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COMPLEX SYSTEMS BIOPHYSICS

Electrochemical Feedback as a Possible Mechanism for Generating the Low-Frequency Component of Bioelectrical Activity of the Brain

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Abstract—A model of electroencephalogram (EEG) generation was proposed to include not only summation of postsynaptic potentials, but also fluctuations in the regulation of a constant potential level. The model explains a number of phenomena observed predominantly in the low-frequency EEG range.

Keywords: electroencephalogram, automatic control, feedback

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INTRODUCTION

The current theory considers summation of postsynaptic potentials responsible for the generation of an electroencephalogram (EEG) [1] and explains a number of observations, while failing to provide a satisfactory explanation to several other EEG phenomena. Their set includes the shape of the EEG signal, which is quite close to sinusoidal in the case of certain rhythms; the frequency spectrum with distinct peaks; differences in frequency spectrum between the EEG and electrocorticogram; the increase in EEG amplitude that accompanies the slowing of biopotential oscillations in pathological conditions; and the situation where rhythms usually thought to indicate a normal state are detected in pathological conditions, such as α-coma.

To explain, it can be assumed that several basically different mechanisms act simultaneously to shape bioelectrical activity. One mechanism, which is currently believed to act alone, is summation of excitatory postsynaptic potentials (EPSPs) with inhibitory ones (IPSPs), while other mechanisms may differ in nature. Different mechanisms generate different frequencies and form different spatial distributions of the electrical potential. This idea was proposed in [2], where ranges of 1–10, 10–100, and greater than 100 Hz were assumed to differ in the mechanism of brain electrical activity generation (the study focused on the 10–100 Hz range and summation of postsynaptic potentials as a mechanism of EEG generation). The lower frequency range includes δ, θ, and α activities, which are diagnostically significant, and is thus of substantial clinical interest. If the mechanism that generates these activities differs from that responsible for higher-frequency ranges its study will help to develop new methods for EEG analysis and to better understand the existing ones. The above range margins are not exact, but rather indicate the order of magnitude of frequency and may change depending on the patient's age, condition, drug effects, etc. In addition, the range may substantially overlap in frequency.

Abbreviations: EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential.

MATHEMATICAL MODEL

The attempt below to explain one of the mechanisms responsible for EEG generation is based on the idea [3] that fluctuations in the level of the constant potential (which is understood as the resting potential on the neuronal membrane) contribute to bioelectrical activity. This potential forms between the inner and outer sides of the neuronal membrane, is approximately 70 mV, and is due to the difference in sodium and potassium ion concentrations. Its generation involves the sodium–potassium pump, which pumps sodium out of the cell in exchange for potassium and creates a concentration gradient. As an action potential (a nerve impulse) forms, sodium channels open and the ion concentration becomes stable [4]. There is no discrepancy between "oscillations" and "constant" because a regulator is essential to maintain constancy in changing conditions of the body function and a regulator is impossible in the absence of fluctuations [5]. The latter idea is understood as follows. A regulator capable of maintaining a necessary level at various loads (an astatic regulator) must work with regard not only for the current deviation, but also to the deviations that occurred previously, thus inevitably generat-

ing fluctuations. The simplest example of such regulators is provided by an integral regulator, where the deviation is integrated over time and change in the parameter under regulation is a function of the resulting integral.

Thus, an intermediate control unit is required for this regulation and a substance may play this role. If a deviation of the regulated parameter leads to the accumulation of a substance, which can be approximated with an integral of the deviation, then the concentration of the intermediate substance affects the change in the regulated parameter. The calcium ion Ca^{2+} can be considered as such an intermediate element, assuming that its intake is determined by the potential-dependent potassium pump and that the sodium–potassium pump is regulated by the Ca^{2+} concentration [6, 7]. The extracellular concentration of calcium is 2.28 mmol/L [7] (for comparison, that of potassium is 2.86 mmol/L); the intracellular calcium concentration is low at rest and substantially increases after an action potential has been generated; calcium is then removed from the cell. Generally speaking, nonlinear functions describe the effects that the potential level exerts on changes in calcium concentration and the calcium concentration exerts on the function of the sodium–potassium pump. Taking a linear dependence as a first approximation yields the following:

$$\frac{dK_{Ca^{2+}}}{dt} = f(P) \approx -a(P - \pi) + b(K_{Ca^{2+}} - \kappa);$$

$$\frac{dP}{dt} = g(K_{Ca^{2+}}) \approx c(K_{Ca^{2+}} - \kappa),$$

where K is the potassium ion concentration; P is the extracellular potential; κ, π, g, and h are the parameters of the linearized model (κ and π are, respectively, the calcium concentration and potential in normal conditions); a and c are the effects that deviations in potential and calcium concentration exert on the rates of changes in calcium concentration and potential, respectively; and b is the diffusion of calcium into surrounding brain structures during its removal. Differentiating the second equation and substituting the first equation into the second one reduce the above system of differential equations to a second-order linear differential equation where $p = P - \pi$:

$$\frac{d^2p}{dt^2} = ac(P - \pi) + bc(k_{Ca^{2+}} - \varkappa) = -w^2p + b\frac{dp}{dt}.$$

The solution of this equation is an exponent with a complex power. Based on Euler's formula $e^{ix} = \cos x + i\sin x$, the exponent can be represented as a damped sinusoidal function in the real region:

$$p(t) = \mathrm{Re}(Ae^{i\omega t - \delta}) = A\cos(\omega t + \varphi)e^{-\delta t},$$

where ω is the imaginary component and δ is the real component of the solutions to the accessory equation $z^2 = bz - w^2$ and the coefficients A and φ are determined by the initial conditions (formally, a sinusoidal function that is not damped or even has an exponentially increasing amplitude is a possible solution, but such solutions appear to be meaningless physiologically).

The resulting fluctuations are assumed to act as a source of the low-frequency range (presumably up to 10–15 Hz) of the EEG. Their spectrum has a relatively sharp peak (depending on the damping decrement δ, i.e., the lower the damping is, the sharper the peak of the spectrum is). The frequency depends on the coefficients of the model and the coefficients are determined, on the one hand, by the availability of ATP, which is utilized by the sodium–potassium pump whose availability depends on oxygenation of respective brain structures, and, on the other hand, on the calcium ion concentration. Both the lack of oxygen and hypocalcemia may cause slow-wave activity or spike-and-wave complexes according to clinical observations [1]. The above dependence may help to assess these important parameters of brain tissue by the EEG, but the mathematical apparatus needs to be developed almost from the beginning for such assessments.

An excitatory signal is necessary for damped fluctuations to occur for a relatively long period of time. If the flow of excitatory signals is of a Poisson process, that is, the next excitatory stimulus is generated independently of the generation of other stimuli, then the signal frequency will correspond to the frequency of a single damped sinusoidal function. If a non-Poisson flow takes place, then this direct dependence is not observed, but the frequency of the resulting signal will depend on the frequency composition of the initial excitatory signal passed through a filter with the amplitude–frequency characteristics corresponding to those of the given regulatory mechanism. The sensory information flow is certainly non-Poisson in character; in the absence of such flow, individual spontaneous impulses are independent and can be approximated with a Poisson process. Therefore, the above mechanism may explain the reason that the α-rhythm becomes detectable when the eyes are closed and changes to high-frequency activity when the eyes are open, the reason that the Rolandic μ rhythm becomes detectable as the contralateral hand is relaxed and disappears as it moves, and the reason that α-coma is observed in severe brainstem injury. A possible interpretation of the last case is that α-coma as an extremely unfavorable prognostic factor may reflect that sensory input to the relatively intact cortex has stopped because of damage to brainstem structures.

A pattern where a rhythm slows and simultaneously increases in amplitude is observed in pathological

conditions (the α-rhythm frequency decreases up to a transition to the θ-rhythm range or δ activity becomes detectable at the site of injury, the perifocal area of a tumor, or in cerebrovascular disorders) and certain functional tests (the Matas test with occlusion of the carotid artery; detection of slow-wave activity suggests insufficient blood supply of the respective hemisphere through collateral vessels). In the above context, these observations mean that the regulator fails to perform its function properly and that, consequently, deviations take more time to eliminate and increase in magnitude (the amplitude of pathological activity). On the other hand, an increase in oxygen supply to brain tissue, for example, during hyperbaric oxygenation leads to a higher frequency of the α rhythm [8].

A description of the electrical field formed during the regulation of the constant potential includes not only dipole components, but monopole ones as well. Therefore, the potential will not decrease with the increasing distance to its source as fast as in the case of a purely dipole source (in inverse proportion to the distance, in contrast to the inverse quadratic relationship observed for dipoles), nor will it depend on the dipole orientation relative to the detector; these issues make it possible to explain the reason that signals from deep sources are successfully recorded. To explain the amplitudes measured from the scalp in the context of dipole sources, one has to reject the volume conduction model [9], whose applied efficiency is well demonstrated, or to assume extremely high potential values for areas close to the source, while such values disagree with intracerebral measurements. The contribution of monopole sources cannot be neglected, as has been noted in the literature [10].

DATA ANALYSIS AND NUMERICAL MODELING

It is necessary to experimentally verify that certain EEG rhythms can be described with the above model and that certain bioelectrical activities are not fully explicable by summation of EPSPs and IPSPs. Because data are sampled at discrete time points by an EEG machine, the above differential equation should be changed to a finite-difference equation:

$$y_t = a_1 y_{t-1} + a_2 y_{t-2} + \varepsilon,$$

where y_t is the observed value of biopotential, a_1 and a_2 are the model coefficients, and ε is the excitatory signal.

The following estimate was obtained for the α rhythm recorded at O_2:

$$y_t = 1.629469 y_{t-1} - 0.928725 y_{t-2} + \varepsilon,$$

which was then used to calculate the frequency ω = 8.99 Hz and the damping decrement δ = 0.0369.

A sequence of random numbers with a normal distribution was used to simulate an EEG (Fig. 1, upper panel; a real EEG is shown at the top and the simulated EEG, at the bottom). Power spectra were calculated for the real and simulated EEGs (Fig. 1, lower panel). A peak in the α range is distinct in both of the spectra. At the same time, the real EEG and especially its spectrum are far richer than the respective simulated curves. The difference is possibly explained primarily by the fact that only one source was assumed in the model, while total activity of many brain structures, including those rather far away from the recording site, is reflected in a real EEG.

When simulation was performed by summing the postsynaptic potentials that were elicited at random time points and had a shape described in the literature (ascending phase, 2–3 ms; descending phase, 10–12 ms), the resulting pattern was absolutely dissimilar to the periodic activity observed in the EEG, but was similar in visual appearance and spectral composition to β activity.

Finally, there is a possibility that oscillations in the δ, θ, and α ranges do not result from EPSPs and IPSPs that arise at random and independently of each other, but are rather caused by pulse trains, so that the train frequency determines the frequencies of the respective rhythms. To test this assumption, activity at rest with the eyes closed was recorded from O_1 and divided into the α (8–13 Hz) and β (15–45 Hz) ranges by digital filtering. Oscillations corresponding in duration and shape to EPSPs and IPSPs would be detectable in the β rhythm frequency range. An envelope curve was calculated for β activity, and possible correlations were analyzed for the signal in the α range or its absolute value with the β rhythm envelope and its absolute value. Significant correlations were not observed between the parameters (Fig. 2). The finding certainly does not demonstrate lack of association between different EEG rhythms, but provides an argument against the idea that low-frequency rhythms form via summation of postsynaptic potentials.

DISCUSSION

The above model is not an alternative to the existing model, which explains the formation of the EEG potential by summation of dipole potentials associated with EPSPs and IPSPs, but rather supplements it by explaining primarily the details of the EEG frequency composition. Following the accepted model, a large number of individual sources producing short pulses are summed to make low EEG frequencies. However, this idea contradicts the linearity of the Fourier transform, which implies that the total spectrum of a set of sources is the sum of the individual source spectra.

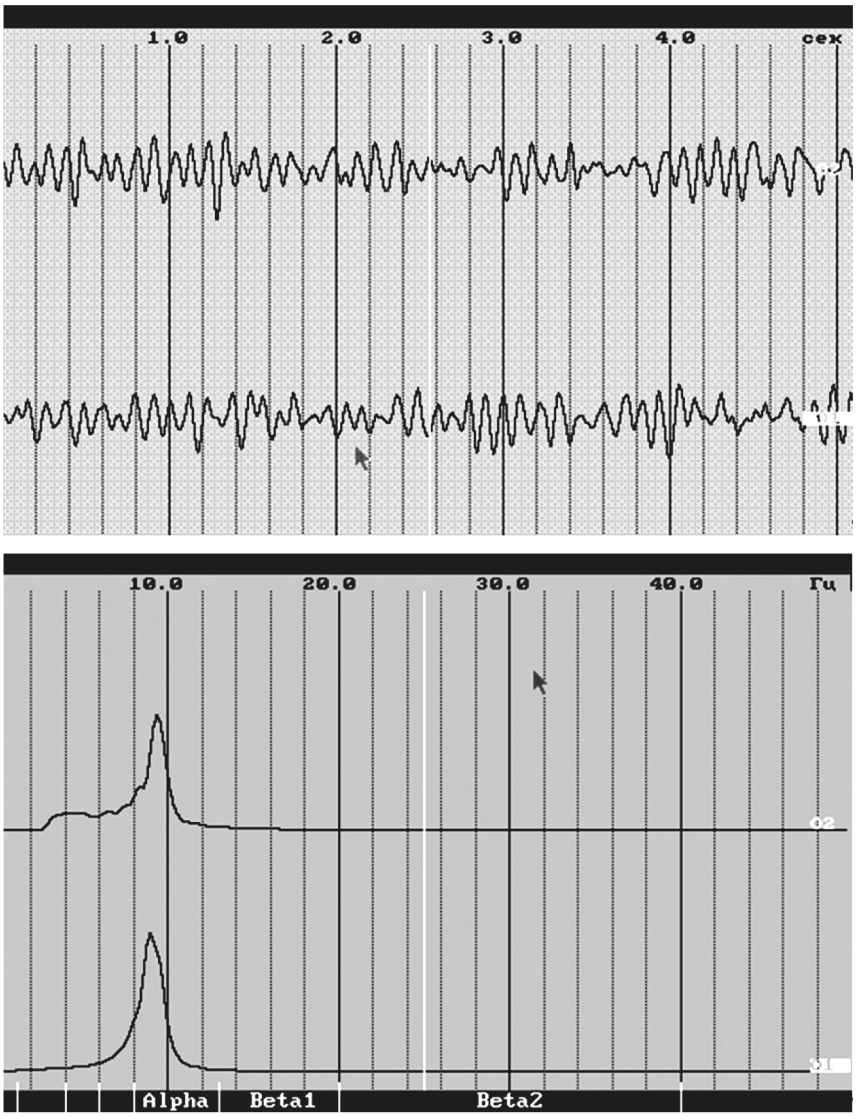

Fig. 1. Real (upper curve) and simulated (lower curve) EEGs (at the top) and their power spectra (at the bottom).

However, the duration of postsynaptic potentials is 10–20 ms, corresponding to oscillations that have a frequency of several tens of hertz, and the frequency of the total signal will be close to the average frequency of these sources. For higher frequencies (β and γ rhythms and spikes) the existing EEG model seems adequate to explain the signal by summation of EPSPs and IPSPs.

The above model of the formation of a low-frequency EEG is of applied significance because the EEG frequency composition has been thought to characterize the patient's condition from early clinical EEG studies. The occurrence of slow rhythms or a slowing of the existing rhythms may point to a pathological process or reflect changes in physiological condition (sleep or anesthesia). Several parameters have found application in this context: the mean or median frequency, spectral edge frequencies (at 90% or 95% of the spectral power), and effective frequency band [11–15]. However, the parameters have been introduced as empirical characteristics of brain bioelectrical activity. The model, which explains the association between the physiological state of brain tissues and the EEG spectral parameters, may have an applied purpose by helping to improve the methods to obtain such parameters.

Although based on extremely simplified assumptions, the model can explain several known EEG phenomena. However, the model cannot explain the generation of specifically shaped signals, such as arch-shaped signals in the μ rhythm or spike-and-wave complexes in epilepsy. Nonlinearities introduced in the model may help to explain these phenomena.

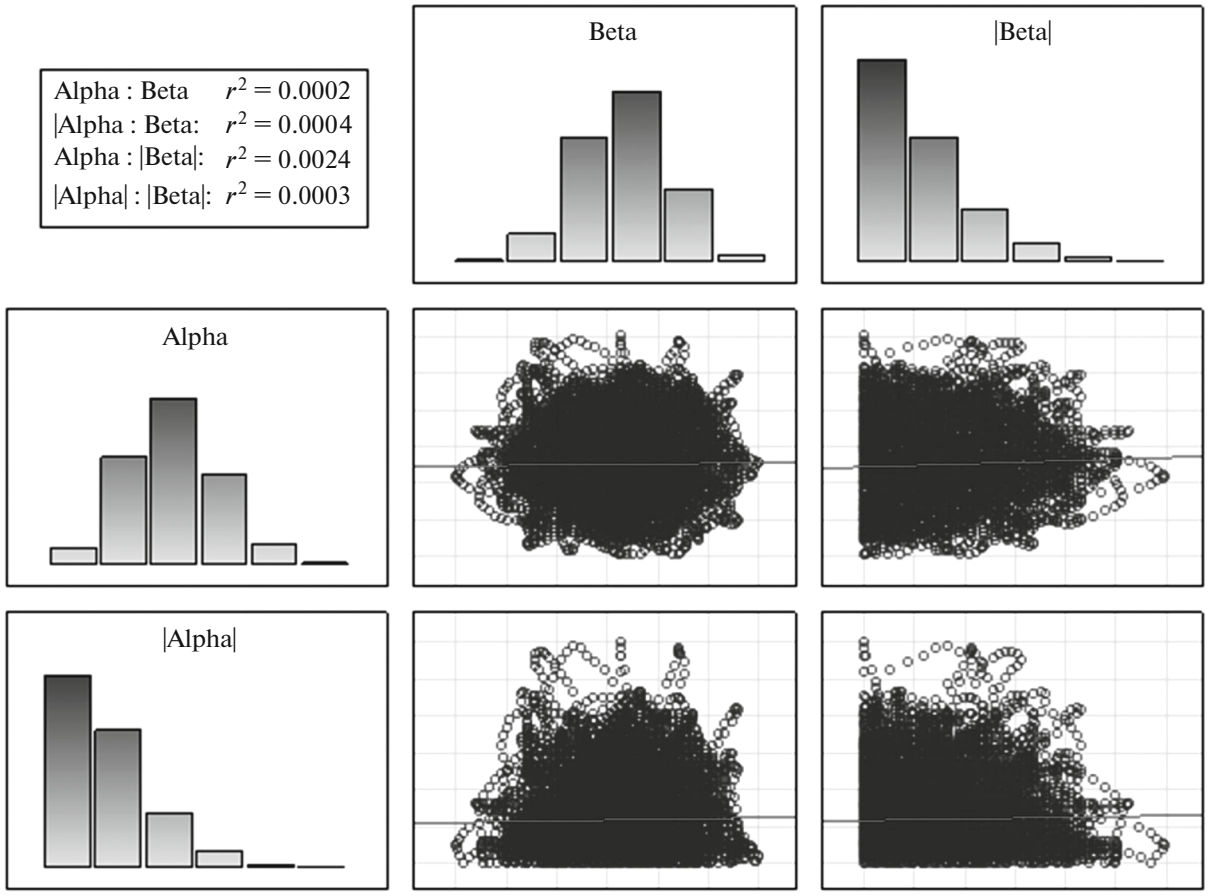

Fig. 2. Correlations between the signal in the α range (Alpha) and the envelope curve of the β rhythm (Beta) or their absolute values (|Alpha| and |Beta|, respectively).

Another open question is related to the interactions among different sources of bioelectrical activity, including their self-synchronization. This model is only the first approximation. To make it more complex and realistic, additional studies are necessary that simultaneously record several different signals (EEG, transcranial oxygenation, and blood flow rate) and compare the data with clinical findings.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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