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Electrochemical Sensors for Digital Medicine and Biology Electrochemical Digitization of Analytical Information Biological Fluids Samples

Sergey V. Sokolkov

* Non-affiliated researcher, Russian Federation.
Correspondence: ssokolkov@yandex.ru

Abstract: Digital medicine based on the integration of all medical data of a particular patient, has become a reality today, thanks to information technology. Traditional medical examinations can be supplemented by assessment results of the oxidative-anti-oxidative (OAO) status of the body [1]. Electrochemical sensors are able to not only determine the integral indicators of the OAO system of the body, but also to depict details of the processes occurring in the system. The main obstacle to the widespread use of electrochemical sensors in medical diagnostics is the extremely small amount of the received information in comparison with tens of thousands of known human diseases. The problem can be eliminated only by rethinking the purpose of electrochemical measurement within the framework of thermodynamics of information processes and information theory. In the information paradigm of electrochemical analysis of biological fluids, a sample is considered as an electrochemical message created by a sensor. The purpose of electrochemical measurement is to obtain information in a volume sufficient to identify the sample composition within the range of possible concentrations of its components. The fundamentals of the thermodynamics of information processes are considered and conclusions that are of practical importance for the development of electrochemical sensors and analyzers are derived. It is shown that potentiostatic control of the sensor is physically impacted by the electromechanical instability of the electrical double layer, which is the main source of sensor signal noise. Estimates are of a minimum amount of analytical signal information required for identification of a sample of a known composition, such as a biological fluid, are provided. Examples of highly informative analytical signals for flowing and stationary samples are presented. Problems related to the visualization of such signals are noted.

Keywords: electrochemistry; analytical signal; noise; trends; identification; classification; fluids samples

1. Introduction

The pandemic has highlighted the serious problems of world medicine - insufficient resources, an unprecedented burden on doctors. Telemedicine techniques, basic home gadgets such as pulse oximeters, not to mention effective portable home diagnostic devices, could really help people. Such devices should be simple, affordable and safe. Electrochemical sensors have long been successfully used for such purposes, for example, most glucometers have electrochemical sensors. However, the diagnostic and prognostic potential of electroanalytics, in comparison with the role played by electrochemical processes in the human body, clearly remains unclaimed.

The problem lies in the low information content of routine electrochemical analysis, usually aimed at measuring the level of one or another metabolite. In the best case, the goal is to determine an integral parameter characterizing the state of any critically important system of a human body, for example, an antioxidant one [2]. More than a dozen actors connected by chains of biochemical transformations can participate in such a system. Consequently, the diagnostic efficiency directly depends on the amount of information about the electrochemical processes in the antioxidant system. It is critically important to understand that information means any experimental data, regardless of their usability significance, that can be reproduced under identical conditions. Of course, the information should be in digital form, which will exclude manual decryption of primary data and will allow fully automating the diagnostic procedure.

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This principle of "experimental presumption" works successfully in practice, for example, in genetic research. Thanks to the development of information technologies, the read but undeciphered human genome, nevertheless, allows doctors to identify genetic diseases and to check the effectiveness of various cancer drugs for a particular patient.

The proposed procedure for electrochemical identification is based on the theory of communication and information and is conceptually different from traditional electrochemical analysis. If we consider a sample as a "chemical information item" or "chemical message", then the task of the sensor is to digitize this information and encode it into some digital image of the sample (a fingerprint, a pattern, a QR code) [3]. This technology is not an analysis in its traditional sense, but rather resembles a method of taking finger prints - dactyloscopy. The more "papillary patterns» are in the print, the more reliable is the identification. A prerequisite for identification is a sufficient amount of a-priori information; in dactyloscopy, this information is contained in the fingerprint database.

In medical diagnostics, the composition of biological samples is known, and homeostasis maintains the concentration of physiologically significant components within fairly narrow limits. The first diagnostic task is to obtain objective information about the variations in the concentrations of physiologically significant components. The optimal ways to solve the first problem are discussed in the article.

The second task is to establish causal relationships between the information received and pathological processes in the human body. This task, which is outside the scope of the article, is solved in the process of analyzing data collected in the national programs of digital medicine.

2. Analytical signal of an electrochemical sensor

The development of electroanalytics took place within the framework of classical analytical chemistry, which assumed the solution of two problems: the determination of the qualitative composition of the sample and the quantitative measurement of the concentration of the sample components. A traditional three-electrode cell allows both tasks to be solved simultaneously. The auxiliary electrode only eliminates the influence of extraneous electrode reactions, while the reference electrode identifies the potential of the working electrode according to the standard potential scale, i.e., provides qualitative analysis (component identification).

Depending on the registered parameter, measurement methods are divided into direct and indirect. With active measurement, the measuring instrument itself has a significant impact on the object under study. If the impact is negligible, then the measurement is considered passive.

Every measurement is a process taking place over time. In electrochemical sensors, the measured concentrations of the sample components are recorded as time-dependent parameter. For electrochemistry, the usual recorded parameter is the electric charge. Such measurement is straightforward because the Faraday charge is directly proportional to the amount of the analyte. The problem is that charge is an integral value that depends on both current and time. For this reason, the recorded parameters can be current and time, as independent physical quantities and their combinations. It will be shown below that the potential of the working electrode is a dependent parameter, since the function i(u) does not satisfy the one-to-one correspondence condition due to the specifics of its nonlinearity.

An analytical signal is the time dependence of the recorded parameter. Moreover, even be time intervals can serve as the recorded parameter.

3. Information in an analytical signal

The primary act of any information process is measurement. The uniqueness of electrochemical sensors is that the measurement can be performed by directly converting an amount of a substance into an electrical charge.

Any signal, in addition to information about the analyzed sample, contains noise. From the primary transducer, the signal is transmitted to the "receiver", where information is separated from noise and, in general, is extracted (decoded). A clear understanding of the measurement purpose allows choosing the correct information decoding algorithm. Leaving the scientific goals outside the scope of the article, let us focus on purely practical measurements, for example, on determining the concentration of one, less often, two or three components of a solution. In the process of routine electrochemical analysis, a researcher, based on a-priori information about the sample, can handle the analytical signal quite freely, for example, limit the range of used potentials, choose the cathodic or anodic reaction, filter the electrical current, subtract the "background line". It means, at own discretion, to separate the experimental information into "useful" and useless. However, in information theory, there is neither "useful" nor "useless" information, but there is only a signal and noise. A signal is that the information that can be reproduced (with a high degree of probability)

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from measurement to measurement under identical conditions. Everything else is noise - a source of random measurement errors. Strictly speaking, the signal contains also systematic and methodological errors (so called conversion errors).

A completely different situation arises during an analysis of samples of unknown composition, for example, natural ones. The absence or insufficient amount of a-priori data does not allow neglecting information about any electrochemical and electrophysical processes occurring on the electrodes. The more information characterizing a sample is collected in one measurement, the higher is the likelihood to identify this sample, or at least to classify it. Obviously, the solution of such a problem requires multiple measurements, also with the involvement of other physicochemical methods of analysis.

The task of classification (identification) of biological samples looks much simpler. The composition of such samples is known in advance, and the concentration of the components is maintained by homeostasis in a fairly narrow range. This makes it possible to formally determine the minimally required amount of information in the analytical signal, which ensures reliable classification (identification) of the sample.

3.1. Assessment of the amount of information required to classify a sample

Let the sample contain *N* electrochemically active analytes. Also known are the reference concentrations C_i of each component, as well as the minimal physiologically significant absolute deviations from the norm

$\Delta C_i = max(C_i) - min(C_i)$.

The number of significant counts for each sample component:

$\alpha_i = \frac{\Delta C_i}{\delta_i}$,

where δ_i is the concentration threshold for the detection of component *i*.

And the amount of a-priori "chemical information" in bits is equal to:

$I_{apri} = \sum_{i=1}^{N} log_2 \frac{\Delta C_i}{\delta_i}$, or $I_{apri} = \sum_{i=1}^{N} log_2 \Delta C_i - \sum_{i=1}^{N} log_2 \delta_i$.

Note that the amount of posteriori information obtained in each measurement cannot exceed the amount of a-priori information: $I_{apri} > I_{apos} \geq 0$.

The accumulation of posteriori information occurs when repeating independent measurements, in our case when using samples from different patients.

4. Electrophysical features of electrochemical sensors

The electrical properties of the interface between the conductor of the first and second kind are unique because they have substantially nonlinear parameters such as conductivity and capacitance. In addition, the interface exhibits its own electrical activity and a distinct hysteresis effect. In sensor applications, it is often necessary to take into account the length of the working electrode and, as a consequence, the distributed nature of the electrical parameters. In fact, we are talking about electrical wave processes in active and nonlinear distributed systems [4].

Such processes have long been of interest to physicists, developers of electronic devices, and biologists [5]. In particular, biologists studying the electrical properties of lipid membranes have encountered their instability. To explain the phenomenon, a simple model of an "elastic" capacitor was proposed [6]. The model also describes well the behavior of the electrical double layer, where similar phenomena are called negative capacitance [7], and the model itself is called an "elastic capacitor". Calculations using the model showed that the φ-control (of the potential) leads to a system instability. The slightest disturbance causes the appearance of potential waves near the electrode surface. The larger the surface area, the greater is the intensity of the waves. However, another type of the control - q control (of the charge) ensures the stability of the system in a wide range of potentials.

The first control mode in electrochemistry is usually called potentiostatic, and the second - galvanostatic.

The theoretical results obtained on the model are well aligned with experiments showing that with potentiometric control of the cell, an increase in the surface area of the working electrode increases both the signal level and the noise level. However, the noise level increases faster than the signal level, therefore, the signal-to-noise ratio decreases [8,9].

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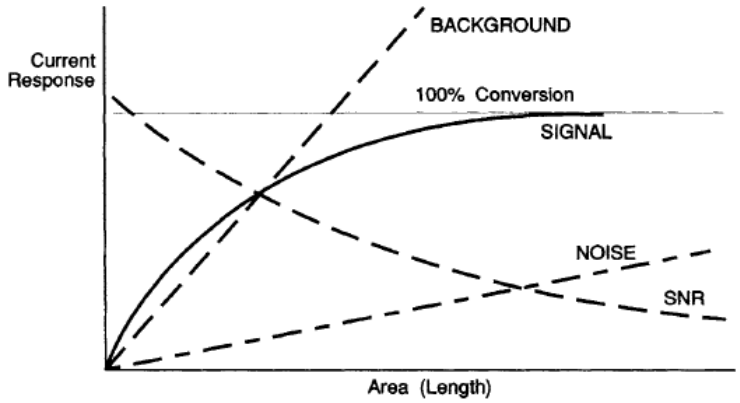

Figure 1. The nature of the change in the main parameters of the analytical signal with an increase in the size of the working electrode [8] (p.50, Fig.6).

It is not surprising that the authors of these publications, published long before the true causes of the noise were established, made the erroneous conclusion that it was impossible to achieve a minimum detection threshold on large electrodes. As shown above, the noise of the instability of the electric double layer is a consequence of the potential control of the cell. It is important to understand the nature of the noise; it is not generated by a potentiostat, but rather caused by an electric double layer on the surface of the working electrode.

Note that the level of thermal fluctuations of the electric charge *q*, which really limit the detection threshold, increases with an increase in the electrode surface area and, as a consequence, with an increase in the capacitance C of the electric double layer [10] (p. 113):

$\overline{q^2} = kTC$, where *k* is the Boltzmann constant, and *T* is the thermodynamic temperature.

However, the cell noise caused by voltage fluctuations $\overline{u^2}$, decreases with an increase in the electrode surface area.

Indeed, $u = \frac{q}{C}$, hence $\overline{u^2} = \frac{\overline{q^2}}{C^2} = \frac{kT}{C}$.

One of the most important parameters that determine the information efficiency of an electrochemical measurement is the conversion coefficient η, which is equal to the fraction of the component participating in the indicator reaction ν_i to the total amount of this substance in the sample ν_0:

$\eta = \frac{\nu_i}{\nu_0}$.

The conversion efficiency at a constant current density $j = const$, and other identical conditions, is proportional to the surface area of the working electrode and the duration of the measurement.

Thus, the absolute detection threshold decreases with an increase in the working electrode surface area and an increase in the measurement duration.

Based on these ratios, it is possible to estimate the root-mean-square values of charge and voltage fluctuations for an electrode with an area of 1 cm^2. The electric capacitance of the electrode is taken to be 10 μF, and the temperature is 300 *K*. Then $\langle q_{sq} \rangle = \sqrt{kTC} = 0{,}2\ pC$. The number of electrons forming such a charge is 2,1 fmol.

Thus, the absolute detection threshold of an analyte in a one-electron reaction is $2.1 \cdot 10^{-15}$ mol.

And the root-mean-square amplitude of thermal voltage fluctuations is $\langle u_{sq} \rangle = \sqrt{\frac{kT}{C}} = 20\ nV$. This value is 8 orders of magnitude less than the potentials used.

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5. Thermodynamics of information processes

In 1871, James Maxwell [11] (pp.308-309) proposed a thought experiment to illustrate the possibility of breaking the second law of thermodynamics. Some being (a demon) able to see the gas molecules, sorts them according to their velocities with the help of a door. In this way, it creates a temperature difference in the two parts of the gas compartment without consuming energy. Maxwell's hypothetical experiment caused a lengthy but fruitful discussion by the most prominent physicists of his time. It is clear that in order to perform an experiment, the being needs information about the speed of each molecule and the ability to control the door. This requires energy consumption and leads to a decrease in the entropy of the gas. The very concept of information was born, inextricably linked with the consumption of energy and a decrease in entropy. Leo Szilard was the first to note the connection between informational and thermodynamic characteristics of an experiment [12]. Leon Brillouin, in his original works, developed this direction, as well as systematized the works of other authors, laying the foundations of the thermodynamics of information processes [13].

For a long time, the thermodynamics of information processes has slowly developed as a purely theoretical direction aimed at establishing the limiting relationships between information characteristics (accuracy, information volume) and thermodynamics (energy, entropy) [14]. The development of sensor networks and systems has stimulated the interest of researchers in this area [15].

The format of the article does not allow for a detailed presentation of the basics of information thermodynamics; therefore, we restrict ourselves to the phenomenological model of physical measurement according to Brillouin.

An electrochemical sensor is an open thermodynamic system [16]. Measurement of the parameters of any physical object is accompanied by the consumption of energy. The energy impact of the measuring device on the thermodynamic system brings it out of equilibrium state and, consequently, reduces the entropy of the system. In the Brillouin model, the decrease in entropy (negentropy) determines the amount of "bound" information. In the process of restoring equilibrium, entropy increases, and "bound" information is converted into "free" information.

Although such a cyclical process is irreversible, it can be follow an analogue of Carnot's theorem, which determines the information efficiency of a measurement.

With regard to electrochemistry, several practical conclusions from this model can be formulated.

The amount of information received in the active measurement is proportional to the decrease in entropy in the object under study (electrochemical cell).

Generalization of Carnot's theorem to information processes allows us to find the threshold rate of transformation of the decrease entropy into information.

The maximum conversion coefficient is achieved during an equilibrium or a quasi-equilibrium process.

The presence of feedback, using the information obtained in the measurement process to control the object (electrochemical cell), significantly increases the amount of information received.

6. Comparison of the information content of electrochemical methods

6.1. Voltammetry

Voltammetry is the most common method for electrochemical analysis of liquids. There are many varieties of the method, which differ, first of all, by the form of potential sweep. Only the potential control and registration of the dependence of the current on the potential remain unchanged.

If we consider a typical voltammogram from the position of information theory, then it cannot be considered as an analytical signal. Firstly, such a dependence $i(u)$ does not satisfy the condition of one-to-one relationship, and secondly, it does not explicitly link to the time scale. Of course, time is present in the signal in an indirect form, through the rate of potential change.

Linear potential sweep is often used, $v = \frac{du}{dt} = const$, where v – sweep speed, and the dependence of the current on the potential is recorded $i(u)$.

The disadvantages of this approach are obvious: firstly, the potential control results in a high level of noise, and secondly, the position of the current peaks is shifted along the potential scale, which complicates the identification of analytes, especially if there are several peaks. Third, the charge-discharge current of the electric double layer increases in proportion to the sweep speed. At the same time, the amplitude of the current peaks also increases, but only in proportion to the square root of the speed. As a result, the conversion efficiency decreases with increasing potential sweep speed.

Such conclusions are confirmed by the example of our recent work [17], in which a sensor on a carbon veil was studied for the determination of ascorbic acid.

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In the work on several voltammograms with a linear potential sweep, an empirical equation was obtained for the dependence of the amplitude of the pulse current i_m on the potential sweep speed v:

$$ln(i_m) = -0{,}5426 \cdot ln(v) + 3{,}6077 \quad (1)$$

Let us express the dependence of the current pulse amplitude on the speed in an explicit form:

$$i_m(v) \cdot= v^{0{,}5426} e^{3{,}6077} \quad (2)$$

For the linear sweep $v = \frac{\Delta u}{\Delta t}$. Let us take the value of the voltage interval comparable to the width of the current peak $\Delta u = 0{,}05V$. Then the time interval corresponding to the passage of the peak $\Delta t(v) = \frac{\Delta u}{v}$.

Let us find the dependence of the charge $\Delta q(v)$ flowing through the electrode at the moment of the maximum current on the sweep speed:

$$\Delta Q(v) = i_m(v)\Delta t(v). \quad (3)$$

Or $\Delta Q(v) = \Delta u \frac{i_m(v)}{v}$ (4)

Note that Δu is actually a scale factor and does not affect the nature of the dependence $\Delta Q(v)$.

$$\Delta Q(v) = 0{,}05e^{3{,}6077} \frac{v^{0{,}5426}}{v} = 0{,}05e^{3{,}6077} v^{-0{,}4574} \quad (5)$$

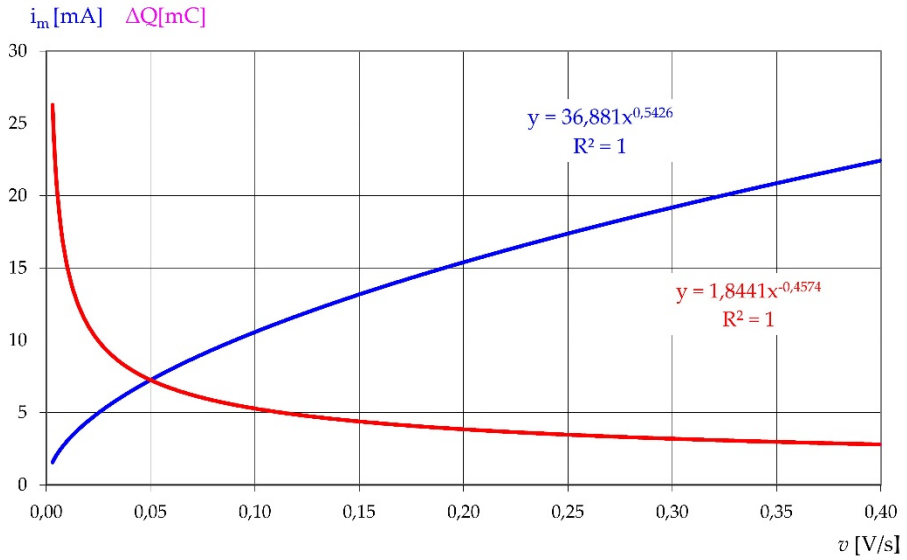

Figure 2. Graphs of the dependence of the amplitude of the current peak (2) and the Faraday charge flowing through the working electrode (5).

The charts clearly demonstrate the opposite tendencies. As the sweep speed increases, the current amplitude increases, and the analytical signal appears to be amplified. However, in this case the conversion efficiency ratio decreases. Consequently, as the sweep speed increases, the amount of information received decreases.

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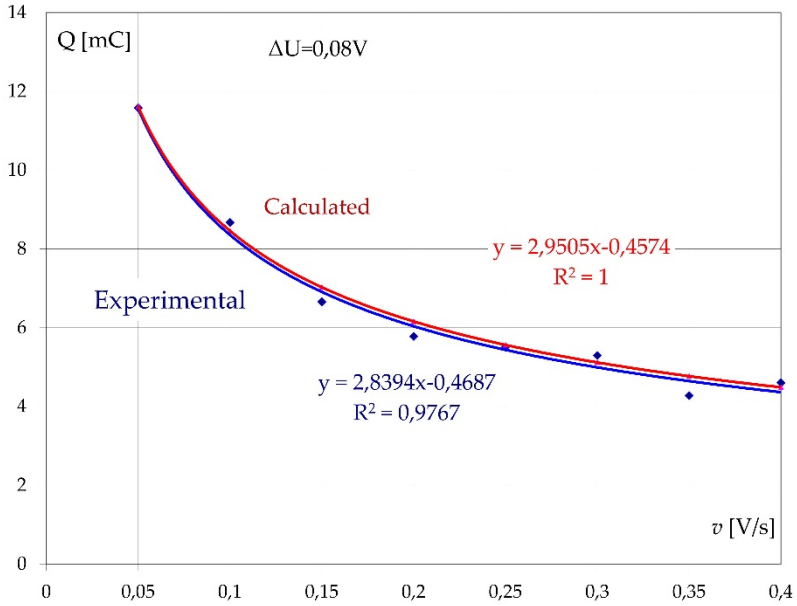

Figure 3. Dependence of the magnitude of the Faraday charge on the sweep speed, experimental data and calculation by equation (4).

6.2. Stripping Voltammetry

Let us consider separately a stripping voltammetry. This truly ingenious method of increasing the information content of a measurement, proposed in 1952 [18], serves as an excellent illustration of the Brillouin model of physical measurement.

The measurement is performed in two steps. First step is preparatory – to perform electrochemical concentration of analytes in potentiostatic mode (φ-control). Let the entropy of the initial state of the solution be S_1. In the process of concentration, some of the ions are reduced, i.e. part of the solute goes into the solid phase, the entropy of the solution decreases to the value S_2.

The change in entropy $\Delta S = (S_2 - S_1) < 0$ is proportional to the total charge of the reduced ions *q*:

$|\Delta S| = \xi|q|$, where ξ – a coefficient of proportionality.

According to the Brillouin model, the amount of "bound" information is proportional to the decrease of cell entropy: $I_{nonfree} = \xi|q|$. During the measurement process, this related information can be converted into "free" information: $I_{free} = \gamma \cdot I_{nonfree} = \gamma\xi|q|$, where γ – coefficient of transformation of entropy into information, similar to a heat engine efficiency coefficient. The information content of the measurement depends on the value of this coefficient, and its maximum value, as for a heat engine, is achieved in the quasi-equilibrium process of returning the solution to its initial state with entropy S_1.

6.3. Scanning coulometry

In 1996-1998, the author participated in an international project to create a portable water analyzer for heavy metals Pb, Cd, Cu. In the course of the project, it was required to solve a very difficult problem: to develop a fully automatic portable electrochemical analyzer of natural samples of unknown composition for use in the field conditions. In this case, it was necessary to use disposable sensors without reference measurement methods. The first stage of the project involved a small team of developers led by the author.

Such a device has not yet been created, but in the past few years our group managed to eliminate a number of fundamental problems and create a working model of a portable water analyzer [19]. The author's method of "scanning coulometry" [20] used in this device made it possible not only to fully automate the measurement process, but also to completely eliminate the subjective factor at the physical level. The analytical signal of the device is a sequence of time intervals that fix the time moments of the system passing through the given points in the coordinates *u-i*. The device does not register neither the dependence of current and potential on time, nor current on potential. In the process of measurement, it does not use any signal filtering and does not require building of a background line.

The measurement control algorithm corresponds to the Brillouin model of physical measurement. At the first stage of measurement, as in stripping voltammetry, the electrochemical accumulation of analytes is carried out on the working electrode in a potentiostatic mode with intensive stirring of the sample.

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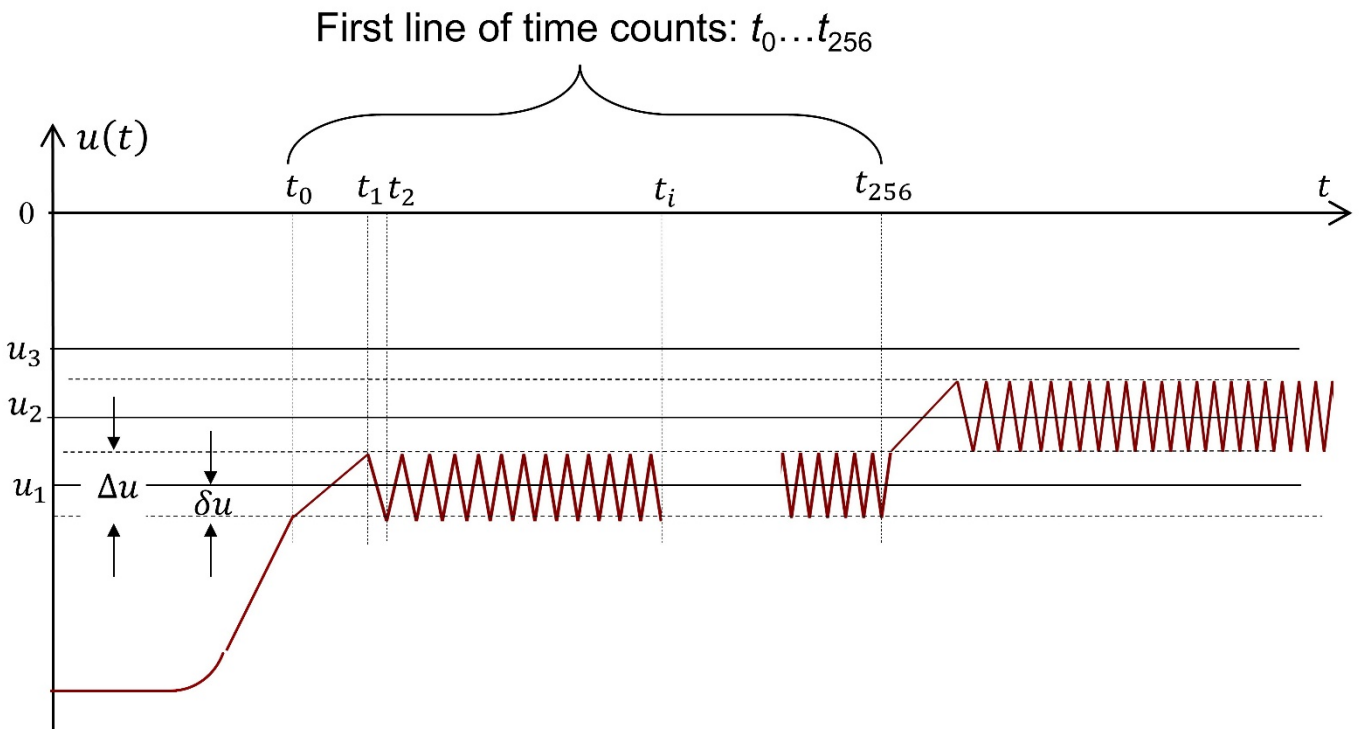

Figure 4. The change of the working electrode potential during time intervals is shown schematically.

The second stage is actually active, adaptive measurement, with feedback (Fig. 4). A galvanostatic control mode is used, with a constant current value. The potential of the working electrode is kept within the predetermined narrow range $2\delta u$ as follows: when one of the limits of the potential range u_2 is reached, the current is inverted. The moment of this event t_1 is recorded by the control panel. The current inversion causes the potential to move to the second limit of the range u_1, upon reaching which the current is inverted and the moment of this event t_2 is recorded. Cycles with current inversion are repeated until the duration of the time intervals stabilizes. This event means that a dynamic equilibrium has been established between two stationary electrode processes: anodic and cathodic.

The analytical signal obtained by this method contains comprehensive information about all electrochemical processes occurring on the electrode. The invariability of the current ensures that the electrode processes are stationary. The total charge corresponding to each time interval is $q_n^{\Xi} = i \cdot \Delta t_n$. The Faraday charge of the sought-for reaction will be less than the total by the value of the charge of the steady-state process.

$$q_n^F = q_n^{\Xi} - q_{\infty} = i(\Delta t_n - \Delta t_{\infty})$$

This eliminates the subjective procedure for subtracting the background line in the entire potential range. The analytical signal also makes it easy to find the fractions of analytes oxidized by the chemical mechanism, the reaction reversibility constants, the quantity of metals restored at the stage of accumulation.

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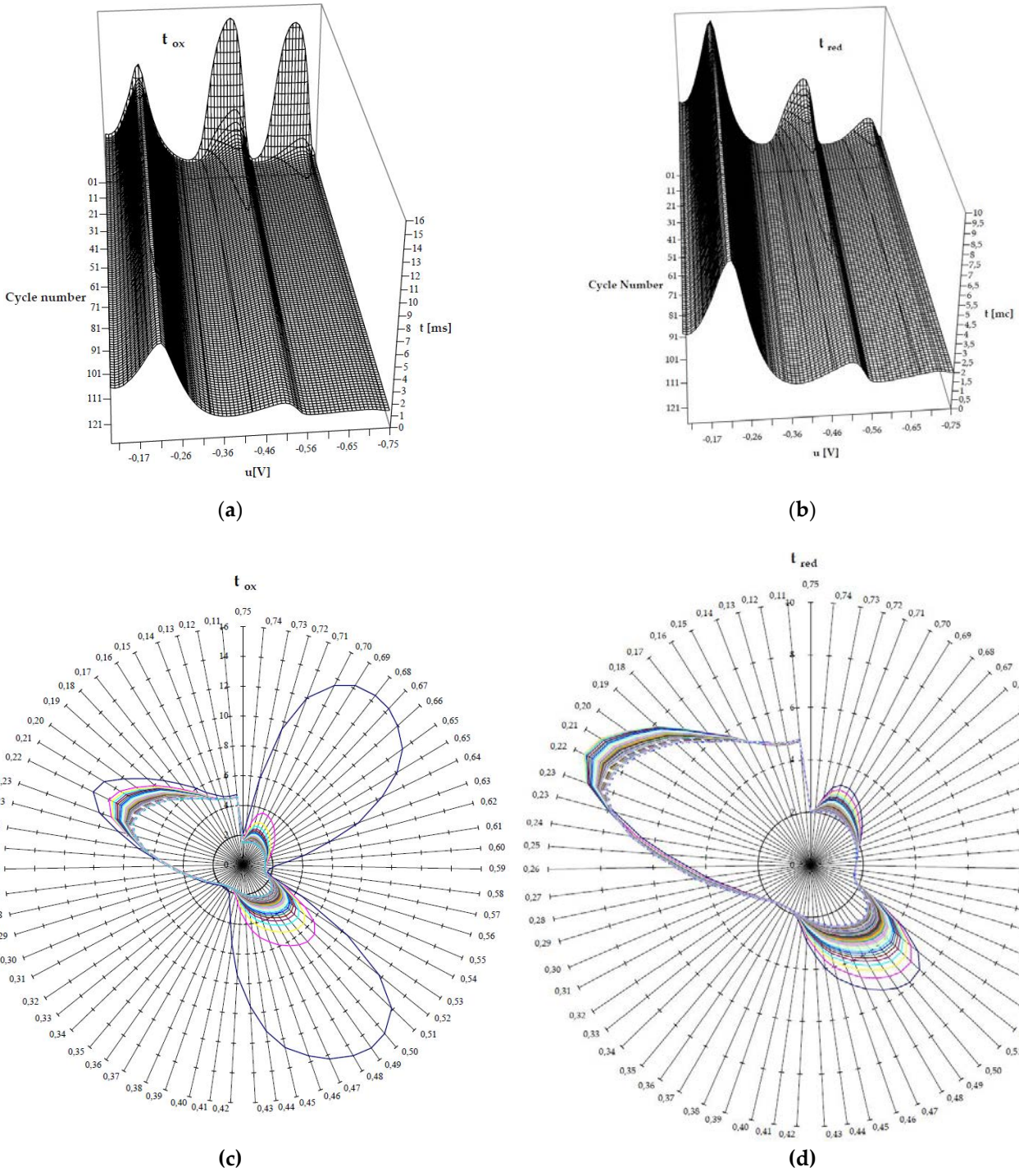

Figure 5. Initial analytical signal of analyzer "ASC-2000". Matrices of time intervals (a,c) -anodic prosses, (b,d) -cathodic prosses.

Figure 5 shows the analytical signal obtained on model samples with concentrations of Cu 10 μg/L, Pb 50 μg/L, Cd 50 μg/L. Acetate buffer. Cell volume 150 μl, i=50 μA. Measurement duration (without the stage of electrochemical concentration) 59.6 seconds.

The main source of methodological measurement error is the uncertainty of the conversion rate. The methodical error can be reduced by bringing the conversion coefficient value as close as possible to 100%.

Based on the analyzer test results on a cell equivalent, the instrumental error was determined, the value of which does not exceed 10^{-9} C.

6.4. Electrochemical analysis with preliminary separation of the sample

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Sample separation is an effective way to increase information content. In accordance with the Brillouin model of physical measurement, the amount of associated information is determined by the change in entropy. During separation, the entropy of the sample ΔS_{sep} decreases, and this decrease is equal to the entropy of the mix ΔS_{mix}.

$$\Delta S_{mix} = -\Delta S_{sep}$$

The higher the degree of separation, the more information is in the analytical signal. The greatest gain comes from high performance liquid chromatography (HPLC), in which electrochemical detectors have been successfully used for a long time. HPLC systems with a range of coulometric detectors are some of the most informative analytical tools available. Such systems allow obtaining 3D chromatograms [21]. Due to the unique carbon electrode with oriented micron channels, the conversion efficiency of the cell in the coulometric mode is close to 99%. Up to 16 similar cells with different potentials of working electrodes can be connected in series to the hydraulic line of the chromatograph. The amount of information received in each dimension increases in proportion to the number of cells. Separation by retention time in the column is supplemented by separation by the potential of the electrochemical reaction, which additionally increases the amount of information obtained. This completely solves the problem of recognizing overlapping chromatographic peaks.

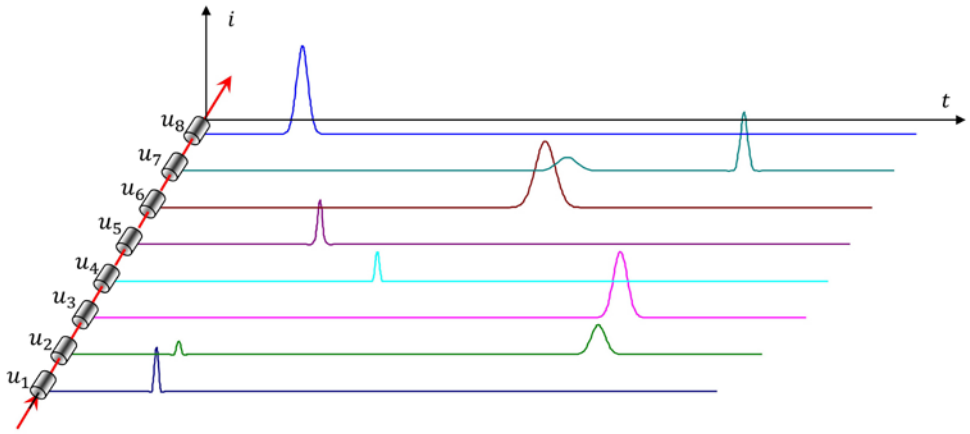

Figure 6. Diagram illustrating the technology of obtaining 3D HPLS chromatograms [21] using multi-electrode array detector.

Of course, such a complex and expensive technology cannot be used in sensors, but it is possible to use a flow cell in the scanning coulometry mode.

In 2005, a team led by the author developed an electrochemical detector for HPLC systems; a double coulometric cell type 5010A P / N70-5560 S / N 5010A-0292 by the firm ESA Inc. (USA) was used as a sensor. The cell has two reference electrodes and two auxiliary electrodes. A working electrode made of carbon material with many longitudinal submicron channels is placed between these electrode systems. Due to the large area of the channels, the conversion efficiency of the working electrode is ~ 99%. The manufacturer uses the cell in the coulometric mode: at a fixed value of the working electrode potential, the current dependence on time is recorded, and the Faraday charge of the reaction is calculated by integrating the current peak.

A mode close to cyclic chronopotentiometry at a given current was used [22]. The potential scale was divided into several adjacent intervals. For each interval, its own current value was set. The analytical signal of the device is a sequence of time intervals that fix the time moments of the system passing through the given points in the coordinates u-i. Thus, a continuous cyclic operation of the cell was ensured.

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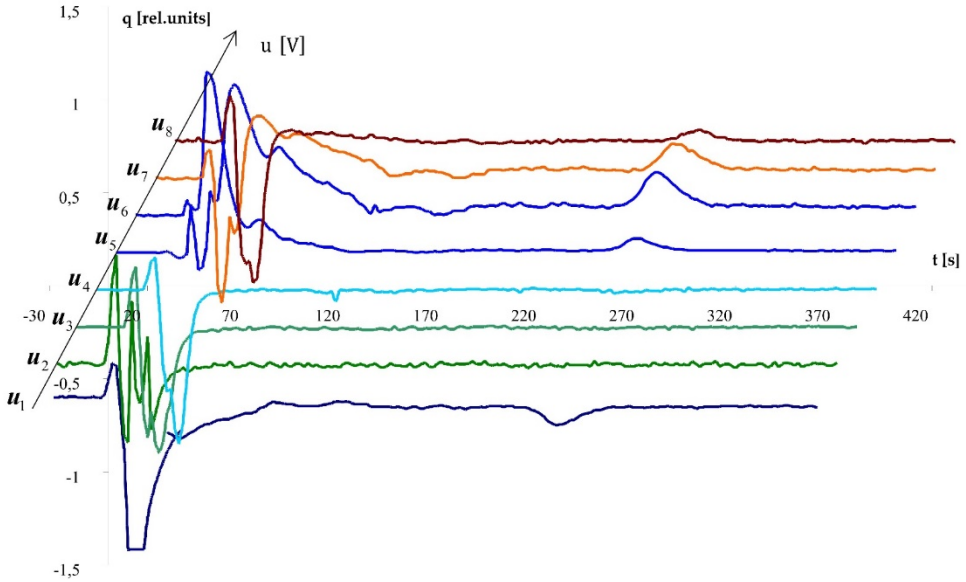

Figure 7. 3D chromatogram obtained with one coulometric cell operating in a cyclic mode (scan mode) [21].

Tests have shown high sensitivity and information content of the detector. The amount of information depends on the number of intervals into which the potential range of the working electrode is divided. During the tests, a slow drift of the background line was detected. Later, this problem was completely resolved.

7. Analytical signal visualization

A large amount of information is required for medical diagnostics based on digital technologies and artificial intelligence. It turned out that there are problems associated with adequate human perception of such volumes of information. Visualization of the analytical signal is important for the researcher, since it allows one to assess the correct operation of the measuring system and to optimize its parameters. The task of visualizing highly informative 3D signals is especially important.

The difficulty of perceiving large amounts of information is often a psychological obstacle to the propagation of modern devices. For example, for the introduction of X-ray tomographs, it was necessary not only to retrain the radiologists, but also to provide for the possibility of visualizing the results in the form of foreshortened X-ray images.

Below are examples of visualization of highly informative analytical signals.

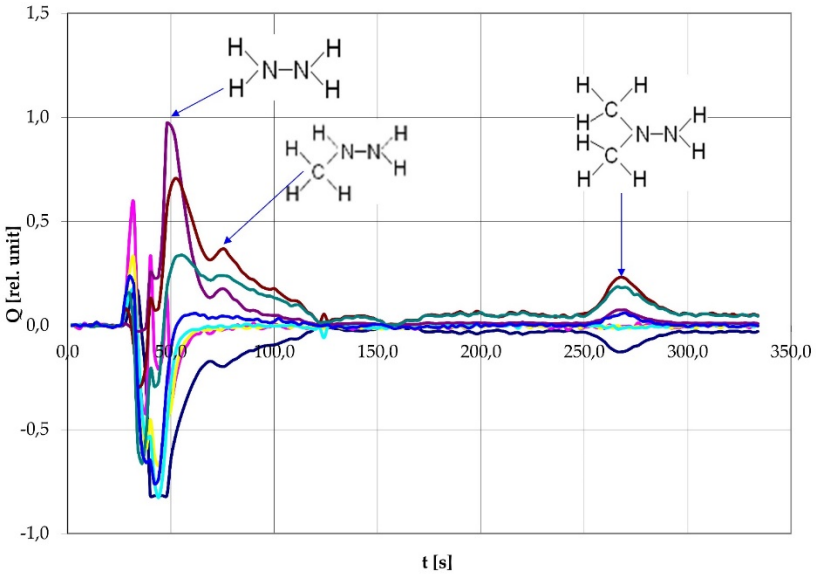

Figure 8. 3D chromatogram obtained by scanning coulometry [22].

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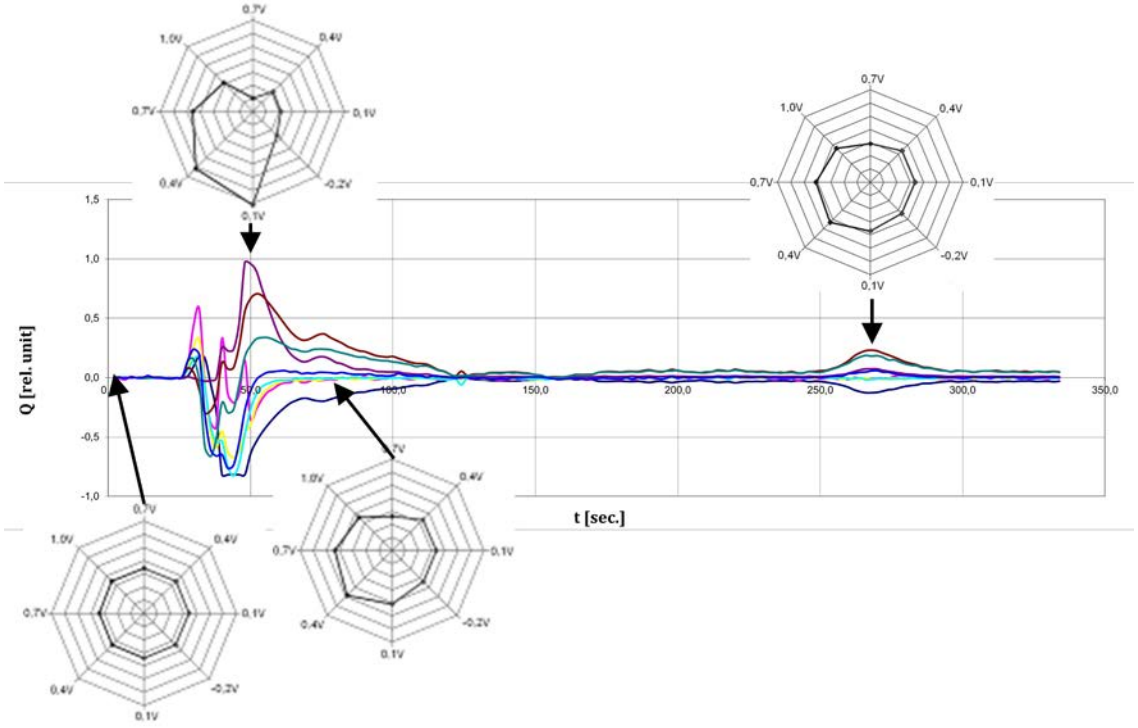

Figure 9. Sections of the 3D chromatogram are shown in polar coordinates corresponding to the retention times of 0, 51, 107, and 270 s [22].

The most striking impression is made by animated analytical signals. An example of one of such animations made by the author is attached to the article.

8. Conclusion

The information paradigm of electrochemical measurement has a number of advantages over classical electrochemical analysis, since it allows:

first, objectively, on the basis of the reproducibility criterion, separate the proper analytical signal from the experimental data, while eliminating the noise;

second, to obtain a significantly greater amount of information about the entire sample, and not just about one component;

third, to use modern IT technologies (neural networks, artificial intelligence) to establish correlations with the most important characteristics of the sample, for example, with toxicity in the ecological environment, or with specific diseases in medicine;

fourth, with the accumulation of experimental data and with training of neural networks, the diagnostic and prognostic potential of the method can be significantly increased.

As for the organization of the measuring process itself, in order to increase the information content of the electrochemical measurement, it is necessary to take into account the following points arising from the thermodynamics of information processes.

Active measurement methods are more informative than passive ones.

Active measurement control is based on the principle of adaptability, based on information obtained directly in the measurement process. Adaptive control allows maintaining a quasi-stationary flow of thermodynamic processes in the sensor, which ensures gaining the maximum amount of information.

The minimum level of intrinsic noise is provided by galvanostatic control of the sensor. Potential control disturbs the stability of the electric double layer, resulting in a high level of intrinsic noise, which increases with an increase in the area of the working electrode.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/Video S1: 3D chromatogram.mp4

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9. References

1. Yan Kazakov, Aleksey Tarasov, Lyudmila Alyoshina, Khiena Brainina. Interplay between antioxidant activity, health and disease. Biointerface Research in Applied Chemistry. Volume 10, Issue 1, 2020, 4893 – 4901

2. Y. Kazakov, M. Khodos, M. Vidrevich, and K. Brainina. Potentiometry as a Tool for Monitoring of Antioxidant Activity and Oxidative Stress Estimation in Medicine. Critical Reviews in Analytical Chemistry, https://doi.org/10.1080/10408347.2018.1496009

3. Sokolkov S.V. Evolution of the analytical signal in electrochemistry from electrocapillary curve to a digital electrochemical pattern of a multicomponent sample. Electrochemical Science Advances, 2022, DOI: 10.1002/elsa.202100212

4. Scott, Alwyn. Active and Nonlinear Wave Propagation in Electronics, Published by John Wiley & Sons Inc 1970-07-22 (1970)

5. A.C. Scott. The electrophysics of nerve fiber. Rev. of Modern Physics, 1975, v.47, №2

6. Crowley, J. M. Electrical Breakdown of Bimolecular Lipid Membranes as an Electrochemical Instability, 1973. Biophys. J. 13:71

7. Michael B. Partenskii and Peter C. Jordan, "Squishy capacitor" model for electrical double layers and the stability of charged interfaces, PHYSICAL REVIEW E 80, 011112 (2009)

8. Duda, C.T., Kissinger P.T. Determination of biogenic amines, their metabolites, and other neurochemicals by liquid chromatography/electrochemistry, In: Methods in Neurotransmitter and Neuropeptide Research. Techniques in the Behavioral and Neural Sciences, Volume 11, Part 1, 1993, Pages 41-82

9. Acworth, I.N., and Bowers, M (1996). An introduction to HPLC-based electrochemical detection: from single electrode to mufti-electrode arrays. In: Progress in HPLC, Volume 6. Acworth, I.N., Naoi, M, Parvez, S., and Parvez, S. (Eds.). VS Press, The Netherlands.

10. Leontovich M.A. Introduction to thermodynamics. Statistical Physics, Moscow, Nauka, 1983

11. J.C. Maxwell, Theory of Heat, p.308-309, London, 1871

12. L. Scilard, Zs. Physik 53, 840 (1929), translation from German 1964. https://doi.org/10.1002/bs.3830090402

13. Leon Brillouin, Science and Information Theory, Academic Press Inc Publishers, New York, 1956

14. R.P. Poplavsky, Thermodynamics of Information Processes, Moscow, Nauka, 1981

15. Stefano Bo et all. Thermodynamic limits to information harvesting by sensory systems. J. Stat. Mech. (2015)

16. Gyorgy Inzelt. Crossing the bridge between thermodynamics and electrochemistry. From the potential of the cell reaction to the electrode potential, ChemTexts (2014) 1:2, DOI 10.1007/s40828-014-0002-9

17. Khiena. Z. Brainina, Maria A. Bukharinova, Natalia.Yu. Stozhko, Sergey V. Sokolkov, Aleksey V. Tarasov, Marina B. Vidrevich. Electrochemical Sensor Based on a Carbon Veil Modified by Phytosynthesized Gold Nanoparticles for Determination of Ascorbic Acid. Sensors 2020, 20(6), 1800; https://doi.org/10.3390/s20061800

18. G. C. Barker, I. L. Jenkins, Analyst, 1952, 77, 685

19. S.V. Sokolkov, P.N. Zagorodnyuk. Portable Electrochemical Analyzers. State of Art and Prospects. Russian Chemical Journal (Journal of Mendeleev Russian Chemical Society) 2001, v. XLV, №5-6, p. 80

20. Sokolkov S.V., Zagorodnyuk P.N., Karzhenkov A.N., Syrsky A.V. Electrochemical Analysis Method. PCT WO 02/46736, 13.06.2002

21. C. N. Svendsen. Multi-electrode array detectors in high-performance liquid chromatography: a new dimension in electrochemical analysis. An International Journal of Analytical and Bioanalytical Science. Review Article. The Analyst, 1993, 118(2), 123 – 129, DOI: 10.1039/AN9931800123

22. Sokolkov S.V. Electrochemical Analysis Method. PCT WO 2007/035130 A1, 29.03.2007.