We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX

CLARIVATE ANALYTICS

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Basic Mechanisms of Cardiac Arrhythmias[1]

Andrey Moskalenko

Additional information is available at the end of the chapter

1. Introduction

1.1. What should the activity of the heart and the action of the heart mean?

The term "*action of the heart*" was discussed in detail in my recent publication [1]. The terms "(any) cardiac activity" or "(any) activity of the heart" should be used only for designation any aimless functioning of the heart. On the other hand, "the action of the heart" or "the cardiac action" should be comprehended as the functioning of the heart that is directed to maintenance of physiological homeostasis, which is the target function in this case. Obviously, the action of the heart can be put into effect only due to a quantity of control loops and guidance loops[2], which all together organize one and indivisible cardiovascular system. Electrical phenomena, that accompany the functioning of the heart and can be recorded by electrocardiography, are nowise satisfying the target of the cardiovascular functioning, because they are but side effects of the *autowave function of the heart* [1, 2]. In English scientific and medical literature, the electrical phenomena to accompany the functioning of the heart are referred to as "the electrical *activity* of the heart" in a good accordance with the remarks above.

Any action of the heart that differs from its normal action ought to be ranked among *cardiac arrhythmias*. The normal action of the heart (the normal cardiac action) should be understood as the averaged round the human population cardiac behavior in comfort conditions. The cardiac arrhythmia arising in comfort conditions is undoubtedly considered to be pathologic. However, different kinds of cardiac arrhythmia arising in conditions distant from the comfort may be either *pathologic* cardiac behavior or normal *adaptive* response of the heart.

1This chapter is mainly based on our previous publication [2], which is revised and renewed for the aims of this book. The chapter contains some materials that have not been available previously to English-speaking readers.

2 Notice that the control is used to maintain a desired output of the system under control, while the guidance is intended for shifting the system from a state A to a state B. See more below.

To make the proper diagnosis of arrhythmia type, one requires a deep understanding of the basic mechanisms of the cardiac action in being normal as well as in its various disorders.

1.2. Has the time come for alteration of the cardiologic paradigm?

Despite major scientific, medical and technological advances over the last few decades, a cure of cardiac arrhythmias remains elusive. As a very appropriate example of the problems of traditional cardiology, which is generally based on physiological approach, is the result of the CAST [3, 4], a multicenter, double-blind, randomized controlled trial, that has revealed a higher rate of death from arrhythmia of the patients treated with antiarrhythmic agents in comparison with the patients assigned to placebo. One of the well-known Russian cardiologists having analyzed a number of multicenter trials came to the conclusion [5] that treatment with antiarrhythmic drugs is prescribed nearly at random; he shared his impression with the following words[3]: "*Potentially any of the known antiarrhythmic drugs can 1) cause an antiarrhythmic effect, 2) not cause it, 3) be arrhythmogenic. And each of these cases happens unpredictably for a patient. Therefore, pharmacological tests are strongly required for selecting not only effective but, at least, harmless therapy for patients with malignant ventricular arrhythmias.*" Another author impressed by the result asserted that antiarrhythmic drugs have "*cost more American lives than the Vietnam War*" [6].

Another convincing example of the same is given to us by the recent discussion about the mechanisms of cardiac fibrillation [7]. The intensity of authors' disappointment is expressed by their writing that the nature of fibrillation remains "*still so puzzling after 160 years of inquiry*". A generally accepted definition of cardiac fibrillation is lacking.

Hence, it remains to add that the history of science gives a lot of resembling examples convincing us that the actual state of affairs suggests a self-evident necessity of drastic alteration of the scientific paradigm that forms the basis of modern cardiology.

1.3. The physiological description of the heart

The discovery of "animal electricity" must undoubtedly be recognized as a very important step in understanding the causes and mechanisms of cardiac disorders. Furthermore, this discovery quickly led to the development of a new language, the *physiological language*, which appeared to be very convenient for a generalized description of such properties of living matter that had been believed to be absolutely different before.

Indeed, what common features between functions of the brain and of the muscles can be found out by somebody without special knowledge? What common, it would seem, can be between muscular power and the power of thought? However, the discovery of the "animal electricity" allowed registering a certain process that can be observed both in nervous and in muscle

---

3 In the original: «потенциально любой из известных антиаритмических препаратов может: а) обеспечить антиаритмический эффект; б) не обеспечить его; в) проявить аритмогенное действие. И все это индивидуально непредсказуемо. Поэтому для больных со злокачественными желудочковыми аритмиями выбор не только эффективной, но и безопасной терапии требует проведения фармакологических проб» [Голицын С.П. Грани пользы и риска при лечении желудочковых нарушений ритма сердца. Международный журнал медицинской практики 2000;(10) 56–64].

tissues; the process was given the name "excitation". Since then the nervous and muscle tissues have been referred to as "excitable tissues". Further development of ideas about excitable tissues made scientists draw some extremely important generalizations of all those experimental data which were collected by the end of the 19th century. It was as long ago as 1900 [8] that T.W. Engelmann, K.F. Wenckebach and H.P. Bowditch postulated the basic properties of the myocardium, namely: 1) automaticity, 2) refractory period, 3) all-or-nothing response, 4) staircase phenomenon. It is the concept of "animal electricity" that has formed the basis for all the subsequent physiological investigations.

Here we will not dwell on the peculiarities of the physiological language used for description of biological objects, as these are written in many textbooks of physiology quite a lot and in detail (for example, see [8–10]). It should only be emphasized that, after replacing the old notion of a special "living substance", the physiological language has entirely dominated among biologists and medical professionals for the whole 20th century.

However, the discussion between modern investigators of the heart reveals faultiness of the cardiologic paradigm, which is constructed owing to the epoch-making discoveries made by the greatest physiologists of the 19th and 20th centuries. The faultiness appears to be caused by our rather simple comprehension how biological systems work, which arose from the historic specificity of scientific knowledge evolution. During 17–19th centuries the science development is known to be mainly grounded on the notions of determinism, with great advantage in applied mechanics to constitute their historical basis. It resulted in permeating the conception, which is referred to as *mechanistic approach*[4] now, into many fields of science. Nor has medicine escaped the common lot, since all modern physiology is per se a manifestation of the mechanistic approach in biology. In accordance with scientific tradition, the phenomena observed in physiology are explained, in the frames of the mechanistic approach, as a result of different simple mechanical movements. The movement of ions through membrane of a biological cell in order to explain the action potential is a good example of the approach. Prevalent endeavors of modern cardiologists to treat cardiac disorders by adjusting membrane channels using one or another drug is another such example.

More and more researchers [11–15] are coming to an increasingly profound understanding that there is a need for an alternative or modified paradigm, in order to consider the multi-systemic nature of the body's function and its environmental interface if new and more effective therapies are to be developed. Recognizing a problem is the first step to its solution...

1.4. Cardiophysics

Over the past few decades, it have been accumulated quite a large number of experimental observations and theoretical results which are poorly fit within the constraints set by the physiological language. These new discoveries were called attention to, which has resulted in both drawing new generalizations of the collected scientific knowledge and developing a new

---

4 To distinguish the "mechanistic approach" and "insight into mechanisms" is extremely important. In the terms of mathematical physics, the mechanistic approach is based on linear description of nature, with the principle of superposition being correct in the frames of this approach; however, non-linear mechanisms are shown to underlie a huge number of natural phenomena (for example, see [16, 17]), and, hence, insight into such non-linear mechanisms is also very desired.

language, the *biophysical* one. For example, while the physiological approach fails to take chaotic dynamics into account, the biophysical way of living system description, mainly based on the theory of dynamical system, has equipped scientists with reliable quantitative methods of studying enorganic phenomena of deterministic chaos. Modern scientific disciplines lead to the conclusion that often adequate comprehension of a complex system requires analyzing not the observed values, but some of its integral characteristics, which can be mathematically obtained as a combination of a number of the observed. Chaotic attractor is a good illustration of how important ideas of modern physics are for cardiology [16–18]. Whether any sort of chaotic attractors correspond to the normal cardiac activity, remains still a very good question. Other crucial phenomena that must certainly be taken into account when treatment for a cardiologic patient is provided are caused by so-called "bifurcation memory", which has attracted special attention of investigators since recently [19–21]. Recent evidence suggests that similar phenomena can be found in the heart [1, 2]. The results of investigating the bifurcation memory in a cardiac model are presented and discussed below.

The following three other examples are intended to illustrate how the use of new biophysical laws has led to a substantially deeper understanding of well-known phenomena, not achievable within the frames of physiology.

Experimental results from studies in electro- and magnetocardiology gave rise to the modern biophysical conception of "*equivalent bioelectric generator*" [22], which is strongly based on classical electrodynamics. The first example is to demonstrate how the conception of "equivalent bioelectric generator" was useful for investigation of the QT dispersion problem. QT dispersion (QTD) is simply defined as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG; since its description in 1990, it has been considered as "undergoing vigorous assessment" for the purpose of early identifying subjects at high risk of sudden cardiac death, because it was supposed that "the interlead QT interval differences within a 12-lead ECG might reflect regional differences in myocardial refractoriness, and that this might predict cardiac dysrhythmias" [23]. Common sense based on the physiological concept seemed to point quite convincingly to the prognostic significance of the phenomenon of QTD, because it is expected that electrophysiological instability of activation and recovery of the myocardium must necessarily be reflected on the surface of the torso in a form of instability of ECG-patterns of the repolarization part of the cardiac cycle. In spite of that, the accurate, from the standpoint of biophysics, study of possible mechanisms of QTD, after problems of the QT-interval genesis were considered in terms of biophysical models of the cardiac electric activity, has led to the conclusion that the duration of the QT-interval (tQT) are the same in each electrocardiographic leads, and the "QT dispersion" phenomenon stems mainly from mistakes in detecting the T-wave end [24, 25]. Electrical activity of the ventricular myocardium in such models is determined only by the equivalent cardiac dipole, which the spatial vector loops QRS and T correspond to. Although the normal work of the heart can be successfully described by a dipole, multipole components are given rise to when cardiac disorders occur. It can be stated therefore that the phenomenon of QTD reflects the contribution of the multipole components in a total picture of the electrical activity of the heart. Let us denote duration of QT in different leads as tQT(l), where l belongs to a set of leads L. The theoretical

consideration within the dipole hypothesis has showed [24] that the QT-duration in different leads, tQT(l), must be exactly equal to each other with the exception, perhaps, of some *very special cases* as well as that, at a low noise level and, consequently, the low threshold of identification the end of the T-wave, it is difficult to expect a large spread of the values tQT(l) measured from leads to leads in a case of vector loops with a *finite radius of curvature*. The differences in tQT(l) observed in practice can be explained only by algorithms used for detecting the T-wave end or the ECG isoline, by choice of the thresholds of identification in relation to the accepted rules of coding the presence of the ECG-waves, or by the actual values of the signal / noise ratio, as well as by measurement errors. Nevertheless, the authors identified a number of factors [25] that can even within the dipole hypothesis result in increasing dispersion of QT-duration both in a sequence of cardiocycles from the same leads and in a set of records of the same cardiac cycle simultaneously registered in the different leads. Two most significant factors are following:

1.   There is no clear correspondence between the positions of electrical and anatomical axes of the heart due to physiologically normal variations in topography of His-Purkinje system.

2.   QT-dispersion also depends on the random rotations of the ventricles relative to the measuring electrodes, for example, during rotation of the heart relative to its anatomical axes.

Hence, the investigation [24, 25] has shown that it is impossible at present to reject the hypothesis of random nature of the QTD changes, since all of these factors that generate QTD changes should be considered as random variables. Regardless of the biophysical result, it is still believed, however, that "increased QT dispersion is associated with increased risk of cardiovascular death" [26].

The second example deals with defibrillation. Cardiologists are known to have been working on the problem of defibrillation for several decades, but desired level of success has not yet been achieved, and the fundamental mechanisms that underlie defibrillation still remain a mystery [27]. At present there is no generally accepted point of view on the mechanisms of postshock arrhythmia induction resulting from unsuccessful defibrillation. A number of factors were assumed among the possible causes of an unsuccessful defibrillation; for example: 1) residual fibrillation activity in areas of weak voltage gradient, 2) new autowave vortices generated by a shock, 3) focal ectopic activity in areas of myocardium traumatized the action of electric current that a defibrillator produces. Suggested in the last years, the new Theory of Virtual Electrodes [28, 29] helps to understand failures of the defibrillation protocols presently in use. One of the most important practical conclusions of the theory is the recommendation to use a biphasic defibrillation stimulus, which can significantly increase the effectiveness of defibrillation. It should be noted that the emergence of new look at defibrillation and the subsequent development of the theory of virtual electrodes became possible only by using one of the fresher biophysical models of such intricate active medium as the myocardium, which is referred to "bidomain model". In addition, several researches [30, 31], which also are carried out in the frames of cardiophysical approach, are aimed at developing new techniques of defibrillation based on suppression of cardiac turbulent dynamics by weak local excitations.

Returning to the results of CAST and other similar investigation, we ought to remind that these results were evident directly from the very early theoretical works of those scientists who can undoubtedly be mentioned among the founders of a new branch of science, cardiophysics. First of all, I mean here the studies by Arthur Winfree [32], who has revealed the principal autowave regimes of the simplest active medium and their dependence on the basic integral parameters of the medium, as well as by Valentin Krinsky and Iury Kokoz [33], who have shown that every active medium should demonstrate the same set of principal autowave regimes, because the corresponding systems of partial differential equation can always be reduced to the simplest one. Taken together these results lead to the obvious conclusion that any manipulation with the membrane ion channels of cardiomyocytes directed to the suppression of ventricular tachycardia by forcing autowave vortices to perform uniform circular motion (which corresponds to monomorphic tachycardia) always results in to the displacement of myocardial state very far from normal, which must inevitably increase patient mortality. Note that the hypothesis about the displacement of myocardial state was confirmed later in an experimental work with lidocaine [34], in good accordance with Winfree's prediction. Another biophysical study [35] demonstrated one more reason why medicines that exhibit strongly pronounced antiarrhythmic properties when affecting single cardiomyocyte increase in 2-3 times the frequency of sudden arrhythmic death in comparison to untreated patients. At first glance, it does seem paradoxical that the same drug has antiarrhythmic effect on isolated cells and pro-arrhythmic effect on the multicellular system (the whole heart). In the computational imitating experiments, the author managed nevertheless to discover that sodium channel blockers can greatly increase the so-called vulnerable period in myocardium, which occurs because of a decrease of velocity of the excitation wave, and also because of reduction of excitability gradient. The next remark deals with ECG diagnostics. Notwithstanding the properties of myocardium are known to affect ECG, the investigation of the dependence of several ECG characteristics on the threshold of excitation, which was carried out by means of mathematical modeling monomorphic arrhythmias in a homogeneous two-dimensional excitable medium, revealed [36] that these arrhythmias appear under both decreased and increased values of the excitation threshold. Hence, this result leads also to the conclusion that medical treatments are prescribed nearly at random when a cardiologist make his or her decision only on the base of ECG analysis without knowing about real changes of the excitation threshold. Generalizing these three biophysical conclusions about medical treatment of tachycardia, should we be surprised that the success of such treatment can hardly be called acceptable?

In addition to remarkable progress in biophysics, another important conceptual breakthrough of science was performed in the field that now is referred to as *nonequilibrium thermodynamics*, "*physics of becoming*" [37] or *synergetics* [38], which "represents a remarkable confluence of many strands of thought, and has become a paradigm in modern culture" [39]. Biological systems are complex and nonlinear, and, therefore, demonstrate complex and nonlinear behavior, which may be chaotic, in many cases; the heart appears to be the same [14, 17, 18, 28, 30, 31].

All these examples should be recognized as proofs of birth of a new science. Thus, we ought to conclude that the 21st century seems to yield a new discipline, which is referred to as

cardiovascular physics[5] or *cardiophysics* (since it combines cardiology with novel achievements of physics). Cardiophysics is an interdisciplinary science that stands at the junction of cardiology and biophysics, with researchers using the methods of, and theories from, physics to study cardiovascular system at different levels of its organization, from the molecular scale to whole organisms. Being formed historically as part of systems biology, cardiophysics is designed to reveal connections between the physical mechanisms, underlying the organization of the cardiovascular system, and biological features of its functioning.

2. Basic biophysical mechanisms of maintaining the action of the heart

2.1. Historical remarks

About fifty year ago, physicists and mathematicians managed to perceive that the processes that take place in a "purely physical" systems (e.g., lasers, or even in boiling water) are similar in some of their properties to the processes observed in the physiology of excitable biological tissues. The understanding came gradually that phenomena such as irritability, conductivity, all-or-nothing response, refractory period etc. are inherent not only exclusively in biological objects, but also typical for non-living nature. It is important to comprehend that the speech here is not about some analogies, but exactly about a new scientific generalization of the accumulated scientific knowledge, and that the generalization made by researchers in respect of particular types of behavior of living and some non-living systems is based on the certain entirely real properties of such systems. This generalization led to the development of a new language, biophysical one, which are more universal and more powerful. The new language has reproduced the description of all that was already described earlier in the physiology, but it also allows in unified terms to represent a wide range of experimental data, the description of which the physiological language performed poorly. The new expanded description of the cardiac action is offered in this chapter further.

Undoubtedly, the term "*autowave*", which refers to a large number of different biological objects, plays one of the most important roles in the new biophysical language.

The first who studied actively the self-oscillations was Academician A.A. Andronov, and the term "*auto-oscillations*" in Russian terminology was introduced by him in 1928. The term "*autowaves*" was proposed in the second half of the 20th century, probably, on the analogy of the previously used "auto-oscillations". The classical axiomatic model of autowaves in myocardium was published in 1946 by Norbert Wiener and Arturo Rosenblueth [40]. During 1970-80, major efforts to study autowaves were concentrated in the Institute of Biological Physics of the USSR Academy of Sciences. A huge role in the study of autowave models of cardiac tissue belongs to D. Noble and members of his team from the University of Oxford [12, 13]. There are a lot of other researchers over the world who contributed to development of the

---

5 For example, there are already the Group of Nonlinear Dynamics & Cardiovascular Physics of the 1st Faculty of Mathematics and Natural Sciences in the Institute of Physics of Humboldt University of Berlin (German) and the Cardiovascular Biophysics Laboratory in Washington University (USA).

theory of the autowave processes, i.e. the processes in the *active media*. Since then, as the peculiar properties of the active media has been understood, the autowave processes attract attention of mathematicians, physicists and biologists, and it turned out, that the experience that had been gained by physiologists before gave a very useful basis for constructing the new bio-physical language for describing phenomena observed in the active media of different nature.

2.2. Mathematical aspects

According to [41], the term "*autowaves*" is used for designation of a self-sustaining nonlinear undulatory process in a non-equilibrium (active) medium, the process remaining unchanged for sufficiently small changes in both the initial and boundary conditions and described by the system of parabolic partial differential equations with a nonlinear free member, which in its general form can be written as follows: $\vec{u}_t = \vec{f}(\vec{u}) + D\Delta\vec{u}$, where $\vec{u}$ is a vector of state variables, $\vec{u}_t$ is the time derivative of the $\vec{u}$, $\vec{f}(\vec{u})$ is a vector of free members (i.e., of nonlinear functions), D is a diagonal matrix of the coefficients that describe diffusion of each component, and Δ is the Laplace operator. Thus, the mathematical apparatus that are often used for describing autowave processes are the equations of the diffusion type with an active nonlinearity (i.e. *reaction–diffusion systems*).

It is impossible here to delve into the details of the mathematical description of autowave processes, but there are an abundance of literature on this topic (for example, see [32, 33, 40–47]). Therefore only those aspects which are the most important for understanding the nature of cardiac arrhythmias will be touched on here. To apprehend distinctly the signification of the term "autowaves", several things should be noted.
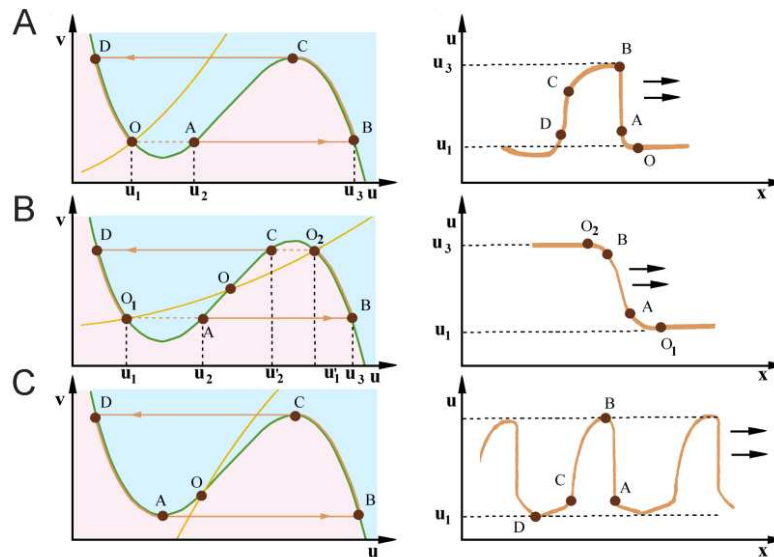

Figure 1. Phase portraits (left column) and the corresponding behavior (right column) of a single element of the active medium: row **A** — excitable, row **B** — bistable, row **C** — self-oscillating element types. Rose area corresponds to $f_1(u, v) > 0$, and blue color highlights the area, where $f_1(u, v) < 0$. See description in the text.

First of all, a general property of such systems, regardless of whether they are of animate or of inanimate nature, is that they consist of external energy sources distributed in the space; and such special systems were called "*active media*". From the thermodynamic point of view, these are open systems far from thermodynamic equilibrium [41]. It is the quality that compels the behavior of the active media to differ fundamentally from that of systems which have been familiar to physicists of the 19th and 20th centuries. Even the waves in active media propagate according to essentially different laws than the well-known acoustic or electromagnetic waves do. Unlike linear waves — such as sound waves, electromagnetic waves and other, which are inherent in conservative systems and mathematically described by linear second order hyperbolic equations (wave equations), — dynamics of an autowave in terms of differential equations can be described by *parabolic equation with nonlinear free member of a special form* (the equation is presented at a few lines above).

It was shown in 1973 [33] that every system of mathematical differential equations describing the process of excitation of biological tissues can be simplified with use of some standard mathematical procedures to only two equations that describe, with an acceptable accuracy, the real object for which the "exact" original system of many equations was composed. It proved that such systems are a very important kind of active media, which has been called "*active media with recovery*" (note, that nerve impulse, which serves typical example of autowaves in the active medium with recovery, was studied as far back as 1850 by Hermann von Helmholtz). Thus, the following system of two equations is recognized to be the base model of the active medium with recovery [41]:

$$\varepsilon \cdot u_t = f_1(u, v) + D_1 \Delta u \tag{1}$$

$$v_t = f_2(u, v) + D_2 \Delta v \tag{2}$$

where $\varepsilon << 1$. $D_2 = 0$ for excitable biological membranes, whereas both the diffusion coefficient, D_1 and D_2, are different from zero for chemical systems. For biological membranes, the meaning of the variables of state is as follows: u corresponds to the membrane potential, and v is the conductivity of the slow component of the membrane current. Although the exact description of a specific sort of active medium can take much more equations (for example, the modern model of the human myocardium consists of more than twenty equations), the most important basic properties of autowave processes are well described already within this basic model of active media.

The next essential moment is that the active media are characterized not only by the connections between the adjacent points of the medium (i.e. by flows of substances and / or energy, such as heat conduction or diffusion, which is described by $D\Delta\vec{u}$ in the system of equations).The concrete form of the free member $\vec{f}(\vec{u})$ is of exceptional importance, because all wave processes are generated by the nonlinear dynamics of the point system $\vec{u}_t = \vec{f}(\vec{u})$, which always must be self-oscillating or potentially self-oscillating. In the base model of the active

medium with recovery, the complicated nonlinear behavior of a single element is described by the free member, i.e. as the function $f_1(u, v)$, which usually has **N**-shaped form (Figure 1). Three simplest types of such elements can be distinguished [17, 42, 43]; one can also say that a single element has three essentially different regimes of its behavior, because it is possible to force the element change its type. These are: *self-excited* (or *self-oscillating*), *excitable* (or *waiting*) and *trigger* (or *bistable*) regimes. Accordingly, there are three types of homogeneous active media composed of these elements.

The *excitable* element (row **A** of Figure 1) has only one stable steady state (the point **O**, which is the intersection of the two null isoclines; a quiescent state of the excitable element corresponds with this point). External impact over a threshold level (i.e., greater than the length of the segment **OA**), can bring the excitable element out from its steady state and force it accomplish a certain evolution (in the phase portrait shown by the orange line) before returning to its quiescent state. An excited element may affect the adjacent elements moving them out from their quiescent state. As a result, an autowave of excitation spreads through the medium. Excitable media like the working myocardium consist of such excitable elements. Hence, it becomes obvious the fallacy of popular opinion that "all cardiac cells have spontaneous firing capacity, but only at a very slow heart rate", the assertion which can be often met in books and papers.

The *bistable* element (row **B** of Figure 1) has two steady states at the points O_1 and O_2, each of which can be whether stable or unstable, while the point O in this case is always unstable. Transitions between the two stationary states occur when an external impact exceeds a certain threshold level (the same way as it does in the excitable element). In such media there can be the *trigger wave* propagation, which switches the media from one steady state to the other. A classic case of such a switching autowave (and, perhaps, the simplest autowave phenomena) is falling dominoes. Another simple example of the bistable medium is burning paper: the switching wave propagates on it in the form of a flame, switching paper from the normal state to its ashes.

The *self-oscillating* element (row **C** of Figure 1) has no stable steady states (the point O in this case is always unstable) and therefore it permanently performs oscillations of certain fixed form, amplitude and frequency. An example of a self-oscillating medium is the sinus node of the heart, in which excitation impulses arise spontaneously. External influence can disturb these oscillations, but, after some relaxation time, all their characteristics, except for the phase, revert to the stable values, although the phase can be changed, resulting in the phase waves spread in the self-excited medium. Such phase waves can be observed in electro-garlands or in certain chemical media.

So it can be clearly seen on the phase portrait of the basic system of equations describing active medium of different types (see Figure 1) that a significant difference between these three types of behavior of an active medium is caused by the quantity and the position of its singular points. The shapes of autowaves observed in reality can be, however, very similar to each other, and therefore it can be difficult to assess correctly the type of element only by the form of its excitation impulse.

It is reasonable that a good number of examples of combined active media, which are composed of different types of elements, can be found everywhere. The heart is just one example of a highly organized combined active medium.

2.3. Pacemakers

The region of a combined active medium which consists of self-oscillatory elements is called the *pacemaker*. This region emits autowaves with a certain stable period. An example of a biological pacemaker in the heart of the human is the sinus node, which is constituted of a group of cells functioning in the self-oscillating mode.

In thin enough layers of the active medium, the pacemaker creates a picture in the form of ring waves diverging from a center (Figure 2). Period of pacemaker oscillations is determined by its intrinsic properties and can be arbitrary, but not less than the absolute refractory period, because a new action potential cannot arise during the absolute refractory period (see below).

If there are a number of self-oscillating elements with different periods in the medium, every element with low-frequency activity is suppressed by the element with the highest frequency [41]. For a long time physiologists have known about the hierarchy of pacemakers in the heart, and the same result was obtained mathematically in the second half of twentieth century. Pacemakers in the heart are the sinoatrial (SA) node, the atrioventricular (AV) node and the bundle of His and Purkinje fibers. The sinoatrial node normally initiates action potentials, simply because it generates impulses slightly faster than the other areas with self-oscillating activity. The remaining pacemakers normally are in a depressed state, which is reflected by physiological language as "latent pacemaker capability." If the SA node is suddenly "out of order", the fastest of the "spare" pacemakers (i.e., the AV node) enters into work, and, as a result, the heart continues its action nearly in normal regime. This duplication of parts of the system is aimed, evidently, to improve its reliability.

However, recent studies [49, 50] have shown that the rhythmic activity of the self-oscillating elements in the group which form the body of the pacemaker is synchronized by more complex laws, and the ascertained earlier variant of synchronization from the element with the highest frequency of the oscillations is only a special case. The problem of the control of cardiac rhythm has been considered in terms of the general theory of the synchronization of relaxation systems, and, as result, the main pathways of the control of cardiac rhythm have been revealed: (1) control with regard for the features of synchronization of relaxation systems during the formation of the unified heart rhythm due to the acceleration of the slow diastole depolariza-tion phase; (2) control by gradual integral increase in the duration of the slow diastole depolarization phase; (3) subsequent synchronization of the rhythm as a delay of the slow diastole depolarization phase.

2.4. Traveling autowaves

The concept "*traveling autowave*" (or "*autowave of excitation*", or "*propagating autowave*") should be considered as generalization made in the new biophysical language of the concept "exci-tation wave", which is understood in the frames of physiology as an electrical wave that
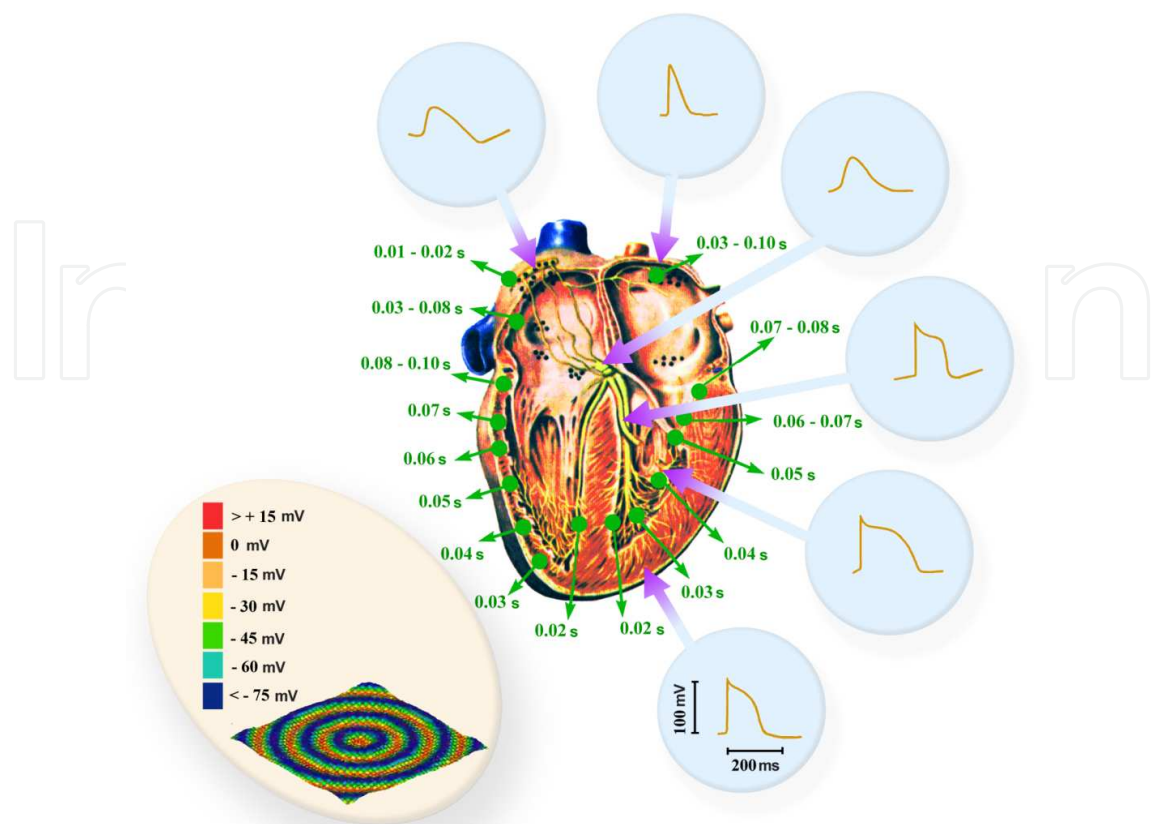
Figure 2. Spatiotemporal organization of the normal cardiac action. Green inscriptions and arrows indicate the time of arrival of the excitation wave in the corresponding region of the heart (using the data published in [48]). Blue incuts show the shape of the traveling wave ("action potential") in different areas of the heart caused by the difference in properties of the elements of the excitable medium that forms the heart tissue. Beige incut demonstrates the normal propagation of the traveling-wave of excitation from the pacemaker area in the center (from the sinus node) towards the edges (through the working myocardium) in a simple simulation model.

propagates along a muscle fiber just before its contraction. Autowaves of excitation are perhaps the most common in nature autowave phenomena, they occur in a variety of physical, chemical and biological objects. According to the earliest investigations [40–42], "traveling autowave" was a designation of the wave processes that have stable ("self-sustaining") parameters, such as speed, amplitude, and pulse shape, independently of initial conditions. It was believed also that "if two autowaves propagate toward each other, they do not pass through each other, like linear waves and solitons do it, but they annihilate in a collision" [41]. Autowaves was believed to be not able to interfere or to reflect from obstacles. These properties were considered as a significant difference of autowaves from the usual electromagnetic or sound waves.

Analysis of the systems of mathematical equations that describe the active medium has given not only a quite good explanation of the phenomena known from physiology, but also has led to the discovery of many new interesting properties of the active media, even in the earliest works. For example, the dependence of the traveling autowave velocity on the curvature of its front was obtained as a result of this analysis: the velocity decreases with increasing curvature,

and there is a *critical value of the curvature*, above which the excitation wave propagation becomes impossible. For example, see [41, 47, 51–53]. The *critical curvature* leads, in particular, to the fact that the excitation autowaves can not pass through an aperture of sufficiently small size in a non-excitable obstacle (e.g., in the postinfarction scar). Other properties of traveling autowaves associated with critical curvature underlie different mechanisms of reentrant tachycardias, which will be considered in more details below.

Another interesting property of active media, which was found out in the earliest works, is that, for periodic autowaves, their velocity decreases with increasing frequency, and explicit expressions for calculating its value were derived. In such a way, it has been shown mathematically that the stationary propagation of autowaves is possible only as long as the wave period T is more than a certain value T_{min}, and that there is a certain mathematical dependence of the wave velocity on the medium properties [54, 55]. When $T < T_{min}$, the propagation occurs in some peculiar manner: though the excitation waves propagate without attenuation, not all of them propagate, but only, for example, every third or fourth wave, depending on T, which is known in cardiology as *Wenckebach periodicity*.

The existence of T_{min} is caused by the fact that the excitation autowave can not propagate until the recovery processes, which are described with the slow variable of the base model, has finished. This property of active media is called refractoriness, and the typical recovery time is called the refractory period.[6] *Refractoriness* is the fundamental property of any object of autowave nature (especially excitable medium) not to respond on stimuli, if the object stays in the specific refractory state. In common sense, *refractory period* is the characteristic recovery time, i.e. the period of time that is associated with the motion of the image point on the left branch of the isoclinic curve $u_t = 0$ (i.e. the segment DO; see row **A** of Figure 1). The *relative refractory period* is understood as the immediately following interval during which initiation of the next action potential is inhibited but not impossible. In the *state of relative refractoriness*, propagation of the next autowave is possible also before the full recovery of the media, but with slightly less velocity depending on the time elapsed since the passage of the previous wave. For periodic pulse, this results in *dispersion*, which is dependence of the autowave velocity on their frequency [44, 56]. If the time interval after the passage of the previous wave is too short, then propagation of the subsequent wave is impossible, so that, for every excitable medium, there is a certain minimal interval between a couple of successive waves, the absolute refractory period. The absolute refractory period is the interval during which the next action potential absolutely cannot be initiated, no matter how large a stimulus is applied. But, even in a fully recovered excitable medium, velocity of the excitation autowaves can not exceed a certain value, which is the maximum value for the medium and which is equal to the velocity of the traveling autowave of zero curvature (i.e. with the flat front, the *flat autowave*). The mathematical details can be found in the suggested literature.

---

6 Let us recall that the existence of the refractory period in the cardiac muscle has been ascertained as long as 1876 by EJ Marey, who was an extremely gifted French researcher in the physiology of the heart. It was he, who also introduced this term as well as who noted that the refractory period of the cardiac muscle lasts conspicuously longer than in skeletal muscle or nerve. In 1906, A.J. Carlson was the first who used the terms "absolute refractory period" and "relative refractory period"[8].

A lot of active media are characterized by the pronounced *relaxantness*, i.e. the time interval of refractoriness is noticeably longer than the time interval of excitation. In the basic model of the active medium with recovery, relaxantness is determined by a small parameter ε [41]. For cardiac tissue, the refractory period exceeds the excitation time approximately 300 times. This leads to the fact that the excitation wave in the heart has a sharp front edge, but has no pronounced trailing edge. The presence of prolonged refractoriness allows to explain, for example, the *annihilation* of the excitation waves when they collide. Because of long refractory tail, where the excitation is not possible, two waves can not pass through each other and die.

However, more recent studies [57–59] have shown that autowaves can exhibit more complicated behavior, and the properties described in the early classical works are observed only in a number of special cases. For example, it was found out that annihilation does not always occur in a collision of autowaves, but under certain conditions autowaves can pass through each other like solitons. Diffraction, reflection and splitting are also possible to observe for autowaves under certain conditions. It was shown that autowave shape and velocity may vary during its spontaneous evolution caused by the bifurcation memory [20, 21]. It was declared [20]:"The general theory of active media remains to be formulated, and practically each in-depth study reveals new types of their dynamics and self-organization. There is no reason to think that these types are unique; on the contrary, the available experience indicates that, once described, a new dynamic regime or bifurcation is thereafter found in other systems, even those that have been investigated for a long time". So it can be expected that further deepening of our knowledge of the properties of autowaves will also help us to understand the failure in the treatment of cardiac arrhythmias.

2.5. Spatiotemporal organization of the normal cardiac action

The main goal of the normal cardiac action is the pumping function of the heart. It is the ordered propagation of the excitation autowave in the myocardium that maintains efficient contraction of the heart, thereby allowing blood to be pumped throughout the body. For the pumping function of the heart to be maintained effective, appropriate *spatiotemporal organization* (STO) of the excitation process is extremely important. The appropriate STO is caused by the very structure of the heart, i.e. by the special spatial arrangement of various autowave elements (cardiomyocytes) with significantly different behavior (which, as mentioned above, is described with use of the nonlinear free member $\vec{f}(\vec{u})$ in the base model of the active medium with recovery). Due to the special spatial structure of the heart as a whole organ, well-known from courses of anatomy and physiology, the only mode of traveling waves initiated from the sinoatrial node occurs in the normal heart during the normal cardiac activity (Figure 2).

It is disorders of the spatiotemporal organization of the process of myocardial excitation and contraction that should be understood as a generalized mechanism of cardiac arrhythmias, which usually manifests with various electrical indications used by doctor to set the correct diagnosis. Note that these ideas are being developed in the concept of the autowave function of the heart [1], which has not yet received a rigorous mathematical formulation.

The simplest examples of disorders of the appropriate STO are various conduction block. The mechanism of partial conduction block has been described above from the biophysical

standpoint. The so called electrical conduction system of the heart should be considered only as an illusive perception of the real complicated active media that builds the body of the heart. The illusion is caused by sincere desire to describe the heart strictly within the frames of the mechanistic approach, which requires that some specific electric wires were searched for. However, there are not any electric wires in the cardiac tissue, which rather presents the network of active elements of different types. Each of these elements can be forced change its type by influence of humoral, nervous or metabolic factors. The target function of the inherent circulatory regulation consists in maintaining the appropriate STO independently from uncontrolled influence of humoral, nervous or metabolic factors. In those cases where the regulation is untenable, pathological states develop leading to disease. For example, additional sources of autowaves, arising from pathological changes of certain areas of the myocardium, can result in severe cardiac arrhythmias.

It is extremely important to understand that the function $\vec{f}(\vec{u})$ may be changed in the same way at various combinations of values of the individual parameters of the cardiomyocyte, but even utterly different combinations of individual parameters may result in the same clinical manifestations of cardiac disorders inasmuch as they are determined by the state of the function $\vec{f}(\vec{u})$ rather than by any of the individual parameters of the myocardium. It is not sodium, potassium, calcium, etc. conductivity of membrane ion channels in cardiomyocytes (as it is usual for physiologists to think) causes the normal cardiac action, but exactly that of their combinations which is optimal for the given conditions of functioning of the organism. It is likely that causes of the cases of unsuccessful pharmacological treatment of cardiac arrhythmias, which were revealed, particularly, in CAST, hide themselves somewhere here.

Hence, cardiac arrhythmia should be considered in a more general way: they occur either as a consequence of disorders of STO, or as a consequence of disorders in inherent circulatory regulation, but not as isolated disorders of the cardiac electrical activity.

3. Basic biophysical mechanisms of cardiac arrhythmias

Since autowave processes were pointed in the role of sources of cardiac arrhythmias, the number of known types of sources of cardiac arrhythmias has increased significantly. This increase is associated not only with discovery of a number of new mechanisms of arrhythmias, but also with distinction of the mechanisms that were equated with each other before. So for *reentry*, a mechanism of arrhythmias known since the 19th century, it is accepted to distinguish now at least five types: (1) running around a ring, (2) spiral wave, (3) autowave reverberator, (4) multiple reverberators, and (5) fibrillation as chaotic behavior of autowave reverberators. In accordance with the classification of principal mechanisms of cardiac arrhythmias that was suggested in [60], the running around a ring as well as the spiral wave should be reckoned among *anatomic reentry*, while the others belong to *functional reentry*.

Altered automaticity, which is the second classical mechanism of arrhythmogenesis, can be divided into (1) *altered normal* automaticity, (2) *abnormal* (or induced) automaticity, and (3)

triggered activity. Regarding *increased automaticity*[7], several new types of automatic nature were also discovered, in addition to the pacemaker activity. These are: (1) induced automaticity, (2) *leading center*, (3) triggered activity by the mechanism of *early afterdepolarization*, and (4) triggered automaticity by the mechanism of *delayed afterdepolarization*.

And each of these mechanisms of arrhythmias can cause disarrangement of the cardiac action, manifesting themselves mostly as ectopic sources of the excitation autowaves. Using new biophysical language, we have attempted to describe below more detailed the currently known types of mechanisms of cardiac arrhythmias.

3.1. Increased automaticity

The term "cardiac automaticity" refers to a biological event characterized by spontaneous process of action potential generation in separate groups of myocardial cells. "Spontaneous" should be understood as being conditioned by intrinsic dynamics, and developing or occurring without apparent external influence, force, cause, or treatment. A spontaneous process is capable of proceeding in a given direction without needing to be driven by an outside source of energy. It is accepted that three different mechanisms may independently underlie cardiac automaticity. These are: (1) the *proper automaticity* of specialized cells of cardiac conduction system, (2) induced automaticity arising or growing under external influences, and (3) triggered activity, which is the automaticity provoked by a series of electrical stimuli.

About the proper automaticity of cardiac conduction system was already told above; it underlies normal cardiac function. It is widely thought that the proper automaticity of specialized myocardiocytes is defined by the capability of cardiac cells to undergo spontaneous diastolic depolarization and to initiate an electrical impulse in the absence of external electrical stimulation. This is so indeed that the specialized conduction system of the heart has the special property of depolarizing without any external influence with a slow, positive increase in voltage across the cell's membrane (the membrane potential) that occurs between the end of one action potential and the beginning of the next action potential. But let's look intently again at Figure 1. Process of spontaneous depolarization corresponds with the motion of the image point from the point D down the left branch of the isoclinic curve $u_t = 0$. It is easy to perceive that a self-oscillating element differs from an excitable or from a bistable element only by the absence of the stable steady state at the point **O**. This difference results in birth of a limit cycle[8], which force the element fire again and again. Hence, it is the limit cycle that should be recognized as the cause of the proper automaticity of the specialized myocardiocytes! And what is more, it is likely that a dynamic system described by the base model can be constructed in such manner that the left branch of the isoclinic curve $u_t = 0$ would go in the other direction

---

7 Some people find it difficult to discern the difference between enhanced and increased cardiac automaticity. It seems that to distinguish between enhanced and increased cardiac automaticity is useful for some reasons. While enhanced cardiac automaticity is referred to reactions of normal adaptation (such as influence of autonomic nervous system because of stress), increased cardiac automaticity is addressed rather to pathological alterations of cardiac tissue properties. Some authors prefer using the term "abnormal induced automaticity" instead of "increased cardiac automaticity" (see for example [60]).

8 In mathematics, in the study of dynamical systems with two-dimensional phase space, a limit cycle is a closed trajectory in phase space.

(i.e. line would go from the right top down to the left), and therefore we would have sponta‐ neous diastolic hyperpolarization, — however, a bistable element would fire again and again even in such a case, because of absence of the stable steady state at the point **O** on the left branch. Thus, acceptance of spontaneous diastolic depolarization as a cause of automaticity seems to be a mistake due to misunderstanding of nature of the self-oscillating automaticity.
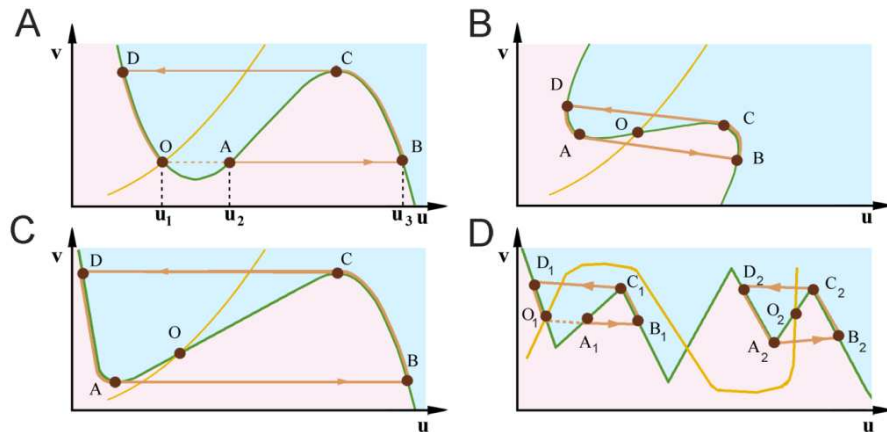

Figure 3. A few examples of increased automaticity caused by transformation of an excitable element in a self-oscillat‐ ing one. Designations are as in Figure 1. It is assumed that the scale is the same in all examples. See description in the text.

Altered normal automaticity is the proper automaticity of cardiac conduction system altered by certain influences. It should be distinguished between primary and secondary permanent increase of frequency of the self-oscillating elements of cardiac conduction system. While the primary increase is conditioned by the processes that have happened inside the cardiomyocyte, and therefore may be rigid against neural and humoral influences, the secondary increase is caused by the neural and humoral influences, and, consequently, is a reversible process. A classic example of the secondary alteration is hyperthyroidism; myocardial infarction provides with examples of the primary alteration.

Induced automaticity is assumed [41] to result from either transforming a waiting regime of certain myocardial area (or even a single cardiomyocyte) in a self-oscillating regime or a sufficient increase of self-oscillating activity of the latent pacemaker cells of the cardiac conduction system. In either case, causes of induced automaticity are similar; among these may be changes of characteristics and ratios of ionic currents in the cell membrane using hormones, poisons, external sources of electric current, etc. Whether the cell spontaneously generates action potential or not, depends on the ratio of incoming and outgoing ion currents. However, as has been stated above, it would be a mistake to assume that it is the spontaneous depolarization after reaching the threshold value of the transmembrane potential that leads to generating spontaneous action potential. Let's look again at Figure 1. The distance between a point of the stable steady state on a branch of the isoclinic curve $u_t = 0$ and the middle section of the same curve (i.e., the segment **OA** in the cases of the excitable regime, as well as the segment O_1A or O_2C in the cases of the triggered regime) corresponds with the threshold value; but it is evident, however, that any saying about the threshold value sounds absurdly in the

case of the self-oscillating regime because no threshold value exists in this case. The illusion that generating spontaneous action potential is caused by the spontaneous depolarization of cardiac cells has spread widely among physiologists only because of their firm intention to stay strictly within the frames of the mechanistic approach. The real cause of transition of an active element from waiting in a self-oscillating regime is such a deformation of its phase portrait which leads to a shift of the point **O** onto the middle section of the isoclinic curve. Changes of the threshold level also occur as a result of one or another deformation of the phase portrait. Specific causes of the phase portrait deformation are similar in either case; these are again poisons, external electric power sources, and other unpleasant things which are almost certain to disagree with a human being, sooner or later.

Figure 3 gives schematically several examples of the deformation of the phase portrait which leads to induced automaticity. The example D is of special interest, because it assumes that two different attractors exist primordially on the phase portrait.[9] While external stimulus remains near the threshold value, the active element behaves in the waiting regime (the attractor at the left side), but the stimulus that sufficiently exceeds the threshold value will throw it in the self-oscillating regime (the attractor at the right side).

It should only be added that latent pacemakers may become sources of arrhythmias, even when their proper automaticity is maintained on the normal level, but, in the cardiac tissue damaged with disease, a low frequency pacemaker is not synchronized by the waves coming from the sinoatrial node. As a result, the distorted ventricular complexes generated by such a source appear out of turn on the background of normal ECG. Mechanism of such arrhythmia (which is a variant of ventricular extrasystole) could be so-called unidirectional block in a damaged site of myocardium [52], when the autowave excitation is capable of spreading in one direction, but is damped propagating in opposite direction. There may be different causes of such unidirectional block; one of these may be the critical curvature, which was discussed above.

In addition, several autowave objects were described under the general title "*leading centers*" [41, 61–65]. In two-dimensional and three-dimensional excitable media, leading centers emit concentric waves similar to the waves initiated by a pacemaker. At least three different mechanisms of leading centers are known from theoretical studies. One of them is described for media consisting of self-oscillatory elements with hard excitation [62]. Such a medium can be at state of rest (i.e. in the waiting regime), but the place of the medium where an external stimulus of suitable amplitude was applied goes into self-oscillating regime and becomes a source of waves. The two other mechanisms of leading centers were described under the titles of "echo" and "partition of the front." The mechanism "echo" in the myocardium was shown in several works [63–65] with use of microelectrode technique. However, the existence of all these types of autowave sources should still be regarded as hypothetical.

The term "*triggered activity*" (TA) is used to refer to a special kind of automaticity when the cells are in the waiting regime and go into self-oscillating regime in response to a stimulus or series of stimuli. Although differences of opinion still exist, there appears to be good agreement that TA is resulted from *afterdepolarizations*, which is understood as the membrane potential

---

9 Similar situation in the corresponding phase portrait (i.e. two attractors) is likely to underlie some types of the atrioventricular nodal reentrant tachycardia, which is discussed below.

oscillations that occur during or immediately following a preceding AP (for more details, see [8, 60]). Based on their temporal relationship, two types of afterdepolarizations are described: early afterdepolarizations (EADs), which occur during phase 2 or 3 of the AP, and delayed afterdepolarizations (DADs), which occur after completion of the repolarization phase. There has been increasing recognition of the role played by TA caused by either EADs or DADs in the genesis of clinical arrhythmias [66, 67–69]. It is widely accepted that phenomena of either type of afterdepolarizations are caused by a variety of conditions that raise the diastolic intracellular Ca^{2+} concentration, resulting in Ca^{2+} mediated oscillations that can trigger a new AP if they reach the excitation threshold. It has been found [70] that the active pumping of calcium ions into cardiomyocytes by the Na^+ / Ca^{2+} exchange current of abnormally increased level is involved in the mechanism of DADs. Therefore, the depolarization is observed after treatment of the myocardium with catecholamines [71], which accelerate the pump, as well as with glycosides (e.g., digitalis) [72, 73], which inhibit the Na^+ / K^+ pump, and this leads in turn to the accumulation of intracellular sodium ions and, hence, enhances the intensity of Na^+ / Ca^{2+} pump [74]. Inhibition of the Na^+ / K^+ pump promotes also the release of Ca^{2+} from the sarcoplasmic reticulum, as well as a number of other processes of molecular level are believed to underlie TA [60].

Although the cause of TA is believed to be the transmembrane potential oscillations exceeding the excitation threshold, closer examination of the phase portrait of the basic model is forcing doubt this widespread opinion. As it has already been argued logically above, the excitation threshold can not play any role for self-oscillatory elements, as it simply does not exist in this regime. This fact motivates to search other, more sensible, explanation. Let's assume that the effect of catecholamines and glycosides results in a significant deformation of the phase portrait, and it is the deformation that is the true cause for the change in behavior of the active elements from waiting into a self-oscillating regime, manifesting it in the triggered activity. An important factor in support of this assumption is the following. In the waiting regime, we have a stable solution of node type at the steady point O; a local *bifurcation* of vector fields on the plane occurs while transiting from the waiting regime into the self-oscillating regime, in which the steady point O loses stability, and a new solution, a limit cycle, arises.[10] Thus, in process of the transition of the steady point O from the left branch to the middle section of the isoclinic curve, the system passes through the state, which is referred to as bifurcation; the bifurcation point is situated at the minimum of the N-shaped isocline. Assume that, under the influence of various substances, the null-isocline $f_2(u, v) = 0$ moves by parallel displacement along the abscissa from left to right in a linear dependence on the concentration of biologically active substances. What will be observed when the system comes to be near the bifurcation condition? Left from the bifurcation point damped oscillations will be observed, which is in a quite good correspondence with afterdepolarizations without TA. On the right we will observe oscillations with increasing amplitude (the movement by escalating spiral, gradually leading off system onto the right branch of the isocline). In other words, the assumption lead to the conclusion that the base system near the bifurcation point behaves just exactly as it is observed in experiments with TA.

---

10 The appearance or the disappearance of a periodic orbit through a local change in the stability properties of a steady point is known as the Hopf bifurcation. For more details, see elsewhere [75].

However, the situation may be even more complicated if we consider the phenomena known under the names of "*stability loss delay for dynamical bifurcations*" or "*bifurcation memory*" [19], recently discovered and still little studied. The essence of the effect of bifurcation memory (BM) lies in the appearance of a special, unusual, type of transition process. An ordinary transition process is characterized by asymptotic approach of the dynamical system from the state defined by its initial conditions to the state corresponding to its stable stationary regime in the basin of attraction of which the system found itself. However, near the bifurcation boundary can be observed two types of transition processes. Firstly, passing through the place of the vanished stationary regime, the dynamic system slows down its asymptotic motion temporarily, "*as if recollecting the defunct orbit*" [19]. And only after a number of revolutions of the phase trajectory in this area of bifurcation memory (which is referred to as "*phase spot*"), the phase trajectory rushes to the state that corresponds to stable steady regime for the system. In other words, the decedent attractor still reveals itself in a certain region near the bifurcations, as if it were still "alive", and this strange situation has contributed to appearance of the third name for the phenomena, "*ghost attractor*" [76]. It is possible that the TA is just another example of the bifurcation memory phenomena. It is hoped that new researches will help to clarify the validity of this hypothesis.

Besides, another very specific new mechanism of arrhythmia is assumed [41], which is the so-called *splitting of the excitation wave*. Passing through the damaged area of the heart, the excitation wave may split into two following each other component. Investigation using special blockers has shown that the first component is caused by activation of Na^+-current, and the second is a delayed activation of the Ca^{2+}-current. The auxiliary component, resulting from this splitting, can be a source of extra cardiac beat.

All these autowave phenomena is supposed to be able act as *ectopic foci*, resulting in *ectopic beat* (or cardiac ectopy). Note that nearly all autowave sources mentioned in this section were detected in experiments on myocardium only at very specific experimental conditions. Nevertheless, the physician should bear in mind that the ectopic foci in the myocardium, which gives the characteristic concentric waves of excitation, can be not only an unregulated latent pacemaker. This remark is entirely correct also regarding so-called *polytopic tachycardias*, which may be based on essentially different mechanisms of ectopia.

3.2. Circulating autowaves (reentry)

The concept of circulation of the excitation wave, which is so important for understanding the mechanisms of a number of types of high-frequency cardiac arrhythmias (tachycardias), has been confirmed experimentally in 1926 by D. Scherf and C. Schockhoff [8], and now it is widely recognized that the circulation of excitation (reentry) is not confined within conducting tissues, but can occur in any region of the heart.

3.3. A single two-dimensional autowave vortex

It is known that reentrant cardiac arrhythmias are often initiated by forming a discontinuous propagating wave of excitation. In sufficiently thin layers (i.e., in two-dimensional media, in mathematical language), it is refractoriness that makes possible the existence of special *circulating autowaves* (Figure 4), which evolve from wave fronts with the free tip originating

from rupture of the wave front. In a thin layer of active medium of sufficiently large extent ("infinite" from the point of view of mathematics, i.e. a layer of such extent when a further increase in the size does not affect the behavior of the object under study), the rotating autowaves take shape of rotating spirals. It was shown already in the axiomatic models of Wiener-Rosenbluth [40] that the discontinuity of a plane wave of excitation, which results from its collision with a sufficiently large non-excitable obstacle, makes the excitation wave revolve around this obstacle. Further studies have shown that the availability of obstacles is not required without fail and that the rotating autowaves also arises when creating the appropriate initial conditions. For example, the inhomogeneity of tissue refractoriness may lead to the fact that at high repetition frequency of the excitation waves the wave front may break on rough-ness of the tail of the preceding wave, and the evolution of these ruptures leads to the formation of rotating autowaves.
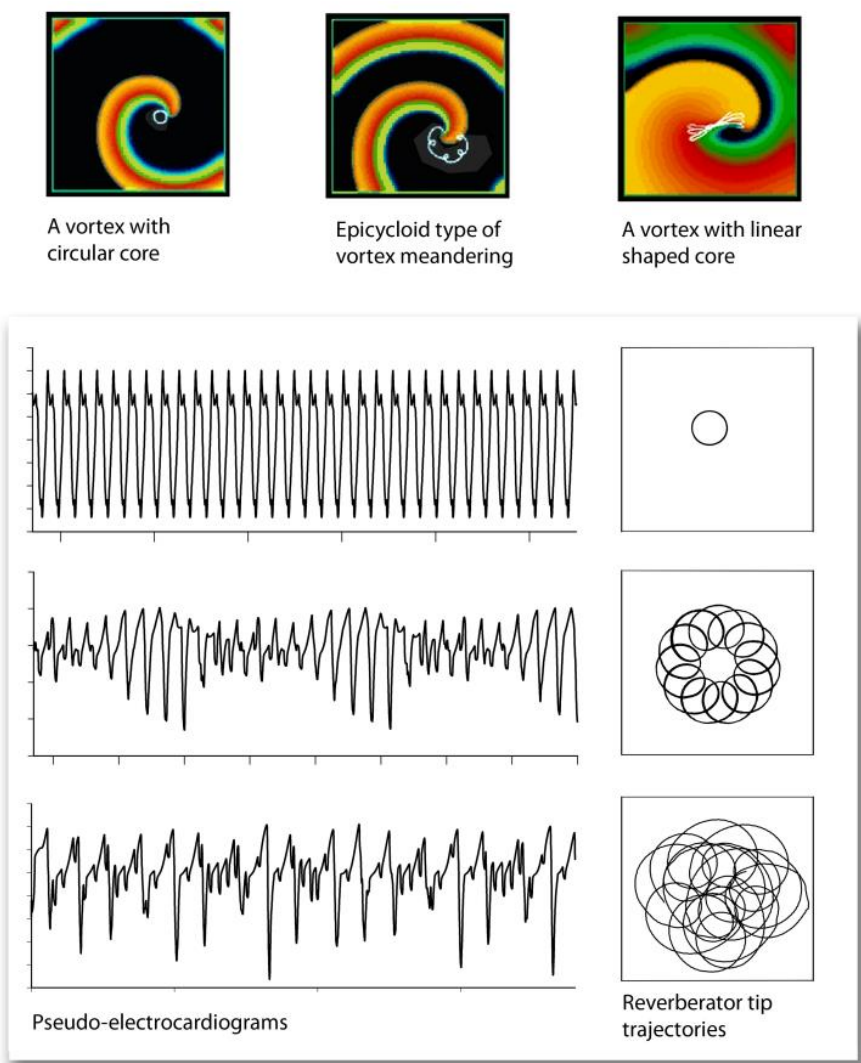

A vortex with circular core

Epicycloid type of vortex meandering

A vortex with linear shaped core

Pseudo-electrocardiograms

Reverberator tip trajectories

Figure 4. Some classic types of reverberator evolution. The inset demonstrates examples of ECG forms for different types of evolution of reverberator: uniform circular rotation (top), meander (middle), and hyper-meander (bottom).

It is customary to distinguish four variants of circulating autowaves (see [8, 41], for example):

1. The *spiral wave*, which is an excitation autowave *revolving around an obstacle*. An example of this is atrial flutter due to the autowave moving around cardiac veins.

2. The *autowave running around the ring* (synonym: one-dimensional circulation regime). Examples of arrhythmias caused by such type of reentry are: (1) the excitation wave circulation between the atria and ventricles through additional atrioventricular path during tachycardia associated with WPW-syndrome; (2) supraventricular tachycardia caused by the excitation wave circulation in the AV node; (3) intraventricular circulations of the excitation wave along path consisting of the specialized cardiac conduction system.

3. The autowave *reverberator*, which is two-dimensional circulation of autowave with its free tip in the plane of the heart wall in the area of myocardium without anatomic obstacle (i.e., *two-dimensional autowave vortex*). In contrast to the circulation around the obstacle, the position of the center of this type of circulating autowaves in this case can move through the cardiac tissue (i.e., it can drift) during arrhythmia. With use of both the multielectrode and optical mapping the existence of such sources of arrhythmias in real myocardium was demonstrated in the SA node as well as in the atrial and ventricular cardiac tissue.

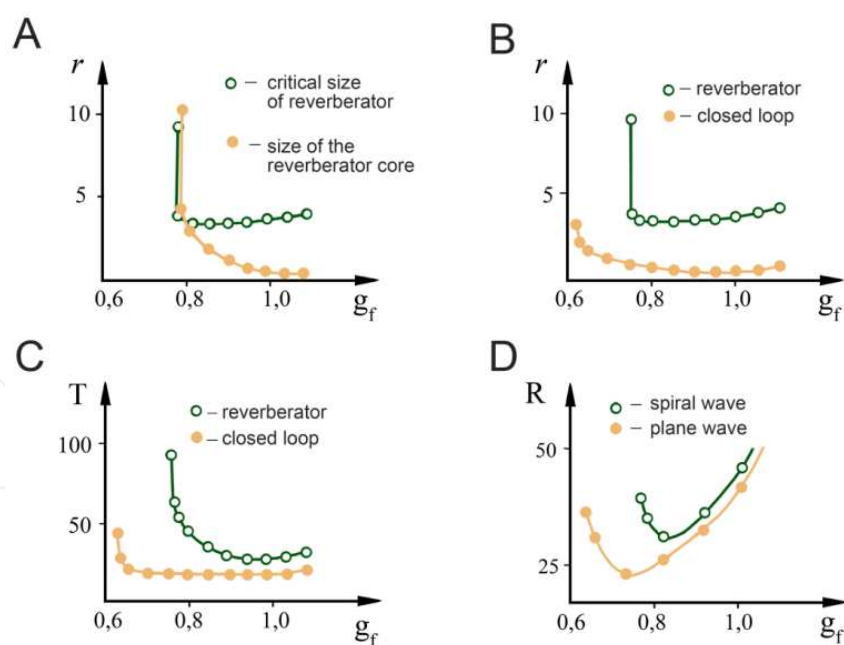4. Autowave *fibrillation*, which is chaotic regime of autowave propagation.

Figure 5. The critical size of reverberator (based on data from [41] obtained by Pertsov and Panfilov for the FitzHugh-Nagumo model). **A**. The relation between the critical size of reverberator and the size of the reverberator core. **B**. The dependences of the critical sizes of reverberator and of the critical size of a closed loop (for an autowave running around the ring) on the conduction of rapid current g_f. **C**. Dependences of the period of the reverberator and of the autowave running around the ring on g_f. **D**. Dependence of the refractoriness of the medium (R) on g_f for the spiral wave (curvature $k=0.83$) and for the plane wave.

It is necessary to pay attention to some of the subtleties of terminology. Various authors can refer to the rotating in two-dimensional medium autowave as "spiral wave", "reverberator", "rotor", "autowave vortex" or even "scroll wave". Note, however, that these terms are not interchangeable synonymous. Briefly, there are the following differences between them. The term "spiral wave" refers usually only to the autowave that revolves around non-excitable obstacle in a medium of sufficiently large extent, that is, in this case, the medium of such size, comparing with which the obstacle is small, but large enough to result in the wave break. The tip of spiral wave moves along the boundary of the non- excitable obstacle. The authors of [41] pointed out: "The most important difference between a reverberator and a spiral wave rotating around the hole, which is similar to reverberator in its form, is that the reverberator is not tied to any structure in the medium. Due to this property, reverberators can appear and disappear at different locations of the medium." Moreover, the autowave reverberators have property to appear not only in the absence of non-excitable obstacles, but also in a completely homogeneous medium (under appropriate initial conditions).

Furthermore, it proved (Figure 5) that refractory period is longer for waves with nonzero curvature (i.e., for reverberators) than for a plane autowave (i.e., the autowave running around the ring), and refractory period of reverberators begins to increase before increase of refractory period of a plane wave, when the excitability of the medium decreases. These and other significant differences of reverberator from circular movement of the excitation wave make us distinguish between these two regimes of reentry.

In the simplest case without drift (i.e., the regime of *uniform circular rotation*), the tip of a reverberator rotates around a fixed point along the circumference of a certain radius (the circular motion of the tip of the reverberator). The autowave cannot penetrate into the circle bounded by this circumference. As far as it approaches the centre of the reverberator rotation, the amplitude of the excitation pulse is reduced, and, at a relatively low excitability of the medium there is a region of finite size in the centre of reverberator, where the amplitude of the excitation pulse is zero (recall that we speak now about a homogeneous medium, for each point of which its properties are the same). This area of low amplitude in the centre of the reverberator is usually called the *core of the reverberator*. The existence of such a region in the center of reverberator seems, at first glance, quite incomprehensible, as it borders all the time with the excited sites. A detailed investigation of this phenomenon showed [41] that resting area in the centre of reverberator remains of its normal excitability, and the existence of a quiescent region in the centre of the reverberator is related to the phenomenon of the critical curvature. In the case of "infinite" homogeneous medium, the core radius and the speed of the rotor rotation are determined only by the properties of the medium itself, rather than the initial conditions. The certain size of the core of the reverberator is conditioned by that the excitation wave, which circulates in a closed path, should completely fit in this path without bumping into its own refractory tail.

The *critical size of reverberator* is understood as the minimum size of the active homogeneous medium in which the reverberator can exist during indefinitely long time. To assess the critical size of reverberator, some authors (e.g., [61]) used the size of the core of the reverberator, supposing that the region of the medium that is adjacent to the core is sufficient for the existence

of sustainable reentry. However, accurate quantitative study of the dependence of the reverberator behavior on conductivity of rapid transmembrane current (which characterizes the excitability of the medium) has revealed [41] that the critical size and the size of the reverberator core are its different characteristics (Figure 5), and the critical size of reverberator is, in many cases, much larger than the size of its core (i.e., reverberator perishes even when its core easily fit within the boundaries of the medium and its drift is absent). It was shown also that, for the same local characteristics of an excitable medium (excitability, refractoriness, etc. given by the nonlinear free member of the base model), there are significant quantitative differences in dependencies of characteristics of the reverberator and of one-dimensional circulation of the autowave impulse, although corresponding curves coincide qualitatively. It is assumed that the earlier growth of the refractory period and of the critical size of reverberator with a decrease of excitability is caused by the curvature of the wavefront of reverberator.

The one-dimensional circulation regime, which is perhaps the simplest case of circulating autowaves, has been studied in greatest detail, and the results help to understand more intricate variants of reentry. In particular, it was shown [55] that the existence of this type of reentry is only possible on condition that the size of the closed loop in which the circulation occurs is greater than a minimal size (the *critical size of the closed loop*). Size of *the core of the reverberator* is usually less than the *critical size of the closed loop* for circular movement, which is associated with the phenomenon of *critical curvature* (Figure 5). Note that, in the normal myocardium (i.e., with normal velocity of excitation autowave, $V \approx 1$ m / sec, and with normal refractory period, $R \approx 0,2$ sec), the wavelength ($V = R \lambda$) is about 20 centimeters, and, therefore, it is difficult, even nearly impossible, for circulating wave to fit in the human heart, if there are not any special conditions. Probability of arising of reverberator in the human heart under normal state of the myocardium is small, but the decreases of refractory period or of the excitation wave velocity (under the influence of metabolism, under the pharmacological influence, etc.) contribute to the appearance of circulating waves in the myocardium.

A reverberator is able to drift freely in medium; besides direction of its drift is caused not only by the properties of the medium, but also largely by its own properties (i.e., the reverberator itself "decides" where to move). In the classical works [32, 42, 77], the following basic types of reverberator behavior in a homogeneous isotropic medium (Figure 4) are distinguished: (1) the regime of *uniform circular rotation* (circular movement), which is the simplest case without drift, with the tip of a reverberator rotating around a fixed point along the circumference of a certain radius; (2) *meander*, which is two-periodic motion of the reverberator in which the trajectory of its tip is similar to a cycloidal curve (epicycloid and hypocycloid); (3) *hyper-meander*, which is a complicated reverberator motion with, probably, chaotic trajectory of its tip. Under special conditions, a vortex with meandering of hypocycloid type can be trans-formed to a vortex with *linear core* [77].

Recently a new form of autowave behavior was found [21], — namely, the transformation of reverberator motion from a two-periodic meander into one-periodic circular rotation due to spontaneous deceleration of reverberator drift. The new autowave behavior, which was called "*autowave lacet*", is likely to result from a phenomenon of so called bifurcation memory. When autowave lacet was discovered, the first question arose: Does the meander exist ever or the

halt of the reverberator drift can be observed every time in all the cases, which are called meander, if the observation will be sufficiently long? The comparative quantitative analysis of the drift velocity of reverberator in the regimes of meander and lacet revealed a clear difference between these two types of evolution of the reverberator: while the drift velocity quickly goes to a stationary value during meander, a steady decrease in the drift velocity of the vortex can be observed during the lacet, in which can be clearly identified the phase of slow deceleration and phase of rapid deceleration of the drift velocity.

The revealing of autowave lacet may be important for cardiology, because the autowave theory predicts the existence of special type of ventricular arrhythmias, conditionally called "*lacetic*" [1, 2], which cardiologists do not still distinguish in diagnostics.

When an autowave propagates in a medium and collides with an obstacle containing a slit, propagation beyond the slit depends on the relationship between the width of the slit and the liminal region. When the slit dimensions are greater than the liminal region, then the wave fragment passing through the slit will continue to propagate. In addition, the ends of the newly formed wave fragment will curl and form counter-rotating autowave vortices, which can results in cardiac tachycardia or fibrillation. [47].

Even more interesting phenomenon caused by the critical curvature effects is *unidirectional conduction* of excitation autowave through a narrow gap in a non-excitable partition arising in the case if the partition edges are arranged at an angle to one another [52].

Variety of forms of behavior of autowave vortices leads to the variety of cardiac arrhythmias, which can be quite ambiguous reflected in the electrocardiograms [1].

At this point, this brief overview of two-dimensional circulating autowaves must be stopped, and more detailed information about their multifarious behavior can be found in the extensive literature.

3.4. Three-dimensional autowave vortices

Even more intricate types of reentry arise "in the three-dimensional case", in the parlance of mathematicians [13, 78–80]. Figure 6 gives examples of three-dimensional organization of reentrant propagation. Direct generalization of an autowave reverberator for the case of three-dimensional space is a *simple scroll*, which rotation occurs around a straight line, called "*filament*". In addition to such a simple three-dimensional autowave reentry, the filament can be arbitrarily curved and possibly even closed (in the latter case, the scroll turns into an *autowave scroll ring*). If the rotational phase of the scroll varies along its filament, the vortex is called "*twisted scroll*". Despite the much greater variety of three-dimensional autowave regimes in comparison with two-dimensional case, it was mathematically proven that there are certain topological restrictions, which reduce significantly the variety of three-dimensional autowave structures. For example, a single twisted scroll ring is impossible; topologically there must be another filament passing through the center of the filament ring [81].
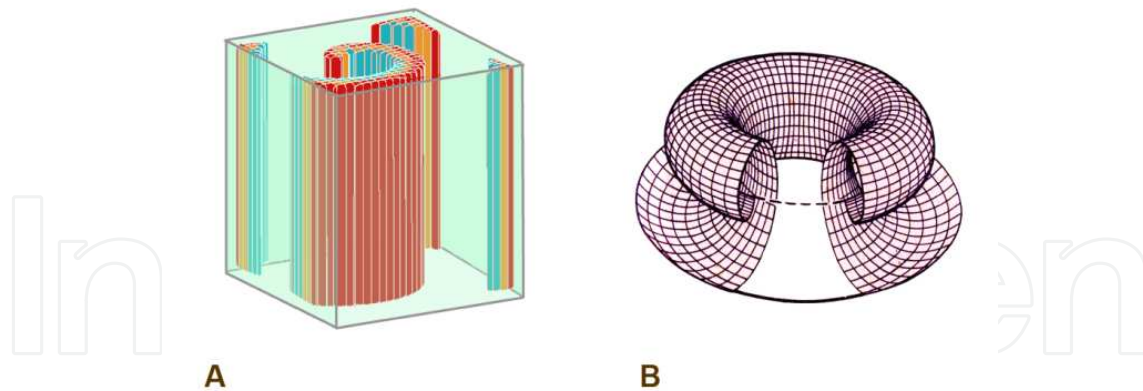
Figure 6. Examples of autowave 3D-vortices: **A** — a simple scroll, **B** — a simple vortex ring.

Although the scroll filament is a bit of a virtual object, it was shown [79] that it has a special property, which has been called *tension* of filaments. A filament with positive tension tends to shorten, similar to an elastic band, and, for example, the autowave scroll ring "shrinks" as a result. When being with negative tension, it increases in size, which eventually ends in multiple twisting of the filament, in its ruptures and in total chaotization of the autowave behavior, — and it looks like ventricular fibrillation (inasmuch as the atrial walls are much thinner, an intricate autowave three-dimensional structure cannot be placed there). The reader should give attention to the fact that the filament tension is a phenomenon caused by the properties of the active medium, and not by the properties of the autowave vortex arising in this medium.

A new mechanism of stabilizing the motion of an autowave vortex was described in the same work for the case of three-dimensional excitable medium with a positive tension of filament; the stabilization occurs due to shortening of the filament attached to the transverse walls of model media. Although ECG manifestations of such stabilization of a vortex motion are not considered in [79], the obvious conclusion in this case is that there would be observed a spontaneous transition of tachycardia from polymorphic to monomorphic type. Thus, stabilization of an autowave three-dimensional vortex with positive tension due to shortening its filament is today the third possible mechanism of such electrocardiographic transformation (the two others are anchoring the autowave vortex in an obstacle and tachycardia of the lacetic type [1]). Note that the anchoring and the lacetic tachycardia are still hypothetical, and their detection in real myocardium requires further research.

3.5. Multiple reverberators and autowave fibrillation

One of the most important results of the study of autowave processes is disclosure of a new mechanism of instability in the active media [30, 42] associated with reproduction of reverberators. As mentioned earlier, wave-fronts sent by reverberator follow closely to each other, and therefore a subsequent wave-front may be broken on the irregularities of the tail of the previous wave-front. It is recognized that (1) reverberators cannot reproduce themselves in a homogeneous medium, and (2) the waves give rise to a new reverberator in an inhomogeneous medium only if the period of these waves is sufficiently small (roughly equal to the relative

refractory period). The latter circumstance is used in physiological experiments to provoke tachycardia: two consecutive pulses are sent through the stimulating electrode, and if the second pulse falls within the "window of vulnerability" (i.e., at the time of relative refractoriness), then an experimental reentrant arrhythmia occurs [34]. It is also assumed that a similar mechanism (collision of an extra wave of excitation to the refractory tail of the previous wave) underlies clinical paroxysmal tachycardias, such as atrial flutter, paroxysmal supraventricular or ventricular tachycardia [8].

It was shown in theoretical studies with use of axiomatic models [41] that another significant property of the reverberator is a finite time of his life in heterogeneous environments. Causes of destruction of reverberator are the same as the causes for its rise, and consist in the inability of steady propagation of excitation waves with high frequency in heterogeneous media. These conclusions are well confirmed in experiments: a reverberator in a homogeneous chemical medium has "infinite" lifetime (limited by depletion of reagents), but in the heart, where there is large heterogeneity, an arising accidentally reverberator usually have time to send only a few wave-fronts.

Thus, there are two competing processes in an inhomogeneous medium: reproduction of reverberators and their death. When the reproduction rate is less than the rate of death, then chaos is impossible, and the medium works in regular mode. In the opposite case, the number of autowave sources begins to grow, leading to chaos. This process reproduces well all main phenomena observed in the heart during fibrillation [41, 42]. Here, similar to the phenomenon of critical mass in the chain reactions, some critical characteristic values appear, above which there is an unlimited reproduction of reverberators. One of these characteristics is the so-called *critical mass of fibrillation*, which is the minimum mass of cardiac tissue, above which fibrillation becomes possible.

The historically first point of view on ventricular fibrillation was that it is a passive process: the jaded heart cannot longer conduct the excitation through the myocardium and only a few Purkinje fibers, after losing control from the pacemaker of higher hierarchy, continue spontaneously to cause asynchronous excitation of myocardial fibers. Currently, though multifocal ectopic activity of ventricular myocardium remains still being considered as a possible mechanism of fibrillation, the main mechanism of ventricular fibrillation is widely recognized to be reentry within the ventricles, which may occur for one cause or another [7, 8, 60,]. Development of ideas about myocardium as an active medium led to significantly different views on the nature of ventricular fibrillation. For example, it has been shown that the ECG that is typical for ventricular fibrillation can be observed resulting from at least two different autowave mechanisms: as a result of coexistence multiple autowave vortices or of a single vortex due to Wenckebach-like frequency division, which in turn is due to some peculiarities inhomogeneity of the active medium [80].

However, such an interesting hypothesis about the nature of ventricular fibrillation as a competing chain reactions of birth and death of reverberators is not received still the merited popularity among researchers and remains without its further development. It is hoped that new researches will give a new development for this hypothesis.

4. Basic mechanisms of adaptation and their abnormalities

Earlier in this chapter we have attempted to show how significantly opportunities of researchers in the interpretation of various phenomena of cardiac action were expanded with using biophysical language, which constitutes a substantial generalization of the experience of two centuries of studies of the heart. But it must be also recognized that the cybernetic language, the basis of which was provided by Norbert Wiener in his classic work [82], is equally useful generalization for aims of cardiology. This section of the chapter is intended for outlining the fundamental cybernetic ideas about the cardiac action and its disorders, with the subsequent text based mainly on Fedorov's[11] work [83], which is scarcely known for English readers.

In the tradition of biophysics, the regulation of heart rate is modeled in isolation; in other words, the heart is assumed to be an autonomous organ, in which its own rhythmic contraction is determined by spontaneous activity of the sinus node myocardiocytes (as it was described above in this chapter), although it is assumed a number of both humoral and neural factors that can modulate this spontaneous activity. In contrast to the pure biophysical approach, cyberneticists used to simulate the regulation of cardiac rhythm as a part of certain regulatory circuits in a more general model of the cardiovascular system rather than isolated.[12] Biological systems contain many types of regulatory circuits, both positive and negative; and construction of a scheme of regulatory circuits, i.e. a typical for traditional physiology descriptive model of regulation, is certainly based on considerations about purpose of functioning of a mechanism or a system that is under studying. Instead the word "purpose", the fixed expression "*physiological role*" (of the system or of the mechanism) is accepted to use in biological sources, the term "*target function*" corresponding with it in the frames of the cybernetic approach.

It is recognized that the most important purpose of functioning of the blood circulatory system (including also external respiration), i.e. the most important "physiological role" of the blood circulation, is the timely delivery of oxygen, nutritious and other substances to all the cells of the body, as well as removal of accumulated metabolites and heat from the tissues; and this ensures maintenance of the internal environment, which surrounds the cells and is necessary for implementation of their metabolism and their biological functions. Open- and closed-loop control as well as a good number of guidance loops is involved in the *inherent regulation* [13] of circulation. It is accepted that the inherent circulatory regulation includes all changes in the cardiovascular system which are directed to preventing or reducing every threatening alteration of the internal environment and metabolism of cells. Consideration of separate mechanisms of the inherent circulatory regulation reveals that the regulation provides it also with achieving an additional goal, which is maintenance of the blood circulation as itself and economization of the blood flow reserve. This substantiates the assignment of the cardiovascular apparatus to the category of a separate functional system of the organism. Besides the

---

11 Viktor FedorovichFedorov carried out this investigation during his work on PhD thesis on the base of the Department of Telemedicine of Medical Center attached to the Presidential Property Management Directorate.

12 By the way, this is one of the reasons why the modern "cardiophysics" is not synonymous with the modern "cardiovascular biophysics".

13 In the original [83]:«автоматическое управление кровообращением».

tasks of control of maintaining the internal environment at the chosen level, the biological inherent regulation includes also mechanisms of self-adjustment (*adaptation*) of the control systems in accordance with changes in the parameters of the biological object or of external influences, as well as mechanisms of automatic selection of the best modes. In view of this the broader term "*inherent guidance*" (or "*self-guidance*") is believed to be more appropriate to describe the functioning of living systems. It should be noted that a human being is charac-terized with a very complex mental activity; on this occasion, P.K Anokhin, a famous Russian physiologist who developed the theory of functional systems [84, 85], pointed out a significant influence of motivation and memory on the result of afferent synthesis, i.e. not physical, but purely informational in its nature stimuli are important for results of inherent circulatory regulation. Hence, the sinus rhythm of the human heart reflects the work of many body systems in normal and pathological conditions, and therefore it is quite reasonable to recognize the possibility of making use of its parameters for constructing a quantitative measure of the quality of individual health.

However, we must here pay attention to the paradoxical situation existing in theoretical medicine today, when any disease (except for the most exotic) is fully described and classified by its stages as well as is easily scaled by its severity, but at the same time a scaling (a set of standardized quantitative measures of the quality) of health is absent, although people widely use in everyday life words of comparing people's health.

According to the new conception of measuring human health [86] that was developed at the Department of Medical and Biological Cybernetics of the Russian State Medical University (Moscow) and was approved by Russian Ministry of Health about two decades ago, the health is understood as "*the system's ability to achieve its aims through its adequate behavior*". Analysis of the ultimate goals of the diverse forms of behavior of living systems can reduce all of these goals to two aims, which are self-reproduction and self-preservation (and keen rivalry between them in the nature is usually resolved in favor of the first). The main idea which was advanced in this connection is to make "*an assessment of individual health or social health (health of a population) on the base of the ability of the living systems to self-development, to self-preservation, to reproduction of offspring as well as to reproduction of the means for implementation of their goals and adequate forms of their behavior*". In the same paradigm, adequate forms of behavior of living systems are grouped as follows:

• self-organization, understood as ability of the system to implement process of dynamic structural and functional self-development with differentiation of some collections of elements for a function;

• adaptability, i.e. the system's ability to adjust itself to changing environmental conditions while retaining its identity and its main functional properties;

• active transformation of the environment (i.e., natural habitat) as a form of adaptation, consequences for the social system should be to create harmony of the noosphere (according to V.I. Vernadsky).

It is easy to see in this construction that self-organization, and active habitat transformation is based on adaptive properties, which are typical for all living things.

In this regard, it is extremely important to remember that adaptive properties of a natural living system is aimed at survival of the biological population[14] as a whole rather than to survival of the single individual in the population, which is conditioned by the process of biological evolution (for instance, by means of natural selection). P.V. Simonov, another illustrious Russian physiologist, has written [87] on this subject: *"mechanism of myocardial infarction has been formed already in the evolution of the relict salmon. As a working hypothesis, we tend to consider cardiovascular pathology of neurogenic origin as a result of a long evolution of one of the mechanisms that enforce the stability and qualitative improvement of the population through the elimination of those individuals that adapts poorly in certain conditions of the existence of our distant ancestors. (...) Since passive animals are often better protected from external dangers (predators, traps, etc.) than individuals with active-searching behavior, natural selection could lead to the accumulation of passive cowards in the population, which would denote regression of the species while increasing its sustainability. This risk of degeneration seems to have been eliminated by means of genetic linkage between the tendency to passive-defensive behavior and susceptibility to cardiovascular and some other psychosomatic diseases. An extreme but striking example of such behavior is suicidal tendency among the subjects with chronic depressive syndrome."* It seems that the recent investigations [88] prove such conclusions. Despite the fact that this context generates a number of ethical issues, which are known as moral dilemmas[15], any ignoring of such biological mechanisms would be a huge mistake.

In the adaptive responses of a biological system (an organism), it is useful to distinguish the ability to implement the process of adaptation, the process itself and its result. Therefore, with respect to adaptive reactions of a human individual, from our point of view, we can formulate the following definitions. *Adaptation* of a human is the process of such adjusting changes of the organism and of the personality under the influence of totality of conditions of habitat that provide an approximation to the optimal values of the efficiency and reliability of implementation of adequate patterns of human behavior. *Adaptedness* is understood as the state of having been adapted, which is also the measure the current result of adaptation. *Adaptability* is the measure that reflects the ability of a biological system to change its adaptedness per unit of time.

Practical experience shows that a high level of adaptedness to certain specific conditions (i.e., high specialization) leads to a loss of adaptability (universality), and vice versa. Consequently, either extreme reduces the reliability of functioning of the organism. On the basis of these theses an individual human health can be defined as follows.

Individual health is a measure that expresses the ratio between adaptedness and adaptability of the individual. At that, the optimal state of health should be understood as a state of satisfactory adaptedness to the specific conditions of the individual existence while maintaining sufficient adaptability (adaptive readiness to a sudden change of conditions).

---

14 A biological species can be considered as a set (in the mathematical meaning) of consanguineous (closely-related) biological populations.

15 In-depth analysis of moral dilemmas was given in [89] recently, so we will not dwell on this issue here.We should only note that similar problems are encountered when finding the optimal balance between the values of the unity of a nation and the values of liberal freedoms.

Consequently, the character of the deviations in the action of the heart from its normal action must be considered from the standpoint of assessment of deviations in state of a human from his or her optimal state of health. How this should be done?

When considering a practically healthy person with the saved in varying degrees adaptive mechanisms, the process of adaptation to functioning in conditions of permissible physical or mental exertion is taking the form of a quasi-linear increase of the corresponding function with an increase in exertion. The linear dependence in coordinates of "stress-response" is broken only in the areas of imperceptible (i.e., while having a subthreshold level of stress) or extreme exertions (i.e., when exhaustion of the reserve of adaptation occurs). In other words, the whole curve "stress-response" reveals a sort of S-shaped dependence (i.e., the logistic sigmoid function). There are five sites that can be identified on this curve (Figure 7). It is obvious that the nature of the load as well as parameters of response may vary in description of the different systems or organs of the human body. It may be a special load, which has an influence only on a number of certain parameters of the organism (e.g., the influence of illumination on the pupil diameter), or a sort of universal load, in response to which the parameters of all or most of the organs and the systems become changed (such as hypoxia). The response parameters need not be primary (measured directly). As those, in some cases, one may make use of the results of mathematical processing of time series of individual primary parameters or even different mathematical combinations of several primary parameters that characterize a particular function of the body. The main requirement for the choice of such parameters is that each parameter showing the response of the organism should change with increasing load like the logistic function and should conform to physiological functions.

It is obvious that the various organs and systems of the body are not necessarily to be in the same functional state. So the pathology of certain organs or systems may result in not only functional, but also structural change of other organs for compensating the reduced function. Therefore, to describe the whole organism by the proposed method, it is required to develop a system of tests that assess separate responses of different organs and systems on a load which is typical for each of them. A specific component of quantitative assessment of the health quality of a particular person can be obtained by making comparison of the slope and the level of saturation of the logistic curve, which corresponds to the response on an adequate load, in a specific plane, which conforms with a specific organ or a specific system, with the average statistical parameters of healthy individuals of the corresponding sex and age group. A set of such "response-planes", each of these with its own parameters (A, B, C, D), enables us to build a system of quantitative assessment of the quality of individual health. By tracking the dynamics of change of the parameters of the curves in each plane simultaneously, we can assess the level of total individual health.

The medical examination should be fulfilled as a three-phase test, comprising the successive phases: 1) initial phase of rest, 2) phase of the individually metered load, and 3) recovery phase. This is caused by the following circumstances.
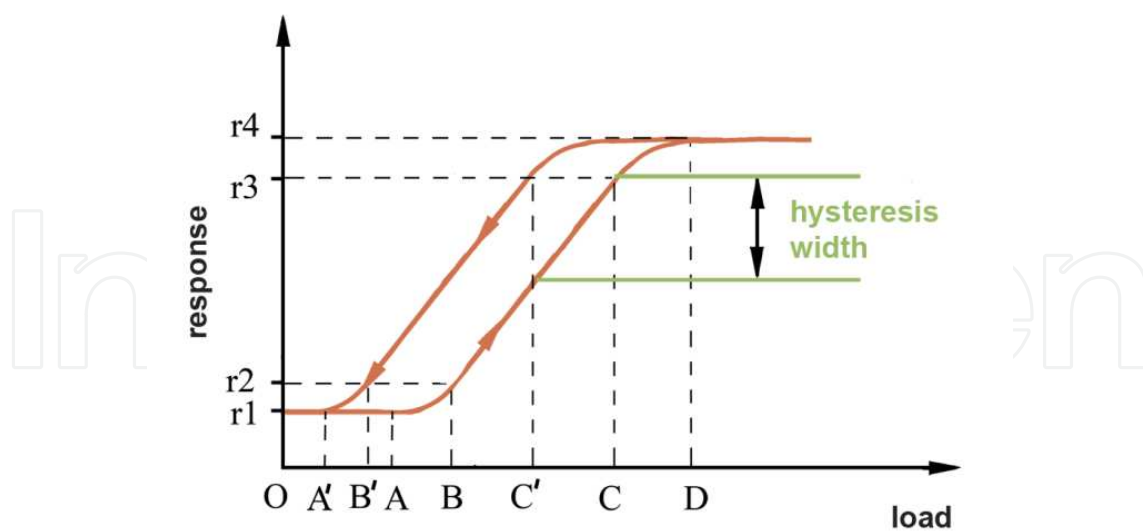
Figure 7. Typical response curves obtained during the testing process with linear increase and subsequent linear decrease of load. Five sections can be identified on each curve: **OA** — the zone of areactivity, when the load is so small that the response is inexpedient; **AB** — the initial nonlinear part of the response, when the specific reaction grows with load increases (can be approximated by a power or exponential functions); **BC** — the zone of linear regulation, when the reaction increase is proportional to the load growth; **CD** — the final non-linear section, when the responding system is approaching exhaustion of resources for adaptation; the section right of **D** corresponds with resource exhaustion response. Arrows show the direction of the process. The projection of the distance between linear sections of the load curve (ascending part of the loop) and the recovery curve (its descending part) on the axis of reactions is taken as the "*width of the hysteresis loop*".
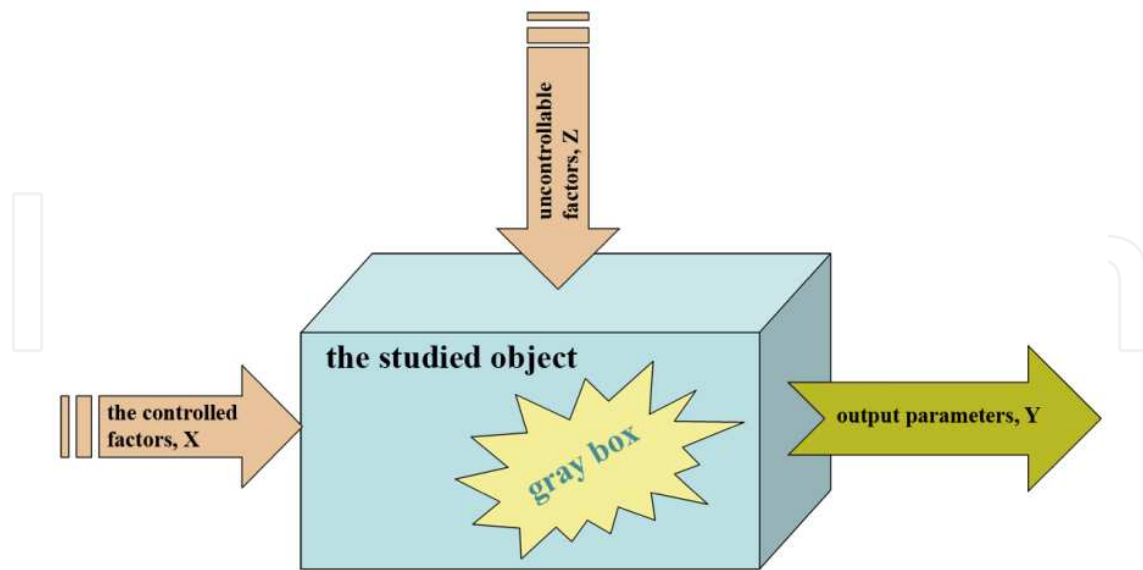

Figure 8. The general scheme of the two approaches (black and gray boxes). **X** — vector of input influences; **Y** — vector of output measured parameters; **Z** — vector uncontrolled influences.

When investigating the complex system (and many researchers are inclined to reckon human organism among supercomplex systems) about the internal structure of which is not known everything that is required to know for predicting its behavior under different conditions, the approaches of "black box" or of "gray box" (Figure 8) are taken to use in cybernetics. Either approach provides for an impact on the studied object by a number of certain controllable factors (the vector of the input parameters) with subsequent registration of the vector of the output parameters. While changing the quantitative levels of the input vector or composition of these parameters, one can observe some changes of the output vector with the aim to find out the transition function, which is inherent in the object under study. In general, we can write the expression $\vec{Y} = F(\vec{X}, \vec{Z})$, i.e. the output parameters are a function of both the input (controlled) impacts and a complex of uncontrolled influences. In our particular case, a doctor or a researcher has a number of certain ideas about the form of the function (or more precisely, a set of models that approximately describe it); in other words, our box is "gray", not "black". However, even when the form of the function F is known exactly, but we do not know anything about the vector $\vec{Z}$, the correct prediction of how the system behavior changes with changing the vector $\vec{X}$ can scarcely be done. As long as the task of a detailed description of the vector $\vec{Z}$, seems to be unsolvable in principle when the cardiovascular system is under the study (since, for example, emotionally significant reflections of the patient have a significant effect on the cardiac rhythm as well as on blood pressure, but they cannot be put under an external control), the only way to solve the problem of revealing the transition function is the way of shifting the conditions of studying the cardiac action to the situation that can be described by the inequality $\vec{X} >> \vec{Z}$ (in the appropriate meaning). To reach the situation, one can either transfer some of the factors from the $\vec{Z}$ to the $\vec{X}$ (if it is possible), or raise the components of the vector $\vec{X}$ to such values when the control system of the biological object being studied will be forced to neglect the influence of $\vec{Z}$ for reasons of self-preservation.

Hence, the testing of a complex system the sufficient information about which is not available should be carried out under the influence of a set of controlled factors (the load) the total effect of which is much higher than that of the unrecorded influences. In other words, the medical examination of the cardiac action should always be performed with the phase of such level of the individually metered load that is physiologically significant for the organism of the examined individual.

No matter how little the test influence is applied, the cardiovascular system, as well as the organism as a whole, functions in a "background mode" nevertheless, in accordance with a great number of the natural laws. So the information about the level of functioning of the organism at rest (at below-threshold loads) is also required, and, therefore, every part of the dependence in coordinates of "stress-response" provides some useful information about the organism.

After canceling any significant load, the system can not instantly jump to its original state because of its inertial properties associated primarily with changes in concentrations of various substances (both hormones and metabolites) in response to the foregoing load. For bringing the substances to their initial concentration, their diffusion, transport and metabolism require some time and energy costs. Hence, the recovery process contains not less information about

the system than its actual response to the load. To assess the response of the load, one of the most convenient models is that one in which a linear increase of load up to a predetermined level followed by a linear decline of load to zero (for example, using veloergometry) is implemented. Curves obtained in this way are reminiscent of the hysteresis loop in descriptions of the magnetization reversal of ferromagnets with high coercivity. The curves from tests with increasing load to a submaximal level have the form shown in Figure 7. The width of the hysteresis loop in this case reflects the adaptability of the reacting system.

The basic mechanisms of cardiovascular regulation, as well as methods for assessing their integrity in the cases when spatial-temporal organization of the heart remains near normality, have been described briefly in this section of the chapter. In such cases, the methods recommended will help more effectively identify persons with weakened adaptive ability at maintenance of normal heart functioning. According to the well-known joke, "healthy people do not exist, there are only people that did still not get the sufficiently full checkup"; and it looks like a great truth.

5. Conclusion: Arrhythmic action of the heart

It has been believed for centuries that cardiac arrhythmia is a sort of pathology, excepting a few variants, caused by these or those disorders of cardiac activity. However, the facts that is set out in this chapter make us become engrossed in our thoughts about many cases when arrhythmia may be a specific sort of normal activity of the heart (and the cardiovascular system in whole), which should be regarded as a normal adaptive response of an organism either on some other health problems, which are different from cardiac problem, or on some specific external signals. And medical treatment in either situation seems to be harmful, and accordingly increases the overall mortality rate from treated cases of arrhythmia (the problem that was addressed in the beginning of the chapter).

In some cases, it has the character of a reversible adaptive response, in other cases it is a compensatory response aimed at replacement of certain lost functions of the organism, and all such cases should be taken as a *normal arrhythmic functioning of the heart*. Certain types of arrhythmias are dangerous to life of the whole organism, because they call forth hemodynamic disturbances, which in turn lead to dysfunction of various vital organs. This group of arrhythmias includes also those that are started up by certain natural hereditary mechanisms of the population dynamics regulation, which should also be recognized, from the viewpoint of the biomedical sciences, as a sort of the normal arrhythmic functioning of the heart. Recall that, according to the hypothesis expressed by P.K Anokhin, even myocardial infarction, at least in some cases, should be considered as a specific adaptive reaction realized through certain mechanisms of intra-population self-regulation. Developing Anokhin's hypothesis, we propose a new special term "*arrhythmic action of the heart*", which should be comprehended as the normal arrhythmic functioning of the heart that is aimed at maintenance of physiological homeostasis under certain specific conditions.

In some other cases, we are often faced with *pathological arrhythmic functioning of the heart*, of course. Therefore, the actual problem of modern medicine is the development of objective methods for discerning arrhythmic action of the heart and *arrhythmic disorders of the action of the heart*

Note that the evaluation of serious cardiac arrhythmias associated with the change in location of the source of excitation waves is even more difficult. For example, the case reported previously [1] engenders thoughts that even the atrioventricular nodal reentrant tachycardia (AVNRT) should be considered in the certain cases as a variant of the normal adaptive response. To observe and to study the normal variants of the AVNRT is harder for two obvious reasons. Firstly, when a human is moving very actively, taking measurements of his or her physiological parameters becomes a very difficult task. Secondly, there are a relatively small number of people in populations of modern societies, who are able to undergo very high physical loads. But it must be assumed that in ancient times, when living conditions were much more rigorous, the normal type of AVNRT could play a vitally important role in providing physiological needs of an actively moving human (during an extremely quick run, for example). It is reasonable to assume that the biological evolution has given our ancestors this normal type of AVNRT as a reserve mechanism for increasing cardiac rate during extremely high physical loads, when it is needed more frequent rhythm of cardiac contraction than the highest possible rhythm of the sinoatrial node. If this hypothesis will be confirmed, clinical cases of AVNRT should be seen rather as a disease resulting from decrease of control from the side of the functional system that regulates the cardiac action, than as pathology of the atrioventricular node.

Another important point is concerned with the widespread conception in the medical community that the arrhythmia must be understood as some abnormalities in the electrical activity of the heart or in conduction of excitation waves through the myocardium. Under this conception, disturbance of other cardiac functions, such as the contractile function, does not relate to cardiac arrhythmias, although can result in arrhythmia of this or that type. This understanding of cardiac arrhythmia is based on traditional rough notions of cause-and-effect relations between processes that underlie the cardiac action. It is traditionally accepted that the process of excitation of the membranes of cardiomyocytes causes contraction of these cells, which in turn leads to the ejection of blood from the heart. Everything here is seems to be simple, logical and understandable, but...

Recent studies [90–92] have demonstrated that the nature in this case also proved to be "smarter" than the human logic built within the frames of the mechanistic approach. The new experimental results reveal the existence of negative feedback, in the terms of cybernetics, between the contractile function of the heart and the process of its electrical excitation, as well as the substantial effect of the mechanical conditions of cardiac contraction on the process of cardiac excitation. In contrast to the rather well-studied nature of the coupling between excitation and contraction, the molecular-cellular mechanisms of *mechanoelectrical feedback* and its physiological and pathophysiological significance are still not completely understood. The authors assert that the mechanoelectrical coupling is physiologically significant for regulation of functioning of normal myocardium, because it provides coordinated changes of the action

potential and of the kinetics of intracellular calcium depending on the mechanical conditions, which is an additional contributing factor of the cardiac muscle adaptation to changing external conditions of mechanical contraction. The same authors acknowledge that arrhythmogenic effects of mechanical impacts are well-known; for example, a sharp shortening or quick mechanical stretches of cardiomyocytes under certain conditions lead to extra action potentials.

Moreover, after studying influence of myocardial heterogeneity on the efficiency of its mechanical function, the same authors come also to unexpected findings. It proved that "different types of mechanical heterogeneity (…) can play a positive or negative role depending on the distribution of heterogeneous properties and on the order the elements of the system are activated" [90]. In pathology, fine coordination of individual characteristics of cardiomyocytes and sequence of their activation can be broken, so that myocardial system becomes disorganized, and its function deteriorates. For example, parts with casual inclusions of hypoxic, hypertrophic and normal cardiomyocytes were observed in the mature myocardium, and therefore it happened that the functional properties of the cells in such a system (particularly, their electromechanical characteristics) were randomly distributed with respect to a sequence of excitation. As a result, the strength of cardiac contraction decreases sharply in such a system, while arrhythmogenic dispersion of repolarization increases. It has been shown that derangement of the accurate sequence of activation of the myocardium can lead to a sharp deterioration in its contractile function, and this fact helps to explain why so often the clinic use of artificial pacemaker does not improve the quality of life of patients. In that way, the complex and diversified investigation brought out clearly that cardiac arrhythmias can result not only from the disorder of the electrical activity of the heart, but also from disorder of its contractile function, and that the most important cause of arrhythmias is a disarrangement in the mechanisms of synchronous interaction between the electrical and mechanical processes in the myocardium.

Consequently, the term *"pathological cardiac arrhythmia" should be understood not only as these or those disorders in electrical activity of the heart, but it is disorders of its functioning as the whole organ*, which is a part of the entire cardiovascular system with its complex regulatory mechanisms.

If disorders in electrical organization of the heart are well compensated by the mechanical properties of multi-cellular system of the myocardium, the heart continues to perform its pump function effectively. On the contrary, very serious disorders of the pump function of the heart, caused by disorders in the accurate organization of the mechanical properties of the myocardial multi-cellular system, can occur even during the "normal" sequence of propagation of electric (i.e. autowave) excitation in the heart. Scientific observation of the heart from this new standpoint of biophysics and cybernetics makes us re-ask the question, in what cases changing the position of the source of excitation waves should be seen as a failure of adaptive mechanisms (i.e., as the disease), and in what cases such sorts of arrhythmia should still considered as a normal effect of adaptive mechanisms or as their side effect. In case of pathological arrhythmias, another task associated with revealing the exact location of failure of adaptation

remains: whether it finds itself in the myocardium or in one of the control loops and guidance loops that serve the cardiac action.

Hence, according to the conception presented here, we must distinguish at least the following groups of pathological arrhythmias:

• arrhythmias that are ranked among normal reactions of adaptation, but, nevertheless, lead to hemodynamic disorders, dangerous for the whole organism (the mechanisms of regulation of population dynamics, for example);

• arrhythmias that result from disorders of adaptation because of disorganization in the chains of regulation of cardiac action;

• arrhythmias that result from disorders of adaptation because of disorganization of the autowave function of the heart.

It must be assumed that these new results will help finally to begin effective treatment of cardiac arrhythmias by restoring the accurate organization of such a complex system which the heart is indeed.

The biophysical language provides a better understanding of the causes of cardiac disorders, because it offers a number of integral characteristics of biological objects, and this is what gives him additional power. The physiological language has become actually a linguistic subset of the biophysical language, and it is quite a natural process in the development of knowledge.

Acknowledgements

Author details

Andrey Moskalenko[*]

The Institute of Mathematical Problems of Biology, Russian Academy of Sciences, Pushchino, Russian Federation

References

[1] Moskalenko, A. Tachycardia as "Shadow Play". In: Takumi Yamada (ed.) Tachycardia. Rijeka: InTech; 2012; ISBN 978-953-51-0413-1. p97–122.

[2] Elkin, Yu. & Moskalenko, A. Basic mechanisms of cardiac arrhythmias. In: Ardashev A.V. (ed.) Clinical Arrhythmology. Moscow: MedPraktika-M; 2009; ISBN 978-5-98803-198-7. p45–74 (*in Russian*).

[3] Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. New England Journal of Medicine 1989;321(6) 406–412. doi:10.1056/NEJM198908103210629.

[4] Brooks M.M., Gorkin L., Schron E.B., Wiklund I., Campion J., Ledingham R.B. Moricizine and quality of life in the Cardiac Arrhythmia Suppression Trial II (CAST II)". Controlled clinical trials 1994;15(6) 437–449.

[5] Golitsyn SP. Borders between benefits and risks in the treatment of ventricular disturbances of cardiac rhythm. International Journal of Medical Practice 2000;(10) 56–64.

[6] Druin Burch. Taking the Medicine: A Short History of Medicine's Beautiful Idea, and our Difficulty Swallowing It. London: Chatto & Windus (Random House); 2009. ISBN: 978-0701182786.

[7] Kurian, T. & Efimov I. Mechanisms of fibrillation: neurogenic or myogenic? Reentrant or focal? Multiple or single? Still puzzling after 160 years of inquiry. J Cardiovasc Electrophysiol. 2010;21(11) 1274–5, ISSN: 1540-8167.

[8] Mandel W. J., editor. Cardiac Arrhythmias: Their Mechanism, Diagnosis, and Management. Philadelphia, Pa: J.B. Lippincott; 1995; ISBN 978-039-75-1185-3.

[9] Schmidt R. F. and Thews G., editors. Human Physiology. Springer-Verlag, Berlin-Heidelberg-New York; 1983; ISBN: 3-540-11669-9.

[10] Sherwood L. Human Physiology: From Cells to Systems. Cengage Learning; 2013; ISBN: 9781133108931.

[11] Crampin EJ, Halstead M, Hunter P, Nielsen P, Noble D, Smith N & Tawhai M. Computational physiology and the physiome project. Experimental Physiology 2004;89(1) 1-26.

[12] Noble D. Modelling the heart — from Genes to Cells to the Whole Organ. Science 2002;295 1678-1682

[13] Noble D. Modelling the heart: Insights, failures and progress. BioEssays 2002;24 1156-1163.

[14] Wessel N, Malberg H, Bauernschmitt R & Kurths J. Nonlinear methods of cardiovascular physics and their clinic application. International Journal of Bifurcation and Chaos 2007;17(10) 3325-3371.

[15] Ewing GW. There is a need for an alternative or modified medical paradigm incorpo-rating an understanding of the nature and significance of the physiological systems. North American Journal of Medical Science 2010;2(6) 246–251.

[16] Loskutov A. Fascination of chaos. Physics – Uspekhi 2010;53(12) 1257–1280.

[17] Loskutov A., Shavarov A.A., Dolgushina E.A., Ardashev A.V. Cardiac tissue as ac-tive media: Invariant characteristics of the theory of dynamical systems and heart rate variability. In: Ardashev A.V. (ed.) Clinical Arrhythmology. Moscow: MedPrak-tika-M; 2009, ISBN 978-5-98803-198-7. p1085–1103 (*in Russian*).

[18] Loskutov A. & Mironyuk O. Time series analysis of ECG: A possibility of the initial diagnostics. International Journal of Bifurcation and Chaos 2007;17(10) 3709-3713.

[19] Feigin, M. & Kagan, M. Emergencies as a manifestation of effect of bifurcation mem-ory in controlled unstable systems. International Journal of Bifurcation and Chaos 2004;14(7) 2439–2447, ISSN 0218-1274.

[20] Ataullakhanov, F., Lobanova, E., Morozova, O., Shnol', E., Ermakova, E., Butylin, A. & Zaikin, A. Intricate regimes of propagation of an excitation and self-organization in the blood clotting model. Physics—Uspekhi 2007;50(1) 79–94, ISSN 1063-7869.

[21] Moskalenko, A. & Elkin, Yu. The lacet: a new type of the spiral wave behavior. Cha-os, Solitons & Fractals, 2009;40(1) 426–431, ISSN 0960-0779

[22] Titomir LI. & Kneppo P. Bioelectric and Biomagnetic Fields. Theory and Applications in Electrocardiology. Boca. Ratón, Florida: CRC Press; 1994. ISBN 978-0849387005.

[23] Sahu P., Lim P.O., Rana B.S. and Struthers A.D. QT dispersion in medicine: electro-physiological Holy Grail or fool's gold? QJM: An International Journal of Medicine 2000;93(7) 425–431. DOI: 10.1093/qjmed/93.7.425.

[24] Baum O.V., Popov L.A., Voloshin V.I., Muromtseva G.A. QT-dispersion: Models and measurements. Bulletin of arrhythmology 2000;(20) 6–17 (*in Russian*). http://www.vestar.ru/atts/1669/166901.pdf

[25] Baum OV., Popov LA., Voloshin VI., Muromtseva GA. QT-dispersion in orthogonal and pseudo-orthogonal lead systems. Bulletin of arrhythmology 2002;(26) 49–56 (*in Russian*). http://www.vestar.ru/atts/983/983baum.pdf

[26] Akintunde AA, Oyedeji AT, Familoni OB, Ayodele OE, Opadijo OG. QT Interval prolongation and dispersion: Epidemiology and clinical correlates in subjects with newly diagnosed systemic hypertension in Nigeria. J Cardiovasc Dis Res 2012;3(4) 290–295. DOI: 10.4103/0975-3583.102705.

[27] Trayanova N. Concepts of ventricular defibrillation. Phil. Trans. R. Soc. Lond. A 2001; (359) 1327–1337; DOI: 10.1098/rsta.2001.0834.

[28] Efimov IR, Cheng YN, Van Wagoner DR, Mazgalev, TN. & Tchou, P. J. Virtual electrode-induced phase singularity: a basic mechanism of defibrillation failure. Circ. Res. 1998;(88) 918–925.

[29] Efimov I.R., Kroll M.W., Tchou P.J., editors. Cardiac Bioelectric Therapy: Mechanisms and Practical Implications. Springer, 2008; ISBN 978-038-77-9403-7.

[30] Luther S, Fenton FH, Kornreich BG, Squires A, Bittihn P, Hornung D, Zabel M, Flanders J, Gladuli A, Campoy L, Cherry EM, Luther G, Hasenfuss G, Krinsky VI, Pumir A, Gilmour RF Jr, Bodenschatz E. Low-energy control of electrical turbulence in the heart. Nature 2011;475(7355):235-9. DOI: 10.1038/nature10216.

[31] Zhuchkova, E., Radnayev, B., Vysotsky, S. & Loskutov, A. Suppression of turbulent dynamics in models of cardiac tissue by weak local excitations. In: Dana S.K., Roy P.K., Kurths J. (eds.) Understanding Complex Systems. Berlin: Springer; 2009; p89–105.

[32] Winfree AT.Varieties of spiral wave behavior: An experimentalist's approach to the theory of excitable media. Chaos 1991;1(3) 303–334, ISSN 1054-1500

[33] Krinskii VI., Kokoz Iu.M. Analysis of the equations of excitable membranes. III. Purkinje fiber membrane. Reduction of the Noble equations to a 2d order system. Analysis of automaticity by nullcline graphs. Biofizika 1973;18(6) 1067-73.

[34] Moskalenko, A. Nonlinear effects of lidocaine on polymorphism of ventricular arrhythmias. Biophysics 2009;54(1) 47-50, ISSN 0006-3509.

[35] Starmer CF. How antiarrhythmic drugs increase the rate of sudden cardiac death. International Journal of Bifurcation and Chaos 2002;12(9) 1953-1968.

[36] Moskalenko, A. & Elkin, Yu. Is monomorphic tachycardia indeed monomorphic? Biophysics 2007;52(2) 237–240, ISSN 0006-3509.

[37] Prigogine I. From Being to Becoming: Time and Complexity in the Physical Sciences. San Francisco: W.H Freeman & Co; 1980. ISBN: 978-0716711079.

[38] Mikhailov A.S. Foundations of Synergetics. Berlin: Springer; 1990.

[39] Bushev M. Synergetics: Chaos, Order, Self-Organization. World Scientific Pub Co Inc.; 1994. ISBN: 978-9810212865.

[40] Wiener N.; Rosenblueth A. The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle. Arch. Inst. Cardiologia de Mexico 1946;16 (3–4) 205–265.

[41] Grekhova, M.T., editor. Autowave processes in systems with diffusion. Gorky: Institute of Applied Mathematics of the USSR Academy; 1981. (*in Russian*).

[42] Krinsky V.I., editor. Self-organization. Autowaves and structures far from equilibrium. Berlin: Springer; 1984.

[43] Mikhailov A.S. Distributed active systems. Berlin: Springer; 1992.

[44] Mikhailov A.S., Krinsky V.I. Rotating spiral waves in excitable media: the analytical results. Physica D 1983; 9: 346-371.

[45] Kopell N. and Howard L.N., Plane wave solutions to reaction diffusion equations. Studies in Appl. Math., 1973;52:291-328.

[46] Kopell N., Reaction-diffusion equations and pattern formation. In Studies in mathematical biology, S. Levin, ed. MAA Studies in Mathematics, Mathematical Association of America, 1978;15:191-205.

[47] Starmer CF. Initiation of excitation waves. Scholarpedia (2007);2(2) 1848, revision #129751. doi:10.4249/scholarpedia.1848

[48] Kechker M.I. Manual of Clinical Electrocardiology. Moscow; 2000. ISBN: 5-900518-24-9 (*in Russian*).

[49] Mazurov M.E. About the formation of the uniform rhythm in the sinoatrial node in the heart. Biofizika 2009;54(1) 81-88 (*in Russian*).

[50] Mazurov M.E. Control of the unified heart rhythm. Biofizika 2009;54(1) 89-96(*in Russian*).

[51] Pertsov A.M., Panfilov A.V., Medvedeva F.U. Instabilities of autowaves in excitable media associated with critical curvature phenomenon; Biofizika 1983;28 100-102.

[52] Rusakov AV, Panfilov AV, Medvinskii AB. Unidirectional block of propagation of a single autowave in a narrow gap and emergence of a two-dimensional reentry depends on geometry of the obstacle and on excitability of the media. Biofizika 2003;48(4) 722-726.

[53] Fast V.G., Kléber A.G. Role of wavefront curvature in propagation of cardiac impulse. Cardiovasc. Res. 1997;33(2): 258-271.

[54] Khramov R.N., Krinsky V.I. Stationary propagation velocities of the stable and unstable impulse. Dependence on membrane ionic currents. Biofizika 1977;22(3) 512. (*in Russian*).

[55] Khramov R.N. Circulation of an impulse in excitable medium. Critical size of the closed loop. Biofizika 1978;23(5) 871. (*in Russian*).

[56] Fife P.C. Singular perturbation and wave front techniques in reaction-diffusion problems. SIAM-AMS Proceedings 1976; 23-50.

[57] Aslanidi O.V. and Mornev O.A. Soliton-Like Regimes and Excitation Pulse Reflection (Echo) in Homogeneous Cardiac Purkinje Fibers: Results of Numerical Simulations. Journal of Biological Physics 1999;25(2-3) 149–164. DOI:10.1023/A:1005119218136

[58] Kozek J., Marek M. Wave reflection in reaction-diffusion equations. Phys.Rev.Lett. 1995;74(11) 2134-2137.

[59] Petrov V., Scott S. K., Shott S. K., Showalter K. Excitablity, wave reflection and wave spliting in a cubic autocatalysis reactio-diffusion system. Phil. Trans. R. Soc. A. 1994;347(1685) 631–642.

[60] Gaztañaga L., Marchlinskia F.E., Betenskya B.P. Mechanisms of cardiac arrhythmias. Rev Esp Cardiol. 2012;65(2) 174-85. DOI: 10.1016/j.rec.2011.09.020.

[61] Allessie M.A., Bonke F.I.M. Schopman F.J.G. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ. Res.*, 1977; 41: 9.

[62] Zaikin A.N., Kawczynski A.L. Spatial effects in active chemical systems. Model of leading center. *J. Non. Equilib. Thermodyn.* 1977; 2 39

[63] Antzelevitch C., Jalife C., Moe G.K. Characteristics of reflection as a mechanism of re-entrant arrhythmias and its relationship to parasystole. *Circulation* 1981;61 182–191.

[64] Lamanna V., Antzelevitch C., Moe G. Effect of lidocaine on conduction through depolarized canine false tendons and on a model of reflected reentry. *J. Pharm. Exp. Ther.* 1982 221 353–361.

[65] Rozanski G., Jafile J., Moe G. Reflected reentry in nonhomogeneous ventricular muscle as a mechanism of cardiac arrhythmias. Circulation 1984; 69 163-–173.

[66] Brugada P., Wellens H.J.J. The role of triggered activity in clinical ventricular arrhythmias. *Pace* 1984; 7: 260–271.

[67] Schechter E., Freeman C.C., Lazzara R. Afterdepolarization as a mechanism for the long QT syndrom. J. Am. Coll. Cardiol. 1984;3(6) 1556-61.

[68] Wit A.L., Rosen M.R. Afterdepolarizations and triggered activity. In: Fozzard H.A., Haber E., Jennings R.B., Kate A.M., Morgan H.E. (eds) The Heart and Circulatory System. New York: Raven Press, Publishers; 1986. p 1449-1490.

[69] Fozzard H.A. Afterdepolarizations and triggered activity. Basic Res. Cardiol. 1992; 87 Suppl 2 105-13.

[70] Kass R.S., Tsien R.W., Weingart R. Ionic basis of transient inward current induced by strophanthidin in cardiac Purkinje fibres. J. Physiol. 1978; 281, 209–226.

[71] Johnson N., Danilo P., Wit A.L., and Rosen M.R. Characteristics of initiation and termination of catecholamine-induced triggered activity in atrial fibers of the coronary sinus. Circulation 1986;74(5) 1168-1179.

[72] Rosen M.R., Gelband H., Merker C., Hoffman B.F. Mechanisms of digitalis toxicity. Effects of ouabain on phase four of canine Purkinje fiber transmembrane potentials. Circulation. 1973;47 681–689.

[73] Ferrier G.R., Saunders J.H., Mendez C. 1973. A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. Circ Res. 1973;32(5):600-609.

[74] Noble D. Ionic mechanisms determining the timing of ventricular repolarization: significance for cardiac arrhythmias. Annals of the New York Academy of Sciences 1992;644(1) 1–22.

[75] Hassard B.D., Kazarinoff N.D., Wan Y.-H. Theory and application of Hopf bifurcation. Cambridge: Cambridge University Press; 1981.

[76] Deco, G; Jirsa, VK Ongoing cortical activity at rest: criticality, multistability, and ghost attractors. J Neurosci 2012;32(10) 3366–75.

[77] Efimov I.R., Krinsky V.I., Jalife J. Dynamics of rotating vortices in the Beeler-Reuter model of cardiac tissue. Chaos, Solitons & Fractals 1995;5(3/4) 513-526.

[78] Keener J.P. The dynamics of 3-dimensional scroll waves in excitable media. Physica D 1988;31(2) 269-276.

[79] Biktashev V.N., Holden A.V., Zhang H. Tension of organizing filaments of scroll waves. Phyl. Trans. Roy. Soc. London, ser A 1994; 347: 611-630.

[80] Biktashev V.N., Holden A.V., Mironov S.F., Percov A.M., Zaitsev A.V. Three-dimensional organisation of re-entrant propagation during experimental ventricular fibrillation. Chaos, Solitons & Fractals 2002; 13(8): 1713-1733.

[81] Mantel R.-M., Barkley D. Parametric forcing of scroll-wave patterns in three-dimensional excitable media. Physica D 2001;149 107–122.

[82] Wiener N. Cybernetics or control and communication in the animal and the machine. New York — London; 1961.

[83] Fedorov V.F. Development of basic techniques of differential chronocardiography. PhD thesis (Dissertation for the degree of Candidate of Medical Sciences). Pirogov Russian State Medical University, Moscow; 2001. (*in Russian*).

[84] Anokhin PK. The essays on physiology of functional systems. Moscow: Medicine; 1975. (*in Russian*).

[85] Anokhin PK. Philosophical aspects of the theory of functional systems. Moscow: Nauka; 1978. (*in Russian*).

[86] Gasparyan S.A. etc. The concept of state health monitoring system of the Russian population. Approved by the Minister of Health, T.B. Dmitrieva and Chairman of the Presidential Committee on Information Policy, A.S. Golubkov. Moscow, 1996. (*in Russian*).

[87] Simonov PV. The emotional brain. Moscow: Nauka; 1981. (*in Russian*).

[88] Cherkashin AK, and Leshchenko Ya A. Mathematical Modeling and Quantitative Analysis of the Demographic and Ecological Aspects of Russian Supermortality. Mathematical Modelling of Natural Phenomena 2011;5(6) 243-258.

[89] Hauser MD. Moral Minds: How Nature Designed a Universal Sense of Right and Wrong. New York: HarperCollins; 2006.

[90] Katsnel'son L.B., Solov'eva O.E., Sul'man T.B., Konovalov P.V., Markhasin V.S. Simulation of mechanoelectrical coupling in cardiomyocytes under normal and abnormal conditions 2006;51(6) 917-926.

[91] Solovyova O.E. Markhasin V.S., Solovyova O., Katsnelson L.B., Protsenko Y., Kohl P., Noble D. Mechano-electric interactions in heterogeneous myocardium: development of fundamental experimental and theoretical models. Prog Biophys Mol Biol. 2003;82(1-3) 207-220.

[92] Kohl P. (Ed.), Sachs F. (Ed.), Franz MR. (Ed.). Cardiac Mechano-Electric Coupling and Arrhythmias. Publisher: OUP Oxford; 2011. ISBN: 978-0199570164