Mathematical Modeling of Atrial Fibrillation

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Electrical activity of the heart during ventricular fibrillation was modeled as a sum of N independent pulse streams with various amplitude-frequency and phase characteristics. The data of computational experiments were compared with the results of actual physiological experiments on dogs. Identification of the model was performed using the least square method. The proposed technique provides the computer simulation for studies of the internal structure of irregularities of atrial fibrillation.

Key Words: *atrial fibrillation; mathematical and computer modeling*

Ciliary arrhythmia occurs as a result of atrial fibrillation (AF). It is the most common cardiac rhythm disturbance associated with impaired propagation of excitation through the atria. As a consequence, functional separation of these departments occurs, and electrical activity of the atria is presented by high-frequency irregular oscillations [1,2]. Various hypotheses were put forward at different times regarding the mechanisms underlying irregularity of atrial electrical activity during fibrillation, such as reentry, ectopic pacemakers, spiral and rotor turbulence leading to the occurrence of the sources of high-frequency periodic activity in certain parts of the atria [4-8]. Experiments using high-resolution endocardial and epicardial optical mapping [3] demonstrated several discrete sites of high frequency periodic activity in atrial myocardium during AF.

In this study, we developed a mathematical model that allows quantifying frequency characteristics of these sources and the degree of synchronization between them.

MATERIALS AND METHODS

The mathematical model was based on the assumption that electrical activity of atria F(t) during AF can be presented as a sum of N independent pulse streams $F_i(t-x_i)$ with rectangular pulse shape, constant frequency (f_i) and amplitude (A_i) and various values of phase shifts x_i between streams:

$$F(t)=\Sigma Fi(t-xi),\ i=1,2,\ldots\ldots N. \quad (1)$$

This model has been implemented as a computer program MODAF, which allows to study the irregular pattern of fibrillatory oscillations during AF under the condition of computational experiment. The program is aimed at studying the dependence of total atrial electrical activity F(t) on the quantitative characteristics of the constituent pulse streams: N, fi, Ai, xi. One hundred and fifty computation experiments were carried out with different variants of combinations of multiple and non-multiple ratios between frequency components. All measurements were carried out in arbitrary units. Frequencies were varied in a range from 1 to 100 arb. units; phase shifts, from 0 to 10 arb. units; total number of streams, from 5 to 10. The amplitudes of pulses of compound streams were set equal to unity. Phase shifts between streams were varied in such a way that all possible phase combination would be taken into account. The peculiarity of this study is the solution of optimization problem, *i.e.* the search for such variant that yields the best fit between the results of computing and the actual physiological experiments. For this purpose, we used the results of our experimental studies performed on dogs. Under nembutal anesthesia (40 mg/kg intraperitoneally) and with the

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exclusion of extracardiac influences, VF was evoked with the facility specially designed at the Laboratory of Experimental Cardiology of P. K. Anokhin Institute of Normal Physiology, Russian Academy of Medical Sciences. A series of test pulses (frequency 100 Hz, pulse duration 5 msec, up to 15 pulses in a series) was applied to the left atrium. After each stimulating effect, the amplitude of pulses was increased by the specified amount until the threshold was reached when AF occurred. Electrograms (EG) were analyzed, recorded from the surface of the atrial myocardium with the suction electrodes. It was assumed that the considered records of fibrillation process are realizations of the random function. The experimental function of the distribution of the amplitudes of fibrillary oscillations was evaluated by given realizations and compared with the theoretical function. Then we searched for the characteristics of the model, which yielded the best fit between computational results and actual physiological experiments. For this purpose, experimental distributions of the amplitudes of fibrillatory oscillations were approximated by theoretical distributions using the method of least squares (MLS). This method was practically implemented by building the histograms of distributions of the amplitudes of fibrillatory oscillations and finding the minimum of the function:

$$D=\sum_{i=1}^{m}[Pi(exp)-Pi(mod)]^2=min, \qquad (2)$$

where i=1, 2,…i, number of columns in the experimental histogram [Pi(exp)] and the histogram calculated by the model [Pi(mod)]; *m*, number of histogram steps. Calculations based on MLS method were performed considering scaling of the amplitude-frequency characteristics of the theoretical EG corresponding to the given experiment. Statistical analysis of experimental and theoretical EG was performed using standard software tools included in the package Excel for Windows 6.0.

RESULTS

Characteristics of compound pulse streams chosen by us can model a wide variety of states of the resulting stochastic signal simulating actual EGs during AF. At first glance, both the calculated and the experimental processes were similar. However, further quantitative analysis of indicators of the amplitude-time ordering exhibited the diversity of the internal structure of the chaos in these processes. This allowed us to solve the optimal problem, *i.e.* to choose from the variety of processes the optimum process, which describes the actual experiment in the best way.

Figure 1 shows examples of theoretical EG of two AF processes (D1 and D2) calculated during the computational experiments, in which atrial EG during AF were simulated by summing 10 composite pulsed streams $F_i(t)$ with frequency and phase characteristics presented in Tables 1, 2. Quantitative parameters of amplitude-time ordering of these processes differ. Process AF D1 (Fig. 1, *a*) has unimodal histogram of the amplitudes of fibrillatory oscillations, and the histogram of the process D2 (Fig. 1, *b*) is bimodal. Statistical characteristics of these processes were also different (Table 2). The process D2 has higher values of variation range and average values of the amplitudes of fibrillatory oscillations compared with the process D1. At the same time, geometry of phase portraits of the process D2 has a higher degree of order than the process D1. This is due to higher synchronization between the composite pulse streams in the process D2: the number of pulsed streams with zero phase shifts is equal to 5 for the process D2 and 3 for the process of D1. The results of computational experiments allow us to conclude that frequency characteristics of the composite pulsed streams and processes of synchronization between them are essential for the forming overall picture of electrical activity of the heart during AF. We have demonstrated wide opportunities of this method regarding the free choice of model parameters in order to identify it, *i.e.* to adjust the parameters of experi-

TABLE 1. Frequency and Phase Characteristics of the Composite Pulse Streams Fi(t) Forming Total Electrical Activity of the Heart During AF for Processes D1 and D2 (see Fig. 1, *a*, *b*)

Frequency and phase characteristics of composite pulse streams, arb. units		Process									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
D1	frequency	17.33	11.33	8.33	6.67	6.67	6.00	5.33	6.33	7.33	7.00
	phase	0	0	0	1	2	3	4	8	9	10
D2	frequency	13.33	9.33	8.67	7.67	7.67	9.67	12.00	19.00	18.33	18.67
	phase	0	0	0	1	0	0	2	1	2	1

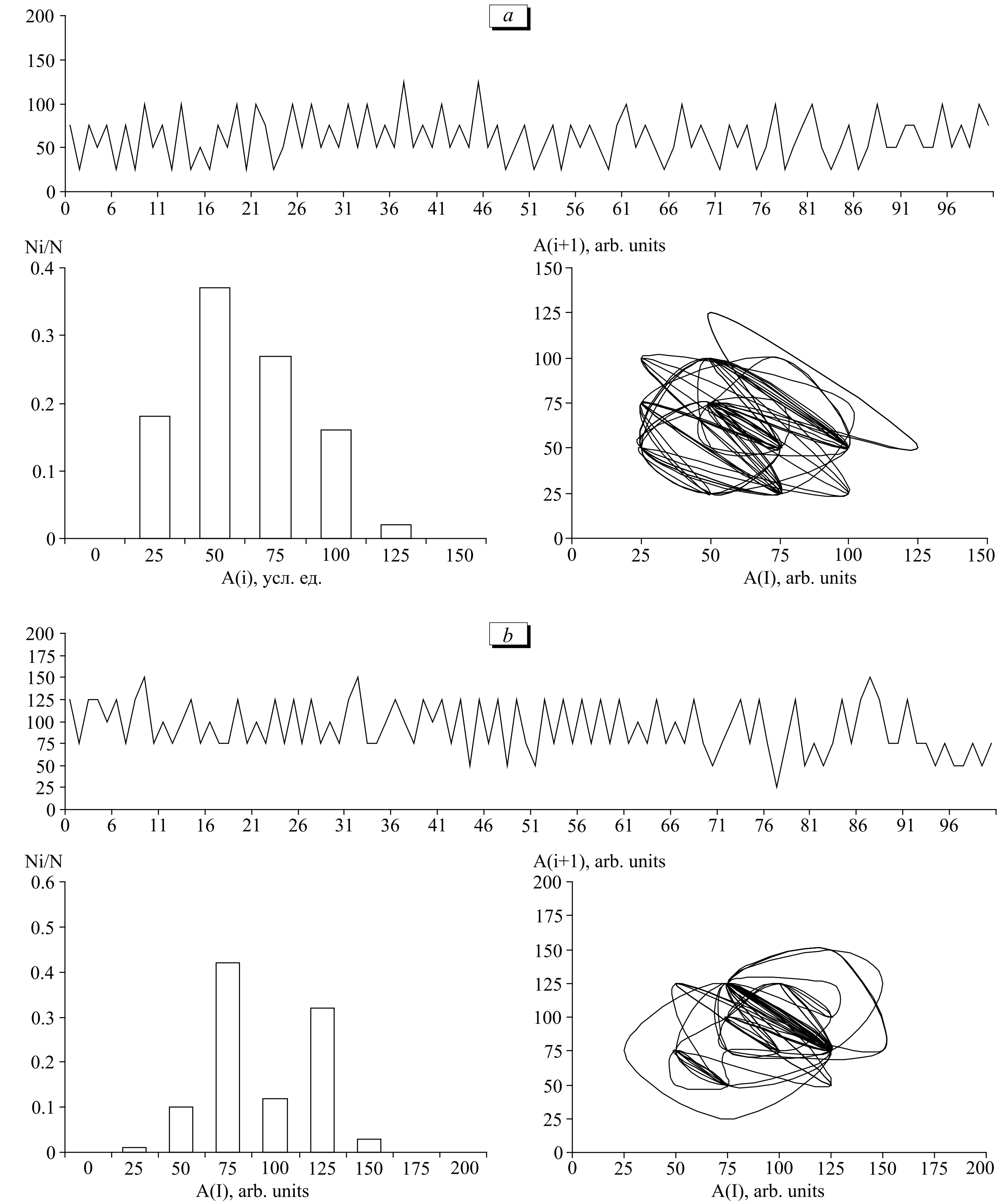

Fig. 1. Theoretical electrograms, histograms of amplitudes of fibrillatory oscillations A(i), and phase portraits of the AF process calculated in the model of the summation of pulse streams with different parameters of synchronization. Model parameters are given in Tables. *a*) variant D1; *b*) variant D2. On the electrograms, the abscissa: the time (arb. units), the ordinate: the amplitude (arb. units). In the histograms: abscissa: amplitude A(i); ordinate: relative number of oscillations with given amplitude Ni/N. In chaosograms (phase portraits): the abscissa: amplitude A(i); ordinate: amplitude A(i+1).

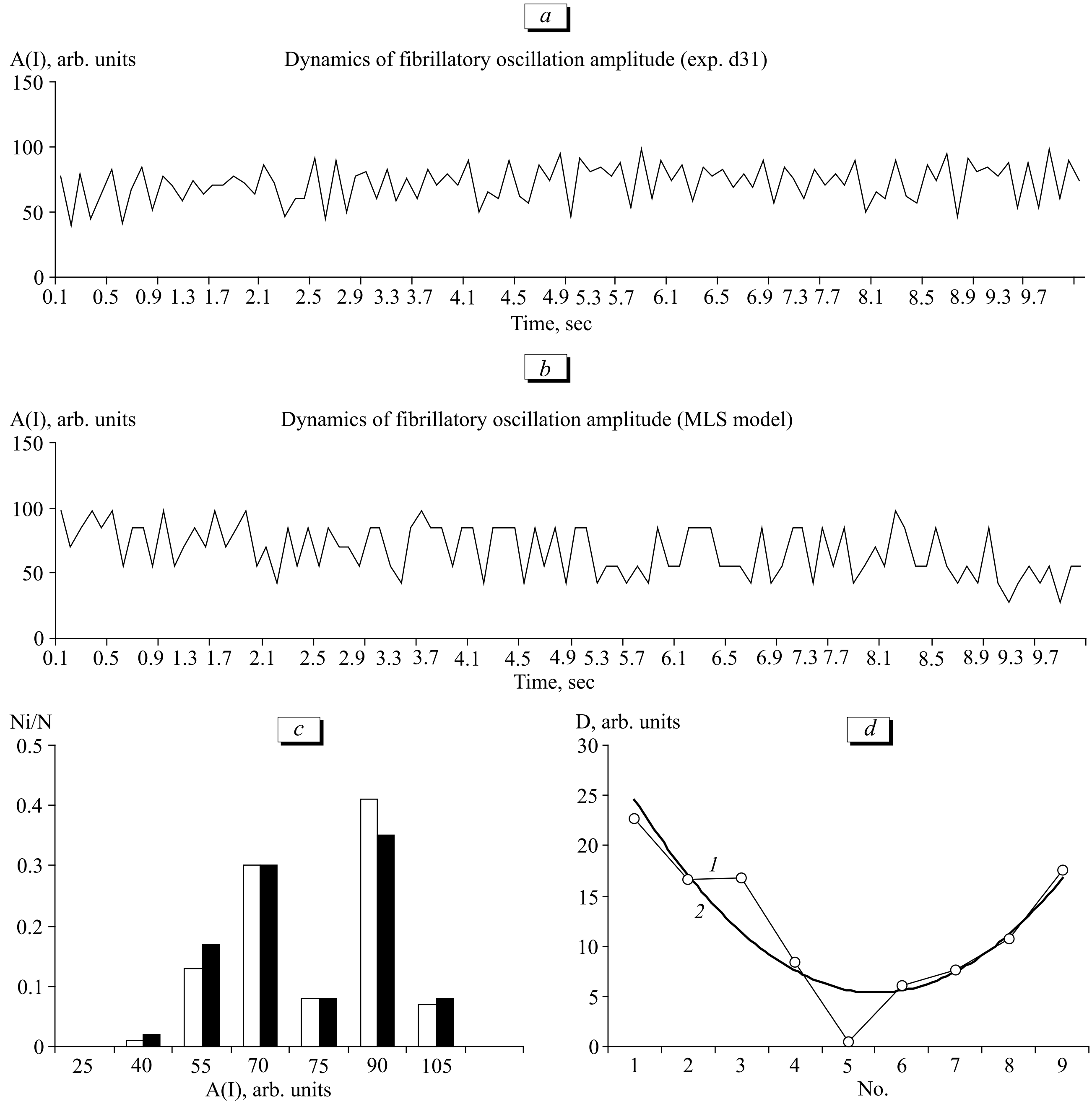

Fig. 2. Modeling approach to experimental data using MLS method. *a*) experimental, *b*) estimated (optimal model) electrograms during AF. Ordinate: amplitude of fibrillatory oscillations (Ai). *c*) experimental and estimated histograms of fibrillatory oscillation amplitudes; light bars: exp. d31; dark bars: model. *d*) model-experiment approximation using MLS method. Ordinate: D values calculated by the formula (**2**) for each variant of the model. *1*) results of computational experiments; *2*) polynomial approximation.

mental AF processes as to approach the parameters of computed process. An example is given of a typical record of the experimental EG of the dog during AF (Fig. 2, *a*). The search for the best theoretical approach of this experimental data was performed using MLK. For this purpose, nine variants of models with different frequency and phase characteristics of composite pulse streams were tested. We have shown the changes of D value calculated in accordance with the formula (**2**) for different variants of models (Fig. 2, *d*). Polynomial approximation of this dependence and finding the minimum of the corresponding curve made it possible to perform the identification of a mathematical model, *i.e.* to find the optimal variant of the model that yields the best approximation to the results of the experiment. Calculations showed that the minimum value of D equal to 0.54 units was achieved as applied to the fifth version of the model, in which the experimental

TABLE 2. Indicators of the Amplitude-Time Ordering of Calculated EG (arb. units)

Process	Average value of the oscillation amplitude	Standard deviation of the oscillation amplitude	Maximum of the oscillation amplitude	Minimum of the oscillation amplitude	Variation of the oscillation amplitude
D1	61.75	25.74	125.00	25.00	100.00
D2	93.25	28.39	150.00	25.00	125.00

AF process was formed of 10 composite independent streams, 6 of which were synchronized (phase equal to 0). These were streams with frequencies as follows: 17.00, 11.33, 9.00, 8.33, 11.00, and 14.00 Hz. Streams with frequencies of 17.67, 15.00, and 14.00 Hz were shifted by phase with respect to previous streams with the shift equal to 2. One stream with a frequency of 9.67 Hz was shifted by phase with the shift equal to 3. The figure 2, *b* shows the calculated EG corresponding to the optimal variant of the model, and histograms of the amplitudes of the fibrillatory oscillations in the model and experiment (Fig. 2, *c*).

Thus, the results of the research have confirmed experimental verification of the hypothesis that there are several discrete local sources of high-frequency periodic activity in the atrial myocardium during fibrillation. The developed mathematical model of AF as well as computational and experimental methods for its optimization enable computer simulation of internal structure of the irregularities of AF process hidden from the experimenter revealing the frequency characteristics of the composite pulse streams and conditions of synchronization between them.

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