33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A Study on Prediction Methods for a Cardiovascular Strong-coupling Simulation

Yuki Hasegawa, Takao Shimayoshi, Akira Amano, Tetsuya Matsuda

Abstract— **We investigated numerical methods for predictors in a multiscale cardiovascular simulation model. The proposed method predicts initial approximations for the iterative convergence calculations of the strong coupling method using the smoothing spline to remove errors from values of past timesteps and using the linear and second-order extrapolation. The new coupling algorithm was used for coupling a left ventricular finite element model to a myocardial excitation-contraction model. We performed experiments with different values for the smoothing parameter λ and with linear and second-order extrapolations. $\lambda = 1$ with the linear extrapolation gave the best results. It reduced computation time by 91% compared to the strong coupling method. With the use of the smoothing spline, distance between the initial approximation and converged solution reduced by 62%, while the average number of iterations reduced by 32%. The smoothing spline can be used to improve the accuracy of predictors and reduce the number of iterations needed for the computation of the convergence procedure.**

I. Introduction

The cardiovascular system is a system in which the heart acts as a pump to circulate blood through a system of vessels. The pump function of the heart is a result of the contraction of myocardial cells. The contraction is brought about by excitation-contraction coupling, a complex interaction of ions and cross-bridges within the cell. As the heart expands and contracts, hemodynamics come into play in which the elasticities of the myocardial wall and blood vessels determine the blood flow through the system. As a result, the cardiovascular system is a complex system composed of the interaction of myocardial electrophysiology, ventricular structural dynamics, and hemodynamics of the circulatory system.

Several models simulate the interaction of excitation-contraction coupling and ventricular deformation[1], [2]. Some models further combine models of the circulatory system to simulate the resistance and compliances of the blood vessels and the resulting interaction of blood flow and the vessels [3], [4], [5]. In these models, each phenomenon of myocardial electrophysiology, ventricular structural dynamics, and hemodynamics is modeled by the individual system of equations. Simulation of the integrated multi-domain model for multiple relating phenomena is called coupling simulation.

Coupling simulation is achieved by coupling calculation of multiple systems of equations. There are two major coupling methods: the weak coupling method and the strong coupling method. The strong coupling method solves the multi-domain equations as a single system. Strong coupling of the cardiac mechanics model have been investigated before[1], [2], [6], [7]. The strong coupling method allows for stable and accurate calculation. However, the coupled models used over-simplified myocardial electrophysiology or structural models to compensate for the computational intensity of the strong coupling method. On the other hand, the weak coupling method uses a simpler and less computationally intensive method in which shared physical quantities are exchanged between timesteps and simulations are performed in parallel. However, instabilities of the weak coupling method have been addressed in the past[1], [3], [6], [7].

Some strategies have been developed to overcome the problems of the weak coupling method. One method used to stabilize the weak coupling method is approximating the force-length equation in the contraction model using a first-order delay equation [1], [3]. This method allows for the ”smoothing” of the calculated myocardial contraction force. However, this solution may not be sufficient in mitigating the effects of the weak coupling method, especially if the equations for excitation-contraction require high precision in its calculation.

With respect to the strong coupling method, in order to reduce computational intensity, a method for improving convergence rate using predictors in cardiovascular simulations was proposed [4]. However, this was done with pressure updates, in which ventricular pressure had to be iteratively updated for the coupling of a ventricular model and circulation model.

In this paper we propose a method to improve the convergency of the strong coupling method by use of the smoothing spline and extrapolation. We demonstrate the method using a multiscale cardiovascular simulation model which includes cell electrophysiology, ventricular deformation, and circulatory hemodynamics. The simulation is also compared with the original strong coupling method.

II. Model Equations

A. Myocardial Excitation-Contraction Model

The electrophysiology of myocardial cells are simulated by the Kyoto model[8] with a modification[3]. The Kyoto model uses the contraction model proposed by Negroni and Lasconi (NL model) [9]. The NL model calculates myocardial contraction force from cross-bridge dynamics of the thick and thin filaments and calcium kinetics of the binding of calcium and troponin. Both the cross-bridge dynamics and calcium kinetics take into account its length

Y. Hasegawa and T. Matsuda are with Graduate School of Informatics, Kyoto Univerisity, Kyoto, 606-8501, Japan (phone:+81-75-753-3373; fax:+81-75-753-3375; e-mail:yhasegawa@sys.i.kyoto-u.ac.jp)

T. Shimayoshi is with ASTEM RI, Kyoto, 600-8813, Japan

A. Amano is with Department of Bioinformatics, Ritsumeikan University, Kyoto, 611-0031, Japan

dependent aspects. Ca^{+2} transients are modeled by equations in the Kyoto model.

The modification in [3] accounts for the instabilities introduced in the force-length equation of the NL model. The force-length equation is stabilized by replacing the equation with a single order delay equation. The myocardial contractile force calculated from the modified version of the NL model remains length dependent. Therefore, the force can be represented as a function of half sarcomere length L: $F_b(L)$.

B. Left Ventricular Structural Dynamic Model

The left ventricular structural dynamic model (LVFEM) is a finite element model which represents the structural deformation of the ventricular wall. Structural deformation is calculated by a balance equation which contains active and passive stresses for each element and LV pressure on the inner wall. The finite element method is used to solve for the balance equation and meet the requirements for the boundary condition of LV volume which is defined by the circulatory model. For simplicity, the balance equation will be written as an implicit function:

$$0 = H(\mathbf{L}, \mathbf{F_b}, P_{lv}, V_{lv}), \tag{1}$$

where $\mathbf{F_b}$ and $\mathbf{L}$ respectively represent vectors of myocardial forces and half sacromere lengths of representative cells for finite elements, and P_{lv} and V_{lv} are LV pressure and volume respectively.

C. Circulatory hemodynamics

The circulatory model calculates hemodynamics and the resulting change in LV volume. Circulatory hemodynamics of pulmonary preload and aortic afterload were modeled using the Windkessel model. We adopted the 3-element windkessel model to simulate the afterload and added a single element for the simulation of the preload. The resulting equation for the modified Windkessel model uses LV pressure as the input variable for the calculation of blood flow.

$$\frac{dV_{lv}}{dt} = Q_{in}(P_{lv}) - Q_{out}(P_{lv}), \tag{2}$$

where the function Q_{in} represents inflow governed by preload which consists of mitral resistance and pulmonary pressure, and Q_{out} is outflow governed by the afterload which consists of aortic compliance, aortic resistance and resistance of the aortic valve.

III. Coupling Methods

1) Strong Coupling: The strong coupling method between the myocardial cell model and LVFEM used in our simulation model will be explained. With this method, the bidomain equations described the myocardial cell model and LVFEM are solved together as a single system. The procdure requires length updates which are performed iteratively. At each iteration step, the following equation is solved with respect to $\tilde{\mathbf{L}}_i^{(t_n)}$.

$$0 = H(\tilde{\mathbf{L}}_i^{(t_n)}, F_b(\mathbf{L}_i^{(t_n)}), P_{lv}^{(t_n)}, V_{lv}^{(t_n)}) \tag{3}$$

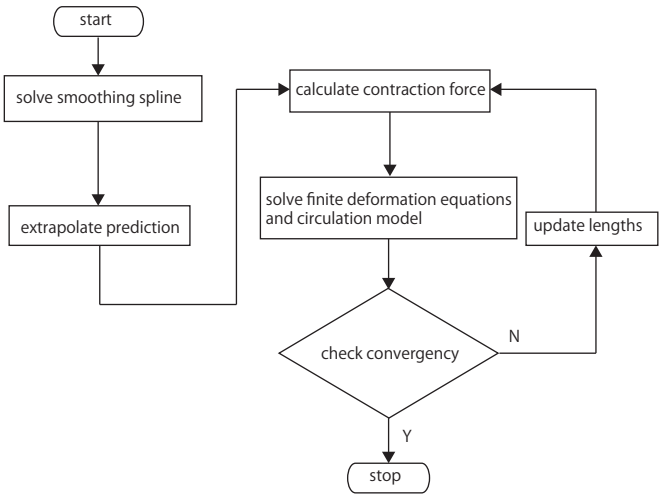

Fig. 1. Flow chart for the proposed coupling method at each timestep

Myocardial contractile force $\mathbf{F_b}$ is calculated with lengths $\mathbf{L}_i^{(t_n)}$. The boundary condition for LV volume $V_{lv}^{(t_n)}$ is calculated in the circulatory model from eq. 2.

At this point, convergence is achieved when the residual of lengths $\mathbf{R_{length}}$ satisifes the convergence tolerance ε_{length}.

$$\mathbf{R_{length}} = \mathbf{L}_i^{(t_n)} - \tilde{\mathbf{L}}_i^{(t_n)} \quad |\mathbf{R_{length}}|_{max} < \varepsilon_{length} \tag{4}$$

If eq. 4 is satisfied, calculation for the nth timestep is complete. If the convergence tolerance is not satisfied, the procedure returns to solving the force equation for $\mathbf{L}_{i+1}^{(t_n)}$ which is updated using the bisection method and eq. 3 is recalculated.

In general, for the initial approximation of lengths, the converged solution for the last timestep is used:

$$\mathbf{L}_0^{(t_n)} = \mathbf{L}^{(t_{n-1})}. \tag{5}$$

2) Weak Coupling: Unlike the strong coupling method, the weak coupling method requires no iterative procedures to be performed. Contractile forces generated by myocardial cells are calculated using sacromere lengths for the last timestep $\mathbf{L}^{(t_{n-1})}$ calculated in the LVFEM.

$$0 = H(\mathbf{L}^{(t_n)}, F_b(\mathbf{L}^{(t_{n-1})}), P_{lv}^{(t_n)}, V_{lv}^{(t_n)}) \tag{6}$$

The circulatory model is solved simultaneously as well for the boundary condition as in eq. 2. The procedure ends here as no convergence calculation is needed.

IV. Prediction Methods for Initial Approximation

The number of iterations to convergence depends on the distance between the initial approximation and the explicit solution. The converged solution at the last timestep works well as the approximation, when displacement between timesteps are small. However, under large displacements this leads to slow convergence of the iterative procedure.

The proposed algorithm adds a predictor to reduce the number of iterations to convergence. This predictor method

employs polynomial extrapolation for prediction and also smoothing splines to correct calculation errors which might effect the extrapolation. This method will be called the proposed coupling method to distinguish it from the strong coupling method.

Fig. 1 is a flow chart of the proposed algorithm for a given timestep. First, smoothing splines are used to reduce residual errors from values in past timesteps. This should mitigate the effects of errors on the predictors. We used a simplified version of the smoothing spline regression function in which the second derivative is calculated by the second-order finite difference method. The smoothing spline requires to solve for the minumum of the following regression function.

$$E_{ss} = \sum_{j=1}^{m} (\mathbf{L}^{(t_{n-j})} - \hat{\mathbf{L}}^{(t_{n-j})})^2 + \lambda \sum_{j=2}^{m-1} (\hat{\mathbf{L}}^{(t_{n-j-1})} - 2\hat{\mathbf{L}}^{(t_{n-j})} + \hat{\mathbf{L}}^{(t_{n-j+1})})^2 \quad (7)$$

As a result, $\{\hat{\mathbf{L}}^{(t_{n-1})} \cdots \hat{\mathbf{L}}^{(t_{n-m})}\}$ will contain the interpolated values of lengths up to the mth past values. The interpolated values are used in the following linear or second-order extrapolation.

$$\mathbf{L}_0^{(t_n)} = 2 \cdot \hat{\mathbf{L}}^{(t_{n-1})} + \hat{\mathbf{L}}^{(t_{n-2})} \quad (8)$$

$$\mathbf{L}_0^{(t_n)} = 3 \cdot \hat{\mathbf{L}}^{(t_{n-1})} - 3 \cdot \hat{\mathbf{L}}^{(t_{n-2})} + \hat{\mathbf{L}}^{(t_{n-3})} \quad (9)$$

After the prediction of initial approximated lengths, the procedure is the same as the strong coupling method described in sec. III.

V. Simulation

A simplified 4-element model was used for the LVFEM model for all experiments. This simplification was necessary to compare each experiment with the strong coupling method, which is computationally intensive.

We tested the proposed coupling method on our cardiovascular simulation system. λ was set to 10^{-3}, 10^{-2}, 10^{-1}, 1, 10^1, 10^2, 10^3. The convergence tolerance for length updates was set to 10^{-4} μM. The number of maximum iterations for each timstep was set to 5 in order to reduce computation time. The predictor was omitted in the beginning of the simulation where past values for $\mathbf{L}$ were not available.

Distance between the initial guess and converged solution d was measured for each timestep. The average distance $\bar{d}$ was calculated. Average number of iteration per time step $\bar{N}$ was also observed to compare convergence efficiency between the coupling methods. Simulation with the strong coupling method was also performed for comparison.

The calculation timestep was set to 0.1 [ms] and each cardiac cycle was set to 400 ms which resulted in a total of 4000 timesteps per cardiac cycle. All simulations were performed on IBM p690 (32CPU, POWER4 1.5GHz).

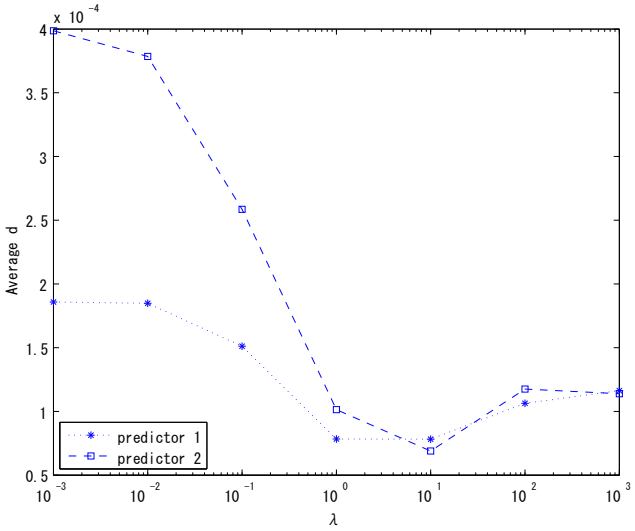

Fig. 2. Average distance between solution and initial value $\bar{d}$

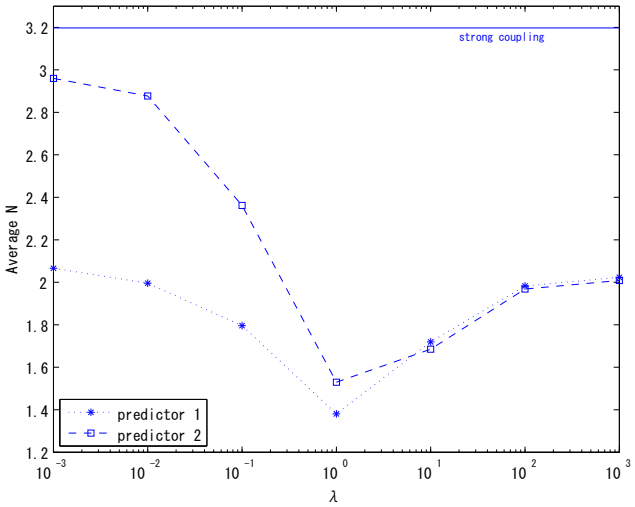

Fig. 3. Average iterations per timestep $\bar{N}$

VI. Results

Total wall clock time for simulation with the proposed coupling method was reduced by 91% compared to the strong coupling method. Fig. 2 shows average distance $\bar{d}$ between the initial estimate and converged solution. $\lambda = 1$ for the linear extrapolation and $\lambda = 10$ for the second-order extrapolation gave the best results. Fig. 3 shows average number of iterations $\bar{N}$ for all experiments. $\lambda = 1$ is the most efficient in terms of average number of iterations. $\bar{N}$ with $\lambda = 1$ for the linear extrapolation was reduced by 57% compared to the strong coupling method.

Table I compares the results of simulations performed with and without the smoothing spline with smoothing parameter $\lambda = 1$. For the linear extrapolation, using the smoothing spline reduced average iterations $\bar{N}$ by 32% and average distance $\bar{d}$ by 62% compared to the results without the

TABLE I

SIMULATION RESULTS PERFORMED WITHOUT THE SMOOTHING SPLINE

	no spline		with spline ($\lambda = 1$)	
	linear	second-order	linear	second-order
$\bar{N}$	2.03	2.96	1.38	1.53
$\bar{d}(10^{-4})$	2.05	4.18	0.784	1.01

smoothing spline. A similar comparison for the second-order extrapolation gave a reduction of 76% and 48% for $\bar{N}$ and $\bar{d}$ respectively. A significant change in wall clock time was not observed.

VII. DISCUSSION

We tested the proposed method with our cardiovascular simulation model and used the weak and strong coupling methods for comparison. Different values for the smoothing parameter λ was tested for both the linear and second-order extrapolations.

Correlation was found between $\bar{N}$ and $\bar{d}$ for both predictors. This indicates that increasing the accuracy of the predictors helps in reducing the number of iterations.

Using the smoothing spline reduced $\bar{N}$ and $\bar{d}$. This indicates that the smoothing spline is effective in increasing the accuracy of the predictors by reducing errors which effect the extrapolation. $\lambda = 1$ was the most efficient for the examined simulation in terms of convergence efficiency and reducing the calculation error.

In fig. 2, $\bar{d}$ increases at both extreme ends of λ. This indicates the following remarks. If the value for the smoothing parameter is too large, then the curve is over-smoothed and the characteristics of the curve is lost. On the other hand, if the value is too small, the oscillation of the curve caused by residual errors makes the extrapolation unstable.

The oscillation of the curve seems to have effected the predictors as well since the linear extrapolation out performed the second-order extrapolation overall. This is most likely due to Runge's phenomenon for extrapolation of high degrees. Linear extrapolation seemed to be more stable for our simulation condition.

The simplicity of the procedure makes the weak coupling method the preferred method when the errors produced by the coupling are nominal. However, it is easy to see that under large displacements the simulation will become unstable and large errors will be produced[1], [6], [7]. The strong coupling method is stable and its computational intensity may be mitigated with the proposed method.

In this paper a combination of the smoothing spline and polynomial extrapolation, which are both well-known and computationally inexpensive, is employed as a predictor. Performances of other predictors are to be evaluated. Another factor not taken into account in the present predictor is the inherent property of our simulation model. Utilization of the model properties may improve prediction accuracy. On the other hand, due to this model independency, the proposed method should be applicable to other multiscale simulations which utilize the coupling procedure as well as different conditions for a particular model. In these cases, the optimal smoothing parameter and degree of extrapolation will depend on the models and conditions.

VIII. CONCLUSION

The proposed coupling method is a modified version of the strong coupling method which reduce the number of iterations to convergence with the use of predictors that employ polynomial extrapolation and the smoothing spline. We found an optimal smoothing parameter which reduced errors and facilitated the iterative procedure. Use of the smoothing spline with this optimal parameter out performed simulations without the smoothing spline.

The method may be used to replace the weak coupling method which may be unstable if the electrophysiology models require high precision in its calculation. Performing the convergence procedure as in the strong coupling method allows for a more stable and accurate calculation.

It may be possible to add an additional implementation for the automatic selection of the smoothing parameter. Much extensive research has been done in this area [10] and it may be beneficial for increasing the accuracy of the predictors since the smoothing spline is applied over varying shaped curves.

REFERENCES

[1] S. Niederer and N. Smith, "An improved numerical method for strong coupling of excitation and contraction models in the heart," *Progress in biophysics and molecular biology*, vol. 96, no. 1-3, pp. 90–111, 2008.

[2] D. Nickerson, N. Smith, and P. Hunter, "New developments in a strongly coupled cardiac electromechanical model," *Europace*, vol. 7, no. s2, p. S118, 2005.

[3] A. Amano, Y. Takada, J. Lu, T. Shimayoshi, and T. Matsuda, "An approximation model of myocardial crossbridge for weak coupling calculation of left ventricle model and circulation model," in *Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE*, pp. 957–960, IEEE, 2008.

[4] R. Kerckhoffs, M. Neal, Q. Gu, J. Bassingthwaighte, J. Omens, and A. McCulloch, "Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonic circulation," *Annals of biomedical engineering*, vol. 35, no. 1, pp. 1–18, 2007.

[5] R. Kerckhoffs, S. Healy, T. Usyk, and A. McCulloch, "Computational methods for cardiac electromechanics," *Proceedings of the IEEE*, vol. 94, no. 4, pp. 769–783, 2006.

[6] J. Whiteley, M. Bishop, and D. Gavaghan, "Soft tissue modelling of cardiac fibres for use in coupled mechano-electric simulations," *Bulletin of mathematical biology*, vol. 69, no. 7, pp. 2199–2225, 2007.

[7] P. Pathmanathan and J. Whiteley, "A numerical method for cardiac mechanoelectric simulations," *Annals of biomedical engineering*, vol. 37, no. 5, pp. 860–873, 2009.

[8] M. Kuzumoto, A. Takeuchi, H. Nakai, C. Oka, A. Noma, and S. Matsuoka, "Simulation analysis of intracellular Na^{+} and Cl^{-} homeostasis during β1-adrenergic stimulation of cardiac myocyte," *Progress in biophysics and molecular biology*, vol. 96, no. 1-3, pp. 171–186, 2008.

[9] J. Negroni and E. Lascano, "A Cardiac Muscle Model Relating Sarcomere Dynamics to Calcium Kinetics," *Journal of molecular and cellular cardiology*, vol. 28, no. 5, pp. 915–929, 1996.

[10] J. Marron, "Automatic smoothing parameter selection: a survey," *Empirical Economics*, vol. 13, no. 3, pp. 187–208, 1988.