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Novel electrochemical sensors with electrodes based on multilayers fabricated by layer-by-layer synthesis and their analytical potential

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The results of studies on layer-by-layer synthesis of multilayers on the electrode surface in order to design electrochemical sensors for the determination of concentrations of inorganic, organic and bioorganic compounds are summarized and analyzed. The principle of the method is discoursed and the key advantages of the approach are highlighted, such as the possibility of single layer synthesis with specified thickness and composition under mild conditions with further fabrication of multilayers. Charge transfer conditions in the layers on the electrode surface between the analyte molecules and electrode redox centres and the operating conditions for the optimal electrode are considered. The role of electrocatalysts and intermediates of these processes is noted. Particular attention is devoted to the methods for synthesis of gold nanoparticles with different diameters. Analytical characteristics for electrochemical sensors are presented and application prospects of the layer-by-layer synthesis to electrode fabrication are discussed.
The bibliography includes 241 references.

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I. Introduction

Electrochemical sensors are centerpieces of chemical sensorics. At present, they are widely used in various fields ranging from analysis of air (in workplace),[1,2] determination of toxic substances and pathogens (in the environment and food) to *in situ* medical analysis of physiological fluids.[3–9]

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The productivity of such devices largely depends on electrochemical processes at electrode surface, which consists of carbon materials, noble metals, conductive oxides, *etc*., dependng on the sensor design and the method for analytical signal generation. Recently, the most efficient electrodes have been fabricated from nanostructured materials.[6,10] The properties of such materials play an important role in sensor application. In particular, they significantly enhance the analytical signal *via* electrocatalysis.

Nanostructured materials are deposited on the electrode surface using known physical and chemical methods including vacuum deposition, sol – gel method,[11] solution deposition, the Langmuir – Blodgett technique,[12] physical adsorption, covalent binding,[13] drop casting,[14] *etc*. In the last 10 – 15 years, layer-by-layer (LbL) synthesis has been among rapidly growing methods. A number of reviews are devoted to apects of application of the LbL synthesis in the design of sensors for detection of organic substances and biologicals.[15–21] However, all of them, except a feature review[16] concerned with specific features of application of gold nanoparticles, do not compare characteristics of the analytical possibilities of this kind of sensors. In fact, there are no reviews on sensors for inorganic analytes.

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The aim of this review is to analyze and summarize information on applications of LbL synthesis to fabrication of electrodes of electrochemical sensors for the detection of a wide range of inorganic and organic analytes including bioorganic ones, as well as to compare their analytical characteristics and to outline the future of the method in question.

The manuscript is arranged as follows. The Introduction is followed by Section II, which describes the LbL synthesis and presents a brief historical survey. In Section III, we consider basic principles of electrochemical and particular amperometric sensors and formulate key problems to be solved to design high-performance† electrodes for electrochemical sensors. Section IV concerns specific features of LbL synthesis which should be taken into account in the design of high-performance electrodes. Sections V to VII are dedicated to evaluation of the sensor analytical possibilities based on electrodes with layers fabricated using LbL synthesis for the detection of inorganic, organic and biological samples.

II. Layer-by-layer synthesis: the essence and brief historical survey

Precision synthesis of layers a few nanometres thick on the surface of a substrate is possible if the following conditions are met: [22]

— the surface of the substrate is covered with a necessary amount of active sites; these sites should react to form a layer whose thickness is governed by the so-called self-saturation effect;

— each newly completed layer exhibits the properties of the reactive substrate in the synthesis of subsequent layers; and

— multistep consecutive synthesis involves an obligatory removal of excess reactants and reaction products upon completion of each step of treatment of the substrate.

This strategy of synthesis of nanostructured materials was first of all implemented in relation to vapour phase deposition of metal oxide layers from volatile metal chlorides; it was called molecular layering [23,24] or atomic layer deposition (ALD).[25,26] Currently, the method is widely used in materials science. Suffice it to say that, according to our estimates, nearly 1100 publications concerning applications of LbL synthesis to the design of new thin-film materials were reported in 2013.

Among various LbL synthesis techniques, synthetic procedures using liquid-phase reactants (solutions of metal salts, colloidal particles and polyelectrolytes) are of great importance. Pioneering studies in this field were carried out by Iler,[27] who used colloidal solutions, by Nicolau [28] and Tolstoy and co-workers [29] (metal salt solutions) and by Decher and Hong [30] (polyelectrolyte solutions). The first review article on the topic was reported in 1993.[31]

Layers are fabricated by the successive ionic layer deposition, colloidal layer deposition and ionic-colloidal layer deposition techniques (SILD, SCLD and SICLD, respectively).[32,33] Experiments are carried out with salts of reactants dissociated in solution (SILD), colloidal solutions including suspensions, micellar and molecular solutions (SCLD) as well as colloidal solutions and salt solutions (SICLD). These synthetic procedures are also treated as polyionic assembly,[34] although in most cases one deals with the synthesis of colloidal particles rather than ions. In addition to LbL synthesis [35] and SILD,[36–38] the term 'successive ionic layer adsorption and reaction' (SILAR) is also used.[39] As can be seen, all these terms do not specify different methods of synthesis that take into account the nature of the reactants.

At present, LbL synthesis using reactant solutions is widely used in nanotechnology in the design of novel types of capsules for drug delivery systems, membranes, corrosion-resistant coatings, electrochromic and magnetic materials, catalysts, *etc*. More than 1500 publications on the subject appeared in 2014.

Operation with liquid-phase reactants offered new prospects for LbL synthesis because the range of such reactants is much wider than that of compounds characterized by high volatility at low temperatures and, usually, the synthesis itself can be conducted under mild conditions (in fact, at room temperature). This additionally extends the range of reactants and supporting electrodes and allows one to study biological systems.

The variety of conditions for the SILD version of LbL synthesis is schematically shown in Fig. 1. Treatment of the substrate with reactant solutions obeys a pattern of a multistep cycle. In the first step, the electrode is treated with the solution of the salt containing a cation from the composition of the growing layer and then the excess reactant solution is removed by washing with a solvent. The next step involves treatment with the solution containing an anion from the composition of the growing layer followed by removal of the excess reactant. The number of cycles depends on the goal of the synthesis.

According to this scheme, for each reactant solution one should choose a specific solvent, the reactant concentration, composition, a supporting electrolyte, a solution pH value, as well as the treatment temperature and duration. At least two reactants and two wash liquids are necessary; their pH values, temperature, presence and concentration of the supporting electrolyte, *etc*. should also be controlled. Therefore, the choice of SILD conditions becomes a much more complicated task. Also, prior to the synthesis one should determine the conditions for pretreatment of the surface of the substrate aimed to ensure adsorption of a reactant resulting in the formation of the first layer.

Thus, the growth of a surface layer in the course of LbL synthesis is possible if the first cycle of deposition on the substrate led to:

— adsorption of the cation- or anion-containing reactant (component of the growing layer);

— stabilization of the adlayer upon removal of excess reactant by washing;

— adsorption of the counterion after treatment with the second reactant solution; and

— stabilization of the completed layer upon removal of the excess second reactant by washing.

The process should result in the formation of a surface layer having new sites for adsorption of the first reactant during the second and subsequent deposition cycles. In other words, the key problem in the synthesis of layers of each composition is to choose appropriate reactants and synthesis conditions that meet the boundary conditions

† By the efficiency of a sensor is meant an operating mode characterized by the best analytical characteristics including sensitivity, limit of detection, stability, linear range and response time.

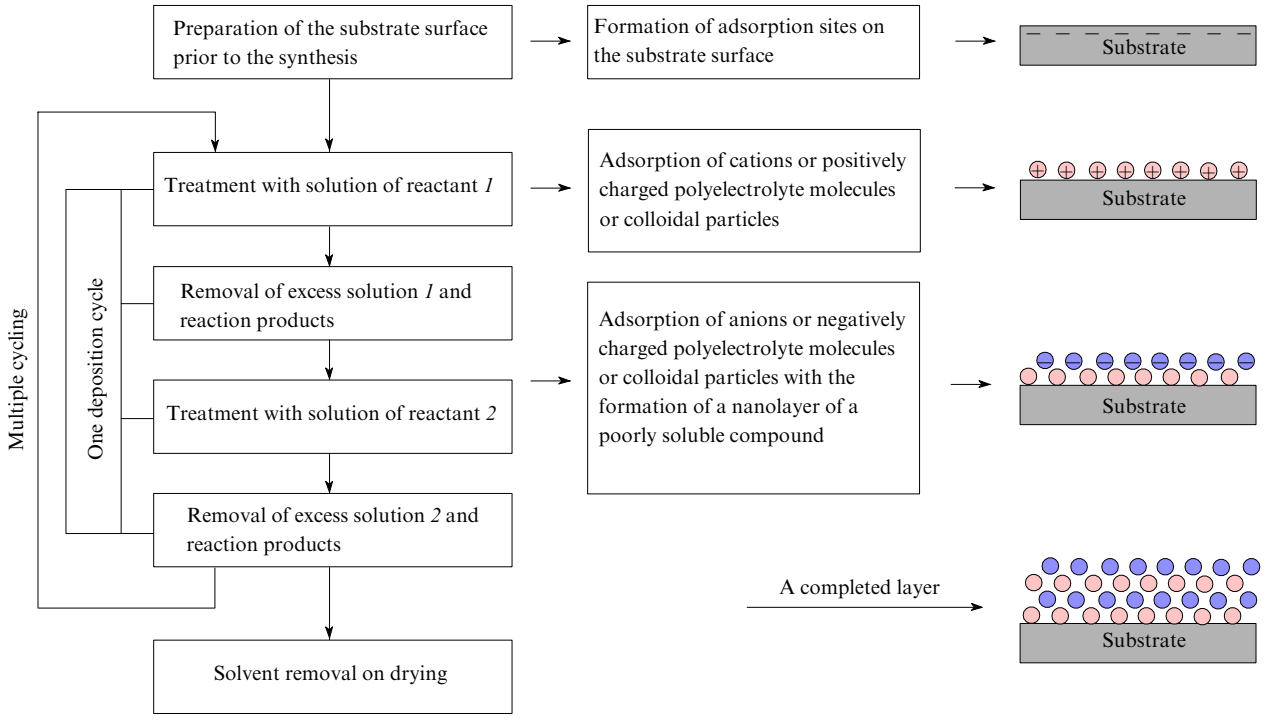


Figure 1. Treatment of the substrate with reactants in the course of LbL synthesis: a schematic.
(*1*, *2*) Salt solutions whose interaction of the surface of a supporting electrode gives rise to a layer of a difficultly soluble compound.

listed above. Clearly, only some out of all possible reactants will meet all the conditions; however, violation of even a single condition for the LbL synthesis will preclude formation of the surface layer after multiple cycling.

Comparing different procedures for the synthesis using reactant solutions, it should be noted that SILD, SCLD and SICLD are different from LbL synthesis or sol–gel technique. Indeed, for the two last-mentioned methods the substrate can also be multiply treated with reactant solutions which leads to formation and buildup of a surface layer whose thickness depends on the number of treatment cycles. The layer thickness will depend on the treatment duration of the substrate with the reactants and on the reactant concentrations; it is these reasons that are responsible for the decrease in the accuracy of maintaining a pre-specified thickness of the layers being synthesized.

III. Electrochemical sensors: principles of operation

A design of an amperometric sensor was for the first time proposed by Clark and co-workers.[40] An oxygen sensor was fabricated and the first enzyme-based glucose biosensor was made. Further progress in the field led to development of a wide variety of electrochemical sensors for the determination of inorganic, organic and biologically active substances. Usually, a modern electrochemical sensor[41] is a device containing a selective membrane (sometimes, a gas gap) with physical separation by the state of aggregation, particle size, *etc.* (Fig. 2). A sensitive layer is the next part of the sensor where chemical or biochemical reactions occur. These processes provide the selectivity of determination. Finally, a transducer (potentiostat) converts the chemical or physical response of the sensitive layer to the measurable (usually, electrical) signal whose value is proportional to the concentration of analyte(s). Often, it is hard to distinguish between the sensitive layer and the transducer because the latter can also act a sensitive layer in some cases.[42] In summary, an electrochemical sensor can be represented as a miniature analytical device containing a membrane for analyte separation, sensitive layer for signal formation and transducer for analytical signal generation.

Instrumental methods used to design electrochemical sensors include potentiometry, amperometry (AM), cyclic voltammetry (CV), electrochemical impedance spectroscopy, coulometry and conductometry. Amperometric sensors are most widely used.

Taking into account the type of reaction proceeding within sensitive layer, sensors are divided into chemical (chemical reactions with selective determination) and biological ones (enzyme reactions or bioselectors).

Three generations of biosensors are most often considered.[4] The first-generation sensors are based on the determination of oxygen released (or consumed) in an enzyme reaction. The second-generation devices contain electron transfer mediators, which reducie the activation energy for electron transfer from the enzyme to the electrode. The third-generation sensors are based on direct electron transfer from the electrode to the enzyme active site or *vice versa*. A new line of modern research related to sensors is to design enzyme-free electrochemical sensors.[42] A key issue in the second- and third-generation biosensors consists in relatively low electrochemical activity of bioanalytes. This is due to large size and rigid structure of biomolecules. Local charge alterations during electron transfer in biomolecules are accompanied by structure-chemical processes with high energy consumption; this leads to high activation energy of the electrochemical step. Therefore, it is electrocatalysis that

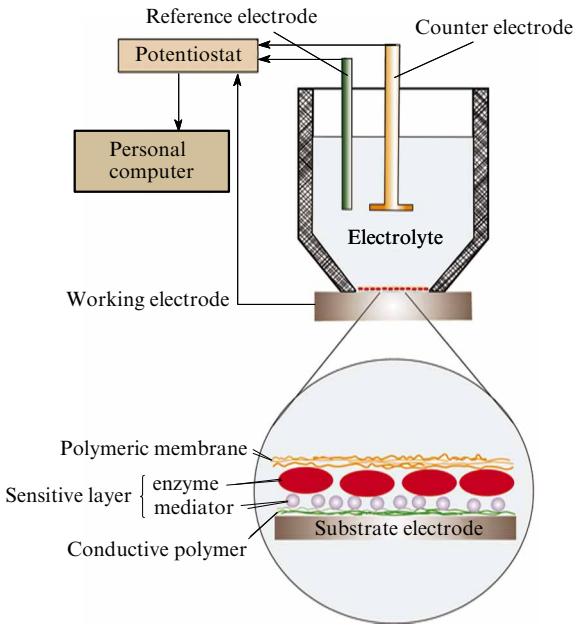


Figure 2. Design of an electrochemical cell and the order of individual layers in the multilayer on the electrochemical sensor electrode surface.

presents a key difficulty in the development of amperometric biosensors.

At present, the most promising electrocatalysts include nanostructured materials.[10,43–45] Application of nanoparticles in electrochemical sensors is a rapidly progressing field of electroanalytical chemistry, as indicated by a large number of reviews on the topic.[15–21,46] The variety of properties of electrodes in these sensors is due to a wide variety of methods for the synthesis of nanoparticles on electrode surfaces. Electrocatalysis allows one to significantly enhance the analytical signal of the sensor and, accordingly, to improve the detection sensitivity of analytes. Metal nanoparticles execute the following important functions in electroanalysis:[18,47] they considerably increase the conducting surface area; they exhibit catalytic properties owing to small particle size; and they directly contact the redox sites of enzymes. It should be noted that the electrocatalytic effect, namely, an increase in the rate constant for electron transfer, can be as high as six orders of magnitude.[10,48] To a first approximation, the most efficient transducer should provide a maximum degree of electron transfer from the electrochemically active sites of the sensitive layer with the maximum catalytic activity to the electrode. The concentration of the electrochemically active sites should be maintained at an optimum level with allowance for the finite rate of diffusion of the analyte components to the surface. The requirement becomes understandable when considering models for diffusion processes for various types of electrodes [49–51] including partially blocked ones (the surface is partially covered with an insulator, *e.g.*, an oxide), electrochemically heterogeneous (the surface is covered with particles of different conductivity), as well as porous electrodes.[52–54] For example, heterogeneous electrodes are represented by glassy carbon electrodes or In–Sn oxide (ITO) electrodes [55,56] whose surfaces are covered with noble metal nanoparticles,[53,54] while porous electrodes are, *e.g.*, those covered with a layer of carbon nanotubes or with polyelectrolytes.[57,58] Clearly, the amplitude of the analytical signal will depend on the electrode surface roughness. Taking into account a large number of parameters influencing the efficiency of electrodes of electrochemical sensors, the design of an optimum electrode is a complicated multiparameter task in materials science of thin-film structures. It should be noted that often, different factors affecting the analytical signal can hardly be included in the analysis of various models in the course of computational experiment, so that prediction of the properties of electrodes faces severe difficulties. Attempts to preset the properties of electrochemical sensors by fabricating layers on their surface by photo- or electropolymerization,[59,60] Langmuir–Blodgett method,[61] drop casting,[62–66] *etc.*, failed because relevant control of the composition and morphology of the surface layers is impossible. In this respect, LbL synthetic procedures become of considerable importance since they enable high-precision specification of the thickness of the layer being synthesized and deposition of all necessary components on the electrode surface, *i.e.*, the synthesis of a multilayer containing, *e.g.*, enzymes or bioselectors, electron transfer mediators, as well as electrocatalysts which provide relatively fast electron transfer from the analyte or mediator to the electrode and (or) membrane. It should be emphasized that LbL synthesis for the first time enables high-precision specification of the thickness of each individual layer in the multilayer and then investigation of the electrochemical response of the sensor. This makes it possible to analyze an array of same-type electrodes and to choose the most efficient items from the standpoint of, *e.g.*, sensitivity. In particular, experiments with electrodes covered with layers of polyelectrolytes, namely, poly(dimethyldiallylammonium chloride) (PDDA) and poly(styrene sulfonate) (PSS), and glucose oxidase were reported.[67] The layers fabricated using LbL synthesis (3 cycles) were characterized by the highest sensitivity and maximum linear range (Fig. 3). Probably, carrying out a specified number of deposition cycles is followed by the formation of a sensitive surface layer with the maximum concentration of the electroactive component and minimum electrical resistance. Deterioration of the sensor characteristics with electrodes fabricated after four and five deposition cycles seems to be due to higher diffusion limitations within the thickest layer and to an increase in its electrical resistance. Summing up, recently, there has been a new promising approach in materials science, which makes it possible to design electrodes for electrochemical sensors. It is based on the synthesis of multilayers, analysis of their electrochemical properties and choice of optimum items among series of same-type electrodes fabricated upon completion of different number of layer deposition cycles.

IV. Layer-by-layer synthesis: specific features that are of importance for the synthesis of multilayers on the surface of electrochemical sensor electrodes

At present, the potential of the SILD, SCLD and SICLD techniques is well studied. Mention may be made of some features that can be used in the formation of multilayers on the surface of electrochemical sensor electrodes. First of all, consider the possibility to synthesize layers on the surface of complex-shape electrodes including microelectrodes and electrodes with rough surface. This feature of LbL synthesis

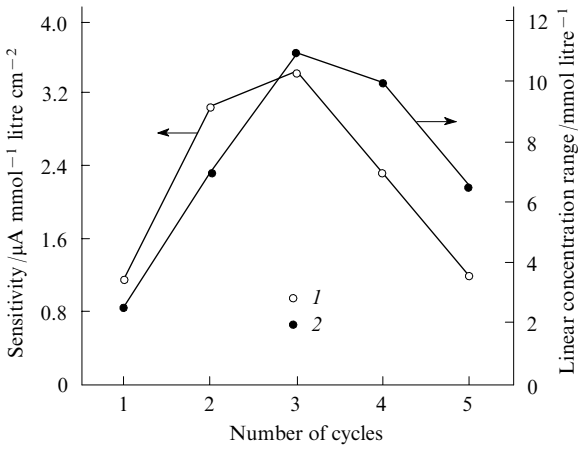


Figure 3. Sensitivity (*1*) and linear concentration range (*2*) plotted *vs.* number of deposition cycles in the course of LbL synthesis of the electrode of an electrochemical glucose sensor.[67]

is due to the fact that in each treatment cycle the new layer is formed within the layer of ions or colloidal particles that are adsorbed on the substrate surface and uniformly cover the surface. By appropriately choosing components for LbL synthesis one can fabricate layers of different composition on the electrode surface and thus create sensors for almost all classes of compounds including inorganic,[68–113] organic,[114–128] biologically active substances and glucose.[129–217] The method enables the synthesis of layers containing all necessary components including mediators, enzymes and other substances responsible for the formation of the analytical signal.

Sensors fabricated by LbL synthesis can conditionally be divided into enzyme-based and enzyme-free ones. In the former case, LbL synthesis can be carried out in mild conditions, usually, at room temperature. This is of great importance for the modification of electrodes of the biosensors containing enzymes and proteins because the biomolecules do not denature and retain their activity on the electrode surface. Nowadays, this approach is widely used in the design of biosensors for cholin,[139,140] glucose,[188–190,192–198,208–217] pyrocatechol,[125,147] phenol,[119,128] ammonia,[73] *etc*. The group of enzymes that can be immediately incorporated into the multilayer under the LbL synthesis conditions includes glucose oxidase,[125,126,181,188–190,192–198,208–217] horseradish peroxidase,[125] phytase,[119] tyrosinase[128] and choline oxidase.[139,140] Also, the sensitive layer fabricated using LbL synthesis may contain proteins and hemins,[92–95,103,104] antigens,[142,144–149,155,184,185] aptamers[173] and other traditionally used components of biosensors.

In the latter case, the analytical signals are generated by the electrochemically active analytes. Enhanced sensitivity is attained using mediators immobilized on the electrode surface[78,80,81,85,87,96,99–101,114,157,161,163–165,171,174] or through catalysis with the surface nanostructured materials, in particular, single- and multi-walled carbon nanotubes (Refs 70, 82, 100, 105, 108, 115, 117, 138, 144, 147, 148, 150, 155, 162, 167, 169, 170, 173–179, 186, 197–207, 217), graphene,[69,74,126,171] as well as platinum,[135,166,177,178] gold (Refs 75, 80, 97, 99–101, 105, 109, 110, 129–132, 138, 143, 145, 149, 171, 185, 89–193, 214), cadmium sulfide[84,165,194] and metal oxide nanoparticles.[133,155,161]

There are two types of sensitive layers with respect to the layer morphology. Namely, an enzyme can be immobilized on the electrode surface (examples are given above) or on the surface of the metal or metal oxide nanoparticles deposited on the electrode. In the latter case, one deals with a larger specific surface area of the sensitive layer and the electrode may exhibit electrocatalytic properties.[81,205] Immobilization of enzymes occurs through their adsorption on the surface of the nanoparticles contacting the electrode[71,102,170,178,192,201,202] or on the polyelectrolyte layers preliminarily deposited on nanoparticles using LbL techniques (Refs 73, 90, 93, 95, 107, 119, 121, 125, 139, 140, 152, 159, 168, 180, 182, 183, 201, 208, 210–213, 216).

Considering immobilization on an electrode, it is desired that the enzyme be on the surface of a conducting substance and contacting the mediator that ensures efficient electron transfer to the electrode. The selectivity of such a sensor abruptly enhances if there is a semipermeable membrane outside of the electrode. The membrane protects the enzyme from the action of undesired components of the solution being analyzed (*e.g.*, ascorbic acid, uric acid and acetaminophen in the case of a glucose sensor based on glucose oxidase). At the same time, glucose, oxygen, hydrogen peroxide and gluconic acid molecules should pass across the membrane with ease (Fig. 4).

A more thorough analysis shows that conducting polymers and semipermeable membranes can be obtained by LbL synthesis using polyelectrolyte solutions. Namely, conducting polymer layers can be fabricated using solutions of PDDA and sulfonated polyaniline (SPAN), poly(ethylene-3,4-dioxythiophene) (PEDOT) and polyethyleneimine (PEI)[218] or polyaniline (PANI),[219] polybutyleneviologen (PBV) and PSS,[220] while semipermeable membranes can be formed using solutions of humic acids (HAs) and $FeCl_3$, HAs and PDDA, PSS and PDDA.[221] The properties of semipermeable membranes can be optimized by varying the number of deposition cycles in the course of LbL synthesis (*i.e.*, by varying the thickness of the layers being synthesized).

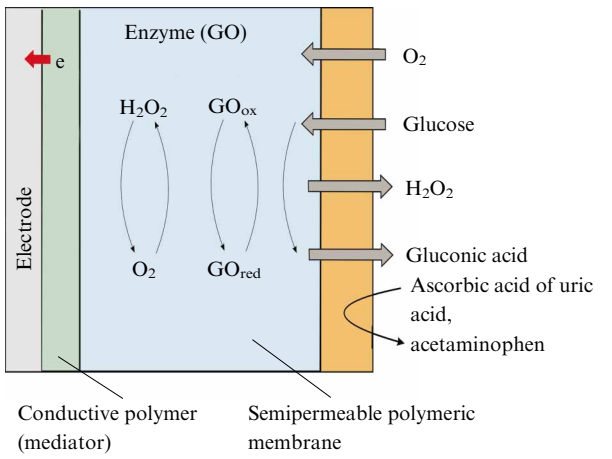


Figure 4. Various diffusion, chemical and electrochemical processes occurring in the multilayer on the electrode surface of a glucose sensor.

Yet another problem in the design of high-performance enzyme-based biosensors is to optimize the conditions for electron transfer from the active site of enzyme to the electrode surface. This case in point is that the redox site of the enzyme is surrounded by a dense protein shell which complicates electron transfer. Optimization is achieved using mediators [81, 107, 140, 169, 182, 195, 197, 206, 210] participating in the redox reactions at the electrode/enzyme interface; they reduce the overvoltage of electrochemical reactions. Possible mediators include various metal ferrocyanides,[81, 87, 114, 140] transition-metal complexes with organic ligands,[83, 85, 149, 157, 201] organic compounds [78, 161, 163, 171] as well as proteins and hemins.[71, 92–95, 101–104, 107] Emphasize that layers of these compounds can also be prepared using LbL synthesis techniques.

Recently, researchers have paid particular attention to electrocatalysis by nanoparticles, in particular, carbon and noble metal (mainly gold) nanoparticles. In this connection, methods of nanoparticle immobilization on the electrode surface are of great importance. For instance, immobilization of colloidal gold particles [222] requires pre-treatment of the surface with a solution of 3-aminopropyltrimethoxysilane to form functional groups with the chelate properties towards Au nanoparticles (Fig. 5 *a*). Gold nanoparticles can also be immobilized on the surface of polyelectrolyte layers obtained by LbL synthesis [223] using the PANI and PSS solutions (Fig. 5 *b*). However, these compounds significantly change the conditions for electron transfer from nanoparticles to the electrode and deteriorate the operating characteristics of the sensor.

Gold nanoparticles can be synthesized on, *e.g.*, the surface of an ITO electrode by consecutive multiple reduction of adsorbed anions $[AuCl_4]^-$ under SILD conditions (Fig. 5 *c* and *d*).[224] Following this approach, treatment of the surface with an $HAuCl_4$ solution is accompanied by adsorption of anions on the positively charged surface sites while treatment with a solution of a reducing agent ($NaBH_4$ or $N_2H_4 \cdot H_2O$) leads to formation of Au^0 nanoparticles. Subsequent multiple treatment with these reactants followed by removal of the excess reactants by washing with water causes the nanoparticle size to increase; however, the particle size can be controlled by varying the number of SILD cycles. If a SnF_2 solution is used as reducing agent, an $Au^0_x \cdot SnO_2 \cdot n\,H_2O$ nanocomposite layer is formed on the surface [225–227] because the redox reaction within the layer of adsorbed ions causes transformation of Au^{3+} and Sn^{2+} cations to Au^0 and Sn^{4+}, respectively (Fig. 5 *d*). The layer thus fabricated represents a mixture of Au^0 nanoparticles and $SnO_2 \cdot n\,H_2O$.

Clearly, Au^0 nanoparticles formed in the reactions (see Fig. 5 *c* and *d*) will be in ohmic contact with the electrode material; we believe this predetermines efficient operation of this type of electrodes.

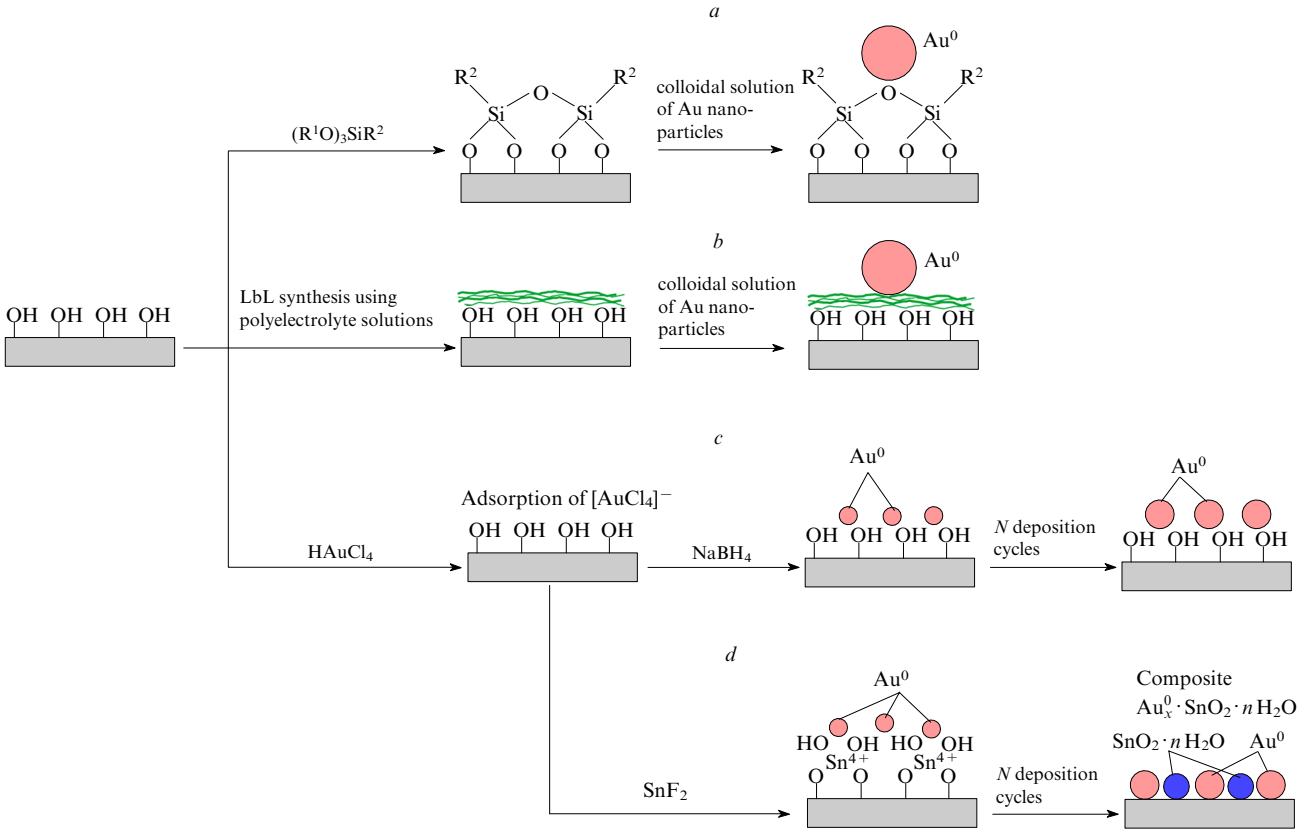


Figure 5. Possible synthetic routes to gold nanoparticles on electrode surface.
Immobilization of Au colloidal particles on the electrode surface through interaction with pre-adsorbed layer of an organic or organometallic compound (*a*); immobilization on the surface of an electrode that was preliminarily covered with a polyelectrolyte layer deposited by LbL synthesis (*b*); and successive reduction of adsorbed $[AuCl_4]^-$ anions during the SILD procedure (*c* and *d*).

Summing up, layers synthesized under LbL conditions and used in the fabrication of electrodes for electrochemical sensors can be constituents of multilayers with specified arrangement of individual components. Emphasize that LbL synthesis provides efficient solutions to most problems that pose in the design of electrochemical sensors (see Section II).

In the text below we will consider the analytical potential of sensors for inorganic, organic and biologically active analytes and glucose.‡

V. Sensors for inorganic compounds

Electrochemical detection of inorganic molecules is most often achieved using sensitive layers comprised of polyoxometalates[68, 72, 76, 77] and various carbon allotropes[91] including graphene,[69, 74] nanodiamonds,[104] as well as single- and multi-walled carbon nanotubes (Refs 70, 82, 85, 98, 100, 105, 106, 179, 204). In addition, noble-metal nanoparticles,[74, 75, 80, 97–101, 105, 106, 109, 110] and transition-metal oxide and sulfide nanoparticles[71, 84, 86, 88, 103] are employed. They have a well-developed surface and are sterically accessible to inorganic analyte molecules. Noble metals (Au, Pt), glasses, ITO layers and carbon materials are usually used as substrates.

The determination of most inorganic analytes usually does not require the presence of enzymes as components of the sensitive layer because selectivity is attained by choosing the detection potential and the analytical signal generated as a result of the electrochemical activity of analytes. Determination of electrochemically inactive ammonia is an exception.[73, 90] Possible electrocatalysts include organic[78, 83, 85, 89, 100, 101, 107] and inorganic mediators,[81, 82, 87, 96] hemins[71, 84, 93–95, 103, 104] and nanostructures.

Among a rather wide range of inorganic compounds that can be determined using electrochemical sensors with multilayers synthesized under LbL conditions, chalcogenides,[72] pnictogenides[68–71, 73, 74] and halides[72, 76] are most often determined. Of considerable interest is highly sensitive determination of hydrogen peroxide and oxygen that play an important role in nature and the determination of solution pH values.

Amperometric determination of nitrites using an electrode based on PDDA-linked multilayers of graphene and cobalt(II) phthalocyanine complex revealed a limit of detection of 8.4×10^{-8} mol litre^{-1} (Table 1). This low value was obtained using graphene layers (graphene favours accelerated electron transfer from reactive sites to the electrode) and a Co^{II} phthalocyanine complex acting as oxidizing agent for the oxidation of nitrites. Amperometric determination of hydrogen peroxide on an electrode covered with multilayers of MnO_2 nanoparticles and choline oxidase cross-linked by PDDA and PAS revealed a limit of detection of 2.2×10^{-8} mol litre^{-1} owing to the high catalytic activity of the MnO_2 nanoparticles. Amperometric determination of oxygen using an electrode modified with multilayers of β-cyclodextrin and gold nanoparticles reduced the limit of detection to 0.05 mg litre^{-1}; the sensitivity increased to 4 nA μmol^{-1} litre (towards nitrites), to 0.62 A mol^{-1} litre cm^{-2} (towards hydrogen peroxide) and to 2.065×10^{-5} A litre cm^{-2} mg^{-1} (towards oxygen).

Electrochemical sensors fabricated by LbL synthesis make it possible to reach lower limits of detection than other types of electrochemical sensors. For instance, the limit of detection of nitrite ions achieved in the determination with an electrode modified with an oxygen-bridged manganese–phenanthroline complex immobilized in Nafion matrix was 6.5×10^{-6} mol litre^{-1}.[228] A similar trend was also observed in the determination of H_2O_2 on an electrode modified by graphene oxide covered with silver nanoparticles immobilized by the drop casting; namely, the limit of detection was 1.099×10^{-6} mol litre^{-1}.[229]

VI. Sensors for organic compounds

When assaying organic analytes, the layer on the electrode surface is most often modified with various carbon allotropes, in particular, carbon nanotubes,[70, 115, 117, 126] or transition-metal hydroxide nanoparticles[120, 128] and platinum-group metal nanoparticles (Pt, Pd).[118, 123, 124, 126] The substrates usually include glasses coated with ITO films and carbon materials. The sensitive layers of these electrodes are mainly composed of nanostructured materials and(or) mediators because the analytical signal is generated upon direct oxidation or reduction of organic compounds on the electrode surface. The processes are catalyzed by components of the sensitive layer; this is the reason for the low limits of detection. In some cases, the sensitive layer may contain enzymes to attain high selectivity.[119, 121, 126, 128]

Modified electrodes are used for the determination of highly toxic, environmentally hazardous compounds (hydrazine, methanol, phenol,[230] aromatics, organic amines). An analysis of these analytes using electrodes with sensitive layers prepared by LbL synthesis revealed relatively low limits of detection (Table 2), *e.g.*, of the order of 5.0×10^{-8} mol litre^{-1} for hydrazine, 0.5 nmol litre^{-1} for phenol and 10^{-9} mol litre^{-1} for organic amines, and a high sensitivity of the order of 1.3×10^{-8} A μmol^{-1} litre. These results can be explained by the fact that the electrodes for the determination of these analytes contain noble metal nanoparticles (Pd, Pt) with high specific surface area; therefore, the catalytic effect and large electroactive surface area leads to enhancement of sensitivity and reduction of the limits of detection.

Using LbL synthesis, one can improve the analytical characteristics of sensors. For instance, when running blood chemistry, ascorbic acid and urea are determined using the glassy carbon electrode covered with a sensitive layer of multi-walled carbon nanotubes cross-linked by PDDA and PDDA–PSS, respectively. The limit of detection was 3×10^{-7} for ascorbic acid and 8×10^{-7} mol litre^{-1} for urea at a sensitivity of about 2.53×10^{-6} A μmol^{-1} litre.[117] Here, carbon nanotubes act as conductors to provide electron transfer from reactive sites to the electrode and thus to ensure the low limits of detection, as well as to increase the electroactive surface area, which improves the sensitivity. Electrochemical sensors with multilayers fabricated on the electrode surface by LbL synthesis exhibit better characteristics than the sensors based on the same materials deposited on the electrode by, *e.g.*, the drop casting. In the latter case, the limit of detection of ascorbic

‡ It should be noted that a biological reaction may result in oxygen or hydrogen peroxide as products; therefore, the studies without specification of biochemical reactions were classified as those devoted to sensors for inorganic compounds. Since there is considerable literature on glucose sensors, these devices are considered separately.

Table 1. Compositions of multilayers prepared by LbL synthesis on electrode surfaces, measuring techniques and characteristics of electrochemical sensors for inorganic analytes.

Multilayer composition	Substrate material	Analyte	Measuring technique [a]	Sensor characteristics					Ref.
				S /A mol^{-1} litre cm^{-2}	RT /s	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
POM – PDDA	C	NO_2^-	CV (−0.4 – 0.4), AM (−0.22)	4×10^{-3} (see [b])	⩽6	55	–	–	68
Graphene/cobalt phthalocyanine – PDDA	GCE	NO_2^-	CV (0.2 – 1.4), AM (0.8)	–	5	–	$(0.1 – 1) \times 10^{-3}$, $(2 – 36) \times 10^{-6}$	8.4×10^{-8}	69
SWNT – OPPy	GCE	NO_2^-	CV (−0.2 – 0.5), AM (−0.77)	–	–	–	–	–	70
Haemoglobin – Fe_3O_4	Pt	NO_2^-	AM (−0.7)	–	–	–	$1.5 \times 10^{-6} – 0.12 \times 10^{-3}$	0.29×10^{-6}	71
		H_2O_2	AM (−0.4)	–	–	–	$0.125 \times 10^{-6} – 0.16 \times 10^{-3}$	3.0×10^{-8}	
POM – PAH – PAA	Au	NO_2^-	CV (−0.2 – 0.4)	5×10^{-4}	–	–	$(0.5 – 70) \times 10^{-3}$	–	72
		ClO_3^-		1.5×10^{-4}	–	–	$(0.9 – 100) \times 10^{-3}$	–	
		$S_2O_8^{2-}$		4.32×10^{-2}	–	–	$(0.05 – 0.8) \times 10^{-3}$	–	
Urease, arginase – PDDA – PSS	Au	NH_3	EIS	–	–	–	–	–	73
Pd nanoparticles – graphene – TMAC	Au	H_2O, NO_2, H_2	CV (−0.4 – 1.4), AM (0.066)	–	–	–	–	–	74
Au nanoparticles – PDDA	GCE	As(III)	CV (0.1 – 0.6)	–	–	–	–	0.48×10^{-6}	75
POM – porphyrins	ITO	ClO_2^-	CV (0.2 – 1.2), AM(0.95)	1.6×10^{-1} (see [b])	–	–	–	13.8×10^{-6}	76
POM – PDDA	C	H_2O_2	CV (0.0 – 0.4)	–	–	–	–	–	77
Naphthol green B – LDH	GCE	H_2O_2	CV (0.2 – 0.6), AM(0.38)	–	–	14	$8 \times 10^{-6} – 1.8 \times 10^{-4}$	0.9×10^{-6}	78
LDH	ITO	H_2O_2	CV (−0.2 – 0.8)	–	–	20	$4.9 \times 10^{-7} – 2.4 \times 10^{-4}$	–	79
Au nanoparticles – thionine	Au	H_2O_2	CV (−0.35 – 0.1), AM (−0.18)	22.8×10^{-3}	–	–	$6.0 \times 10^{-6} – 1.1 \times 10^{-3}$	5.8×10^{-6}	80
Copper hexacyanoferrate	(F-Sn) oxide	H_2O_2	CV (0.0 – 1.2), AM (0.0 V)	3×10^{-2}	–	–	–	–	81
MWNT – polythionine – iron oxide	GCE	H_2O_2	CV (−0.6 – 0.3), AM (−0.5)	2.74×10^{-3}	–	–	$(0.099 – 6.54) \times 10^{-3}$	0.0536×10^{-3}	82
Cobalt tetrasulfophthalocyanine – PDDA	Au	H_2O_2	CV (−0.2 – 0.5)	–	–	14	$(1 – 20) \times 10^{-6}$	0.4×10^{-6}	83
Haemoglobin – CdS nanoparticles – chitosan	GCE	H_2O_2	CV (−0.9 – 0.3), AM (−0.4)	–	–	–	$0.125 \times 10^{-6} – 1.20 \times 10^{-3}$	0.083×10^{-6}	84
Iron phthalocyanine complex – PABS – MSWNT	Au	H_2O_2	CV (−0.1 – 0.6)	0.87×10^{-3} (see [b])	–	–	–	5.5×10^{-4}	85
MnO_2 – PDDA – PAS	GCE	H_2O_2	AM (0.25; 0.45)	0.377	–	–	$4.5 \times 10^{-8} – 1.0 \times 10^{-4}$	2.2×10^{-8}	86
Prussian blue nanoparticles – PAH	Glass	H_2O_2	AM (0.2)	–	–	–	–	–	87
TiO_2 – PAH	PGE	H_2O_2	CV (−0.2 – 0.6)	–	–	–	–	–	88
TiN – 1-(3-aminopropyl)-3-methylimidazolium bromide	GCE	H_2O_2	CV (−0.8 – 0.5), AM (−0.35)	3.80×10^{-1}	–	–	$1.0 \times 10^{-6} – 2.1 \times 10^{-3}$	–	89
GOX – PDDA	GCE	H_2O_2	CV (−0.05 – 0.5), AM (0.2)	–	–	–	$(0.1 – 0.8) \times 10^{-3}$	–	90

Table 1 (contitued).

Multilayer composition	Substrate material	Analyte	Measuring technique [a]	Sensor characteristics					Ref.
				S /A mol^{-1} litre cm^{-2}	RT /s	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
Mesoporous carbon SMK-3	GCE	H_2O_2	CV (−1.0 – 0.3)	–	–	30	$(1.2-57)\times10^{-6}$	0.6×10^{-6}	91
Myoglobin – PSS	GE	H_2O_2	CV (−0.6 – 0.2)	0.62	–	–	$(1-70)\times10^{-6}$	–	92
Myoglobin – PDDA	PGE	H_2O_2	CV (−0.8 – 0.2), AM(−0.1)	1.606×10^{-3}	–	–	$(10-130)\times10^{-6}$	5×10^{-6}	93
Haemoglobin – PAH, PSS, PS	GCE	H_2O_2	CV (−0.8 – 0.2)	4.3×10^{-1}	–	–	$2.5\times10^{-6}-1.2\times10^{-4}$	2.1×10^{-7}	94
Haemoglobin – PDDA – mesoporous aluminum	GCE	H_2O_2	CV (−0.7 – 0.1), AM (−0.3)	–	–	15	$1.0\times10^{-6}-1.86\times10^{-4}$	10^{-7}	95
Prussian blue – PDDA	ITO	H_2O_2	CV (−0.2 – 1.0), AM(−0.1)	–	–	–	$(0.5-3.5)\times10^{-3}$	0.1×10^{-3}	96
Au nanoparticles	GCE	H_2O_2	CV (−0.5 – 0.8)	$(6.339\pm0.156)\times10^{-2}$ (see [b])	–	–	$5.0\times10^{-6}-1.0771\times10^{-3}$	–	97
			AM (−0.3)	$(2.452\pm0.230)\times10^{-2}$ (see [b])	–	–	$1.4745\times10^{-3}-2.5362\times10^{-2}$	–	
Au nanoparticles – chitosan – MWNT	GCE	H_2O_2	AM (−0.2)	9.221×10^{-2}	–	–	$1.5\times10^{-6}-5.1\times10^{-4}$	9.0×10^{-8}	98
Au nanoparticles – polyviologen	Au	H_2O_2	CV (−0.6 to −0.31)	0.48	–	–	to 35×10^{-3}	10^{-6}	99
Cyt c – Au nanoparticles – ionic liquid – MWNT	GCE	H_2O_2	AM (−0.2)	–	–	–	$5.0\times10^{-5}-1.15\times10^{-3}$	3.0×10^{-6}	100
Cyt c – Au nanoparticles	ITO	H_2O_2	AM (−0.1)	–	–	–	$(0.1-0.4)\times10^{-3}$	0.5×10^{-6}	101
HRP – titanate nanolayers	GCE	H_2O_2	CV(−0.8 – 0.2)	0.78	–	–	$2.1\times10^{-6}-1.85\times10^{-4}$	0.7×10^{-6}	102
Haemoglobin – Fe_3O_4 – chitosan	ITO	H_2O_2	CV (−0.9 – 0.3)	–	–	–	$(0.77-160)\times10^{-6}$	–	103
Haemoglobin – nano-crystalline diamonds	GCE	H_2O_2	AM (−0.3)	–	–	–	$0.5\times10^{-6}-0.25\times10^{-3}$	0.4×10^{-6}	104
Au nanoparticles – PDDA – MWNT	GCE	O_2	CV (−0.4 – 1.4)	–	–	–	–	–	105
Pt nanoparticles	SWNT	CO_2	CV [c]	–	–	–	0 – 1	–	106
Cyt c – laccase – mercapto-undecanoic acid, polyaspartic acid	Au	O_2	CV (−0.35 – 0.3)	–	–	–	–	–	107
MWNT – PEI	C	O_2	CV (−0.5 – 1.0)	–	–	–	–	–	179
β-Cyclodextrin – Au nano-particles	Au	O_2	AM (−0.15)	–	–	60	0.2 – 6.5 (see [d])	0.05 (see [d])	109
Au nanoparticles	GCE	O_2	CV (−0.3 – 0.6)	–	–	–	–	–	110
FeTsPc – FeT4MPyP	GCE	O_2	AM (−0.15)	2.065×10^{-5} (see [e])	–	10 [f]	0.2 – 6.4 (see [d])	0.06 (see [d])	111

Table 1 (contitued).

Multilayer composition	Substrate material	Analyte	Measuring technique [a]	Sensor characteristics					Ref.
				S /A mol^{-1} litre cm^{-2}	RT /s	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
POM – PDDA	C	See [g]	Potentiometry, CV (−1 – 0), reproducibility, 3 mV	69 ± 2 (see [h])	⩾7	⩾90	–	10^{-14}	112
POM – PDDA	C	See [g]	CV (−1.2 – 0.2)	72.1 ± 0.4 (see [h])	–	–	–	–	113
SWNT – PDDA	Au, Cr	See [g]	Conductometry (pH)		–	–	0 – 9 (see [i])	–	204

Note. Notations are as follows: S stands for sensitivity, RT stands for response time, STB stands for stability, LR stands for linear range, LOD stands for limit of detection, POM stands for polyoxometalates, GCE stands for glassy carbon electrode, EIS stands for electrochemical impedance spectroscopy, SWNT stands for single-walled carbon nanotubes, OPPy stands for overoxidized polypyrrole, PAH stands for polycyclic aromatic hydrocarbons, PAA stands for polyacrylamide, TMAC stands for *N*-[(trimethoxysilyl)propyl]-*N*,*N*,*N*-trimethylammonium chloride, LDH stands for layered double hydroxide, MWNT stands for multi-walled carbon nanotubes, PABS stands for poly(acrylonitrile butadiene styrene), MSWNT stands for a mixture of multi- and single-walled carbon nanotubes, PGE stands for pyrolytic graphite working electrodes, PAS stands for poly(*p*-acetoxystyrene), GOX stands for glucose oxidase, SMK-3 is a type of mesoporous carbon, GE stands for graphite electrode, PS stands for polystyrene, Cyt c stands for Cytochrome C, HRP stands for horseradish peroxidase, FeTs stands for iron(II) tetrasulfonated phthalocyanine and FeT4MPy stands for iron(III) tetrakis(*N*-methylpyridyl)porphyrin.

[a] Here and in Tables 2 – 4, numbers in parentheses denote the potential measuring range (for CV) and the fixed potential (for AM) in Volts.

[b] The dimensionality is A mol^{-1} litre.

[c] The potential response of the circuit is 0.2 V.

[d] The dimensionality is mg litre^{-1}.

[e] The dimensionality is A mg^{-1} litre cm^{-2}.

[f] Number of measurements.

[g] Determination of pH.

[h] The dimensionality is mV (pH)$^{-1}$.

[i] In pH units.

Table 2. Compositions of multilayers prepared by LbL synthesis on electrode surfaces, measuring techniques and characteristics of electrochemical sensors for organic analytes.

Multilayer composition	Substrate material	Analyte	Measuring technique /V	Sensor characteristics			Ref.
				S /A mol^{-1} litre	LR /mol litre^{-1}	LOD /mol litre^{-1}	
Prussian blue – CMC – PAH – PANI	Au	Ascorbic acid	CV (0.0 – 0.5)	–	$(0-50)\times10^{-3}$	10^{-3}	114
MWNT – PDDA	C	The same	CV (-0.1 – 0.4), AM (0.2)	3×10^{-7}	5×10^{-10} – 7×10^{-8}	–	115
Naphthol green B – LDH	ITO	"	CV (0.2 – 0.8)	–	$(1.2-55.2)\times10^{-6}$	0.51×10^{-6}	116
SWNT – CO – PPy	GCE	"	CV (nitrite, 0.0 – 1.2),	–	2×10^{-5} – 10^{-3}	4.6×10^{-6}	70
		Dopamine	CV (-0.2 – 0.5),	–	1×10^{-6} – 5×10^{-5}	3.8×10^{-7}	
		Uric acid	AM (nitrite, 0.77)	–	2×10^{-6} – 10^{-4}	7.4×10^{-7}	
MWNT – PDDA – PSS	C	Ascorbic acid	CV (-0.2 – 0.5), AM (0.1)	2.27	5×10^{-5} – 10^{-3}	3×10^{-7}	117
		Dopamine	AM (0.25)	1.237×10^{-1}	$(50-350)\times10^{-6}$	1.5×10^{-7}	
		Uric acid	AM (0.35)	2.53	$(50-800)\times10^{-6}$	8×10^{-7}	
Au nanoparticles – PVA – Os	GCE	Ascorbic acid	CV (-0.2 – 0.5)	–	$(0.1-4.5)\times10^{-3}$	–	118
Phytase – PAH – ITO (see [a])		Phthalic acid	CV (-0.1 – 0.9), AM (0.6)	–	$(0.5-2)\times10^{-3}$	0.19×10^{-3}	119
$Ni(OH)_2$ – $Co(OH)_2$	ITO	Urea	CV (-0.2 – 0.7), AM (0.4)	3.2×10^{-3} (see [b])	–	–	120
Urease – chitosan – PANI	C	pH	Potentiometry	53 (see [c])	4 – 8 (see [d])	–	121
		Urea		70 (see [e])	10^{-4} – 10^{-1}		
Mesoporous SiO_2 – PDDA	GCE	Nitroaromatics	VA (-1.0 to -0.1)	–	10^{-9} – 10^{-7}	10^{-9}	122
Pd nanoparticles – PANI (see [a])	GCE	Hydrazine	CV(-0.5 – 0.5)	–	3.0×10^{-7} – 3.5×10^{-4}, 5.0×10^{-4} – 1.2×10^{-2}	5.0×10^{-8}	123
Pd nanoparticles – PANI	GCE	"	CV (-0.8 – 0), AM (-0.32, -0.2, 0.2)	5.4×10^{-2}	40×10^{-6} – 10^{-3}	0.42×10^{-6}	124
GOX – HRP – PAH – PSS	GCE	Pyrocatechol	AM	76.82×10^{-3}	$(6-60)\times10^{-6}$	0.9×10^{-6}	125
		p-Phenylenediamine		1.6×10^{-3}	$(0.6-68.4)\times10^{-6}$	0.35×10^{-6}	
		o-Phenylenediamine		1.30×10^{-2}	$(0.8-46.8)\times10^{-6}$	0.28×10^{-6}	
		m-Phenylenediamine		8.17×10^{-2}	$(8.5-42.5)\times10^{-6}$	1.76×10^{-6}	
		Aniline		1.29×10^{-2}	$(10.5-73.5)\times10^{-6}$	1.97×10^{-6}	
GOX – PDDA – S/graphene oxide	ITO	Organic amines	CV (0.2 – 1.3)	–	5.0×10^{-7} – 5.0×10^{-4}	10^{-9}	126
Pt nanoparticles – PAMAM	ITO	Methanol	CV (0 – 1.2)	–	–	–	127
Tyrosinase – nanozeolite – PDDA	ITO	Phenol	AM (-0.2)	–	1.0×10^{-8} – 1.8×10^{-5}	0.5×10^{-9}	128

Note. Notations are as follows: CMC stands for carboxymethylcellulose, PVA stands for polyvinyl alcohol, VA stands for voltammetry, PANI stands for polyaniline and PAMAM stands for 4-polyamidoamine (PAMAM) dendrimer.

[a] STB is 15 days.

[b] The dimensionality is A mol^{-1} litre cm^{-2}.

[c] The dimensionality is mV (pH)$^{-1}$.

[d] In pH units.

[e] The dimensionality is mV (pU)$^{-1}$; pU is the urea concentration exponent.

acid on a graphene oxide-modified glassy carbon electrode was 6.45×10^{-6} mol litre^{-1} (Ref. 231) while the limit of detection of urea on chemically synthesized, urease-modified ZnO nanorods was 10^{-5} mol litre^{-1}.[232]

VII. Sensors for biologically active substances and glucose

High intensity of modern research (first of all, in the field of medical diagnosis) using electrochemical biosensors can be explained by their advantages over other methods. These are:

— relatively high selectivity achieved by 'tuning' the composition of the sensitive layer to a particular analyte;

— no sample preparation step;

— the possibility of operation with minimum volumes of biological liquids; and

— low cost; this allows biosensors to be used in screening tests for the most common diseases.

The development of electrochemical biosensors imposes strict requirements on the nanomaterials to be used as electrode components; the most important of them include no denaturation of biomolecules upon immobilization on the electrode surface, inertness in the reactions with analytes and stability with time. Usually, such materials include noble metal (Au, Pt) nanoparticles,[129–132,135,138,143,145,166,171,177,185] carbon nanotubes,[132,138,141,144,146–148,162,167,171,177,185] or, more rarely, transition-metal oxides and sulfides.[133]

The sensitive layer of sensors for biologically active substances may contain bioselectors that can vary depending on the type of biological or biochemical interaction responsible for the generation of the analytical signal. In particular, the detection of DNA is based on complementary interaction with oligonucleotides, aptamers,[129,135–138,173] while immunoassay is based on gene–antigen interaction;[142,144–149,155,184,185] both the direct reaction and inhibition of the enzyme reaction are utilized in enzyme assay. No information on bacterial and tissue sensors fabricated by LbL synthesis are available; clearly, this is due to inaccessibility of these systems to the approach in question.

Biological assays considered in this review are carried out to timely diagnose various diseases including cancer as well as viral and infectious diseases. Most analytes are determined in blood. In particular, dopamine is determined to diagnose schizophrenia and Parkinson's disease. The determination of dopamine using an ITO electrode covered with a layer comprised of poly(acrylic acid) and CeO_2 nanoparticles was characterized by a limit of detection of 10^{-8} mol litre^{-1} and an improved sensitivity of 2.292 μA μmol^{-1} litre (Table 3). In a similar study using electrochemical sensors based on Au–Pt nanoparticles prepared by pulsed laser ablation the limit of detection reduced to 6×10^{-8} mol litre^{-1} only. Pyrocatechol is detected in order to determine the amount of cholesterol and to control the formation of pyrocatecholamines, which prevent the development of various genetic diseases and neoplasms. The limit of detection of pyrocatechol in biological samples obtained using electrochemical sensors with an ITO electrode modified with layers of lutetitum bis(phthalocyanine) and polycyclic aromatic hydrocarbons fabricated by LbL synthesis (two deposition cycles) was 3.75×10^{-7} mol litre^{-1} at a sensitivity of 2.0×10^{-8} A μmol^{-1} litre. An electrochemical sensor based on nanoporous gold was prepared by etching Au–Si alloy; it is characterized by a limit of detection of 5×10^{-7} mol litre^{-1}.[233] The determination of alpha-1-fetoprotein is aimed at identifying liver diseases (cirrhosis, hepatitis) and monitoring pregnancy. The lowest concentration of alpha-1-fetoprotein determined using an Au electrode modified with Pt nanoparticles, Prussian blue, chitosan and MWNT (LbL synthesis, 10 deposition cycles) was ~0.08 ng ml^{-1} at a sensitivity of 1.53 μA ng^{-1} ml. Determination of alpha-1-fetoprotein on the electrodes modified with Au–Fe_3O_4 heterostructures fabricated by thermal decomposition reduced the limit of detection to 2.3 pg ml^{-1}.[234]

In recent decades, oncological diseases have been an important reason for increased number of deaths worldwide, namely, the annual number of deaths from cancers exceeds 50% of the number of the newly discovered cases.[235] The frequency of cancer doubled between 1975 and 2000; also, a total of 12% of deaths were due to cancer in 2000. Often, relevant early diagnosis, prompt laboratory monitoring of cancer treatment efficacy and forecast for the development of the disease, based on quantitative laboratory parameters are impossible. In spite of high research activity in the field, there has been insufficient progress; in particular, biomarkers for various types of cancer are not widely used.[236,237] A diagnostic perspective is associated with the use of circulating DNA that can be found in human plasma (blood serum) as cancer biomarker. Analyses of DNA are aimed to identify various viruses, as well as oncological and genetic diseases. The limits of detection of DNA can be as low as 0.6 fmol litre^{-1}. It should be noted that all sensors for biological analytes are characterized by short-term stability and high performance.

The diagnosis of cancer is based on the use of electrochemical sensors whose analytical signal is generated owing to antibody–antigen interaction. For instance, carcinoembryonic antigen is determined to identify lung cancer and cancers of other internal organs. The limit of detection of this antigen using an Au electrode modified with layers of Au nanoparticles, multi-walled carbon nanotubes, chitosan and thionine, was 0.01 ng ml^{-1} at a sensitivity of ~4.69 μA ng^{-1} ml. This electrochemical sensor is second to a sensor based on nanoporous gold and graphene structures for which the limit of detection was 3.5×10^{-13} mol litre^{-1}.[238]

The analytical characteristics of sensors for the determination of biologically active compounds fabricated by other methods are at least competitive with the sensors fabricated by LbL synthesis. This can be explained by complexity of LbL immobilization of bioselectors. The authors of most studies considered below used LbL synthesis to fabricate layers of nanostructures and binders; only one sensitive layer was deposited.

A wide practical application of glucose sensors is due to the fact that recently, diabetes has been a progressive disease. According to WHO data, nearly 350 million people worldwide have diabetes and in 2030, diabetes will rank 7th in the list of human diseases that lead to death.[239] Accurate measurements and thorough monitoring of blood glucose are of crucial importance for relevant diagnosis and treatment of diabetes. A typical blood test in a glucose meter requires a small amount of blood taken from the finger. Blood is brought to a disposable test strip under the action

Table 3. Compositions of multilayers prepared by LbL synthesis on electrode surfaces, measuring techniques and characteristics of electrochemical sensors.

Multilayer composition	Substrate material	Analyte	Measuring technique /V	Sensor characteristics				Ref.
				S /A mol^{-1} litre	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
Oligonucleotides – Au nanoparticles – PDDA	GCE	DNA	VA (0.0 – 0.7)	–	–	2.2×10^{-13} – 2.2×10^{-9}	3.20×10^{-14}	129
Au nanoparticles – mercaptopropionic acid	Au	DNA	PM	–	–	–	–	130
Au nanoparticles – GSGHs	ITO	DNA	CV (0.1 – 0.7)	–	–	10^{-11} – 5×10^{-7}	–	131
L-Lysine – Cyt c – Au nanoparticles – chitosan	GCE	DNA	VA (−0.4 – 0.0)					132
HRP – Fe_3O_4 nanoparticles – PDDA – PSS	Au	DNA	CV (−0.1 – 1.5), AM (−0.1 V), Coulometry (−0.1)	–	7	5×10^{-11} – 5×10^{-7}	7.1×10^{-12}	133
Oligonucleotides – Pt nanoparticles, C – PDDA	Au	DNA	AM (−0.1)	–	–	10^{-15} – 10^{-11}	0.6×10^{-15}	135
Oligonucleotides – Ru^{III} – PDDA	GCE	DNA	VA (0.6 – 1.2)	–	–	–	–	136
Oligonucleotides – mercaptopropionic acid – zirconia	Au	DNA	CV (−0.4 to −0.1)	–	–	–	–	137
Oligonucleotides – thiol-modified MWNT – Au nanoparticles	Au	DNA	CV (−0.2 to −0.6)	–	–	5×10^{-10} – 1.0×10^{-11}	6.2×10^{-12}	138
Choline oxidase – MnO_2 – PDDA – PAS	GCE	Choline	AM (0.25; 0.45)	$(59\pm3)\times10^{-3}$ (see [a])	–	3.0×10^{-7} – 1.0×10^{-4}	300×10^{-9}	86
Choline oxidase – PEI – PDDA (see [b])	Pt	"	AM (0.6)	3.79×10^{-3}, 9.04×10^{-3}	–	5×10^{-7} – 1.0×10^{-3}	0.5×10^{-6}	13
Choline oxidase – 6-*O*-ethoxytrimethylaminochitosan – Prussian blue (see [c])	Pt	"	AM (0.0)	8.86×10^{-2} (see [a])	60	5×10^{-7} – 1.0×10^{-4}	5×10^{-7}	140
MWNT – PDDA	GCE	Thiocholine	AM (0.3)	–	–	1.5×10^{-6} – 7.5×10^{-5}	7.5×10^{-7}	141
Integrin β1 (antigen) – chitosan	GCE	*E. coli*	EIS	252.1 (see [d])	–	1.0×10^{4} – 2.0×10^{6} (see [e])	3.5×10^{3} (see [e])	142
Thionine – chitosan – Au nanoparticles – MWNT	SiO_2	*E. coli*	CV (−0.6 – 0.2)	–	–	–	250 (see [e])	148
Au nanoparticles – MWNT – chitosan – thionine	Au	CEA	CV (−0.6 – 0.2)	–	91	0.5 – 15.0 (see [f]); 15.0 – 200.0 (see [f])	0.01 (see [f])	144
Au nanoparticles – TiO_2 nanoparticles – thionine	Au	CEA	CV (−0.4 – 0.2)	–	60	1.0 – 80.0 (see [f]); 0.2 – 80.0 (see [f])	0.20 (see [f]); 0.07 (see [f])	145
Antigen – MWNT – PDDA – PSS	GCE	CEA	CV (−0.2 – 0.6)	4.69×10^{-6}, 0.51×10^{-6} (see [g])	30	0.1 – 2.0 (see [f]), 2.0 – 160 (see [f])	0.06 (see [f])	146
Antigen – alkaline phosphatase – SWNT – PDDA	GCE	CEA	CV (−0.3 – 0.3)	–	–	$(0.1-1000)\times10^{-3}$ (see [f])	0.04×10^{-3} (see [f])	147
Antigen – Prussian blue – MSWNT – PEI – chitosan	Au	CEA	CV (−0.1 – 0.4)	–	–	0.5 – 2.0 (see [f])	0.08 (see [f])	148

Table 3 (continued).

Multilayer composition	Substrate material	Analyte	Measuring technique /V	Sensor characteristics				Ref.
				S /A mol^{-1} litre	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
Antibodies – Au nanoparticles – tris(2,2′-bipyridyl)cobalt(III) – Nafion	Pt	Hepatitis B	CV (−0.3 – 0.7), AM (−0.35)	–	–	0.05 – 4.5 (see [h])	0.015 (see [h])	149
β-Cyclodextrin – MWNT – chitosan	GCE	Dopamine	CV (−0.1 – 0.5)	2.313	30	$(0.1 – 25) \times 10^{-6}$	0.06×10^{-6}	132
Carbon nanoparticles – (TDA) – SiCl	ITO	"	CV (−0.2 – 0.7), AM (0.45)	2.51 (see [a])	10	$(0.4 – 6) \times 10^{-6}$	0.135×10^{-6}	151
GOX – PADA	GCE	"	CV (−0.2 – 0.6)	2.292, 8.32×10^{-1}	20	$(1 – 60) \times 10^{-6}$, $(1 – 120) \times 10^{-6}$	0.02×10^{-6}, 0.27×10^{-6}	152
Poly(acrylic acid) – CeO_2 nanoparticles	ITO	"	AM (0.585)	–	–	$(4 – 16) \times 10^{-6}$	10^{-8}	153
Polyaniline – phthalocyanine (Fe, Ni, Cu)	ITO	"	CV (−0.8 – 0.4)	–	–	–	–	154
Antibodies – MWNT – PDDA	Au, Cr	MV	CV (−0.5 – 0.5), IMP	–	–	–	–	155
HRP – haemoglobin – LDH	ITO	Pyrocatechol	CV (−0.8 – 1.0)	–	–	6.0×10^{-6}–1.7×10^{-4}	5×10^{-6}	156
Lutetium(III) bis(phthalo cyanine) – PAH	ITO	"	CV (−0.5 – 1.2), AM (0.3)	2×10^{-2}	–	$(0 – 900) \times 10^{-6}$	3.75×10^{-7}	157
Concanavalin A – HRP	Au	"	AM (−0.05)	1.6	–	$(6.0 – 48) \times 10^{-6}$	0.6×10^{-6}	158
HRP – PAH	Au	"	AM (−0.05)	4.89×10^{-2}	–	$(6.0 – 120) \times 10^{-6}$	0.7×10^{-6}	159
Cl-Pyrocatechol – PAMAM	Au	"	EIS	–	–	–	–	160
Methylene blue – Au nanoparticles – thiourea	GCE	CG	CV (−0.7 – 0.2)	–	60	–	0.3 IU ml^{-1}	161
Pt nanoparticles – Prussian blue – MWNT – chitosan	Au	Alpha-1-fetoprotein	CV (−0.1 – 0.6)	1.53×10^{-6} (see [g]), 0.11×10^{-6} (see [g])	15	0.1 – 15 (see [f]), 15 – 200 (see [f])	0.08 (see [f])	162
CdS nanoparticles – poly(Congo red)	GCE	"	CV (−0.7 – 0.1), AM (−0.3)	–	30	0.30 – 250 (see [f])	0.12 (see [f])	163
Ferrocenemethanol – PANI	C	"	CV (0.0 – 0.5) AM (0.025)	–	15	5 – 20 (see [f]); 20 – 150 (see [f])	2 (see [f])	164
Au nanoparticles – thionine – Nafion	Au	"	CV (−0.6 – 0.2)	–		1 – 250 (see [f])	0.56 (see [f])	165
Glutamate dehydrogenase – Pt nanoparticles – PAMAM (see [i])	GCE	GA	CV (−0.6 – 0.6) AM (0.2)	–	28	$(0.2 – 250) \times 10^{-6}$	10^{-8}	166
MWNT – sulfonylated PDDA (see [i])	GCE	Cysteine	CV (0 – 1.1), AM (0.8)	2.78×10^{-9} 1.38×10^{-8}	10 –	20×10^{-6} – 1.3×10^{-3} 230×10^{-6}	– 0.3×10^{-6}	167
HRP – PSS, PAH	Au	"	CV (−0.4 – 0.6) AM (−0.15)	–	60	$(0.1 – 23.5) \times 10^{-6}$	0.02×10^{-6}	168
β-Lactamase – hematein – MWNT – chitosan	GCE	Penicillin	CV (−0.4 – 0.6) AM (0.2)	–	–	9.3×10^{-6} – 1.0×10^{-3} $(1.0 – 2.6) \times 10^{-3}$	50×10^{-9}	169

Table 3 (continued).

Multilayer composition	Substrate material	Analyte	Measuring technique /V	Sensor characteristics				Ref.
				S /A mol^{-1} litre	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
DNA aptamer – MWNT	ITO	Thrombin Lysozyme	CV (0.0 – 0.7)	–	24 21	0.3 – 165 (see [f]) $0.2 - 1.66 \times 10^{-3}$	0.14 (see [f]) 0.17 (see [f])	170
Toluidine blue – graphene – Au nanoparticles	GCE	Thrombin	CV (-0.6 – 0.2)	–	–	$(0.001 - 80) \times 10^{-9}$	0.33×10^{-12}	171
Thrombin aptamer – Au nanoparticles – thionine – Nafion	Au	"	CV (-0.5 – 0.0)	–	–	$(0.12 - 0.48) \times 10^{-9}$	0.04×10^{-9}	172
Acetylcholin esterase – SWNT – PDDA	GCE	Carbaryl	CV (-0.2 – 1)	–	–	from 10^{-7} (see [k])	10^{-9} (see [k])	173
Hemin – MWNT – PADA (see [j])	GCE	L-Tyrosine	CV (0.0 – 1.0), AM (0.8)	3.1×10^{-1} (see [a])	–	$(0.1 - 28.8) \times 10^{-6}$	0.01×10^{-6}	174
MWNT – PDDA – PSS	C	Acetaminophen	CV (-0.1 – 0.7), AM (0.3)	3.35×10^{-6}	21	–	5.0×10^{-7}	175
Cholesterol esterase – MWNT – PDDA	C	Cholesterol	CV (-0.8 – 0.2) AM (-0.4)	1.365×10^{-4}	21	$(0.2 - 1) \times 10^{-3}$	30×10^{-6}	176
Cholesterol esterase – MWNT – Pt nanoparticles – chitosan – PSS	Au	"	AM (0.1)	–	–	$(0.001 - 3) \times 10^{-3}$	5×10^{-6}	177
Cholesterol esterase – Pt nanoparticles – MWNT	ITO	"	AM (0.7)	8.7×10^{-3} (see [a])	–	$(0.005 - 10) \times 10^{-3}$	0.0028×10^{-3}	178
Acetylcholin esterase – MWNT – PADA – PAMAM – Au	GCE	Carbofuran	CV (-0.2 – 0.8)	–	21	$4.8 \times 10^{-9} - 0.9 \times 10^{-7}$	4.0×10^{-9}	179
GOX – PDDA	GCE	Sildenafil	CV (-0.2 – 0.5)	–	20	$2.0 \times 10^{-8} - 5.0 \times 10^{-7}$, $5.0 \times 10^{-7} - 5.0 \times 10^{-5}$	–	180
GOX	Pt	Carbamazepine	CV (1.0 – 1.5)	–	–	$10^{-5} - 5 \times 10^{-4}$	2.75×10^{-5}	181
Glutathione reductases, glucose 6-phosphate dehydrogenase – PEI – ferrocene	GCE	NADP Glucose-6-phosphate	AM (0.5)	–	–	$(0 - 0.2) \times 10^{-3}$ $(0 - 0.16) \times 10^{-3}$	– –	182
Laccase – PEI	GCE, Pt	*p*-Phenylenediamine	CV (0.0 – 1.0)	–	–	–	–	183
Antibiotin IgG – Os – PAH	Au	Horseradish peroxidase biotin	CV (0.0 – 0.5)	–	–	–	–	184
Anti-albumin – Au nanoparticles – polytyramine	Au	Albumin	EIS	–	–	$6.8 \times 10^{-12} - 6.8 \times 10^{-3}$ (see [k])	6.8×10^{-12} (see [k])	185
MSWNT	GUME	Estradiol	CV (0.0 – 0.8)	–	–	$2.0 \times 10^{-8} - 2.0 \times 10^{-6}$ (see [k])	1.0×10^{-8} (see [k])	186

Note. Notations are as follows: GSGHs stands for mesoporous graphene/silica (nanosheets), (TDA)SiCl stands for tetradecyldimethyl[3-(trimethoxysilyl)propyl]ammonium chloride, CEA stands for carcinoembryonic antigen, MV stands for metapneumovirus, CG stands for chorionic gonadotropin, GA stands for glutamic acid, GUME stands for gold ultramicroelectrode, PADA stands for polyadamantyl acrylamide, PM stands for potentiometry and IU stands for the international unit of measurement of the amount of a substance, which is based on its biological activity.

[a] The dimensionality is A mol^{-1} litre cm^{-2}. [b] RT = 15 s. [c] RT = 10 s. [d] The dimensionality is Ω (number of cells)$^{-1}$ ml. [e] Number of cells per ml. [f] The dimensionality is ng ml^{-1}.

[g] The dimensionality is A ng^{-1} ml. [h] The dimensionality is μg ml^{-1}. [i] RT = 3 s. [j] RT = 5 s. [k] The dimensionality is mg litre^{-1}.

Table 4. Compositions of multilayers prepared by LbL synthesis on electrode surfaces, measuring techniques and characteristics of electrochemical glucose sensors.

Multilayer composition	Substrate material	Measuring technique /V	Sensor characteristics					Ref.
			S /A mol^{-1} litre cm^{-2}	RT /s	STB /days	LR /mol litre^{-1}	LOD /mol litre^{-1}	
GOX – Au nanoparticles – chitosan	Au	CV (−0.1 – 0.7), AM (0.7)	5.55×10^{-4} (see [a])	–	–	–	–	187
GOX – Au nanoparticles – PAMAM – PVAC [b]	ITO	CV (0.0 – 1.0)	$(3.36 \pm 0.02) \times 10^{-5}$	–	–	–	17×10^{-6}	188
GOX – Au nanoparticles – PAMAM – PVAC [b]	ITO	CV (−0.5 – 0.1), AM (0.0)	1.11×10^{-7}	–	–	–	1.9×10^{-6}	189, 190
Au nanoparticles	Au	CV (−0.05 – 0.55)	–	–	–	–	–	191
GOX – Au nanoparticles	Au	AM (0.4)	–	–	–	–	–	192
GOX – Au nanoparticles – polyelectrolytes	Au	CV (−0.2 – 0.8), AM (0.3)	$(1.927 \pm 0.05) \times 10^{-2}$	–	–	–	2.3×10^{-6}	193
Au nanoparticles – thionine	Au	CV (−0.35 – 0.1), AM (−0.18)	–	–	–	to 3×10^{-3}	3.5×10^{-5}	80
Copper hexacyanoferrate	(F-Sn) oxide	CV (0.0 – 1.2), AM (0.0)	0.33×10^{-6}	–	–	to 5×10^{-6}		81
GOX – CdS nanoparticles – PAMAM	Pt	CV (−1.0 – 1.0), AM (0.5)	1.83×10^{-3}	–	–	10^{-6} – 2.5×10^{-3}	10^{-6}	194
GOX – Os – PAH	Au	CV (0.1 – 0.5)	–	–	–	–	–	195
GOX – Pt nanoparticles – chitosan	GCE	CV (−0.6 to −0.2), AM (0.3)	–	–	30	1.2×10^{-6} – 2.0×10^{-3}	4.0×10^{-7}	196
GOX – HRP – Concavalin A – MWNT – pectin	Au	CV (−0.4 – 0.6), AM (−0.15)	–	–	8	2.0×10^{-6} – 1.7×10^{-4}	2.5×10^{-7}	197
GOX – MWNT – polyhistidine	GCE	AM (0.7)	$(1.94 \pm 0.03) \times 10^{-3}$ (see [a])	12	15	2.5×10^{-4} – 5.0×10^{-3}	2.2×10^{-6}	198
Polylysine – laccase – MWNT	ITO	CV (0.05 – 0.75)	–	–	–	to 30×10^{-3}	–	199
GOX – MWNT – PEI	GCE	CV (−0.7 – 0.0)	1.07×10^{-1}	–	–	to 0.3×10^{-6}	–	200
GOX – SWNT – PVA – Os	C	CV (−0.1 – 0.5), AM (0.3)	1.6×10^{-2}	–	30	$(0.5 – 6.0) \times 10^{-3}$	0.1×10^{-3}	201
SWNT – PVA – Os	C	CV (−0.1 – 0.5), AM (0.3)	3.2×10^{-2}	–	–	$(0.3 – 10) \times 10^{-3}$	0.3×10^{-3}	241
GOX – MWNT	C	AM (0.6)	3.82×10^{-2} (see [a])	–	–	5×10^{-4} – 1.5×10^{-2}	0.9×10^{-4}	202
GOX – MWNT – PANI	ITO	CV (0.0 – 0.5), AM (0.4)	3.97×10^{-3} (see [a])	–	21	$(1 – 9) \times 10^{-3}$	0.06×10^{-6}	203
SWNT – PDDA	Au, Cr	Conductometry (pH), AM (glucose, −1.0; −1.5)	2.84×10^{-2} (see [a])	–	–	$(2 – 10) \times 10^{-3}$	–	204
MWNT – PDDA	GCE	CV (−0.5 – 0.5)	–	–	21 – 28	15×10^{-6} – 6×10^{-3}	7.0×10^{-6}	205
		AM (−0.1)	–	–	–	$(15 – 120) \times 10^{-6}$		
GOX – NH_2 – MWNT – aminocystamine	Au	CV (−0.8 – 0.2), AM (−0.3)	7.46×10^{-3}	–	21	$1 – 7 \times 10^{-6}$	8×10^{-6}	206
GOX – SWNT – PDDA	Pt	CV (0.0 – 0.6), AM (0.6)	6.38×10^{-2}	–	30	50×10^{-6} – 12×10^{-3}	4×10^{-6}	207
GOX – HRP – PAH	ITO							208
GOX – HRP – thiourea	GCE	CV (−0.65 to −0.3), AM (0.3)	5.73×10^{-3}	–	–	$(50 – 600) \times 10^{-6}$	6×10^{-6}	209
GOX – HRP – cystamine	Au	CV (0.0 – 0.5), AM (0.28)	5.11×10^{-3}	4	28	$(1 – 8) \times 10^{-3}$	9×10^{-6}	210
GOX – PDDA – Nafion	GCE, Pt, C	AM (0.6)	9.6×10^{-3}	–	28	$(0.05 – 7) \times 10^{-3}$	20×10^{-6}	211
GOX – PDDA	GCE	CV (−0.05 – 0.5)	–	–	–	–	–	212
GOX – dodecylbenzenesulfonic acid	Ag	AM (−0.1)	7.2×10^{-4}	–	–	$(1 – 8) \times 10^{-3}$	1.55×10^{-4}	213
GOX – Au nanoparticles – chitosan – PANI	Pt	AM (0.6)	5.55×10^{-4} (see [a])	–	–	$(0.5 – 16) \times 10^{-3}$	7×10^{-6}	214
GOX – ZnO nanoparticles	ITO	AM (−0.2)	–	–	–	$(0.1 – 9) \times 10^{-3}$	1.94×10^{-6}	215
GOX – PEI	PGE	CV (−0.8 – 0)	7.6×10^{-1} (see [a])	–	–	$(0.5 – 8.9) \times 10^{-3}$	50×10^{-6}	216
GOX – mercaptopropionic acid – PDDA – PSS – MWNT	Au	AM (−0.2)	–	–	–	to 5×10^{-3}	58×10^{-6}	217

[a] The dimensionality is A mol^{-1} litre.

[b] PVAC stands for poly(vinylsulfonic acid).

of capillary forces. Most test strips contain glucose dehydrogenase or glucose oxidase immobilized on a printed electrode, and their operation is based on enzyme reactions.

In recent decades, there has been research activity on the development of more efficient continuous, both invasive and noninvasive, methods for the determination of glucose.[240] The enzyme-based and enzyme-free methods for the determination of glucose using electrodes whose surface is covered with multilayers (usually, noble metals and carbon allotropes) have nothing to give each other, but the enzyme-free sensors are more stable than the oxidase-based ones. Experiments with electrodes covered with multilayers comprising glucose oxidase, horseradish peroxidase, concanavalin A and multi-walled carbon nanotubes (obtained by LbL synthesis, 10 deposition cycles) revealed a decrease in the limit of detection to 2.5×10^{-7} mol litre^{-1} and an increase in sensitivity to $\sim$0.1 A mol^{-1} litre cm^{-2} (Table 4).

VIII. Conclusion

A large array of experimental data discussed in this review indicates that LbL techniques, that is, SILD, SCLD and SICLD can be efficiently used to synthesize layers on electrode surfaces. These techniques are relatively simple, reliable and cheap. They allow one to fabricate multilayers that cannot be formed on the surface of electrodes including microelectrodes using other methods. Multilayers can comprise layers of so-called hybrid compounds containing, *e.g.*, carbon nanotubes, graphene or various noble metal nanoparticles. A salient feature of the design of multilayers consists in the possibility of 'tuning' their composition and order of individual layers by varying the synthesis protocol taking into account recommendations obtained after examination of test results.

Layer-by-layer synthesis enables the formation of sensitive layers in sensors for almost all classes of analytes. Clearly, progress in this method (in particular, determination of synthesis conditions for layers of new compounds and their multilayers, development of the known synthetic procedures, and their adaptation to, *e.g.*, the formation of layers on the local surface of microelectrodes) will offer prospects for the design of novel highly sensitive and selective electrochemical sensors for a wide range of analytes. Seemingly, the most important aspect in further applications of LbL synthesis is to proceed to fabrication of operation-ready electrochemical sensors with electrodes covered with multilayers comprising, *e.g.*, a sensitive layer, a mediator, a transducer and a membrane whose thickness is preset in order to obtain a maximum sensor response. This will enable transformation of research-only activity to the development of technologies for the design of high-performance sensors within the framework of the same synthetic strategy.

It should be noted that the decisive role in the development of novel large-scale methods of synthesis of supporting electrodes will be played by a distinctive feature of LbL synthesis, namely, the possibility of carrying out the reaction simultaneously on the surface of a large number of substrates; this undoubtedly will reduce the cost of the end product.

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