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An Approximation Model of Myocardial Crossbridge for Weak Coupling Calculation of Left Ventricle Model and Circulation Model

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Abstract— **It is necessary to use complicated myocardial cell model and heart model to evaluate the regional energy production and consumption which leads to the unrealistic computational time. In this research, a left ventricle (LV) simulation model was constructed which includes accurate myocardial cell model. In order to simulate the model in realistic time, we introduced an approximation model of the crossbridge model which can be calculated with weak coupling calculation. The LV model was combined with a circulation model to validate the proposed model by calculating the hemodynamics parameters and ventricular energetics indices. The ESPVR (End Systolic Pressure Volume Relation) showed linear relation, and also the PVA - ATP consumption relation showed linear relation which are widely known as the physiological characteristics of mammalian hearts. From these results, we can say that the model can be used as a model for physiological simulation experiments which are related to the ventricular energetics.**

I. INTRODUCTION

Since many heart diseases are considered to come from the lack of the balance between the energy (ATP) production and consumption, it is very important to evaluate energetics of heart. The computer simulation of heart model with an accurate cell model is expected to be a power tool for such research. However, the computational cost of such model becomes very high since the accurate left ventricle (LV) model constructed from the accurate myocardial cell model and the LV tissue model needs to be calculated by the strong coupling calculation due to their physiological characteristics.

In this research, we propose a LV simulation model which can be used to evaluate regional and global energy production and consumption. The model includes an accurate myocardial cell model. In order to simulate the model in realistic time, we introduced an approximation model of the crossbridge mechanics model which can be calculated by weak coupling calculation.

A circulation model was combined with the model to validate the hemodynamic characteristics of the proposed model by calculating the hemodynamics parameters and ventricular energetics indices. The ESPVR (End Systolic Pressure Volume Relation) showed linear relation and also the PVA - ATP consumption relation showed linear relation which are widely known as the physiological characteristics of mammalian hearts which were difficult to reproduce in previous heart simulation researches.

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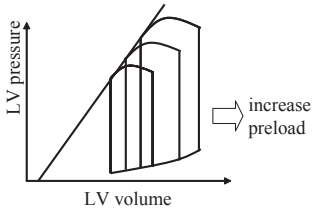

Fig. 1. Pressure volume loop under different preload.

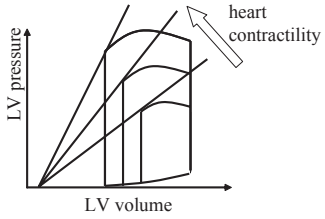

Fig. 2. Pressure volume loop under different heart contractility.

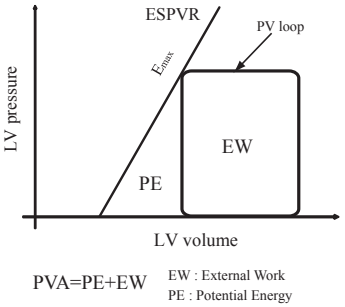

Fig. 3. PV Area (PVA)

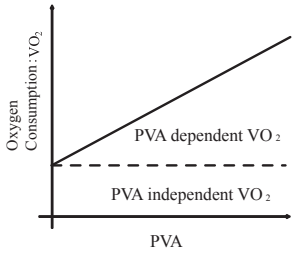

Fig. 4. PVA-VO_2 relation

II. BACKGROUNDS

The pressure volume (PV) loop of LV are widely used to evaluate the heart performance which changes according to the afterload and the preload. The end diastolic pressure increases according to the increase of the preload which results in the increase of the stroke volume (Fig.1). The end systolic pressure increases according to the increase of the afterload which results in the decrease of the stroke volume.

Various PV loops can be obtained by providing various preloads and afterloads. It is widely known that the end systolic pressure volume points of LV distribute on a linear line [1]. This relation is called ESPVR (end-systolic pressure-volume relation) and the angle of this linear line is called E_{max} (maximum elastance). E_{max} is known to increase according to the increase in the heart contractility [1] (Fig.2). The physiological range of E_{max} of excised canine LV is reported to be 4.2 to 10.8[mmHg/ml] by Suga et al. [2]. Sunagawa et al. also reported that the canine E_{max} is 5.4 ± 1.00 [mmHg/ml] [3].

The closed loop area of a PV loop is called external work (EW) which corresponds to the external work of LV. Also the triangle area between an ESPVR and a PV loop is called potential energy (PE). The pressure volume area (PVA) is defined as the sum of EW and PE (Fig.3). PVA

TABLE I

LIST OF THE FUNDAMENTAL MODELS.

Element	Model	Species	Reference
cardiac cell	Kyoto model	guinea pig	[5]
left ventricle	Ring Shape	canine	[6]
tissue material	Mooney-Rivlin	canine	[7]
circulation	Nikos model	canine	[8]

is widely known to be linearly related to the ventricular oxygen consumption (VO_2) from many animal experiments [1] (Fig.4).

III. COUPLING CALCULATION OF LV MODEL AND CIRCULATION MODEL

A. Fundamental models

One of the most accurate myocardial cell model is Kyoto model [5] which is the only model which can calculate ATP consumption and production. Most of the physiological parameters are known to be related with body weight by a special function which is known as the allometric scaling [4]. Since the baseline RR interval of Kyoto model is 400[msec] which is close to the canine RR interval, it is natural to think that the physiological properties of Kyoto model is close to those of canine ones. Therefore, we used Kyoto model as canine cardiac cell model. The fundamental models of the proposed LV model are described in Table I.

B. Calculation scheme of the model.

The contraction model proposed by Negroni and Lascano (NL model) [9] is incorporated in Kyoto model. By denoting the concentration of the crossbridge states that develop force by [TCa*] and [T*], the contraction force F_b is represented by the following equation.

$$F_b = A(L - X)([TCa^*] + [T^*]) \tag{1}$$

Note that $A(= 1800[\mathrm{mN/mm^2}/\mu\mathrm{m}/\mu\mathrm{M}])$ is a constant which represents crossbridge spring constant. L represents half sarcomere length. The term $L-X$ represents the crossbridge elongation where X shortens according to the following equation.

$$dX/dt = B(L - X - h_c) \tag{2}$$

Note that B (=1.2[1/msec]) is a constant which represents crossbridge sliding rate. h_c is a constant.

Parallel elastic component of NL model is represented as follows.

$$F_{p,NL} = K_p(L_0 - L)^5 \tag{3}$$

In the physiological range, this equation can be approximated by the linear elastic component which can easily be modeled by many finite element solvers. Therefore, we used linear elasticity for the parallel elastic component which can be represented as follows.

$$F_p = K_l(L_0 - L) \tag{4}$$

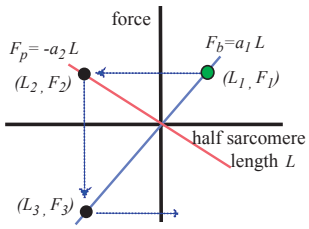

Fig. 5. Resulting sarcomere length and crossbridge force under weak coupling calculation.

Finally, from the following balance equation, we can calculate the sarcomere length i.e. tissue strain.

$$F_b = F_p + F_{ext} \tag{5}$$

Here, the term F_{ext} represents LV tissue stress which is related with LV blood pressure.

There are two types of calculation method in the coupling simulation: one is the strong coupling calculation, and the other is the weak coupling calculation. The strong coupling calculation gives accurate results however, the calculation time becomes large especially in the case of calculating complex simulation model. On the other hand, the calculation time becomes small for weak coupling calculation, however the accuracy of the result becomes low and in some case unstable.

In our model, the calculation step of these two methods can be described as follows.

strong coupling calculation:

$$\begin{aligned} &A(L^{(t_n)} - X^{(t_n)})([TCa^*]^{(t_n)} + [T^*]^{(t_n)}) = \\ &K_l(L_0 - L^{(t_n)}) + F_{ext}^{(t_n)} \end{aligned} \tag{6}$$

weak coupling calculation:

First, calculate contraction force from sarcomere length at time t_{n-1}.

$$F_b^{(t_n)} = A(L^{(t_{n-1})} - X^{(t_n)})([TCa^*]^{(t_n)} + [T^*]^{(t_n)}) \tag{7}$$

Then, calculate sarcomere length at time t_n.

$$F_b^{(t_n)} = K_l(L_0 - L^{(t_n)}) + F_{ext}^{(t_n)} \tag{8}$$

In the coupling calculation of a LV model and a circulation model, the weak coupling calculation is known to become unstable in some case. Therefore, strong coupling calculation is used in most case.

C. Condition of unstable calculation

Here, the condition of the unstability in the weak coupling calculation of NL model and the LV model is analyzed. For the simplicity, we only consider NL model and the LV mechanical model in this analysis.

The contraction force of NL model is described by equation (1) and the tissue passive force is described by equation (4). By denoting $a_1 = A([TCa^*] + [T^*])(a_1 > 0)$ and $a_2 = K_l(a_2 > 0)$, both forces can be denoted as follows.

$$F_b = a_1 L,\ F_p = -a_2 L \tag{9}$$

Here we assume that the half sarcomere length and the contraction force at time $t = 1$ be denoted as L_1, F_1. In the weak coupling calculation, the half sarcomere length at time $t = 2$ (L_2) is calculated from F_1 and the equation $F_p = -a_2 L_2$. Using this length, the contraction force at time $t = 2$ (F_2) is calculated from equation $F_2 = a_1 L_2$. By iterating these steps, the track of the half sarcomere length and the contraction force becomes as in Fig.5.

$$\begin{aligned}
(L_1, F_1) &= (L_1, a_1 L_1) \\
(L_2, F_2) &= (-a_1/a_2 L_1, a_1 L_1) \\
(L_3, F_3) &= (-a_1/a_2 L_1, -a_1^2 L_1) \\
&\vdots \\
(L_n, F_n) &= \begin{cases} \left((-a_1/a_2)^{n-1} L_1, (-a_1/a_2)^{n-1} a_1 L_1\right) \\ \qquad\qquad (n : odd) \\ \left((-a_1/a_2)^{n} L_1, (-a_1/a_2)^{n-1} a_1 L_1\right) \\ \qquad\qquad (n : even) \end{cases}
\end{aligned} \tag{10}$$

From this result, we can find that the weak coupling calculation becomes unstable if $\dfrac{a_1}{a_2} > 1 \Leftrightarrow a_1 > a_2$ which means that if the contraction force becomes larger than the tissue passive force, the calculation becomes unstable.

IV. Stable weak coupling calculation by the crossbridge approximation model

A. Approximation model

The weak coupling calculation is effective for reducing the computational time, however, the accuracy of the calculation results become low and in the myocardial cell and LV tissue coupling, the calculation becomes unstable. To overcome this problem, we propose a crossbridge approximation model.

In the force calculation equation (equation (1)), X changes according to equation (2). From these equations, X can be recognized as the first order delay variable of L. Note that by denoting the input signal as e, output signal as y, Laplace transformed variables of e and y as $E(s)$ and $Y(s)$, the first order delay system can be denoted as follows.

$$G(s) = Y(s)/E(s) = K\frac{1}{1+Ts} \tag{11}$$

Here, K is called the gain, T is called the time constant. By the inverse Laplace transformation, equation (11) is transformed into following equation.

$$y + T\frac{dy}{dt} = Ke \Leftrightarrow \frac{dy}{dt} = \frac{Ke - y}{T} \tag{12}$$

If we consider $e = L - h_c$, $y = X$, $K = 1$ and $T = 1/B$, then equation (2) becomes equivalent to equation (12).

Since this first order delay system is stable in weak calculation, we construct a crossbridge approximation model with this formulation. Here we replace $L - X$ in equation (1) by the constant h_c, and the number of crossbridge is calculated by the following first order delay system.

$$F_b = A \cdot h_c \cdot y \tag{13}$$

Here, y satisfies the following equation.

$$\frac{dy}{dt} = \frac{[TCa^*] + [T^*] - y}{T} \tag{14}$$

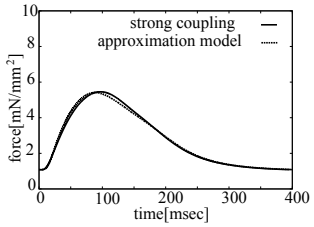

Fig. 6. Isotonic (noload) contraction.

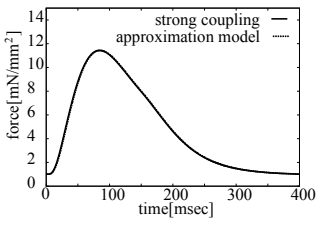

Fig. 7. Isometric contraction.

In the case of the isometric (fixed cell length) condition, the sarcomere length is fixed ($L = \text{const}$). In this case, the developed force is proportional to the number of crossbridge that means there is no delay in contraction force compared to the number of crossbridge.

To reproduce above characteristics, the time constant T is defined to be proportional to the sarcomere length change as follows.

$$T = \alpha|dL/dt| + \beta \tag{15}$$

Note that β was set to a small number compared to the maximum value of $\alpha|dL/dt|$.

B. Experimental results of the approximation model

Resulting developed force of the isotonic (free contraction) and the isometric condition with the strong coupling and the weak coupling with the proposed approximation model are presented in Fig.6 and Fig.7, respectively. The difference in the resulting total ATP consumption of both models were less than 1 %. From these results, we can say that the accuracy of the weak coupling calculation result for the approximation model is very high.

V. Experimental results

Pressure volume loop and the ATP consumption were evaluated for the proposed model by providing different preload and afterload values.

We used a ring shaped finite element model for the LV model which has 80 elements in the circumferential direction and 5 layers in the transmural direction. The myocardial cells are aligned with the circumferential direction. The LV volume was assumed to be proportional to the inner area of the ring where the end-diastolic volume was set to be 54[ml] according to the physiological value [6]. We used the Mooney-Rivlin material for the tissue where the corresponding Young's modulus was set to be 50[kPa]. The distribution of the cellular excitation time was determined by calculating the excitation propagation model with the same LV model.

The aortic compliance (C) was set to 0.25[ml/mmHg], and the characteristic impedance (R) was set to 2000, 3000, 4000 [mmHg·msec/ml] according to the published physiological values [8]. The preload (E_v) was set to 4.0, 7.0, 10.0[mmHg] according to the published physiological values [10]. 10 heart cycles were calculated with the model and the result of the last cycle was evaluated. The calculation time step

TABLE II

RESULTING HEMODYNAMIC PARAMETERS.

Variable	Target	Simulation results
HR(bpm)	115-150	150
LVEDV(ml)	42-65	53
LVEDP(mmHg)	3.6-16.1	4-10
LVESV(ml)	21-40	43.7-48.4
LVESP(mmHg)	69-110	43.9-65.1

HR:Heart rate, LVEDV:left ventricular end-diastolic volume, LVEDP:left ventricular end-diastolic pressure, LVESV:left ventricular end-systolic volume, LVESP:left ventricular end-systolic pressure

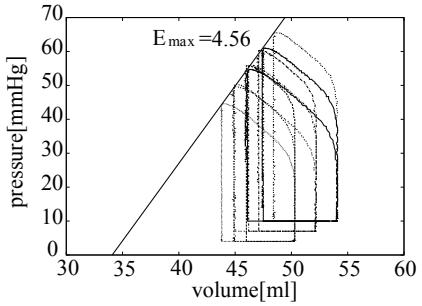

Fig. 8. Resulting pressure volume loop under 9 preload and afterload.

TABLE III

ATP CONSUMPTION AND AREA OF PRESSURE VOLUME LOOP.

pre-load	after-load	ATP_{CB}	ATP_{other}	ATP_{total}	EW	PE	PVA
4.0	2000	22.9	37.0	59.9	206	186	407
4.0	3000	24.3	37.0	61.3	219	213	449
4.0	4000	25.5	37.0	62.5	250	255	497
7.0	2000	24.7	37.0	61.7	221	231	476
7.0	3000	26.5	37.0	63.5	263	292	537
7.0	4000	27.7	37.0	64.7	273	313	572
10.0	2000	26.5	37.0	63.5	262	275	535
10.0	3000	28.4	37.0	65.4	281	323	595
10.0	4000	29.8	37.0	66.8	282	370	643

Units: preload, [mmHg]; afterload, [mmHg·msec/ml]; ATP, [mM]; EW, PE, PVA, [ml·mmHg].

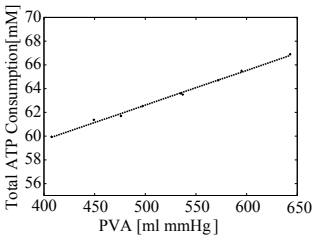

Fig. 9. Resulting relation between PVA and total ATP consumption.

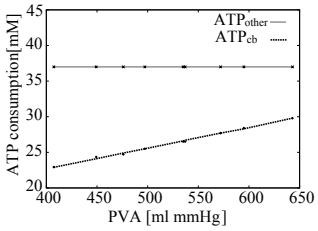

Fig. 10. Resulting relation between PVA and ATP consumptions in cross-bridge and other components.

was 0.1[msec], and the total calculation time with IBM p690 (96CPU, PowerPC 1.5GHz) was about 60 min.

Resulting hemodynamic parameters are presented in Table II with the published experimental values [6][2][10]. Corresponding pressure volume loops are presented in Figure 8. From this result, we can recognize that all the end-systolic pressure volume point coincide in single line where R^2 was 0.989. Corresponding E_{max} was 4.56[mmHg/ml] for these results.

In Kyoto Model, ATP consumption is calculated at the crossbridge and the ion transporters. Here we define ATP_{CB} as the ATP consumption at the crossbridge, and ATP_{other} as the ATP consumption at the ion transporters. Resulting ATP consumption and EW, PE and PVA for different afterloads and preloads are presented in Table III. The relation between PVA and the total ATP consumption is presented in Fig.9. Also the relation between PVA and ATP_{CB}, ATP_{other} are presented in Fig.10. From these results we can recognize that only the crossbridge ATP consumption is linearly related to PVA. Note that there is no clear relation between the total ATP consumption and EW or PE.

VI. CONCLUSIONS

We proposed an approximation model of the crossbridge model which can be stably calculated by the weak coupling calculation. From the experimental results, the model showed very good agreement with the animal experimental results.

The results show that the model can be used for evaluating the energetics of heart. The results imply that the mechanism of the linear relation between PVA and ATP consumption is not simple since the relation between the PVA and EW or PE are not linear. The analysis of this relation is the important future work.

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