Прикладные задачи нелинейной теории колебаний и волн

Известия высших учебных заведений. Прикладная нелинейная динамика. 2021. Т. 29, № 3
Izvestiya Vysshikh Uchebnykh Zavedeniy. Applied Nonlinear Dynamics. 2021;29(3)

Article
DOI: 10.18500/0869-6632-2021-29-3-356-364

Using a mathematical model of cardiovascular system for preparing surrogate data for testing methods of phase synchronization analysis

E. I. Borovkova[1,2,3], *Yu. M. Ishbulatov*[1,2,3], *A. N. Hramkov*[1]✉, *A. S. Karavaev*[1,2,3]

[1]Saratov State University, Russsia
[2]Science Research Institute of Cardiology of Saratov State Medical University n.a. V. I. Razumovsky, Russia
[3]Saratov Brunch of Kotelnikov Institute of Radioengineering and Electronics, Russia
E-mail: rubanei@mail.ru, ishbulatovyurii94@gmail.com, ✉anhramkov@gmail.com, karavaevas@gmail.com
Received 1.11.2020, accepted 23.12.2020, published 31.05.2021

Abstract. The *aim* of present research is refinement of the parameters and statistical properties of methods for diagnosing phase synchronization areas based on the dependence of the instantaneous phase difference of oscillations on time. *Methods*. Two methods are compared that allow one to identify of synchronization modes based on the dependence of the instantaneous phase difference of oscillations on time: a method based on an estimate of the phase coherence coefficient and a method based on a linear approximation of the instantaneous phase difference in a sliding window and an estimate of the slope of the approximating straight line. The phase synchronization of the low-frequency (0.04–0.15 Hz) components of the time series of interbeat intervals and blood pressure is analyzed. A mathematical model of the cardiovascular system is used to generate an ensemble of test data when analyzing the statistical properties of methods of phase synchronization analysis and refining their parameters. Test data is generated by modulating the coupling parameters between the autonomic control loops of blood circulation in the model, providing the known presence and absence of synchronization modes. *Results*. During the analysis of the model data, the values of the method parameters were refined. The sensitivity and specificity of the methods were evaluated. A higher sensitivity of the previously proposed method for detecting phase synchronization intervals in the analysis of non-stationary time series of the cardiovascular system is shown. *Conclusion*. In the analysis of non-stationary time series of the cardiovascular system shown the higher sensitivity of the method for detecting phase synchronization intervals, what based on a piecewise linear approximation of the instantaneous phase difference in a sliding window and an estimate of the slope of the approximating straight line.

Keywords: phase synchronization, mathematical model, low frequency, autonomic control, heart rate variability, blood pressure, sensitivity, specificity, receiver-operating-characteristic curve.

Acknowledgements. This work was supported by Russian Foundation for Basic Research, grant No. 20-02-00702 and grant No. 19-32-90206.

For citation: Borovkova EI, Ishbulatov YuM, Hramkov AN, Karavaev AS. Using a mathematical model of cardiovascular system for preparing surrogate data for testing methods of phase synchronization analysis. Izvestiya VUZ. Applied Nonlinear Dynamics. 2021;29(3):356–364. DOI: 10.18500/0869-6632-2021-29-3-356-364

Научная статья
УДК 530.182, 004.942
DOI: 10.18500/0869-6632-2021-29-3-356-364

Использование математической модели сердечно-сосудистой системы для приготовления суррогатных данных при тестировании методов диагностики синхронизации

Е. И. Боровкова[1,2,3], *Ю. М. Ишбулатов*[1,2,3], *А. Н. Храмков*[1]✉, *А. С. Караваев*[1,2,3]

[1]Саратовский национальный исследовательский государственный университет им. Н. Г. Чернышевского, Россия
[2]Саратовский государственный медицинский университет им. В. И. Разумовского, Россия
[3]Саратовский филиал Института радиотехники и электроники им. В. А. Котельникова РАН, Россия
E-mail: rubanei@mail.ru, ishbulatovyurii94@gmail.com, ✉anhramkov@gmail.com, karavaevas@gmail.com
Поступила в редакцию 1.11.2020, принята к публикации 23.12.2020, опубликована 31.05.2021

Аннотация. *Цель* настоящего исследования – уточнение параметров и статистических свойств методов диагностики участков фазовой синхронизации по зависимости мгновенной разности фаз колебаний от времени. *Методы*. Сопоставляются метод, основанный на оценке коэффициента фазовой когерентности, и метод, основанный на кусочно-линейной аппроксимации мгновенной разности фаз в скользящем окне и оценке углового коэффициента наклона аппроксимирующей прямой. Анализируется фазовая синхронизация низкочастотных (0.04–0.15 Гц) компонент временных реализаций кардиоинтервалограммы и артериального давления. Математическая модель сердечно-сосудистой системы используется для генерации ансамбля тестовых данных при анализе статистических свойств методов диагностики фазовой синхронизации и настройки их параметров. Тестовые данные генерируются при модуляции параметров связи между контурами автономного контроля кровообращения модели, обеспечивая заведомое наличие и отсутствие режимов синхронизации. *Результаты*. В ходе анализа данных модели были уточнены значения параметров методов. Оценены чувствительность и специфичность методов. *Заключение*. Показана более высокая чувствительность метода диагностики фазовой синхронизации, основанного на кусочно-линейной аппроксимации мгновенной разности фаз в скользящем окне и оценке углового коэффициента наклона аппроксимирующей прямой, при анализе нестационарных временных рядов сердечно-сосудистой системы.

Ключевые слова: фазовая синхронизация, математическая модель, низкая частота, автономный контроль, вариабельность сердечного ритма, кровяное давление, чувствительность, специфичность, рабочая характеристика приёмника.

Благодарности. Работа выполнена при поддержке РФФИ, грант № 20-02-00702 и грант № 19-32-90206.

Для цитирования: *Боровкова Е. И., Ишбулатов Ю. М., Храмков А. Н., Караваев А. С.* Использование математической модели сердечно-сосудистой системы для приготовления суррогатных данных при тестировании методов диагностики синхронизации // Известия вузов. ПНД. 2021. Т. 29, № 3. С. 356–364. DOI: 10.18500/0869-6632-2021-29-3-356-364

Introduction

The works [1–7] show the importance of studying the phase synchronization between the processes of autonomic baroreflex control of heart rate variability and blood pressure (BP) for understanding the fundamental principles of the functioning of the cardiovascular system and solving applied problems of medical diagnostics. Low-frequency (LF) components of interbeat intervals (RR-intervals) and BP signals are often used as a source of information about these processes [8]. We have previously shown that the LF components of the RR-intervals and BP signals are characterized by strong non-stationarity and chaotic dynamics, which manifests itself in the alternation presence and absence of synchronization modes [1, 9, 10]. Moreover, the relative time of synchronization modes is important for the diagnosis and therapy of various circulatory pathologies, as well as understanding the peculiarities of the interaction of complex nonlinear elements of the human body [1, 4–7, 11, 12].

When studying the phase synchronization of complex systems of biological nature according to their time series, there is always a problem of choosing the methods of phase synchronization analysis and refining their parameters. The complexity of the systems under study and the nonstationarity and noisiness of the analyzed signals make it difficult to diagnose synchronization and can lead both to masking the synchronization modes and to false detection of synchronization modes [13, 14].

Therefore, the purpose of the work is analyzing the statistical properties of methods of phase synchronization analysis and refining their parameters that allows you to identify areas of phase synchronization between the RR-intervals and BP signals in the LF range.

The known methods of diagnostics of synchronization are distinguished by various advantages, disadvantages and peculiarities of their use, which a priori make it impossible to use a number of such methods for solving worthwhile goals. A number of well-known methods, for example, synchrograms [15] and calculation of the instantaneous frequency ratio [16], claim to qualitatively analyze the dynamics and their formalization to determine the boundaries of synchronization sections is difficult. Methods based on information-theoretic approaches [17] require long stationary time series and cannot be used to analyze the systems under study.

The paper compares two methods that allow one to identify of synchronization modes based on the dependence of the instantaneous phase difference of oscillations on time: a method based on an estimate of the phase coherence coefficient [18] and a method based on a linear approximation of the instantaneous phase difference in a sliding window and an estimate of the slope of the approximating straight line [1].

The selected methods are widely used for diagnostics of synchronization in radiophysical systems, nonlinear reference oscillators, systems of biological nature, including analysis of signals from the central nervous system and cardiovascular system [1, 19, 20].

The first problem typical for the analysis of the biological processes under study is the lack of objective information on the location of synchronization intervals. The second problem is the impossibility of recording long-term experimental records, which are necessary to obtain reliable statistical conclusions. These problems were solved by generating test data using a specially developed mathematical model that simulated the alternation of areas of synchronous and asynchronous behavior of processes of autonomic baroreflex control of heart rate variability and mean arterial pressure.

1. Model

We modified the mathematical model from work [21], which simulates the phase synchronization of the processes of autonomic baroreflex control of heart rate variability and mean arterial pressure.

The dynamics of the processes under study is described by two self-oscillators with delayed first-order feedback, which generate self-oscillations with a frequency of about 0.1 Hz. Additionally, the interaction of the studied processes is influenced by the dynamics of the main heart rate, mean BP, elastic properties of the aorta, peripheral vascular resistance, adrenaline concentration in the vessels and heart, the activity of two groups of baroreceptors, the respiration process and other parameters of the model. In [15], the values of the model parameters are proposed, which make it possible to describe the functioning of the studied control processes in a healthy person in a standing position. Due to the structure of the model in this mode, 100% synchronization is observed between the investigated autonomic control processes.

However, the reduction to zero of the coefficients responsible for the effect of the sympathetic and parasympathetic links of autonomic control on heart contractility, peripheral vascular resistance, heart rate, allows us to describe the mode of autonomic blockade. In this mode, 100% desynchronization is observed between the investigated autonomic control processes.

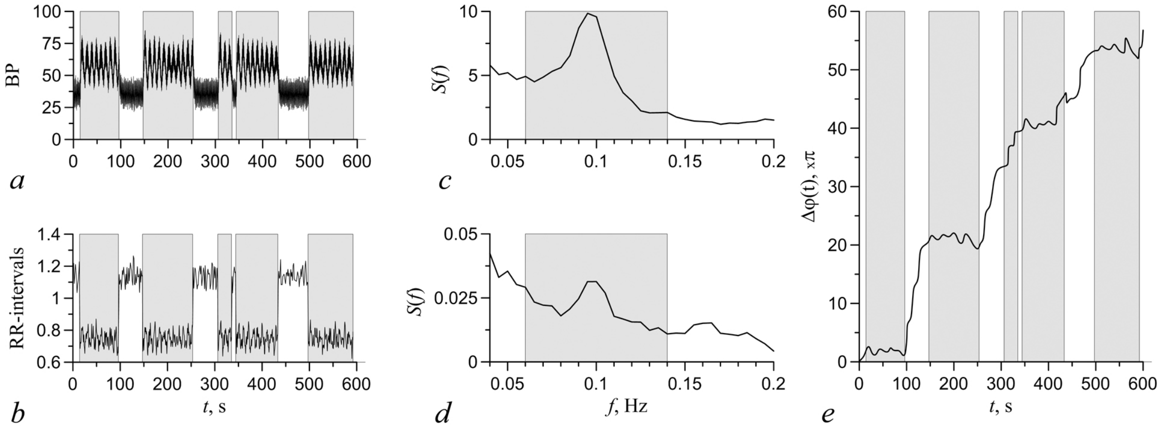

Fig. 1. *a* – Fragments of the BP signal of model. *b* – Fragments of RR-intervals of model. *c* – Fourier power spectra of the BP signal of model. *d* – Fourier power spectra of RR-intervals of model. *e* – Differences of instantaneous phases of RR-intervals and BP. In (*a, b, e*) gray bars mark the true areas of phase synchronization. In (*c, d*) gray bars mark the boundaries of the LF-band

When generating model time series by changing the parameters of the model, we alternated the mode of functioning of the studied processes of a healthy person in the standing position and the mode of autonomic blockade. The duration of the intervals of blockade and normal functioning reproduced the statistics of the distributions of the duration of the intervals of synchronization and areas of asynchronous behavior of the studied control processes, which were evaluated in [22].

As a result, we obtained temporal realizations of the blood pressure signal and RR-intervals, for which information about the position of the phase synchronization intervals was known. The duration of the data was about 10,000 characteristic oscillation periods. In Fig. 1, *a, b* fragments the signal RR-intervals and BP of model, gray bars mark the true areas of phase synchronization are shown.

To extract the phases RR-intervals and BP, we filter them in LF-band with band-pass filter 0.06–0.14 Hz in accordance with the method proposed in [10]. In Fig. 1, *c, d*, Fourier power spectra the signal RR-intervals and BP of model, gray bars mark the boundaries of the LF-band are shown. Then, we calculated the instantaneous phases $\varphi_x(t)$ and $\varphi_y(t)$ for these rhythms using the Hilbert transform [23] and their phase difference $\Delta\varphi(t) = \varphi_x(t) - \varphi_y(t)$. In Fig. 1, *e* the differences of instantaneous phases of RR-intervals and BP are shown. In Fig. 1, *e*, it can be seen that sections of phase synchronization, in which the phase difference fluctuates around a certain constant value, alternate with sections of asynchronous behavior, in which the phase difference increases.

2. Methods of phase synchronization analysis

We compared two methods for finding the boundaries of the synchronization sections using the phase difference signal.

The first method is based on the calculation in windows of duration b seconds sliding along the temporal implementation of the phase synchronization index ρ [24]. As a result, ρ_i is calculated for the moment t_i corresponding to the middle of the window. By shifting the window by one point along the temporal realization of $\Delta\varphi(t)$, ρ_{i+1} is calculated for the time instant t_{i+1}. Regions of phase synchronization, in which the dependence of the $\Delta\varphi(t)$ is a flat plateau, correspond to the regions with the value of ρ_i close to unity. Phases of phase synchronization are identified if $\rho_i \geqslant \rho_0$, where ρ_0 is the threshold value of the phase synchronization index p, and the duration of such an interval is at least l. b, ρ_0 and l are free method parameters. Further, when mentioning this method, we will use the “method ρ”.

The second method is based on a piecewise linear approximation of the instantaneous phase difference in a sliding window and an estimate of the slope of the approximating straight line α [1]. The method is as follows. In a window with a width b, using the least squares method, a linear approximation of the dependence of the difference of the instantaneous phases $\Delta\varphi(t)$ is carried out. As a result, for the moment of time t_i corresponding to the middle of the window, the slope of the approximating straight line α_i is calculated. By shifting the window by one point along the temporal realization of $\Delta\varphi(t)$, we calculate the tilt angle α_i for the moment of time t_{i+1}. The regions of phase synchronization, on which the dependence of the $\Delta\varphi(t)$ is a flat plateau, correspond to the regions with a small value of the slope coefficient $\aleph$. Phase synchronization sections are identified if $|\alpha_i| \leqslant |\alpha_0|$, where α_0 is the threshold value of the slope coefficient α, and the duration of such an interval is at least l. b, $\aleph_0$ and l are free parameters of the method. In what follows, when referring to this method, we will use the "method α".

The choice of parameters for methods for analyzing complex experimental signals is a nontrivial task that requires taking into account the features of specific systems under study. In this case, as a rule, the choice of parameters is a compromise between the requirements for specificity, that is, the probability of not detecting a false synchronization interval (1-FPR – false positive results) and sensitivity, that is, the probability of detecting a synchronization interval where it is actually present (TPR – true positive results) method [25]. Therefore, in the course of comparing the methods, their parameters were taken over wide ranges with TPR and 1-FPR estimates. For the method α: we went α_0 over the interval $[0; 0.1]$ with a step of 0.001. The value $\alpha_0 = 0$ corresponds to the horizontal section of the phase difference, $\alpha_0 = 0.1$ corresponds to an increase in the $\Delta\varphi(t)$ by π radians over a characteristic period. For the ρ: ρ_0 method, we went over the interval $[0.6; 1.0]$ with a step of 0.004. The value $\rho_0 = 1.0$ corresponds to a δ-peak in the distribution of the phase difference, and $\rho_0 = 0.6$ is often chosen as an empirical estimate of the lower threshold of the index value corresponding to phase synchronization. For all algorithms, the parameters of the sliding window width b were sorted out in the range [1; 40] seconds with a step of 1 second. The minimum length of the synchronization region l was selected in the range [10; 40] seconds with a step of 10 seconds (1 characteristic period).

3. Results

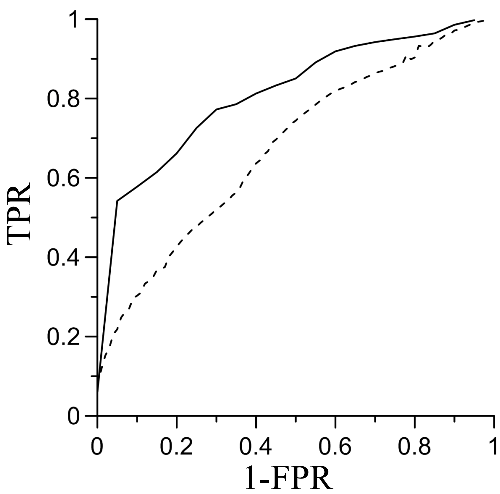

Fig. 2. Receiver operating characteristic, characterizing the ratio between the proportion of true positive leads (TPR) and false positive leads (1-FPR) about the presence of phase-locked areas. Solid line is for method α. Dotted line is for method ρ

As a result of the analysis, using a priori information about the position of the phase synchronization sections, ROC-curves (receiver operating characteristic) were constructed, characterizing the ratio between the proportion of true positive leads (TPR) and false positive conclusions (1-FPR) about the presence of phase synchronization sections. In Fig. 2, the result of the method comparison is presented. The solid line corresponds to the method α. The dotted line corresponds to the method ρ. Each point on the graphs gives information about what sensitivity (TPR) a given method provides for a given specificity (1-FPR). For example, the upper left corner of the graphs (TPR = 100 and 1-FPR = 0) corresponds to the ideal case of error-free detection of synchronization regions.

It can be seen that the solid ROC curve always remains above the dashed ROC curve. This indicates that the method α demonstrates a higher sensitivity than the method ρ.

Figure 2 shows that the method α, in contrast to the method ρ, can provide TPR at 0.7 and 1-FPR at 0.3. Such TPR and 1-FPR are acceptable characteristics of the method when solving problems of medical diagnostics. Method α parameter areas providing TPR = 0.7 and specificity = 0.7: $\alpha_0 \in [0.003; 0.004]$, $b \in [15; 40]$ seconds, $l \in [10; 30]$ seconds.

Conclusions

In the course of the ROC analysis, the methods of searching for phase synchronization regions were compared. It is shown that when studying the phase synchronization between the signals of RR-intervals and BP in the low-frequency range, the method based on approximating the phase difference with a line in a sliding window and estimating the slope of the approximating line demonstrates a better ratio of sensitivity and specificity than the method based on the calculation in sliding window phase synchronization index. The range of parameters of the method was revealed, providing sensitivity at the level of 0.7 and specificity at the level of 0.3, which is necessary for the analysis of signals of a biomedical nature.

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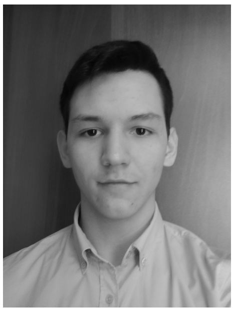
Боровкова Екатерина Игоревна – родилась в Саратове (1989). Окончила факультет нано- и биомедицинских технологий Саратовского государственного университета (2012). Защитила диссертацию на соискание учёной степени кандидата физико-математических наук на тему «Разработка и апробация методов определения границ интервалов синхронизации по нестационарным временным рядам» по специальности «Радиофизика» (2018, СГУ). Должности – доцент кафедры динамического моделирования и биомедицинской инженерии Саратовского государственного университета им. Н. Г. Чернышевского, научный сотрудник отдела продвижения новых кардиологических информационных технологий Саратовского государственного медицинского университета имени В. И. Разумовского. Научные интересы – методы обработки и анализа сигналов сложных систем. Опубликовала свыше 20 научных статей по указанным направлениям.

Россия, 410012 Саратов, ул. Астраханская, 83
Саратовский национальный исследовательский государственный
университет имени Н. Г. Чернышевского
E-mail: rubanei@mail.ru
ORCID: 0000-0002-9621-039X

Ишбулатов Юрий Михайлович – родился в Саратове (1994). Окончил факультет нано- и биомедицинских технологий Саратовского государственного университета (2017). Должность – младший научный сотрудник отдела продвижения новых кардиологических информационных технологий Саратовского государственного медицинского университета имени В. И. Разумовского. Научные интересы – математическое моделирование биологических систем. Опубликовал свыше 20 научных статей по указанным направлениям.

Россия, 410012 Саратов, ул. Астраханская, 83
Саратовский национальный исследовательский
государственный университет имени Н.Г. Чернышевского
E-mail: ishbulatovyurii94@gmail.com



Храмков Алексей Николаевич – родился в Саратове (2000). Студент 3 курса факультета нано- и биомедицинских технологий Саратовского государственного университета. Должность – лаборант кафедры динамического моделирования и биомедицинской инженерии Саратовского государственного университета им. Н. Г. Чернышевского. Научные интересы – методы разработки нейросетей.

Россия, 410012 Саратов, ул. Астраханская, 83
Саратовский национальный исследовательский
государственный университет имени Н.Г. Чернышевского
E-mail: anhramkov@gmail.ru

Караваев Анатолий Сергеевич – родился в Саратове (1981). Окончил факультет нелинейных процессов Саратовского государственного университета (2004). Защитил диссертацию на соискание учёной степени кандидата физико-математических наук на тему «Восстановление параметров систем с запаздыванием по временным рядам» по специальности «Радиофизика» (2007, СГУ). Получил ученое звание доцента по специальности «Радиофизика» (2018). Защитил диссертацию на соискание учёной степени доктора физико-математических наук на тему «Математическое моделирование механизмов функционирования и синхронизация элементов системы кровообращения» по специальности «Математическое моделирование» (2019, СГТУ). Должности – профессор кафедры динамического моделирования и биомедицинской инженерии Саратовского государственного университета им. Н. Г. Чернышевского, старший научный сотрудник отдела продвижения новых кардиологических информационных технологий Саратовского государственного медицинского университета имени В. И. Разумовского, старший научный сотрудник лаборатории нелинейной динамики Саратовского филиала Института радиотехники и электроники им. В. А. Котельникова РАН. Научные интересы – радиофизические устройства регистрации и анализа сигналов биологических объектов, разработка программного обеспечения для персональных компьютеров и цифровых сигнальных процессоров. Опубликовал свыше 20 научных статей по указанным направлениям.

Россия, 410012 Саратов, ул. Астраханская, 83
Саратовский национальный исследовательский
государственный университет имени Н.Г. Чернышевского
E-mail: karavaevas@gmail.ru
ORCID: 0000-0003-4678-3648