

THE FUTURE OF VOLTAMMETRY

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It is exactly one hundred years ago when the first paper about the development of polarography was published in 1922. Polarography is considered a predecessor of voltammetry, and this iconic electrochemical technique was designed by the Nobel laureate Jaroslav Heyrovsky. In this short review, the aim is to highlight some of the most important achievements of voltammetry so far. While hints are given to some of the most important theoretical works related to various electrode mechanisms in cyclic voltammetry and pulse voltammetric techniques, a critical part is written that should help to improve the communication between theoretical and experimental electrochemists. Since a main application of voltammetry is in the field of constructing biosensors, some of the major achievements and several drawbacks of applying voltammetric techniques in designing sensors are discussed. In a small part of this review, the role of nanomaterials in voltammetry is also considered. As scanning electrochemical microscopy (SECM) seems to be most promising instrumental system that will bring voltammetry a step closer to probing real biological systems, critical aspects about the weaknesses of this technique are also briefly discussed. In the final outlooks, we present a set of directions in which voltammetry will develop in the coming years. The paper is written in a way to motivate younger electrochemists to get more involved in exploring the voltammetry.

Keywords: cyclic voltammetry; pulse voltammetric techniques; biosensors; nanomaterials; scanning electrochemical microscopy

ИДНИНА НА ВОЛТАМЕТРИЈАТА

Точно пред сто години, во 1922 година, е публикуван првиот научен труд што го опишува развојот на нова електрохемиска техника наречена поларографија. Поларографијата се смета за претходник на волтаметријата и оваа техника е дизајнирана од страна на добитникот на Нобелова награда Јарослав Хејровски. Главната цел во овој краток прегледен труд е да се прикажат некои од најголемите достигнувања во волтаметријата. Покрај дадените информации за некои од најважните теоретски трудови што се однесуваат на објаснувањето на својствата на различни механизми во циклична волтаметрија и во пулсни волтаметриски техники, претставена е и критична дискусија што треба да помогне во комуникацијата помеѓу теоретските електрохемичари и истражувачите што работат на полето на експериментална електрохемија. Бидејќи главната апликација на волтаметријата е во дизајнирањето на биосензори, претставени се најголемите достигнувања на ова подрачје, а дискутирани се и недостатоците од примената на волтаметријата во дизајнирањето на електрохемиски сензори. Во мал дел од прегледниот труд е опишана и улогата на наночестичките што се применуваат во електрохемиските експерименти. Бидејќи скенирачката електрохемиска микроскопија е најсофистицирана волтаметриска техника што треба да ја доведе волтаметријата чекор поблиску до испитувањето на електрохемиските својства на биолошките микросистеми, во трудот е даден и критички осврт на слабите страни на оваа техника. На крајот од овој прегледен труд се дадени насоки во кои волтаметријата би можела да се развива во наредните години. Овој прегледен труд е напишан со цел да ги мотивира младите електрохемичари да ги користат поинтензивно можностите на волтаметријата.

Клучни зборови: циклична волтаметрија; пулсни волтаметриски техники; биосензори; наноматеријали; скенирачка електрохемиска микроскопија.

1. INTRODUCTION

It was in 1959 when an electrochemist (Jaroslav Heyrovsky) was awarded the Nobel Prize for the first time for his achievements in developing "polarography".¹ Since then, it took exactly 60 years for another electrochemical achievement to be awarded the Nobel Prize for Chemistry in 2019, this time for work related to the development of lithium-ion batteries.² Meanwhile, electrochemistry and especially voltammetry made tremendous progress in many areas of research.³⁻⁷ Even though voltammetry has made a huge impact in many different scientific fields (physics, chemistry, pharmacy, medicine, biofuel cells, environmental protection, etc.), it must be admitted that it is still considered by many as a sort of "secondary research technique".⁸ The fact is that voltammetric systems are among the cheapest instrumental devices that are already available in many research laboratories. With the newest electrochemical systems developed in the last 10 years, one can afford an entire voltammetric device (i.e., potentiostat plus electrochemical cell with all electrodes included) for less than 4000 US \$. Moreover, most of the voltammetric experiments are not time-consuming and can be performed using a very easy and cheap protocol. Because the electrode transformation of a given analyte in voltammetry can be linked to various phenomena such as phase transformation, adsorption, coupled chemical reactions, mass transfer effects, and many more,³⁻⁵ the interpretation of voltammetric outputs is often a very challenging task, even for the skilled electrochemists. Because the core of every electrochemical experiment is an evaluation of certain physical parameters, from the experimental data obtained, one should make a suitable mathematical model that will reveal the most probable behavior of the system that is considered under defined experimental conditions. Once the mechanism of the electrode transformation is revealed, the corresponding data analysis will drive the evaluation of the physical parameters of the studied system. Mathematical modelling in voltammetry is not a simple task, and most of the troubles met by experimental electrochemists come from the appropriate interpretation of the theoretical voltammetric data. Indeed, voltammetry has been applied to study various systems, ranging from small ions³⁻⁵ to bulky proteins,⁹⁻¹² and it is incorporated as a working

technique in many electrochemical systems. In this short overview, hints are given to some of the most important voltammetric achievements, while some of the major puzzling aspects of practicing voltammetry are also critically discussed.

2. RESULTS AND DISCUSSION

Exactly 100 years ago, the Czech electrochemist Jaroslav Heyrovsky designed the first electrochemical device with the capacity to obtain insights into the redox transformation of substances that exchange electrons with an electronic conductor in experiments performed under a defined potential difference.¹ *Polarography* was the name of that electrochemical technique, for which the Nobel Prize was awarded to J. Heyrovsky in 1959. Nowadays, polarography (using the dropping mercury as a working electrode) is almost completely removed from most of the electrochemical labs, and it is almost entirely replaced by voltammetry in all novel commercial electrochemical systems. Voltammetry is an electrochemical technique that uses solid working electrodes made mainly of graphite, gold, or platinum.³ In the time that it was designed (in the late 1950s), polarization of the working electrodes in voltammetry was achieved by applying a bias having a linear or cyclic form. The latter paved the way for the design of *cyclic voltammetry*, one of the most familiar voltammetric techniques both for mechanistic and kinetic characterizations.^{3,13-17} Cyclic voltammetry is, even nowadays, a first choice in studying different electrode mechanisms. Moreover, many physical phenomena such as adsorption, phase transformation, or chemical reactions that occur at/nearby a working electrode can be successfully recognized and characterized by cyclic voltammetry.^{3-5,16,17} Because of its ability to obtain deeper insight into the nature of all the above-mentioned phenomena, cyclic voltammetry is often designated as "electrochemical spectroscopy".¹⁷ A valuable historical overview on polarography and cyclic voltammetry can be found in.¹⁸ With respect to the theories developed on cyclic voltammetry until now, a large number of mathematical models of "diffusional" and "surface" electrode mechanisms, in which the electrode transformations are associated with preceding, intermediate, follow up, dimerization, or regenerative chemical reactions at planar electrodes, rotat-

ing electrodes, microelectrodes, and rough-surface electrodes, simulated for single and multiple electron transfer steps have been presented in the literature.^{3-5,13-16,19-50} The majority of the cyclic voltammetric theories have been developed by prominent names in theoretical electrochemistry, such as M. Olmstead, R. Nicholson, J. M. Saveant, A. Bond, E. Laviron, J. Heinze, A. Bard, Ch. Amatore, R. Compton, K. Oldham, Anson, M. Lovrić, F. Scholz, F. Armstrong, A. Molina, S. Komorsky-Lovrić, L. Bieniasz, I. Shain, J. O'Dea, J. Osteryoung, V. Mirčeski, L. Faulkner, and many more. Since the mid 1960s, there have been permanent efforts to design novel voltammetric techniques with similar abilities to cyclic voltammetry for diagnostics of electrode mechanisms but with much better performances in sensitivity than cyclic voltammetry. The last was accomplished by launching of the so-called "*pulse voltammetric techniques*", which were designed in a way to achieve superiority by measuring the desired "Faradaic currents" over the unwanted "charging currents" in voltammetric experiments. By applying potential in the form of pulses with defined characteristics and by measuring the current in a small time-frame at the end of the applied pulses, one achieves significant domination of Faradaic currents over the charging currents.⁵¹⁻⁵³ Nowadays, there are several commercially available pulse voltammetric techniques in modern potentiostats, i.e., differential pulse voltammetry (DPV), square-wave voltammetry (SWV), normal pulse voltammetry (NPV), differential square-wave voltammetry (DSWV), or cyclic square-wave voltammetry (CSWV).^{3,51-56} All pulse voltammetric techniques have a different form of applied potential pulses, and they also differ in the current sampling procedure. In the short list of theoretical electrochemists who developed scores of theories for different mechanisms in pulse voltammetric techniques,^{3,51-53,57-90} the names of outstanding electrochemists such as Janet Osteryoung, John J. O'Dea, Milivoj Lovrić, Valentin Mirčeski, Richard Compton, Alan Bond, Zbigniew Stojek, Hiroaki Matsuda, Šebojka Komorsky-Lovrić, Angela Molina, Jan Myland, Samuel Kounaves, Stephen Feldberg, Robert Osteryoung, Craig E. Banks, and many more can be found. To the present day, there are several thousands of scientific papers related to various theoretical aspects of different electrode mechanisms studied under conditions of some voltammetric technique. Regardless of the algorithm used, the major task of all theoretical works is to provide diagnostic criteria to recognize some phenomenon at a defined electrode mechanism.

Moreover, it is up to theoretical electrochemists to provide working curves that will clearly portray the most relevant results of their studies. In addition, they should propose methodologies for getting access to physical parameters that are relevant to the considered mechanism. In scores of the theoretical works considered in voltammetric conditions, one finds valuable methodologies that allow access to kinetic and thermodynamic parameters relevant to the studied systems. While in most of the theoretical voltammetric works, there is a comprehensive explanation of the mathematical algorithms used, troubles are mainly met by explanations of the theoretical results in a language that is understandable for the experimentalists. There is a general impression that the majority of the theoretical results are not easily received by many experimentalists working in voltammetry. What is expected from the theoreticians in their further theoretical works is to propose a working protocol or some type of guidance in which they will give hints to experimentalists on designing a proper voltammetric experiment. This will help experimentalists to evaluate the physical parameters of relevance in light of the theoretical results. Unfortunately, this part is missing in many valuable theoretical voltammetric papers, and that aspect must be improved soon.

One of the most important applications of voltammetry is in the design of specific biosensors.^{5,91-93} *Voltammetric biosensors* are devices that take advantage of the sensitivity of a particular electroanalytical method and the inherent selectivity of the defined biological system. In most voltammetric biosensors, a defined biological substance, commonly attached to the surface of the working electrode, has the ability to recognize its specific counterpart (the analyte) present in the voltammetric cell. An eventual chemical interaction between these two systems might produce an electrical signal that will be proportional to the analyte concentration. This event can be amplified and detected, and it will be displayed in a specific pattern on recorded voltammograms. In last 25 years, a huge impact of voltammetry on the field of biosensor design has been witnessed.⁹¹⁻⁹⁴ Because many recent reviews report on a large number of voltammetric sensors, we refer the readers to some of those excellent works.⁹¹⁻⁹⁶ At this point, it is worth mentioning one remarkable achievement of voltammetry in probing the chemical features of so-called redox proteins and enzymes.⁹⁷ The technique, named "*protein-film voltammetry*" (PFV), introduced by Armstrong et al.⁹⁸⁻¹⁰¹ is seen as a cornerstone of voltammetric methodologies de-

signed to obtain insight into the chemistry of water-insoluble redox enzymes that keep their activity even after being immobilized on the surface of a working electrode. In the last 20 years, scores of relevant theoretical^{98–112} and experimental papers^{98–102,110,113–120} have been published reporting on the mechanism of action between various redox enzymes and defined substrates, thus paving the way to getting access to kinetic and thermodynamic parameters of many enzyme-substrate interactions. Due to the selectivity of redox enzymes to interact with a defined substrate only, protein-film voltammetry was also used to design specific voltammetric biosensors [see review 121 and the references therein, for example]. Although remarkable progress has been achieved in understanding the chemistry of some lipophilic redox enzymes by using a simple voltammetric setup, the number of proteins and enzymes studied experimentally with PFV remains quite limited.^{102,110,121} The hindrances in electron communication between the working electrode and the redox active center(s) that are deeply hidden in the bulky protein structure are seen as major limiting factors for the broader use of PFV in enzymatic biosensing. In addition, deactivation/inhibition of some proteins often happens when they are brought in contact with the material of the working electrode.

For achieving a better selectivity and sensitivity of voltammetric biosensors, it was inevitable that steps towards *modifications of surfaces* of commercially available working electrodes would be undertaken. *Polymerization* methods at the electrode's surfaces were seen as an initial step in improving some of the performances of the working electrodes.^{122–124} Furthermore, the discovery of *metal-based nanoparticles* and their application as modifiers of different electrode surfaces was the next step forward in the era of the development of voltammetric biosensors.^{125–135} However, a real revolution in improving the overall performances of commercial working electrodes and their intensive application in developing voltammetric biosensors happened some 20 years ago. This period coincides with the year in which 2D *graphene* was isolated in a separate form.¹³⁶ The introduction of this carbon-type material in electrochemistry, which is characterized by amazing elasticity and flexibility and highly expressed thermal and electrical conductivity, brought quick positive feedback in developing scores of voltammetric biosensors.¹³⁷ Because the graphene structure can be rolled and wrapped quite easily, many carbon-based nanomaterials with outstanding physical performances were derived from graphene, such as the

fullerenes, carbon single-walled nanotubes, carbon multiwalled nanotubes, quantum nanodots, and nanoplatelets.¹³⁸ Very soon, it was recognized that these graphene-based nanostructures exhibit amazing improvements over the performances of the material of working electrodes used in voltammetry.¹³⁸ An inherent property of all graphene-based nanoforms is their overexpressed ability to interact with a large number of biomolecules, hence serving as a platform for the attachment of many specific functional groups on their surface.^{136,138} The so-called "functionalization" of the graphene-based nanostructures leads to the creation of a bio-modified nanoplatform on the surface of the working electrodes that is made a key platform in specific molecular recognitions in voltammetric biosensors.^{136,138–140} In the last couple of years, several excellent reviews already reported on many voltammetric biosensors based on carbon nanotubes or fullerenes.^{137–145} Next to their use in chemistry and pharmacy, scores of voltammetric biosensors using graphene-based nanoforms have been designed for quantification of systems relevant in clinical biochemistry and molecular diagnostics, such as glucose, urea, DNA, hemoglobin, and other important biomolecules detected in physiological fluids.^{142,146,147} Moreover, because specific antibodies can be attached to the surface of graphene-based nanoforms, several voltammetric biomarkers have also been constructed, reported to be suitable in medical diagnostics.^{148–150} From most of the voltammetric studies presented so far, it seems that the future of voltammetry will be closely linked to the further development of current and novel forms of various nanoparticles.

The biggest expectations for the broader application of voltammetry in biological microsystems came some 30 years ago, when *scanning electrochemical microscopy* (SECM) was introduced by A. J. Bard.¹⁵¹ SECM is a hybrid-type of microscopic-electrochemical technique that can detect a redox activity even from single cells present in water solution.¹⁵² In SECM, by using an ultra-microelectrode (with diameter of 20 μm or smaller) that is polarized at a defined potential, it is possible to detect the redox activity of defined species present in a very limited part of some biological or chemical system. The SECM has been applied so far in important research areas such as corrosion,¹⁵³ surface modification,¹⁵⁴ medical diagnostics,¹⁵⁵ and biosensor development.¹⁵⁶ Even very precise topographies of some carcinogenic cells have been achieved by applying the SECM in experiments with single cells.¹⁵⁷ A comprehensive overview about the basic principles and achieve-

ments of SECM can be found in.¹⁵⁸ Although there are several reports of using the SECM for reliable diagnostic cancer studies on single cells,^{152,156–158} it seems that due to the practical problems that arise from fragile ultra-micro electrodes, whose surface can get easily contaminated when working in a complex matrix of biological systems, the broader application of this technique is far below its real potential. Indeed, one needs researchers skilled both in microscopy and electrochemistry to get relevant data from the experiments performed with quite expensive SECM instrumentation. The very high price (more than 100 000 US \$) seems to be another limiting factor for using the SECM to study electrochemical systems of broader interest. These are the most probable reasons why there are "only" about 2500 papers published in which the SECM was explored in the last 33 years.

3. OUTLOOKS FOR THE FUTURE

This year coincides with the 100th anniversary of the first work published on the development of the predecessor of voltammetry, i.e., polarography.¹ Without exaggeration, voltammetry is the most versatile instrumental technique that is already applied in hundreds of thousands of studies related to various phenomena observed during electrode transformation of important physiological and chemical systems. In the last 30 years, one witnesses the rapid progress of voltammetry in understanding processes of corrosion, in environmental analysis, in designing sensors relevant to biomedicine, in developing biofuel cells, in characterizing novel materials, in separation and analyses in many industrial processes, in understanding the ion-transfer processes across a liquid-liquid interface,^{159,160} and many more. The role of voltammetry in biosensor development has been recognized significantly in the last 20 years. This coincides with the development of various metallic and graphene-based nanoparticles that have superior physical properties compared to the commercial material from which the working electrodes are made. Although about tens of thousands of voltammetric sensors are reported every year for the detection of DNA, proteins, enzymes, hormones, glucose, and many other physiological systems, regrettably, only few voltammetric biosensors have been transformed into commercially applicable devices. Interesting information existing in the literature is that there are more than 20 000 reports of different enzymatic and non-enzymatic voltammetric sensors developed for glucose detection in blood, but none is still designed for commercial purposes.

The same also holds true for the majority of voltammetric biosensors for other physiological and chemical systems. A major reason for these discrepancies is the fast contamination of the working electrode's material when applying these conductors for probing complex biological samples. A huge potential in overcoming these problems is seen in metallic nanomaterials and especially in graphene-based nanoparticles and their ability to host specific substrates on their surfaces that can recognize only a single defined target in complex biological matrixes. It will also be a challenging task to develop multi-functionalized nanomaterials, where several different substrates will be attached at a single nano-platform. This will open up the possibility of designing voltammetric biosensors capable of simultaneously quantifying different biomolecules and permanently monitoring complex biological samples. In the last couple of years, many fast and reliable analytical tools have been designed for the detection of Covid-19. In that respect, voltammetry has made rapid progress in the field of virus detection, and several reliable voltammetric sensors for the detection of Covid-19 have already been reported.^{161–164} It seems that voltammetric devices are quite suitable for the development of an inexpensive platform for rapid diagnosis of Covid-19. Now, it seems very likely that the future of voltammetry in the 21st century will be closely tied to the development of new nanomaterials. With respect to achieving a better sensitivity of the voltammetric techniques, novel materials, and novel types of modifications of working electrodes should be designed. In addition, one expects that novel voltammetric techniques with new forms of the applied potential should be designed, as those reported recently^{72,77,88} that will contribute to better analytical sensitivity. Because voltammetry turns quickly to the nano-world, it will be a challenging task for the theoreticians to start considering the theories of voltammetry at the molecular level. Indeed, one expects to see, in the near future, a large number of so-called "interdisciplinary theories", in which molecular dynamics simulations, quantum mechanics, and electrochemical theories will be intersecting. Performing voltammetry experimentally is probably not very difficult, but understanding voltammetry is definitely not an easy task. It is up to all electrochemists to transfer their knowledge to younger generations and to make voltammetry a research technique of the first choice. In Figure 1, we give a visual scheme for the possible directions in which voltammetry will develop in the 21st century. Happy 100th anniversary to polarography and voltammetry.

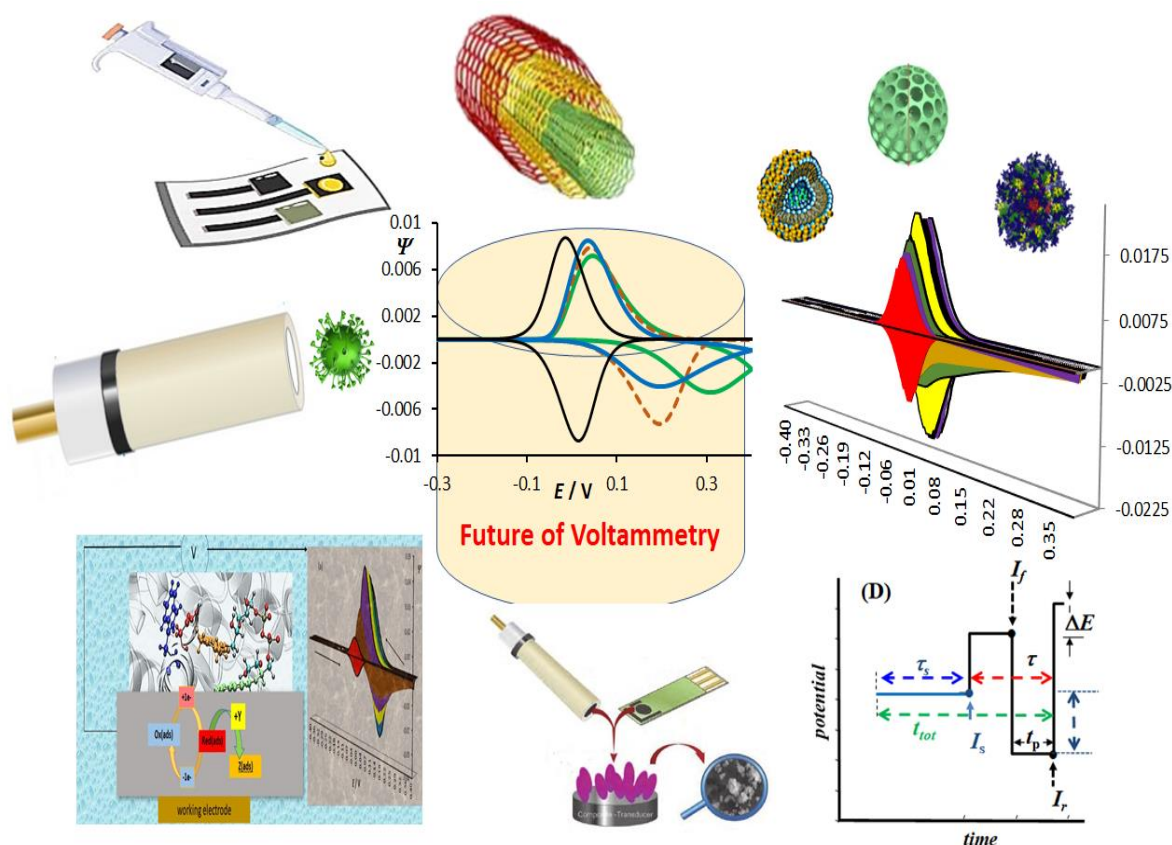


Fig. 1. Possible directions in which voltammetry will develop in the 21st century

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