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Solving the Inverse Problem of Relationship Between Action Potentials and Field Potentials in Cardiac Cells

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Multiple electrode array (MEA) systems are the instrument platforms being used for cardiac extracellular electrophysiology investigation. Key applications of MEA technology are disease modeling and screening of drug effects. To solve these problems the efforts of many scientists are directed to signal processing and analysis of field potentials (FP) measured with MEA systems. However, it should be noted the complexity of interpretation of MEA information in non-invasive field potentials measurements of cardiac cells compared to invasive action potential (AP) recordings obtained using patch clamp technology. This study is devoted to the mathematical determination of the relationship between the signals of the electrical activity of cardiomyocytes: internal AP and external FP. Derivation of equations for transfer functions between AP and FP is based on field theory. This article provides a solution to the inverse problems of the relationship between AP and FP. Numerical experiments demonstrate the results of the inverse transformation of simulated field potentials signals. To denoise the potentials of the extracellular field of cardiomyocytes, the method combining wavelet transform and processing in eigensubspaces of cardiac cycles is used. The proposed method, based on transfer functions, can be used to determine AP parameters and expand the capabilities of data analysis in MEA systems for diagnosing heart disease and assessing cardiac toxicity during drug development.

Key words: MEA system; cardiomyocyte; action potential; field potential; inverse problem of electrocardiography; cardiac toxicity assessment; wavelet denoising; lab-on-chip technology; human-induced pluripotent stem cells

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Introduction

In recent years, multiple electrode array (MEA) technology has been used in a wide range of applications: cardiac electrophysiology, neurobiology, and bio interfaces research. The MEA systems record, amplify, and analyze signals from biological samples in vitro: neuronal or cardiac cultures stem cells, and ex vivo retina. These multichannel systems, consisting of a PC, an interface board, and a MEA headstage, have the ability to analyze the recorded signals using the included data acquisition software. The MEA technology is based on an idea from the 1970s when scientists discovered that signals of the electrical activity of biological objects can be recorded extracellularly as the field potentials (FP). At the same time, the classic patch clamp technology with an intracellular recording of the action potential (AP) is used for electrophysiological studies. Although this technology is the 'gold standard', it is not suitable in the early stages of research because it requires skilled technicians and is a low-throughput system [1–4].

Now, MEA systems are a non-invasive state-of-the-art tool in electrophysiological research, and the main applications of MEA technology are disease modelling and screening for drug effects. Scientists [2] studied the influence of drugs and the relationship between FP and AP experimentally by simultaneously recording FPs and APs of cardiomyocytes plated on a multi-electrode probe of MEA system and by using a VSD (voltage-sensitive FluoVolt dye) optical imaging system. Authors [3] present approach to record and to precisely control the activity of neurons. Their method allows for parallel measurements, which combine an extracellular high-density microelectrode array for extracellular recording and stimulation, with intracellular patch clamp recording. In article [4] authors describe the use of perforated MEAs to record responses from the retina.

MEA technology is widely used in cardiac electrophysiology research due to its advantages: long-term extracellular experiments with repeated recordings for hours, low required skills and fast results. In addition, network information of signal propagation

and spatial distribution allows to get a map of cardiac excitation patterns with microelectrode arrays.

1 Literature review and problem statement

Multiple electrode array systems are developed for cardiac electrophysiology research to examine newly developed drugs for potential cardiac toxicity in preclinical safety pharmacology and arrhythmia modeling.

The large number of reviews [5–7] in pharmaceutical drug market is linked with lengthening of the QT interval on the surface ECG. The QT interval on the ECG characterizes the duration of the heart electric systole, which normally correlates with heart rate and may depend on the age and gender [8]. In accordance with [7] prolongation of the QT interval is a major drug safety problem, which is defined by the Food and Drug Administration (FDA). Many investigations [8–12] are devoted to the study of the relationship between prolongation of the QT interval and drug-induced potentially lethal ventricular arrhythmia Torsade de Pointes.

It is known [9, 10], that the increase of delayed repolarization, which affects the QT prolongation, early afterdepolarizations (EADs) and ectopic beats are risk factors under standard cardiac safety screening. A classical electrophysiological method for determining these risk factors is the patch clamp. However, this method is characterized by complex and low-throughput measurements.

Many scientists carry out their research with human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), that are a useful medium for performing of arrhythmia risk assessments of new drugs [7, 13–18]. In [13, 14] authors described medium- to high-throughput non-invasive assay MEA platform, used to detect external FP in electrically active hiPSC-CMs. It was suggested to use FP measurement and evaluation for examination pharmacological toxicity of newly developed drugs and to analyze combinations of compounds on cardiomyocytes. In addition, the results of the study [14] showed the effect of application of hiPSC-CMs for "personalized" drug screening due to their identity with genomic background and genetic mutations of the patient.

The QT interval on the surface ECG represents the summation of action potentials (APs) of ventricular myocytes; therefore, in the majority of cases, cardiac pharmacological toxicity evaluation of newly developed drugs is performed by electrophysiological methods with measurements of AP parameters: amplitude and action potential duration (APD). Changes in the AP may induce many types of arrhythmias, among which the most dangerous is Torsade de Pointes, which is described by significant lengthening of APD.

The action potential reflects the flow of ion currents of cell membrane through specialized channels made of protein complexes [8]. Drug dependent changes in cardiomyocytes' APs can be caused by alterations of currents for Na^+ and Ca^{2+} ions (I_{Na} and I_{Ca}) or several of currents for K^+ ions (the rapidly activated I_{Kr} and slow activated I_{Ks}) [13].

The measurement of the cardiac AP and all ionic currents by the classical electrophysiological patch clamp method has been studied over several decades [13]. Prolongation or shortening of AP repolarization can lead to the corresponding modulation of the QT interval. The most commonly investigated parameters in determining of AP changes are the AP amplitude (APA), the resting membrane potential (RMP), the maximal rate depolarization (Vmax) and AP duration at 50% and 90% of repolarization (APD50, APD90 respectively). However, to measure these parameters accurately the experienced operators are required.

Many investigations [13, 14, 17] are devoted to multiple electrode arrays, which have been developed to measure electrical activity in neural and cardiac cells. Now MEAs are being increasingly used to analyze pharmacological toxicity of newly developed drugs. Measurement, based on the MEAs, is non-invasive and user-friendly method with medium- to high- throughput that records the cardiac extracellular FPs instead of intracellular APs.

In accordance with [13, 14] prolongation or shortening of FP duration (FPD) corresponds to measured APD90, but other parameters are difficult to extract from FPs although they contain a high level of information. In [13] extraction of this information have been performed on the basis of relationship (transfer function) between the AP and the FP. The authors have conducted an analysis of this relationship by comparing simulated APs with measured FPs in hiPSC-CM (exposed to drugs with known effects) using an electrical circuit model.

So, each of the used methods for early identification of the arrhythmia risk has advantages and limitations. Authors [17] offered comprehensive screening strategies, based on the combination several different in vitro assessments using integrated platform (multiple electrode array, patch clamp, cellular impedance, motion field imaging, and Ca transient systems), that will allow researchers to increase cardiac safety. Furthermore, this multi-parametric platform of cardiac cells should have all the assessments evaluated simultaneously to predict cardiac disease.

The translation of external FPs to cardiac internal APs is complex, so in practice the accurate assessment of drug risks to the heart is still challenging [13, 14]. Moreover, the concordance between clinical outcome and prediction principles using assay platform, based on the MEAs and hiPSC-CMs is still unsatisfactory [18].

Therefore, to get more useful information about the parameters of FP pulses the study and development of new approaches to interpretations of measured FPs and new signal processing methods should be performed. Due to the importance of the FP morphology assessment, the method for the inverse transforms of AP and FP signals must be developed. In addition, to analyze cardiomyocytes' FP, obtained by means MEA technologies, the detection method to get undistorted morphologies of FP and to interpret experimental functional properties of cardiomyocytes in drug screening and disease modeling should be offered.

2 Determination of mathematical relationship between action potentials and field potentials

According to the basics of electrocardiography it is known, that surface electrodes can detect the small currents, which represents part of membrane activation of many cardiac cells [19]. Consider a monopole current source located in a homogeneous medium with conductivity σ, Fig. 1. Since the source current I spreads uniformly in space, the current density $\vec{J}$ on a sphere of radius r centered at the location of the current monopole is equal to:

$$\vec{J} = \frac{I}{S}\vec{e}_r = \frac{I}{4\pi r^2}\vec{e}_r, \tag{1}$$

where S is the sphere area, $\vec{e}_r$ is the normal vector to the sphere surface.

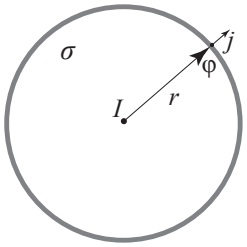


Fig. 1. Monopole current source in a homogeneous medium

The current density $\vec{J}$ is related to the vector of the electric field strength $\vec{E}$ at a point on the surface of the sphere by Ohm's law:

$$\vec{J} = \sigma\vec{E}.$$

Considering that $\vec{E} = grad\ \varphi$, where φ is the potential at the observation point, we have:

$$\vec{J} = -\vec{e}_r\sigma\frac{\partial\varphi}{\partial r}. \tag{2}$$

If the size of the cell is much smaller than the distance to the observation point, then the current flowing through the cell membrane is:

$$I = I_K + I_{Na} + I_{Ca} + I_l = -C_m\frac{du_m}{dt}, \tag{3}$$

where I_K is the potassium current, I_{Na} is the sodium current, I_{Ca} is the calcium current, I_l is the component of the current of other ions and the leakage current through the membrane, C_m is the cell membrane capacitance, u_m is the membrane voltage.

Combining (1), (2), and (3), and taking into account that the potential depends only on the distance from the cell to the observation point and does not depend on the observation angle, we get:

$$C_m = \frac{du_m}{dt} = 4\pi r^2\sigma\frac{d\varphi}{dr}. \tag{4}$$

Consider two observation points located at distances r_1 and r_2 from the cell, Fig. 2. Integrating (4) on the segment $[r_1, r_2]$ we obtain:

$$\int_{\varphi_1}^{\varphi_2} d\varphi = \frac{C_m}{4\sigma\pi}\frac{du_m}{dt}\int_{r_1}^{r_2}\frac{dr}{r^2}. \tag{5}$$

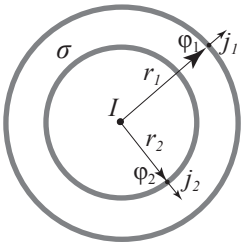


Fig. 2. Illustration to definition of potentials φ_1, φ_2 at the observation points (at distances r_1 and r_2 respectively)

From (5) we get:

$$\varphi_2 - \varphi_1 = \frac{C_m}{4\sigma\pi}\frac{du_m}{dt}\left(\frac{1}{r_2} - \frac{1}{r_1}\right), \tag{6}$$

where φ_1, φ_2 are potentials at the observation points, respectively, at distances r_1 and r_2.

Expression (6) is valid at every moment of time. To find the time dependence of the voltage on the cell membrane, one can integrate expression (6) over time. As a result, we have:

$$u_m(t) = u_0 + \frac{4\pi\sigma r_1 r_2}{C_m(r_2 - r_1)}\int_0^t(\varphi_2 - \varphi_1)dt, \tag{7}$$

where u_0 is the voltage across the membrane at a time $t = 0$.

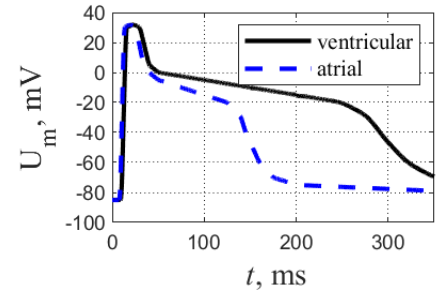
Thus, in order to find the voltage on the cell membrane from the measured potentials in the extracellular space at distances r_1 and r_2 from the cell, it is enough to integrate the difference in the measured potentials over time.

3 Results

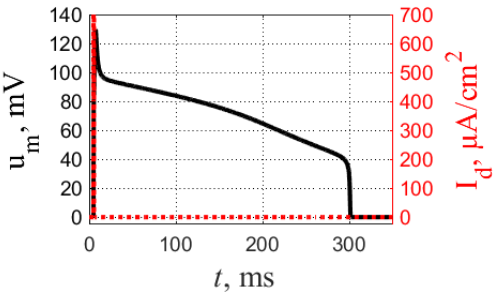
One of the advantages of MEA systems [1–3] is the ability to perform non-invasive FP measurements. However, in main applications of MEA technology, the interpretation of non-invasive information about FPs should be interconnected with invasive AP measurements.

The goal of our study was to focus on the relationship between internal and external signals of cardiac electrical activity. Numerical experiments have been performed with simulated AP and FP signals using reviewed equations for transfer functions between AP and FP. The solution for the relationship between AP and FP has been provided.

To simulate AP signal the proposed in [20] model of cardiac electrical activity at the level of cardiomyocyte have been used. The simulated AP signals for atrial and ventricular cardiomyocytes are demonstrated in Fig. 3a. For numerical experiments, the parameters of the AP signal for ventricular cardiomyocytes have been chosen according to our previous model studies [20].



a)

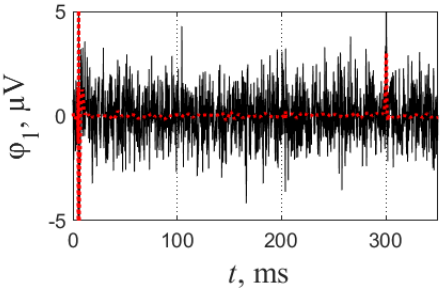


b)

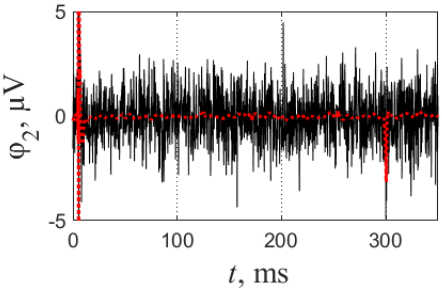
Fig. 3. Simulated action potentials: a) AP for atrial and ventricular cardiomyocytes [20]; b) the variable part of the simulated AP signal for ventricular cardiomyocytes

The direct problem of relationship between APs and FPs has been solved in accordance with the methodology for determining extracellular fields given in [19]. The variable part of the simulated AP signal (Fig. 3b) has been converted to FP_1 and FP_2, which describe the signals at points on the surface, located at the distance r_1 and r_2, respectively. Then obtained potentials FP_1 and FP_2 were investigated taking into account white Gaussian noise (Fig. 4a, b).

Subsequent noise filtering has been made using the wavelet transform and the method combining wavelet denoising and processing in eigensubspaces, proposed in [21]. In numerical experiments denoising techniques with wavelet function "db4" and decomposition to 4 levels have been performed.



a)



b)

Fig. 4. Potentials φ_1, φ_2 at observation points at distances r_1 and r_2: a) potential φ_1 with white Gaussian noise (SNR = 20 dB) (solid black line) and denoised potential φ_1 (dotted red line); b) potential φ_2 with white Gaussian noise (SNR = 20 dB) (solid black line) and denoised potential φ_2 (dotted red line)

Then the inverse problem of relationship between APs and FPs (Fig. 5) has been solved and mathematical equation (7) has been used to find the time dependence of the voltage on the cell membrane $u_m(t)$ (Fig. 6). To solve the inverse problem following parameter values were used: r_1=0.001m, r_2=0.002m [1–3], σ=1.35S/m [22].

4 Discussion

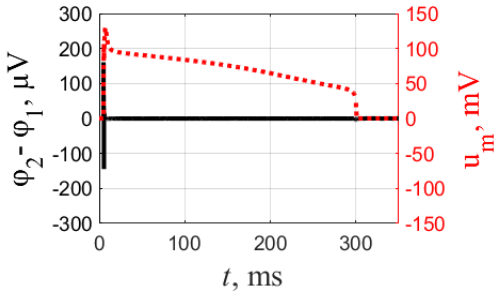
The reconstructed AP demonstrated good consilience with original AP by preserving the signal power and morphology (Fig. 6). The assessment of quality of reconstruction was performed by comparing the values of relative root mean square error (RRMSE) of original and reconstructed APs for different signal to noise ratios (SNR) of noised FP signals and different methods for denoising:

$$RRMSE = \sqrt{\frac{\sum_{i=1}^{n}(u_{mi} - u^*_{mi})^2}{\sum_{i=1}^{n} {u^*_{mi}}^2}} \cdot 100\%,$$

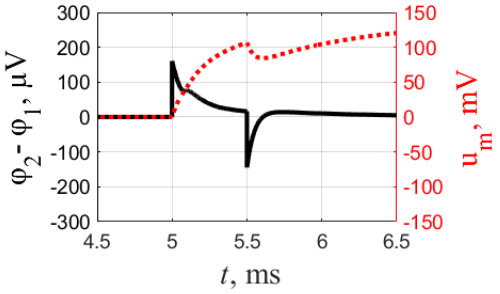
Table 1 RRMSE between the original APs and the APs reconstructed from the denoised FPs for different SNRs and denoising methods

Denoising methods	RRMSE (%)		
	SNR 20 dB	SNR 30 dB	SNR 40 dB
Wavelet denoising (Daubechies 4, db4, level 4)	45.5931	15.2860	4.7973
Eigensubspaces	12.4047	3.9514	1.2429
Wavelet denoising (db4) + Eigensubspaces	10.7778	3.5210	1.1122

where u_{mi} is the original AP's signal, u^*_{mi} is the reconstructed AP's signal, n is the signal length, i is the number of the data point in the signal.



a)



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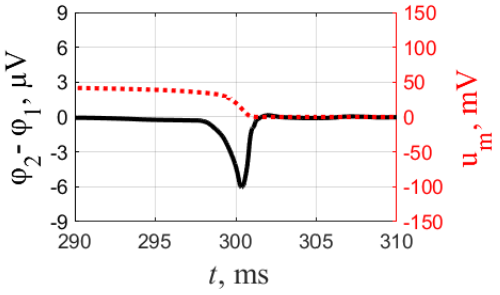

c)

Fig. 5. Relationship between the field potential (black solid line) and action potential that was reconstructed from it (red dashed line): a) a full cycle; b) depolarization phase; c) repolarization phase

Denoising with wavelet transform at SNR = 40 dB showed good results with RRMSE = 4.8%, however using wavelet denoising with lower SNR resulted in considerable increase of RRMSE. Method using eigensubspaces and a method combining wavelet denoising and processing in eigensubspaces [21] both proved to be more effective in reducing RRMSE (Table 1). SNR range of 20 dB and higher was chosen based on the SNR measured from the MEA recordings of the real FP of hiPSC-CM [23].

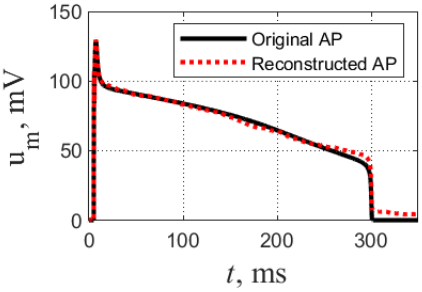

Fig. 6. Simulated action potentials: original (solid) and reconstructed (dotted) by solving the inverse problem

Conclusion

Due to the importance of the FPs morphology assessment the relationship between cardiomyocytes' AP and FP has been proposed on the basis of field theory. Inverse problem of relationship between AP and FP has been solved and mathematical relations have been confirmed by numerical experiments. Proposed method could significantly increase the amount of information extracted from MEA measurements. In addition, to identify extracellular field potentials of cardiomyocytes the method based on wavelet transform and signal processing in eigenvectors' basis of cardiac cycles has been used. This complex method would allow us to get undistorted morphologies of FP and to interpret experimental functional properties of cardiomyocytes in drug screening and disease modeling.

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Розв'язання оберненої задачі взаємозв'язку між потенціалами дії та потенціалами поля в серцевих клітинах

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Багато-електродні масиви (БЕМ) – це поширений інструмент в дослідженнях позаклітинної електричної активності серцевих клітин. Ключовими областями використання БЕМ є фармакологічні дослідження та моделювання захворювань. Під час досліджень в цих областях зусилля багатьох вчених направлені на аналіз та інтерпретацію позаклітинних потенціалів (ПП) отриманих за допомогою систем з БЕМ. Однак, слід зазначити складність інтерпретації інформації БЕМ у вимірах неінвазивного ПП серцевих клітин порівняно з інвазивними записами потенціалу дії (ПД) на основі технології патч-кламп.

Метою цієї роботи є математичне визначення взаємозв'язку між внутрішньоклітинними ПД та зовнішніми ПП. Для цього було поставлено та розв'язано обернену задачу із взаємовідношення ПД та ПП, а саме – розрахунок ПД на основі ПП. Виведення рівнянь для передавальної функції між ПП та ПД було виконано на основі теорії поля. Для отримання більш корисної інформації про параметри імпульсів ПП в роботі виконано дослідження комплексного підходу до обробки виміряних ПП сигналів.

На основі числових експериментів з симульованими ПП було показано успішні результати використання отриманої передавальної функції для реконструкції ПД.

В реальних умовах після вимірювання сигнали ПП мають певну ступінь зашумлення, тому перед трансформацією в ПД до симульованих ПП було додано білий шум. Для знешумлення потенціалу позаклітинного поля кардіоміоцитів було використано вейвлет-перетворення, обробку у власних підпросторах та комбінацію цих методів.

Запропонований метод, заснований на передавальних функціях, може бути використаний для отримання ПД та його параметрів на основі ПП, і, таким чином, може розширити можливості аналізу електричної активності серцевих клітин в системах БЕМ. Комплексний метод знешумлення, що показав високу ефективність на симульованих ПП може бути використаний і на реальних сигналах для отримання неспотворених морфологій ПП, що дозволить проводити більш якісну інтерпретацію функціональних властивостей ПП серцевих клітин в дослідженнях з використанням систем БЕМ.

Ключові слова: БЕМ система; кардіоміоцити; потенціал дії; позаклітинний потенціал поля; обернена задача електрокардіографії; теорія поля; вейвлет-знешумлення; метод власних підпросторів; технологія «лабораторії на чіпі»; індуковані людиною плюрипотентні стовбурові клітини

Решение обратной задачи взаимосвязи потенциалов действия и потенциалов поля в клетках сердца

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Много-электродные массивы (МЭМ) - это распространенный инструмент в исследованиях внеклеточной электрической активности сердечных клеток. Ключевыми областями использования МЭМ являются фармакологические исследования и моделирование заболеваний. При исследованиях в данных областях усилия многих ученых направлены на анализ и интерпретацию внеклеточных потенциалов (ВП), полученных с помощью систем с МЭМ. Однако, следует отметить сложность интерпретации информации МЭМ в измерениях неинвазивного ВП сердечных клеток по сравнению с инвазивными записями потенциала действия (ПД) на основе технологии патч-кламп.

Целью настоящей работы является математическое определение взаимосвязи между внутриклеточными ПД и внешними ВП. Для этого была поставлена и решена обратная задача взаимоотношения ПД и ВП, а именно - расчёт ПД на основе ВП. Вывод уравнений для передаточной функции между ВП и ПД был выполнен на основе теории поля. Для получения полезной информации о параметрах импульсов ВП в работе выполнено исследование комплексного подхода к обработке измеренных ВП сигналов.

На основе численных экспериментов с модельными ВП были продемонстрированы успешные результаты использования полученной передаточной функции для реконструкции ПД. В реальных условиях после измерения сигналы ВП имеют определенную степень зашумления, поэтому перед трансформацией в ПД к модельному ВП был добавлен белый шум. Для удаления шума потенциала внеклеточного поля кардиомиоцитов были использованы вейвлет-преобразование, обработка в собственных подпространствах сердечных циклов и комбинация этих методов.

Предложенный метод, основанный на передаточных функциях, может быть использован для получения ПД и его параметров на основе ВП, и, таким образом, может расширить возможности анализа электрической активности сердечных клеток в системах МЭМ. Комплексный метод удаления шума, показавший высокую эффективность на модельных ВП может быть использован и на реальных сигналах для получения неискаженной морфологии ВП, а также позволит проводить более качественную интерпретацию функциональных свойств ВП сердечных клеток в исследованиях с использованием систем МЭМ.

Ключевые слова: МЭМ система; кардиомиоциты; потенциал действия; внеклеточный потенциал поля; обратная задача электрокардиографии; теория поля; вейвлет преобразование; метод собственных подпространств; технология «лаборатория на чипе»; индуцированные человеком плюрипотентные стволовые клетки