Вісник Тернопільського національного технічного університету
https://doi.org/10.33108/visnyk_tntu
Scientific Journal of the Ternopil National Technical University
2023, № 4 (112) https://doi.org/10.33108/visnyk_tntu2023.04
ISSN 2522-4433. Web: ***visnyk.tntu.edu.ua***

UDK 004.942:53.05-617.735

METHODS OF CONSTRUCTING ALGORITHMS FOR COMPARATIVE TEST STATISTICAL VERIFICATION OF MATHEMATICAL MODELS OF BIOOBJECT RESPONSES TO LOW-INTENSITY STIMULI

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Summary. *The paper presents the results of the construction of algorithms for comparative test statistical testing of mathematical models of responses of a bioobject to low-intensity stimuli, which is an oscillating function with relaxation. In addition, due to the hierarchically primary role of the mathematical model among the used means of this test, the possibility of determining the quality of the response evaluation method is substantiated.*

Key words: *biological object, low intensity excitation, mathematical model, estimation, statistical test.*

https://doi.org/10.33108/visnyk_tntu2023.04.082 *Received 26.09.2023*

Statement of the problem. In the biomedical field, there is a growing trend towards applications of automated telemetry and screening technologies (Health Affairs, V.21, Nr.5 (2001):33-41). These technologies are used in monitoring the functional state and managing the functions of bioobjects, which is mandatory in biotechnical systems for the synthesis (growing) of bioobjects, and include procedures for automated active electrophysiological research. Effective in such studies is the use of informational influence on the biological object (Pressman A. S., Yanenko A. F., Rojas J. C., Gonzalez-Lima F.) – test irritation with ultra-low intensity. As a result of such irritation, a biosignal (feedback) is obtained, the shape parameters (morphological parameters) of which are used in the control systems of the bioobject synthesis. With low-intensity irritations, the non-invasiveness of their impact on the biological object increases, and the informativeness of the response of the biological object increases. However, then the requirements for statistical evaluation of the response form increase, as the ratio of response energies and noise decreases [1]. In addition, the initial, latent (hidden) delay in the appearance of the response, which stochastically changes with each stimulus, is more pronounced (Alpern M., Hodgkin-Huxley, Donner Cristian, Mitchell Grossberg, Nickalls RW.). This phenomenon reduces the reliability of the statistical evaluation of the response form. There is an important, scientific and practical problem of improving the method of statistical evaluation of morphological response parameters. The fundamental role is played by the adequacy of its mathematical model.

Analysis of the well-known results of the research. Evaluation of biosignals during active electrophysiological studies is mostly based on the use of variants of additive-multiplicative biosignal complexes with stationary normal noise. In order to take into account the non-stationarity specific to biosignals, a mathematical model in the form of a periodically-correlated process and corresponding methods of preparing biosignals [2, 3, 9, 10] were used. However, known mathematical models of biosignals and methods of preparing their registers for further processing turned out to be ineffective for responses to low-intensity stimulation, since then the computational complexity of automating active electrophysiological studies increases significantly. Therefore, improving the mathematical model of the bioobject's

Corresponding author: Evhenia Yavorska; e-mail: kaf.bt@tntu.edu.ua response to low-intensity stimuli and methods of preparation for statistical evaluation of its morphological parameters with predicted probability is an urgent scientific task. Its solution will ensure the improvement of biotechnical synthesis systems and preclinical screening of biological objects.

The Objective of the work. The purpose of the work is to improve the mathematical model of the response of a bioobject to low-intensity stimuli and the methods of preparing a series of responses during the statistical evaluation of the morphological parameters of this response with predicted probability.

Computer simulation of the response. Statistical testing of the methods of statistical assessment of the response by the classical method and using the Hilbert transformation was performed by repeatedly generating test ensembles of responses taking into account the latent stochastic delay and noise.

The study of methods for ensuring the coherence of responses of a biological object to its irritation was carried out by means of statistical tests of general populations (ensembles) of these responses. The improvement of the quality of the evaluation of the mathematical expectation of feedback when using the Hilbert transformation of the feedback ensemble was confirmed [4]. Research results are provided for the automation of information and analytical systems of active bioobject research due to their lower complexity. The study of methods for ensuring the coherence of responses of a biological object to its irritation was carried out by means of statistical tests of general populations (ensembles) of these responses. The improvement of the quality of the evaluation of the mathematical expectation of feedback when using the Hilbert transformation of the feedback ensemble was confirmed. Research results are provided for the automation of information and analytical systems of active bioobject research due to their lower complexity.

Computer simulation of features of the structure of the mathematical model. Ensuring the coherence of feedback in their ensemble when evaluating feedback for this ensemble is the main stage of automation of feedback evaluation. To automatically ensure the coherence of responses, it is necessary to establish the beginning of their active part – the oscillatory process. The main difficulty of this procedure is the need to optimally estimate the value of the end of the latent response period for its preparation (synchronization) for its selection for further coherent statistical processing.

Response modeling is based on the fact that a bioobject is a dynamic, non-linear object, its behavior is stochastic, smooth, non-erosive [5]. The computer model is adequately represented by the algorithm of the computational method of solving the stochastic differential equation with consideration of noise. An ordinary differential equation with nonlinearity was used for this purpose to study the characteristics of the response.

The response $s(t)$ to the test stimulus $\delta(t)$ with the latent part added at the beginning was studied – the readings of the oscillatory function with relaxation were directly calculated [5]:

$$s_r(\mathrm{m}T_d) = e^{-\alpha m T_d}\sin(2\pi\,\mathrm{m}T_d/\mu), \tag{1}$$

hidden at the beginning (Fig. 1).

$$x_{lr}(\mathrm{t}) = \begin{cases} s_l(\mathrm{t}), 0 < t \le \tau \\ s_r(\mathrm{t}), \tau < t < \theta' \end{cases} \tag{2}$$

It is marked here: marked: τ - the duration of the hidden response, θ - response time. Here, and further $t = mT_d, m = \overline{1, int\left(\frac{\theta}{T_d}\right)}$, T_d - the discretization period, μ - the number of counts per oscillation period.

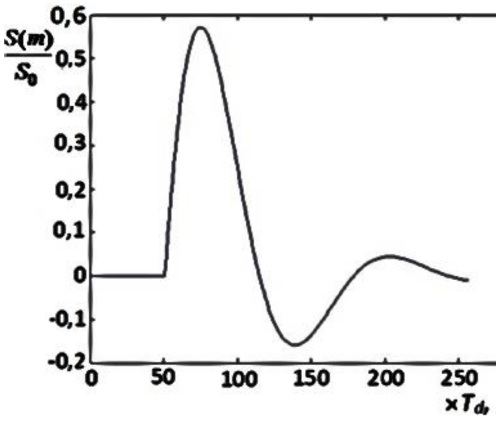


Figure 1. A graphical representation of a computer model of deterministic response

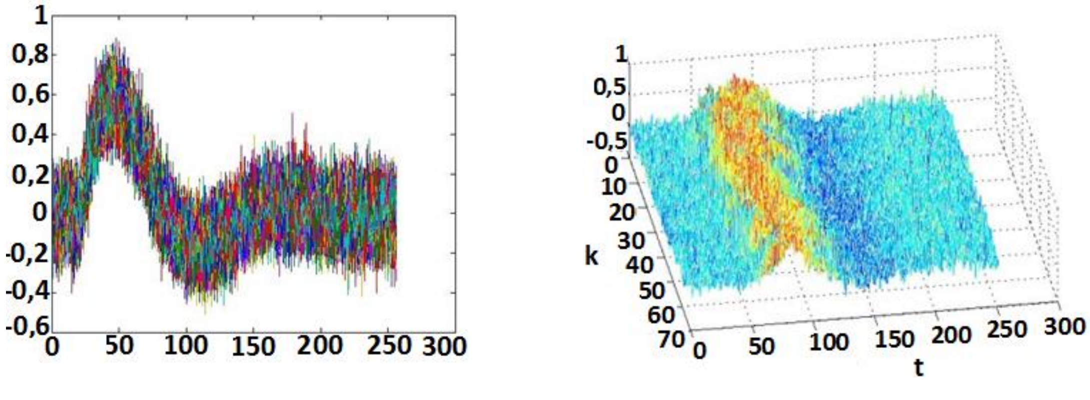
Since low-intensity irritations of the biological object are more informative, observation noises begin to appear $n(t)$ – uncorrelated with the main trend $s_{lr}(t)$ of change, the energy of which does not depend on the intensity of irritation, it becomes necessary to perform a series $k = \overline{1, K}$ of experiments (irritations) (Fig. 2), then:

$$x_k(\mathrm{t}) = \begin{cases} s_l(\mathrm{t}) + n_k(t), \ 0 < t \le \tau_k \\ s_r(\mathrm{t}) + n_k(t), \ \tau_k < t < \theta' \end{cases} \tag{3}$$

where noise n_k and oscillation τ_k delay time are random, normal according to mathematical expectations and variances m_n, σ_n and m_τ, σ_τ:

$$n_k(\mathrm{j}), \tau_k, \mathrm{j} = \overline{1, M}, \text{ normal distribution:} \hat{m}_x(\mathrm{j}) \ , \ \hat{\sigma}_x^2(j) \tag{4}$$

and evaluate the feedback on this ensemble (Fig, 3).



(a)

(b)

Figure 2. An ensemble of test responses (a) and (b) with noise

The probabilistic measure of noise in biomedical research is represented by the Gaussian probability distribution [6] of their values, with mathematical expectations and variances $m_n(t), \sigma_n^2(t)$ and $m_\tau(t), \sigma_\tau^2(t)$ generated by software. Therefore, to increase the reliability of the response assessment $\hat{s}(t)$, before coherent assessment of responses in the ensemble $x_k(\mathrm{t})$ synchronize, preferably interactively – by visual observation of the displayed ensemble.

Since it is necessary to use at least several tens of responses to ensure the quality of the assessment of the ensemble response, it causes significant difficulties due to the significant invasiveness of the study of the bioobject and synchronization through visual observation of the ensemble on the display.

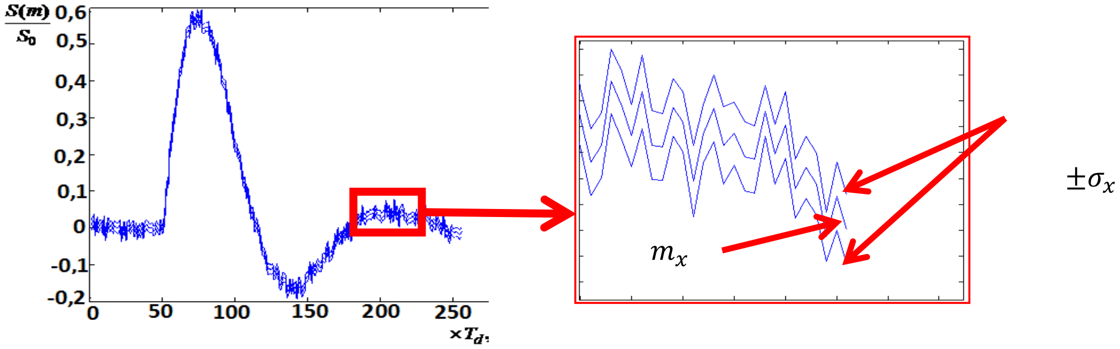
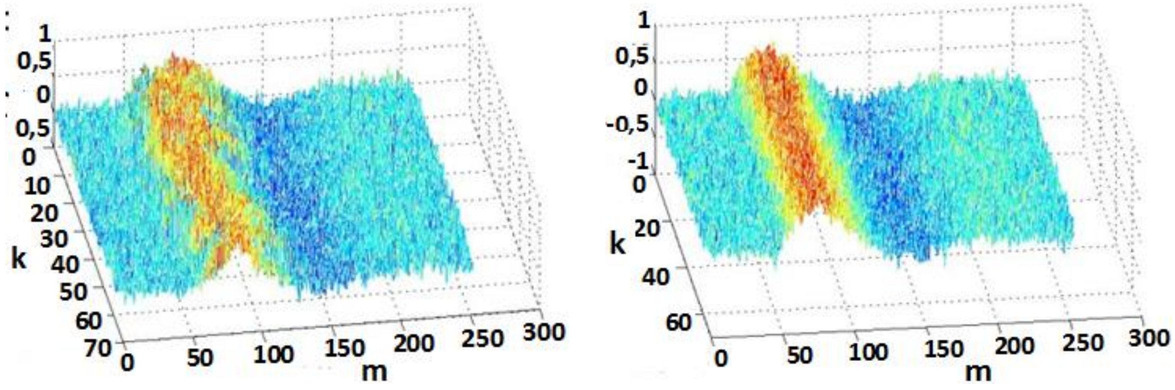


Figure 3. Graphic representation of coherent assessment of response ensembles

To eliminate the established difficulties of interactive synchronization, it must be automated.

Construction of algorithms for methods of preprocessing (synchronization) of an ensemble of bioobject reactions for synchronization of these reactions. In computer test modeling, the values $\tau_k \equiv int\left(\frac{\theta}{T_d}\right)$are determined programmatically or generated (for example, by the Matlab function normrnd (m, σ), so they are known. For computer modeling, they can be considered unknown stochastic parameters τ_k. Therefore, the incoherence of feedback is modeled programmatically, similar to the same modeling as noise.

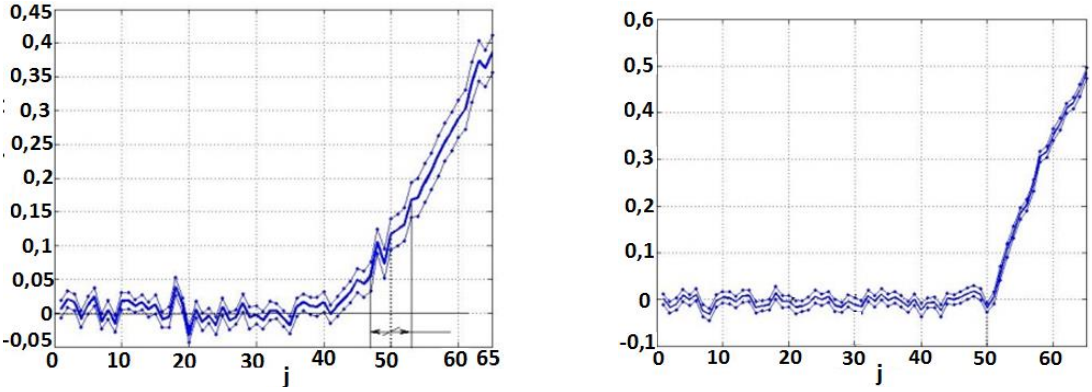
Figure 4 shows graphs of response ensembles x_{km} obtained by computer simulation for stochastic (a) and coherent (b), when there is no noise n_k and the delay value is deterministic. At the same time, the parameters of the main trend s_r(m)=$e^{\alpha m T_d}$ sin$(2\pi$m$T_d)$ of reviews are as follows: α – coefficient reassurance, T_d the discretization period, m=$\overline{1, M}$, $T_d = \frac{1}{M}$, $K = 64, M = 256, \alpha = 0.1$. Stochastic parameters of graphs: a) $m_\tau = 50, \sigma_\tau = 10, m_n = 0, \sigma_n = 0.1$; b) $\tau = 50, m_n = 0, \sigma_n = 0.1$.



(a) (b)

Figure 4. Graphic representation of simulated ensembles:
a – non-coherent responses, and b – coherent responses

Estimates of mathematical expectation and root mean square deviation $m_s(j) \pm \sigma_s(j), j = \overleftarrow{1,J}$ obtained for ensembles (a) and (b) are shown in **Figure 5** where it is shown that in order to ensure a coherent assessment of the mathematical expectation of an incoherent ensemble of samples, the threshold value $h(j) \triangleq m_s(j) \pm \sigma_s(j), j = \overleftarrow{1,J}$ (the feedback with the index j of this value) has a larger root mean square deviation than for the ensemble of coherent samples, and increasing the number of samples is not effective enough to improve this estimate.



(a) (b)

Figure 5. Graphs of evaluations $m_s(j) \pm \sigma_s(j)$ of reviews of the biological object to low-intensity irritation (ensembles (a) and (b), Figure 4)

The property of symmetry of the ensemble of coherent responses was used to automatically ensure coherence [7]. For symmetrization, each response is shifted cyclically until its value becomes the $\geq h$ optimal threshold value. Thus, reviews are registered starting from the reference number $m \approx \tau_k \triangleq m_k$. The method of increasing the effectiveness of coherent evaluation is built on the conceptual basis of ensuring the synchronicity of sample implementations by achieving ensemble symmetry relative to the plane that divides the ensemble into two ensembles equal in number of samples. The criterion of symmetry is a functional of the type $F(\widehat{m}_x, \hat{\sigma}_x)$, which is achieved by minimizing it. A number of heuristic algorithms for their synchronization of different complexity and efficiency can be built for the automated processing of an ensemble of responses.

Estimation of computational complexity of synchronization methods. Automation of assessment of the response of a biological object to low-intensity irritation is by definition performed by technical (computational) means. Computing tools are based on hardware and software components, which manifest the corresponding parts of computing complexity – hardware and time (time required to execute the program). The set of all these means constitutes two corresponding subsets that intersect with respect to the function of «calculations» (execution of algorithms) - hardware, software and «mixed». The efficiency of calculations is determined by their computational complexity, and the efficiency of the main function (automated feedback assessment) also depends on operational conditions (ensuring the performance of this function - non-invasiveness, reliability of the assessment result, etc.). Thus, it follows from here the need to quickly perform calculations - to ensure automated assessment of response while obtaining a reliable assessment result non-invasively. Similar problems in various fields were noticed at the beginning of the intensive introduction of computer technology, when the issue of algorithmization and computational methods of solving problems based on a mathematical model (solving systems of differential equations in partial derivatives, etc. by computational methods) or obtaining a simple expression was discussed solution by «analytical» transformations and corresponding calculations.

For a long time, the construction of a «fast» algorithm was perceived as a way out of the presented dilemma, however, it soon became clear that the algorithm for solving a problem can be made fast if the processor of the computing device contains complex commands in its command system, or a method for solving the problem that is implemented the algorithm ensures the required speed of this solution (this also applies to the combination «method – command system»). As a rule, there are several methods of solving a problem corresponding to different such properties. But, theoretically, it turned out to be more correct to lay a mathematical model of the problem (in particular, ensuring the required speed) as the basis for achieving the desired goal. This also follows from the definition of a mathematical model (mathematical object adequate to the modeled object to ensure an effective solution to the actual problem) [8]. That is, in the hierarchy of building algorithms, mathematical modeling, mathematical models occupy a higher step. Therefore, the value of computational complexity (in the appropriate notation, for example, Landau – asymptotic complexity) logically follows from mathematical modeling. The latter depends on the correct specification of the problem – the identification of a sufficient number of facts and connections between them that do not contradict the laws of nature).

When solving the problem of automated, effective assessment of the bioobject's response to low-intensity stimulation, it was established that traditionally, the mathematical model of a biosignal was used to represent it in its own, biophysical space – a deterministic function of a real variable. Replacing such a representation with a stochastic process turns out to be inefficient due to the presence of a stochastic, initial latent response period (the studied biosignal). Due to the requirement of operating conditions (evaluation of morphological response parameters) and other biosignal representations (in energy space, spectral, etc.) are inadequate to this requirement. Therefore, an idea arose regarding the use of holomorphic representations of the biosignal, in particular, as an analytical function.

Automation is a mode that consists of the process of achieving the required values of its parameters. The achievement of these values is established by calculating the values of its criterion. The value of the average value of the root mean square deviation was reasonably chosen by this criterion. The calculation of this value during the coherent evaluation of the response is at most polynomial in complexity.

The computational complexity of the statistical test trial of response evaluation using the Hilbert transformation depends on the selected option of this use, Figure 6. Thus, the computational complexity of the test trial determines the complexity of preliminary preparation (synchronization), if the Hilbert transformation is not used, or the complexity of the Hilbert transformation, if general-purpose computing tools are used. When using specialized processors with an appropriate command system or processors built on the conceptual basis of automata, the complexity of the Hilbert transformation (convolution) can be neglected.

The computational complexity of evaluating the response during the operation of the appropriate systems for evaluating the morphological parameters of the bioobject's response to low-intensity stimulation depends on the chosen option of applying the Hilbert transformation during statistical testing using a mathematical model of the response of a specific bioobject.

So, the paper substantiates the possibility of solving the task of automating the visual analysis of the data of an active study of a biological object with less complexity with the preliminary symmetrization of the ensemble of these data.

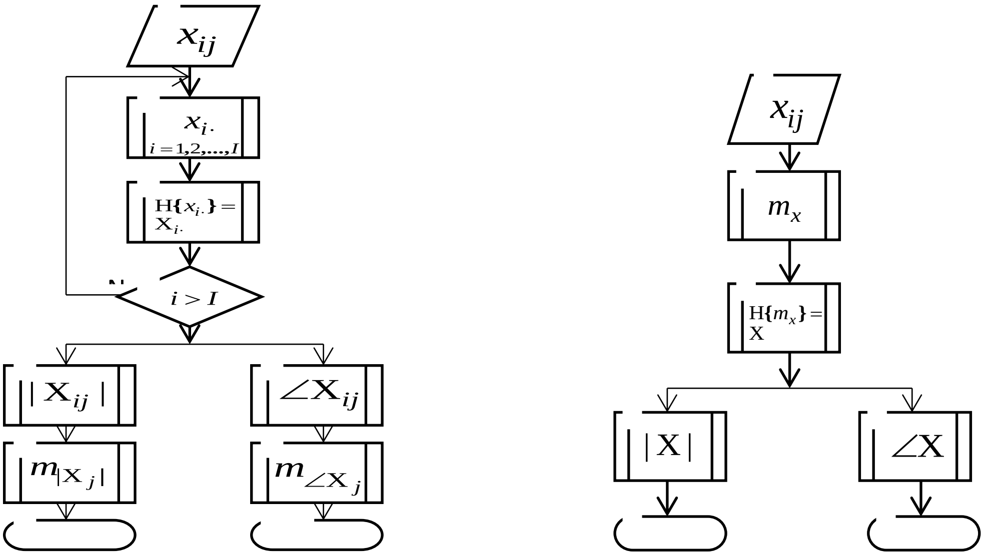


Figure 6. Scheme of options for using the Hilbert transform to determine the value of the index for the synchronization of responses in the ensemble

It has been studied that the use of a preliminary representation by their Hilbert transform of an ensemble of narrow-band responses simplifies the algorithms for evaluating the ensemble response.

In the case when the conditions for the presentation of narrowband signals by the Hilbert transform are not fulfilled, it is necessary to use the methods of numerical extremal search for the characteristic values of the data of the active experiment.

The resulting algorithms enable computer modeling of options for ensuring the coherence of biosignal samples in information-analytical biotechnical systems of other purposes.

To evaluate the effectiveness of using an improved mathematical model due to the stochasticity of feedback evaluations, it is advisable to use methods of statistical testing based on the Bayesian concept of probability theory and a variant of the average risk criterion - which makes it possible to establish the probability of its approval at a given probability of erroneous deviation of the feedback evaluation result.

Conclusions. Due to the invariance to time translations of the spectral density of its power, and hence the dispersion of the response estimate, the optimality functional of this estimate serves as the mathematical expectation of its mean square deviation. This means that the result of the statistical test should be considered the latter. The results of statistical tests of two models make it possible to use the statistical theory of choosing a solution from an alternative [7].

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УДК 004.942:53.05-617.735

МЕТОДИ ПОБУДОВИ АЛГОРИТМІВ ПОРІВНЯЛЬНОЇ ТЕСТОВОЇ СТАТИСТИЧНОЇ ПЕРЕВІРКИ МАТЕМАТИЧНИХ МОДЕЛЕЙ ВІДПОВІДЕЙ БІООБ’ЄКТА НА СТИМУЛИ НИЗЬКОЇ ІНТЕНСИВНОСТІ

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Резюме. *Наведено результати побудови алгоритмів порівняльної тестової статистичної перевірки математичних моделей відповідей біооб’єкта на стимули низької інтенсивності, що є осцилюючою функцією з релаксацією. Крім того, зважаючи на ієрархічно першорядну роль математичної моделі серед використовуваних засобів цього тесту, обґрунтовано можливість визначення якості методу оцінювання відповіді. Стан розвитку й тенденції математичного моделювання біосигналу, існуючі* *методи підготовки ансамблю біосигналів до виконання статистичного оцінювання біосигналу та верифікація отриманої оцінки, дали змогу обґрунтувати вибір напрямку вдосконалення математичної моделі відгуку біооб'єкта на низькоінтенсивне подразнення та підготовки серії відгуків для оцінювання форми відгуку. Автоматизація оцінювання реакції біологічного об'єкта на подразнення низької інтенсивності за визначенням здійснюється технічними (обчислювальними) засобами, які базуються на апаратних і програмних компонентах, які виявляють відповідні частини обчислювальної складності – апаратне забезпечення і час (час, необхідний для виконання програми). Випливає необхідність швидкого виконання розрахунків – забезпечення автоматизованого оцінювання відповіді при отриманні надійного результату оцінювання неінвазивним шляхом. Встановлено, що обчислювальна складність підготовки ансамблю з використанням перетворення Гільберта для статистичного оцінювання відгуку не відрізняється від обчислювальної складності підготовки за евристичними припущеннями, проте оцінка відгуку тоді більш достовірна; при збільшенні кількості відгуків якісні характеристики оцінки (зокрема, її достовірність) покращуються. Завдяки інваріантності до часових трансляцій спектральної щільності його потужності, а, отже, дисперсії оцінки відповіді функціонал оптимальності цієї оцінки служить математичним сподіванням її середнього квадратичного відхилення. Це означає, що результат статистичного тесту слід вважати останнім. Результати статистичних перевірок двох моделей дають змогу використати статистичну теорію вибору рішення з альтернативи.*

Ключові слова: *біологічний об'єкт, збудження низької інтенсивності, математична модель, оцінка, статистичний тест.*

https://doi.org/10.33108/visnyk_tntu2023.04.082 *Отримано 26.09.2023*