

Chapter 2

Theoretical Background of Electrochemical Analysis

Abstract An electrode is a conductor or semiconductor, which directly contacts the electrolyte solution. In an electrochemical system, the input and output are both realized through an electrode. The substrate materials of the commonly used electrodes include noble metals (platinum, gold, silver, etc.), mercury, various kinds of carbon materials and semiconductor materials. Since the electron transfer rate between proteins and electrode surfaces is usually prohibitively slow, due to the burying of the electroactive prosthetic groups of most proteins in the electrically insulated peptide backbones and adsorptive denaturation of proteins on electrode surface, chemically modified electrodes (CMEs) are developed to facilitate the electrochemical analysis of the biomacromolecules and cells. Meanwhile, different electrochemical techniques are employed to meet the requirements of different bioassays.

Keywords Electrode substrates • Chemically modified electrodes • Cyclic voltammetry • Differential pulse voltammetry • Electrochemical impedance spectroscopy • Chronocoulometry

2.1 Electrode Substrates

The basis of electrochemical analysis is the reaction on an electrode surface. Since the working electrode substrates can strongly influence the efficiency of the reactions, the properties of electrode substrates are of great significance for successful electrochemical analysis.

So far, a variety of electrode substrates have been exploited. Noble metals, mercury, carbon and semiconductor materials are commonly used electrode materials. Some composite materials with excellent characteristics have also been employed for electrode substrates, such as platinum-dispersed titanium, tantalum and niobium. Besides, electrode materials with small dimension (e.g., a nanometer level) may greatly enhance the electron transfer rate and thus have superiority in lots of applications. For example, nanocrystalline tin oxide electrodes have been constructed to study the electrochemistry of certain redox proteins [1, 2].

Since different functional groups on electrode substrate possess different physical and chemical properties as well as biocompatibility, a protein usually exhibits

extremely different electrochemical performance on different electrode substrates. Therefore, choosing appropriate electrode substrate is crucial for successful electrochemical analysis. While the obtained experimental results can help researchers choose suitable substrate for specific applications, prediction of the utility of electrode substrate can also be helpful, which is mainly based on two factors. One is the redox behavior of the target analyte, and the other is the background current over the potential range applied in the measurements. Meanwhile, some other factors should also be considered, such as the electrical conductivity, mechanical properties, toxicity, cost, etc.

2.1.1 Metal Electrodes

Nobel metals such as platinum, gold and silver have been widely used as electrode substrates. Noble metal electrodes can offer very favorable electron transfer kinetics and a wide anodic potential range. The cathodic potential window of these electrodes is usually restricted due to the low hydrogen overvoltage. However, the formation of surface oxide or adsorbed hydrogen layers may lead to high background currents, which strongly affect the kinetics of the electrode reaction. To solve this problem, a pulse potential cycle should be performed before electrochemical experiments [3]. Here, we will briefly discuss several typical metal materials.

The chemical properties of gold electrode and platinum electrode are very stable. Meanwhile, pure gold or platinum materials are easily obtained, and the electrodes can be conveniently manufactured. Therefore, these electrodes become most popular metal electrodes. Silver is also good electrode substrate, which is usually used for the preparation of chemically modified electrodes (CMEs) in various electrochemical researches [4–8]. Moreover, some proteins such as cytochrome *c* (cyt *c*) may exhibit the capability of direct electron transfer on silver electrode, so silver substrate has also been directly used for protein analysis [9].

Besides noble metal electrodes, some other metals have also been employed as electrode substrates. For instance, copper electrode and nickel electrode have been constructed for the detection of carbohydrates or amino acids in alkaline media. Compared with platinum or gold electrodes, these two kinds of electrodes possess a stable response for carbohydrates at constant potentials [10]. In addition, alloy electrodes like platinum–ruthenium and nickel–titanium electrodes have also been reported, which are often used for the preparation of fuel cells, owing to their bifunctional catalytic mechanism [11].

2.1.2 Mercury Electrodes

Mercury is a classic electrode material. With high hydrogen overvoltage, it can extend the cathodic potential window. Meanwhile, mercury electrodes possess highly reproducible, renewable and smooth surface, which is very beneficial in

electrochemical analysis. So, a variety of mercury electrodes including dropping mercury electrode, hanging mercury drop electrode and mercury film electrode have been developed. Among the mercury electrodes, dropping mercury electrode is the most commonly used one. The main advantage of dropping mercury electrode is that the electrode can be self-renewing, so it does not need to be cleaned or polished before each experiment. Moreover, each drop of mercury has an uncontaminated and uniform surface. Nevertheless, the toxicity of mercury and the limited anodic range have restricted the application of dropping mercury electrode and the other mercury electrodes in the analysis for biologic species. Therefore, the colleagues have exploited some related solid amalgam electrodes for the biologic analysis.

2.1.3 Carbon Electrodes

A family of carbon materials have been widely used as electrode substrates to make various electrodes. Due to the soft properties of carbon, these electrodes surface can be easily renewable for electron exchange. Carbon materials also have broad potential window, low background current, rich surface chemistry and comparative chemical inertness. The cost of carbon materials is also very low. Therefore, carbon electrodes are currently widely used, and a large number of research projects are even focused on the relationship between structure and reactivity of carbon electrodes. The commonly used carbon electrodes include pyrolytic graphite electrode (PGE), glassy carbon electrode (GCE), carbon paste electrode, carbon fiber electrode and electrodes composed of carbon composites. All these electrodes have the basic structure of a six-membered aromatic ring and sp^2 bonding. One difference between these carbon electrodes is the relative density of the edge and basal planes of the surface which affects the electrochemical reactivity at electrode surface. For example, an elegant cyclic voltammogram of cyt *c* can be obtained at an edge plane PGE [12] and GCE [13], while only a very small response can be obtained on a basal plane PGE.

2.2 Chemically Modified Electrodes

In many research works, proteins under investigation are usually immobilized onto the surface of an electrode. However, this immobilization procedure may denaturalize most proteins with the conformational change, which may affect the further analysis of the proteins. Therefore, bare electrodes are not ideal interfaces to obtain direct electrochemistry of most proteins; thus, CMEs are developed to improve the situation. CMEs emerged in 1973 when Lane and Hubbard modified various olefine compounds on clean platinum electrode through chemisorption, which significantly changed the electrochemical response of the electrode [14, 15]. Since then, CMEs have been developing rapidly to investigate the direct electrochemistry of proteins and the mechanisms of redox reactions. The fabrication of CMEs is to immobilize

molecules with specific functions on the ordinary electrode surface by chemical or physical methods. Proteins deposited on the surface of the CMEs can then retain their biologic activities to some extent; thus, electrochemical performance of the electrode can be improved for the analysis of proteins. For example, thiol compounds can be covalently attached to the surface of gold electrode through the formation of metal–S (Au–S) bond [16]. This process has then introduced some new functional groups not only for the improvement of biocompatibility but also for the later electrostatic interaction. Therefore, biologic analysis by using the CMEs can be conducted.

2.2.1 Conducting Polymer–Modified Electrodes

Conducting polymers are organic polymers with metallic conductivity or semiconductor properties. Since the discovery of high conductivity in doped polyacetylene in 1977 [17], numerous well-characterized and ordered conducting polymers have been exploited; thus, many conducting polymer–modified electrodes have been prepared for the analysis of proteins and cells.

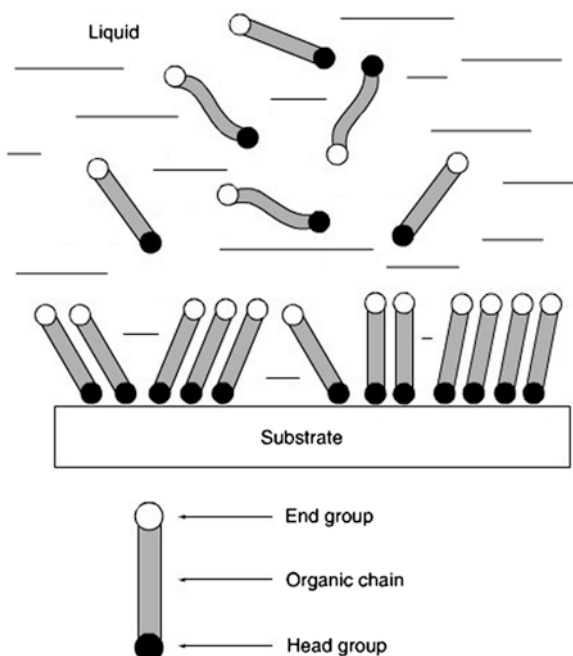
The preparation of conducting polymer–modified electrode is often realized via in situ electropolymerization from monomer solution. Moreover, the properties of polymers can be modulated by attaching different chemical groups to the monomers before polymerization. Therefore, these chemical groups may participate in molecular recognition or electrocatalytic reaction, which can help the polymers become efficient molecular interfaces between electrodes and solution. Meanwhile, conducting polymer nanowires have also been synthesized and applied in the fabrication of resistance sensors and molecular electronic devices for the analysis of proteins and cells [18].

There are many advantages of conducting polymer–modified electrodes. On the one hand, most proteins can well function in non-aqueous media with high activities [19]. On the other, conducting polymers usually contain electronic states that can be reversibly occupied and emptied with electrochemical techniques [20], which can facilitate the electrochemical measurements of analysis for proteins and cells.

2.2.2 Self-Assembly Monolayers

Self-assembly is a term to describe processes that a number of spatially disordered objects arrange themselves in an ordered pattern via local interactions. The interactions include ionic bond, covalent bond, metallic bond, as well as weak interactions (e.g., hydrogen bond, van der Waals force and π – π interaction). The self-assembly system is not freestanding. It needs solid support, so electrode is an excellent support which can further play more function roles. Figure 2.1 illustrates the formation a self-assembly monolayer (SAM) on a substrate surface.

Fig. 2.1 Schematic representation of the formation of a self-assembly monolayer at a substrate. Reprinted with the permission from Ref. [22]. Copyright 1995 American Chemical Society



Self-assembly has been a widely studied surface modification technology, so SAM has been rapidly developed since the late 1980s and used in many scientific fields such as material science, molecular biology and medicine [21, 22]. Some properties like the injection across the interface between the monolayer and the electrode have been determined by molecular orientation and packing at the interface [23, 24]. Meanwhile, it has been known that the functions of the devices fabricated with SAMs usually depend on the deposition of the SAMs [25–27].

SAM has a lot of advantages. For instance, the formation of a SAM just requires a simple procedure, and the monolayer is chemically stable and biocompatible for electrochemical analysis. Moreover, proteins can be immobilized on the SAM-modified electrode with much more appropriate orientation compared with the adsorption on a bare electrode or in a polymer, overcoming the problem of denaturalization of proteins. Some electro-inactive reagents can also be used to help the formation of a SAM. Besides, a SAM can induce proteins to form an appropriate orientation, so the electron transfer rate between proteins and electrode can be largely accelerated accordingly [28].

2.2.3 Nanomaterial-Modified Electrodes

Nanomaterials possess at least one dimension sized from 1 to 100 nm [29]. They possess not only unique geometric, mechanical, electronic and chemical

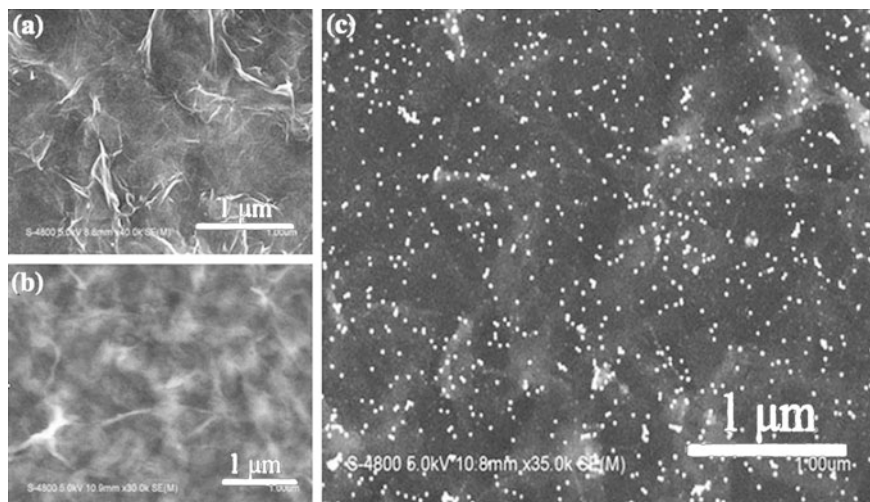


Fig. 2.2 Scanning electron microscope images of **a** graphene, **b** polythionine/graphene and **c** AuNPs/polythionine/graphene film. Reprinted from Ref. [37], with kind permission from Springer Science + Business Media

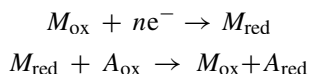
properties, but also properties different from macroscopic materials, such as quantum effect, surface effect, small size effect, etc. These properties have greatly prompted a broad range of applications of nanomaterials in medicine, electronics, biomaterials, environmental science, energy production and biosensors [30–44].

Nanomaterial-modified electrodes have many advantages over the traditional material-modified electrodes. Firstly, nanomaterials offer huge specific surface area for the immobilization of more functional molecules on the electrodes (Fig. 2.2). Secondly, some semiconductor nanomaterials may act as promoters of electrochemical communications, accelerating the electron transfer rate between proteins and electrodes. Thirdly, some biocompatible nanomaterials can help proteins or cells maintain their activities on the electrode for a long period. Therefore, a variety of nanomaterials have been synthesized and characterized for the performance of electrochemical analysis for proteins and cells. The frequently used nanomaterials include metal nanomaterials, especially gold nanoparticles (AuNPs), metallic oxide/sulfide nanomaterials, carbon nanotubes (CNTs), especially multiwalled carbon nanotubes (MWCNTs) and graphene, etc. Moreover, nanocomposite materials, consisting of two or more types of nanomaterials, have also been exploited.

2.2.4 Mediator-Modified Electrodes

Redox reactions on the surface of an electrode can be accelerated by using a suitable electron transfer mediator [45, 46]. The function of the mediator is to facilitate

the charge transfer between the electrode and the analyte. The reaction can be described as follows, in which M represents the mediator and A is the analyte:



Compared with bare electrodes, mediator-modified electrodes have the following advantages. Firstly, it can reduce the overpotential of the analyte and the possible interfering background current. Secondly, the response of current signal can be enhanced; thus, lower detection limit can be achieved. Thirdly, adsorption of the analytes and the products can be eliminated. Therefore, the sensitivity and selectivity of the analysis by using mediator-modified electrodes can be greatly improved.

Up to now, a lot of studies have been carried out for electrochemical analysis of various substances, including proteins, by using the electrodes modified with different kinds of mediators. For instance, sensitive and selective detections of dihydronicotinamide adenine dinucleotide (NADH) [47–49], ascorbic acid [50–53], cyt c [54–56] and hydrogen peroxide [57–60] have been achieved with the help of the corresponding mediators modified on the surfaces of PGE, GCE, gold electrode or platinum electrode.

2.2.5 Sol–Gel Technology

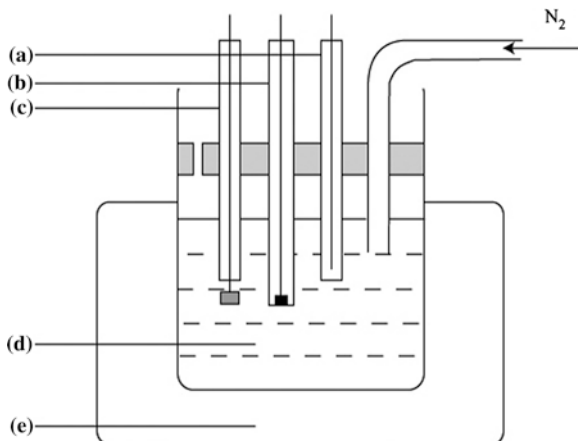
The sol–gel process is a wet-chemical technique, which has been widely used in materials science and ceramic engineering. This technique can fabricate an integrated three-dimensional network of materials like metal oxides from a colloidal solution via hydrolysis and polycondensation reactions [61]. Inorganic silica sol–gel materials are traditional sol–gel matrices, exhibiting excellent properties such as chemical inertness, high thermal stability and tunable porosity, etc. Nanomaterials have also been often used in the fabrication of complicated sol–gel three-dimensional networks. Since the formed structure of sol–gel matrix can maintain the native functional characteristics of the immobilized proteins [62, 63], a variety of studies have been conducted for the analysis of protein and cells based on sol–gel technology [64–67].

2.3 Electrochemical Cell

An electrochemical cell is used to generate voltage and current from chemical reactions or induce chemical reactions by the input of electrochemical signals. The most commonly used electrochemistry system is the three-electrode system consisted of working electrode, reference electrode and auxiliary electrode [68, 69]. Schematic illustration of the three-electrode system has been shown in Fig. 2.3. The

Fig. 2.3 Schematic diagram of an electrochemical three-electrode system:

a the reference electrode,
b the working electrode,
c the counter electrode, **d** the working solution, **e** constant temperature bath



working electrode makes contact with the analyte. Its surface is the place where the reaction occurs. After the working electrode is applied with a certain potential, the transfer of electrons between electrode and analyte takes place. The current observed at the electrode will pass through the auxiliary electrode for balance. Inert conducting materials such as platinum and graphite with comparably large surface areas are usually used to make auxiliary electrode. The reference electrode has a known reduction potential, while no current passes through it. It only acts as a reference when measuring the working electrode potential. Silver–silver chloride and the saturated calomel reference electrodes are commonly adopted in the three-electrode system. To avoid the contamination of the sample solution, the reference electrode can be insulated from the sample reaction via an intermediate bridge.

2.4 Electrochemical Measuring Techniques

For electrochemical analysis of biologic substances, various electrochemical signals such as current, potential, charge and impedance have to be generated via biorecognition or biocatalysis processes, which are further related to the concentration of the analytes. So, the most commonly used electrochemical measuring techniques should be briefly discussed, including cyclic voltammetry, differential pulse voltammetry (DPV), electrochemical impedance spectroscopy and chronocoulometry [68, 69].

2.4.1 Cyclic Voltammetry

Cyclic voltammetry may provide the information of the thermodynamics of redox processes, adsorption processes and the kinetics of electron transfer reactions. It is the

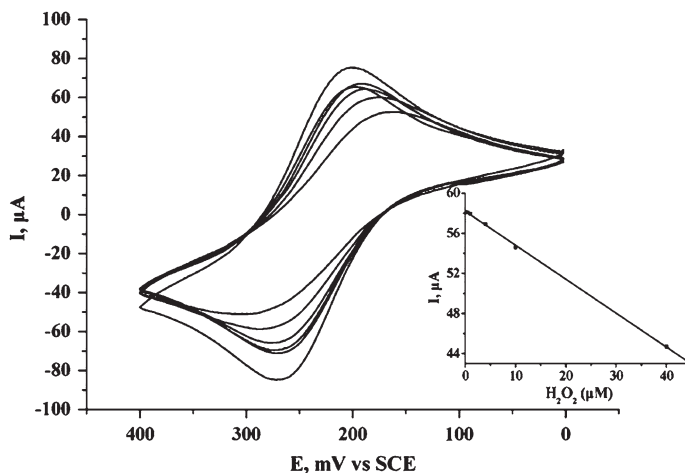


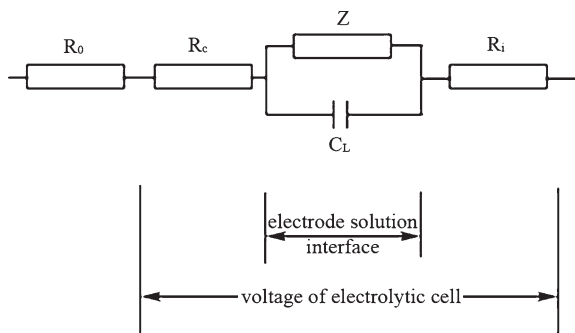
Fig. 2.4 Cyclic voltammograms of $\text{K}_4\text{Fe}(\text{CN})_6/\text{K}_3\text{Fe}(\text{CN})_6$ solution obtained at Au/cysteamine/AuNPs electrodes upon the treatment by the AuNPs growth solution consisting of 0, 0.1, 1, 10, 100, 1,000 μM H_2O_2 (from outer to inner). Inset shows the linear relationship between the cathodic peak current and the concentration of H_2O_2 . Reprinted with the permission from Ref. [38]. Copyright 2006 American Chemical Society

most widely used measuring technique in electrochemical analysis. In a typical cyclic voltammetry, the impulse potential is ramped linearly versus time and a pair of well-defined redox peaks are observed. Single or multiple cycles can be performed depending on the requirements of specific analysis. During cyclic voltammetric scanning, analytes or the redox centers of proteins will carry out certain electron communication with the electrode under various potentials and the currents may be proportional to the concentration of the analytes. Figure 2.4 shows a series of cyclic voltammograms of $\text{K}_4\text{Fe}(\text{CN})_6/\text{K}_3\text{Fe}(\text{CN})_6$ solution obtained at an Au/cysteamine/AuNPs electrode with the treatment by AuNPs growth solution containing different amount of H_2O_2 . The peak currents are inversely proportional to the concentration of H_2O_2 [38], demonstrating cyclic voltammetry a fine quantitative analytical method.

2.4.2 Differential Pulse Voltammetry

DPV is a derivative of linear sweep voltammetry and staircase voltammetry, which is extremely useful to detect trace levels of organic and inorganic analytes. In this technique, there are a series of regular voltage pulses superimposed on the potential linear sweep or stair steps. Just before each potential change and late in the pulse life, the currents are recorded. The current difference is then plotted against the applied potential. In the differential pulse voltammogram, the height of the current peak can be directly proportional to the concentration of corresponding

Fig. 2.5 The basic equivalent circuit of electrochemical impedance spectroscopy of an electrolytic cell



analytes. The peak potential varies with different analytes, which can also be used to distinguish the detected species. DPV can not only help improve the sensitivity of the detection and the resolution of the voltammogram, but also provide information about the chemical form of the analytes, such as oxidation and complexation status, which is very important for an analysis. Therefore, this technology has also been widely used for the electrochemical analysis of proteins and cells.

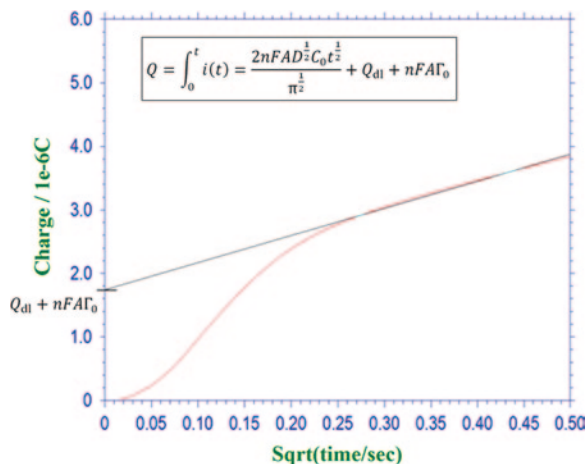
2.4.3 Electrochemical Impedance Spectroscopy

Electrochemical impedance spectroscopy detects the dielectric properties of a medium over a range of frequencies. The obtained data can be plotted in a Bode plot or a Nyquist plot. The electrochemical process on an electrode can be simulated to an equivalent circuit consisting of resistors and capacitors. Applied alternating voltage can generate alternating current from the electrochemical reaction on the electrode. The same alternating current can be produced if the voltage is applied on an equivalent circuit. Therefore, the electrochemical behavior on the electrode is equivalent to a resistance, known as Faraday impedance (Z). Figure 2.5 describes the basic equivalent circuit of the electrochemical impedance spectroscopy of an electrolytic cell. C_L represents the capacitance of the electric double layer on the electrode, R_i represents the internal resistance of the electrolytic cell, R_c represents the polarization resistance of the electrode itself and R_0 is the resistance of the electrolytic cell circuit. Usually, R_c and R_i are small, which can be neglected. Electrochemical impedance spectroscopy can not only probe into the features of the surfaces of CMEs, but also reveal the information about the reaction mechanism of an electrochemical process.

2.4.4 Chronocoulometry

Chronocoulometry is a technique measuring the relationship between charge and time, involving stepping the potential of the working electrode from the

Fig. 2.6 Chronocoulometric curve and corresponding formula



value at which no faradaic reaction occurs to the value at which the surface electroactive species concentration is zero. The adsorption phenomenon can also be characterized by chronocoulometry. In an electrochemical system, the function of the charge (Q) of the surface-confined redox species and the time (t) is described in the Cottrell expression as is shown in Fig. 2.6, in which n represents the number of electrons per molecule in the reduction, F is the Faraday constant (C/equiv), A is the electrode area (cm^2), D is the diffusion coefficient (cm^2/s), C_0 is the bulk concentration (mol/cm^3), Q_{dl} is the capacitive charge (C) and $nFA\Gamma_0$ is the charge from the reduction of redox marker on the electrode. Γ_0 represents the amount of redox marker on the electrode. When $t = 0$, the detected charge is the sum of the double layer charging and the surface excess terms. Under certain experimental condition, Q_{dl} is constant, so the quantitative determination of electroactive species adsorbed on the electrode can be achieved.

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Electrochemical Analysis of Proteins and Cells

Li, G.; Miao, P.

2013, IX, 69 p. 42 illus., 17 illus. in color., Softcover

ISBN: 978-3-642-34251-6