Modeling of Human Myocyte Active Contraction: A Review

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Abstract: The paper presents the mathematical modeling of the excitation contraction phenomena in single cardiac cells. Particular emphasis was placed on three models: the Hill model, the Huxley model and the Land model. Further literature was reviewed concerning the mathematical modeling of the myocyte cardiac cells. This included the Hunter model, which presented the passive active mechanics of the cardiac muscle suitable for use in the continuum mechanics models of the entire heart; the Rice Filament model, which approximated the activation and generation of force in cardiac myofilaments and; Vasileiou’s work, which described the coupling between mechanical contraction and electrical excitation in cardiac cells. As a starting point, descriptions of fundamental models were obtained along with their underlying mathematical modelling describing the processes behind excitation and contraction in cardiac cells. The Hill model representing muscle behavior, as well as the Hodgkin-Huxley model representing excitation, are fully considered due to their significance in mathematical physiology literature and as the basis for many models of cells.

Keywords: Human myocyte, mathematical modeling, cardiac cell,

1. Introduction

The active contraction of the myocyte is crucial for the pumping functionality of the heart. The activities involved in the active contraction of the cardiac muscle are complex, hence require the development of mathematical models. The mathematical models developed for the active contraction of the myocyte provide a unique technique for integrating many pathways in order to understand its contraction mechanisms. In addition, mathematical modelling can also shed light on the cardiac function at an organ level [1]. In this work, we will focus on the mathematical modeling of the active contraction of the cardiac myocyte cells.

Mathematical and computational modelling have long played a key role in understanding the physiology of the heart. Researchers have developed various models of myocyte contraction in the cardiac muscles, such as the Hill model and the Huxley model [2]. A recent example is that developed by Land et al [3], in which they described the development of a cardiac contraction model based on novel measurements of tension development in human cardiomyocytes. In their study, experimental data from human cardiac myocytes at body temperature were used, and they further embedded their myocyte contraction model into a whole-organ pump function.

The Land model includes troponin C kinetics, tropomyosin kinetics, and a three- state crossbridge model that accounts for the distortion of cross bridges, as well as the cellular viscoelastic response. Each component is parameterized using experimental data collected in human cardiomyocytes at body temperature [3]. The study further revises the model of tension generation in the skinned isolated myocyte, to replicate reported tension traces generated in intact muscle during isometric tension and to provide a model of human tension generation in multi-scale simulations. This process requires changes to calcium sensitivity, cooperatively, and crossbridge transition rates, the model is further applied within multi-scale simulations of biventricular cardiac function, and they refined the parameterization within the whole organ context, with the purpose of obtaining a healthy ejection fraction [8]. This process reveals that crossbridge cycling rates differ between skinned myocytes and intact myocytes. The mathematical models studied in this work can be used to analyze other behaviors of myocyte cells.

2. Background of Myocyte Active Contraction

The heart is one of the main organs in the body which facilitates various processes for the effective functioning of the body, as shown in Fig. 1. It is, however, one of the simplest organs in the human body because its function involves the pumping of blood to different parts of the body through expansions and contractions of its muscles [4]. The contraction and expansion of the human heart are estimated to occur 2.5 billion times in a human
lifetime; a mechanical or electrical failure of the heart could lead to either death or slowed biological activities in the body. Electrical signals spread from the sinoatrial node using the bundle of His and Purkinje network. Purkinje network has its ends connected to the endocardium on the ventricles. From these connections, an electrical signal can spread using the myocardium [2]. This is the muscle tissue which is the main substance in the heart walls leading heart contraction. It is, therefore, essential to examine the mechanism of the cardiac muscles through the creation of a mathematical model to allow efficient analysis.

Figure 1: General heart anatomy, cited from [8].

2.1 Cardiac Muscle Cells (Myocyte)

The cardiac muscle cells are also known as the cardiac myocytes; they are the muscle cells which make up the cardiac muscle. The cells measure about 100 – 150 µm long and 15 – 20 µm in diameter. The muscle cells have the capability to translate the electrical signals into mechanical contraction. In this work, the primary focus is on cardiac muscle cells. These are cells whose contraction makes it possible for the heart to pump blood, and have two main functional properties [2]. These properties are electric excitability and mechanical contractility.

The voltage-gated Ca$^+$ channels (see Fig. 2) are opened through action potential, making it possible for the Ca$^+$ to enter into the cell. This leads to an additional release of the Ca$^+$ from the sarcoplasmic Reticulum, passing through the ryanodine receptors [3]. The high Ca$^+$ concentration helps in transforming the myofilaments structure, which makes it possible for the thick filament to bind and tag on the thin filament, and leads to muscle contraction. This Ca$^+$ driven alteration of an electrical stimulus into mechanical force is what is known as the excitation-contraction coupling, as shown in Fig. 2 [1].

This muscle cell is composed of myofibrils, which are made up of myofilaments. The myofibrils further contain repeating microanatomic units referred as sarcomeres, which represent the core contractile units of the cardiac myocyte. The sarcomere is the region of myofilament structures between two Z-lines, and the distance between Z-lines (i.e., sarcomere length) ranges from about 1.6 to 2.2 µm. The sarcomere is composed of thick and thin filaments [5]. Chemical and physical interactions between the actin and myosin cause the sarcomere to shorten, and therefore the myocyte

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contracts during the process of excitation-contraction coupling.

2.2 Sliding Filament Theory

The interactions between actin and myosin serve as the basis for the sliding filament theory of muscle contraction. The mechanism of the cardiac muscle cells in humans is similar to the nerve cells in terms of conducting action potentials along the surfaces of the membranes. However, muscle cells tend to convert the electrical signals into mechanical actions of contraction and expansion to facilitate the pumping action of the heart. Myocyte contraction is a complex process which involves activation of ionic currents, including L-type Ca$^{2+}$ current, through which Ca$^{2+}$ enters the cell and causes Ca$^{2+}$ release from the intracellular Ca$^{2+}$ store, the sarcoplasmic reticulum [2].

![Figure 2: Ca$^{2+}$ transport in ventricular myocytes. The plot depicts the time course of the action potential, Ca$^{2+}$ transient, and contraction, cited from [6].](image1)

![Figure 3: The myofibril structure, cited from [6].](image2)
The cardiomyocyte is composed of myofilbr bundles containing sarcomeres, the contractile cell units, consisting of thick and thin myofilaments, myosin and actin proteins, as shown in Fig. 3. At the micro scale, the exchange of calcium between cytosol and the sarcoplasmic reticulum influence the interaction of these myofilaments, and which onsets the shortening of the sarcomeres and drives the process of excitation contraction of the whole cardiac cell [6]. During excitation, the depolarization of the sarcolemma induces the influx of extracellular calcium into the cardiomyocytes; the increase of intracellular calcium acts as the main role in the cardiac electrical activity and leads to contraction of the cardiac myocytes [10], and this section will review existing literature concerning the mathematical modeling of the myocyte cardiac cells of the human heart during active contraction. Numerous mathematical models of human skeletal muscles have been developed. However, none of them have been adopted generally and each of them is applicable to a specific purpose. Mathematical models form a basis for understanding the functions and interactions in the heart and make it possible to simulate experiments that are not feasible otherwise with current measurement technologies.

2.3 Myocyte Contraction Modelling

Various research has been conducted in order to develop a mathematical model of the active contraction of the cardiac myocytes [10], and it was implicitly included by assuming that cross-bridges exist from the myoplasm and outside the cells through the sarcolemma [6]. During excitation, the depolarization of the sarcolemma induces the influx of extracellular calcium into the cardiomyocytes; the increase of intracellular calcium induces more Ca$^{2+}$ to be released from the sarcoplasmic reticulum; cytosolic Ca$^{2+}$ ions bind to troponin-C and activate the myofilaments [7].

The thin filaments are made up of three proteins which are actin, troponin and troponymosin. Each actin has a single myosin binding site. During contraction, myosin heads form a crossbridge with the actin, the main contractile elements in a muscle [9]. Contraction occurs when the cross-bridges bind and creates a force which causes the thin filaments to slide along the thick filaments. The cross-bridges cycling acts as the basis for movement and force generation in the myocyte. The basic cross-bridges muscle contraction cycle is represented in Fig. 4, and the following is a basic description of the cycle:

- Active site on actin is exposed as Ca$^{2+}$ binds to the troponin.
- The myosin heads make a cross-bridges with actin.
- The myosin head bends in the event of the power stroke with ADP and phosphate being released.
- A new ATP molecule joins to the myosin head leading to the cross-bridges detaching.
- ATP is hydrolysed to become the ADP and phosphate. This returns the myosin to a grounded position.

![Figure 4: The cross bridge contraction cycle](image)

Excitation-contraction coupling in the heart is defined as a process in which electrical stimulus is changed into a muscle contraction. The Ca$^{2+}$ plays a major role in the cardiac electrical activity and acts as the activator of myofilaments leading to contraction. The T tubule is depolarized through action potential and leads to the L-type Ca$^{2+}$ opening. This leads to the inward Ca$^{2+}$ current ICa flowing through. Ca$^{2+}$, which goes into cells, leads to release of the additional Ca$^{2+}$ through the ryanodine receptors RyR. This is through the Ca$^{2+}$-induced Ca$^{2+}$ release, CICR. The Ca$^{2+}$ spreads and binds the myofilaments. The spread is through the myoplasm which leads to contraction. Finally, the Ca$^{2+}$ exists from the myoplasm and outside the cells through ATP.

To create the quantitative model of a cross-bridges binding, it is vital to know the number of actin binding sites which are available in a single cross-bridge. The main assumptions to be made are whether the cross-bridges has a single available site, or an endless array of available sites for binding.

The Hill and Huxley models are two of the core mathematical models for the muscle. The Hill model, which was developed in 1938, is limited by its inability to provide an accurate description of the behavior of all parameters of the muscle. As such, the Hill model is based on the elastic and contractile elements only. However, the Hill equation is used in the development and analysis of other muscle models. The Huxley model is purely based on the kinetics of the cross-bridges and forms the basis for many models of muscle behavior. The Huxley model considered dynamics of the filaments within muscle and the probability of establishing cross-bridges. The distribution function $n(x,t)$ described the distribution of attached cross-bridges, i.e. the rate of connections between myosin heads and actin $f_i$ is, as a function of cross-bridge length $x$. The force dependence on velocity is implicitly included by assuming that cross-bridge attachment and detachment are time-dependent processes. The Huxley model produced a more accurate analysis of the active contraction of the cardiac muscles, compared to the Hill model. However, the accuracy of the Huxley model is limited by various assumptions, made by Huxley during its development.

Early empirical models of cardiac muscle mechanics were modified versions of the skeletal muscle models of Hill [1], which combined a contractile element obeying a hyperbolic force-velocity relation, a passive series elastic element and a passive parallel...
elastic element. The Hunter model was developed in 1999 by Hunter et al [11], and presented the passive active mechanics of the cardiac muscle suitable for use in the continuum mechanics models of the entire heart. The model is based on an extensive review of experimental data from a variety of preparations and species, at temperatures from 20 to 27 degrees. Experimental tests included isometric tension development, isotonic loading, quick-release, length step and sinusoidal perturbations. The model, however, deals only with the rather limited range of experimental tests available at that time.

The Rice Filament model was developed by Rice et al [12], and was based on the Huxley model of the cardiac muscles. The Rice Filament model approximated the activation and generation of force in cardiac myofilaments using the cytosolic transient of calcium as an input. The fraction of cross-bridges that can bind strongly and produce force depends on the overlap of the thin and thick filaments [1]. They defined the single-overlap function for the thick filament SOVF\(_\text{thick}\), as the fraction of thick filaments that are opposed to single overlap filaments, and this is used to calculate the maximal activated force. On the other hand, the SOVF\(_\text{thin}\) is defined as the single overlap thin filaments for interactions of the thin filament length. In this case, the SOVF\(_\text{thin}\) is used in evaluating the binding of calcium to Troponin. Following equations represent the mathematical formulation of the SOVF\(_\text{thin}\) and SOVF\(_\text{thick}\) interactions in the cardiac muscle.

\[
\text{SOVF}_{\text{thin}}(x) = \frac{2 \times \text{length}_{\text{overlap}}(x)}{\text{length}_{\text{thick}} - \text{length}_{\text{overlap}}},
\]

\[
\text{SOVF}_{\text{thick}}(x) = \frac{2 \times \text{length}_{\text{overlap}}(x)}{\text{length}_{\text{thin}}},
\]

where, length\(_{\text{overlap}}\), length\(_{\text{thick}}\) and length\(_{\text{thin}}\) represent the lengths of the thick, thin filaments and the paller region respectively. Also, x is the sarcomere length, and length\(_{\text{overlap}}(x)\) is the length of the hole single-overlap region [2]. Other factors that feature in the model include passive force, viscosity, a mass term, and a linear series elastic element. Titin contributes to the passive force which functions as a restoring force to reduce the total tension below the rest length. In addition, the viscosity of the muscle filament is set to the experimental mean values, while the mass terms act in reducing the instantaneous changes in the shortening velocity of the muscle [1]. Finally, the elastic factor in the model stimulates the effects of the compliant end connections.

The Land model incorporated an experimental data set collected from skinned human cardiac myocytes, including the passive and viscoelastic properties of isolated myocytes, the steady-state force calcium relationship at different sarcomere lengths, and changes in tension following a rapid increase or decrease in length, and after constant velocity shortening. This data set is, to our knowledge, the first characterization of length and velocity-dependence of tension generation in human skinned cardiac myocytes at body temperature [3]. The Land model used experimental data to develop a computational model of contraction and passive viscoelasticity in human myocytes. It includes troponin C kinetics, troponyosin kinetics, a three-state crossbridge model that accounts for the distortion of crossbridge, and the cellular viscoelastic response [3]. Each component is parameterized using real experimental data, collected in human cardiomyocytes at body temperature. Furthermore, they confirmed that properties of length-dependent activation at 37°C are similar to other species, with a shift in calcium sensitivity and increase in maximum tension [3]. The model of tension generation in the skinned isolated myocyte was used to replicate reported tension traces generated in intact muscle during isometric tension, and to provide a model of human tension generation for multi-scale simulations. This process required changes to calcium sensitivity, and crossbridge transition rates [3]. The model was applied within multi-scale simulations of biventricular cardiac function and further refined the parameterization within the whole organ context, based on obtaining a healthy ejection fraction.

Vasileiou’s work described the coupling between mechanical contraction and electrical excitation in cardiac cells, using models that represent excitation-contraction phenomena in single cardiac cells. Particular emphasis was given to two recent models of electrophysiology and mechanical contractility, the GPB and the Rice Filament models, respectively [12]. The Rice Filament model described activation and force generation in cardiac myofilaments and is used to simulate the contraction of the cardiac muscle. On the other hand, the GPB model aimed to simulate excitation-contraction coupling phenomena for the Ca handling and ionic currents in the human ventricular myocyte. Vasileiou coupled the GPB and the Rice Filament models to simulate excitation-contraction coupling phenomena in healthy cardiac cells [12]. The study further simulated the mechanical contraction of a failing human myocyte.

Basically, all these mathematical models possibly have given assistance to improve our understanding of the analysis of the active contraction of the human cardiomyocyte.

3 Conclusion

Developing physiologically realistic heart models is complicated by many challenges [13], such as the complex anatomical geometry, nonlinear material responses of the myocardium, fluid-structure interaction, and issues across different length/function scales. In the last several decades, many nonlinear models of cardiac mechanics have been developed using the finite element (FE) method. Muscle cells function in a similar manner to nerve cells in terms of their ability to conduct action potentials along their membrane surfaces. In addition, muscle cells have the ability to translate the electrical signal into a mechanical contraction, which enables the muscle cell to perform work.
The current work focused on reviewing the mathematical models of the cardiac myocytes’ active contraction. Various models have been developed based on existing studies and various concepts about the functionality of the cardiac muscle in humans [14]. The functionality of the heart is enabled by the cardiac muscles that contract to promote the flow of blood to different parts of the body. In this work, we reviewed the Hill model and Huxley model for general muscle cells. The Hill model was examined based on the outcome of the mathematical analysis of the contraction of the cardiac muscle. The Hill model establishes the relationship between force and velocity in the cardiac myocytes [15]. However, the Hill model is limited by the absence of the interaction of the sarcomere elements in its development. The Hill model was developed before the details of the sarcomere anatomy were known, and was based on Hill’s observations that when a muscle contracts against a constant load, the relationship between the constant rate of shortening velocity and the load is well described by the force velocity equation.

The literature was reviewed concerning the mathematical modelling of the myocyte cardiac cells. This included the Hunter model, which presented the passive active mechanics of the cardiac muscle suitable for use in the continuum mechanics models of the entire heart; the Rice Filament model, which approximated the activation and generation of force in cardiac myofilaments and; Vasileiou’s work, which described the coupling between mechanical contraction and electrical excitation in cardiac cells. As a starting point, descriptions of fundamental models were obtained along with their underlying mathematical modelling describing the processes behind excitation and contraction in cardiac cells. The Hill model representing muscle behavior, as well as the Hodgkin-Huxley model representing excitation, are fully considered due to their significance in mathematical physiology and as the basis for many models of cells.

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