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Reproducing Nonlinear Force Velocity Relation of Myocardial Tissue by a Nonlinear Parallel Elastic Component

Yutaka NOBUAKI*, Yu KAMEI*, Jianyin LU‡, Takao SHIMAYOSHI§, Satoshi ISHIKAWA¶, Akira AMANO*
Hidetoshi KOTERA†, Tetsuya MATSUDA*
*Graduate School of Informatics, †Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto, Japan 606-8501
‡Leading Project for Biosimulation, Kyoto University, Shimogyo-ku, Kyoto, Japan 600-8815
§ASTEM Research Institute of Kyoto, Shimogyo-ku, Kyoto, Japan 600-8813
¶Mechanical Design and Analysis co, Tokyo, Japan 182-0024

***Abstract*— To realize precise simulation of the left ventricular motion, it is important to utilize an accurate myocardial tissue model which can reproduce various characteristics of myocardial tissue contraction. In this study, we show that the nonlinear characteristics of the passive myocardial tissue property is the essential nature of the nonlinear force-velocity relation and present a formulation for hyperelastic physiological tissue property. Experimental results of our myocardial tissue simulation with the hyperelastic material property proposed are in good agreement with the reported force-velocity relation of real tissue.**

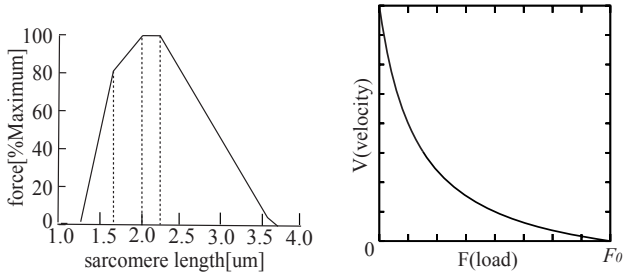
I. INTRODUCTION

To explore the knowledge on biological mechanisms, quantitative and integrated study of each biological element is necessary. Despite the rapid advancement in the accumulation of quantitative data from biological elements, integrated systems are still not analyzed very well.

Biosimulation has proved to be a powerful tool for the analysis of complex biological functions[1] and is of great importance for the investigation of coupled biological models. Since the heart is an essential organ that drives blood circulation in the body, it is a major target for biological simulation[2][3]. Heart motion is characterized by high complexity. To realize accurate simulation of the left ventricular motion, incorporation of an accurate myocardial tissue model, which can reproduce various characteristics of myocardial tissue contraction, is of importance.

The contraction model proposed by Negroni and Lascano (NL model)[4] enables reproduction of the force-velocity relation(FVR) and the force-length relation(FLR). In their model, the active contraction force is linearly related to the quantity of crossbridge extension. The passive force generated by the parallel elastic component (PEC) is nonlinearly related to the half sarcomere length. When the finite element method is used to calculate myocardial tissue deformation, the PEC in the NL model must be implemented as a material property of the mechanical model. This fact indicates the importance of evaluating the characteristics of the myocardial tissue contraction model using the finite element method.

In this study, we experimentally analyzed the relation between the characteristics of the FVR and the PEC, in order to propose a nonlinear hyperelastic formulation of the nonlinear material property which can analytically reproduce the nonlinear FVR. Simulation results obtained with the proposed hyperelastic material property are presented to demonstrate the accuracy between the simulation results and the reported experimental results.



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

Fig. 1. Experimental data of two typical myocardial tissue characteristics: (a) Force-length relationship derived from isometric contraction experiments and (b) force-velocity relationship which results from isotonic contractions.

II. THE CHARACTERISTICS OF MYOCARDIAL TISSUE AND MYOCARDIAL TISSUE SIMULATION

A. Characteristics of myocardial tissue contraction

The relationship between peak contraction force and sarcomere length, referred to as force-length relation, is acquired from isometric contraction experiments(Fig.1(a))[5]D

The relationship between the shortening velocity V and an applied load F, called force-velocity relation, can be determined using isotonic contraction experiments(Fig.1(b))D This relation is described using the following Hill's equation[6]D

$$(F+a)(V+b) = (F_0+a)b \tag{1}$$

Here, a, b and F_0 are constants which are determined by musclar tissue properties.

The shortening velocity of the instantaneous shortening experiment is defined as the shortening velocity of the isotonic contraction. In the experiment, both ends of the myocardial tissue are fixed at the beginning. A certain time interval after stimulation, one end of the tissue is released and a load is attached. Shortening velocity is measured after another fixed time period[7]DA great number of reports dealing with force-velocity relation is available . The force-velocity relation is known to be affected by the initial half sarcomere length before release (L_{init}) and the time interval (t_r) between stimulation and release.

Noble et al. reported that the maximum load and the maximum shortening speed increase and the nonlinearity of

the force-velocity relation increases when the half sarcomere length approches the length at which the peak contraction force is generated (Fig. 2(a))[8]DBodem et al. reported that in their measurement of the FVR with different t_r, the tangential slope of the force velocity curve decreases as t_r approaches the point of force generation (Fig.2(b))[9]D

B. Elements of myocardial tissue simulation

The simulation model of the myocardial tissue contraction is constructed by complex combination of many elements. In this study, we realized the myocardial tissue simulation by using an electrophysiological model that reproduces the membrane potential and various ion concentrations, a myocardial tissue contraction model that considers the mechanism of the contraction force generation, and a mechanical myocardial tissue model that represents mechanical properties of the myocardial tissue, such as elasticity.

1) Electrophysiological model for a myocardial cell: For the electrophysiological cell model, the "Kyoto model"[10] proposed by Noma was used. The "Kyoto model" enables accurate reproduction of the aforementioned membrane potential and ion concentrations.

2) Myocardial tissue contraction model: If myocardial tissue is activated by specific electrical stimulation, the intracellular Ca concentration increases rapidly and the contraction force is generated. A well-known model for the latter is the NL model. In this model, the mechanical relation between the force and the half sarcomere length is included. The contraction force $F_b[mN/mm^2]$ is incorporated as follows:

$$F_b = K_{CB}(L-X) \tag{2}$$

Note, that K_{CB} is a coefficient which is calculated by a biochemical Ca kinetics model, and X is the difference between the half sarcomere length and the crossbridge length h.

For the parallel elastic component, the force F_p is calculated using the following equation:

$$F_p = -\sigma(L) = K_p(L_0-L)^5 \tag{3}$$

$K_p = 140{,}000[mN/mm^2/\mu m^5]$ is the passive stiffness of the myocardial cell and L_0 is the half sarcomere length in resting state. If the myocardial cell is loaded with an external force $F_{ext}[mN/mm^2]$, the half sarcomere length is given by the following equation:

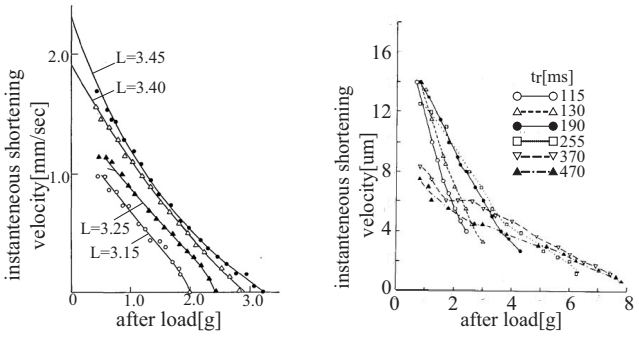
$$F_b = F_p + F_{ext} \tag{4}$$

The crossbridge returns to its steady state with following velocity:

$$dX/dt = B(h-h_c) \tag{5}$$

where $B = 1.2[1/ms]$ is the velocity parameter and $h_c = 0.005[\mu m]$ is the crossbridge length in steady state.

3) Myocardial mechanical model: In the 3D mechanical model, the contraction force calculated by the electrophysiological model is incorporated as the contraction force along the cell orientation. The mechanical deformation is calculated using the finite element method.



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

Fig. 2. Experimental data of instantaneous shortening: (a) Force-velocity relationship as measured by Noble et al[8] and (b) force-velocity relationship as measured by Bodem et al[9]. The time of the peak force generated is 450[ms].

III. NONLINEAR CHARACTERISTICs OF THE PARALLEL ELASTIC COMPONENT AND FORCE-VELOCITY RELATION

A. Analysis of force-velocity relation in the NL model

To evaluate the effect of the PEC on the FVR, we analyzed the FVR derived from the mathematical model equations, first assuming linear elastic material characteristics, then nonlinear hyperelastic material characteristics as PEC property.

We define the half sarcomere length at time t as $L^{(t)}$. Note that t_r, t_r^-, and t_r^+ represent the release time, the time immediately before, and after the release, respectively. The half sarcomere length $L^{(t_r^-)}$ before releasing the fixed part corresponds to the initial half sarcomere length L_{init}. By using these variables, the shortening velocity V in the instantaneous shortening experiments at time t can be calculated as follows.

If we assume that K_{CB} is constant during the time period in consideration, the following relation can be derived from equation (4):

$$K_{CB}(L-X) + \sigma(L) = F_{ext} \tag{6}$$

where $\sigma(L)$ is the material property of myocardial tissue. Differentiation yields:

$$K_{CB}\frac{dL}{dt} - K_{CB}\frac{dX}{dt} + \frac{d\sigma}{dt} = 0 \tag{7}$$

Using following relation,

$$\frac{d\sigma}{dt} = \frac{d\sigma}{dL}\frac{dL}{dt} \tag{8}$$

we derive:

$$\frac{dL}{dt} = \frac{K_{CB}}{K_{CB} + d\sigma/dL}\frac{dX}{dt} \tag{9}$$

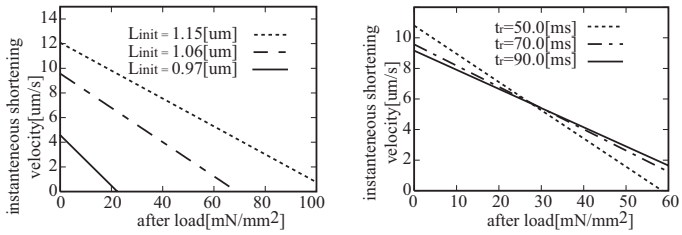
When the linear elastic material is used as the PEC material propertyC the passive force $F_p^{(t)}$ can be calculated by:

$$F_p^{(t)} = -\sigma(L^{(t)}) = K_p(L_0 - L^{(t)}) \tag{10}$$

where K_p is a constant coressponding to the Young's modulus. From equations (2) and (5), the contraction force is determined:

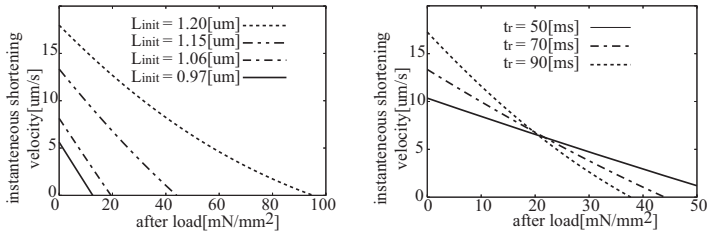
$$F_b^{(t)} = K_{CB}(L^{(t)} - X^{(t)}) \tag{11}$$

$$dX/dt|_t = B(L^{(t)} - X^{(t)} - h_c) \tag{12}$$



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

Fig. 3. Numerical analysis results of instanteneous shortening using a linear elastic body: (a) Force-velocity relationship with changing L_{init} at $t_r = 70.0[ms]$ and (b) force-velocity relationship with changing t_r in the case of $L_{init} = 1.06$



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

Fig. 4. Numerical analysis results of instantaneous shortening using a hyperelastic body: (a) Force-velocity relationship of changing L_{init} at $t_r = 70.0[ms]$ and (b) force-velocity relationship of changing t_r in the case of $L_{init} = 1.15$

Combining equations (4), (10), (11) yields following relation between contraction force $F_b^{(t)}$, extension force $F_p^{(t)}$ and external force $F_{ext}^{(t)}$:

$$L^{(t)} = \frac{K_{CB}X^{(t)} + K_pL_0 + F_{ext}^{(t)}}{K_{CB} + K_p} \tag{13}$$

Since the half sarcomere length is constant before release time $t = t_r^-$, we can describe

$$L^{(t_r^-)} = X^{(t_r^-)} + h_c \tag{14}$$

$$dX/dt|_{t=t_r^-} = 0 \tag{15}$$

Immediately after release, the applied load F_a becomes the external force $F_{ext}^{(t)} = F_a(t \geq t_r^+)$. Thus, at $t = t_r^+$

$$L^{(t_r^+)} = \frac{K_{CB}X^{(t_r^+)} + K_pL_0 + F_a}{K_{CB} + K_p} \tag{16}$$

$$dX/dt|_{t=t_r^+} = B(L^{(t_r^+)} - X^{(t_r^+)} - h_c) \tag{17}$$

$$X^{(t_r^+)} = X^{(t_r^-)} \tag{18}$$

Then the velocity can be described as

$$\begin{aligned} dX/dt|_{t=t_r^+} &= B(L_E^{(t_r^+)} - X^{(t_r^+)} - h_c) \\ &= B\left(L_E^{(t_r^+)} - X^{(t_r^-)} - h_c\right) \\ &= B\left\{L_E^{(t_r^+)} - \left(L_E^{(t_r^-)} - h_c\right) - h_c\right\} \\ &= \frac{B}{K_{CB} + K_p}\left(F_a - F_{ext}^{(t_r^-)}\right) \end{aligned} \tag{19}$$

From equations (9), (19) and since $d\sigma/dL = K_p$, the shortening velocity $V^{(t_r^+)}$ at $t = t_r^+$ is calculated.

$$V^{(t_r^+)} = \frac{dL}{dt} = \frac{B \cdot K_{CB}}{(K_{CB} + K_p)^2}\left(F_a - F_{ext}^{(t_r^-)}\right) \tag{20}$$

The equations above show, that FVR becomes linear, regardless of L_{init} or t_r, when assuming linear elasticity as tissue characteristics.

When using nonlinear material property, following velocity is obtained:

$$V^{(t_r^+)} = \frac{dL}{dt} = \frac{dL}{dX}\frac{dX}{dt}$$

$$\begin{aligned} &= \frac{K_{CB}}{K_{CB} + d\sigma/dL}B(h - h_c) \\ &= \frac{K_{CB}(B(L^{(t_r^+)} - X^{(t_r^+)}) - Bh_c)}{K_{CB} + d\sigma/dL} \\ &= \frac{BF_a - B\sigma(L)^{(t_r^+)} - K_{CB}Bh_c}{K_{CB} + d\sigma/dL} \end{aligned} \tag{21}$$

Since the velocity of X is constant immediately after release,

$$K_{CB}(L_E^{(t_r^+)} - X^{t_r^-}) + \sigma(L_E)^{(t_r^+)} = F_a \tag{22}$$

From equations (15), (22), the half sarcomere length immediately after release $L^{(t_r^+)}$ can be calculated by providing $L^{(t_r^-)}$ and F_a. Inserting $L^{(t_r^+)}$ into equation (21), we can estimate the shortening velocity at $t = t_r^+$. The shortening velocity at the next time point $t = t_r + \Delta t$ can be calculated by inserting $L^{(t_r+\Delta t)}$ into equation (21), with $L^{(t_r+\Delta t)} = L^{(t_r^+)} - V^{(t_r^+)} \times \Delta t$. Recursive calculation allows for estimation of the shortening velocity $V^{(t_a)}$ at any measuring time $t = t_a$.

B. Hyperelastic body

To obtain accurate simulation results, the choice of equation (3) for the material property in the finite element method would be appropriate. However, this material is not available in general finite element solvers. From this reason, we defined a nonlinear hyperelastic material property that is widely available in numerous finite element solvers.

Following hyperelestic material that was based on the myocardial tissue experiments from the report of Lin et al[11] was used in this study:

$$W = C_1(e^Q - 1), \quad Q = C_2(I_1 - 3)^2 \tag{23}$$

Note, that I_1 is the first strain invariant. In equations (23), the material property is determined by C_1 and C_2, which directly defines the stress-strain relation.

Fitting equation (3) with the functions given above in a least squares sense, we derived $C_1 = 11.5$ and $C_2 = 5.6$. These values are in the range of the material properties reported by Lin et al.

The FVR was analyzed with the above formulation. The FVR for the different L_{init} and t_r are shown in Fig.4(a), (b). Time steps of $1.0[ms]$ were used for velocity measurement . In Fig.4(a), we can see that the nonlinearity of FVR increases when L_{init} approaches to L_{max}. This results coincides well with the report of Noble et al.[8]. Fig.4(b) shows that the FVR is affected by t_r, and the tangent of FVR becomes

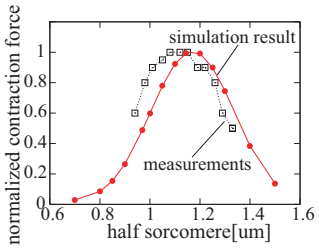


Fig. 5. Simulation result of the force-length relation

flatter when t_r approaches the maximum force generating time. These results agree with the report of Bodem et al.[9]

IV. EXPERIMENTAL RESULTS

A. Experimental conditions

By using above hyperelastic formulation, we performed isometric contraction and instanteneous shortening experiments. The geometrical model of the finite element method was a hexahedral cube of size $1\times1\times1[mm]$. The myocardial cells in a single cube are assumed to align in the same direction. The resting length of the cell L_{init} was $0.97[\mu m]$.

1) Isometric contraction: By fixing the nodal displacement of both ends of the geometrical shape model, we evaluated the force length relation and compared it to the results obtained from physiological experiments with cardiac cells of a guinea pig. The resting length of the physiological experiment was $0.94[\mu m]$.

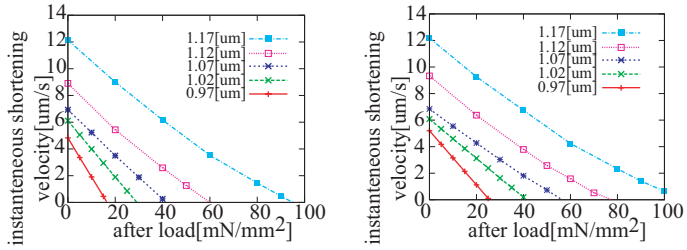
2) Instantaneous shortening: We performed an instantaneous shortening simulation to evaluate the effect of t_r, the interval from the excitation time to the release time, and the initial sarcomere length L_{init} on the FVR.

B. Results

1) Isometric contraction: The experimental results of isometric contraction are shown in Fig.5. The physiological experimental data of the guinea pig are given in the same figure (solid line). Each contraction force is normalized by the peak value. In our simulation model, the peak force was generated with the half sarcomere length at $1.15-1.20[\mu m]$ while in the real experiment, the length was approximately $1.10-1.15[\mu m]$.

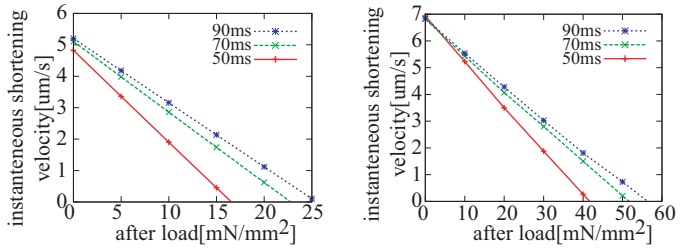
2) Instantaneous shortening: For the assesment of FVR, an average velocity during the period from 1.5[ms] to 2.5[ms] after release was used. The FVRs for different L_{init} with $t_r=50[ms]$ and $90[ms]$ are shown in Figs.6(a)C(b). The FVRs for the different t_r with $L_{init}=0.97[\mu m]$ and $1.02[\mu m]$ are shown in Figs.7(a)C(b).

Figs.6(a), (b), demonstrate that the FVR is affected by L_{init}. The FVR is almost linear for $L_{init}=0.97[\mu m]$ and $1.02[\mu m]$. For isometric contraction, L_{max} in our model was $1.15-1.20[\mu m]$. In the instantaneous shortening experiment, the maximum velocity V_{max} and the maximum contractable load F_0 increase when L_{init} approaches to L_{max}. Similarly, the nonlinearity of FVR increases. These results agree with the reported experimental data by Noble et al.[8]. In Figs.7(a), (b), we show that the FVR is also affected by t_r. When t_r approaches to the time of maximum force generation, the tangent slope of FVR flattens. This results matches the experimental data reported by Bodel et al.[9].



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

Fig. 6. Simulation results of changing L_{init}:(a) $t_r=50[ms]$ and (b) $t_r=90[ms]$.



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

Fig. 7. Simulation results of changing t_r:(a) $L_{init}=0.97[ms]$ and (b) $L_{init}=1.02[ms]$.

V. CONCLUSION

In this study, we showed that nonlinear material property is necessary for reproduction of the nonlinear force velocity relation of the myocardial tissue. We first demonstrated this fact by analyzing the electrophysiological cell model and the mechanical model. The simulation results confirmed our assumption.

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