A Bio-Inspired Computational Model of Cardiac Mechanics: Pathology and Development.

Thesis by

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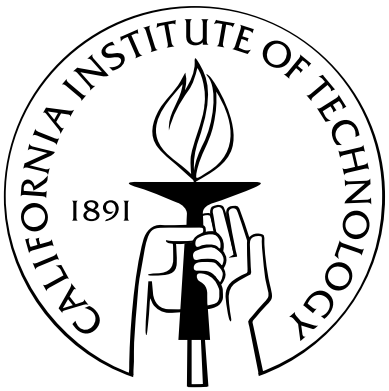

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Abstract

In this work we study the function and development of the myocardium by creating models that have been stripped down to essentials. The model for the adult myocardium is based on the double helical band formation of the heart muscle fibers, observed in both histological studies and advanced DTMRI images. The muscle fibers in the embryonic myocardium are modeled as a helical band wound around a tubular chamber. We model the myocardium as an elastic body, utilizing the finite element method for the computations. We show that when the spiral band architecture is combined with spatial wave excitations the structure is twisted, thus driving the development of the embryonic heart into an adult heart. The double helical band model of the adult heart allows us to gain insight into the long standing paradox between the modest, by only 15%, ability of muscle fibers to contract, and the large left ventricular volume ejection fraction of 60%. We show that the double helical band structure is the essential factor behind such efficiency. Additionally, when the double helical band model is excited following the path of the Purkinje nerve network, physiological twist behavior is reproduced. As an additional validation, we show that when the stripped down double helical band is placed inside a sack of soft collagen-like tissue it is capable of producing physiologically high pressures.

We further develop the model to understand the different factors behind the loss of efficiency in heart with a common pathology such as dilated cardiomyopathy. Using the stripped down model we are able to show that the change to fiber angle is the much more important factor to heart function than the change in gross geometry. This finding has the potential to greatly impact the strategy used in certain surgical procedures.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

Heart disease is the leading cause of death in America [1] and in the rest of the developed world. The American Heart Association (AHA) has promoted cardiovascular research for more than half-a-century, yet more than a million people suffer from heart attacks each year. Amazing progress has been achieved in medicine, allowing for both open chest surgeries (such as coronary artery bypass surgery) and less invasive procedures to be used in preventing fatalities caused by heart disease. There are many stages of heart disease, and in most of them the patients exhibit clear symptoms, such as shorteners of breath and fatigue. However, by the time such symptoms appear unrecoverable damage has likely been done to the heart. According to AHA guidelines, patients in stage B of heart disease are not yet exhibiting symptoms, but have structural remodeling of the myocardium [2, 3]. This makes diagnosis of patients in this stage a challenge, yet crucial to our ability to correct the damage with non-invasive means. Through dedicated work, doctors and scientists have found risk factors, such as high blood pressure and high cholesterol. Still, no current technology has the capability of diagnosing the initial stages of heart failure, because of our limited understanding of the mechanics of heart failure. So what do we know?

1.1 Background

1.1.1 Physiology of the human heart

The human heart beats about once every second, or more than two and a half billion times during an average lifetime. The heart is very adaptive, providing sufficient amounts of blood to our body while we rest or strenuously exercise. This biological pump has evolved to be amazingly efficient, to adjust and to correct itself in a wide range of situations. The heart exhibits this flexibility and agility in response to mechanical stimuli from the first stages of development.

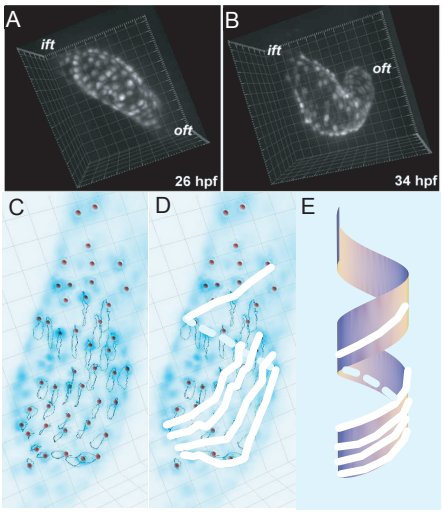

Figure 1.1: Three-dimensional reconstruction of a transgenic embryonic zebrafish heart at (A) 26 hours past fertilization and (B) 34 hours past fertilization. The inlet and outlet have been labeled. At both ages, analyzed region is mostly located in the ventral side towards the left lateral direction. (C) The trajectories of the fluorescent myocardial cells are tracked and marked at 26 hours post. The reconstruction was obtained by acquiring 40 optical sections (3 m intervals) at high speed (151 fps) with a confocal microscope (Zeiss LSM 5 LIVE). These sections were synchronized using a wavelet-based registration algorithm. (D) Shows possible direction of the fibers consistent with the trajectories of the myocytes. (E) A helical band is shown for comparison. (A)&(B) Produced by Michael Liebling and Arian S. Forouhar; (C) Produced by Abbas Moghaddam.

1.1.1.1 Heart development

At initial formation, the embryonic heart is a tube with two sulcus [4]. It starts beating on the twenty second day after conception. The initial form of the heart – a tubular pump – is often studied using fish embryonic hearts as model systems [5, 6]. It has been found that the muscle cells in the wall of the embryonic heart tube are arranged in a helical fiber framework [7, 8] (see figure 1.1).

Fibers wound around a cylinder have been studied as far back as the 1950s in worm locomotion [9, 10]. It was discovered that, for a given length of fiber and cylinder radius, the greatest volume change at a given fiber length change could be achieved at a helix angle of 55°. In these studies of worms, it was assumed the fibers were rigid and the muscles would be acting either radially or longitudinally. However, even the authors point out that diagonal muscles cannot be modeled by such a system. In the embryonic tubular heart, the diagonal fibers are active and their arrangement could impact both the efficiency of the early pumping and the further development.

Indeed, soon after the embryonic heart starts to beat, it begins its road to an adult heart by starting to loop. The driving mechanism for this change has not been fully understood. The heart tube goes through a sequence of bending and twisting transformations, first going into a “c” loop, then an “s” loop that is “matured,” after which the main architecture of the four chamber heart is

discernible [11]. This looping have been experimentally modeled using elastic tubing and compared to direct images from chick embryos [12]. However, the simulations performed by Manner et al. start at the "c" loop stage and explore the mode of rotation of the looping heart, not the driving forces necessary for such a deformation. By the eighth week, with the looping complete, some of the chamber walls are remodeled and the heart takes on the form of the four chamber pump.

1.1.1.2 Adult heart anatomy

The heart has four chambers: right and left ventricles, plus right and left atria. The atria chambers receive blood and pump it into the ventricles. The left atrium and ventricle are separated by the Mitral valve, which is sometimes also called the A-V valve. The right atrium and ventricle are separated by the tricuspid valve. The right ventricle (RV) and the left ventricle (LV) are the main pumping mechanisms of the heart. The right ventricle pumps the blood into the pulmonary system through the pulmonary valve. The left ventricle supplies the systemic circulation through the aortic valve, which leads into the the aorta (the main aortic vessel) [13]. A heart goes through a cardiac cycle during each heart beat. The cardiac cycle is divided into two distinct periods: systole and diastole. During systole, the heart contracts pumping blood out of the ventricles. While during diastole, the heart relaxes and the ventricles are filled with blood from the atria.

The two ventricles are separated by the septum. The plane where the ventricles meet the atria is called the basal plane. The other end of the heart, the lowest point, is called the apex. The outside surface of the heart is, for ease of terminology, divided into four surfaces. The anterior, or sternocostal, surface mainly bounds the right ventricle. The right pulmonary surface is formed by the right atrium. The left pulmonary surface bounds the left ventricle from the side of the left lung. The diaphragmatic, or inferior, surface bounds the left ventricle from the diaphragm side.

The heart is surrounded by a fibrous sack called the pericardium. The pericardium prevents the heart from over dilating (expanding too much). The pericardial cavity is the small space between the heart and the pericardium wall. On the outside of the heart there is a thin layer of tissue called the epicardium. The inside of the chambers is lined with a similar tissue called the endocardium. The myocardium is the main musculature of the heart and is between these two linings [14].

1.1.1.3 Myocardium architecture

The myocardium is a matrix, consisting of collagen, muscle and some other proteins. There are three types of cardiac muscle: atrial and ventricular types, plus the excitatory and conductive muscle fibers. The atrial and ventricular types behave very similarly to skeletal muscle, although the duration of contraction is much longer. The excitatory and conductive muscle fibers, which exhibit rhythmicity and varying rates of contraction, provide a fine tuned control of the rhythmical beating of the heart. The excitation of the heart muscles is controlled through the specialized

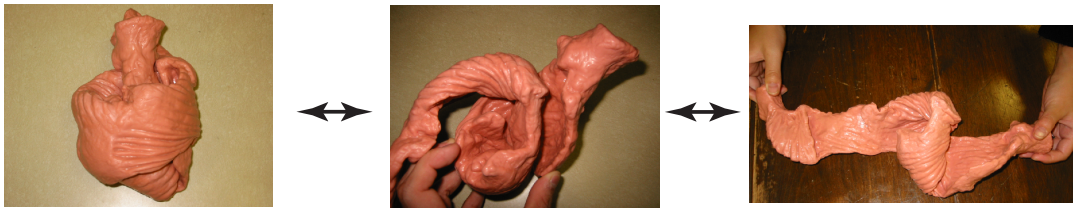

Figure 1.2: The photograph of the Torrent-Guasp heart model.

conductive system of the heart called the Purkinje system [15]. The excitation starts at the sinus node in the right atrium, moves to the A-V node located in the septum, where it is delayed and then passed into the ventricles going from the apex of the heart towards the outside and up through the heart walls. The different types of muscle and collagen cells are organized into muscle fibers called myofibrils. These fibers can contract by about 15% [16]. This biological constraint is very important when considering the efficiency of the heart, and we will come back to it many times.

The three dimensional layout of the fibers in the myocardium is not random. The heart has been described as a helical arrangement of fibers as far back as 1600s by Lower [17]. In 1891, Krehl described the multiple spirals formed by the muscle bands [18]. In 1933, some of these spirals were connected by Rob and Rob, creating a helical framework for the myocardium [19]. In 1969, using then cutting edge imaging technology, Streeter mapped the fiber orientation in the free wall of the left ventricle. He found that the fiber angle linearly varies from the endocardium to the epicardium [20]. It was proposed from these findings that the myocardium consists of sheets of helical fibers with changing orientation from the epicardium to the endocardium [16]. Another histological study done in the early seventies by Torrent-Guasp was aimed at isolating the muscle fibers from the collagen network. He showed that the muscle fibers are combined into a single band, which is wound about the two ventricles in a double helical arrangement [21]. The photographs of a cast of a heart that has been unwrapped are shown in figure 1.2. Most recently, the fibers in the heart were mapped using magnetic resonance imaging [22]. Figures 4 through 6 of the paper by Zhukov and Barr [22] show the fibrous network to be more complex than a simple combination of sheets. Another MRI study, in which Helm et al. were able to isolate the muscle fibers in the images, using DTMRI [23], showed an arrangement more closely resembling a helical band than sheets of fibers [24]. It has been realized that the way these fibers are arranged has a great impact on heart function [25, 26].

1.1.1.4 Functional properties of the left ventricle

The volume of the relaxed left ventricle is about 130 mL. During each of its two and a half billion beats, the left ventricle of the heart pumps out about 70 mL of blood, or in other words about 60% of its volume (this volume exchange ratio is commonly referred to as the ejection fraction). This

number gains new meaning when we recall that the muscle fibers providing for this volume ejection can only contract by 15%. One interesting fact is immediately evident from this information: if the muscle fibers were arranged circumferentially around the LV, the highest possible ejection fraction would be about 30% (see appendix A.1 for the calculation).

The pressures in the cardiovascular system are measured relative to the atmosphere, therefore all the pressures quoted in this manuscript will be the gauge pressures. The pressure in the left ventricle ranges from 0 Pa to 1.7×10^4 Pa (≈ 130 mmHg). Between 0 Pa and 1.3×10^4 Pa (≈ 100 mmHg), the contraction is isochoric, or in medical terminology isovolumetric. When the pressure in the ventricle reaches 1.3×10^4 Pa (≈ 100 mmHg), the aortic valve opens and the ejection of the blood begins. The ejection of the blood continues until the pressure in the ventricle falls back below 1.2×10^4 Pa (≈ 90 mmHg). The pressure continues to fall isovolumetrically until about 1.3×10^3 Pa (≈ 100 mmHg), when the mitral valve opens and filling begins. By the end of the cycle the pressure in the ventricle is back to zero.

As the heart performs its pumping function, it moves within the pericardium sack. The base of the heart is constrained by the vessels from rotating in the basal plane, while the apex of the heart is prevented from moving up or down. The remaining movement can be characterized by the twisting of the left ventricle. As is evident from the advanced imaging done of the heart, the dynamics of the left ventricle are not as simple as squeeze and release, which brings us to another interesting parameter that characterizes the dynamic behavior of the left ventricle pump: the twist. The twist is the rate of change of the angle of rotation in the left ventricle from the apex to the base. The heart gradually twists during systole as the left ventricular volume decreases, then, while the volume remains almost constant, there is rapid "un-twisting." The volume then increases with almost no change in twist. This hysteresis loop behavior has been documented by many studies, and it has been shown to be altered in damaged hearts [27–32]. The variations of twist during the cardiac cycle have also been shown to change with age [33]. This is an important observation because solid mechanics suggests the twisting of the left ventricle to be most likely responsible for the efficient operation of the heart [34, 35]. To intuitively convince yourself of this, consider the energy efficiency of two purely analytical pump models: one that operates by twisting, and the other that operates by squeezing. It is relatively easy to show that twisting can be more efficient at any giving ejection fraction (see appendix B for calculations). Therefore, through out this work we will use the twisting behavior as a gauge of the appropriateness of our models.

1.1.1.5 Pathologies

With the heart's intricate design and its non-stop operation, it is no wonder that more people suffer from heart problems as life expectancy increases. Early diagnosis of heart disease is widely recognized as one of the important steps in battling the high mortality rates of patients suffering from heart

failure. The earlier the patient is diagnosed, the better the chances of halting the progress of heart failure.

Many types of MRI protocols can give high quality images of the heart, and are mostly used to diagnose the morphological and static aspects of the heart, but not the underlying causes of the symptoms that different diseases exhibit. Indeed, physicians primarily rely on correlation and statistical analysis, rather than an understanding of the mechanisms behind the disfunction.

For example, it is well known that Hypertrophic Cardiomyopathy produces a thickening of the heart muscle, usually at the septum below the aortic valve and in the left ventricle. However, it has not been clearly demonstrated how these changes lead to reduced heart function (especially during exercise) [36].

Another area that would benefit from a deeper understanding of cardiovascular mechanics is the surgical restorative procedures. For example, dilated cardiomyopathy is sometimes treated with cardiac surgical anterior ventricular endocardial restoration procedure. However, while there are studies showing that it is reliable, it would benefit greatly from a better understanding of the mechanical properties of the arrangement of the muscle fibers [37]. Another example is a surgical procedure called cardiomyoplasty, in which surgeons place healthy muscle tissue around the heart in an effort to aid it while it recovers from damage. However this procedure does not have a good success rate [38].

Each type of heart disease is a complex combination of many factors. For example the dilated cardiomyopathy mentioned above usually develops after an infarction. In an infarction part of the heart muscle, to which the blood flow was cut off, dies. The dead muscle has different mechanical properties than healthy tissue, thus impacting the performance of the heart [39]. As the heart attempts to compensate the ventricle is remodeled. However without assistance it cannot recover back to its healthy shape.

To gain a better understanding of the causes of these diseases, many studies have been performed on healthy hearts and ones with pathologies. Not only values for left ventricular ejection fraction, pressure and twist, but a range of other data are available, including longitudinal, circumferential and radial strain measurement, material property measurements, data on rotations and pressure measurements [16, 40]. All of these data are available for comparison with models.

1.1.2 Modeling the Heart

Modeling of the heart started long before computers were around to aid in the process. As soon as Streeter came out with his findings on helical fiber arrangement, an analytical model was constructed to show the importance of such structures [41]. In this work, Sallin showed that a shell shrunk by contracting the length of fibers on its surface produces high enough ejection fraction only if the fibers are helical. By necessity, these analytical models could only handle one shell and had unrealistic

boundary conditions.

Modeling the heart in general presents a problem of scales. The active element in the heart, the muscle cells, can only contract by a small amount of 15%, yet the global structure deformations are large. With the advance of computing technology, it became possible to approach this problem. Two distinct methods have been used to strive for a solution.

The first, is the immersed boundary method developed by Peskin et al. [42, 43]. This is a general way to simulate elastic materials interacting with fluids. While this is very interesting computationally, it is not yet possible to create models with realistic conditions. Also, using this method it is not possible to account for the preexisting stresses in the fibers. In this method the authors can achieve the proper ejection fractions, however the strain they put on the material greatly exceeds the ones observed physiologically.

The second method is based on the histological studies done by Streeter et al. and utilized the finite element method to model the solid structure of the heart. These models assume that the myocardium consists of concentric shells with varying fiber directions. Meaning, that the epicardium and endocardium will have axially directed fibers, while the fibers in the middle will be directed circumferentially [16, 35, 44]. These models have been modified and developed extensively to simulate both volume and pressure inside the left ventricle.

The paper by Vendelin et al. shows how these models can be used to optimize the fiber organization with strain, stress, or ATP consumption. However, even the most optimal models provide less than 40% ejection fraction [45].

The blood flow in combination with the left ventricular wall motion is studied using fluid-structure interaction finite element method in a paper by Watanabe et al. [46]. The authors are able to reproduce the relationship between pressure and volume in the left ventricle. However, the structure maximal contraction is assumed to correspond to the ejection fraction of 60%. In other words, they assume that the walls of the left ventricle will contract by a large enough strain to accommodate the physiological ejection fraction. This phenomenological approach made sense for this study, since it was looking at the changes in blood flow with arrhythmia, but it does not answer the question of how such a high ejection fraction is possible with the contractile limit on the muscle fibers [46].

The major advances in computational modeling of the heart based on the sheet model have been done in the McCulloch group [47, 48]. They have created a comprehensive model for the three-dimensional heart that allows for large elastic deformation and keeps the strain in the fibers to below 20%. To create more reliable constitutive relations the three dimensional strains inside the myocardium were measured [49]. As a result constitutive relations for the different tissues in the heart were formulated [16, 50]. However, the maximal ejection fraction achieved with this model is less than 40% [51].

The models based on the finding by Streeter, have been getting progressively more complicated.

In the paper by Kerckhoffs et al. [52], the researchers added the circulatory system to the cardiac model by coupling a finite element model for the ventricles and a circulation model for the circulatory system. This provided better accuracy for the relationship between pressure and volume in the left ventricle for multiple beats. However, the maximal left ventricular ejection fraction in this model was still below 45%, which is borderline heart failure [52].

In the papers by Usyk et al. [53, 54], the authors considered a three dimensional cardiac models with electromechanics for normal and dilated failing hearts. The maximal ejection fraction for the healthy system is below 45% in this model. It is unsurprising that the ejection fractions are very low for the dilated heart model ($< 30\%$). However, it is interesting to note that the authors make no attempt to measure the twist of the left ventricle to verify that the model corresponds to the physiological dilated hearts in its motion.

None of these models answer the simple question of how it is possible for the heart to achieve a 60% ejection fraction without the fibers constructing over their physiological limit of 15%.

1.2 Overview of the Present Work

In modeling the heart we took a different approach. We wanted to create the simplest possible model that would still capture the main functionality of the heart. This would allow us to isolate the dominant structures in the myocardium and to gain a deeper understanding of at least some pathologies. To do so, we turned to the histological model proposed by Torrent-Guasp and focused on bands of muscles. We follow the previous modeling work by assuming that the heart tissue can be modeled as an elastic body. In other words, all the chemical and electrical processes are lumped together into an elastic relation that has approximately the same phenomenological response as the biological tissue. We used our models to study both the embryonic hearts and the adult heart. In this we approach the problem from a number of different directions.

1.2.1 Modeling of helical muscle bands

We present a framework for modeling biological pumping organs based on coupled spiral elastic band geometries and active wave-propagating excitation mechanisms. Two pumping mechanisms are considered in details by way of example: one in the shape of a simple tube, which represents a embryonic fish heart, and another, more complicated structure with the potential to model the adult human heart. Through finite element modeling, different elastic contractions are induced in the band. For each version the pumping efficiency is measured and the dynamics are evaluated. We show that by combining helical shapes of muscle bands with a contraction wave, it is possible not only to achieve efficient pumping, but also to create desired dynamics of the structure. As a result we match the function of the model pumps and their dynamics to physiological observations.

We then take a look at the problem from the developmental point of view. What causes the heart to loop in an embryo?

1.2.2 Spiral elastic bands and development

We explore the heart phylogeny – the development of the heart from embryonic to adult shape. For the shape change (from tubular to four chamber) to be initiated, a mechanical twist needs to be present in the embryonic heart tube. We show that the helical shape of the muscle fibers in the embryonic heart is a necessary but an insufficient condition for the transformation to occur. It is also necessary for the excitation pattern to be in the form of a spatio-temporal wave. We illustrate that such a combination, while producing twist, does not negatively impact the heart's ability to work as a pump.

Our next step is to look at the twist quantitatively.

1.2.3 Adult Heart Model: Ejection Fraction and Twist

Simple models have always been highly appreciated for their ability to isolate the dominant factors of a system. Surprisingly, this concept has never before been applied to modeling of the myocardium. Here, we report a computational study of the heart's spiral structure modeled as a closed elastic double helix band with active local excitation following the physiological activation pattern. This model is reduced to basic essentials, allowing us to focus on the dominant structure of the heart. By means of finite element computational modeling we address two features of heart mechanics and, most importantly, their timing relationship: one of them is the ejection volume efficiency and the other is the twist of the heart. The corner stone of our approach is the assumption that the double helical muscle fiber band represents the dominant active macrostructure behind the function of the myocardium. We show that this double helical model easily reproduces a physiological maximal ejection fraction of up to 60% without exceeding the limit on local muscle fiber contraction of 15%. Moreover, a physiological ejection fraction can be achieved independently of the excitation pattern. The left ventricular twist is also largely independent of the type of excitation. However, the physiological relationship between the ejection fraction and twist can only be reproduced with Purkinje type excitation schemes. Our results indicate that the proper timing coordination between twist and ejection dynamics can be reproduced only if the excitation front originates in the septum region near the apex. This shows that the timing of the excitation is directly related to the efficient pumping operation of the heart and give credence to the possibility of using twist as an important diagnostic tool.

We also show that the simple model can be used to study the cause of pathological symptoms.

1.2.4 Modeling pathologies in the heart

In a common heart pathology, dilated cardiomyopathy, the ventricular chamber undergoes a complex remodeling that changes the shape of the ventricle and the architecture of the fibers in the myocardium. In order to effectively surgically reconstruct the heart it is necessary to understand the relative impact of these changes on heart function. Here we present a series of simulations that model different pathological changes separately. We use the sensitive relationship between twist of the ventricle and its ejection fraction to judge the functional impact of the different damage types. We show that the anomalies found in the relation between torsion and ejection fraction for dilated cardiomyopathy are predominantly caused by the damage to the architecture of the myofibrils of the heart, rather than gross geometry.

As the last step we show that this arrangement of muscle fibers is capable of producing high enough pressures to provide efficient pumping to the circulatory system.