

SEEING THE HEARTBEAT

FROM MATTEUCCI'S RHEOSCOPIC FROG TO
IMAGE-GUIDED ARRHYTHMIA ABLATION

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The study of the heart's electrical activity is not only matter for medical doctors. It is a fascinating intellectual adventure bringing together different disciplines from biology to medicine to physics. It initiated in Italy in 1842 when the rheoscopic frog of the physicist Carlo Matteucci for the first time signalled an electrical current accompanying the heartbeat. Then the story continued with the advent of sensitive galvanometers allowing picking up the heart activity from the external surface of the body. A further step was the discovery and exploration of the electrical cardiac circuitry by means of endocardial catheters and a number of ingenious tricks. Not only. That was also the time when the rhythm disturbances could be electrically domesticated. Up to now, when seeing the rhythm inside the heart in multicolour artistic maps is become a reality that may also help to cure heart diseases.

1 A cardiac pump primer

The human heart is a four-chambered muscular pump. With barely the size of a clenched fist, it enables an unidirectional blood flow of about 5-6 litres per minute in a closed circuit formed by a complex network of pipes approximately as long as two and a half the terrestrial circumference. Actually it is composed of two pumps connected in series and corresponding to the right and left sides of the heart (fig. 1). The right-side pump supplies the low-pressure (~ 2.2 kP), low-resistance and high-compliance circuit that moves the blood through the pulmonary circle where it releases carbon dioxide and acquires oxygen. The left-side pump sustains a circuit characterized by high pressure (~ 13 kP), high resistance and low compliance. This circuit creates the systemic circulation designed to reach, within a distance of no more than $10 \mu\text{m}$, all the roughly 10^{14} cells of the human body: a population ten thousand times the world population. The systemic circulation performs an efficient "door-to-door"

distribution of integrated services by exchanging mass (nutrients, oxygen and waste products of metabolism), energy (including heat), momentum and communication signals. All these services are finely tuned in space and time by controlling the blood distribution according to the specific metabolic and/or functional needs of the different regions of the body. A control system optimizes the limited resources available by following a well-defined prioritization scheme which is based on how essential each region is to sustain the life of the whole organism.

Both the right- and left-side pumps are made of muscle fibres and work as chambers of variable volume. Due to their proper spatial arrangement [1] the fibre's linear shortening results into a chamber volume reduction that generate potential energy (blood pressure) and kinetic energy (blood flow). In order to assure an efficient pumping function the synchronism of the fibres stretching is carefully controlled through an electrical triggering system. Each cardiac pump,

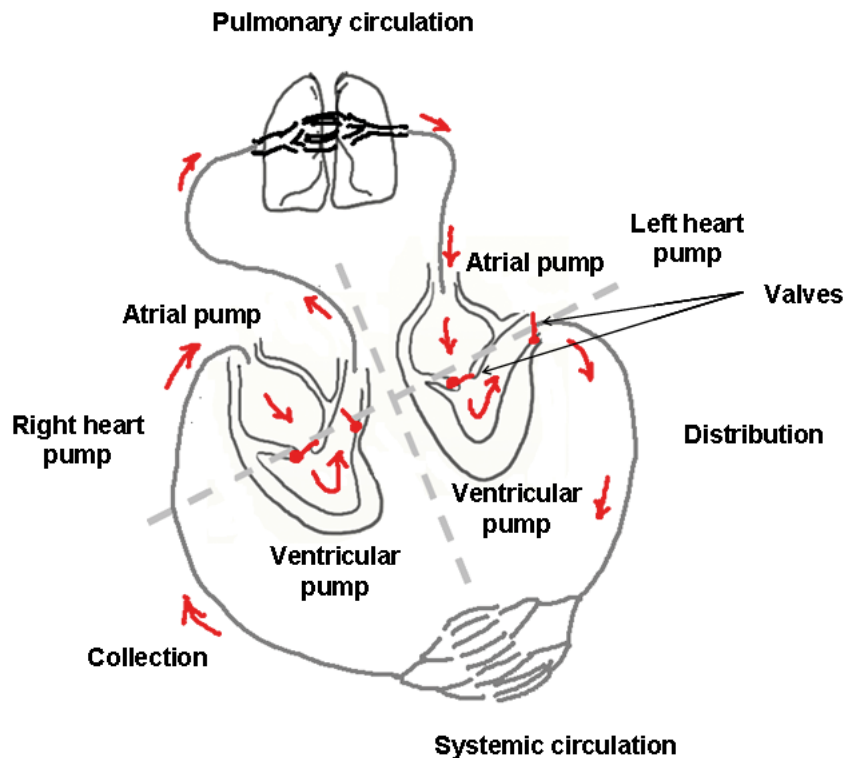


Fig. 1 Scheme of the human blood circulation. Right and left heart pumps are shown separated. Red arrows indicate the verse of the unidirectional blood flow.

right and left, is further constituted by two pumps in series that work sequentially. A smaller upper chamber, atrium, collects the blood coming from the external circuit and fills the lower chamber, ventricle, which is about twice the size of its corresponding atrium (fig.1). The unidirectional flow from atrium to ventricle and from ventricle to the external circuit is secured by inlet and outlet valves in both ventricles. In summary, the heart pump has four contractile chambers connected in series and operating cyclically, by means of an alternation of contraction (systole) and relaxation (diastole). The period of the cardiac cycle is about 860 ms in an adult at rest but it decreases during exercise or excitement and changes in various abnormal conditions. The four-chamber architecture is functionally organized so that both atria and ventricles contract simultaneously but ventricular systole must be delayed of about 150 ms with respect to atrial systole to allow the atria contribute to the ventricular filling.

2 Electrical waves in the heart muscle - Physical methods, industrial instruments and the dawn of electrocardiography

Cardiac muscular contractions are electrically activated and their mechanical concerted action, resulting in efficient pump function, is triggered by electrical impulses. The first recorded report of an electrical current accompanying the heartbeat was published in 1842 by the Italian physicist Carlo Matteucci. He used the Galvani nerve-muscle preparation known as "rheoscopic frog": an ancestor of the

modern biosensors in which the cut nerve of a frog's leg operated as electrical sensor and twitching of the muscle was the visual sign of electrical activity. Matteucci indeed observed that, if the nerve of the preparation was laid across a beating heart, the muscle contracted in synchrony with the cardiac rhythm [2]. Afterward the studies on the electrical activity of the heart paralleled the successes achieved in developing new methods and instruments for measuring electrical currents. In fact the sensitivity and time constant requirements needed to measure the currents flowing in biological preparations were beyond the limits of the available instrumentation, but the joint contribution of both pure physics laboratories and telegraphic and power industries enabled to hit the mark. Thereby physiologists initiated to characterize the electro-mechanical properties of animal hearts. Very soon they discovered that the electrometers could sense the cardiac electrical activity of mammals, including man, from the external surface of the body without the need to gain direct access to the heart. By using an instrument, originally designed by William Thomson (Lord Kelvin) [3] to satisfy the necessities of the emerging submarine telegraphy industry, in 1876 Alexander Muirhead obtained the first successful recording from a human heart. But Muirhead did not publish the results and not even carried out further physiological work: he became a successful telegraph engineer [4]. The first report on cardiac electricity recorded from the body's surface was published by Augustus Waller in 1887 and the recording was called "cardiogram" [5]. He used a pair of zinc electrodes, covered

by chamois leather and moistened with brine, strapped front and back on the chest and connected with a Lippmann's capillary electrometer. Among Waller contributions were the description of the cardiac signal variability depending on the electrode location, its interpretation by modelling the heart as an electrical dipole and the observation that ventricles do not beat simultaneously in every portion. Indeed the contraction takes place progressively, as a state of action traversing the whole ventricle mass bottom up, beginning at the apex and terminating at the base (fig. 4). Despite the fact that many of the instruments used in the early studies we have described were derived from industrial instruments, the activities performed with them remained confined to laboratory experiments. No one foresaw their clinical potentiality until Willem Einthoven who, instead, was firmly convinced of the widespread feasibility of clinical electrocardiograms, and promoted a number of improvements and refinements in the recording technique. In those days the electrometer's major drawback was the long response time, thus the recording of the rapid variations of potential accompanying the heartbeat demanded frustrating graphical corrections [5]. Since high sensitivity and short response time were also the requirement for submarine telegraphy in 1897 the French electrical engineer Clement Ader built a new amplification system called string galvanometer [6]. With this apparatus the rate of telegraphic transmission on the long cable from Brest (France) to Saint-Pierre (off Newfoundland, Canada) raised from 400 to 600 signals per minute. Einthoven string galvanometer was inspired to Ader's design but introduced new solutions to increase its sensitivity. Einthoven's instrument comprised a thin silver-coated quartz filament of 0.003 mm diameter placed between two electromagnets. An electric current passed through the filament and produced a little movement of only 0.06 mm when a maximum potential of 3 mV was applied across it. The filament movement was amplified by means of a high-quality optical system with 600× magnification projecting its shadow on the recording system. The string galvanometer provided readings of quality higher than its precursor, the capillary electrometer, but the whole instrument was very large and bulky. It filled two rooms, included an enormous water-cooled electromagnet, and required five people to operate it. Nevertheless Einthoven was convinced of the clinical value of the new instrument and to circumvent the need to move the patients from the Leyden University Hospital to his laboratory he installed a 1.5 km long cable to connect the two structures and called telecardiograms the recorded signals. Einthoven not only assembled the first practical galvanometer for recording the heart's electrical activity in humans, but also introduced the first standardization for the recording sites, gave a very detailed description of the Electro-Cardio-Graphic traces (ECG) and contributed to establish the basis for their interpretation. In 1924 he was rewarded with a Nobel Prize in medicine for "the discovery of the mechanism of the

electrocardiogram". Since then electrocardiography attracted some of the brightest minds interested in both the basic knowledge of the heart function and the clinical diagnoses of its dysfunctions. In the physiological laboratories the new reliable electrocardiographs added to the already available sphygmomanometers and polygraphs. This made it possible to see the heart at work. Thereby the correlation of ECG with both electrical activity directly recorded on the exposed heart and intracardiac pressure provided quite quickly a deeper insight into the normal heart rhythm and its major irregularities or arrhythmias. Clinical translation of the new findings was equally rapid and the study of arrhythmias developed in an explosive way.

3 A look into the heart's electric circuitry

ECG interpretation is a challenging task. In physical terms it is the problem of determining the electric source of the signals measured at the body surface. The rationale for its diagnostic use is the assumption that a pathologic condition by affecting the source could be detected as a modification of the measured signals. Thereby the question facing the clinicians is the solution of the inverse problem that, as is well known since Hermann von Helmholtz analysis in 1853 [7], does not have a unique solution. In other words the external measurements alone are not enough to identify the source without imposing some constraint. The founding fathers of electrocardiography, Waller and Einthoven, modelled the source as a single dipole located near the centre of the heart and varying its magnitude and orientation during the cardiac cycle. The ECG's interpretation task was then approached by dividing it into two steps. At first the physiopathological knowledge set up the relation between electrical heart activity and source dipole vector. The next step, of a purely physical nature, relates the source model with the measured potentials. However the limits of this simple model became very soon clear as the results of extensive experimental investigations disclosed the anatomical and physiological complexity of the genesis and propagation of electrical impulses in the heart (see box 1). To overcome the above limitation Frank Wilson proposed two improvements. He augmented the number of recording sites by introducing six unipolar electrodes placed on the torso. Furthermore he replaced the single-dipole model of the source with a more realistic one constituted by a uniform dipole layer. The new model accounted for the effect of the excitation wave propagating in the heart on the potential recorded on the torso with unipolar electrodes. This model laid the theoretical foundation for interpreting ECG that is still widely used even if more refined approaches are now available [8]. In any case much of the clinical analysis follow an empirical approach based on the physician's experience to link the observed signal pattern to a typical one belonging to a catalogue of patterns associated with clinical disorders.

BOX 1

Normal spreading of the electrical waves and cardiac arrhythmias

The role of cardiac cells is to contract once triggered by an electrical impulse, called action potential, and to transmit the impulse to neighbouring cells via local circuit currents (fig. 2). For this reason they belong to the class of excitable cells. In their resting state they are electrically polarized with the inside roughly 90 mV negative with respect to the outside due to a different ionic concentration between inside and outside compartments. Charge separation is maintained by an insulating membrane about 6 nm thick and with a specific capacitance on the order of magnitude of 10^{-2} F/m². Among the great variety of proteins housed in the membrane two types are mandatory to bestow excitability on the cell. The first type includes the ion pumps which use metabolic energy to transport some ions into the cell and others outside against their concentration gradients. The second type is a family of naturally occurring nanotubes, or ion channels, that provide the specific conducting pathways for ions of different sort. All membrane proteins experience local electric fields amounting to some ten million volts per meter. Under the action of this intense field it is not surprising if some ion channels are able to sense the electric field and to respond to its variation by modulating the dynamics of their conformational changes that open or close the transmembrane pathways for the charged ions. Consequently these voltage-sensitive ionic channels present a voltage- and time-dependent conductance. They open independently of each other nevertheless they act synergistically. As in the same patch of membrane different channels share a common membrane potential, they result mutually coupled through their voltage-dependent conductance. With the above ingredients the resulting cell behaviour, or excitability, is the production of an action potential in response to a trigger stimulus over a well-defined voltage threshold. The form of the action potential (fig. 2) is an initial rapid voltage change from the resting state to an excited state (excitatory or depolarization phase) followed by a much longer recovery or repolarization phase. The pulse shape does not depend on the stimulus strength or duration; rather it is due to the sequence of coupled molecular events responsible for the recovery of the resting state. Also the action potential duration does not depend on the stimulus; it establishes a first time interval (absolute refractory period) during which the cell is not retriggerable at all, followed by a relative refractory period. During this second time interval another action potential can be elicited by an external

stimulus, but with a higher threshold whose value relaxes gradually to its normal level.

The first biophysical model for the membrane of an excitable cell was published in 1952 by Alan Hodgkin and Andrew Huxley [9] in summary of their intensive investigation on the current flow through the membrane of the giant nerve fibre of the squid. The framework for this model is described by the circuit diagram in fig. 3 that takes into account the membrane capacitance and includes a few separated ionic currents. The sodium and potassium currents, which present voltage- and time-dependent conductance, are represented in the scheme by a variable conductance whereas the leakage current, which lumps all other contributions to the membrane current, is described as a constant conductance. Moreover every current branch also includes a specific electromotive force accounting for the equilibrium potential due to the concentration gradient of that particular ion. Assuming a space clamp condition, that is an equipotential membrane, and in the absence of external stimuli, the relationship between the membrane potential V_m and ionic currents is

$$(1) \quad -C_m \frac{dV_m}{dt} = J_{ion} = G_{Na} P_{Na}(V_m, t) (V_m - E_{Na}) + G_K P_K(V_m, t) (V_m - E_K) + g_L (V_m - E_L),$$

where C_m is the specific membrane capacitance and J_{ions} is the total density of ionic current. G_{Na} and G_K are the maximal conductances per unit area of the sodium and potassium channel, respectively, g_L is the leakage conductance per unit area. All specific conductances are expressed in mS/cm². E_{Na} , E_K , and E_L are the equilibrium potentials for the corresponding ions. P_{Na} and P_K are the opening probability of the sodium and potassium channel, respectively. Their voltage- and time-dependence are expressed by first-order ordinary differential equations of the type

$$(2) \quad \frac{dP_i}{dt} = f(P_i, V_m).$$

The Hodgkin and Huxley model not only succeeded in describing the generation and propagation of action potentials in the nerve of the squid as a non-linear phenomenon arising from voltage-dependent conductance, but it was a seminal work that opened an extremely fruitful route towards the modelling of the great variety of excitable cells, including the cardiac ones.

The great majority of cardiac cells follow the general scheme described above thus sharing the property of excitability. However cells belonging to distinct regions of the heart

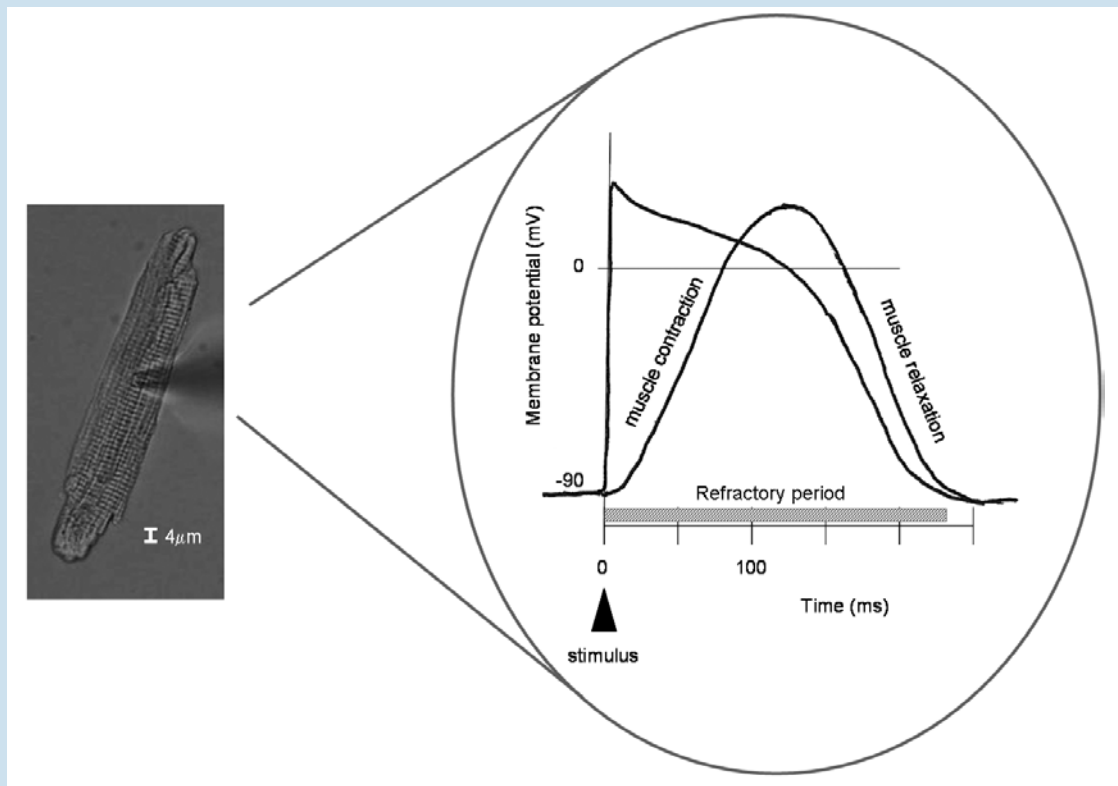


Fig. 2 Electrical and mechanical activity in an isolated cardiac cell. The image on the left represents a microscopy view of a cardiomyocyte enzymatically isolated from a guinea pig ventricle. The shadow on the image is due to microelectrode contacting the cell to record the action potential. The scheme on the right side shows a typical ventricular action potential with a superimposed mechanical contraction associated with it.

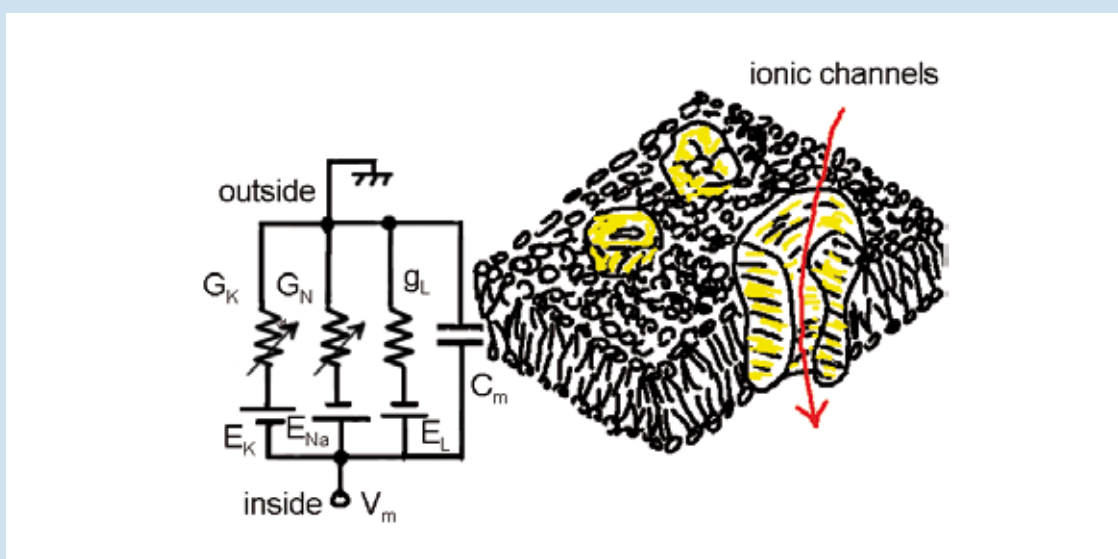


Fig. 3 Equivalent circuit of the Hodgkin-Huxley model. Right side: a cartoon illustrating an excitable membrane patch. Ionic channels and membrane proteins are embedded into the lipid bilayer modelled by the capacitor C_m . Left side: equivalent circuit of an excitable membrane.

present variations in some characteristics resulting in different shape and duration of their action potentials (fig. 4). For instance the cells of the nodes are characterized by an unstable resting potential that slightly drifts towards the excitation threshold, granting them spontaneous oscillatory properties or pacemaking function.

In healthy hearts, the cardiac rhythm originates in the sinoatrial node, a small region with a volume of about 70 mm^3 located in the upper part of the wall of the right atrium. The spontaneous electrical discharge of this primary pacemaker is responsible for setting the heart rate to 60–100 beats per minute under normal circumstances. The firing of the sinoatrial node suppresses the automatic activity of other groups of slowly beating cells located in the atrio-ventricular node and Purkinje fibres and called latent or secondary pacemakers. Conversely the latter ones can drive the heart

activity if the sinus node fails to beat. From the sinoatrial node the cardiac impulse spreads with a velocity of about 0.5 m/s throughout the right and left atria along privileged directions determined by the cell architecture. Then the impulse reaches the atrio-ventricular node, which is the sole conductive pathway connecting the atrial and ventricular chamber. With a conduction velocity of 0.05 m/s the nodal cells impose a critical delay in impulse propagation, thereby allowing sufficient time for complete atrial depolarization and contraction prior to ventricular depolarization and contraction. After exiting the atrio-ventricular node the electrical impulse is fastly conducted along the bundle of His with a conduction velocity of 2 m/s . At the end of the bundle of His the conduction pathway splits into two bundle branches which first run down the interventricular septum then branch out to produce numerous Purkinje fibres. With a

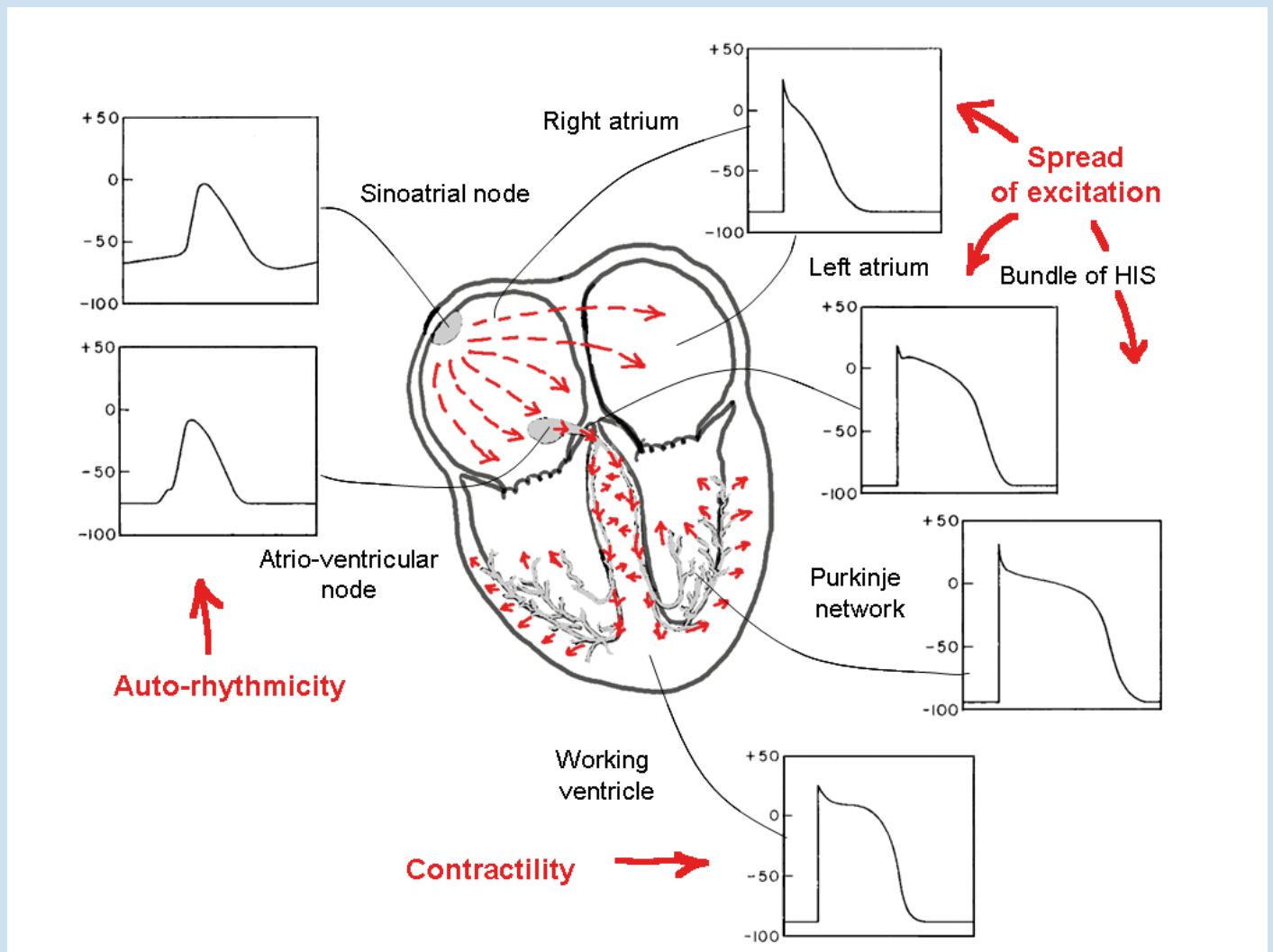


Fig. 4 The conduction system of the heart. The red arrows indicate the normal activation sequence. The insets illustrate the shapes of the action potentials recorded in different sites along the conduction pathway. Left-side insets refer to auto-rhythmic nodal cells characterized by unstable diastolic potentials and slow depolarization phase. Right-side insets refer to conduction cells characterized by stable diastolic potential and fast depolarization phase.

conduction velocity of 4 m/s these fibres provide a rapid and uniform distribution of the impulse to the whole mass of the ventricles, causing them to contract synchronously. Considering that in an average lifetime the heart beats more than two and a half billion times it is not surprising if some time it breaks down. In those circumstances electrical dysfunctions are very common and may be quite serious. The normal sequence of impulse formation and conduction as described above fails replaced by an arrhythmia which is a slower (bradycardia) or more rapid (tachycardia) rhythm. Intensive experimental and clinical investigations unravelled many types of arrhythmia's mechanisms in form of disorders of impulse formation, impulse conduction, or a combination of both. Among them a particular role is played by the re-entrant excitations or more simply re-entry which has been associated to many severe forms of tachycardia as well as to both atrial and ventricular fibrillations, the main cause of premature death in the developed world. The re-entry occurs when the impulse can propagate back into a previously depolarized area that has recovered excitability. In such a case, depending on the tissue properties of conduction and refractoriness, the impulse may propagate indefinitely around the re-entrant circuit, thus becoming an anomalous high-frequency oscillator. If the new imposed rate is so fast that the heart's pumping efficiency is impaired, the arrhythmia may become life-threatening. The impulse propagation in a population of cardiac cells could be modelled as an excitable medium [10] that is a space-distributed dynamical system constituted of elements which possess the property of excitability described above. Moreover neighboring elements interact with each other by diffusion-like local transport processes. For the cardiac cells the local coupling is due to specific proteins which provide resistive intercellular bridges or gap junctions. Thereby the excitable medium is able to support propagation of undamped solitary excitation waves, as well as wave trains. Several models of excitable media have been developed to describe the cardiac tissues with different aims and with different degrees of complexity regarding the cells behaviour, the cell-to-cell signal propagation and the cell arrangement in a space-structured tissue. (For a review see ref. [11].) With reference to cell behaviour, there are models aimed to capture the essential electrical property of excitability followed by recovery, as in the FitzHugh-Nagumo equations that are a modification of the well-known model of the van der Pol relaxation oscillator. On the other extreme of complexity there are detailed biophysical models taking into account more than twenty channels as well as other molecular components like ion pumps and exchangers. With regard to signal propagation a cellular automaton is the simplest model on the shelf. It consists of a regular

discrete lattice of cells where each cell is characterized by a state determined by a set of simple rules. The cells evolve in discrete time steps the future state of each cell being dictated by its present state and by the state of a finite number of neighbouring cells. Figure 5 illustrates an example of cellular automaton that we have used to model atrial arrhythmias [12]. Despite the model simplicity, the automaton can simulate the main features of the non-linear wave propagation as shown in fig. 6, where a few patterns relevant for the understanding of the arrhythmia mechanism are presented. In panel A a point source generates concentric waves in a homogeneous medium. Panel B describes the one-dimensional propagation along a ring of cardiac tissue. The parameters have been selected so that the ring circumference be greater than the wave velocity multiplied by the refractory period, thus allowing the impulse to circulate perpetually without dying out. The simulation reproduces the mechanism known as anatomical re-entry. It occurs in various clinically observed arrhythmias where the impulse can circulate around a non-conducting tissue, like a scar after myocardial infarction, or through an anomalous circuit made possible for instance by the presence of an accessory atrioventricular connection. A different form of re-entry does not require tissue inhomogeneity but regions with functionally different properties. Such situation occurs in the presence of steep excitability gradients that provide the substrate for unidirectional functional block and conduction back into repolarized tissue. Panel C shows the formation of a spiral wave which can rotate around a functional obstacle in a two-dimensional plane. The spiral waves can be stable as in panel C or it will be subject to destabilize itself. The latter case may either result in an arrhythmia termination or in the induction of a more complex pattern as in panel D. In such case the re-entrant wave form first breaks into multiple spirals, then the spirals degenerate into an irregular pattern with multiple colliding waves known as fibrillation. Returning to excitable media modelling and increasing in model complexity, the cardiac tissue may be replaced by distinct intracellular and extracellular spaces considered as continua, described by the same coordinate system and characterized by conductivity tensors. The cell membrane, with its particular descriptive model, separates both spaces at each point. In the three-dimensional version of this bidomain model the current density in each space is

$$\begin{aligned}
 \nabla \cdot \mathbf{J}_i &= -\nabla \cdot (\mathbf{G}_i \nabla \Phi_i) = -Sv (C_m (\partial V_m / \partial t) + I_{ion}) + I_{ext}^i, \\
 (3) \quad \nabla \cdot \mathbf{J}_e &= -\nabla \cdot (\mathbf{G}_e \nabla \Phi_e) = -Sv (C_m (\partial V_m / \partial t) + I_{ion}) + I_{ext}^e, \\
 V_m &= \Phi_i - \Phi_e,
 \end{aligned}$$

where the subscripts i and e denote the intracellular and extracellular spaces, respectively, \mathbf{J} the current density per

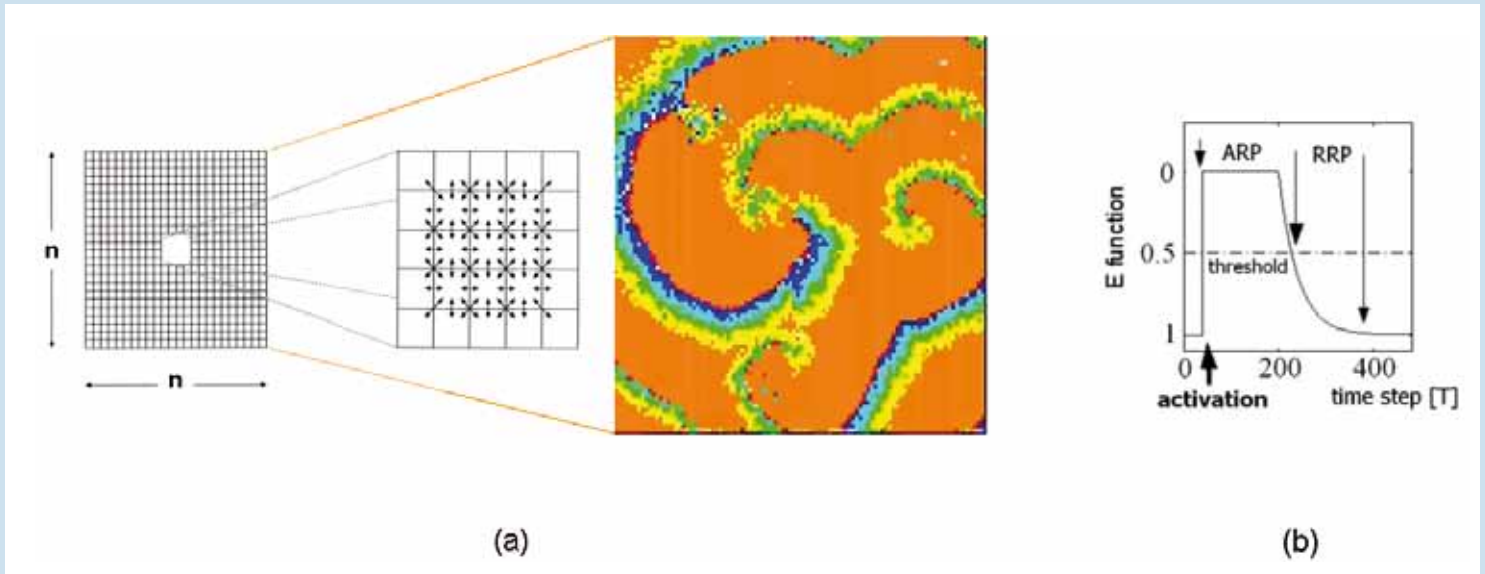


Fig. 5 The cellular automaton model. (a) Lattice and connectivity. The model is constituted by 100×100 units, each connected to eight neighbours. (b) Changes in excitability function E in a single cell following its activation. ARP = absolute refractory period. RRP = relative refractory period.

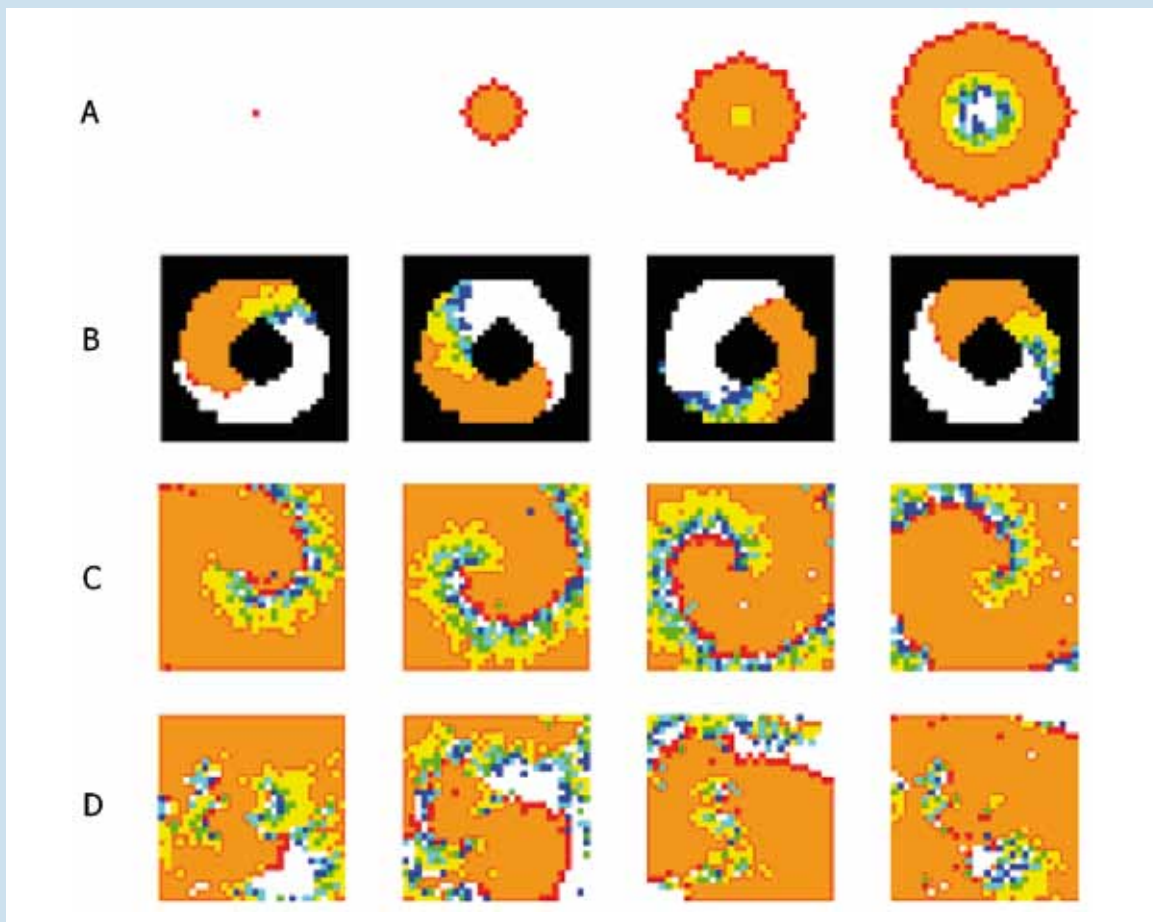


Fig 6 Wave propagation patterns in excitable media: radial propagation (A), circus movement along a fixed ring (B), stable spiral wave (C), multiple-wavelet propagation (D). Simulation obtained with a two-dimensional cellular automaton model as in fig. 5.

unit volume, \mathbf{G} the conductivity tensors, S_v the surface-to-volume ratio for the cells, C_m the specific membrane capacitance, I_{ion} the membrane current per unit area, I_{ext} the externally applied currents per unit volume in the intracellular and extracellular spaces. The I_{ion} current has to be described with one of the cell behaviour models mentioned before. The one-dimensional version of this bidomain model is illustrated in fig. 7. A simplified version of eq. (3) may be obtained if the extracellular potential Φ_e is assumed to be zero. This is the case called monodomain model which reduces the cardiac-tissue description to the well-known cable equation developed by Lord Kelvin in the 1850s to describe the signal decay in submarine telegraphic cables.

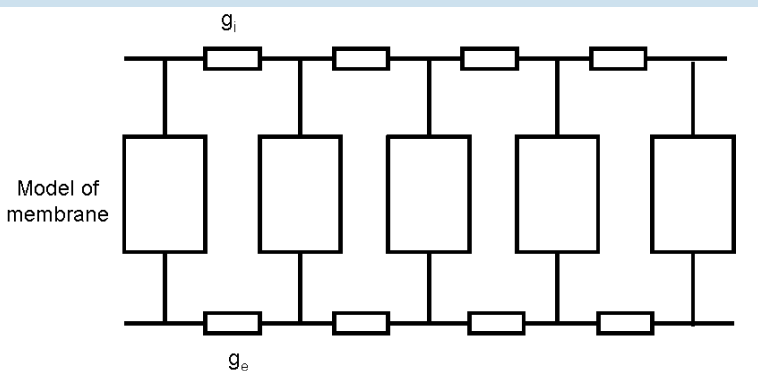


Fig. 7 Equivalent circuit of cardiac tissue: continuous bidomain one-dimensional cable.

As illustrated in box 1, the electrophysiological mechanism responsible for the initiation and maintenance of cardiac arrhythmias may be quite complex. In many cases the ECG pattern alone cannot discriminate among competing mechanisms demanding for different therapies. A major breakthrough in understanding human cardiac arrhythmias came in the late 1960s and opened new avenues in their management. In 1929 Werner Forssmann, a 25-year-old surgical trainee, demonstrated on himself the feasibility of a direct access to the right atrium through a urethral catheter placed into a vein in his arm. He inaugurated the new field of human cardiac catheterization and launched the systematic exploration of normal and abnormal hemodynamics. But Forssmann's demonstration suggested also to some cardiologists the possibility to use intracardiac catheters to record electrical activity directly from inside the heart. The signals detected on the endocardium, or electrograms, allowed mapping the cardiac activation: for the first time the human heart's electric circuitry could be disclosed and the arrhythmia's mechanisms as well. Soon afterward Furman and Robinson were able to stimulate the heart by connecting an intracardiac catheter to a stimulator and Scherlag succeeded in recording the activity of the thin His bundle (see box 1) by modifying the bandwidth of the recording amplifier from 0.1–200 Hz of the standard ECG to 40–500 Hz. It was the dawn of clinical electrophysiology with the setting of specific laboratories dedicated to the management of complex rhythm disturbances. There the arrhythmias may be reproduced in controlled conditions with proper stimulation protocols, investigated to find out their underlying mechanisms and terminated with appropriate electrical stimuli or drugs (see box 2). Thereby clinical electrophysiological laboratory rapidly shifted the arrhythmia's treatment approach in the direction of a truly personalized medicine that is looking at identifying the arrhythmia's mechanism in each specific patient in order to choose the better treatment. Such approach was firmly rooted on the scientific paradigm based on data collection, formulation of hypotheses and their experimental testing. In this job a strict cooperation between physicists and cardiologists produced a significant added value in terms of experimental methodology, instruments development, real-time analysis of a large amount of data, biophysical modelling and simulation.

BOX 2**The clinical electrophysiological laboratory - Where clinical and basic scientific skills meet to treat the arrhythmias**

An electrophysiological study is a diagnostic test aimed to identify the mechanism and location of an arrhythmia and recommend the best method of treatment based on the results of the study. In a baseline study, two-to-four catheters are placed into the right side of the heart via the systemic vascular tree under X-ray fluoroscopic control (fig. 8). A number of electrodes embedded in the terminal part of each catheter contact the internal surface of the heart thus recording the local electrical activations or intracardiac electrograms. By recording from multiple locations in the heart, the conduction time from one location to another can be measured. Furthermore the same electrodes can also be utilized to pace the tissue and the combined use of pacing and recording allows assessing conduction and refractoriness in different locations.

In addition, re-entrant arrhythmias can be intentionally triggered, their location mapped and response to therapy evaluated. Both pharmacological and antiarrhythmic pacing therapies can be submitted to acute testing for efficacy and safeness during the studies.

An alternative antiarrhythmic therapy undertaken in the clinical electrophysiological laboratory is cardiac ablation. In this procedure a special electrode placed on the distal tip of the catheter delivers RF energy to a target tissue considered responsible for the arrhythmia. The effect is a resistive heating producing a thermal injury (fig. 9). This neutralizes, or ablates, the nearby cardiac cells creating a block which the electrical impulses can no longer cross. A successful procedure thus interrupts the arrhythmia and prevents its relapse. However some arrhythmias are more easily treated with catheter ablation than others. Success rate in stable arrhythmias with predictable anatomic locations is over 90% but the ablation of more complex arrhythmias, including atrial fibrillation, continues to pose a major challenge.

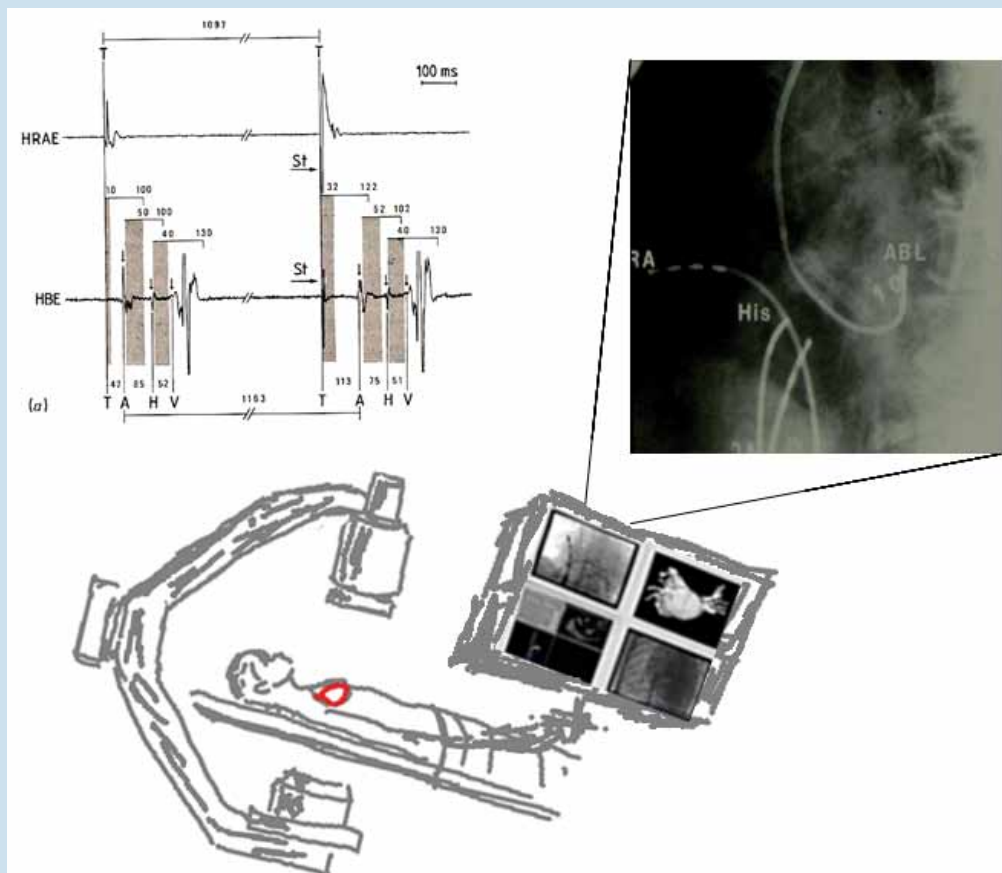


Fig. 8 The set-up of a clinical electrophysiological laboratory for baseline studies. Main components: fluoroscopy suite, catheters, recording and stimulation system. The inset (a) show two typical electrograms recorded in the high right atrium (HRAE) and His bundle (HBE) together with the principal conduction intervals.

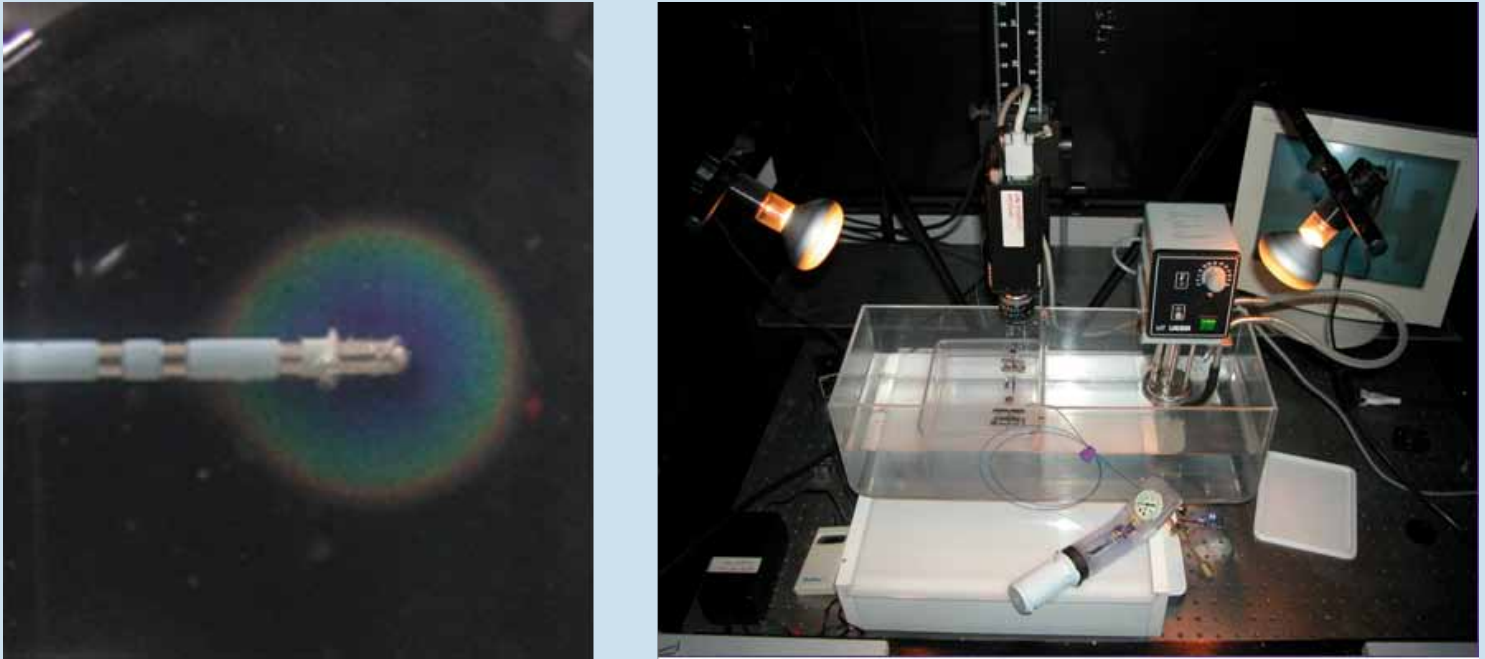


Fig. 9 Dosimetric characterization of an ablation catheter. The heating pattern on the left. The dosimetric set-up on the right.

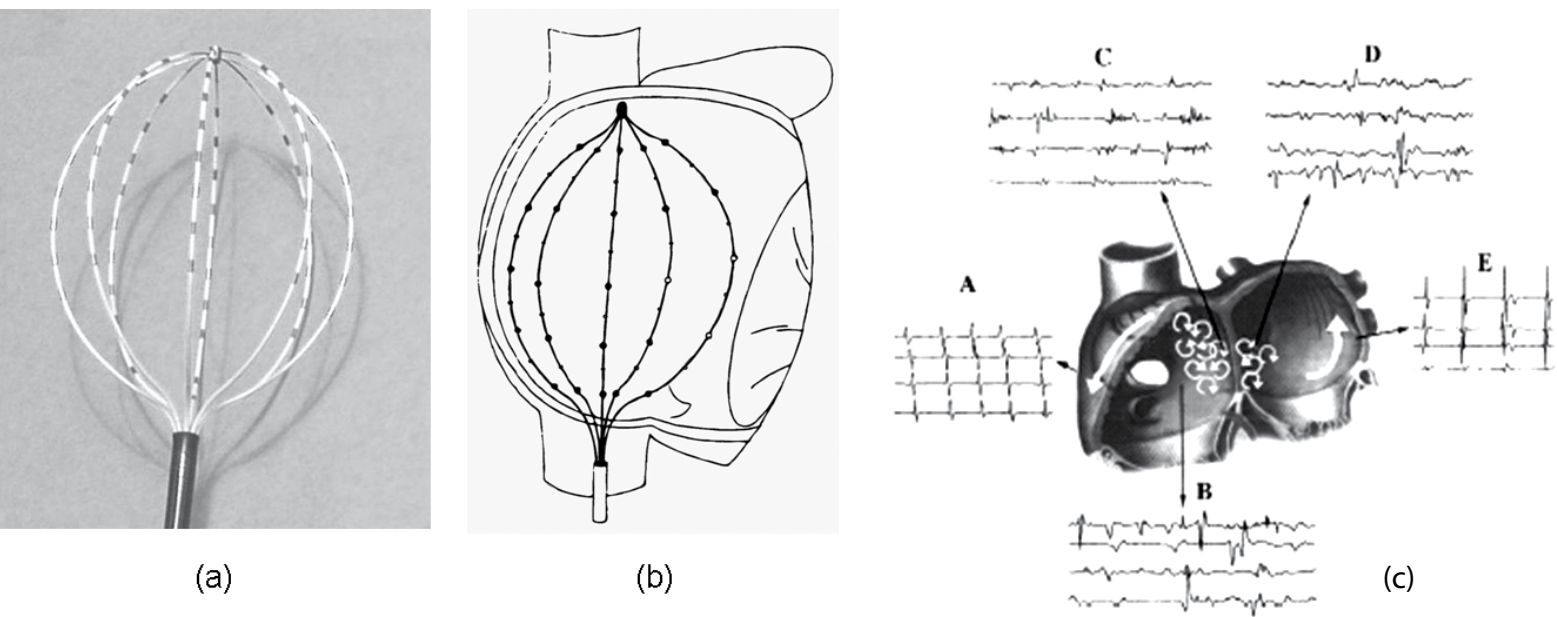


Fig. 10 Basket catheter. Image of the deployed catheter (a). Scheme of the catheter positioned in the right atrium (b). Snapshot of electrograms recorded in different positions during an episode of atrial fibrillation (c).

The main problems are the exact definition of the mechanism underlying the arrhythmia and, when it is known, the difficulty to target it. To overcome the latter limitation new mapping systems have been developed with the aim to gain higher anatomical information and more precise and reproducible catheter ablation positioning. A comprehensive discussion of this important point may be found in [13]. Here, as an example, two mapping systems in use in the cardiology units we are cooperating with are presented. In **fig. 10**, a basket catheter (Constellation catheter, EP Technologies, Boston Scientific) which allows the simultaneous recording of up to 64 electrograms is illustrated. The electrodes are mounted on eight flexible splines, each carrying eight electrodes equally spaced 4 mm apart. Once positioned into the cardiac chamber, the splines are expanded and the electrodes contact the endocardial surface allowing the electrograms recording. The second mapping system is shown in **fig. 11**. It provides a sequential sampling of the inner surface of the cardiac chamber through a steerable roving catheter. Triangulation of spatial location of the catheter tip is derived by the

electromagnetic signals emitted at different frequencies by three coils placed under the patient back. Three receiving coils, specifically oriented, are embedded in the catheter tip allowing real-time detection and display of the tip catheter position and direction. As this mapping system is not an imaging technique, at the very beginning of the procedure few anatomic locations fluoroscopy are localized by fluoroscopy and taken as a reference to create the model of the mapped chamber. Then, during the procedure, the system produces a surface geometry of the cardiac chamber by real-time processing the recorded spatial positions. Electrophysiological information is acquired by the catheter simultaneously with the anatomical one. Electrocardiogram signals or intracardiac recordings can be used as electrical reference to construct a colour-coded activation time map displayed on the anatomical reconstruction. As an alternative, the local electrogram amplitude may be placed, in colour code, on the map allowing the delineation of areas of low amplitude, scar, and fully viable myocardium. In both cases the whole map is therefore called electro-anatomical map.

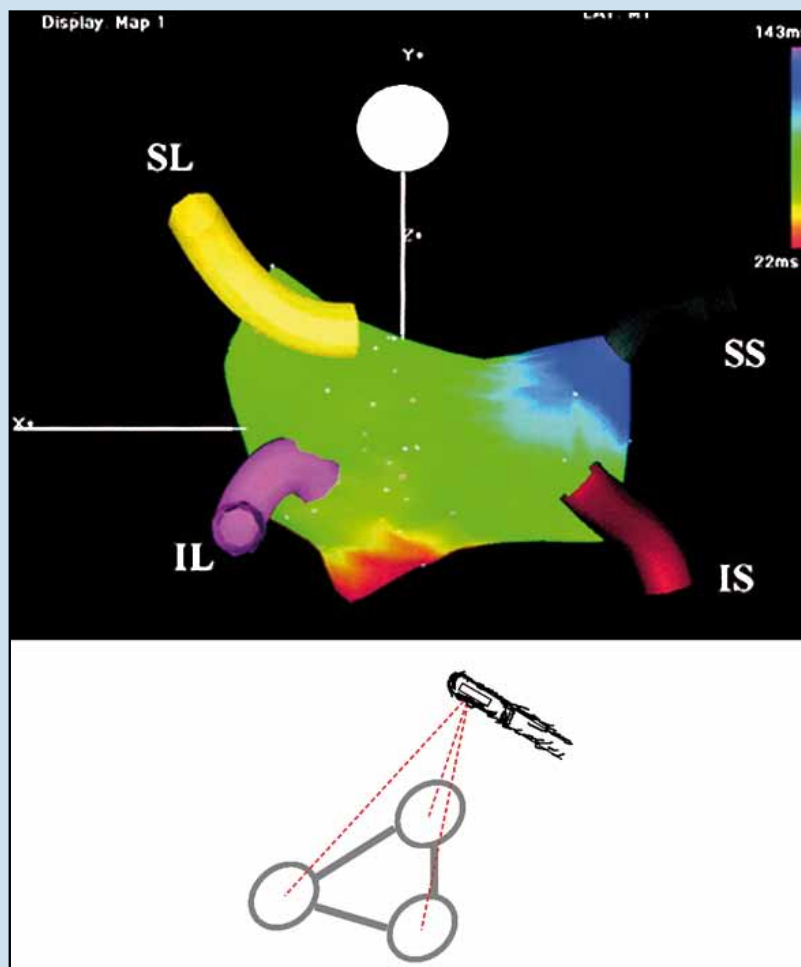


Fig. 11 Electro-anatomical map. Bottom: scheme of triangulation for the spatial location of the catheter tip. Top: colour-coded activation map.

4 Multimodal image integration for understanding atrial fibrillation mechanisms and planning the treatment

In order to give an idea of the current approach to arrhythmia's treatment in the setting of a clinical electrophysiological laboratory, our experience on the study of atrial fibrillation in cooperation with the cardiology departments in Trento and Asti will be briefly described. It is worth noting that atrial fibrillation is a common cardiac disorder affecting up to 10% of individuals aged over 70 years. During the arrhythmia the electrical activity of the atria is highly disorganized and any coherent mechanical contraction is lost. The consequent stasis of blood in the atria may promote clot formation and occurrence of thromboemboli which tend to propagate to different districts, potentially leading to infarction. As a matter of fact atrial fibrillation is associated with a 5–6-fold increase in the incidence of stroke. In addition during atrial fibrillation the ventricular rate is no more under physiological control being determined by the interaction between atrial rate and filtering action of the atrio-ventricular node. The result is a rapid and highly irregular ventricular rate with a consequent reduced cardiac output leading to a number of adverse hemodynamic outcomes including congestive heart failure and tachycardia-related cardiomyopathies. Last but not least, atrial fibrillation is a progressive disease. Its tendency to progress from paroxysmal to chronic forms has been well documented as a positive feedback due to the concurrent action of electrical, contractile and structural remodeling [14]. An impressive number of experimental and clinical studies have been devoted to explore the mechanism underlying this clinically relevant arrhythmia. The results of the first studies, dated in the early twentieth century, did not agree on a single cause for the arrhythmia. Different experimenters proposed, in competition, the multiple rapid discharges of ectopic foci distributed throughout the atria, a single re-entry circuit or the coexistence of multiple functional re-entrant circuits, respectively. Over the past 50 years, multiple re-entrant circuits, or multiple wavelets, have been the dominant model of atrial fibrillation, while the other hypotheses fell largely into disfavour. According to such model, fibrillation is considered fundamentally as a turbulent and self-sustaining process, resulting from the random propagation of multiple wavelets in an inhomogeneous excitable medium. The process is independent of the initiating event, while emphasis is put on the properties of the excitable medium as a substrate of the arrhythmia which may favour the wavelet propagation patterns. Short refractory period and slow conduction velocity have been recognized as determinant factors for initiation and maintenance of the fibrillation. In fact both conditions combine to bring about functional circuits of small dimensions. A great tissue's mass, as in

enlarged atria, is a further favourable situation since a higher number of re-entrant circuits can be accommodated. The therapeutic application of the multiple-wavelets hypothesis has been the successful termination of the arrhythmia in a number of patients after surgical isolation of the re-entrant pathways through a tissue compartmentalization, known as maze procedure. The rationale is a tissue mass reduction in each compartment below the value which is able to sustain fibrillation. Nevertheless in the last fifteen years a large number of both experimental and clinical observations reopened the debate on atrial fibrillation mechanisms suggesting that all three mechanisms initially considered may play a role in the genesis and maintenance of the arrhythmia. Ectopic activity became again fashionable when an important ectopic activity originating in proximity of the pulmonary vein orifices was discovered in patients with fibrillating atria. Moreover, in animal models, a single-circuit re-entry which sustains the arrhythmia has been documented. According to these observations, atrial fibrillation should be triggered by either the activities of a small number of discrete generators like focal sources or a single-circuit re-entry. Otherwise its maintenance depends on the interactions between the high-frequency wavefronts produced by primary generators and the spatial properties of the atrial tissue described as a fibrillatory conduction. Such condition has been the subject of deep experimental and clinical investigations. Animal studies have suggested that the intricate three-dimensional structure of the atrium may be an essential component contributing to the complexity of the propagation pattern observed during fibrillation. Moreover the heterogeneity of refractory periods and excitability could play a major role in both the initiation of re-entrant activity and the fragmentation of wavefronts.

However the detailed molecular and cellular mechanisms underlying the above properties remain a mystery to be investigated at many levels of integration, from the molecular level to the whole body. Hence, fibrillation initiation and perpetuation still pose intriguing and clinically relevant questions demanding the contribution of diverse disciplines including physics.

In summary, the current view of the fibrillation mechanisms regards atrial fibrillation as a "complete" arrhythmia since it seems to involve all known arrhythmia mechanisms. However the interrelation between different mechanisms is not known and the relative contribution of each mechanism to the arrhythmia's pathogenesis has to be clarified. Effective prevention and treatment of atrial fibrillation would require targeted treatment modalities that are difficult to find facing its complex multifactorial pathogenesis. Medications are only marginally effective in treating this arrhythmia, and have the potential for serious side effects, including life-threatening pro-arrhythmia. Conversely catheter mapping and ablation

procedures (see box 2) offer a treatment option that is gaining an increasing favour. However, a number of clinical investigations describe the procedures as quite complex and time-consuming with variable efficacy rates depending on the patient selection. In other words the success of a clinical ablation strongly depends on the correct identification of the arrhythmia mechanism in each patient. This is a very demanding task for cardiologists alone. Hence there is plenty of room for physicist' contribution in the field of cardiac arrhythmias studies. Not only in understanding the biophysical mechanisms, but also in introducing innovative solutions in the electrophysiological laboratory. Two examples, taken from the recent activity of our group, may help to illustrate possible interdisciplinary cooperation in this field. In several studies the presence of complex fractionated atrial electrograms has been correlated to an electrophysiological substrate favourable to sustain

fibrillation. Therefore such functional substrate has been proposed as a target site for ablation. As part of the more general problem of identification of non-anatomical targets, the specific question is how to quickly identify the above region with precision. To this purpose, a number of quantitative methods have been devised to characterize the complexity/organization of atrial endocardial signals. Among them, the morphological approach proposed in [15] quantified the regularity of single electrograms as the presence of activation wave forms with stable morphology (wave similarity analysis). This quantitative index obtained in this way is a signature of the local dispersion of the electrophysiological properties of the tissue. Mapping the index evidenced substantial differences in the dispersion of electrophysiological characteristics between early and advanced forms of fibrillation (fig. 12). Such finding is in agreement with the different aptitudes for arrhythmia

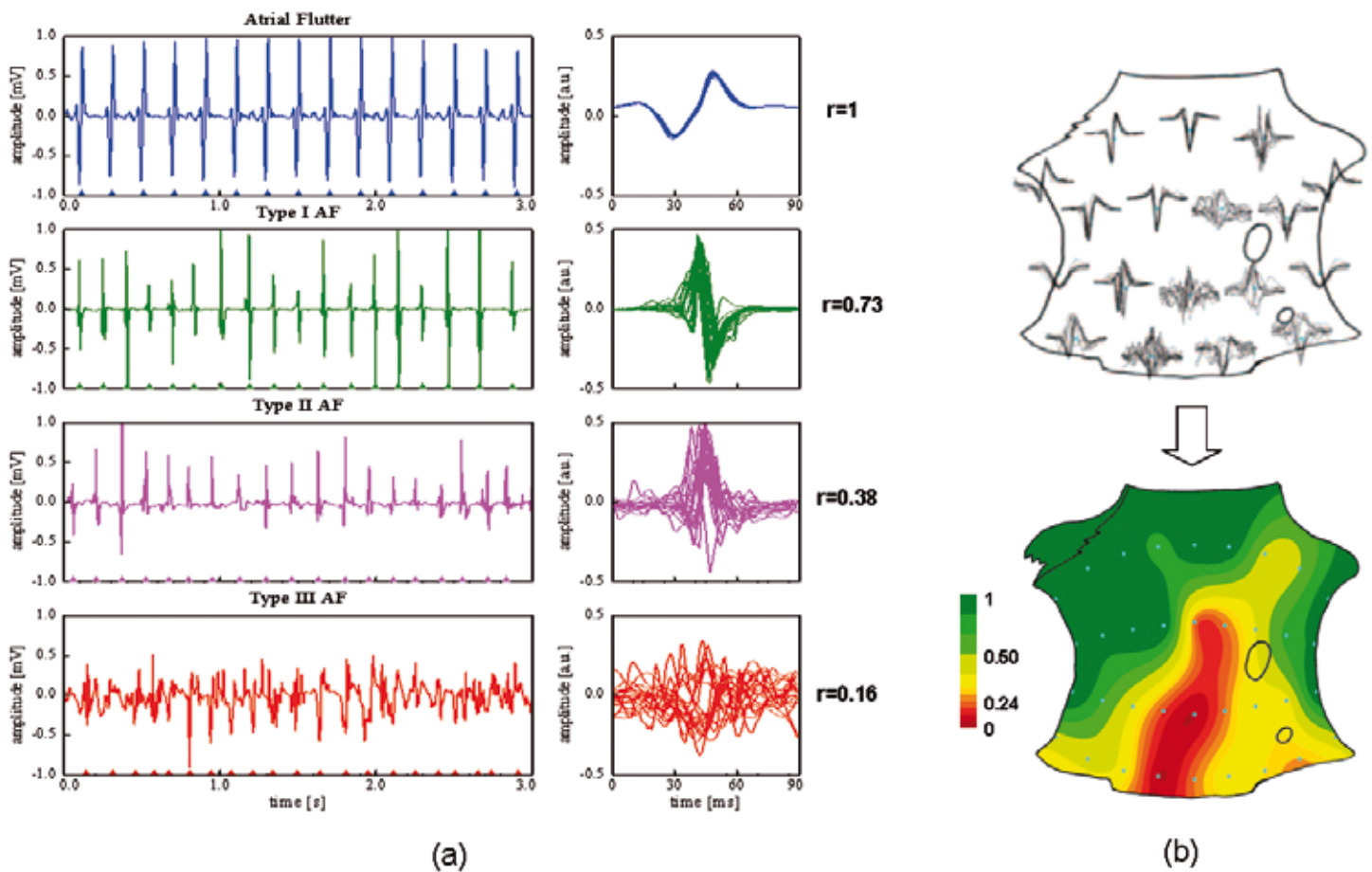
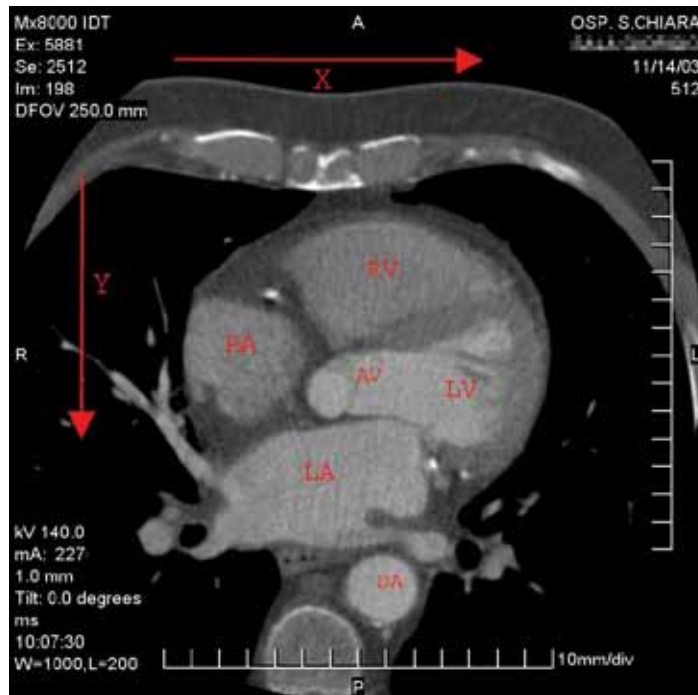


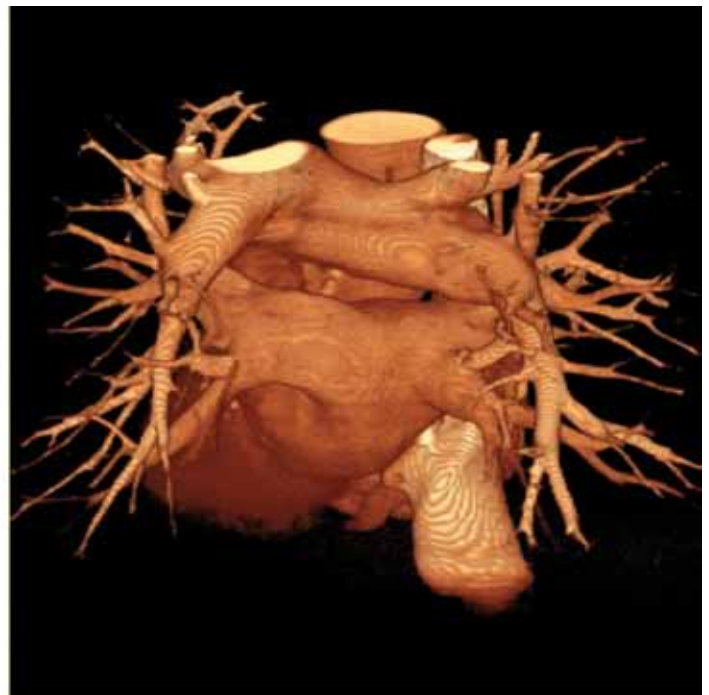
Fig. 12 Quantification of the similarity of fibrillatory waves recorded by a basket catheter in the human right atrium. (a) Wave morphology similarity of different electrograms manually classified by expert cardiologists following the standard methods. From top to bottom: atrial flutter, type-I, type-II, and type-III atrial fibrillation. (b) Construction of wave similarity maps during atrial fibrillation. Top: Spatial distribution of wave form complexity during AF shown by superimposition of activation waves. Bottom: Corresponding wave similarity map. The values of the similarity index are colour coded with green indicating high-similarity and red low-similarity values.

domestication predicted from experimental studies and computer simulation and observed in the clinical setting [16]. Another important problem, common to all the image-guided clinical procedures, is the real-time image integration. While this field is well developed in the area of brain imaging, cardiac motion of the heart and interpatient variability of anatomical features, make the registration of cardiac images a unique challenge. In the context of the ablative procedure of atrial fibrillation recent studies indicate the need for a high-resolution anatomical and electrical characterization of the left atrium as the more critical chamber. A pre-procedural imaging obtained with multi-detector computed tomography or magnetic resonance tomography may offer the required anatomical resolution. In collaboration with the cardiology and radiology units of Trento Hospital we developed specific segmentation techniques and we obtained highly resolved

three-dimensional anatomical reconstructions of the left atrium (fig. 13) [17]. The images collected during the last three years indicate a large interpatient morphological variability and the presence of unusual anatomies related in particular to the number and branching structure of the pulmonary veins, the most usual site of anomalous high-frequency sources of electrical activity during atrial fibrillation. However a detailed anatomical reconstruction is not enough to implement the ablation. An optimal strategy would thus be to integrate the three-dimensional detailed morphological images with the sparse endocardial electro-anatomic maps obtained with the interventional system through the process of registration. To this purpose, we have developed a fully automated strategy [18]. Anatomical and electrical images reside in different image spaces. By means of a parameterized geometric transformation the second space is transformed into the first one. Then a stochastic parallel search process



(a)



(b)

Fig. 13 Isolation of left atrial surface from cardiac multidetector CT images. (a) Mediastinum CT slice showing the contrast enhanced bloodstream within cardiac chambers. LA: left atrium. RA: right atrium. LV: left ventriculum. RV: right ventriculum. AV: aortic valve. DA: descendent aorta. (b) Inner surface of the left atrium as extracted with the proposed segmentation procedure.

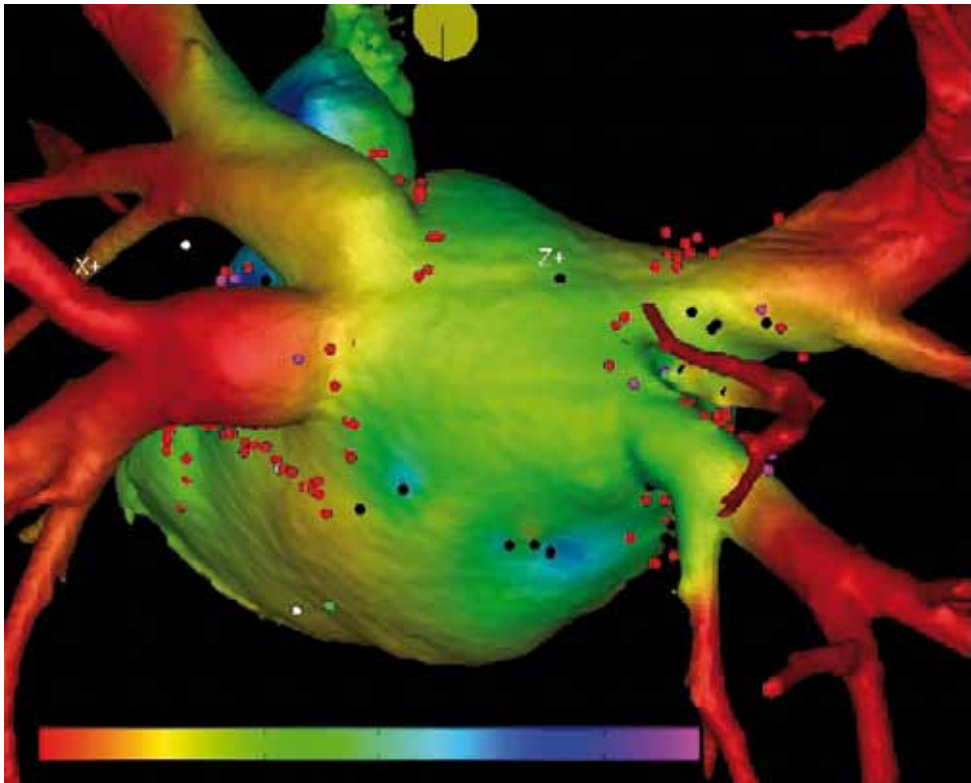


Fig. 14 Example of integrated multimodal map obtained by registration and fusion of the CT left-atrium anatomic surface with an electro-anatomical voltage map.

is performed in order to find the best parameter set which minimizes the misalignment between the points of the electro-anatomical map and the segmented tomographic surface. The subsequent fusion of electrophysiological data on the reconstructed atrium surface is obtained through a radial basis function interpolation (fig. 14).

The anatomic reconstructions integrated with electrical/functional maps are currently in use in the cardiology unit of Trento. The first results indicate a significant improvement in the arrhythmia mechanism elucidation, as shown in [19], but a full clinical evaluation is underway. In the meanwhile a further development points to complement the images with arrhythmia simulations done on the real atrial geometry. The common denominator of both imaging and simulation techniques is the integration of anatomical and electrophysiological information in order to gain a thorough, patient-specific description of the arrhythmic episodes with the hope that the new insights will be translated into improved therapeutic approaches.

Conclusions

Since Matteucci's first historical experiment, the study of the electrical activity of the heart evolved as a fascinating multidisciplinary adventure bringing together biologists, clinicians and physicists. It always required experimental skill to conduct difficult experiments, to develop front line

instruments, to disentangle the intriguing large amount of data. This was valid when Einthoven and Lorentz laboratories were next door in Leyden as it is nowadays. Moreover when in the 1960s the non-linear properties of cardiac-tissue excitability were discovered a further avenue was inaugurated to welcome the dynamicist's contribution. The parallel between non-linear dynamical aspects of the heart and other well-defined physical systems gave birth to a huge amount of new concepts and tools in the cardiac-arrhythmias arena. Thus the hundred and sixty eight old story is far from being concluded. It is in a sort of second childhood where many fronts of innovative researches, improvement in technology and the importance of heart diseases to human conditions should lead to exciting developments in coming years.

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