pp.153-155, 1998.

[2] LeGrice B.I and Hunter P and Young A and Smaill B: "The architecture of the heart:a data-based model," Phil. Trans. R. Soc. Lond(A), 359, pp.1217-1232, 2001.

[3] Costa KD and Jeffrey W. Holmes and McCulloch AD: "MODELING CARDIAC MECHANICAL PROPERTIES IN THREE DIMENSIONS," Phil Trans Royal Soc, 2001.

[4] MARKO VENDELIN, PETER H. M. BOVENDEERD, THEO ARTS, JURI ENGELBRECHT, AND DICK H. VAN CAMPEN: "Cardiac Mechanoenergetics Replicated by Cross-Bridge Model," Annals of Biomedical Engineering, Vol. 28, pp. 629-640, 2000.

[5] K. Sugiura, J. Okada, H. Hukunari, H. Watanabe, T. Hisada: Computer simulation of blood flow, left ventricular wall motion and their interrelationship by fluid-structure interaction finite element method, *JSME International Journal Series C*, Vol. 45, No. 4, 2002.

[6] D. Noble, D. DiFrancesco: A model of cardiac electrical activity incorporating ionic pumps and concentration changes, *Phil. Trans. R. Soc. Lond. Biol.*, Vol. 307, pp. 353–398, 1985.

[7] A.F. Huxley, A.L. Hodgkin: A quantitative description of membrane current and its application to conduction and excitation in nerve, *Journal of Physiology*, Vol. 117, pp. 500–544, 1952.

[8] Y. Rudy, C.H. Luo: A dynamic model of the cardiac ventricular action potential i. simulation of ionic currents and concentration changes, *Circulation Research*, Vol. 74, pp. 1071–1096, 1994.

[9] Shinobu KURATOMI, Kyoichi ONO, Satoshi MATSUOKA, Nobuaki SARAI and Akinori NOMA: Role of individual ionic current systems in ventricular cells hypothesized by a model study, *Japanese Journal of Physiology*, Vol. 53, pp. 105 – 123, 2003.

[10] A. F. Huxley: "MUSCLE STRUCTURE AND THEORIES OF CONTRACTION," Prog. Biophysics and Biophysical Chemistry, 7:255-318, 1957.

[11] A. Negroni and C. Lascano: Concentration and elongation of attached cross-bridges as pressure determinants in a ventricular model, *Journal of Molecular and Cellular Cardiology*, Vol. 31, pp. 1509 – 1526, 1999.

[12] A. Landesberg and S. Sideman: "Mechanical regulation of cardiac muscle by coupling calcium kinetics with cross-bridge cycling: a dynamic model," Am J Physiol Heart Circ Physiol 267: H779-H795, 1994.

[13] FB Sachse, KG Glänzel, G Seemann: "Modeling of Protein Interactions Involved in Cardiac Tension Development," IJBC, 13, pp.3561-3578, 2003.

[14] B. H. Smaill, P. M. F. Nielsen, I. J. Le Grice and P. J. Hunter: Mathematical model of geometry and fibrous structure of the heart, *the American Physiological Society*, 1991.

[15] e-cell Masaru Tomita, Kenta Hashimoto, Kouichi Takahashi, Tom Shimizu, Yuri Matsuzaki, Fumihiko Miyoshi, Kanako Saito, Sakura Tanida, Katsuyuki Yugi, J. Craig Venter, Clyde A. Hutchison: "E-CELL: Software Environment for Whole Cell Simulation," Genome Informatics, 1997.

[16] Sarai N and Amano A and Matsuoka S and Matsuda T and Noma A: "Development of the cardiac cell model by applying object-oriented methods," IEEE EMBC, 2003.

[17] Shimayoshi T and Hori K and Lu J. Y and Amano A and Matsuda T: "A Software Environment for Simulators Suitable for Complex Biological Analysis," IEEE EMBC, pp.3047-3050, 2004.

[18] A. M. Katz: "Physiology of the Heart," Lippincott/Williams & Wilkins, 2001.