Topical Mathematical Problems in Electrotherapy of the Heart

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Summary

An approach to solve several topical mathematical problems of cardiac electrotherapy is presented. Based on this approach, a problem of patient state recognition by intracardiac impedance measured with a pacemaker is considered. A method for analyzing monophasic action potentials (MAP) is suggested that is intended for the investigation of atrial tachycardia initiating processes. It is shown that practical algorithms can be constructed which recognize supine, resting, exercise, and overpacing patient states satisfactorily. The suggested method for MAP analysis allows to calculate characteristic media parameters, the behavior of which changes essentially if the heart rate changes from sinus rhythm to tachycardia. The results of the study can be applied to the development of cardiac pacemakers and defibrillators.

Key Words

Intracardiac impedance, closed loop regulation, atrial tachycardia, monophasic action potential, recovery of operators

Introduction

Progress in electrotherapy of the heart more and more shows a trend towards development of active electronic implants that are becoming more automatic. This enhanced automaticity implies fast and adequate monitoring of the state of the heart, choice of appropriate therapeutic measures, and predictability of intervention outcomes. Further progress is hardly possible without an improved understanding of the nature of cardiovascular regulation, accurate measurement of relevant heart monitoring signals, and the development of fast, advanced algorithms for signal processing and decision making. This is a truly challenging problem for specialists in different fields of science and engineering where mathematics is one of the main and most powerful tools.

The difficulty of the task lies in both the complexity of the object and the impossibility to win full information by applying the restricted number of methods that are acceptable without heavy intervention. As a complex nonlinear system governed by multi-level regulation mechanisms, the heart follows very complex dynamics that possess both deterministic-chaotic and stochastic features of an external as well as an internal nature. The main function of the heart is to adapt blood flow to metabolic needs. Due to the environmental exposure, the metabolic needs change continuously. This is one of the ways the heart dynamics become stochastic. Another source of stochastic behavior is of intrinsic nature, caused by the complexity of the body's control mechanisms and the complex nature of the medium where relevant processes take place (e.g., the tremendous number of myocardium cells, the diffusion character of their excitation, the stochastic character of the underlying biochemical processes). Nevertheless, the heart may be described by a simplified linear model as an ideal biomechanical pump demonstrating highly regular oscillations with minimum energy consumption in more or less stationary states.

Governed by the electromechanical coupling mechanism, the elastic properties and, thus, the contraction force of the myocardium (inotropy) are matched to the contraction frequency (chronotropic function of the heart) [1]. This feature has been successfully utilized to restore closed loop regulation of cardiac function in chronotropically insufficient patients with still intact inotropic function. Myocardial contractility changes derived through unipolar right ventricular impedance measurements are used as a sensor signal to adjust the pacing rate to the hemodynamic requirements of the body. Discrimination of different contractility states is key to the successful implementation of the method.

Another important problem in cardiac monitoring is to find relevant arrhythmia predictors. Due to the interplay of different phenomena (chemical, electrical, mechanical), fatal consequences may occur if only one of the systems of the heart, e.g., the electrical one, is malfunctioning. In most cases, a pathological myocardium substrate with disturbed intercellular spread of excitation (cellular action potential diffusion) provokes and maintains heart arrhythmia. The electrical subsystem might be disturbed either by a considerable slowing of the action potential conduction [2] or by triggered automaticity that leads to unpredictable, ectopic impulses. Uncoupling of gap junctions is supposed to be the major underlying mechanism in a variety of pathologic states [3, 4].

Due to electrical nature of cardiac contractions, most of the important information on the state of the heart is gained through electrical measurements, e.g., through intracardiac electrograms in the form of monophasic action potentials (MAP) or the myocardial evoked response to pacing. Advanced methods of electrical cardiac mapping with the aid of electrode nets allow to reconstruct the whole picture of the electrical excitation of the heart and, thus, to reveal conduction disturbances. This is hardly possible with the aid of an implantable device and one or two electrodes. Still, the possibility exists to study dynamical features of a few electrical signals and via the analysis of their waveform and timing, to win information about the arrhythmogenic state of the heart.

Several studies have revealed that cardiac arrhythmias are preceded by characteristic changes of the MAP waveform [5,6]. Rotors or vortex extensions of action potentials have been shown to occur just before the transition to fibrillation, a disorderly pattern of action potential propagation [7]. This is the background to seek for mathematical methods that will enable an early recognition of pending arrhythmia while working with a restricted number of intracardiac electrical signals.

Description of Mathematical Methods

In various scientific fields (engineering, geophysics, medicine), problems of object investigation (diagnostics) arise where a direct examination is impossible, but it is possible to use indirect information. We can derive this information from the signals produced by an object and recorded in the form of reograms, electrograms, etc. [8]. In favorable cases, we know how signal morphology reflects an object state and, consequently, we can evaluate the object state based on the signal form. Unfortunately, it is usually only poorly understood or not understood at all how an object state influences the signal morphology. In such cases, we have to rely on our experience of dealing with the objects under investigation or (if it is possible) to perform a series of experiments to collect statistics, i.e., to find a relation between object state and signal morphology for a sufficiently large number of objects.

The problem of information recovery by data can be formulated as follows. Let ***B*** = *{B}* be a set of objects. We are interested in the value of a feature essential to the object (scalar or vector) *b* = *b(B) for B* ***Î B***. In other words, our interest is a mapping

$$b: \quad B \longmapsto b(B)$$

of an object set into feature space. A signal *F(B)* arises as a consequence of the activity of object B or of our operations with the object during an interval *[0,T]*

$$B \longmapsto F(B) = \{f(B,t):\ 0 \leq t \leq T\}\ ; \qquad (1)$$

here *f(B,t)* is a value of a signal, t is an appropriate parameter (time, voltage, etc.) determined by the essence of a problem. It is assumed that the signal *F(B)* can be measured at any point *t* ***Î*** *[0,T]* or at least at the points of a dense grid

$$\{t_1, t_2, \ldots, t_M\} = \{t_j\}_{j=1}^{M} \subset [0,T]$$

that allows to detect features of signal behavior. We denote by ***F*** a set

$$\mathcal{F} = \{F = F(B):\ b \in \mathcal{B}\}$$

of all the signals under consideration. The problem is to determine a value of a feature essential to the object *b(B)* from the measured signal $F = F(B)$ with required precision ***e*** > 0, i.e., to construct a mapping

$$\beta : \ F \longmapsto \beta(F)$$

such that

$$\|\beta(F(B)) - b(B)\| < \varepsilon, \qquad (2)$$

where ||×|| denotes a norm ("measure of difference"), e.g., a Euclidean norm. The source information for practical solutions of this problem is collected statistics, i.e., sets

$$\mathcal{B}_N = \{B_j\}_{j=1}^{N} \subset \mathcal{B}, \ \ \{b(B_j)\}_{j=1}^{N}, \ \ \{F_j = F(B_j)\}_{j=1}^{N}$$

of objects B_j, of feature values $b(B_j)$, and of corresponding signals $F(B_j)$, $(j = 1,...,N)$. Based on these data, our aim is to construct a mapping of the known signal set $\{F_1,...,F_N\}$ into the feature space, satisfying (2), and to approximate this mapping by a "simple" mapping p from an appropriate set $P = \{p\}$ of easily calculable mappings defined by the set ***B*** of objects under consideration.

The main difficulty of this approximation problem is that the domain of the mapping β is the functional set ***F*** with maybe infinite dimension. But when dealing with real signals, we have to approximate functions defined on a subset of space $\boldsymbol{R}^M$ of finite dimension. Consequently, the infinite-dimensional domain ***F*** of β must be replaced by a finite-dimensional set. The simplest way is to replace every signal $F = f(t)$ by the vector $F_M = (f(t_1),...,f(t_M))$. Unfortunately, if the signal has a complex structure, then the corresponding vector reflects the features for large M only. On the other hand, for a good approximation of the function (1), we need to know its values for a satisfactorily great number of objects, in other words, to have "rich statistics". Statistics are often very poor in practical problems. For cases of this sort, the described method for reducing β to a finite-variant function is inapplicable. We have to find other ways to replace the infinite-dimensional domain ***F*** by a finite-dimensional set on the base of similarity or general principles of related fields (physics, mathematics, physiology, etc.).

Exactly this situation takes place in case of the two problems described below. These problems have a great importance for electrotherapy of the heart. We found a small number of numerical characteristics $\{x_1(F),...,x_M(F)\}$ of the signal that allow to evaluate β*(F)* (patient state) with satisfactory precision. In fact, $X = \{x_1(F),...,x_M(F)\}$ is a set of functionals on ***F*** that are more informative in comparison with functionals of the form $x_j(F) = f(t_j)$ (t_j Î $[0,T]$). In other words, selection of these sets of parameters allows to describe the signal $F = F(B)$ as a set of its features.

Use of Intracardiac Impedance for Discrimination of Patient State

Source information (statistics) is available in the form of intracardiac impedance curves measured in four patient states:

- rest supine ("SUP");
- rest sitting ("RST");
- exercising ("EXR");
- overpacing in rest ("OVR").

An example of the forms of these impedance curves is shown in Figure 1.

The problem is to analyze impedance curves in order to discriminate patient states.

The curve morphology changes obviously with changing patient state, but these changes are "individual" and may take opposite directions for different patients. That is the main difficulty of the problem.

We introduced a set of parameters $x_j = x_j(B,s)$ (here *B* is a patient and *s* Î *{SUP, RST, EXR, OVR}* is a patient state). Using linear combinations of these parameters, it is possible to "separate" the positions under consideration in pairs. Figure 2 shows a behavior of one of these parameters, namely, of the first derivative of the best linear L_2-approximation to the impedance curve.

All together, we selected 25 parameters (M = 25) describing both curve morphology and changes of impedance in the course of time. All the parameters

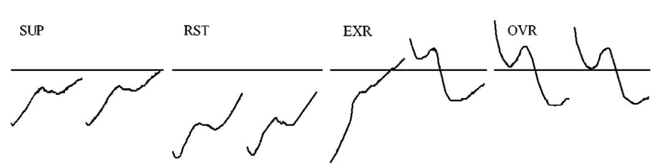

Figure 1. Example of intracardiac impedance curves for different states. For every cardiac cycle, there is an "interval" of fixed length during which the measurements were made.

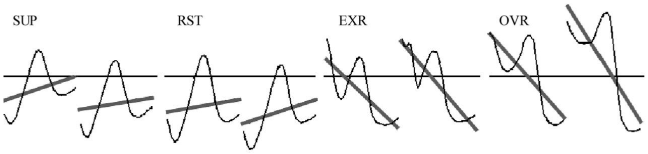

Figure 2. The impedance curves and the best linear L_2-approximations. The first derivatives of these linear functions decrease from SUP to OVR for most of the patients.

State pairs	Separation error	%
SUP and RST	6	8.45
SUP and EXR	3	4.22
SUP and OVR	0	0
RST and EXR	4	5.6
RST and OVR	0	0
EXR and OVR	1	1.4

Table 1. Separation errors and percentages for various state pairs.

were calculated on the base of 15 consecutive cardiac cycles. We considered data from 71 patients.

Based on an information degree analysis of the numerical characteristics of the impedance curves, a set of weight coefficients $\{a_1,...,a_M\}$ is selected and a linear functional

$$f_{s',s''}(B,s)=\sum_{j=1}^{M}\alpha_j x_j(B,s)$$

is constructed for each pair of states; here s', s'' are states, and a set of coefficients of functional $f_{s',s''}$ is optimized to separate them. We understand under the term "separation" a property of the constructed functional to hold the inequality

$$f_{s',s''}(B,s')<f_{s',s''}(B,s'') \tag{3}$$

for a maximal possible number of patients. Thus, we construct the vector $\{a_1,...,a_M\}$ for each pair of states. The important fact is that not more than 12 parameters are included into each separation, i.e., the coefficients α_j are zeros for a number of parameters. On the other hand, the subsets of parameters with non-zero weight differ for different pairs of states.

The table below shows results of separation by constructed functionals for each pair of states. Separation error here is the number of patients that the inequality (3) does not hold for.

Analysis of the Monophasic Action Potential Signal in Tachycardia Onset

The MAP is a signal that appears as a result of excitation propagation in the myocardium. Thus, the myocardium state and especially features of the myocardium excitation process must affect MAP signal properties. In the frame of the described approach, the problem of analyzing processes that initiate tachycardia reduces to the problem of finding MAP signal parameters that change essentially if the heart rate changes from sinus rhythm to tachycardia.

The characteristics of the MAP signal allow its representation in the form of a vector-function with the amplitude and phase changing in the course of time. Analysis of this function behavior gives an opportunity to calculate the characteristic medium parameter that is determined by excitation medium properties.

Figure 3 shows the results of analyzing an MAP that was registered on the right atrium wall during two episodes of atrial tachycardia [6]. Figure 3a shows the MAP signal, Figure 3b depicts values of the characteristic medium parameter q calculated for different phas-

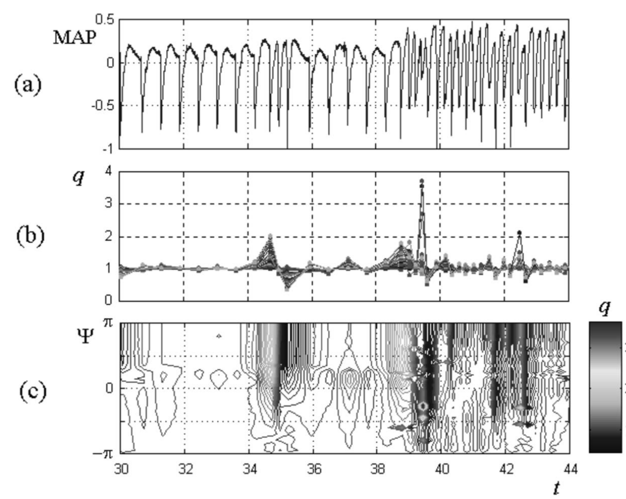

Figure 3. Analysis example of an MAP electrogram that was registered on the right atrium wall during two episodes of atrial tachycardia. (a) MAP signal, (b) characteristic parameter q, (c) level lines of parameter q.

es, Figure 3c shows level lines of dependence of the parameter $q = q(t,\Psi)$ on time t (in seconds) and phase Ψ of the MAP signal. All three figures are coordinated in time.

As one can see from the example, values of the characteristic medium parameter are concentrated at $q = 1$ for sinus rhythm, but q increases with the tachycardia onset, and a dependence of q on the MAP signal phase appears. The obtained results show that the representation of the MAP in the form of vector function provides new opportunities for investigating tachycardia onset processes and tachycardia prediction.

Conclusion

The main solution steps for problems of interest are listed below:

- Collect "statistics".
- Study the relation object — signal — feature value on the basis of the collected statistics.
- Represent the informative features of the signal in the form of numerical characteristics.
- Select weights that reflect the information degree of the parameters well.
- Find an analytical dependence of a feature on the characteristics. Choose a class of "simple" mappings and approximate.
- Develop algorithms for signal processing, calculating characteristic parameters, and computing of an approximate value of the desired feature using the characteristic parameter.

Real signals are always measured with an error. Investigating problems of this type, we must apply the results and methods of approximation theory in such a way that the best approximation of unbounded operators by bounded ones, an optimal recovery of operators, and an approximation of functions (using different approximating sets) are achieved, and methods of regularization of ill-posed problems are used.

It is obvious that success can be achieved only by cooperation of mathematicians and specialists that are experienced in dealing with the object under investigation.

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