People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

Ecole Nationale Polytechnic

Environmental engineering department

Master's mémoire

Advanced Electrochemical Processes used for health purposes

Presented by: **Thinhinane IGUER**

Under the directions of: Mr. N. Mameri Professor (ENP)

Publically presented and defended in (17/July /2017)

Jury :

President	Mr H.GRIB,	Professor (ENP)
Examinator	Mr Derouiche,	Professor (ENP)

ENP 2017

People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

Ecole Nationale Polytechnic

Environmental engineering department

Master's mémoire

Advanced Electrochemical Processes used for health purposes

Presented by: **Thinhinane IGUER**

Under the directions of: Mr. N. Mameri Professor (ENP)

Publically presented and defended in (17/July /2017)

Jury :

President	Mr H.GRIB,	Professor (ENP)
Examinator	Mr Derouiche,	Professor (ENP)

ENP 2017

Dedications

I dedicate this modest work

To my dear parents, I can never thank you enough for everything you do for me and also for all the sacrifices and your efforts. May god keep you for me, long life to you.

To my dear sister Kahina, you are my corner of serenity, thank you!

To my twin sister Dyhia, we once shared our date of birth, today I would like to share this memory with you.

To my dear brothers Amirouche, Massinissa, Jugurtha and his wife Samia, Koussaila and Youva; you are the best!

Thanks to Karim for always being there.

To all persons who helped do this work.

To my cousin, stay always joyful!

To the whole Iguer family.

Finally, I want to dedicate this work to all the people I love.

Thinhinane

Thanks

After giving thanks to God the Almighty, I would like to thank everyone with whom I have been able to exchange for the realization of this work. In particular:

Mr Nabil Mammeri, Professor at the National Polytechnic School of Algiers, for his precious help and patience.

I would also like to thank Mr Derouiche and Mr Grib, professors at the Ecole Nationale Polytechnique, for having accepted to be a member of this honorable jury.

Finally, I would like to thank everyone who helped me in the near or far for this work.

مختصر

الرجال، من خلال أنشطتهم، قد تلوث الكوكب ومعظم هذه الملوثات لها العديد من الآثار على الصحة. وتشمل تقنيات إزالة التلوث العمليات الكهروكيميائية. وتستخدم هذه العمليات أيضا للتشخيص الطبي والعلاج. وتركز هذه الدراسة الببليوغرافية على استخدام التقنيات الكهروكيميائية لأغراض صحية. نتائج هذه الدراسة تظهر بوضوح أن هذه العمليات هي التأثيرات في إزالة التلوث والتشخيص الطبي والعلاج الطبي. وقد ساعدت هذه التقنيات، المرتبطة بتكنولوجيات النانو، على تطوير أجهزة وتقنيات وأجهزة متناهية الصغر جعلت من السهل تقييم الحالة الصحية حتى من قبل الشخص البسيط

الكلمات الدالة: الكهرباء، العمليات، الصحة، السرطان، التحليل.

Résumé

Les hommes, par leurs activités, ont pollué la planète et la plupart de ces polluants ont plusieurs répercussions sur la santé. Les nouvelles techniques de dépollution comprennent les procédés électrochimiques. Ces procédés sont également utilisés pour le diagnostic et la thérapie médicale. Cette étude bibliographique porte sur l'utilisation de techniques électrochimiques avancées dans le domaine de la santé. Les résultats de cette étude montrent clairement que ces procédés sont efficaces dans l'élimination de la pollution, le diagnostic médical et la thérapie médicale. Ces techniques, associées aux nanotechnologies, ont aidé à développer de nouveaux dispositifs, techniques et micro-appareils qui ont rendu la santé plus facile à évaluer même par les simples citoyens.

Mots clés: électrochimie, procédés, santé, cancer, analyses.

Abstract

Men, by their activities, have polluted the planet and most of these pollutants have several impacts on health. Pollution removal techniques include electrochemical processes. These processes are also used for medical diagnosis and therapy. This bibliographic study focuses on the use of electrochemical techniques for health purposes. Results of this study show clearly that these processes are effectives in pollution removal, medical diagnosis and medical therapy. These techniques, associates with nanotechnologies, helped develop new devices, techniques and micro devices that made health easier to assess even by the simple person.

Key words: electrochemistry, processes, health, cancer, analysis.

Table Of Content

TABLE OF CONTENT

Chapter 3: Electrochemical disease therapy.

LIST OF TABLES

LIST OF FIGURES

Abbreviations

AC: Alternative Current

Ach: Acetylcholine

ACV: Alternating Current Voltammetry

AdSV: Adsorptive Stripping Voltammetry

AFP: α-Fetoprotein

ALP: Alkaline Phosphatase

AMP: Adenosine Monophosphate

AOP: Advanced Oxidation Process

APE: Apurinic/Apyrimidinic Endonuclease

ATP: Adenosine Triphosphate

BDD: Boron Doped Diamond

CA: Chronoamperometry

CC: Chronocoulometry

CE: Capillary Electrophoresis

CEA: Carcinoembryonic Antigen

CES: Cranial Electrotherapy Simulation

Ch: Choline

CNT: Carbon Nanotube

CP: Chronopotentiometry

CV: Cyclic Voltammetry

DA: Dopamine

DC: Direct Current

EAOP: Electrochemical Advanced Oxidation Process

EC: Electro-Coagulation

ED: Electro Dialysis

EF: Electro Fenton

EGFR: Epidermal Growth Factor Receptor

EIS: Electrochemical Impedance Spectroscopy

EML: Essential Medicine List

EP: Epinephrine

EW: Electrolyzed Water

GDE: Gas Diffusion Electrode

Glu: Glutamate

GST: Glutathione-S-transferase

HAAs: Halo Acetic Acids

HP: Hydrogen Peroxide

HPL: Human Plancal Lactogen

IDDS: Implantable Drug Delivery System

LDH: Lactate Dehydrogenase

LOD: Limit of Detection

LP: Linear Probe

LSV: Linear Sweep Voltammetry

MDM: Murine Double Minute

MDR: Multidrug Resistance

MIPs: Molecularly Imprinted Polymers

MMP: Matrix Metallopeptidase

MPs: Magnetic Particles

NA: Nucleic Acid

NAD: Nicotinamide Adenine Dinucleotide

NE: Norepinephrine

PED: Paper-based Electrochemical Device

PGE: Pencil Graphite Electrode

PNAs: Peptide Nucleic Acids

PSA: Prostate-Specific Antigen

ROS: Reactive Oxygen Species

SCCA: Squamous Cell Carcinoma Antigen

SELEX: Systematic Evolution of Ligands by Exponential Enrichment

THM: Trihalomethanes

UA: Uric Acid

Introduction

Introduction

Men's activities have a significant effect to the environment. Most of them led to its degradation that has grown to the point that the health of many people and of ecosystems is seriously threatened. In 2012, 23% of all deaths were attributable to the environment (Prüss-Üstün et al, 2016). So to protect both environment and public health, these contaminants must be removed. Although several water, wastewater and soil treatment technologies are available and have been applied for a long period, most of these technologies consume huge amount of energy. To overcome this problem, new technologies that utilize the concepts of electrochemistry were developed. Electrochemistry for health concerns doesn't stop to the pollution removal. Indeed it is also widely used in medicine. The detection of clinically relevant molecules, including small molecules, nucleic acids, and proteins, is fundamental to understanding their biological and physiological functions and to developing clinical diagnostics. Many electrochemical based devices and techniques were developed for rapid and effective detection of those molecules for diagnosis sakes.

One death every 40 seconds is due to suicide and for every six deaths, one is due to cancer. So electrochemistry was also used for therapeutic techniques and purposes. It was, in fact, used to develop new techniques such as targeting techniques for cancer therapy and other disorders like depression.

This is a large and rapidly advancing field, and this work attempts to provide a comprehensive coverage of the last few years of progress of the various uses of advanced electrochemical processes in health.

This work is subdivided to three major chapters:

- ✓ The first chapter concerns electrochemical processes used for pollution removal;
- ✓ The second chapter concerns electrochemical techniques used for medical analysis and diagnosis purposes;
- ✓ And the last chapter concerns electrochemical techniques used for therapeutic purposes.

Chapter I

Preventing disease through healthy environments

1. Introduction:

The voluntary or involuntary contributions of men's activities to the environment led to its degradation that has grown to the point that the health of many people and of ecosystems is seriously threatened. A simple view of the substances involved in the pollution arena allows one to note that most of them can normally be subject to either an oxidation or a reduction (Souza et al, 2016). In 2012, 12.6 million deaths globally, representing 23% of all deaths, were attributable to the environment. When accounting for both death and disability, the fraction of the global burden of disease due to the environment is 22%. In children under five years, up to 26% of all deaths could be prevented, if environmental risks were removed. Some diseases due to environment are listed in Table1 (Prüss-Üstün et al, 2016):

Table 1: Diseases due to environmental risks

Disease	Causes	Proportion of the disease attributable to the environment
Diarrhoeal diseases	Water, sanitation, hygiene and agricultural practices	**57%**
Malaria	Environmental management to reduce vector proliferation and contact between vectors and humans	**42%**
Neonatal conditions	Air pollution, mothers' exposure to secondhand tobacco smoke, water and sanitation in birth settings	**11%**
Cancers	Air pollution, management of chemicals, radiation and workers' protection	**20%**
Unipolar depressive disorder	Occupational stress, work-life imbalance	**11%**
Cardiovascular diseases	Household and ambient air pollution, secondhand tobacco smoke, chemicals	**31%**

Likewise, many organic and inorganic compounds lose their toxicity upon oxidation or reduction. Such an electron transfer can frequently be achieved on an electrified surface (electrode); this opens a wide door for the electrochemical treatment or destruction of pollutants. Indeed, many treatment technologies are being developed for both soil and water treatment to minimize the effects of pollutants occurrence on the environment and public health (Souza et al, 2016).

2. Electrochimical processes in water and waste water treatments:

Even if most chemicals present in drinking water are of health concern only after extended exposure of years, rather than months (the principal exception is nitrate), it is important to treat those waters. For example, elevated nitrate concentrations can cause acute asphyxiation of infants (methemoglobinemia), congenital malformations and an increase in the risk of developing cancer (Wisniewski et al, 2001).

These chemicals are present as a consequence of natural occurrence (constituent) or from a variety of anthropogenic sources (contaminant). Different sources of chemicals in drinking-water are categorized like the following (World Health Organization, 2017):

- Naturally occurring chemicals (including naturally occurring algal toxins) Rocks and soils (e.g. calcium, magnesium but also arsenic and fluoride, cyanobacteria in surface water)
- Chemicals from agricultural activities (including pesticides) Application of manure, fertiliser and pesticides; intensive animal practices
- Chemicals from human settlements (including those used for public health purposes e.g. vector control) is Sewage and waste disposal, urban runoff, fuel leakage, chemicals from industrial activities such manufacturing, processing and mining
- Chemicals from water treatment and distribution Water treatment chemicals; corrosion of and leaching from, storage tanks and pipes, by-products of chemical treatment

Although several water and wastewater treatment technologies are available and have been applied for a long period, most of these water treatment technologies consume huge amount of energy from carbon-based energy sources, which are non-renewable and contribute to carbon dioxide emissions processes, promising, relatively new technologies that utilize the concepts of electrochemistry are also available such as electro coagulation (EC), electro oxidation and electro floatation… etc.

Electrochemical processes used for pollution removal in order to preserve health will be more detailed in this chapter.

2.1. Electro coagulation

Although using electricity for water treatment applications goes back to the 19th century, when EC was used for the treatment of drinking water in the United States, they were found impractical due to the high capital and electricity cost required (Chen, 2004). During the past two decades, electrochemical wastewater treatment technologies started to regain importance as an environmentally friendly option that generates minimal sludge requires no chemical additives and minimal footprint without compromising the quality of the treated water. One of the first applications of this process for environmental and health purposes was by Mameri et al in 1997 for fluoride removal from drinking water because high fluoride concentrations cause fluorisis, molting enamels…etc (mameri et al, 1997).

2.1.1. Advantages and limitations of electro coagulation

A. Advantages:

- Water treated by EC has appreciable properties: the water has an acceptable taste; it is clear, colorless and odorless;
- EC flocs are similar to chemical flocs except that EC flocs tend to be larger, contain less bound water, are acid resistant and more stable, and can thus be separated more quickly by Filtration.
- In comparison with conventional coagulation-flocculation, EC has the advantage of eliminating the smallest colloidal particles: the smaller particles have a greater probability of being coagulated due to the electric field Sets in motion.
- Since no chemicals are added, there is no chance of secondary pollution due to high concentration of chemicals as in CC/CF

B. Disadvantages

- "Sacrificial" electrodes are dissolved in the waste water as a result of their oxidation, which requires the regular replacement of these electrodes. - The use of electricity can be expensive in some places. - An impermeable oxide film can form on the cathode, which leads to a loss of efficiency of the EC unit. The EC technique requires the treated wastewater suspension to have a high conductivity.

- Regular replacement of sacrificial anode used in EC is necessary since the anode dissolves into the solution.
- Cathode passivation can occur which decreases the efficiency of the EC process
- In some areas where electricity is not abundant, the operating cost of EC can be expensive

2.1.2. Applications of electro coagulation

The use of electro coagulation EC has been widely applied successfully by various researchers for the treatment of effluents of various kinds:

- Water containing heavy metals: Heavy metals are discharged from several industries and wastewater containing heavy metals are challenging to treat as they are non-biodegradable and some metals are toxic. Heavy metals: include cadmium, chromium, zinc, lead, mercury and arsenic.

Mameri et al. (1997). Studied the removal of fluoride ions in South Algerian by bipolar electro coagulation using aluminum electrodes. They were able to reduce the fluoride concentration from 6.0 to less than 0.8 mg / L-1, thus achieving a reduction rate of about 90%. The EC was used for the removal of nitrates and phosphates, found in surface waters and soil. Electro coagulation offers the possibility of purifying the waste water from its content in heavy metals (chrome, zinc, lead...).

- Tannery and textile industry wastewater: Tannery and textile industry effluent is highly contaminated with organics, chromium and different types of dyes. Chromium on its own is a major concern as it may oxidize to Cr^{6+}, which is carcinogenic and toxic. The presence of dyes also renders the water quality very poor by preventing the passage of sun light; it is also known to be highly stable, toxic and may resist chemical and biological degradation.

Babu et al., (2007) studied the removal of chromium in a tannery and textile industry effluent by a continuous mode reactor constituted of an iron anode and an aluminum cathode; they were able to reduce the chromium concentration of 46% rate.

- Food industry wastewater: Food industry consumes larger amounts of water for each ton of product compared to other industries. Various contaminants are found in wastewater

from food industry depending on the sector but the general characteristics of wastewater are being highly biodegradable and nontoxic with high suspended solids, COD and BOD. In the case of meat processing industry, color, oil and grease are other concerns

- Paper industry wastewater: Paper industry consumes large amounts of water and the effluent is usually blackish in color and highly contaminated with lignin, COD, BOD, organics, suspended solids and arsenic.
- Refinery wastewater: Includes wastewater generated from petroleum refineries and petrochemical industries. It usually contains high level of aromatic and aliphatic hydrocarbons, chemicals, dissolved solids, BOD and COD.

El-Naas et al (2014) studies the removal of COD in a refinery waste water, they used a continuous mode mono polar electro coagulation units combined with other units with both aluminum electrodes. They obtained an elimination rate of 97% on DCO.

- Produced water: Produced water is the largest by product by volume produced from oil and gas industry. Although the composition of produced water depends on the nature of produced hydrocarbon, the geological characteristics of the field, and the method of extraction, it is usually very saline and contains various contaminants including production chemicals, dispersed and dissolved oils, dissolved gases and different minerals.

Electro coagulation has been applied as pretreatment of margins (rejects from the olive oil production industries) where the majority of phenolic compounds responsible for dark color, phytotoxicity, etc., have been polymerized.

2.2. Electro Fenton:

Advanced oxidation processes (AOPs) have proved to be a suitable alternative for rapid degradation of recalcitrant and non-biodegradable compounds in water. Among them, electrochemical advanced oxidation processes (EAOPs) have received great attention over the last decade as an effective and suitable technology for the remediation of wastewater contaminated with toxic and persistent organic pollutants. One of the most attractive EAOPs is the electro Fenton process (EF), in which H_2O_2 is formed by the two-electron reduction of dissolved O_2 at a suitable carbonaceous cathode, such as graphite, carbon felt, reticulated vitreous carbon, gas diffusion electrodes (GDE), boron-doped diamond (BDD), carbon nanotubes, activated carbon fiber, and so on. BDD electrodes are currently the most powerful and preferred anodes for electrochemical oxidation (Barhoumi et Al, 2017). In fact, EF

process is a combination of coagulation and oxidation mechanisms which simultaneously occur at electrochemical cell (Jaafarzadeh et Al, 2016).

2.2.1. Advantages and limitations

EF process can be considered ecologically friendly; simple to handle and economical since catalytic processes are involved and no chemical reagent is needed except molecular oxygen from compressed air (Trevin et al, 2003).

Even though E-Fenton process is very efficient, it has some limitation such as the demand for high electrical energy, resulting in high operating costs.

2.2.2. Applications of electro Fenten

Electro-Fenton process can be used for the treatment of wastewater effluents and landfill leachate effluents containing toxic organic pollutants such as phenol, azo dyes azobenzene methyl red, methyl orange and alizarine red used in textile industry, aniline…Etc. (Zhang et al, 2002; Zhang et al, 2005, Trevin et al, 2003, Brillas and Casado, 2002, Cerisola, Panizza and Carizola, 2009).

2.3. Electrosorption:

Electrosorption is a novel technology for removing ionic species from aqueous solutions. The basic concept of electrosorption is to force charged ions moving toward oppositely charged electrodes by imposing an electric field (Ying et al, 2002). In 1997, Mameri et al, suggested this process for fluoride removal from drinking water. (mameri et al, 1997).

The electrosorption capacity strongly depends on the surface properties of the electrode materials such as their conductivity, surface area, and pore size distribution. As typical porous materials, carbon based materials including activated carbon, carbon fibers, carbon aerogels, and carbon nanotubes are always favorites to be employed as electrosorptive electrodes due to their good conductivity, high surface area, and suitable pore size distribution. Recently, graphene has emerged as a material with interesting low-dimensional physics and potential applications have been actively pursued, such as nanoelectronics and nanocomposites (Pan et al, 2009).

2.3.1. Advantages and limitations

Because of this reversibility, electrosorption offers several advantages over other conventional technologies. Unlike ion exchange, no acids, bases, or salt solutions are required for regeneration of the surface, thereby substantially reducing the amount of secondary waste. Compared with thermal processes, such as evaporation, electrosorption consumes less energy to achieve similar results. (Ying et al, 2002). Electrosorption also does not need high-pressure pumps and membranes which are necessary for reverse osmosis and electrodialysis (Pan et al, 2008).

An example of disadvantages is that with activated carbon electrodes, the most used electrode material, several practical problems are encountered. For example, significant fractions of the activated carbon surface may be occluded in electrodes that use polymeric binders (Ying et al, 2002).

2.3.2. Applications of electrosorption

Electrosorption has been shown to be a promising technology for the removal radionuclides, metal ions, and anions such as nitrates and iodide (Ying et al, 2002). Researchers have shown good removal efficiency of metal ions by activated carbon beds (Ying et al, 2002). Mameri et al have applied this process for fluoride removal from drinking water in Algerian Sahara (Mameri et al, 1997).

2.4.Electrodialysis

Due to the shortage of drinking water and the deterioration in its quality several processes have been developed to remove the ions and impurities contained. A technology used for the ions removal is the electrodialysis, which uses an electric field gradient and ion-exchange membranes to promote the movement of ions from treated water to a suitable compartment (Enciso et al, 2017). It was used, for the first time, for the recovery of phenylalanine from an industrial waste stream (Mameri et al, 1999)

2.4.1. Advantages and limitations

The advantages of ED over other separation processes includes low energy cost, versatility in term of wide variety of feed streams that can be utilized with minimum requirement of pre-treatment, easier and low cost of maintenance and higher membrane life.

Recent development has resulted in the significant usefulness of the ED technique for producing safe drinking water and for the separation of hazardous chemicals from water (Imran Khan et al, 2016)

2.4.2. Applications of electrodialysis

The main applications of ED process are the purification of salty water, the separation and concentration of high value chemicals and for health purposes it is used in the removal of toxic effluents (Imran Khan et al, 2016). One of the most hazardous effluents present in water are heavy metals**.** In fact most heavy metals are very toxic and thus cause great health and environmental damage. The conventional techniques for metal ions abatement, such as hydroxide precipitation, or direct electro-reduction do not provide sufficient removal efficiency and as a consequence secondary treatment processes are required downstream. That's why electrodialysis is generally used in this case (Mahmoud and Hoadley, 2012).

Examples of application of this process include nitrate removal, boron elimination, desalination of brackish water, nitric acid concentration, glycerin recovery, fluoride reduction, etc (Wisniewski et al, 2001; Ibanez, 2004, Zeni et al, 2005).

2.5. Electrochemical disinfection

Pollution of natural water, which is primary resource for survival of mankind, is evidently gaining concerning scale. Vulnerability of open springs, waterfowls, natural lakes, artificial accumulations as well as natural wells (open and underground waters) is direct consequence of ever increasing pollution of environment. Besides unacceptably increased concentrations of physico-chemical constituents in raw water, new emerging problem is bacterial, i.e. microbiological water pollution. Within water treatment, process of disinfection has highly important role (P*avlović et Al*, 2014)

More than that in food industry, washing is still an essential step in the production of fresh produce to mainly remove dirt, debris and cell exudates after cutting. More than that, one of its alleged functions is to decrease the microbial load of the product, to which a disinfectant (chlorine is the most common used one) is usually added in order to improve water disinfection potential.

More than 20 years ago, Adams and co-workers (Adams et Al, 1989) already warned on the limited efficacy of chlorine to reduce the microbial load of lettuce. Even though its use

has many advantages in comparison with its potential alternatives, especially the low price but it has many drawbacks like the generation of trihalomethanes (THMs) and haloacetic acids (HAAs) (World health organization, 2017). Medical researches confirm that increased amount of chlorine in drinking water leads to increased probability for tumor development in digestive organs, and bladder and colon cancers and mutations (P*avlović et Al*, 2014)

Further works tried to find disinfectants more efficient than chlorine. But the results found so far have been unsuccessful and even though some microbial inactivation is achieved in fresh products immediately after washing with disinfectants, its overall effect tends to disappear during storage due to a faster growth of the epiphytic micro biota.

Recent studies have highlighted electrolyzed water (EW) as one of the potential substitutes. EW is a solution generated by passing a dilute salt solution, generally NaCl through an electrolytic cell, which contains free chlorine as the main microbial inactivation agent.

Many authors have summarized the advantages of EW over chlorine such as: on-site and simple production, cheap and easy-to-find raw materials (water and NaCl), low operational expenses and a lower THM generation. The latter is because EW produces several disinfectants besides chlorine; therefore it can have the same disinfection effectiveness at lower free chlorine concentrations. Furthermore, cell electrodes, especially boron-doped diamond electrodes, are able to oxidize organic matter, decreasing in this way the environmental impact of fresh produce industry wastewater discharges. Its main disadvantage is the cost of the electrolytic cell, which has however diminished in the last years due to technological improvements to the point that can be nowadays competitive (Allende et Al, 2016).

For drinking water treatment, some authors like P*avlović* used silver, which is known to destroy microorganisms even in small concentration (ppb), in electrochemical way to destroy all known water bacteriological contaminants. They proved it is efficient in water systems like water sources, traps, reservoirs, pools…etc (P*avlović et Al*, 2014).

3. Soil Electro remediation

Pollution of top and subsurface soil, as well as underneath groundwater has been one of the consequences of industrial activities and has a significant effect on people's health; electro kinetic processing has been an emerging technology offering advantages for a wide variety of pollutants being either organic or inorganic; as well as its versatility of being

applied in soil wetting conditions ranging from unsaturated to saturated; one of the main advantages of this technology is the fact that this process can be applied to low permeability soils, like clays.

Initially electro kinetics was applied for soil consolidation but it was later applied as a remediation procedure. For remediation purposes, it requires having a wetted soil in which electrodes are inserted and terminals are connected to a power source. As soon as an electric field is generated, electrode reactions take place producing protons at the anode and hydroxide at the cathode; concentration of these ions increases exponentially creating and acid front which moves from anode to cathode, and a basic front moving from cathode to anode; during its passage through the soil protons and hydroxides interact with sorbed pollutants releasing them into solution. Soluble ion transport occurs by three mechanisms: 1) Diffusion due to concentration gradients, 2) Convection due to fluid movement and 3) Migration due to the electric field.

3.1.Advantages and limitation:

A sample of initial published results (Acar et al, 1994; Hamed et al, 1991; Khan & Alam, 1994; Kim et al, 2002; Pamucku et al 1990; Pamucku & White, 1992; Reddy et al, 1999) is enough to claim that this method is highly efficient on restoration actions for clayey soils having very low heavy metal concentrations, for which regular mining procedures would result very expensive; although, for this method one of the minuses is the time required to get metal removals above 90%. Most of these studies report soil characterization providing information about: sand, clay, silt content; organic matter as well as hydraulic permeability.

In order to improve the process and get shortening of experimental times, applied efforts have covered a wide set of conditions. Some examples of reported research have addressed for modifying pH and current density (Hamed& Bhadra, 1997), chemical conditioning of electrode wells (Reed et al, 1995; Murillo-Rivera et al, 2009), cation inclusion (Colleta et al, 1997), as well as addition of complexing (Yeung et al, 1996) and lixiviant agents (Cox et al, 1996); another approach has been the inclusion of reactive barriers into the soil matrix (Cundy & Hopkinson, 2005; Ruiz et al, 2011).

4. Conclusion

As a result of this bibliographic study, it appears that the application of electro chemical processes has been very diverse, contributing to the elimination of several compounds of different origins but which are linked by their negative impacts on the environment and health.

More than that the same electrochemical reactors can often be used for a more than one purpose and these reactors are e*asy for automation*, optimization, monitoring, and control. Contrary to other techniques or processes like incineration, supercritical oxidation, wet oxidation, etc., electrochemical techniques normally do not require high temperature or pressure (*Ibanez, 2004)*.

Some of the major impediments to the commercialization of electrochemical processes include low current efficiencies and limited space-time yields (i.e., quantities of removed contaminant per unit volume and unit time), which consequently lead to high energy consumptio (Radjenovic et al, 2012).

Even if electrochemical processes have many advantages they also have some limitation such as (*Ibanez, 2004)*:

- Electrode materials that may be prone to erosion, complexation, oxidation, wearing, or inactivation.
- The production of gases from the above decomposition (hydrogen and oxygen) may form explosive mixtures.
- The best electrode materials in terms of durability and inertness frequently involve precious metals, and this increases costs.
- The cost of electricity in many areas is prohibitive. Initial capital investment may be large.

New hybrid processes were applied for more specific removal or to enhance the performance of treatment.

Chapter II

Electrochemistry in medical diagnostics

1. Introduction

Rapid progress in identifying biomarkers that are hallmarks of disease has increased demand for high-performance detection technologies. The detection of clinically relevant molecules, including small molecules, nucleic acids, and proteins, is fundamental to understanding their biological and physiological functions and to developing clinical diagnostics. These molecules carry out many biological functions, including storing and transmitting genetic information, regulating biological activities, transporting small molecules, and catalyzing reactions. Moreover, they can be used as biomarkers in the diagnosis of many diseases. Clinical analysis is no longer performed exclusively in clinical laboratories. Instead, it is routinely carried out in several settings, including hospital point-of-care settings, by caregivers in nonhospital settings, and by patients at home. Electrochemical detection systems are ideally suited for these new applications. (Labib et al, 2016)

2. Classical techniques

2.1. Electrophoresis

This technique is considered to be one of the oldest but most used electrochemical techniques. There are many kinds of electrophoresis, among them capillary electrophoresis (CE). CE was initially developed for protein analysis, so as to propose a faster method and generating fewer band deformations than conventional electrophoresis. Numerous problems related to the adsorption of proteins on silica capillaries and their solubility have initially hampered the development of the technique in the field of analysis of proteins and macromolecules in general. Progress in this area has been particularly important. Furthermore, the scope of CE has been considerably extended, in particular to the analysis of small molecules, by implementing the numerous modes of separation of this technique. Thus, the technique currently covers the field of analysis of small molecules, neutral or charged, polar or apolar, organic or inorganic, and that of biological macromolecules (Taverna et al, 2003).

2.2. Potentiometry

It is an analytical method that links an electrode potential measurement to a species activity in solution. The corresponding electrode is referred to as the indicator electrode. The indicator electrode chosen as a function of the nature of the solute to be determined is included in a galvanic chain comprising a reference electrode and one or two electrolytes.

The major advantage is that this technique allows rapid measures and the measurement doesn't change the composition of the solution and it allows simultaneous measurement of one or more parameters.

The major disadvantage of potentiometry is its (relative) lack of accuracy. The other imprecision factor is most evident with membrane electrodes. It is also related to the uncertainty about the exact value of the activity coefficients of the ions under the operating conditions of the measurement; the potential of the electrode varies according to the activity of the species, whereas it is often the concentration values that are sought (Durand, 2010).

3. New electrochemical techniques

Electrochemistry is shown to be quite compatible with micro analytical systems for biochemical assays, because of its attractive merits such as simplicity, rapidity, high sensitivity, reduced power consumption, and sample/reagent economy (Zhang et Al, 2009).

Electrochemical sensing strategies have the potential to achieve rapid, sensitive, selective, and low-cost detection of biomolecular analytes relevant to clinical diagnosis and monitoring treatment of disease. The sensing platforms have been successfully transitioned from the central lab to the point-of-care for the detection of small molecules, such as glucose and lactate, using enzymatic approaches. In contrast, detection of larger biomolecules, such as nucleic acids and proteins, requires further innovation to overcome challenging problems related to nonspecific adsorption of nontarget molecules and lack of enzyme/analyte pairs for many analytes (Labib et al, 2016).

3.1. Electrochemical sensors

Electrochemical biosensing investigates a specific biological event (e.g. Antibody–antigen binding) using a combination of biological receptor substances (antibody, enzyme, DNA, nucleic acid, etc.) and electrochemical methods of signaltransduction. Biosensors based on amperometric, potentiometric, impedimetric and capacitive transducers can be easily found (Zhang et Al, 2009).

Electrochemical nanobiosensors have attracted significant attention using nanoscale materials as electrodes or as biomolecular tracers, and have been applied in areas of disease diagnostics and detection of infectious organisms and biothreat agents. With the growth of nanotechnology new opportunities are provided for biosensors construction and for developing novel electrochemical bioassays. It has been demonstrated that carbon nanotube (CNT) can enhance the electrochemical reactivity of important biomolecules, promote the electron transfer reactions of proteins, accumulate important biomolecules and alleviate surface fouling effects. Many kinds of nanoparticles, such as metal, oxide and semiconductor nanoparticles have been employed for constructing electrochemical biosensors. The significant functions provided by nanoparticles include immobilization of biomolecules, catalysis of electrochemical reactions, enhancement of electron transfer between electrode surfaces and proteins, labeling of biomolecules and even acting as reactant (Zhang et Al, 2009).

The rapid progress of nanomedicine, especially in the field of medical diagnostics, has motivated the development of new devices and/or arrays which can be combined with biological materials for specific medical applications (Cancino et al, 2014).

3.2.Electrochemical biosensors

These analyses, microelectrodes integrated in the miniaturized devices especially micro fluidic chips, have been widely employed to conduct electrical manipulation of fluids and biochemical analytes such as DNA, proteins, cells, microorganisms, nanoparticles, and possibly single molecules in aqueous solutions. Analytical biosensors have emerged as efficient alternatives for the detection of innumerous diseases, because of their high

specificity and the convenience of detecting the electrochemical signals produced by the presence of an analyte using portable equipment (Zhang et Al, 2009; Cancino et al, 2014).

The benefits of using biosensors can be attributed to their simple preparation procedures, relatively low cost, versatility, and selectivity for quantification of various compounds of interest. Furthermore, the miniaturization of detection systems and development of disposable sensor units have also attracted considerable attention (Cancino et al, 2014).

An electrochemical biosensor is an integrated, highly selective recognition device that provides analytical information, wherein a transducer transforms the signal generated in the reaction of the analyte with a biological element such as an immobilized enzyme, antibody/antigen, plant or animal tissue, or a microorganism into an electronically measurable signal (Cancino et al, 2014, Labib et al, 2016).

Various analytes of environmental, medical, biological or pharmaceutical interest can be monitored using an electrochemical biosensor. In electrochemical biosensors, the biological material is directly immobilized on a electrode by adsorption, covalent bonding, or encapsulation within a coating layer of a permeable conductive polymer or cross-linked reagent. These diverse strategies of immobilization lead to biosensors with different architectures such as monolayer, multilayers and thin films. (Cancino et al, 2014).

3.2.1. Types of Electrochemical Biosensors

Electrochemical techniques discussed in this work can be organized into five main types, including voltammetric/amperometric, impedimetric, conductometric, potentiometric, and field-effect transistor-based biosensors. The principles behind each approach are outlined below (Zhang et Al, 2009; Labib et al, 2016).

3.2.1.1. Voltammetric/Amperometric Biosensors

These biosensors apply a potential to a working electrode versus a reference electrode and measure the current. The current arises from electrolysis by means of an electrochemical reaction at the working electrode and is limited by the mass transport rate of the reactant

molecules from the bulk solution to the electrode interface. Many techniques are use those principles such as (Labib et al, 2016):

- Linear Sweep Voltammetry (LSV): the electrode potential is varied at a constant rate throughout the scan, and the resulting current is measured.
- Alternating Current Voltammetry (ACV): during ACV an alternating potential is added to the DC potential ramp used for LSV.
- Cyclic Voltammetry (CV): it is widely used for the study of redox processes, monitoring reaction intermediates, and stability assessment of reaction products.
- Chronoamperometry (CA): In CA, the current response is studied as a function of time after a potential step, large enough to initiate a chemical reaction, is applied to an electrode
- Chronocoulometry (CC): In a CC experiment, the charge used in an oxidation or reduction reaction is measured and plotted versus to time.
- Chronopotentiometry (CP): CP is a technique in which a constant current, or a current step, is applied to the electrode and the resulting potential change is monitored over time.
- Pulse Methods: to improve the speed and sensitivity, many forms of potential modulation have been developed. Differential pulse voltammetry and square wave voltammetry are widely used.
- Preconcentration and Stripping Techniques: these techniques have the lowest detection limits of any of the commonly used electrochemical techniques. The three most commonly used preconcentration and stripping techniques include anodic stripping voltammetry (widely used for the determination of trace metals and has a detection limit of parts per trillion), cathodic stripping voltammetry (used to analyze inorganic anions and halides), and adsorptive stripping voltammetry(many organic and inorganic species can be analyzed using AdSV). Even though each technique has its own unique features, all have two steps in common. First, the target analyte in the sample solution is concentrated onto the working electrode. In the second step, the preconcentrated analyte is stripped from the electrode surface by the application of potential and measured. Potential waveforms can be used in the stripping step, such as linear sweep,

differential pulse, and square wave. The most common are the differential pulse or square wave due to their abilities to discriminate against charging current. In addition, square wave has the added advantages of rapid scan rate and enhanced sensitivity as compared to differential pulse.

3.2.1.2. Impedimetric Biosensors

Electrochemical impedance spectroscopy (EIS) determines the resistive and capacitive properties of materials upon perturbation of the system by a small amplitude sinusoidal AC excitation signal(Labib et al, 2016).

3.2.1.3. Conductometric and Capacitive Biosensors

Conductometric biosensors measure changes in the electrical conductivity of a sample solution as the composition of the solution changes during a chemical reaction. They often include enzymes whose charged products cause changes in the ionic strength of the sample solution (Labib et al, 2016).

3.2.1.4. Potentiometric Biosensors

They measure the potential of an electrochemical cell while drawing negligible current. These sensors usually contain an electrochemical cell with two reference electrodes capable of measuring the potential across an ion-selective membrane that reacts with the charged ion of interest. Biological elements such as enzymes are commonly integrated into potentiometric sensors to catalyze the reaction that forms the ion, which can be detected by the underlying electrode (Labib et al, 2016).

3.2.1.5. Field-Effect Transistor-Based Biosensors

They detect a change in source-drain channel conductivity arising from the electric field of its environment. The electrical conductance of the channel is proportional to its carrier density, and this is readily sensed via the change in the source-drain voltage−current(Labib et al, 2016).

Of all of these methods, voltammetric approaches are the most widely deployed. This type of measurement strategy has the most flexibility, and the signals that are generated are straightforward to interpret (Labib et al, 2016).

3.2.2. Biosensor Recognition Elements

Molecular recognition is central to biosensing. Initially, biosensor recognition elements were obtained from living systems. However, many recognition elements are synthetic and have been prepared in the laboratory. The recognition element plays a crucial role in the overall biosensor performance and selectivity toward a particular analyte (such as antibodies, antibody fragments, enzymes, receptors, lectins, whole cells, peptides/proteins, nucleic acids, aptamers, peptide nucleic acids, locked nucleic acids, and molecularly imprinted polymers). All the elements stated below are detailed in the following (Labib et al, 2016):

- Antibodies: frequently, sensor design makes use of antibody sandwiches, where capture antibodies are immobilized onto the surface of the sensor, while labeled reporter antibodies bind to the analyte to provide a signal.
- Antibody Fragments: for sensing applications, only the antigen-binding fragment of the antibody is required for biomolecular recognition.
- Enzymes: they are catalytic proteins with an active site that has some features similar to those of antigen-binding fragment of antibodies, that is, exquisite specificity for certain molecules, known as their substrates. Of all enzyme recognition element-based biosensors, glucose biosensors are the most widely studied and used.
- Receptors: they are transmembrane and soluble proteins that bind to specific molecules called ligands to initiate a specific cellular response
- Lectins: they represent a broad family of proteins involved in many biological processes. They generally exhibit strong binding affinities to specific carbohydrates, known as glycans. Their specific binding has been exploited in biosensor design.
- Whole Cells: generally microbial cells, in those sensors, the whole cellular machinery functions as a recognition system for the target analyte.

- Peptides/Proteins: a number of peptide- and protein-based electrochemical sensors have been described in the literature, many of which feature impressive sensitivity and selectivity.
- Nucleic Acids: in classical nucleic acid-based sensors, the biorecognition process involves noncovalent interactions between bases of complementary nucleic acid strands and is manifested by hybridization between an immobilized capture probe and a complementary target sequence. The immobilized nucleic acid could be either a stem-loop probe (SLP) or linear probe (LP)
- Aptamers: they are nucleic acid ligands that are isolated from libraries of oligo-nucleotides by an in vitro selection process called systematic evolution of ligands by exponential enrichments (SELEX). The selectivity and binding affinity of aptamers can be similar to those of the corresponding antibodies. A variety of electrochemical aptamer-based sensors (aptasensors) have been fabricated to detect a plethora of analytes ranging from small molecules to large microorganisms and cells.
- Peptide Nucleic Acids (PNAs): they are synthetic DNA analogues with a polyamide backbone instead of the sugar phosphate backbone. The uncharged nature of PNAs is mainly responsible for the thermal stability of PNA−DNA hybrids as compared to DNA−DNA equivalents. Hence, they can be used for the detection of double-stranded DNA (dsDNA) directly without thermal denaturation.
- Molecularly Imprinted Polymers (MIPs): it is a method for making selective binding sites in synthetic polymers using molecular templates. They have been successfully utilized to develop sensing platforms for small molecules (200−1200 Da range).

3.3. Integrated Electrochemical Assays

As compared to carrying out electrochemical analysis in bulk solution, microfluidics can speed up the interaction between the recognition element and the target analyte by reducing the distance required for interaction. This is realized by microfluidic platforms are fabricated from inorganic materials, polymers, and paper. The choice of material depends on the application, detection system, fabrication facility, cost, and other factors including thermal conductivity, sealing properties, and resistance to different chemicals. Within the past few

years, paperbased microfluidic devices have been widely used as a lower-cost microfluidic platform (Labib et al, 2016).

- PDMS-Based Microfluidic Devices: PDMS is one of the most widely used elastomers as it is cheap, elastic, and cures at low temperature. In recent years, several PDMS-based microfluidic devices were designed to allow for efficient capture of circulating tumor cells. Several PDMS-based microfluidic devices integrated with electrochemical sensors have been developed for the analysis of clinically relevant proteins, such as prostate-specific antigen, interleukin 6, C-reactive protein, and apolipoprotein E.
- PMMA-Based Microfluidic Devices: PMMA is widely known under the name lucite and Plexiglas. PMMA-based mutlilayered devices can be completely fabricated in few hours. PMMA-based microfluidic devices integrated with electrochemical sensors have been employed for the analysis of clinically relevant proteins, such as α-fetoprotein and aminoterminal pro-B-type natriuretic peptide.
- Paper-Based Microfluidic Devices: Paper is a flexible, cellulose-based material that has recently emerged as a promising microfluidic substrate. Electrochemical detection in paper microfluidics was first demonstrated using a three-electrode design to analyze clinically relevant small molecules, such as glucose, lactate, and uric acid in human serum. Integration of electrochemical detection into paper-based microfluidic devices has led to the development of several lowcost, easy-to-use portable diagnostic devices. Paper-based microfluidic devices integrated with electrochemical sensors have been used in the analysis of clinically relevant small molecules, such as glucose, lactate, and uric acid, and proteins, such as carcinoembryonic antigen, α-fetoprotein, cancer antigen 125, and immunoglobulins.

4. Electrochemical analysis of small molecules

Clinically relevant endogenous small molecules and ions include neurotransmitters, metabolites, vitamins, amino acids, dietary minerals, and other small biomolecules.

4.1. Neurotransmitters

They are endogenous chemical messengers that transmit, enhance, and convert specific signals between neurons and other cells (dopamine, acetylcholine, serotonin, epinephrine, norepinephrine, nitric oxide, glutamate, and tryptamine…). A variety of electrochemical methods are available for the measurement of these analytes both in vitro and in vivo (Labib et al, 2016).

- Dopamine (DA): DA is a catecholamine neurotransmitter widely present in the central nervous system. Altered levels of DA have been implicated in several neurological disorders including Parkinson's disease and schizophrenia (Labib et al, 2016).

A voltammetric immunosensor for DA was designed on the basis of magnetic particles (MPs) coated with anti-DA monoclonal antibody. Carbon nanotubes (CNTs) were adsorbed on the surface of the MPs. The magnetic entrapment of the CNT/MP hybrids onto a gold screen-printed electrode placed on top of a magnet allowed for straightforward electrochemical sensing of DA by exploiting CNTs as a wiring tool. Cyclic voltammetry (CV) permitted the determination of DA level with a limit of detection (LOD) of 120 nM (Baldrich and Munoz, 2011)

An enzymatic implantable microbiosensor is also available for in vivo monitoring of DA. The biosensor was fabricated using tyrosinase enzyme immobilized in a biocompatible matrix comprising chitosan and ceria-based metal oxides, and was deposited onto the surface of a carbon fiber microelectrode. This amperometric sensor demonstrated an LOD of 1 nM (Njagi et al, 2010).

As compared to conventional electrochemical methods, the nanoelectronic device lowered the LOD of DA to 100 pM and did so even in the presence of other chemical analogues (Labib et al, 2016).

- Acetylcholine (ACh): ACh is a neurotransmitter that acts as a key link in the communication between the neurons in the spinal cord and the nerve skeletal junctions in vertebrates. A variety of neuropsychiatric disorders such as Parkinson's disease, myasthenia gravis, and Alzheimer's disease are correlated with dysfunctional ACh regulation (Labib et al, 2016).

An enzymatic microbiosensor for choline (Ch) and ACh was constructed using an electropolymerized film. Two ACh-specific enzymes were coimmobilized onto the surface of the electropolymerized modified carbon fiber microelectrode. This amperometric sensor permitted the analysis of ACh and Ch levels, with a LOD of 45 nM (Khan et al, 2012).

- Epinephrine (Ep): Ep, also known as adrenalin, is a hormone and neurotransmitter secreted by the medulla of the adrenal glands. It is mainly responsible for activating the sympathetic system associated with the energy and excitement of the fight-or-flight response (Labib et al, 2016).

An MIP-based sensor for Ep was constructed using CNTs bearing a terminal monomeric unit and entailing N-hydroxyphenyl maleimide functionality as a polymeric network with simultaneous imprinting of Ep as a template molecule. The MIP was cast onto a pencil graphite electrode (PGE). Using DPASV, the Ep level was determined with a LOD of 10.9 nM (Prasad et al, 2013).

- Norepinephrine (NE): NE, also known as noradrenalin, is a hormone and neurotransmitter released from the sympathetic neurons to affect the heart. As a stress hormone, NE affects the amygdala in the brain where attention and vigilant concentration are controlled. In addition, NE also underlies the fight-or-flight response along with Ep by directly increasing the heart rate, triggering the release of glucose from energy stores and increasing the blood flow to skeletal muscles (Labib et al, 2016).

An MIP-based sensor for NE was constructed by electropolymerizing o-aminophenol on the surface of a GCE in the presence of NE. Using SWV, the detection was increased with a LOD of 490 pM (Rosy et al, 2014).

- Nitric Oxide (NO): NO is a transcellular messenger molecule that mediates various physiological and pathological events in the biological system. NO is released by most cancer cells and normal cells under drug stimulation and in the course of disease development. Nevertheless, it is very challenging to detect NO in real-time due to its low concentration, high diffusivity, and fast decay (Labib et al, 2016).

An enzymatic approach was described for NO detection in biological fluids using an amperometric sensor. The method permitted a sensitive detection of NO, with a LOD of 0.1 nM (Jiang et al, 2013).

- Glutamate (Glu): Glu is a major excitatory neurotransmitter in the central nervous system. It is involved in the main aspects of brain functions and plays a principal role in neural activation. Excessive glutamate in brain fluids is indicative of acute brain insults such as traumatic brain injury and stroke (Labib et al, 2016).

An enzymatic amperometric sensor for Glu was constructed using glutamate oxidase immobilized onto a composite film of carboxylated MWCNTs, GNPs, and chitosan, preformed on the surface of a gold electrode with a LOD of 1.6 μM.

- Tryptamine: this monoamine alkaloid found in trace amounts in the brains of mammals is believed to play a role as a neurotransmitter or neuromodulator. Tryptamine acts as a nonselective serotonergic receptor agonist and releasing agent for DA (Labib et al, 2016).

A MIP specific for tryptamine was synthesized by electropolymerizing p-aminobenzoic acid in the presence of the template, tryptamine. The MIP was deposited onto a graphene electrode modified with polypyrrole-sulfonated graphene and hyaluronic acid-modified MWCNTs. Amperometric measurements permitted the quantification of tryptamine with a LOD of 74 nM (Xing et al, 2012).

4.2. Metabolites

Metabolites include glucose, uric acid, urea, cholesterol, lactates, hydrogen peroxide, creatine, creatinine, ketone bodies, xanthine, and hypoxanthine. One member of this molecular class, glucose, is perhaps the largest success story in the application of electrochemical sensing methods to clinical applications. The widespread use of electrochemical glucometers is a clear example of how the cost-effectiveness and robustness of electrochemical sensors can be leveraged in commercial products (Labib et al, 2016).

- Glucose: diabetes is a worldwide public health problem. This metabolic disorder is caused by insulin deficiency and is reflected by blood glucose concentrations higher or lower

than the normal range. The first and second generations of commercial glucose sensors were based on the immobilization of glucose oxidase enzyme onto an electrode surface. Mediators were employed for electron transfer between the enzyme and electrode surface. Direct electron transfer between the enzyme and the electrode surface was introduced in third generation glucose sensors. The selectivity of these sensors is excellent; however, problems such as enzyme denaturation and subsequent reduction in reproducibility after storage can arise. Alternative nonenzymatic glucose sensors are therefore of considerable interest; however, these require alkaline aqueous conditions during measurement, and this is not suitable for in vivo glucose sensing applications (Labib et al, 2016).

To facilitate glucose monitoring without the need for blood sampling, an enzymatic amperometric sensor was designed facilitating glucose measurement in tears. Using only 4−5 μL of tear fluid, the sensor had a LOD of 1.5 μM (Batra et al, 2013).

A microfluidic paper-based electrochemical device (μPED) was developed to quantify the glucose level in various biological fluids such as serum, blood, and urine.

- Lactose: Lactose is a disaccharide hydrolyzed by the lactase enzyme in the digestive system into the monosaccharides, glucose and galactose. The lactose level in blood can be used in the diagnosis of gastrointestinal malignancies (Labib et al, 2016).

An enzymatic-based amperometric sensor for lactose was prepared by immobilizing β-galactosidase enzyme in a layer-by layer film of poly (ethylene imine) and poly(vinyl sulfonate) followed by film deposition onto a Prussian blue-coated ITO electrode. The sensor had a LOD of 1.1 mM (Campos et al, 2014).

- Uric Acid (UA): UA is the major nitrogenous molecule in urine and has been associated with a variety of clinical disorders. Elevated UA level in blood, also called hyperuricemia or Lesch−Nyhan syndrome, may result in gout and other pathological conditions, including obesity, diabetes, high blood pressure, and kidney and heart diseases. One of the major problems inherent in direct biological determination of UA results from the interference caused by other biomolecules of close oxidation potential such as ascorbic acid (Labib et al, 2016).

An enzymatic amperometric sensor for UA was fabricated using ferrocene-induced electroactivated uricase enzyme deposited within a Nafion film onto a GCE. Electro-activation of uricase was achieved using CV through the electrostatic interaction between the Fc molecules and tryptophan residues within the hydrophobic pockets in the enzyme. The sensor had a LOD of 230 nM (Ghosh et al, 2015).

- Cholesterol: Monitoring cholesterol is of great importance, especially for people with a high risk of developing heart diseases. Determination of blood cholesterol is required for the diagnosis of atherosclerosis and for estimation of the risk of thrombosis and cardiovascular disorders (Labib et al, 2016).

A MIP-based voltammetric sensor for cholesterol was fabricated by mixing MIP-coated MWCNTs, graphite powder, and silicon alkoxide, followed by packing the formed mixture into the electrode cavity of a Teflon sleeve. Linear sweep voltammetry (LSV) allowed for the quantification of cholesterol with a LOD of 1 nM (Tong et al, 2013).

- Lactate: The level of lactate in blood is used in the clinical diagnosis of respiratory insufficiency, shock, and acute cardiac disorders. In addition, lactic acidosis is known to accompany tissue hypoxia, left ventricular failure, and drug toxicity (Labib et al, 2016).

An amperometric lactate biosensor was constructed using lactate oxidase enzyme immobilized in a mucin/albumin hydrogel matrix preformed onto the surface of a platinum electrode. This biosensor has a LOD of 0.8 μM (Romero et al, 2010).

- Hydrogen Peroxide (HP): Reactive oxygen species (ROS) are important intracellular signaling molecules, mainly regulating DNA damage and cell apoptosis. However, accumulation of ROS in cells leads to oxidative stress that may be linked with a variety of pathological conditions such as neurodegenerative disorders, Alzheimer's disease, autoimmune diseases, and cancer. HP is the most common type of ROS (Labib et al, 2016).

An enzymatic voltammetric biosensor for HP was engineered by embedding a HRP enzyme in a cross-linked 3D polymer matrix bearing a mobile osmium redox and permitting the diffusion of the substrate. This biosensor had a LOD of 1 nM (Suraniti et al, 2014).

- Creatine: Creatine is an amino acid derivative synthesized in the kidneys, liver, and pancreas. Most of the stored creatine is converted to phosphocreatine which represents a major energy storage form in the body. The creatine level in blood and urine is clinically used as an indicator of muscle damage (Labib et al, 2016).

An enzymatic amperometric sensor for creatine was fabricated using a mixture of creatinase and sarcosine oxidase coimmobilized onto the surface of a carbon paste electrode modified with Fe3O4 nanoparticles. This sensor exhibited two linear dynamic ranges extending from 0.2 to 3.8 μM and from 9 to 1200 μM, with a LOD of 0.2 μM (Kacar et al, 2013).

- Creatinine: Creatinine is a byproduct of muscle metabolism and represents an important indicator of renal functions (Labib et al, 2016).

An enzymatic amperometric sensor for creatinine was prepared using a mixture of three enzymes, including creatinine aminohydrolase, creatine aminohydrolase, and sarcosine oxidase, coimmobilized onto a composite film of ZnO nanoparticles/chitosan/carboxylated MWCNTs/polyaniline, deposited on the surface of a platinum electrode. The sensor had a LOD of 0.5 μM (Wen et al, 2014).

- Ketone Bodies: Ketone bodies are biomarkers for diabetes that has progressed to severe ketoacidosis (Labib et al, 2016).

A nonenzymatic voltammetric sensor for acetone was fabricated using a ZnO nanoparticles-coated GCE. This sensor had a LOD of 68 μM (Khan et al, 2011).

4.3.Vitamins

Vitamins are organic compounds and vital nutrients required by living organisms in limited amounts to perform diverse biological functions. In the last few years, several electrochemical sensors have been developed for the analysis of a variety of vitamins such as biotin (vitamin B7 or H), ascorbic acid (AA, vitamin C), folic acid (vitamin B9), riboflavin (vitamin B2), pyridoxine (vitamin B6), and 25-hydroxyvitamin D (Labib et al, 2016).

- A voltammetric immunosensor for biotin was developed using an antibiotin antibody immobilized onto the surface of a boronic acid-modified screen-printed gold electrode via the

interaction between boronic acid and the carbohydrate moiety of the antibody (Ho et al, 2010).

- An enzymatic amperometric sensor for AA was fabricated using an ascorbate oxidase enzyme immobilized between an inner and outer film of poly (3,4-ethylenedioxythiophene) and MWCNTs-coated Nafion, respectively. This detector has a LOD of 87 nM (Wen et al, 2012).
- A MIP-based voltammetric sensor for AA was prepared by incorporating AA as a template molecule during the electrochemical copolymerization of o-phenylenediamine and o-aminophenol followed by electrochemical reduction in ammonium aqueous solution. Using DPV, the LOD was of 36.4 μM (Kong et al, 2014).

4.4. Amino Acids

Amino acids are the building blocks of proteins and are essential for cell function. They play a variety of roles in nutrition and whole-body homeostasis, including nucleic acid synthesis, metabolic regulation, cell signaling, osmoregulation, acid−base balance, and reproduction. Analysis of amino acids is required for the diagnosis and management of inherited metabolic disorders affecting more or one amino acids, such as tyrosinaemia, cystine-lysinuria, homocystinuria, hyperglycinaemia, phenylketonuria, and citrullinaemia. An increase in the total level of plasma amino acids can be a sign of kidney failure, Reye syndrome, ketoacidosis, and fructose intolerance. A decrease in the total level of plasma amino acids might be caused by malnutrition, rheumatoid arthritis, nephrotic syndrome, Huntington's disease, and fever. In the last few years, a variety of electrochemical sensors have been developed for the analysis of amino acids such as arginine, cysteine, glutamic acid, histidine, homocysteine, leucine, lysine, methionine, phenylalanine, tryptophan, and tyrosine (Labib et al, 2016).

- An enzymatic amperometric sensor for L-lysine was designed on the basis of the impregnation of L-lysine oxidase in a diamond paste. This sensor has a LOD of 4 pM (Stefan-van Staden et al, 2012).
- A voltammetric aptasensor for phenylalanine was constructed using a phenylalanine-specific aptamer immobilized onto a gold electrode. Using DPV, the LOD was of 1 nM (Omidinia et al, 2014).

- A voltammetric sensor for L-histidine was fabricated using a specific L-histidine-dependent DNAzyme modified with a ferrocene tag at the distal end. Using SWV, the LOD was of 0.1 pM (Li et al, 2011).

4.5. Dietary Minerals

Dietary minerals are chemical elements required by living organisms other than the four essential elements. These minerals have key roles in several biological functions such as energy production, bone mineralization, nerve and muscle functions, and immunity (Labib et al, 2016).

- A protein-based impedimetric sensor for calcium ions was constructed using porcine S100A12 protein immobilized onto a polyvinyl butyral-coated gold electrode (Oliveira et al, 2011).
- A MIP-based sensor for cadmium and copper ions was fabricated by modifying a PGE with a dual-ion imprinted polymer in a sol−gel matrix. Using DPASV, this sensor had a LOD values were 0.4 and 0.5 nM for cadmium and copper ions, respectively (Bali Prasad et al, 2014).
- A volatmmetric sensor for calcium ions was engineered using a gold microparticle-modified GCE. This sensor catalyzed the electrochemical reduction of alizarin red after complexation with calcium in alkaline solution. Using DPV, it had a LOD of 0.5 μM (Yang et al, 2015).

4.6. Other Small Molecules

Other biologically relevant small molecules have been detected using electrochemical methods include nicotinamide adenine dinucleotide, adenosine monophosphate, adenosine triphosphate, glutathione, heparin, and 3,4-dihydroxy-o-phenylalanine (levodopa) (Labib et al, 2016).

- Nicotinamide Adenine Dinucleotide (NAD). NAD is an important coenzyme found in all living cells. It exists in two forms, including an oxidized (NAD+) and a reduced form (NADH). The rate of NADH in cancer cells is higher than that in normal cells, and thus it can be used as a biochemical marker in the analysis of new cancer therapeutics. Its levels can

provide information that enables the selection of appropriate drugs for Parkinson's disease, Alzheimer's disease, and major depression diseases (Labib et al, 2016).

A nonenzymatic amperometric sensor for NADH was fabricated using a platinum microwire modified with hierarchically driven iridium oxide nanowires. The sensor had a LOD of 5 μM (Shim et al, 2012).

- Glutathione: Glutathione, an important thiol tripeptide antioxidant in cells, exists in two forms: one is a reduced form (GSH), and the other is an oxidized form (GSSG). High levels of GSSG are associated with asthma, chronic renal failure, diabetes, Alzheimer's disease, Parkinson's disease, and macular degeneration (Labib et al, 2016).

A DNA-based voltammetric sensor for GSH was designed on the basis of the ability of GSH to chelate Hg(II) and displace it from the thymine-Hg(II)-thymine complex formed between methylene blue tagged DNA probes immobilized onto a gold electrode surface (Lotfi Zadeh Zhad and Lai, 2014).

5. Electrochemical analysis of nucleic acids

5.1. Application of Nucleic Acid Analysis in Diagnostic Medicine

The analysis of specific nucleic acids sequences is of central importance in clinical medicine. Pathogens responsible for infectious disease can be rapidly and specifically identified via their nucleic acids (NAs), and molecular-level information can be collected on cancer and other diseases through sequence-level analysis. This is a challenging area. The presence of pathogen-specific NAs is routinely used for rapid diagnosis of infectious diseases. More than that, the formation and growth of cancerous tumors involves an accumulation of genetic and epigenetic changes in DNA. At the molecular level, a cancer cell can be distinguished from a healthy cell by abnormalities in structure or expression of certain genes. While leukemia and lymphomas are associated with relatively few but highly specific genetic abnormalities, solid tumors frequently comprise multiple specific and nonspecific abnormalities. The discovery of fetal cfNAs in maternal plasma and serum has opened new venues for parental diagnosis of neurological disorders, preterm labor, fetal-maternal hemorrhage, preeclampsia, polyhydramnios, invasive placentation, sex-linked disorders, fetal

rhesus-D (RhD) status, and fetal chromosomal aneuploidies. Also, fetal RhD genotyping is routinely used for parental diagnosis. Furthermore, placentalderived mRNA species, such as human placental lactogen (hPL), corticotrophin-releasing hormone (CRH), and the β-subunit of human chorionic gonadotropin (βhCG), can be detected in maternal plasma, and their expression is correlated with the corresponding protein product levels. In addition to cfNAs in plasma and serum, DNA in urine represents another tool for molecular analysis. For example, microsatellite alterations have been detected in the urine of patients suffering from renal cancer, prostate cancer, and bladder cancer. Tumor-associated mRNA was first detected in the plasma or serum of cancer patients with nasopharyngeal carcinoma, melanoma, breast cancer, follicular lymphoma, and hepatocellular carcinoma (Labib et al, 2016).

5.2. Electrochemical Detection of Clinically Relevant Nucleic Acids

Several approaches exist for the detection of nucleic acids, including sensors modified with a MIP specific to a nucleic acid sequence. The use of nanostructured transducers could enhance the sensitivity significantly by improving the interaction between the recognition element and the target analyte (Labib et al, 2016).

5.2.1. DNA Detection Strategies.

- Genomic DNA: the analysis of disease-specific gene mutations in DNA is desired because these genes have high mutation frequency in many tumor types and are associated with cancer progression (Labib et al, 2016).

Genosensors based on electrochemical detection have been a promising development in this area. These analytical devices exhibit high specificity and sensitivity and can be applied for the early detection of many genetic diseases, in pathology, food safety and in various other fields. Disposable genosensors are used to detect pesticides,microbiological diseases, toxic algae, and untreated raw biological samples like serum and urine. DNA sensors based on guanine oxidation have been reported to detect pesticides such as malathion and chlorpyrifos by monitoring changes in the DNA redox properties or by employing an electro-active analyte intercalated on a DNA layer. Pencil graphite, carbon nanotubes modified with graphite, and screen-printed graphite electrodes were employed to monitor DNA hybridization in specific

sequences of Hepatitis B and C virus for early diagnoses of the infectious agents.(Cancino et al, 2014)

An amperometric sensor for single nucleotide polymorphisms (SNPs) was constructed using a DNA tetrahedron structure. This 3D nanostructure was strongly anchored on a gold electrode by the three thiol-modified 55-mer DNA strands at the base of the "pyramid", leaving a freestanding 80-mer capture probe at the top (Pei et al, 2010).

- Epigenetic Alterations: heritable changes in gene expression that do not depend on the DNA sequence are referred to as "epigenetic" (Labib et al, 2016).

A voltammetric method was developed for methylated DNA relied on the conversion of C into U using sodium bisulfite. Using CV, 0.1 μM methylated DNA sequences were successfully measured. Using EIS in another study permitted the detection of methylated GSTP1 sequences down to 29 nM (Topkaya et al, 2012).

A facile electrochemical DNA biosensor using isorhamnetin (ISO) indicator for detection of the sequence-specific detection of BCR/ABL fusion gene related to chronic myelogenous leukemia was developed (Zhong et al, 2014).

- Microsatellites: Microsatellites, often referred to as short tandem repeats (STRs), are repetitive DNAtriplets that form variable-length stretches of DNA. They can be found at many locations within the human genome. To date, more than 12 human genetic diseases including Huntington disease (triplets CAG-CTG), myotonic dystrophy (CTG-CAG), fragile X syndrome (CGG-CCG), and Friedreich ataxia (GAATTC) have been found to be associated with the expansion of trinucleotide repetitive sequences such as CTG, CGG, or GAA repeats (Labib et al, 2016).

An impedimetric sensor was developed for the detection of XCG trinucleotide repeats (X: C, T) using a naphthyridine carbamate dimer (NCD) of nucleic acids immobilized onto the surface of a gold electrode (He et al, 2014).

- Viral DNA: a DNA virus is a virus in which the genetic material is DNA and replicates using a DNA-dependent DNA polymerase. Viruses, such as Epstein−Barr virus

(EBV), hepatitis B virus (HBV), and human papillomavirus (HPV), are etiological factors in several malignancies, including nasopharyngeal carcinoma, cervical cancer, head and neck squamous cell carcinoma, Hodgkin's disease, and lymphoid malignancies (Labib et al, 2016).

A voltammetric sensor for the HPV DNA sequence HPV16E7p was fabricated using an anthraquinone-labeled pyrrolidinyl PNA probe immobilized onto the surface of a chitosan-modified screen-printed carbon electrode. Hybridization with the viral DNA was studied by measuring the electrochemical signal of the anthraquinone label using SWV (Jampasa et al, 2014).

- Mitochondrial DNA: Human cells contain several hundreds of copies of mitochondrial DNA (mtDNA) that encodes respiratory chain subunits, tRNAs, and rRNAs. Over 150 mutations with documented pathogenicity have been identified within the human mtDNA. Several mutations have been observed in patients with lung cancer, bladder cancer, head and neck cancer, and colorectal carcinoma (Labib et al, 2016).

An impedimetric sensor was fabricated to monitor the PCR amplification of mitochondrial Cytochrome c oxidase gene using a forward primer immobilized onto the surface of a GCE precoated with a polymerized film of pyrrole and pyrrolylacrylic acid. This sensor permitted the detection of as few as 2 copies μL^{-1} (Aydemir et al, 2015).

5.2.2. RNA Detection Strategies.

The analysis of messenger RNAs and microRNAs is the focal point of the electrochemical RNA analysis area. RNA sequences that are important targets for cancer monitoring, infectious disease diagnosis, and organ transplant assessment have all been analyzed electrochemically using a variety of approaches (Labib et al, 2016).

- Messenger RNA (mRNA): mRNA is the intermediate between genes encoded by DNA and the final protein products. Tumors typically exhibit aberrant mRNA expression, and hence mRNA can be used as a marker for cancer monitoring. In breast cancer patients, the level of CCND1 mRNA has been identified in patients with poor survival and who were nonresponsive to tamoxifen (Labib et al, 2016).

A voltammetric sensing platform was developed for detection of the BCR-ABL mRNA, which is associated with chronic myeloid leukemia. This platform was based on amino acid/ nucleic acid chimeras (ANAs) immobilized onto the surface of an array of nanostructured gold microelectrodes (Vasilyeva et al, 2011).

- MicroRNA (miRNA). miRNAs are a class of small noncoding RNA molecules that regulate the expression of target genes at the post-transcriptional level by either translational repression or degradation of mRNAs. Altered expression patterns of miRNAs have been observed in many diseases, including cancer, cardiovascular diseases, diabetes, rheumatic diseases, and neurological disorders (Labib et al, 2016).

A hybridization-based voltammetric sensor for miRNA was fabricated using a DNA capture probe immobilized onto the surface of MWCNTs-PAMAM dendrimer-coated GCE. This sensor had a LOD of 0.5 fM (Li et al, 2015).

6. Electrochemical analysis of proteins

The contents of human plasma represent secretions coming from all body tissues and may feature markers of physiological and pathological processes. Plasma contains tens of thousands of core proteins which are the biological molecules most ubiquitously affected in diseases. Clinically relevant protein markers include tumor, cardiac, hepatic, inflammatory, and other biomarkers that do not fall into the previous categories (Labib et al, 2016).

Sensitive and specific detection of protein, especially disease related biomarkers, has attracted increasing attention in both biomedical research and clinical diagnosis. As an alternative to antibody, small molecule that can bind to protein through a special interaction has become an appealing recognition element in biosensing, and terminal protection by using small molecule-linked DNA as probe has provided a new insight for protein detection. Besides the high selectivity from small molecule protein interaction, well designed probe DNA can pave the way for signal transduction, acquisition and even amplification, which can greatly improve the flexibility and sensitivity of protein detection. Consequently, different signal amplification techniques and signal readout approaches have been attempted to develop

highly specific, sensitive and robust detection for target proteins based on the terminal protection (Zhao et Al, 2014).

6.1. Tumor Markers

They represent one of the most valuable tools of early cancer detection, classification, staging, progression monitoring, and assessment of resistance to chemotherapy. There are more than 200 distinct diseases associated with cancer affecting different parts of the body. In the absence of a tumor, the tumor markers usually exist at low levels (Labib et al, 2016).

- Prostate-Specific Antigen (PSA): PSA is one of the first tumor markers that has been used for screening and diagnosis of prostate cancer.

A displacement-based voltammetric immunosensor for PSA was developed using an anti-PSA antibody immobilized onto the surface of a MWCNTs-modified GCE, where the antibody was coupled with polytyrosine-tagged PSA. Using DPV, a LOD of 2.2 ng L^{-1} was achieved (Gao et al, 2010).

- Carcinoembryonic Antigen (CEA). CEA is a cell surface glycoprotein that has been used for the clinical diagnosis of breast, lung, pancreatic, gastric, colon, and ovarian tumors (Labib et al, 2016).

A displacement-based voltammetric immunosensor for CEA featured an anti-CEA antibody-modified graphene sensing platform.The immobilized antibody was coupled with multiarmed star-like platinum nanowires modified with CEA and HRP. Using DPV, a LOD of 5 ng $L^{-1}$was achieved (Su et al, 2011).

- α-Fetoprotein (AFP): AFP is an oncofetal glycoprotein that has been used for the clinical diagnosis of hepatocellular carcinoma, teroblastoma, and liver carcinoma (Labib et al, 2016).

A sandwich-based immunosensor for AFP and CEA was designed using anti-AFP and anti-CEA antibodies coimmobilized onto the surface of GNPs-modified GCE using an L-cysteine chitosan derivative. Using DPV, LOD values of 80 and 50 ng L^{-1}, respectively were achieved (Song et al, 2010).

- Cancer Antigen (CA): a variety of cancer-related antigens are currently being explored for the clinical diagnosis of cancer, including CA50, CA125, CA15-3, CA19-9, CA27.29, CA72-4, CA242, and CA549. CA125 is a membrane mucin-like glycoprotein, and its elevated level is used for monitoring of epithelial ovarian tumors (Labib et al, 2016).

A voltammetric immunosensor for CA125 was fabricated using an anti-CA125 antibody immobilized onto the surface of cystamine-modified gold microelectrodes array chip. Using DPV, the level of CA125 was quantified down to 0.1 kU L^{-1} (Das et al, 2011).

- Squamous Cell Carcinoma Antigen (SCCA): SCCA is a glycoprotein that has been used for the clinical diagnosis of cervical cancer (Labib et al, 2016).

A sandwich-based voltammetric immunoassay for SCCA was performed in a magnetically controlled microfluidic device. The assay was designed using an anti-SCCA antibody-functionalized magnetic mesoporous nanogold/thionine/NiCo2O4 hybrid as a capture probe and a HRP-conjugated anti-SCCA antibody conjugated with nanogold/graphene nanosheets as a signaling tag. With DPV a LOD of 1 ng L^{-1} was achieved (Li et al, 2011).

Many other sensors were developed for the detections of other markers such as Neuron-Specific Enolase (NSE; lung cancer marker), Human Epididymis-Specific Protein 4 (HE4; lung and ovarian cancers markers),Ferritin (breast and pancreatic cancers, hepatocellular carcinoma, and Hodgkin's lymphoma), Calcitonin (Ct, medullary thyroid carcinoma), Human Chorionic Gonadotropin (hCG, choriocarcinoma, and testicular cancer), Urokinase Plasminogen Activator (uPA; breast, prostate, ovarian, and squamous cell carcinoma), Glutathione-S-transferase (GST; gastric, esophageal, colonic, pancreatic, hepatocellular, and biliary tract cancer), Alkaline Phosphatase (ALP; leukemia, lymphomas of B cell origin, and osteoblastic bone tumors, Paget's disease, osteomalacia) and many others (Labib et al, 2016).

A novel electrochemical sensor based on the functionalized multiwalled carbon nanotube (f-MWCNT) was successfully developed by Karthik et al (Karthik et al, 2016) for the sensitive and selective determination of non-steroidal prostate anti-cancer drug nilutamide

in tablet and blood serum samples. This technique manifested a good reproducibility and stability. In addition a very low detection limit (0,2 nM) was achieved.

6.2. Cardiac Markers

- Troponin I (cTnI): cTnI has been recognized as the "gold standard" cardiac marker for diagnosis of myocardial infarction (Labib et al, 2016).

A sandwich-based voltammetric sensing platform was reported in which an alkaline phosphatase-conjugated secondary antibody was utilized.Among several phosphatase substrates and products tested, L-ascorbic acid 2-phosphate and ascorbic acid have met the requirements for obtaining a high signal-tobackground ratio. Using CV, the LOD of the immunosensor was 10 pg L^{-1} with redox cycling of ascorbic acid with TCEP (Zhou et al, 2010).

- Myoglobin (Mb): Mb is a heme-containing protein found in all muscle cells, it acts as a valuable marker for acute myocardial infarction (Labib et al, 2016).

A voltammetric aptasensor for Mb was constructed using a Mb-specific aptamer immobilized onto the surface of a reduced graphene oxide/CNTs-functionalized screen-printed electrode. Using CV, the LOD was 34 ng L^{-1} (Kumar et al, 2015).

- Amino-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP): NT-proBNP is an inactive peptide whose level in the blood is used for diagnosis of congestive heart failure and prognosis of heart failure. And is useful marker of the rejection after heart transplantation (Labib et al, 2016).

A voltammetric immunosensor for NT-proBNP was fabricated using the Fab fragment of a NT-proBNP-specific monoclonal antibody modified with magnetic nanoparticles and captured by a magnet placed under the surface of a gold electrode. Using CV, a LOD 30 ng L^{-1} was achieved (Yi et al, 2011).

Other biosensors are used for other markers such as: Creatine Kinase-Myocardial Band (CK-MB; cardiac injury, acute myocardial infarction), Apolipoprotein B-100 (ApoB-100; coronary artery disease), P-Selectin (cardiovascular disorders such as hypertension,

coronary artery disease, and atrial fibrillation), Heart Fatty Acid-Binding Protein (H-FABP; acute myocardial injury) and many others (Labib et al, 2016).

6.3. Hepatic Markers

- Alanine Transaminase (ALT): Elevated levels of ALT in serum (>40 U L^{-1}) have been associated with a range of hepatic disorders, including hepatitis, liver cancer, and alcohol toxicity (Labib et al, 2016).

A peptide-based impedimetric sensor for ALT was constructed using an ALT-specific peptide modified with a C terminal cysteine and immobilized onto the surface of a gold electrode. This approach facilitated the determination of ALT levels down to 92 μg L^{-1} (Wu et al, 2014).

- γ-Glutamyl Transpeptidase (GGT): Elevated serum GGT (>40 U L−1) is generally used as an indicator of liver disorders, such as biliary obstruction, alcohol toxicity, and exposure to certain drugs. Recently, several studies have demonstrated that higher serum GGT levels are associated with cardiovascular risk factors and certain types of cancer (Labib et al, 2016).

A voltammetric sensor for GGT was fabricated using a glutathione substrate immobilized onto the surface of a gold electrode through interaction between the thiol group of glutathione and the gold surface. Using CV, GGT levels were determined down to 5 kU L^{-1} (Chen et al, 2012).

- Bilirubin (BR): BR can be used to assess liver functions and identify various liver diseases, such as jaundice and cirrhosis (Labib et al, 2016).

An enzyme-based amperometric sensor for BR was fabricated using bilirubin oxidase enzyme immobilized on the surface of zirconia-coated silica nanoparticles/chitosan composite predeposited onto a gold electrode. This sensor had a LOD of 58.5 ng L^{-1} (Batra et al, 2013).

- Human Serum Albumin (HSA): HSA is the most abundant protein in human serum. It is essential for maintaining the osmotic pressure. An increased HSA level is widely established as one of the earliest prognostic markers for liver diseases, such as liver cirrhosis as well as kidney and cardiovascular disorders (Labib et al, 2016).

An impedimetric immunosensor for HSA was constructed using an anti-HSA antibody immobilized onto the surface of a screen-printed gold electrode. The LOD was 0.2 mg L^{-1} for this albumin sensor (Chuang et al, 2011).

6.4. Inflammatory Markers

- C-Reactive Protein (CRP): CRP is found in the blood of healthy individuals at levels below 3mg L^{-1}, rising by 2 or more orders of magnitude in response to inflammation or infection (Labib et al, 2016).

An impedimetric sensing platform for CRP used an anti-CRP antibody or affimer immobilized onto the surface of a gold electrode (Johnson et al, 2012).

- Tumor Necrosis Factor-α (TNF-α): TNF-α is an extremely potent inflammatory peptide cytokine produced by the cells of the immune system. When overproduced, the TNF-α plays a major role in chronic inflammatory diseases, such as atherosclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, Alzheimer's disease, and ankylosing spondylitis (Labib et al, 2016).

A voltammetric aptasensor for TNF-α was fabricated using a methylene blue-labeled TNF-α specific aptamer immobilized onto the surface of a gold electrode. With SWV a LOD of 10 μg L^{-1} was achieved (Liu et al, 2013).

6.5. Other Protein Markers

- Antibodies

In the past few years, an explosion in the number of electrochemical sensors targeting antibodies that are present in blood or at the surface of cells has occurred. For example, analysis of diagnostically relevant antibodies is the central core for the detection active pathogens and monitoring of disease progression and responsiveness to therapy. Also, anti-DNA antibodies are important markers for the diagnosis of several autoimmune diseases, such as systemic lupus erythematosus. Furthermore, the determination of antigliadin antibodies from human serum samples is of vital importance for the diagnosis of celiac disease (Labib et al, 2016).

For example, a peptide-based voltammetric sensor for anti-HIV-1-p24 capsid protein antibody was fabricated using a methylene bluemodified peptide immobilized onto the surface of a gold electrode. Using ACV, the antibody level was quantified within the linear range from 750 μg L^{-1} to 15 mg L^{-1}, with a LOD of 750 μg L^{-1} (Gerasimov et al, 2011).

- Hemoglobin (Hb): Hb deficiency can be caused either by a decreased amount of hemoglobin molecules, as in anemia, or by the reduced ability of Hb to bind O2. Other common causes of low hemoglobin include nutritional deficiency, bone marrow diseases and kidney failure (Labib et al, 2016).

A voltammetric sensing platform for Hb was presented on the basis of red blood cells or raw blood cells immobilized onto the surface of a GCE coated with a Nafion film (Toh et al, 2014).

- Retinol-Binding Protein (RBP). RBP is a lowmolecular- weight protein found in human plasma and urine. Urinary RBP is an important marker for the early detection of proximal tubular dysfunction, which is closely associated with some serious diseases, such as diabetes mellitus and hypertension (Labib et al, 2016).

A voltammetric immunosensor for urinary RBP was fabricated using an anti-RBP antibody immobilized onto the surface of a gold electrode modified with Ag/bovine serum albumin composite microsphere. EIS and DPV were utilized for the analysis of RBP within the linear range from 50 μg L−1 to 4.5 mg L^{-1}, with a LOD of 18 μg L^{-1} (Hu et al, 2012).

Chapter III

Electrochemical disease therapy

1. Introduction

The updated list WHO Essential Medicines List (EML) adds 30 medicines for adults and 25 for children including several new drugs, such as two oral cancer treatments, a new pill for hepatitis C that combines two medicines, a more effective treatment for HIV as well as an older drug that can be taken to prevent HIV infection in people at high risk, new paediatric formulations of medicines for tuberculosis, and pain relievers (WHO-6 June 2017 | Geneva)

New treatment techniques are studied some of them are under clinical study, either to improve the quality of life patient or, in desperate cases, just to relieve them from the pain. One of the most interesting techniques studies is electrochemistry.

2. Electrochemistry in neuropathy and mental related diseases

2.1. Diabetes neuropathy

Peripheral neuropathy is a common complication of diabetes, affecting more than 50% of patients with more than 10 years of diabetes duration. It has been estimated that up to 20% of patients with Diabetes suffer from painful neuropathy. Numerous pain management protocols have been advocated to ameliorate neuropathic pain. These have included antidepressants, anticonvulsants, α-adrenergic agonists, aldose reductase inhibitors, intravenous… etc. Apart from those protocols, various non- pharmacological therapies had been tried to reduce the diabetic neuropathic pain, among them electrotherapy. Many studies tried to evaluate the efficacy of electrical nerve stimulation for the management of chronic painful neuropathy in patients with type 2 diabetes.

Shanmugam et al fount that almost 85% of painful neuropathic patients felt the symptomatic reduction of the pain (Shanmugam et al, 2017)

2.2. Anxiety disorders and depression

Anxiety disorders are the most common mental disorders with lifetime prevalence rates ranging from 13.6% to 28.8%. According to a World Health Organization report anxiety disorders generally develop before the age of 35 in 80–90% of cases. It has also been shown that about 50–60% of depressed individuals also meet the lifetime criteria of an anxiety disorder and that anxiety disorders can be causal factors for later developing depression. Patients who have an

anxiety disorder with depression have an increased number of suicide attempts compared to those without depression. Medication is the standard treatment for anxiety disorders. While these medications can be helpful, compliance is often compromised due to the adverse effects these medicines have on the patient including weight gain, gastro intestinal and sexual difficulties, insomnia, and severe headaches. Due to the non-compliance issue, new and effective treatments that have minimal side effects are needed for the treatment of anxiety and depression. Cranial electrotherapy stimulation (CES) can be used as an adjunct to the pharmacological approach and psychotherapy or as an alternative therapy. CES is a non invasive brain stimulation prescriptive medical treatment that uses the application of pulsed, low amplitude electrical current to the head via electrodes placed on the earlobes (Barclay and Barclay, 2014).

This technique is prescribed for US Service Members and veterans for the treatment of anxiety, PTSD, insomnia and depression. Kich et al (Kirch et al, 2011) studied the effectiveness and safety of CES treatment and found that the majority of participants reported ≥ 50% clinical improvement. They also found that individuals who were not taking any prescription medication rated CES more effective than those who taking also medication prescription. It has also been shown that this is effective for Bipolar Patients (Amr et al, 2013).

3. Electrochemistry in tumor therapy

For the following reasons, among all non transmissible diseases, we focus in this bibliographic research on cancer. Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Approximately 14 million new cases are registered in 2012. The number of new cases is expected to rise by about 70% over the next 2 decades. Globally, nearly 1 in 6 deaths is due to cancer. Approximately 70% of deaths from cancer occur in low- and middle-income countries. Late-stage presentation and inaccessible diagnosis and treatment are common (WHO's 21st expert committee report, Mars 2017).

3.1. Cancer therapy

Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other

organs, the latter process is referred to as metastasizing. Metastases are a major cause of death from cancer. These changes are the result of the interaction between a person's genetic factors and 3 categories of external agents, including:

- physical carcinogens, such as ultraviolet and ionizing radiation;
- chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant), and arsenic (a drinking water contaminant); and
- biological carcinogens, such as infections from certain viruses, bacteria, or parasites.

A correct cancer diagnosis is essential for adequate and effective treatment because every cancer type requires a specific treatment regimen that encompasses one or more modalities such as surgery, radiotherapy, hormonotherapy and chemotherapy.

Current cancer therapy usually involves intrusive processes including application of catheters to allow chemotherapy, initial chemotherapy to shrink any cancer present, surgery to then remove the tumor(s) if possible, followed by more chemotherapy and radiation. The purpose of the chemotherapy and radiation is to kill the tumor cells as these cells are more susceptible to the actions of these drugs and methods because of their growth at a much faster rate than healthy cells, at least in adults (Brannon-Peppas and Blanchette, 2004).

An overview of literature let us think that chemotherapy and other treatment techniques face a variety of difficulties such as MDR (multidrug resistance) which represents the capability of the targeted cell to become insensitive towards therapy treatments after prolonged exposure to permeability glycoproteine (effluxes a large number of therapeutic out of the cell).

To overcome these difficulties, the advances in treatment of cancer are progressing quickly both in terms of new agents against cancer and new ways of delivering both old and new agents such as the two oral cancer medicines (dasatinib and nilotinib) recently added to the WHO EML for the treatment of chronic myeloid leukaemia that has become resistant to standard treatment. In clinical trials, one in two patients taking these medicines achieved a complete and durable remission from the disease. The effectiveness of the treatment is directly related to the treatment's ability to target and to kill the cancer cells while affecting as few healthy cells as

possible (Arap et al, 1997; Brannon-Peppas and Blanchette, 2004, WHO's 21st expert committee report, Mars 2017).

3.2. Electrochemical treatment

Electrochemical treatment is one of the alternative modalities for tumors treatments. It is a therapy in which tumour tissue is treated with direct current through the use of electrodes placed withing the tumour zone. When tissue is electrolysed, electrical energy is converted into chemical energy through electrochemical reactions at the electrodes. In the first applications the parameters important in the process were still uncertain (De Abreu, 2002). Further researches suggested various mechanisms to explain how direct electric current destroys tumor cells. Although, it is generally accepted this treatment induces electrolysis, electroosmosis and electroporation in tumoral tissues. However, action mechanism of this alternative modality on the tumor tissue is not well understood. Although the principle of electrochemical treatment is simple, a standardized method is not yet available.

This treatment is noted for its great effectiveness, minimal invasiveness, local effect and low cost. Several studies have been conducted worldwide to evaluate the antitumoral effect of this therapy. In all these studies a variety of biochemical and physiological responses of tumors to the applied treatment have been obtained. It constitutes a good therapeutic option for patients that have failed the conventional oncology methods (Holandino et al, 2013).

3.3. Targeted therapies

Neoplastic tissues may be divided into three sub compartments: vascular, interstitial and cellular.

The vascularization of tumors is heterogeneous, showing regions of necrosis or hemorrhages as well as regions which are densely vascularized in order to sustain an adequate supply of nutrients and oxygen for rapid tumor growth. Tumor blood vessels present several abnormalities in comparison with normal physiological vessels.

Macromolecular transport pathways across tumor vessels have been shown to occur via open gaps, vesicular vacuolar organelles (VVO) and fenestrations. The pore cutoff size of several tumor models has been reported ranging between 380 and 780 nm. The tumor interstitial compartment is predominantly composed of a collagen and elastic fiber network. The transport of

an anticancer drug in the interstitium will be governed by physiological (i.e. pressure) and physicochemical properties of the interstitium and by the physicochemical properties of the molecule (size, configuration, charge, hydrophobicity) itself.

Thus, to deliver therapeutic agents to tumor cells in vivo, one must overcome the following problems:

(i) Drug resistance at the tumor level due to physiological barriers (non cellular based mechanisms), (ii) drug resistance at the cellular level, and (iii) distribution, biotransformation and clearance of anticancer drugs in the body (M Wahab et Al, 2016; Y Xie et Al, 2016).

3.3.1. Achieving targeting by avoiding reticulo endothelial system (RES)

Nanoparticles will usually be taken up by the liver, spleen and other parts of the RES depending on their surface characteristics. Particles with longer circulation times, and hence greater ability to target to the site of interest, should be 100 nm or less in diameter and have a hydrophilic surface in order to reduce clearance by macrophages (Brannon-Peppas and Blanchette, 2004).

3.3.2. Tumor-specific targeting

Tumor-activated prodrug therapy uses the approach that a drug conjugated to a tumor-specific molecule will remain inactive until it reaches the tumor. These systems would ideally be dependent on interactions with cells found specifically on the surface of cancerous cells and not the surface of healthy cells. Limitations exist due to the lower potency of some drugs after being linked to targeting moieties when the targeting portion is not cleaved correctly or at all (Brannon-Peppas and Blanchette, 2004).

The ideal antigen should be expressed on all tumor cells but not expressed on critical host cells. There should be no mutation or variation and it should be required for cell survival or for a critical cellular function(Brannon-Peppas and Blanchette, 2004).

Gene expression may be inhibited by small interfering RNA (siRNA) via thewell-controlled enzyme-mediated gene silencing mechanism. The Nobel Prize (medicine) in 2006 reiterated the commitment of global research to RNAi. Ten years later, combination of anticancer drugs with therapeutic miRNA and siRNA has emerged as a promising anticancer strategy. But this strategy

can't reach its goal without delivery vectors. Among the available delivery systems, biodegradable polymeric nanoparticles have been the most successful delivery platforms used in drug/nucleic acid combinations. When properly designed, such polymeric drug nanoparticles have several advantages, including simple production and high drug contents that makes them suitable for clinical translation. Moreover, many studies highlight self-immolative materials as powerful approach for drug or nucleic acid delivery due to smart and amplified release of cargos upon encountering a suitable trigger. Therefore, polymeric nanoparticles composed of self-immolative polymeric prodrugs are expected to offer a promising platform for drug/nucleic acids combination. (Wahab et Al, 2016; Xie et Al, 2016). In fact, hydrophilic groups incorporated in the polymeric micelles can extendin vivo half-life of siRNA to ensure adequate accumulation in tumors, be exchanged forcations that electrostatically interact with siRNA.

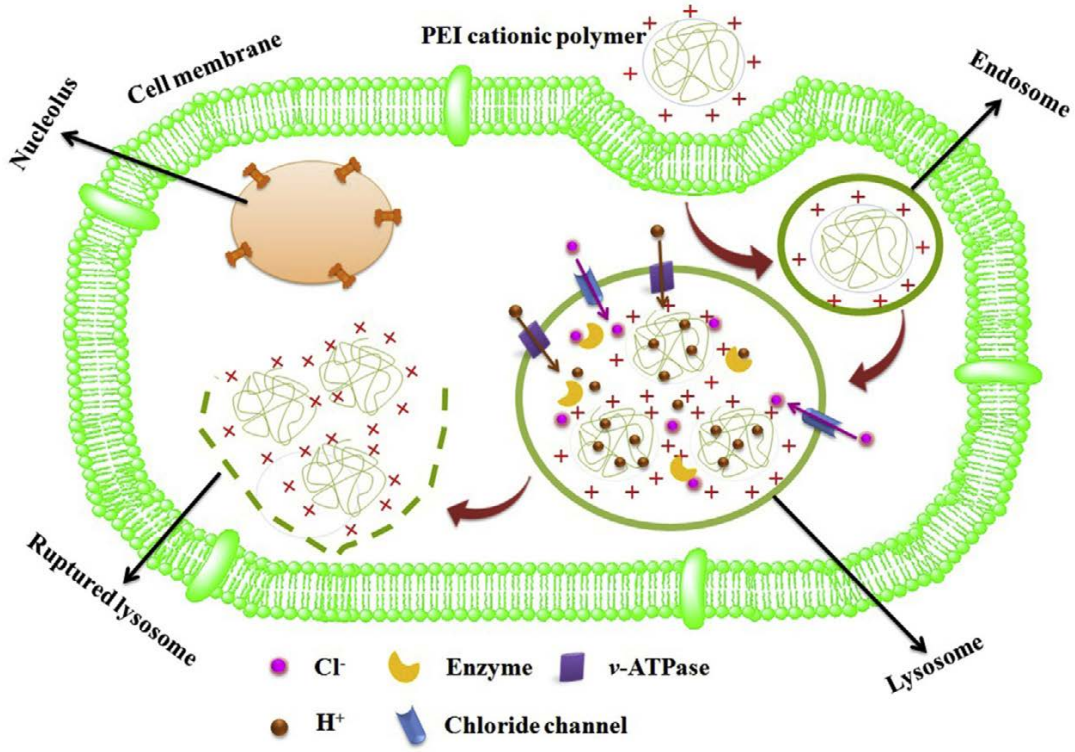

Figure 1. The proton sponge effect of cationic polymers. Polyethylenimine is the best example of a cationic polymer exhibiting the proton sponge effect,which enables the avoidance of endosomal/lysosomal degradation and, hence, the successful cytosolic release of siRNA.

During the past few decades, the development of polymeric micelles to deliver a range of entities fromchemotherapeutics to oligonucleotides, antibodies, siRNA,and DNA, has undergone a rapid evolution. This approach may aid in the delivery ofimaging mediators and agent sensitive to distinct signals that are produced either externally or within the tumor microenvironment, and therefore allows for the tempo-ral and spatial regulation of payload release. (Amjad et al, 2016)

3.3.3. Targeting through angiogenesis

Angiogenesis is a process vital to the continued development of a tumor mass. This process has been the subject of intense research due to its role in cancer development and has proven to be the result of numerous interactions between regulators, mediators and stimulatory molecules. These molecules regulate the proliferative and invasive activity of the endothelial cells that line blood vessels (Brannon-Peppas and Blanchette, 2004).

Because so many different molecules are involved in angiogenesis there are many potential targets for therapy. Some examples of therapeutic strategies include limiting endothelial proliferation and motility, increased expression of angiogenesis inhibitors and use of molecules such as soluble VEGF receptor to try and decrease the amount of angiogenesis stimulatory factors at the tumor site (Brannon-Peppas and Blanchette, 2004).

3.4. Delivery of specific agents

3.4.1. Paclitaxel

Paclitaxel is a microtubule-stabilizing agent which promotes polymerization of tubululin causing cell death by disrupting the dynamics necessary for cell division. It has neoplastic activity especially against primary epithelial ovarian carcinoma, breast, colon, and non-small cell lung cancers. It could be incorporated at very high loading efficiencies, nearing 100%, using the nanoprecipitation method using acetone and PLGA. Cellular studies showed up to a 70% loss of viability in NCI-H69 human small cell lung cancer cells at levels as low as 0.025 μg/ml (Brannon-Peppas and Blanchette, 2004).

3.4.2. Doxorubicin

One of the most potent and widely used anti-cancer drugs is doxorubicin which works by inhibiting the synthesis of nucleic acids within cancer cells. Doxorubicin has a number of undesirable side effects such as cardiotoxicity and myelosuppression which leads to a very narrow therapeutic index. Various researchers have studied ways to target doxorubicin delivery to cancer tissues or at least to diminish its side effects. Conjugates of dextran and doxorubicin have been encapsulated in chitosan nanoparticles of ∼100 nm diameter (Brannon-Peppas and Blanchette, 2004).

Organometallic chemistry has allowed the design and emergence of a new class of metalbased bioactive molecules and a variety of drugs used or still tested against cancer. This approach has been successfully used to design ferrocifens. These complexes involve a ferrocenyl group covalently grafted onto the tamoxifen skeleton, the current gold standard for endocrine breast cancer therapy. Based on the same strategy, several original ruthenocene- and osmocene-tamoxifen derivatives have been recently synthesized and successfully tested against breast and other cancer cells. The development of such potent metallodrugs was made possible thanks to the accurate mechanistic understanding of the metallodrugs activation provided by the synergistic combination of electrochemical and biological approaches (Amatore et al, 2017)

Also, Villar et al, (Villar et al, 2017) presented a new strategy using a new molecules they named glutamoptosis as a tumor suppressor. This technique needs to be more envestigated.

3.5. Targeting to specific organs or tumor types

One of the greatest challenges is defining the optimal targeting agent or agents to selectively and successfully transport nanoparticle systems to cancerous tissue. These strategies also then rely on the targeting agents capability to bind to the tumor cell surface in an appropriate manner to trigger receptor endocytosis. The therapeutic agents will thereby be delivered to the interior of the cancer cell.

3.5.1. Breast cancer

An example of the type of work which can be done to identify the ideal ligands for targeting is the development of a strategy to select internalizing antibodies from phage libraries. This technique was used to identify two antibodies (F5 and C1) to the breast tumor cell line SK-BR-3 that bind to ErbB2, a growth factor that is overexpressed in 20–30% of human breast carcinomas and also in other adenocarcinomas

3.5.2. Liver

A promising receptor for liver targeting is the asialoglycoprotein receptor (ASGP-R, galactose receptor). Work by Kim et al (Kim et al, 2003) describes nanoparticles that use the galactose moiety from lactobionic acid, biotin and diamine-terminated poly(ethylene glycol) which exhibit in vitro release of A11-trans-retinoic acid (a model cancer drug) at a fairly constant rate over 1 month.

3.6. Imaging for cancer

Many of the same techniques used to target delivery of drugs to cancerous tissues may also be used to target imaging agents. In fact, as targeted delivery systems approach the stage where they can be used clinically, primary assessment of the utility of a particular formulation in a particular patient may be made with imaging agents to verify that the delivery system goes primarily to the cancerous tissues.

3.7. Applications of electrochemical techniques

Many electrochemical treatments exist such as the treatments of Benign Prostatic Hyperplasia which affects old people generally, in fact for this particular disease many treatments were developed such as Transurethral Electrosurgical Vaporization and Transurethral Electrochemical Treatment of the Prostate which uses catheters in case surgery is contraindicated. (Koshiba et al, 2000)

4. Self powered delivery system

The development of nanoparticles led to a rapid growth of micro scale implantable devices which are applied in diagnostic sensing, stimulating tissues/organs, monitoring body functions, imaging, and delivering drugs have been demonstrated.

For example, implantable drug-delivery system (iDDS) has made localized treatment feasible with high drug delivery efficiency and great controllability in delivery time and rate. Such devices are useful in the treatment of diabetes, ocular disease, and cancer. So far, most of these devices need an external power source such as lithium-ion batteries for activation.

To overcome this challenge of continuously powering an iDDS, it is critical to find a sustainable powering solution. On one hand, wireless power transmission is being studied. Researchers have demonstrated the use of metal coil in the device to harvest energy from radio-frequency signal generated from a transmitter for powering a drug-delivery pump. But in this method, a complicated external signal generator/transmitter is needed and the working conditions for remote power transmission are strict. On the other hand, implantable materials that harvest energy from chemical, mechanical, electrical, and thermal processes in the human body have been demonstrated, such as using biochemical reaction, the electric potentials in human body, mechanical movements of body parts, and the vibration of organs using piezoelectric nanogenerator. However, none of these solutions are applied in implantable drug-delivery applications due to their relatively large footprint and small output.

Recently, researchers have invented the triboelectric nanogenerator (TENG). TENG offers an effective method to harvest ambient mechanical energy and transfer it into electricity. Its working principle is based on the combination of contact electrification and electrostatic induction. It has a simple structure, thus it can be greatly miniaturized and fabricated using soft materials. At the same time, it generates a strong output that ranges up to a few milliwatts (mW). Therefore, it can be implanted to harvest the energy from body/organ's motion and engineered as an ideal power source for implantable biomedical devices. Scientific efforts made by Peiyi et al, (Peiyi et al, 2017) have made possible the development of the first TENG-based self-powered iDDS for drug-delivery applications which is an electrochemical micro fluidic pump powered by TENG represented in Fig 2.

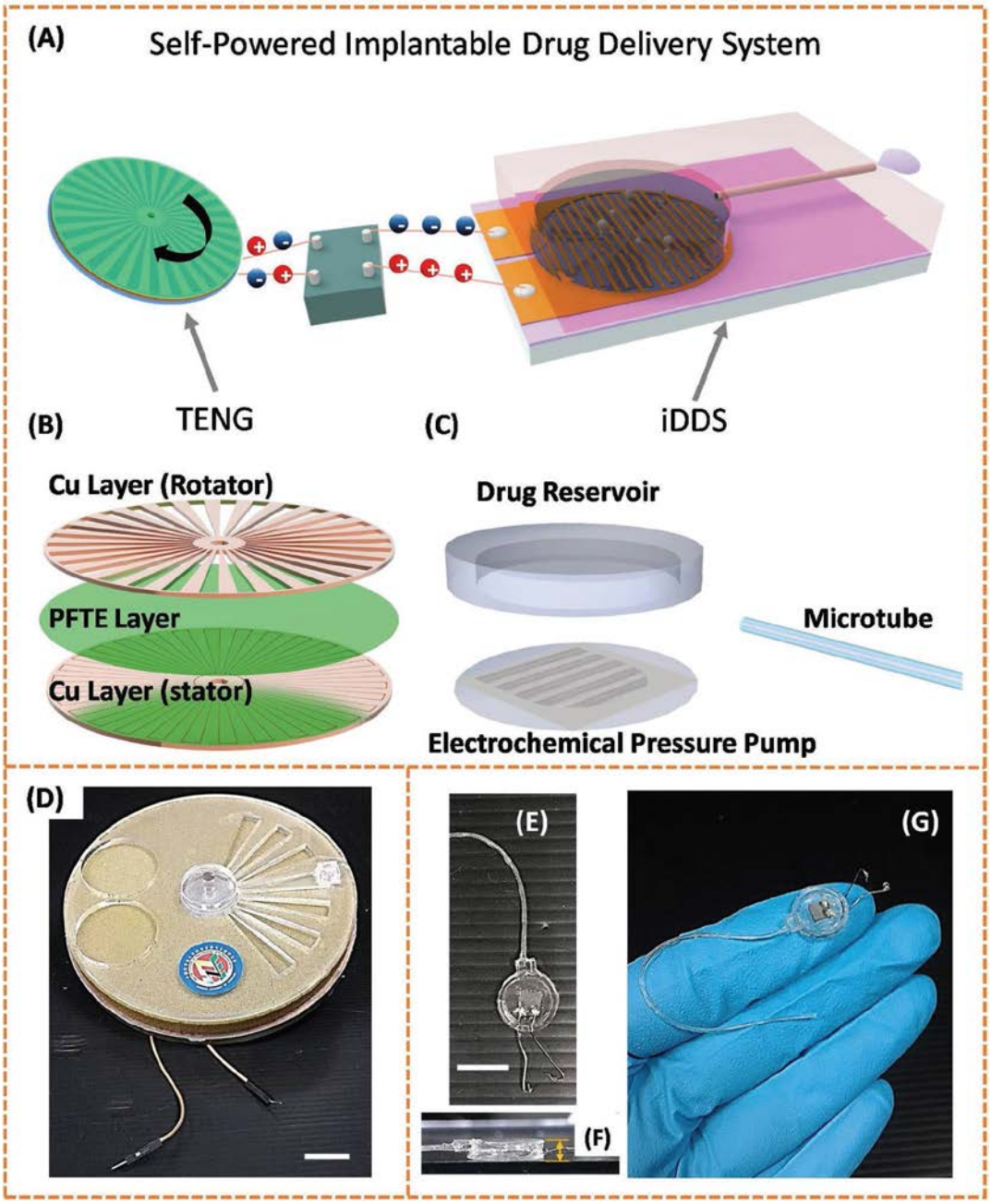

Figure 2 . Structural designs and photographs of the TENG and the iDDS. A) Schematic illustration of the TENG-based iDDS. B) Schematic illustration of the parts in TENG. C) Schematic illustration of the parts in iDDS. D) Photograph of the TENG packaged in glass epoxy. The scale bar indicates 10 mm. E) Photograph of the iDDS. The scale bar indicates 10 mm. F) Side-view photograph of the iDDS. The thickness measured is 2 mm. G) Photograph of the iDDS on a human hand.

Conclusions

Conclusions

As a result of this bibliographic study, it appears that the application of electro chemical processes for health purposes has been very diverse. They were used for the elimination of many pollutants of different origins but which are linked by their negative impacts on the environment and health.

More than that the same electrochemical reactors can often be used for a more than one purpose and these reactors are easy for automation, optimization, monitoring, and control. Contrary to other techniques or processes like incineration, supercritical oxidation, wet oxidation, etc., electrochemical techniques normally do not require high temperature or pressure.

New hybrid processes were applied for more specific removal or to enhance the performance of treatment, the hybrid processes can be more effectives than electrochemical processes used by their own.

In the medical field, the detection of several disease markers and the diagnosis of many diseases is processed using electrochemistry.

Electrochemical processes were also used for the development of many devices based on nanomaterials and nanotechnologies that helps the medical analysis systems to be more effective and fast. Those clinical analyses are no longer performed exclusively in clinical laboratories. Instead, they are routinely carried out in several settings, including hospital point-of-care settings, by caregivers in nonhospital settings, and by patients at home. these detection systems are ideally suited for these new applications.

Electrochemical devices are proved to be effective for many disease therapies for either mental or body diseases. The effectiveness of electrotherapy for depression was studied a lot but no technique standard was approved. At high current this same technique was used to treat tumors by phenomenon of electrolysis, electrophoresis… etc

Conclusions

With the development of nanotechnologies, many tumors therapies were developed to overcome the problems of classical treatment techniques like chemotherapy. This new techniques focus on targeting the tumor itself. Their effectiveness of these treatments is directly related to their ability to target and to kill the cancer cells while affecting as few healthy cells as possible.

The principal of targeting techniques relies on the recognition of those tumors by drug carriers. They uses the approach that a drug conjugated to a tumor-specific molecule will remain inactive until it reaches the tumor. These systems would ideally be dependent on interactions with cells found specifically on the surface of cancerous cells and not the surface of healthy cells (recognition of tumor cells).

In fact, implantable drug-delivery system (iDDS) has made localized treatment feasible with high drug delivery efficiency and great controllability in delivery time and rate. The problem of these systems is that most of these devices need an external power source such as lithium-ion batteries for activation which means other risks for patients. Electrochemical processes have, once again, brought the solution to this problem by the development, earlier in 2017, of the first self-powered iDDS for drug-delivery applications.

Akrama M. and Hoadley A., 2012. An evaluation of a hybrid ion exchange electrodialysis process in the recovery of heavy metals from simulated dilute industrial wastewater. water research 46(2012)3364-3376.

Amatore C., Labbee E., Buriez O., 2017. Molecular Electrochemistry: a Central Method to Understand the Metabolic Activation of Therapeutic Agents. The Example of Metallocifen Anti-Cancer Drug Canditates. Current Opinion in Electrochemistry (2017), doi: 10.1016/j.coelec.2016.12.003.

Amjada M.W., Kesharwanib P., Arun K, 2017. Recent advances in the design, development, and targeting mechanisms of polymeric micelles for delivery of siRNA in cancer therapy. 2016. Progress in Polymer Science 64 (2017) 154–181.

Amr M., El-Wasify M., Elmaadawi A.Z., Roberts R.J., El-Mallakh R.S., 2013. Cranial Electrotherapy Stimulation for the Treatment of Chronically Symptomatic Bipolar Patients . Journal of ECT, Volume 29, 2013. DOI: 10.1097/YCT.0b013e31828a344d.

Aydemir N., McArdle H., Patel S., Whitford W., Evans C.W., Travas-Sejdic J., Williams D.E., 2015. A Label-free, sensitive, real-time, semiquantitative electrochemical measurement method for DNA polymerase amplification (ePCR). Anal. Chem. 2015, 87, 5189−5197.

Baldrich E., Munoz F.X., 2011. Carbon nanotube wiring: a tool for straightforward electrochemical biosensing at magnetic particles. Anal. Chem. 2011, 83, 9244−9250.

Barclay T.H., Barclay R.D., 2014. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. Journal of Affective Disorders164(2014)171–177.

Barhoumia B., Olvera-Vargasb H., Oturanb N., Huguenota D., Gadrie A., Ammare S., Brillasd E., Oturanb M.A., 2017. Kinetics of oxidative degradation/mineralization pathways of theantibiotic tetracycline by the novel heterogeneous electro-Fentonprocess with solid catalyst chalcopyrite. 2017. Applied Catalysis B: Environmental 209 (2017) 637–647.

Batra B., Lata S., Rana J.S., Pundir C.S., 2013. Construction of an amperometric bilirubin biosensor based on covalent immobilization of bilirubin oxidase onto zirconia coated silica nanoparticles/ chitosan hybrid film. Biosens. Bioelectron. 2013, 44, 64−69.

Batra B., Pundir C.S., 2013. An amperometric glutamate biosensor based on immobilization of glutamate oxidase onto carboxylated multiwalled carbon nanotubes/gold nanoparticles/chitosan composite film modified Au electrode. Biosens. Bioelectron. 2013, 47, 496−501.

Bogdanov M., Matson W.R., Wang L., Matson T., Saunders-Pullman R., Bressman3 S.S., Flint Beal M., 2008. Metabolomic profiling to develop blood biomarkers for Parkinson's disease. Brain (2008), 131, 389-396.

Bouaziz I., Hamza M., Sellami A., Abdelhedi R., Savall A., 2017. New hybrid process combining adsorption on sawdust and electroxidation using a BDD anode for the treatment of dilute wastewater. Separation and Puri_cation Technology, Elsevier, 2017, vol. 175, pp. 1-8.

Brannon-Peppas., Blanchette., 2004. Nanoparticle and targeted systems for cancer therapy. Advanced Drug Delivery Reviews 64 (2012) 206–212.

Brillas E., Casado J., 2002. Aniline degradation by Electro-Fenton and peroxi-coagulation processes using a flow reactor for wastewater treatment. Chemosphere 47 (2002) 241–248.

Campos P.P., Moraes M.L., Volpati D., Miranda P.B., Oliveira O.N., and Ferreira M., 2014. Amperometric detection of lactose using beta-galactosidase immobilized in layer-by-layer films. ACS Appl. Mater. Interfaces, 2014, 6, 11657−11664. 123, 1625−1630.

Cancino J., Janegitz B.C., Zucolotto V., 2014. Disposable biosensors for clinical diagnosis. Journal of Nanoscience and Nanotechnology, Valencia : American Scientific Publishers-ASP,v.14,n.1,p.378-389.

Chasta H., Goyal R.N., 2014. Molecularly imprinted sensor based on o-aminophenol for the selective determination of norepinephrine in pharmaceutical and biological samples. Talanta 2014, 125, 167−173.

Chen G., Ni S., Zhu S., Yang J., Yin Y., 2012. An electrochemical method to detect gamma glutamyl transpeptidase. Int. J. Mol. Sci. 2012, 13, 2801−2809.

Chuang Y.H., Chang Y.T., Liu K.L., Chang H.Y., Yew T.R., 2011. Electrical impedimetric biosensors for liver function detection. Biosens. Bioelectron. 2011, 28, 368−372.

Das J., Kelley S.O., 2011. Protein detection using arrayed microsensor chips: tuning sensor footprint to achieve ultrasensitive readout of CA-125 in serum and whole blood. Anal. Chem. 2011, 83, 1167−1172.

DURAND G., 2010. Potentiométrie – Définitions et principes généraux. Techniques de l'Ingénieur, 2010 Réf. : P2115 V2.

Enciso R., Delgadillo J.A., Domínguez O., Rodríguez-Torres I., 2017. Analysis and validation of the hydrodynamics of an electrodialysis cell using computational fluid dynamics Desalination 408 (2017) 127–132

Gao Y., Cranston R., 2010. Polytyrosine as an electroactive label for signal amplification in electrochemical immunosensors. Anal. Chim. Acta 2010, 659, 109−114.

Gerasimov J.Y., Lai R.Y., 2011. Design and characterization of an electrochemical peptide-based sensor fabricated via″click″ chemistry. Chem. Commun. 2011, 47, 8688−8690.

Ghosh T., Sarkar P., Turner A.P., 2015. A novel third generation uric acid biosensor using uricase electro-activated with ferrocene on a Nafion coated glassy carbon electrode. Bioelectrochemistry 2015, 102, 1−9.

Gomez-Lopez V.M., Gil M.I., Allende A., 2017. A novel electrochemical device as a disinfection system to maintain water quality during washing of ready to eat fresh produce. 2016. Food Control 71 (2017) 242e247

GRIB H., BELHOCINE D., LOUNICI H., PAUSS A., MAMERI N., 1999. Desalting of phenylalanine solutions by electro dialysis with ion-exchange membranes 1999 Journal of Applied Electrochemistry 30: 259-262, 2000.

Guivarch E., Trevin S,. Lahitte C., Oturan K.T., 2003. Degradation of azo dyes in water by Electro-Fenton process. 2002. Environ Chem Lett (2003) 1:38–44. DOI 10.1007/s10311-002-0017-0.

Hassaan M.A., El Nemr A., 2017. Health and Environmental Impacts of Dyes: Mini Review. Environment and Sustainability. Vol. 1, No. 3, 2017, pp. 64-67. doi: 10.11648/j.env.20170103.13.

He H., Peng X., Huang M., Chang G., Zhang X., Wang S., 2014. An electrochemical impedance sensor based on a small molecule modified Au electrode for the recognition of a trinucleotide repeat. Analyst 2014, 139, 5482−5487.

Ho J.A., Hsu W.L., Liao W.C., Chiu J.K., Chen M.L., Chang H.C., Li C.C., 2010. Ultrasensitive electrochemical detection of biotin using electrically addressable site-oriented antibody immobilization approach via aminophenyl boronic acid. Biosens. Bioelectron. 2010, 26, 1021−1027.

Holandino C., Ciria H., González M., Zamora L., Cabrales L., González G., De Oliveira L., Zanella R., Buzaid A., Parise O., Brito L., Teixeira C., Gomes M, Moreno G, da Veiga V., and Telló M., 2013. Antitumor effects of electrochemical treatment. Chin J Cancer Res. 10.3978/j.issn.1000-9604.2013.03.03, 2013 Apr; 25(2): 223–234. PMCID: PMC3626978.

Hu C., Yang D.P., Xu K., Cao H., Wu B., Cui D., Jia N., 2012. Core/shell microspheres as an electrochemical interface for sensitive detection of urinary retinal-binding protein. Anal. Chem. 2012, 84, 10324−10331.

Jampasa S., Wonsawat W., Rodthongkum N., Siangproh W., Yanatatsaneejit P., Vilaivan T., Chailapakul O., 2014. Electrochemical detection of human papillomavirus DNA type 16 using a pyrrolidinyl peptide nucleic acid probe immobilized on screen-printed carbon electrodes. Biosens. Bioelectron. 2014, 54, 428−434.

Jiang S., Cheng R., Wang X., Xue T., Liu Y., Nel A., Huang Y., Duan X., 2013. Real-time electrical detection of nitric oxide in biological systems with sub-nanomolar sensitivity. Nat. Commun. 2013, 4, 1−7.

Johnson A., Song Q., Ko Ferrigno P., Bueno P.R., Davis J.J., 2012. Sensitive affimer and antibody based impedimetric label-free assays for C-reactive protein. Anal. Chem. 2012, 84, 6553−6560.

Kacar C., Erden P.E., Pekyardimci S., Kilic E., 2013. An Fe3O4- nanoparticles-based amperometric biosensor for creatine determination. Artif. Cells, Nanomed., Biotechnol. 2013, 41, 2−7.

Khan A., AbdelGhani S., 2012. Multienzyme microbiosensor based on electropolymerized o-phenylenediamine for simultaneous in vitro determination of acetylcholine and choline. Biosens. Bioelectron. 2012, 31, 433−438.

Khan S.B., Faisal M., Rahman M.M., Jamal A., 2011. Lowtemperature growth of ZnO nanoparticles: Photocatalyst and acetone sensor. Talanta 2011, 85, 943−949.

Kim I.S., Kim S.H., 2003. Development of polymeric nanoparticulate drug delivery systems: evaluation of nanoparticles based on biotinylated poly(ethylene glycvol) with sugar moiety, International Journal of Pharmaceutics 257 (2003) 195–203.

Kirsch D.L., Price L.R., Nichols F., Marksberry J.A., Platoni K.T., Psy D., 2011. Efficacy of Cranial Electrotherapy Stimulation for Anxiety, PTSD, Insomnia and Depression: US Military Service Members and Veterans Self Reports. The American institute of stresse, 2011.

Kong Y., Shan X., Ma J., Chen M., Chen Z., 2014. A novel voltammetric sensor for ascorbic acid based on molecularly imprinted poly(o-phenylenediamine-co-o-aminophenol). Anal. Chim. Acta 2014,809, 54−60.

Kumar J.V., Karthik R., Sasikumar R., Chen S.M., Elangovan A., Muthuraj M., Muthukrishnan P., Al-Hemaid M.A., Ali M.A., Elshikh M.S., 2016. A highly sensitive and selective electrochemical determination of non-steroidal prostate anti-cancer drug nilutamide based on f-MWCNT in tablet and human blood serum sample, 2016, Journal of Colloid and Interface Science 487 (2017) 289–296

Kumar V., Shorie M., Ganguli A.K., Sabherwal P., 2015. Graphene-CNT nanohybrid aptasensor for label free detection of cardiac biomarker myoglobin. Biosens. Bioelectron. 2015, 72, 56−60.

Labib M., Sargent E.H., Kelley S.O., 2016. Electrochemical Methods for the Analysis of Clinically Relevant Biomolecules. DOI: 10.1021/acs.chemrev.6b00220.

Li F., Peng J., Zheng Q., Guo X., Tang H., Yao S., 2015. Carbon nanotube-polyamidoamine dendrimer hybrid-modified electrodes for highly sensitive electrochemical detection of microRNA24. Anal. Chem. 2015, 87, 4806−4813.

Li H., Lu T., Pan L., Zhang Y., Sun Z., 2009. Electrosorption behavior of graphene in NaCl solutions. 2009. Journal of Materials Chemistry. DOI: 10.1039/b907703k

Li L.D., Chen Z.B., Zhao H.T., Guo L., 2011. Electrochemical realtime detection of L-histidine via self-cleavage of DNAzymes. Biosens. Bioelectron. 2011, 26, 2781−2785.

Li Q., Tang D., Tang J., Su B., Chen G., Wei M., 2011. Magnetocontrolled electrochemical immunosensor for direct detection of squamous cell carcinoma antigen by using serum as supporting electrolyte. Biosens. Bioelectron. 2011, 27, 153−159.

Liu Y., Zhou Q., Revzin A., 2013. An aptasensor for electrochemical detection of tumor necrosis factor in human blood. Analyst 2013, 138, 4321−4326.

LiX., Jin X., Zhao N., Angelidaki I., Zhang Y., 2017. Efficient treatment of aniline containing wastewater in bipolar membrane microbial electrolysis cell-Fenton system. Water Research (2017), doi: 10.1016/j.watres.2017.04.047.

Mameri N., Bariou B., Nicolas S., Grib H., Belhicine D., Addour L., Lounici H., 1997. Study of a new technique for fluoride removal from water 1997 Desalination 114(1997)241-251.

Mameri N., Bouhezila F., Hariti M., Lounici H., 2011. Treatment of the OUED SMAR town landfill leachate by an electrochemical reactor Desalination 280 (2011) 347–353.

Mameri N., Lounici H., Belhocine D., Grib H., Piron D.L., Yahiat Y., 2001. Defluoridation of Sahara water by small plant electrocoagulation using bipolar aluminium electrodes (2000) Separation and Purification Technology 24 (2001) 113–119.

Mameri N., Yeddou A.R., Lounici H., Belhocine D., Grib H., Bariou B., 1997. Defluoridation of septentional Sahara water of north africa by electrocoagulation process using bipolar aluminium electrodes 1997 Wat.Rees.Vol 32, No, 5.pp,1604-1612,1998.

Maxwell E.J., Aaron D.M., Whitesides G.M., 2013. “Paper-Based Electroanalytical Devices for Accessible Diagnostic Testing.” MRS Bulletin 38 (04) (April): 309–314. doi:10.1557/mrs.2013.56. http://nrs.harvard.edu/urn-3:HUL.InstRepos:12388523.

Miomir G., Pavlović L., Pavlović M.M., Nikolić N.D., 2014. Electrochemical Removal of Microorganisms in Drinking Water .2014. Int. J. Electrochem. Sci., 9 (2014) 8249 – 8262.

Moreira F.C., Boaventura A.R., Brillas E., Vilar J.P., 2017. Electrochemical advanced oxidation processes: a review on their application to synthetic and real wastewaters. Appl. Catal. B Environ. 202, 217e261.

Njagi J., Chernov M.M., Leiter J.C., Andreescu S., 2010. Amperometric detection of dopamine in vivo with an enzyme based carbon fiber microbiosensor. Anal. Chem. 2010, 82, 989−996.

Oliveira M.D., De Melo C.P., Oliva G., Andrade C.A., 2011. Development of impedimetric and optical calcium biosensor by usingmodified gold electrode with porcine S100A12 protein. Colloids Surf., B 2011, 82, 365−370.

Omidinia E., Shadjou N., Hasanzadeh M., 2014. Aptamer-based biosensor for detection of phenylalanine at physiological pH. Appl. Biochem. Biotechnol. 2014, 172, 2070−2080.

Pan L., Wang X., Gao Y., Zhang Y., Chen Y., Sun Z., 2008. Electrosorption of anions with carbon nanotube and nanofibre composite film electrodes. 2008, Desalination 244 (2009) 139–143.

Panizza M., Cerisola G., 2009. Electro-Fenton degradation of synthetic dyes water research 43(2009)339–344.

Pei H., Lu N., Wen Y., Song S., Liu Y., Yan H., Fan C., 2010. A DNA nanostructure-based biomolecular probe carrier platform for electrochemical biosensing. Adv. Mater. 2010, 22, 4754−4758.

Pimentel M., Oturan N., Dezotti M., Oturan M.A., 2008. Phenol degradation by advanced electrochemical oxidation process electro-Fenton using a carbon felt cathode Applied Catalysis B: Environmental 83 (2008) 140–149.

Polewczyk A., Kutarski A., Tomaszewski A., Polewczyk M., Janion1 M., and Polska K., 2013. Late complications of electrotherapy — a clinical analysis of indications for transvenous removal of endocardial leads: a single centre experience. 2013; 71, 4: 366–372.

Prasad B., Jauhari D., Verma A., 2014. A dual-ion imprinted polymer embedded in sol-gel matrix for the ultra trace simultaneous analysis of cadmium and copper. Talanta 2014, 120, 398−407.

Prasad B.B, Prasad A., Tiwari M.P., Madhuri R., 2013. Multiwalled carbon nanotubes bearing 'terminal monomeric unit' for the fabrication of epinephrine imprinted polymer-based electrochemical sensor. Biosens. Bioelectron. 2013, 45, 114−122.

Prüss-Üstün A., Wolf J., Corvalán C.F., Bos R.V., Neira M., 2016. Data Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. World Health Organization Repport. ISBN 978 92 4 156519 6 (NLM classification: WA 30.5)

Radjenovic J,. Bagastyo A., Rabaey., Batstone M., Gernjak W., Mu Y., Rene A., Escher R.B., Poussade Y., Keller J., 2012. Electrochemical Treatment of Problematic Water Recycle Waste Streams. 2012 Urban Water Security Research Alliance Technical Report No. 82.

Romero M.R., Ahumada F., Garay F., Baruzzi A.M., 2010. Amperometric biosensor for direct blood lactate detection. Anal. Chem. 2010, 82, 5568−5572.

Shackerya I., Patila U., Pezeshkib A., Shindea N.M., Kanga S., Imb S., Juna S.C, 2016. Copper Hydroxide Nanorods Decorated Porous Graphene Foam Electrodes for Non-enzymatic Glucose Sensing. Electrochimica Acta 191 (2016) 954–961

Shanmugam A., Jayapackiam T., Bronson S.C., 2017. Effectiveness of electrotherapy in chronic painful diabetic neuropathy. J. Evolution Med. Dent. Sci. 2017;6(17):1317-1322, DOI: 10.14260/Jemds/2017/286.

Shim J.H., Lee Y., Kang M., Lee J., Baik J.M., Lee C., Kim M.H., 2012. Hierarchically driven IrO2 nanowire electrocatalysts for direct sensing of biomolecules. Anal. Chem. 2012, 84, 3827−3832.

Song Z., Yuan R., Chai Y., Zhuo Y., Jiang W., Su H., Che X., Li J., 2010. Horseradish peroxidase-functionalized Pt hollow nanospheres and multiple redox probes as trace labels for a sensitive simultaneous multianalyte electrochemical immunoassay. Chem. Commun. 2010, 46,6750−6752.

Souzab F., Quijornaa S., Lanzab M., Sáeza C., Nizaresa P., Rodrigoa M.A., 2016. Applicability of electrochemical oxidation using diamond anodes to the treatment of a sulfonylurea herbicide. Catalysis Today (2016).

Staden R.I., Nejem R.M., van Staden J.F., Aboul-Enein H.Y., 2012. Amperometric biosensor based on diamond paste for the enantioanalysis of L-lysine. Biosens. Bioelectron. 2012, 35, 439−442.

Su B., Tang D., Tang J., Cui Y., Chen G., 2011. Multiarmed star-like platinum nanowires with multienzyme assembly for direct electronic determination of carcinoembryoninc antigen in serum. Biosens. Bioelectron. 2011, 30, 229−234.

Suraniti E., Ben-Amor S., Landry P., Rigoulet M., Fontaine E., Bottari S., Devin A., Sojic N., Mano N., Arbault S., 2014. Electrochemical monitoring of the early events of hydrogen peroxide production by mitochondria. Angew. Chem., Int. Ed. 2014, 53, 6655−6658.

Taverna M., Le Potier I., Morin P., 2003. Électrophorèse capillaire - Applications Techniques de l'Ingénieur, 2003 Réf. : P3367 V1.

Toh R.J., Peng W.K., Han J., Pumera M., 2014. Direct in vivo electrochemical detection of haemoglobin in red blood cells. Sci. Rep.2014, 4, 6209.

Tong Y., Li H., Guan H., Zhao J., Majeed S., Anjum S., Liang F., Xu G., 2013. Electrochemical cholesterol sensor based on carbon nanotube molecularly imprinted polymer modified ceramic carbon electrode. Biosens. Bioelectron. 2013, 47, 553−558.

Topkaya S.N., Ozkan-Ariksoysal D., Kosova B., Ozel R., Ozsoz M., 2012. Electrochemical DNA biosensor for detecting cancer biomarker related to glutathione S-transferase P1 (GSTP1) hypermethylation in real samples. Biosens. Bioelectron. 2012, 31, 516−522.

Vasilyeva E., Lam B., Fang Z., Minden M.D., Sargent E.H., Kelley S.O., 2011. Direct genetic analysis of ten cancer cells: tuning sensor structure and molecular probe design for efficient mRNA capture. Angew. Chem., Int. Ed. 2011, 50, 4137−4141.

Villar V.H., Nguyen T.L., Terés S., Durán V., 2017. Escaping mTOR inhibition for cancer therapy: Tumor suppressor functions of mTOR, Molecular & Cellular Oncology, DOI: 10.1080/23723556.2017.1297284.

Wen T., Zhu W., Xue C., Wu J., Han Q., Wang X., Zhou X., Jiang H., 2014. Novel electrochemical sensing platform based on magnetic field-induced self-assembly of Fe3O4 Polyaniline nanoparticles for clinical detection of creatinine. Biosens. Bioelectron. 2014, 56, 180−185.

WHO (World Health Organization), 2011. Brief guide to analytical methods for measuring lead in blood. WHO. SBN 978 92 4 150213 9.

WHO (World Health Organization), 2017. Chemical mixtures in source water and drinking-water. Geneva Repport: Page 3; Licence: CC BY-NC-SA 3.0 IGO.

Wisniewskia C., Persinb F., Cherif T., Sandeauxb R., Grasmicka A., and Gavachb A., 2001. Denitrification of drinking water by the association of an electrodialysis process and a membrane bioreactor: feasibility and application Desalination 139 (2001) 199–205.

Xing X., Liu S., Yu J., Lian W., Huang J., 2012. Electrochemical sensor based on molecularly imprinted film at polypyrrole-sulfonated graphene/hyaluronic acid-multiwalled carbon nanotubes modified electrode for determination of tryptamine. Biosens. Bioelectron. 2012, 31, 277−283.

Xiong X.G., Patra P., Hu J., Wu P., 2016. Biochip with Cu-Graphene Glassy Carbon Electrode for Glucose Sensing (2016) University of Bridgeport.

Yang J.X., He Y.B., Lai L.N., Li J.B., Song X.L., 2015. Electrochemical sensors using gold submicron particles modified electrodes based on calcium complexes formed with alizarin red S for determination of Ca (2+) in isolated rat heart mitochondria. Biosens. Bioelectron. 2015, 66, 417−422.

Yi W., Liang W., Li P., Li S., Zhang Z., Yang M., Chen A., Zhang B., Hu C., 2011. Application of a Fab fragment of monoclonal antibody specific to N-terminal pro-brain natriuretic peptide for the detection based on regeneration-free electrochemical immunosensor. Biotechnol. Lett. 2011, 33, 1539−1543.

Ying T.Y., Yiacoumi K.L., Tsouris C., 2002. Electrosorption of Ions from Aqueous Solutions by Nanostructured Carbon Aerogel. 2002. DOI: 10.1006/jcis.2002.8314

Zeni M., Riveros R., Melo K., Primieri R., Lorenzini S., 2005. Study on fluoride reduction in artesian well—water from electrodialysis process Desalination 185 (2005) 241–244.

Zhad H.R., Lai R.Y., 2014. A Hg(II)-mediated ″signalon″ electrochemical glutathione sensor. Chem. Commun. 2014, 50, 8385−8387.

Zhang H., Huang C.P., 2002. Treatment of landfill leachate by Fenton oxidation process, Chin. J. Chem. Eng. 19 (2002) 128–131.

Zhonga G.H., Yea J.X., Baia F.Q., Fud F.H., Chena W., Liua A.L., Lina X.L., Yuan-Zhong Chenb., 2014. Electrochemical biosensor for detection of BCR/ABL fusion gene basedon isorhamnetin as hybridization indicator. Sensors and Actuators B 204 (2014) 326–332.

Zhou F., Lu M., Wang W., Bian Z. P., Zhang J. R., Zhu J.J., 2010. Electrochemical immunosensor for simultaneous detection of dual cardiac markers based on a poly(dimethylsiloxane)-gold nanoparticles composite microfluidic chip: a proof of principle. Clin. Chem. 2010, 56, 1701−1707.