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An inverse problem approach to identify the internal force of a mechanosensation process in a cardiac myocyte

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ABSTRACT

Mechanosensation and mechanotransduction are fundamental processes in understanding the link between physical stimuli and biological responses which currently still remain not well understood. The precise molecular mechanism involved in stress and strain detection in cells is unclear. Sarcomeres are the contractile machines of a cardiac myocyte and two main sarcomeric components that are directly involved in the sensation and transmission of mechanical stimuli are titin and filaments (thin and thick). Titin is known as the largest protein in biology with a mass of up to 4.2 MDa. Its flexible region (I-band region) may function as a length sensor ($\varepsilon = l/l_0$) while its Z-disc domain may be involved in the sensation of tension and stress ($\sigma = F/A$). Filaments act as contractile machineries by converting biochemical signals into mechanical work which in response cells either shorten or relax. Based on these considerations and a qualitative understanding of the maladaptation contribution to the development of heart failure, an inverse problem approach is taken to evaluate the contractile force in a mathematical model that describes mechanosensation in normal heart cells. Different functional forms to describe the contractile force are presented and for each of them we study the computational efficiency and accuracy of two numerical techniques.

1. Introduction

Cardiovascular disease is the leading global cause of death worldwide with an estimated 17.3 million deaths per year expected to exceed 23.6 million per year by 2030 [1]. The cause of cardiac hypertrophy is known to be from mechanical overloading of cardiac myocytes (induced by, e.g., hypertension or myocardial infarction). There has been at least 230 different mutations identified to cause more than 10 different human diseases [2,3]. A growth factor treatment was used in heart failure patients but was not successful in avoiding the loss of cardiac myocytes. This may indicate the lack of knowledge of the underlying molecular events and thus hindering interference [4]. However, there has been studies that suggest mutations in genes are linked to defects in mechanosensation and mechanotransduction [5]. A comprehensive review on mechanosensation and mechanotransduction in the pathogenesis of heart failure can be found in Linke and Knoll (2010), Knoll and Marston (2012) and Buyandelger et al. (2014) [3–5].

The functional link between cardiac myocyte loss and regeneration as well as the influence of mechanical forces on these events still remain poorly understood [6]. Regeneration and loss are associated with cardiac hypertrophy and its reverse, cardiac atrophy, where there is an increase or decrease in cell size, respectively. This poses a tremendous challenge for every cell since it requires new sarcomeres to be added or removed (growth in 3 dimensions) and membrane constituents to increase or decrease (growth in 2 dimensions) which also cause an increase or decrease in physical stress, respectively. This leads to significant remodelling processes including changes in angiogenesis and the composition of the extracellular matrix [7]. Considering these changes, membrane and cellular components have to change proportionately to find a new equilibrium only within possible limits [8,9].

The development of heart failure can lead to a loss of contractile performance (i.e. the cell's ability to contract and relax). This results in a significant difference in contractile force between normal and heart failure cells. Cellular models that are able to generate realistic contraction patterns in heart cells will be very helpful in understanding diseased-induced alterations in contractile properties. These models contribute to the understanding of cardiac cell contractility in both physiological and pathological contexts at single cardiac myocyte level and may lay the foundation for quantitatively understanding the mechanism of heart failure.

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In this paper, one aim is to make use of a previously published model that could be used to measure the contractile force in a single cell and propose an inverse problem approach to evaluate the contractile force. This approach could become a useful tool in studying disease-induced alterations in contractile properties at single cardiac myocyte level. The model has been derived based on physical laws and linear elastic theory linking to the sarcomere dynamics (Sections 2 and 3). A brief biological background of the sarcomere dynamics with linkages to the role of intracellular Ca^{2+} dynamics in triggering the contractile mechanism is reviewed (in Section 2) with emphasis on the three important processes and features that contribute to active, passive and viscous forces in muscle contraction: calcium-induced calcium release (CICR), sliding filament theory and the giant molecule titin. The other aim is to provide the origins of the model and encourage future developments. In Section 4, two numerical techniques (i.e. Quantum-behaved Particle Swarm Optimisation (QPSO) and Gauss-Newton (GN)) are used to identify the contractile force and cases are presented in which different functional forms for the contractile force are used. Section 5 is a comparison (i.e. comparing computational accuracy and efficiency) of the results obtained for each case study using either QPSO or GN and wherever suitable a hybrid of these two. The suitability of the method and function in each case are discussed with some possible further improvements in Section 6.

2. Excitation-contraction mechanism in normal heart cells

A single muscle cell consists of sarcomeres, each of which extends from one Z-line to the neighbouring Z-line and contains many parallel thin and thick filaments as illustrated schematically in Fig. 1. Thin filaments consist of actin, tropomyosin and C-, I- and T-troponins [10] (two of which are shown in Fig. 1). Thick filaments are mainly composed of myosin and myosin binding proteins [10] (Fig. 1).

The excitation-contraction mechanisms in the cardiac muscle are coordinated by an autonomous electrical activation generated in the sino-atrial node and propagated through the heart wall [11,12]. The membrane goes through depolarisation which causes the opening of voltage-gated channels on the sarcolemma for the influx of Ca^{2+} into the cell triggering a release of Ca^{2+} from the sarcoplasmic reticulum (SR) into the surrounding sarcoplasm [13]. This phenomenon is known as CICR.

The release of Ca^{2+} from the SR binds to TnC sites (Fig. 1) which causes a conformational change in tropomyosin and releases the inhibitory subunit TnI. The troponin/tropomyosin complex shifts to the centre of the groove between actin monomers allowing actin-myosin interaction [14–16]. Myosin heads form crossbridges with

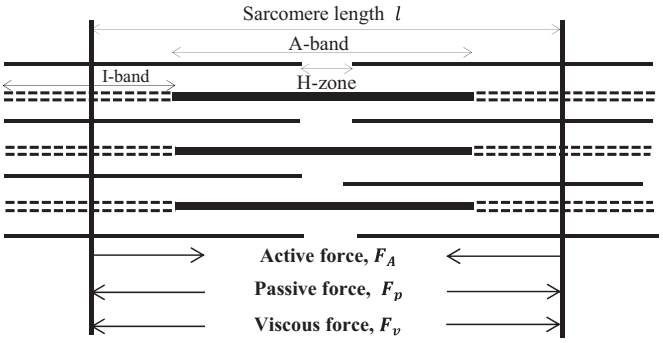

Fig. 2. Mechanical model of the sarcomere with directions of active force, F_A, passive force, F_P, and viscous force, F_v, during shortening.

actin by attaching to these active site and perform power strokes by pulling the actin filaments towards the centre of the sarcomere [17]. A series of power strokes causes these filaments to slide along each other (giving rise to the sliding filament theory) thus shortening the muscle [17]. This is the mechanism that is known to cause muscle contraction. However, uncertainties remain associated with the termination of the release of the CICR mechanism which is important for diastolic refilling of the heart [18,19]. Ca^{2+} that is released from the SR appears as Ca^{2+} sparks which propagate as waves throughout the cardiac myocytes. The effects of this in full width cardiac myocyte has recently been experimentally and theoretically investigated [20]. Here a stochastic model for calcium concentration has been used to model the stochastic behaviour of calcium release from channels and was compared to the experimental results. This is known to cause perturbations in the cellular mechanical response which is yet to be studied.

Thin filaments extend from the Z-lines through to the I-bands (where it overlaps with the thick filaments) and terminate on either side of the H-zone (Fig. 2). Thick filaments are connected to the Z-lines through the protein titin and are anchored at the M-line located at the centre of the sarcomere (Figs. 1 and 2) [11]. The sliding filament theory was originally proposed by two papers published consecutively: first by Huxley and Niedergerke (1954), and the other by Huxley and Hanson (1954). They believed that the observed changes in the cross striations of muscle during contraction implied that the actin and myosin filaments are arranged in parallel in the A-band and in the absence of ATP there would be crossbridges formed between them during muscle contraction. In both contraction and stretching, the A-band region remained relatively constant in length until the sarcomere reached the length of the A-band where beyond this point further shortening would fold up the ends of the myosin whereas the I-band

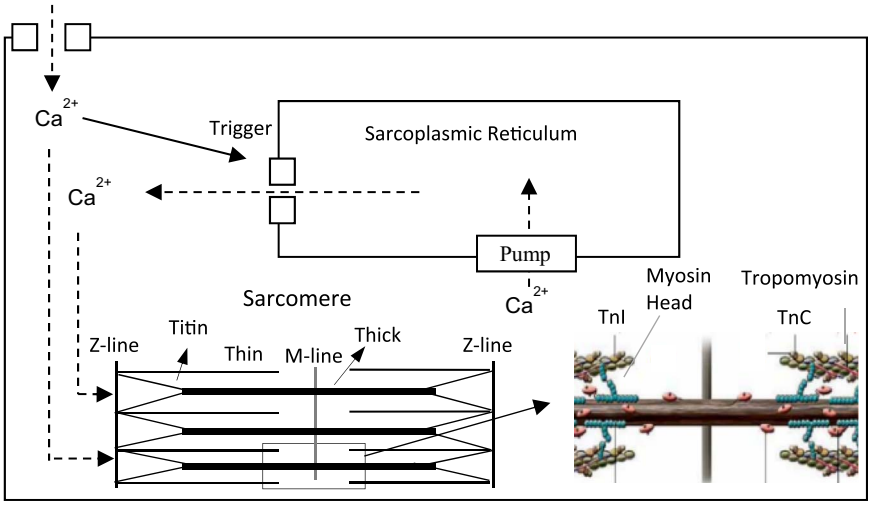

Fig. 1. Schematic view of the influx and outflux of calcium in a cardiac myocyte and the CICR process. Ca^{2+} released from the sarcoplasmic reticulum (SR) binds to TnC (leading to contraction) and then Ca^{2+} unbinds from TnC and is pumped back into the SR (during relaxation). Higher magnification around M-line is adapted from [10].