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科研費
KAKENHI

科学研究費助成事業　　研究成果報告書

令和　２ 年　 ８ 月 １９ 日現在

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研究課題名（和文）Computer modeling of cardiac conduction system with nonlinear oscillators

研究課題名（英文）Computer modeling of cardiac conduction system with nonlinear oscillators

研究代表者
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研究成果の概要（和文）：心臓伝導系の拡張不均質振動子モデルを開発しました。モデルは、人工的なRRタコグラム、HRV、付加ノイズ、呼吸周波数ベースラインワンダーを備えた、リアルな12誘導ECGを生成します。また、非線形微分方程式に基づいて房室（AV）ノードの二重経路の簡略化モデルを開発しました。モデルは、さまざまなAV二重経路伝導現象を再現します。 AVノードモデルをテストして、パラメーターを最適化しました。心房細動時の房室結節機能に対するAC信号の影響を調査しました。興奮性モデルの修正に基づいて非線形発振器のモデルを提案し、予備シミュレーションを実行しました。オープンソースのMATLABコードが公開されました。

研究成果の学術的意義や社会的意義
我々が開発した心臓伝導システムの単純な異種コンピューターモデルは、正常および病的なリズムに対応する現実的な12誘導心電図を正確に再現できます。このモデルは、全体的な心臓の電気的活動を研究するのに適しており、心臓の主要部分間の相互作用の調査を可能にします。このモデルは、「ICD」や人工ペースメーカー検証およびテストハードウェアなど、心臓の電気的機能のリアルタイムシミュレーションを備えた低電力ハードウェアシステムで使用できます。また、教育や研究の目的にも使用できます。

研究成果の概要（英文）：We developed extended heterogeneous oscillator model of cardiac conduction system which can demonstrate various situations of cardiac electrical activity. The model generates realistic 12 lead ECG with artificial RR-tachogram, frequency-domain characteristics of HRV, normally distributed additive noise and a baseline wander that couple the respiratory frequency. We also developed simplified model of atrioventricular (AV) node dual pathway, based on nonlinear differential equations. The model reproduces AV dual pathway conduction phenomena: normal behavior, pacemaking, reentry, excitation propagation decay, and filtering function. We tested our AV node model to optimize its parameters. We investigated the effect of sinusoidal AC signals on AV node function during atrial fibrillation. We propose a model of nonlinear oscillator based on our modification of excitable model and performed preliminary simulations. Research papers and open source MATLAB/Simulink code were published.

研究分野：生体医工学

キーワード：heart model　computer modeling　cardiac　conduction system　nonlinear equation　dual pathway　atrioventricular node

１．研究開始当初の背景

The nonlinear analysis of ECG signals is commonly used in studies of cardiac and cardiovascular diseases. For the modeling of the electrical processes in the heart, various modeling approaches with different levels of details have been proposed and utilized. Most of the models describe functioning of the heart on the cellular level. Simulations on 2D or 3D tissue slabs produce pseudo electrograms, while 3D biventricular, atrial, or whole-heart models coupled with torso model can yield more realistic ECG signals. These models are based on either rule-based or reaction-diffusion approaches for simulation of excitation wave propagation and require a lot of computational resources.

There is a different class of models, which describe of heartbeat dynamics in general with a set of ordinary differential equations. Some of the models generate synthetic ECG signals using a dynamical system on a circle without considering structure of the cardiac conduction system. Such oscillator models are focused on the generation of transmembrane action potentials and the study of their synchronization, bifurcation, and chaos, but only a few are intended for calculation of realistic ECG.

A mathematical model for the generation of ECG signals with appropriate heart rate variability (HRV) spectra has been the subject of many research efforts. Different models that include the effects of sympathetic and parasympathetic system in the heart rate, using a statistical approach have been proposed. Given the importance of information obtained from ECG recordings for medical education and equipment testing some hardware and software simulators that offer the generation of ECG signals from all 12 leads (or some of them) have been published. However, such implementations keep shortcomings in the amplitudes, ranges, waveforms, and intervals of the produced signals. Most of developed ECG signal generators reproduce only Lead II signal with physiologically right timing and profile characteristics. Such artificial ECG simulators are based on sampled waveform previously stored in memory. Therefore, they do not provide a useful tool to a dynamical interpretation of abnormalities in the cardiac conduction system.

The atrioventricular (AV) node is key part of cardiac conduction system that coordinates appropriate relationship between atria and ventricles, creating a delay to facilitate efficient pumping of blood, protecting ventricles from atrial tachyarrhythmias, and functioning as a subsidiary pacemaker in the case of sinoatrial (SA) node dysfunction. The very important feature of the normal AV node is its built-in dual –fast (FP) and slow (SP) – pathway. The SP and FP interplay may result in a clinical arrhythmia known as AV nodal reentrant tachycardia, the most common form of paroxysmal supraventricular tachycardia. Despite numerous experimental studies and clinical observations, the electrophysiological behavior of AV node remains not fully understood.

Currently there are very few AV models of dual conduction pathway. The detailed multi-variable cardiac transmembrane cellular models allow investigation of the heart rhythm properties but are too complex and usually do not have the ability to effectively simulate cardiac electrical activity during arrhythmia in real time.

２．研究の目的

The goals of this project are the following.

1. Extension of our recent heterogeneous nonlinear oscillator model of cardiac conduction system by including an artificial RR-tachogram with HRV spectrum. The modified model is capable to generate all the standard 12 leads representing human body surface ECG. Additionally, we introduce ambient noise and the respiratory frequency into baseline wander, to reproduce realistic ECG signals.

2. Development of a simplified dual pathway model of AV node which should be fast enough to allow the study of cardiac conduction phenomena at a time scale of thousands of heart beats in real time, contain as small a number of elements as possible, and be able to reproduce various cardiac phenomena without significant changes in its basic structure. We also optimized the dual pathway model structure to provide acceptable balance between the realistic physiology, structural simplicity, and efficient real-time computation, especially taking into account future hardware model implementation with less powerful microcontrollers. We simulated the influence of sinusoidal AC electrical signals on cardiac electrical conduction system operation, which can serve as an alternative method of defibrillation.

３．研究の方法

We use as a starting point the model of cardiac conduction system consisting of sets of heterogeneous nonlinear oscillators, which represent electrical responses of main natural pacemakers and atrial (AT) and ventricular (VN) muscles. Sinoatrial node, atrioventricular node, and His-Purkinje (HP) system are represented by modified Van der Pol (VdP) type oscillators connected with time-delay coupling, and are given by sets of ordinary differential equations. The description of the electrical responses of AT and VN muscles under the stimulation by the pacemakers is based on modified FitzHugh-Nagumo equations. The net ECG waveform is calculated as a composition of muscle electrical responses (雑誌論文 1,2).

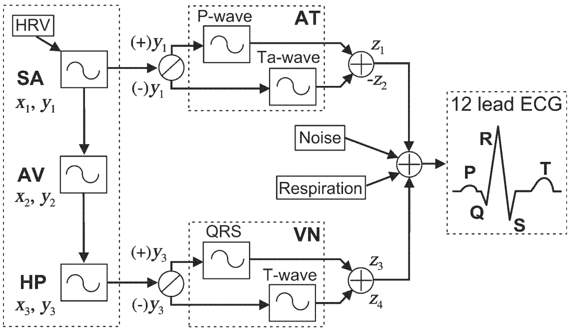

Fig. 1. General scheme of the developed 12-lead ECG model.

ECG tachogram signals with specific statistics such as the mean and standard deviation of the HR and frequency-domain characteristics of HRV incorporated the effect of both RSA and Mayer waves in the power spectrum by generating RR intervals having a bimodal power spectrum consisting of the sum of two Gaussian distributions.

We synthesized the ECG waveform for each of 12 standard leads for normal and pathological cases, as well as fit it to individual characteristics of a subject considering weighted linear combination of the depolarization and repolarization responses. The weighting coefficients for each lead were obtained by a fitting procedure with real ECG's. For this purpose, we used a supervised learning algorithm called *perceptron* which is the simplest type of artificial neural network (雑誌論文 3).

We incorporated simplified AV node dual pathway block into our basic cardiac heterogeneous oscillator model (Fig. 2). The pathway elements - peripheral sinoatrial node (PSA), FP and SP units, and proximal AV node (PAV) are represented by nonlinear excitable Aliev-Panfilov equations. The excitation is initiated in the central sinoatrial node (CSA), then propagates through PSA to atrial muscles and FP (9 units) and SP (19 units) pathways, reaches PAV, and though distal atrioventricular node (DAV) proceeds to His-Purkinje system and further to ventricles. The CSA and DAV are represented by modified VdP equations. The parameters of the model equations were scaled to produce amplitudes and durations of action potentials close to corresponding natural cardiac pacemaker cells (雑誌論文 4,5).

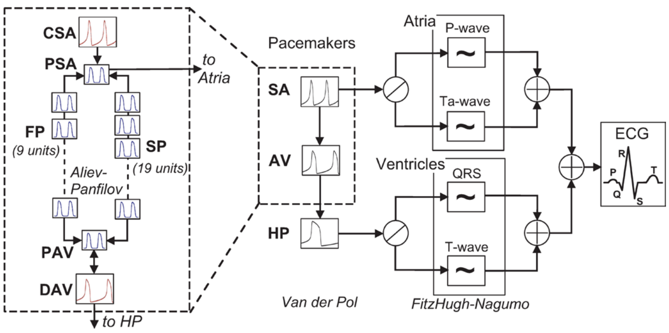

Fig. 2. Scheme of the incorporation of proposed AV node dual pathway model block into our basic model of cardiac conduction system.

To investigate the effect of AC stimulation on the AV node block performance during the atrial fibrillation, we applied a train of chaotic stimuli from atria side of the model with randomly changed stimulus. Then sinusoidal AC signals with amplitudes less than the excitation threshold were added (Fig. 3). The trains of stimuli were exactly the same for all the cases to clearly reveal the effect of AC signal application (雑誌論文 6).

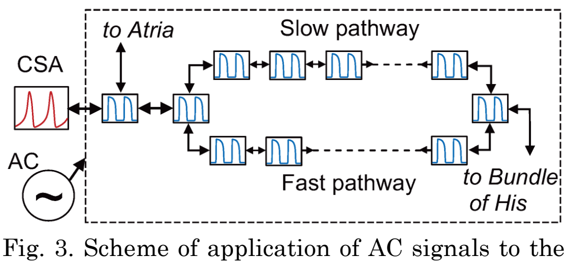

Fig. 3. Scheme of application of AC signals to the AV node dual pathway model.

All the models were developed in MATLAB/Simulink environment.

４．研究成果

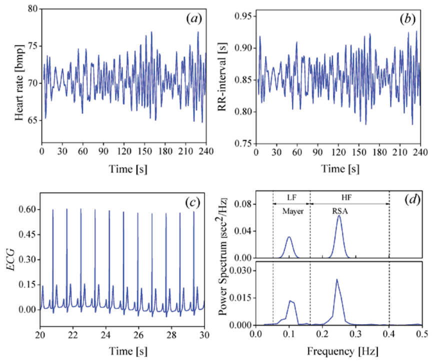

Fig. 4. Analysis of RR-intervals from R-peak detection of the ECG signal generated using the proposed method. (a) Variation of instantaneous heart rate, (b) RR-intervals, (c) calculated ECG signal, and (d) power spectra of the RR-intervals: top - obtained with (4) and bottom - from the calculated ECG.

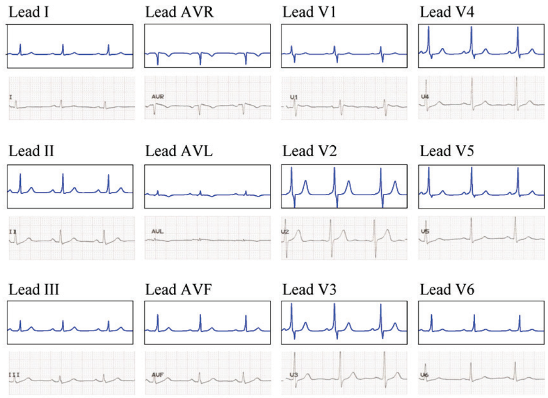

Fig. 5. Calculated 12 lead ECG signals with specific statics in the heart rate, obtained with the proposed model (top panels). Real ECG signals are shown for comparison (bottom panels).

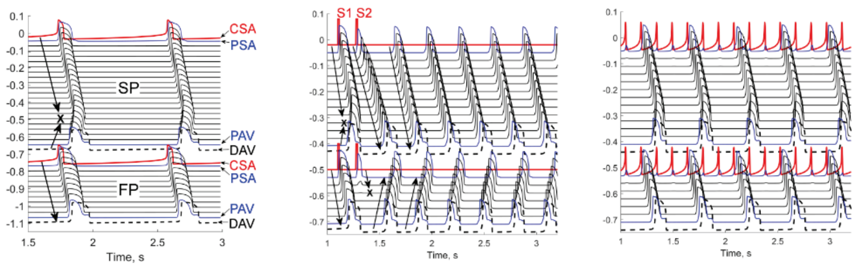

Fig. 6. Normal pacing at 70 bpm (left) and S1-S2 protocol stimulation (middle) with reentry, and filtering function (right).

We developed heterogeneous oscillator model of cardiac conduction system able to generate the 12 lead ECG signals with appropriate heart rate variability spectra. The model incorporates an artificial RR-tachogram with specific statistic on the heart rate with both respiratory sinus arrhythmia and Mayer waves introduced in the HRV spectrum (Fig. 4). Ambient noise and a baseline wander were added to account for observational uncertainty of real ECG signals. The proposed model reproduces QT and RR intervals variations similar to clinically observed ECGs. The model is capable to simulate accurately realistic ECG characteristics, even local pathological phenomena (Fig. 5) (雑誌論文 1,2).

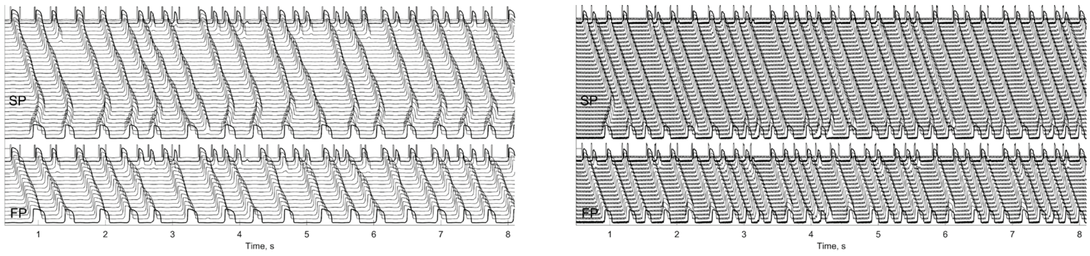

Fig. 7. AC stimulation of AV node during atrial fibrillation 5 Hz amplitude 2 a. u. (left), and 50 Hz amplitude 30 a. u. (right).

We considered and compared three model variants with different number of pathway node elements. All tested models were able to reproduce normal cardiac signals conduction, AV node automaticity, reentry, and filtering function (Fig. 6) (雑誌論文 4,5).
We investigated the effect of application of sinusoidal AC signals on the atrioventricular node during atrial fibrillation using nonlinear differential equation model. The obtained results demonstrated that the AC application affects the AV node performance during arrhythmia changing the nodal filtering function depending on AC signal amplitude and frequency (Fig. 7) (雑誌論文 6).

５．主な発表論文等

〔雑誌論文〕　計6件（うち査読付論文　4件／うち国際共著　6件／うちオープンアクセス　3件）

１．著者名 Quiroz-Juarez MA, Jimenez-Ramirez O, Vazquez-Medina R, Ryzhii E, Ryzhii M, Aragon JL	４．巻 17(4)
２．論文標題 Cardiac conduction model for generating 12 lead ECG signals with realistic heart rate dynamics	５．発行年 2018年
３．雑誌名 IEEE Transactions on Nanobioscience	６．最初と最後の頁 525-532
掲載論文のDOI（デジタルオブジェクト識別子） 10.1109/TNB.2018.2870331	査読の有無 有
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１．著者名 Quiroz-Juarez MA, Jimenez-Ramirez O, Vazquez-Medina R, Ryzhii E, Ryzhii M, Aragon JL	４．巻 -
２．論文標題 ECGHOSM (ECG Heterogeneous Oscillator Simulation Model) [Source Code]	５．発行年 2018年
３．雑誌名 Repository: Code Ocean (www.codeocean.com)	６．最初と最後の頁 -
掲載論文のDOI（デジタルオブジェクト識別子） 10.24433/co.a3c92666-8674-4cf7-801f-0ed0a927d7b6	査読の有無 無
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１．著者名 Quiroz-Juarez MA, Jimenez-Ramirez O, Vazquez-Medina R, Ryzhii E, Ryzhii M, Aragon JL	４．巻 -
２．論文標題 Fitting Algorithm for Cardiac conduction model for generating 12 lead ECG signals with realistic heart rate dynamics [Source Code]	５．発行年 2018年
３．雑誌名 Repository: Code Ocean (www.codeocean.com)	６．最初と最後の頁 -
掲載論文のDOI（デジタルオブジェクト識別子） 10.24433/co.9132bcf4-173b-463d-8770-58e623b4e3c5	査読の有無 無
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Ryzhii M, Ryzhii E	４．巻 144524
２．論文標題 Development of Simplified Model of Atrioventricular Node with Dual Pathway	５．発行年 2018年
３．雑誌名 Proc. IEEE Int. Conf. on Bioinformatics and Biomedicine (BIBM 2018)	６．最初と最後の頁 2800-2802
掲載論文のDOI（デジタルオブジェクト識別子） 10.1109/BIBM.2018.8621149	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Ryzhii M, Ryzhii E	４．巻 1372
２．論文標題 Optimization of Dual Pathway AV Nodal Conduction Model	５．発行年 2019年
３．雑誌名 Journal of Physics: Conference Series	６．最初と最後の頁 12078
掲載論文のDOI（デジタルオブジェクト識別子） 10.1088/1742-6596/1372/1/012078	査読の有無 有
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１．著者名 Ryzhii M, Ryzhii E	４．巻 -
２．論文標題 Simulation of the Effect of AC stimulation on Atrioventricular Node with Nonlinear Model	５．発行年 2020年
３．雑誌名 Proc. of 11th Conference of the European Study Group on Cardiovascular Oscillations (ESGCO)	６．最初と最後の頁 9158159
掲載論文のDOI（デジタルオブジェクト識別子） 10.1109/ESGCO49734.2020.9158159	査読の有無 有
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〔学会発表〕　計4件（うち招待講演　0件／うち国際学会　4件）

１．発表者名 Ryzhii M,　Ryzhii E
２．発表標題 Simulation of various cardiac conduction phenomena with Matlab/Simulink model
３．学会等名 21st International Conference on Circuits, Systems, Communications and Computers (CSCC 2017)（国際学会）
４．発表年 2017年

１．発表者名 Ryzhii M,　Ryzhii E
２．発表標題 Simplified model of cardiac atrioventricular node based on nonlinear heterogeneous oscillators
３．学会等名 5th Int. Conf. on Mathematics and Computers in Sciences and Industry, MCSI 2018（国際学会）
４．発表年 2018年

１．発表者名 Ryzhii M, Ryzhii E
２．発表標題 Development of Simplified Model of Atrioventricular Node with Dual Pathway
３．学会等名 2018 IEEE Int.Conf. on Bioinformatics and Biomedicine, BIBM 2018（国際学会）
４．発表年 2018年

１．発表者名 Ryzhii M, Ryzhii E
２．発表標題 Optimization of Dual Pathway AV Nodal Conduction Model
３．学会等名 International Conference on Biomedical Engineering (ICoBE 2019)（国際学会）
４．発表年 2019年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
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研究協力者	アラゴン　ホセ・ルイス (Aragon Jose L.)	メキシコ国立自治大学・教授	