An iterated map model with CaMKII feedback in modeling the force frequency relationship of a cardiac cell

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Received 10 July 2022; Revised 22 August 2022; Accepted 10 October 2022; Published 28 October 2022.
DOI: https://doi.org/10.54939/1859-1043.j.mst.82.2022.142-149

ABSTRACT

Experiment data on isolated rat hearts shows that the transient behaviors after switching pacing intervals are very complicated with increasing, decreasing, and rebound of the contraction force. The strength of contraction in the heart muscle is strongly related to intracellular free Ca2+ mediated by an action potential. This behavior can be explained by calcium cycling inside the excitable cardiac myocytes coupled with their action potential. The previous and recently proposed models can only explain a short period of time after changing the pacing frequency. Our aim is to develop a simple feedback model based on the role of the enzyme CaMKII to describe the whole dynamic picture captured from experiments.

Keywords: Cardiac myocyte; Feedback; Rat heart; CaMKII; Calcium.

1. INTRODUCTION

A cardiac myocyte model is an important tool for researchers due to the fact that it allows them to study the human heart in a controlled environment. The cardiac model is also useful for studying cardiac arrhythmias, drug effects, and other cardiac functions & conditions. Another potential use for the myocyte model is in the development of new cardiac treatments to see how well new treatments would affect the heart's cells [1-3]. Despite the potential uses of the myocyte models, it is not perfect and needs to be improved over time.

There are lots of cardiac cell models for different types of cardiac cells, types of animal and human [4]. Some of them are rather simple with few variables, such as the action potential duration model Fitz Hugh-Nagumo model [5, 6]; however, most of the present models are complicated with many variables and parameters. Also, models can be classified as detailed ionic models [7, 8] and discrete map models [9, 10]. In fact, the discrete map model is the simplification of the detailed ionic model, where the variables are averaging over one period (1 heartbeat) of which in the detailed ionic model [9].

In heart cell activities, cardiac excitation-contraction coupling (E-C coupling) is one of the most important processes for the heart's contraction and relaxation [11, 12]. It involves a series of complex signaling pathways in which many proteins play an essential role in the E-C coupling process, such as myosin, actin, troponin, calmodulin, etc. [11-13]. Ca2+/calmodulin dependent protein kinase II (CaMKII), which is activated by calcium (Ca2+), plays an important role in the regulation of these signal transduction pathways in cardiomyocytes. However, the role of this enzyme was not considered carefully in the previous models.

In isolated rat heat experiments, after switching the pacing rate, the transient behaviors of the contractile force are quite complicated and cannot be explained by present cardiac cell models [4, 7-9]. The earlier models can only account for a small number of beats following a step shift in

frequency and steady state. For instance, the transient behaviors between the first beat and the first few hundred beats following a frequency change have never been taken into account [7-9]. The transient response to a step change of pacing interval (inverse of pacing rate) is always accompanied by transient changes in contractile force and in [Ca2+]i signaling [14-16], which has been less considered. It is also well known that the cardiac contractile force, in a wide range of normal activity, is linearly proportional to the free Ca2+ concentration inside the cell [11]. That's why, in this work, we work with Ca2+ concentration instead of pressure (or contractile force).

In this study, to explain our experimental findings, we propose a new map model feedback for the transient behaviors based on the role of calcium/calmodulin-dependent protein kinase phosphatase (CaMKII). The CaMKII target in this model is release-reuptake processes which then affect the interplay between ionic currents and intracellular [Ca2+]. Our new study says it has been found to be adequate to explain well observations in experiments of isolated rat hearts.

2. MODEL

The model that we developed here is basically based on the iterated map model proposed by Qu and Shiferaw [9]. The map model is a simplification of a detailed ionic model, in which every variable in the map averages over one period (1 heartbeat) of the detailed ionic model. Schematically, the cardiac cell model is given in figure 1(A), and the discrete variables for the model are shown in figure 1(B).

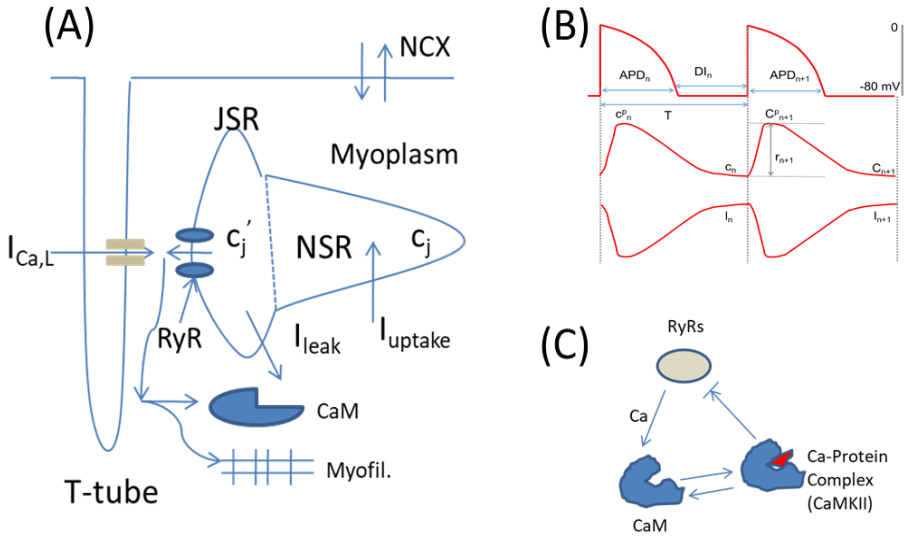

Figure 1. *(A) Schematic illustration of cardiac cell with electrical contraction coupling, in which $I_{Ca,L}$ represents L-type Ca current; NCX represents Na-Ca exchange; SR represents sarcoplasmic reticulum- the Ca2+ stored inside the cell (divided into SR is divided into two small compartments, named by network SR (NSR) and junctional SR (JSR) that contain the release unit RyRs); RyR represents ryanodine receptors of SR Ca release channels; SERCA represents sarcoplasmic-endoplasmic reticulum Ca ATPase or SR Ca uptake pump; CaM represents Ca2+/calmodulin dependent protein kinase. (B) Variable definitions: APD, DI, and stimulation period T; diastolic Ca (cn, cnp) at the end of each beat, peak cytoplasmic Ca (cp), and Ca released (r) from the SR and SR Ca load (l) at the end of each beat, illustrated for the n^{th} and $(n+1)^{th}$ beat. (C) Simple illustration of the formation and regulation of CaMKII.*

Briefly, the electrical-chemical process in one cycle (one period) works as follows: the first is excitation, the depolarization of plasma membrane voltage rising, that triggers the opening of the membrane L-type calcium channel in the T-tube for calcium ion flowing into the cell. This influx

of calcium will trigger to open the RyRs, the release units of SR (sarcoplasmic reticulum) calcium store, then large amounts of calcium from the SR store are released into cytosol (the environment inside the cardiac cell). These calcium ions, including influx calcium from L-type calcium channels, go through myofilament (the contraction unit) to cause contraction. After contraction, the calcium is released from the myofilament, then a large amount (70-90%) is pumped back to SR, and the other is sent to the outside cardiac cell through some ways (Na-Ca exchange, potassium pump, …) [9, 11, 12]. The flow of calcium is represented by arrows in figure 1(A). Our improvement in the model is that a small amount of calcium is bound to Ca2+/calmodulin dependent protein kinase (CaM) to form an active CaMKII as graphically shown in figure 1(A) and 1(C).

The governed equations of this model are given by:

$$\begin{cases} a_{n+1} = f(d_n) + p(c_{n+1}^p)a_n \\ l_{n+1} = l_n + q(d_n)g(l_n)F(CM_n) + u(T)h(c_{n+1}^p) \\ b_{n+1} = b_n + \eta(a_{n+1} - a_n) - \kappa[c_n - c(T)] \end{cases} \quad (1)$$

where, $c_{n+1}^p = c_n + q(d_n)g(l_n)$. For more details and explanations of this model, please see [9].

This model and other present models give rich dynamics of the complexity of the heart system. However, they all failed to explain the transient dynamics after step pacing in an isolated rat heart. That is the main reason for us to develop the model to involve the role of CaMKII, this enzyme is activated by and sensitive to the concentration of Ca2+. Ca2+/calmodulin dependent protein kinase II (CaMKII) targets many processes and units inside the cardiac myocyte, such as [11, 13]. However, in this work, the role of Ca2+ release from SR is the most important process that affects the contraction of myofilament (then the cell); we only focus on the role of CaMKII in regulating RyRs (Ryanodine receptor – Release unit) – the Ca2+ release unit of the Ca2+ store SR. The formation and dissociation and the regulating role of CaMKII are presented graphically in figure 1(C). Normally, if too much Ca2+ is released, then the enzyme is highly activated. This tends to negatively regulate back to RyRs to reduce the release. On the other hand, if too small amounts of Ca2+ are released from RyRs, then the low-activated enzyme will signal to RyRs to enhance the release of Ca2+. In the model, the calcium release at beat $(n+1)^{th}$ is represented by q(dn)g(ln), then the target of the CaMKII regulation will be this term.

The improved model is given by the following equations:

$$\begin{cases} a_{n+1} = f(d_n) + p(c_{n+1}^p)a_n \\ l_{n+1} = l_n + q(d_n)g(l_n)F(CM_n) + u(T)h(c_{n+1}^p) \\ b_{n+1} = b_n + \eta(a_{n+1} - a_n) - \kappa[c_n - c(T)] \\ CM_{n+1} = CM_n + \xi[r_{n+1} - r_0(T)] \end{cases} \quad (2)$$

The CaMKII concentration at beat n^{th} is denoted by CMn. The change in time of this quantity is given by the last equation of the Eqs. (2) above, where the new complex is formed if the Ca2+ release is larger than the steady state release at pacing interval T, and vice versa, part of the complex will be dissolved.

The regulating effect of CaMKII to RyRs is shown in the second equation of Eqs. (2) through a function $F(CM_n)$ of the form:

$$F(CM_n) = e^{-\varsigma(CM_n - CM_0)} \quad (3)$$

In which ς is the regulating parameter, and CM_0 is the concentration of the complex at the steady state.

In fact, the last equation of Eqs. (2) makes some change to the free calcium (Ca2+ free) during release r_{n+1}; however, with the choice of very small parameter ζ, the amount of Ca2+ bound with CaM to form CaMKII active is relatively small in comparison to calcium release. We can consider this as a small perturbation.

3. RESULTS AND DISCUSSION

3.1. Experimental data in isolated rat hearts

In order to keep the heart alive for 6 - 10 hours, the rat heart is taken out from its body and placed in the Langendorff system, using Krebs-Henseleit solution (a solution of nutrition and artificial oxygen at 37 ^{o}C.). For more details about the setup and data measurements in experiments, see [17, 18]. The rat heart was studied for 2 - 4 hours while it was still in healthy condition.

In order to use and compare with the iterated map model, the experimental data is processed to obtain peaks of left ventricular pressure (LVP), then we have LVPmax (denoted by P) – now we will work with the beat number. After that, LVPmax is rescaled and normalized to a dimensionless unit in the range from -1 to 1 by the formula $P_{rescaled}(n) = \left(P(n) - P_{SS}\right) / |P_1 - P_{SS}|$, where P(n) is the peak of LVP at beat number n^{th}, P_{ss} is the steady state value of P, P_1 is the pressure of the first beat after switching pacing interval.

Some novel and important findings are presented below: Figure 1 shows the time course of the transient response to step pacing in an isolated rat heart. Figure 2 shows the rescaled LVPmax for different step changes in pacing intervals (10%, 20%, and 30% of the initial pacing interval). Figure 3 shows the normalized LVPmax change (Pex-P1) vs. Period difference (ΔT = T0-T0), where T0 is the initial pacing interval, and T is the interval after switching. We can see that these quantities.

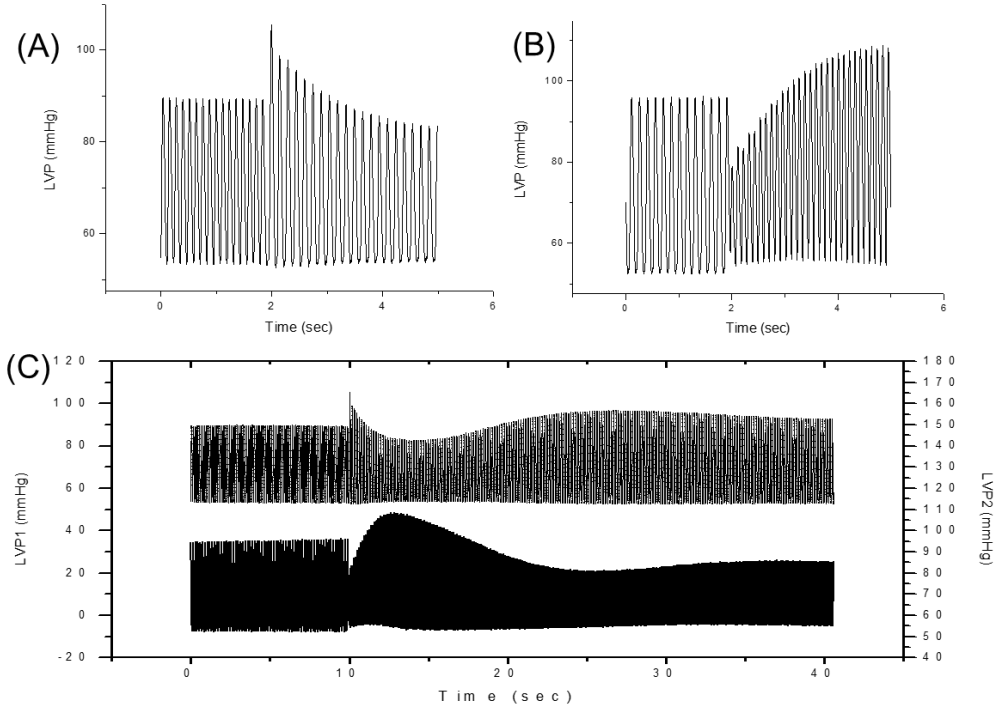

Figure 2. *Time course of the transient response to the step pacing in isolated rat heart. (A) The short period of time for step increasing of pacing interval from 150 ms to 195 ms; (B) for decreasing the pacing interval from 150 ms to 105 ms; and (C) shown for a longer time to see more characteristics. All subfigures: the x-axis is time in seconds (s), and the y-axis represents left ventricular pressure in mmHg.*

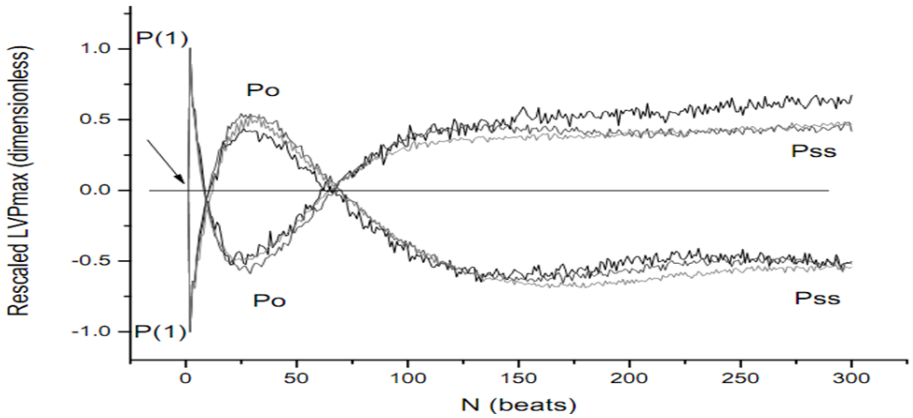

Figure 3. *In this graph, the rescale LVPmax for a different step change in pacing intervals (10%, 20%, and 30% of initial pacing interval); the x-axis is the discrete time in terms of beat number N.*

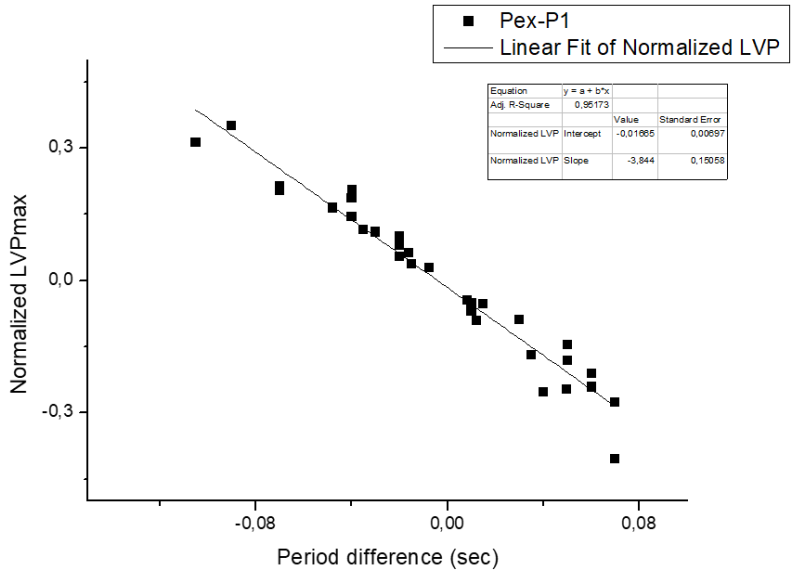

Figure 4. *Normalized LVPmax vs. Period different ΔT. The filled square dots are the difference between the maximum/minimum of the LVPmax (Pex or P_0 in figure 3) and the rescale LVPmax at the first beat after switching pacing P_1.*

3.2. Numerical results of the improved model

The numerical results of our improved model with CaMKII regulation are computed with the set of parameters that are chosen for small hearts like the rat heart [9].

Figure 5 is the numerical computation for the original Qu-Shiferaw 2007 model [9]. In comparison to the experimental results in figure 3, there is no agreement between the model and experiment. The rescaled calcium for contraction curves shows a simple monotonic increasing/decreasing behavior, then saturating more than 50 beats after switching the pacing interval.

The experimental results for different step pacing intervals in figure 3 are reproduced in figure 6 with our improved model. In both experiments and the model, the step change of pacing intervals is respectively +/- 10%, +/- 20%, and +/- 30% of the initial pacing interval of 150 ms. CaMKII regulation parameters are ζ=0.01, ς=0.06, which means just 1% of the change in calcium release each cycle is bound to CaM to form active CaMKII. By comparing figure 3 and figure 6, it is clear that the model results are fitted very well with the experiments.

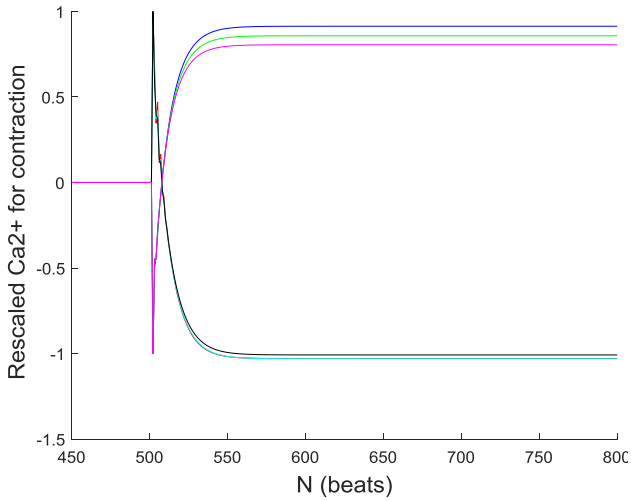

Figure 5. *Numerical computation for original Qu-Shiferaw model. The X-axis is discrete time in beats, the y-axis is the rescaled Ca2+ for contraction, which is proportional to contractile force or rescale LVPmax. The pacing interval is switched at beat 500th.*

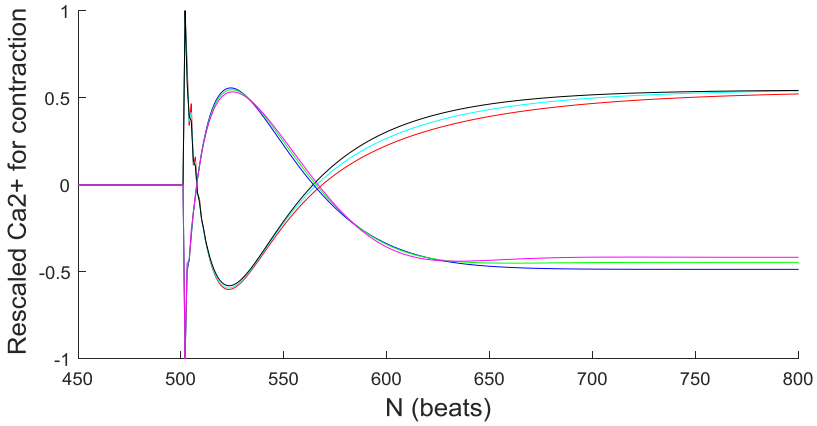

Figure 6. *Numerical computation for our improved model with CaMKII regulation. Axes' properties are the same as in figure 5.*

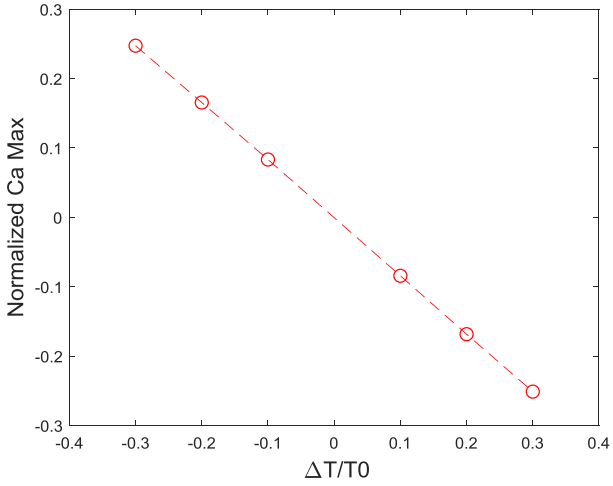

Figure 7. *Normalized rescaled CaMax vs. relative period different $\Delta T/T_0$.*

Another result is shown here in figure 7, which is the difference between rescaled Ca2+ extreme (min/max) and the rescaled Ca2+ of the first beat after switching the pacing interval. In comparison to the experimental data in figure 4, we can see there is good agreement between the model result and the experimental result.

4. CONCLUSIONS

Our improved iterated map model is adequate in explaining the complicated, slow, non-monotonic response of the contractile force in isolated rat hearts. Our discovery is novel and has yet to be replicated by existing models. The integration of the regulatory role of CaMKII in cardiac myocyte models has been less considered so far. More and more experimental evidence shows that they cannot be explained by previous models without CaMKII regulation.

However, our model has some limitations. First, the CaMKII regulation target is only RyRs – the release unit of SR store, while the enzyme CaMKII has multiple targets such as calcium uptake (back to SR store), L-type calcium channel, NCX exchange, etc. Second, the model is a single cell model and assuming that all of the contractile cells in the ventricle are synchronized very well, then we can use the single cell model for the whole heart mode. Despite the limitation, our improved model with CaMKII regulation is very good in explaining experiments in isolated rat hearts. Further experiments on different animals need to be carried out to verify this model. Also, the future development of this model is necessary to take into account other CaMKII regulation targets.

Acknowledgment: *This research is funded by Graduate University of Science and Technology, Vietnam Academy of Science and Technology, under grant code number: GUST.STS.ĐT2020-VL04.*

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TÓM TẮT

Mô hình tế bào tim gián đoạn tích hợp phản hồi CaMKII trong mô phỏng quan hệ tần số với lực co bóp cơ tim

Dữ liệu đo từ thí nghiệm trên tim chuột bị cô lập, sau khi thay đổi đột ngột nhịp tim, cho thấy các phản ứng nhất thời không đơn điệu phức tạp với việc tăng, giảm (giảm/tăng) và phục hồi của lực co bóp. Hoạt động co bóp của cơ tim liên quan chặt chẽ đến ion Ca2 + tự do trong nội bào, được điều chỉnh bởi hiệu điện thế hoạt động xuyên màng. Các biểu hiện này có thể được giải thích bởi chu trình canxi bên trong các tế bào tim trong mối liên hệ hữu cơ với điện thế hoạt động xuyên màng của chúng. Các mô hình tế bào tim cho đến nay chỉ có thể giải thích một khoảng thời gian ngắn, khoảng 20 nhịp tim, sau khi thay đổi tần số nhịp đập. Trong nghiên cứu này, chúng tôi là phát triển một mô hình tế bào tim đơn giản tích hợp phản hồi, dựa trên vai trò điều khiển của enzyme CaMKII để mô tả hầu hết các hiện tượng thu được từ thực nghiệm.

Từ khóa: Tế bào tim; Phản hồi; Tim chuột; Hoạt chất CaMKII; Ion can-xi.