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MATHEMATICAL MODELLING OF CARDIAC PHENOMENA: ARRHYTHMIAS, CELL ENERGETICS, AND CONTRACTION

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Abstract. Mathematical modelling can be successfully used in cardiac research. We give an overview of our studies in this field in the general framework of knowledge in order to reflect our ideas more precisely. The studies of the cardiac phenomena performed by us are focused on three aspects: (a) regulation of the heart by means of electrical activation of the cardiac conducting system; (b) energy transformation from different chemical forms to mechanical form by means of oxidative phosphorylation, intracellular energy transport, and mechanical contraction of the myofibrils; and (c) mechanical contraction of the heart wall leading to the efflux of blood into the coronary system.

Key words: heart, nonlinear dynamics, electrical activation, cellular bioenergetics, mechano-energetics.

1. INTRODUCTION

In recent years it has become clear that interdisciplinary studies combining physiology and mathematics can facilitate the understanding of extremely complicated phenomena. For example, a series of simulations of heart dynamics based on mathematical modelling largely influenced by the theoretical background of current cardiology has been carried out in the 1990s [1,2]. The methods of contemporary nonlinear dynamics such as bifurcation analysis have proved suitable for the study of on-steady biological processes [3,4]. The application of the state-of-the-art numerical algorithms makes it possible to handle spatio-temporal systems

such as the intracellular energy fluxes or mechanical contraction of the muscle on a qualitatively higher level than that achieved by numerical methods commonly used in biology [5,6].

The heart can be studied from different aspects. For example, one can treat the heart as a "black box" which consumes energy taken from the surrounding environment and releases mechanical energy – blood flow – together with heat (Fig. 1). Great advantages of the "black box" method are its simplicity and its idea of treating the heart as a unity. However, the phenomenological knowledge collected by this method is far from being sufficient for developing new drugs or methods of medical treatment.

Another extreme would be to handle the heart as a bunch of billions and billions of cells with all the tissue-specific geometric, electrophysiological, biochemical, and mechanical subtleties involved. Such a "complete" model of the heart could be defined as an ultimate goal of the heart research that will still remain a mere fiction for a long time.

Commonly, the heart is considered as a set of separate functional blocks. Figure 1 shows one possible way of dividing the heart processes into such blocks which are briefly commented on below. The electrical, as well as mechanical activity of the heart, is affected by the central nervous system through its sympathetic or vagal activity together with the release of hormones. These factors influence the processes in the cardiac conducting system resulting in changes in the heart rate. In addition, they regulate the Ca^{2+} release in the activation process, leading to changes in contractility. The electrical activation of the myocardial tissue triggers the chemomechanical contraction processes on the cellular level. This results in the contraction of the heart muscle and produces the blood flow together with blood pressure. Blood pressure affects through the baroreceptors directly the central nervous system closing the loop. It is known that the contracted heart muscle closes temporarily the blood supply to itself by compressing the coronary arteries. Through this mechanism, the contraction affects the supply of oxygen to the cardiac cells, more specifically, to the mitochondria that are responsible for producing most of the energy available for the contraction process in the form of adenosine triphosphate (ATP). The ATP produced by mitochondria through oxidative phosphorylation is then transported to myofibrils, where its energy is consumed in the activation-controlled contraction process closing another loop. Figure 1 shows how the processes on the three different levels – the organ level, the tissue level, and the cellular level – can be linked to each other. Such partitioning allows different laboratories around the world to focus on a particular phenomenon in heart physiology and to achieve considerable expertise in the particular field [1–3,7].

To illustrate the successful use of mathematical modelling in cardiac research, we give an overview of the recent studies performed at the Institute of Cybernetics, Tallinn, under the supervision of Prof. J. Engelbrecht. Our studies of the cardiac phenomena are focused on three aspects: (a) regulation of the heart by means of

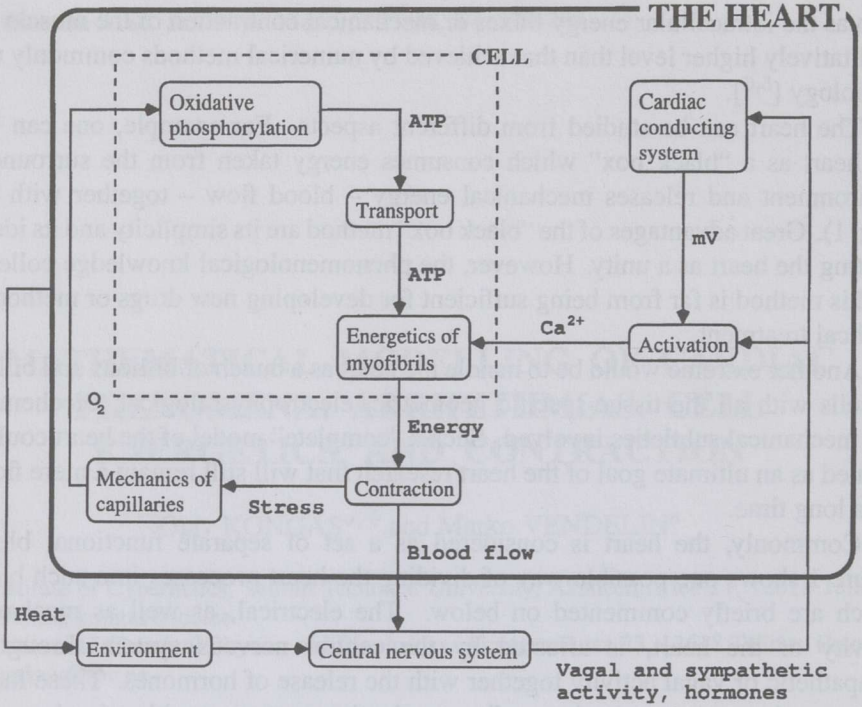

Fig. 1. Simplified functional scheme of the heart.

electrical activation of the cardiac conducting system; (b) energy transformation from different chemical forms to mechanical form by means of oxidative phosphorylation, intracellular energy transport, and mechanical contraction of the myofibrils; and (c) mechanical contraction of the heart wall leading to the efflux of blood into the coronary system (Fig. 1).

2. CONDUCTING SYSTEM

The sick heart can be bistable, exhibiting coexisting modes such as normal behaviour and reentry tachycardia. In terms of nonlinear dynamics, these two modes can be viewed as coexisting attractors, because without any change in external factors, for example vagal or sympathetic activity, or drug level, the heart can function in either mode. The switch between the modes can occur by temporary disturbances like ectopic beat or the impulse from an artificial pacemaker or defibrillator. The reentry mechanism, either anatomical or functional, is possible only in the tissue with certain size and geometry together with a proper velocity of the activation front and a repolarization time [8,9].

Recently, several publications have appeared both on the experimental [10,11] and theoretical [12–15] works demonstrating the bistability in very small portions of cardiac tissue or even on a single cell (non-reentrant bistability). In these cases the bistability emerged purely due to the nonlinearity in the dependence of ion channels on intermembrane voltage and involved neither geometric nor intercellular conductivity aspects. In guinea pig ventricular cells, the bistability was reported for low driving frequencies of 1–2 s [10,11]. Purkinje fibres revealed the so-called electrotonic inhibition, a special form of bistability with 1:1 or 1: 0 response modes [16]. In experimental studies, the bistability was detected by demonstrating the hysteresis in the activation patterns with respect to control parameters.

In the model studies, Landau et al. [13] and Vinet and Roberge [14] used the ionic models of a single undriven ventricular cell to demonstrate the bistability mechanism for the self-oscillatory cell with raised resting potential. They detected only the simplest possible mechanism for the bistability – the folding of the membrane potential amplitude curve with respect to the control parameters. In their cases, the hysteresis loops were formed by attractors annihilated in saddle-node bifurcations. These authors used contemporary continuation and bifurcation software to trace the attractors with respect to control parameters.

Our study introduced three new aspects in addition to the above theoretical considerations. First, the Purkinje tissue was modelled [17–21]. Second, the periodically driven model was treated [22–24], and the bistability in the frequency range typical of tachycardias was demonstrated [19,25]. Third, the more complicated bifurcation scenarios, including the global bifurcations leading to the bistability were found [25–27].

The bistability on the cellular level can, in principle, induce the bistability on the tissue level, which causes the bistability of the cardiac conducting system during tachyarrhythmias. Therefore, the bistability phenomenon can complicate the interpretation of ECG recordings and it should be taken into account in modelling on tissue level. However, first, the bistability phenomenon should be tested on a more sophisticated model of Purkinje cells (e.g., the DiFrancesco–Noble model [28]), with majority of the known ion currents involved.

3. INTRACELLULAR ENERGY FLUXES

The energy metabolism is the basis of the cell life. By now, basic mechanisms of cellular metabolism are well described and even illustrated by metabolic charts. All this information has been accumulated by using isolated and purified enzymes. After isolation, these enzymes are usually studied in diluted solutions. This is why the kinetics of the homogeneous enzyme systems has been used for the description of the biological systems. For example, the Michaelis–Menten type dependence on the adenosine diphosphate (ADP) concentration in cytoplasm has been used in an attempt to describe the regulation of cellular respiration. Experimental studies,

however, did not confirm this assumption [29]. The reason for this is that, in contrast to the diluted solutions, in living cells all enzymes function in the cellular structures such as biological membranes and multi-enzyme complexes. In these structures all components influence the behaviour of one another. This results in new phenomena like substrate and enzyme compartmentation and metabolic channelling, which determine the mechanisms of cellular regulation of metabolic and energy fluxes. The quantitative methods of the description of such compartmentalized processes *in vivo* are absent, in spite of their importance.

The first *dynamic* model of oxidative phosphorylation was proposed by Holtzhütter et al. [30]. The model was able to simulate two kinds of experiments with the suspension of mitochondria: the "oxygen pulse" experiment after full anaerobiosis, and an experiment with fully respiring mitochondria in the presence of externally added ADP. Another dynamic model was proposed by Korzeniewski and Froncisz [31]. During the last decade this model has been continuously improved to describe various experiments with suspension of mitochondria and mitochondria of hepatocytes and skeletal muscle cells in *in vivo* conditions [32]. The model is able to predict the oxygen consumption rate VO_2 as a function of the energy consumption.

Several models have been proposed that take into account some aspects of the metabolic and physical structure of the energy production, transport, and utilization system, including the non-equilibrium state of creatine kinase (CK) [33–35]. Aliev and Saks [36] proposed a model of mitochondrial regulation in the heart muscle. The model has been used to demonstrate the metabolic fluxes in various compartments and to simulate the "knock-out" experiments with bioengineered mice with selectively inhibited CK isoenzyme expression. An interesting result of this study is that, in addition to mitochondrial CK (Mi-CK), also myofibrillar CK functions in a non-equilibrium manner during systole. None of the models of energy fluxes mentioned in this section compute the oxygen consumption rate VO_2 as a function of the ATP consumption rate by using the kinetic equations for the respiratory chain.

Recently, our group developed the first model for cardiac cell [5,37] that is able to compute the oxygen consumption rate VO_2 as a function of ATP hydrolysis rate. The model makes use of the kinetic description of respiratory chain complexes.

From this research we have drawn the following two conclusions [5]. First, during the increasing workload close to its maximum possible value, both normal and Mi-CK inhibited heart cells should undergo a considerable increase in intracellular ADP which puts mitochondria to work with maximum possible VO_2. Second, the restricted diffusion in the intracellular environment with experimentally estimated diffusion coefficients (tenfold lower than characteristic of water) can lead to considerable ADP oscillations and ADP gradients in myofibrils. This suggests that ADP, together with inorganic phosphate, may participate in the regulation of oxidative phosphorylation by feedback mechanism. These conclusions are, of course, just theoretical predictions until they are experimentally verified.

4. MECHANICAL CONTRACTION

At present, the analysis of the mechanical contraction of the heart wall often takes into account the fibre orientation and electrical activation pattern of the heart, but usually it is assumed that contractile element concentration is homogeneous across the heart wall when the normal functioning heart wall is simulated. On the basis of these assumptions several mathematical models have been constructed to study deformation and stress development in the heart ventricle [38]. However, taking into account the inhomogeneity of the oxygen supply into the heart wall, the assumption about the homogeneous concentration of the active contractile element in the heart wall is doubtful.

The mechanical contraction of the heart muscle is constantly supported by the influx of oxygen from the surrounding blood vessel system. The blood vessels form a fractal-like structure in the myocardium wall which allows spatially heterogeneous blood perfusion of the muscle [39,40]. This heterogeneity of the blood flow results in an inhomogeneous regional oxygen supply to the heart wall even in the normal functioning conditions and seems to be correlated with the concentration of the active contractile elements. Indeed, recent experiments have shown that the local metabolism–perfusion mismatch during partial coronary stenosis is not correlated with the variations in the local blood flow; instead, there is a clear correlation with the relative reduction of the local blood flow [41]. The influence of the oxygen supply on the mechanical contraction regulation in normal functioning conditions as well as in pathological conditions remains open to discussion. Several experimental studies on this subject have been published [42,43] and several are in progress; however, the lack of the mathematical models of the mechanical contraction together with a shortage of the substrate supply on the tissue level makes it difficult to take full advantage of the experimental data. Indeed, it is hard to analyse simultaneous measurements of the heart wall surface (epicardium) deformation, regional blood flow, and oxygen consumption without an appropriate mathematical model. Our project is focused on the development of the mathematical model of the mechanical contraction of and oxygen supply to the heart wall region and on quantitative analysis of the referred experiments.

The simulation of the heart wall contraction and energy consumption has to be based on a good mathematical description of the properties of the heart muscle tissue, active stress development, and energy consumption by the heart muscle, in particular [44]. Commonly, the cross-bridge model is used to compute the stress and energy consumption since (a) it is in good correlation with the current understanding of the actin and myosin filament interaction and (b) the energy consumption is clearly defined by this type of a model. However, the Huxley-type cross-bridge models usually fail to replicate the basic property of the heart muscle: linear dependence of the energy consumption on the stress-strain area (SSA). The SSA is a specific area in the stress-strain (SS) diagram, surrounded by the end-systolic SS relation line, the end-diastolic SS relation line, and the systolic segment of the SS trajectory for a contraction. The computed dependence is highly nonlinear and

different for isometric and isotonic contractions [45,46], contradicting the results of experimental studies [47].

The goal of our study was to replicate the linear relation between energy consumption and the SSA in a wide range of cardiac muscle loading conditions. It is shown in [6] that the measured linear dependence of ATP consumption on the SSA in the isometric and isotonic cases can be simulated by the self-consistent model [48,49] if an advanced model of myosin–actin interaction activation is used and appropriate cross-bridge rate constants are selected. The computed active stress development is in good correlation with the experimentally measured stress [50] in isometric contraction and isotonic contraction. Our model reproduces two key properties of the heart muscle: (a) energy consumption depends linearly on the SSA, (b) this dependence is almost the same for the isometric and isotonic contractions [6]. To the best of our knowledge, this is the first Huxley-type model that predicts linear ATP consumption dependence on the SSA.

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TEOREETILISED SÜDAMEALASED UURINGUD

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On antud lühiülevaade Tallinnas Küberneetika Instituudis professor J. Engelbrechti juhendamisel tehtavatest teoreetilistest südamealastest uuringutest, mis on keskendunud kolmele südame füsioloogia aspektile: a) südame rütmi reguleerimine erutustekke- ja juhtesüsteemi aktiveerimise kaudu; b) energia muundamine erinevatest keemilistest vormidest mehaanikalisse vormi oksüdatiivse fosforüleerimise, rakusisese energiatranspordi ja müofibrillide kontraktsiooni kaudu; c) vere pumpamiseks vajalik südamelihase mehaaniline kontraktsioon.