International Journal of Latest Research in Science and Technology **ISSN (Online):2278-5299**
Volume 11, Issue 1: Page No.1-5 (2022)
https://www.mnkjournals.com/journal/ijlrst/index.php

MODELING AND SIMULATION STUDY OF ELECTROCHEMICAL SENSOR FOR GLUCOSE CONCENTRATION MEASUREMENT IN CLINICAL DIAGNOSIS

Babatunde S. Emmanuel[1], Stella A. Emmanuel[2]
[1]Senior Lecturer, Department of Electrical and Electronic Engineering, Lead City University, sbemmenuel@yahoo.com, Nigeria.
[2]Principal Research Fellow, Chemistry Advanced Research Centre, Sheda Science and Technology Complex (SHESTCO), sa.emmanuel2016@gmail.com, Nigeria.

Received : 25 January 2022; Accepted : 08 February 2022 ; Published : 10 March 2022

Abstract: ***This paper presents the modeling and simulation study of an electrochemical blood glucose sensor for clinical diagnosis. The working principle of the proposed sensing device is based on amperometry, that is, the measurement of electric current from a chemical reaction process. An applied voltage to the working and reference electrodes of the sensor resulted in the oxidation of glucose in the analyte sample, and the current due to this oxidation is measured at the electrode. As the input glucose concentration increases from 0.1M to 0.9M in the modeled glucose biosensor, the output response in terms of average current density increases linearly from 0.75 A/m^2 to 7.8 A/m^2. The linearity of response is a desirable property for an efficient measurement system.***

***Keywords*-:** Electrochemical, sensor, glucose, amperometry, diagnosis.

I. INTRODUCTION

In biomedical applications, electrochemical sensors have been extensively used especially for clinical diagnosis. An example of such sensors is the glucose biosensor commonly employed in glucometers or glucose monitoring devices. In recent times, research efforts have focused on the design and development of efficient sensor devices, by virtue of the urgent need for real time monitoring of health conditions. In line with the contemporary demand for continuous measurement of concentration of biochemicals in the body, electrochemical sensors provide a way for the design of reliable measuring devices with improved performance in terms of sensitivity, accuracy, linearity of response, precision and stability. By way of simple definition, an electrochemical sensor is the sensing element of a measurement device that converts chemical measurand into an electrical output signal for clinical diagnostic analysis. The sensor is often made up of two basic parts, namely, chemical detection or sensing and electrical transducer which converts the chemical input into electrical output that can be calibrated by modern electrical instruments [1].

A. Glucose Electrochemical Biosensor

The measurement of the concentration of glucose in the blood or in a solution is carried out by devices that are operated based on the concept of electrochemical transduction. To perform glucose concentration measurement, electrochemical test strips are employed. The measurement process involves placing a little drop of target glucose solution or blood sample on the electrochemical test strip. The test strip is typically composed of an enzyme known as glucose oxidase which reacts with the glucose in the solution sample to produce gluconic acid. This then reacts, with another mediator compound in the testing strip. This chemical reaction product creates the flow of electrical current through the blood sample collected on the strip. The magnitude of this current determines the amount of glucose in the blood sample. Thus, the chemical reaction process involving glucose in the presence of an enzyme produces electrons. These electrons which are collected at the electrodes are measured and it is required that the resulting charge density should be proportional to the concentration of glucose in the solution. The current can be measured using a current-to-voltage converter and an analogue to digital converter (ADC). The variation in the electrical output is measured as a variation in the concentration of glucose in the solution.

B. Amperometric and Potentiometric Principles

The basic methods for electrochemical sensing include: amperometric and potentiometric methods. Amperometric sensing method produces current output. In this method, oxidation or reduction reaction of chemical analyte at the working electrode occurs. This results in the gain or loss of

electrons at the electrode surface. The electric current generated due to electrons exchanges at the electrodes can be measured and it is proportional to the analyte concentration. The output current measured in the amperometric sensing process is related to area of electrode; number of electrons exchanged, Faraday constant, diffusion coefficient; thickness of the diffusion layer; and concentration of the analytes. Common application example includes glucose sensors. The benefits of amperometry include reduced detection limit, simplicity, reduced analysis time and reduced cost [2][3]. On the other hand, potentiometric electrochemical sensing process is based on the measurement of the output voltage between the electrode and the reference electrode. In this sensing process, ion selective electrodes are used as sensors. Application example include oxygen sensors and pH sensors [2]. However, the focus of this study is on the amperometric principle based enzymatic glucose sensor.

II. LITERATURE REVIEW

Amperometric principle for electrochemical sensing has been employed in the design and development of glucose biosensors in recent times. Sridara et al [2] proposed an amperometric glucose concentration biosensor which was non-enzymatic. The design was based on carbon nanodots and copper oxide (CuO) nanocomposites. Electron microscopy and infrared spectroscopy were employed to characterize the physicochemical properties of the sensor. According to Paik et al [4], glucose biosensor based on amperometric principle was designed using glucose oxidase (GOx) embedded in zinc oxide (ZnO). The effect of interferences was highly reduced on the performance of the sensor. Pinyou et al [5] reported the implementation of a thermo-responsive biosensor design for the amperometric detection of glucose concentration. Gold working electrodes were employed at 28 °C glucose solution temperature. The output response was determined as a function of temperature.

Nanocomposite based enzymatic glucose biosensor was reported by Rakhi et al [6]. The electrocatalytic properties of nanoparticles were harnessed by the biosensor for efficient enzymatic reaction. This design produced an amperometric response as a measure of glucose concentration in the analyte solution. Liu et al [7] developed a carbon nanohorns based glucose level biosensor. The sensor encapsulates GOx in the Nafion composite film. Ferrocene monocarboxylic acid acted as a redox mediator in the design. The electrocatalytic activity of the biosensing system with respect to glucose was reportedly good. Kucherenko et al [8] developed a twin biosensor system with one for sensing glucose level on the basis of glucose oxidase and the other to monitor hexokinase. Platinum disc electrodes were used as amperometric transducers with polyphenilenediamine membrane deposit on the platinum electrodes surface to prevent sensitivity to extraneous electroactive substances.

Electro-polymerization of pyrrole with glucose oxidase on a hydrogel coated platinum electrode was presented by Kotanen et al [9] as a viable amperometric biosensor for glucose. The proposed technique for application in biosensor design was reported to possess the capacity to quantitatively add enzyme catalytic bioactivity to metal or semiconductor biointerfaces of biosensors. Ang et al [10] developed an enzyme-electrode amperometric glucose sensor where glucose oxidase (GOx) was immobilized on chitosan membrane on a platinum working electrode. High retention activity was shown by the immobilized enzyme as well as good stability. Nanocomposites were used to construct electrochemical biosensors for the amperometric detection of glucose concentration indirectly from the concentration of hydrogen peroxide by Xiang et al [11, 18]. The enzymic biosensor produced a high selectivity and stability features, as well as showed great promise for application in the detection of glucose.

Other studies have also focused on non-invasive blood glucose measurement. Cabedio et al [11, 12] presented a study that showed that variations in the glucose level in blood is proportional to the permittivity property of blood. Additionally, it was experimentally shown that the dielectric property of blood varies more as the changes in the concentration of blood glucose than concentration changes of other blood compound elements [13], [14]. Hence, it was proposed that these variations in concentration level can be sensed by a microwave transducer due to the relation between its frequency response and the dielectric properties of the materials it is in contact with [15]. Therefore, since non-enzymatic sensor does not contain biological components, it was reportedly unaffected by storage factors such as lifetime, temperature, humidity, solvent and other interferences [16]. However, the challenges of selectivity and accuracy still exist.

The goal of this study is the modeling and analysis of the output response of an enzymatic electrochemical glucose biosensor. An enzymatic and invasive electrochemical glucose sensor can be defined as a device that uses specific biochemical reactions mediated by isolated enzymes to monitor the concentration of glucose in the blood through a process of electrochemical transduction [17, 18]. Two basic components of all biosensors include:

1. Ligand: Biological recognition element that facilitates specific binding or biochemical reaction with the target analyte.
2. Transducer: Signal conversion unit.

A. Theoretical Formulation

As a result of the thick protein layer surrounding the enzyme glucose oxidase (GOx), direct transfer of electrons is not feasible between its redox center and the electrode surface. Additionally, due to the limitation of oxygen dependence in the enzymatic reaction process which produced reduced upper limit linearity in device response, the design has replaced oxygen as a natural electron acceptor with a synthetic electron acceptor which is reportedly more efficient in carrying electrons from the redox center to the electrode surface. Therefore, in order to improve the electrical contact between the redox center of GOx and electrode surfaces, an artificial mediator has been employed for the purpose of electron transfer. This was reported by Wang [22] as follows:

$$\text{glucose} + \text{Gox}_{(ox)} \rightarrow \text{gluconic acid} + \text{Gox}_{(red)} \quad (1)$$

$$\text{Gox}_{(red)} + 2\text{M}_{(ox)} \rightarrow \text{Gox}_{(ox)} + 2\text{M}_{(red)} + 2\text{H}^{+} \quad (2)$$

$$2\text{M}_{(red)} \rightarrow 2\text{M}_{(ox)} + 2e^{-} \quad (3)$$

In the set of chemical (1) to (3) , $M_{(ox)}$ is the mediator oxidized form and $M_{(red)}$ is the mediator reduced form. The reduced form is re-oxidized at the electrodes, producing a current output proportional to blood glucose concentration while regenerating the oxidized form of the mediator (equation 3). Electron transfer mediator employed for the design in this work is the ferricyanide compound for easier diffusion of electrons to the electrode surface. This innovation minimizes the interference of oxygen in the enzymatic reaction process. If the rate of electron diffusion through the mediator is higher than the reaction rate between oxygen and the enzyme, blood glucose concentration can be measured to a large extent of specificity and selectivity without the interference of other coexisting electroactive species.

For the proposed glucose biosensor design, ferricyanide, that is hexacyanoferrate (III) was employed as the oxidant for the enzymatic reaction due to its fast kinetics at the electrode as opposed to glucose oxidase. This is because of the need to measure current output without any interference of natural oxidant, namely, oxygen. Ferricyanide was used as the mediator or chemical oxidant because it is an electron acceptor. In the absence of a mediator in the electrochemical system, molecular oxygen accepts the electrons donated by the substrate to produce hydrogen peroxide [19], [21]. Ferricyanide reduces to ferrocyanide when it accepts electrons from substrate. Consequent upon this, the concentration of glucose is determined by the oxidation of ferrocyanide on electrode surface. The reversible chemical reactions that take place before and after application of a potential of 0.4V at the electrode surface are as depicted [19], [20]:

$$Fe(CN)_6^{3-} + e^- \leftrightarrow Fe(CN)_6^{4-} \quad (4)$$

Studies have shown that the ferro-ferricyanide redox couple is an effective oxidation-reduction potential buffer for the determination of redox potentials for biometric systems. The benefits of this include relative ease of preparation, and stability of potential with respect to time. The measured output signal is the magnitude of current due to the reduction of the ferricyanide enzymatically produced. GOx catalyzes the oxidation of glucose in the presence of chemical oxidant ferricyanide which is reduced to ferrocyanide in a continuous cycle oxidized back to ferricyanide at the surface electrode. Hence, the concentration of ferricyanide, which is measured amperometrically is proportional to the initial concentration of glucose [19, 20].

B. Diffusion Equations

The diffusion equation describes the diffusion of species or energy starting at an initial time, with an initial spatial distribution and progressing over time. The simplest example has one space dimension in addition to time.

$$\frac{d\rho}{dt} = D\nabla^2\rho \quad (5)$$

$$\frac{dN}{dt} = K_F(N_0 - N)\rho_s \quad (6)$$

$As\ K_F \rightarrow \infty\ and\ As\ \rho_s \rightarrow 0$

$$N(t) = \rho_0 t^{9(D_F)} \quad (7)$$

Where:

ρ_0 = Initial analyte density

D_F = Fractal dimension of electrode surface

ρ = Analyte density

t = Settling response time

N = Number of analyte molecules or analyte concentration

x = diffusion distance

$$\rho_{(x,t)} = \rho_0 \text{erf}\,(x/2\sqrt{Dt}) \quad (8)$$

$$\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-y^2}dy \quad (9)$$

$$N(t) = \rho_0 t^{9(D_F)} \int_0^\infty [\rho_0 - \rho_{(x,t)}]dy = \rho_0\sqrt{\frac{4}{\pi}}\sqrt{Dt} \quad (10)$$

Sensor current response - Butler-Volmer equation

$$I = A_e q(K_F\rho_{s,R} - K_B\rho_{s,O}) \quad (11)$$

Where:

A_e = Surface area of electrode

$q(K_F\rho_{s,R})$ = Reduction process reaction

$q(K_B\rho_{s,O})$ = Oxidation process reaction

K_F = Forward reaction rate

K_B = Backward reaction rate

Therefore, amperometric biosensor current response is linearly proportional to the concentration of the analyte.

$$I(t) = \left[\frac{e^{(1-\alpha)f(E_A-E_0)}}{\frac{1}{K_O}+\frac{A_e}{C_{D(t)}}(e^{(1-\alpha)f(E_A-E_0)}-e^{-\alpha f(E_A-E_0)})}\right] \quad (12)$$

Where:

A_e = Effective area of electrode surface

$C_{D(t)}$ = Diffusion capacitance

The amperometric current response is proportional to the diffusion capacitance as $\frac{1}{K_O} \rightarrow 0$

III.METHODOLOGY

The methodologies employed in this work is depicted by the workflow shown in Figure 1.

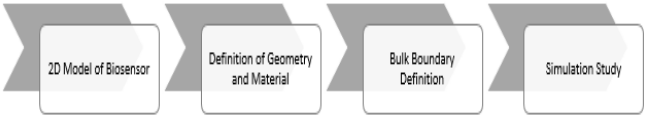

Figure 1: Methodological Workflow for the Simulation Study of Glucose Biosensor

The modeling and study of the amperometric output characteristic of glucose biosensing system was carried out using COMSOL Multiphysics in two-dimensional (2D) space, to create, analyze, and visualize the electrochemical behaviour of the system. 2D model parameters defined for the glucose biosensor include the dimension of geometry, and sensor electrodes and boundary conditions. The mesh was also defined for finite element analysis which is necessary for the steady state study of the model. In the simulation, the current response of the system to a constant potential set at +0.4 V applied at the working electrode was calculated. The values of currents generated at different glucose concentrations in the analyte solution were also measured.

The geometry of the 2D space model was defined as a unit cell of solution above an interdigitated electrode with a width of 100 μm and length of 1000 μm. At the top of the unit cell is a bulk boundary where the surface glucose concentration is assumed to be equal to the bulk concentration in the target solution of the analyte. The bottom of the unit cell is sectioned by four points into separate electrode and insulator boundaries as follows:

Table 1: Dimension of model geometry

Model Geometry	Dimension
Unit Cell	100 x1000 μm
Working Electrode	37.5 μm < *x* < 62.5 μm
Left Reference Electrode	*x* > 12.5 μm.
Right Reference Electrode	*x* < 87.5 μm
Left Insulator Layer	12.5 μm < *x* < 37.5 μm
Right Insulator Layer	62.5 μm < *x* < 87.5 μm

The working electrode is at the center of the cell. The unit cell contains half of each of the two reference or counter electrodes at the fringes of the working electrode. A solid insulator separates the working and counter electrodes. The steady state analysis of the output current generated in proportion to the concentration of glucose in solution was carried out. The value of glucose concentration is gradually varied and the electrical output response of the sensor is measured. The proposed glucose sensor structure employed silver/silver chloride (Ag/AgCl) electrodes held at +0.4 V. This was used to monitor the enzymatic ferro-ferricyanide redox couple which is an effective oxidation-reduction potential buffer. Glucose oxidase catalyzes the oxidation of glucose in the presence of chemical oxidant ferricyanide which is reduced to ferrocyanide and oxidized back to ferricyanide in a continuous cycle at the surface electrode. The initial values of sensor model parameters are shown in Table 1.

Table 1: Defined values for model parameters

Model Parameters	Values
External glucose concentration	0.005 mol/m³
Ferrocyanide concentration	0.001 mol/m³
Ferricyanide concentration	50 mol/m³
Maximum rate of reaction (V_{max})	0.015 mol/(m³·s)
Michaelis-Menten constant (K_m)	0.5 mol/m³
Reference exchange current density (i_{0ref})	9.6485E7 A/m²

Linearity is a major performance metric adopted for evaluation of the response of the proposed biosensor. This is in terms of the relationship between the range of measurable values of current output response and varying values of target analyte.

IV. RESULTS AND DISCUSSIONS

Figure 2 shows the concentration profile for the ferrocyanide ion in the unit cell modeling the glucose biosensor. Ferrocyanide is generated in the solution between the electrodes and bulk by the enzyme catalyzed oxidation of glucose. It reacts at the working electrode in the center of the unit cell to generate the output response current used to measure the concentration of glucose. Ferrocyanide is regenerated at the counter electrodes at the fringes of the cell.

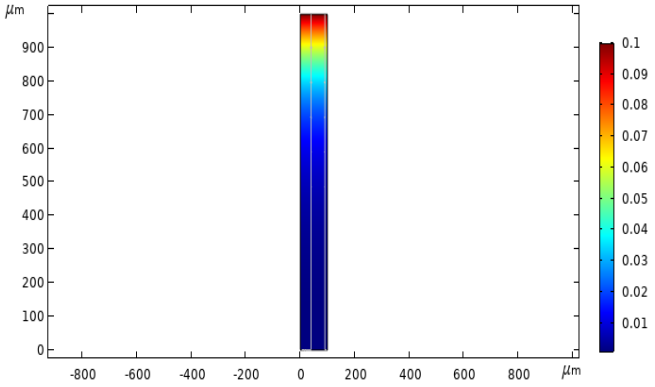

Figure 2: Concentration profile of ferrocyanide ion

The diffusion of ferrocyanide from the counter electrode to the working electrode represent reduction-oxidation process where a single redox reaction is driven in opposite directions at two electrodes with a small geometric separation. This redox reaction produces an output current that is linearly proportional to the varying concentration of glucose in the analyte solution as shown in Figure 3.

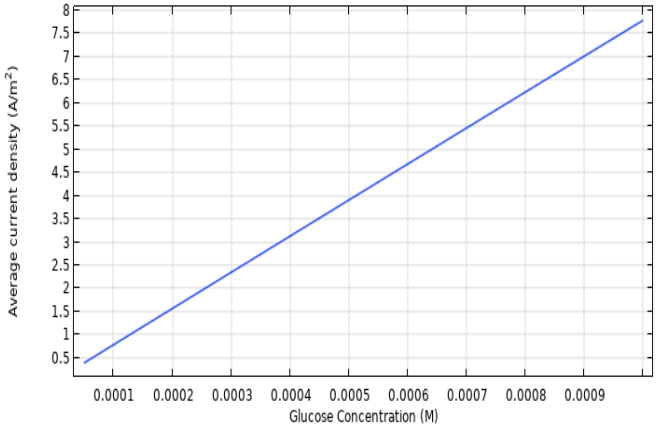

Figure 3: Plot of Average Current Density Against Glucose Concentration

As shown in Figure 3, as the input glucose concentration increases from 0.1M to 0.9M in the modeled glucose biosensor, the output response in terms of average current density increases linearly from 0.75 A/m² to 7.8 A/m². The linearity of response is a desirable property for an efficient measurement system.

V. CONCLUSION

In conclusion, the paper presents the modeling and simulation study of an enzymatic blood glucose sensor for clinical diagnosis. The working principle of the biosensor is based on amperometry which is the measurement an electric current from a chemical reaction process. A voltage is applied to the working and reference electrodes of the sensor and this resulted in the oxidation of glucose in the analyte sample, and the current due to this oxidation is measured at the electrode. The output measurement of the device showed that there is a linear relationship between the glucose concentration and the average current density output of the biosensor.

ACKNOWLEDGMENT

The authors gratefully acknowledge the management of the Lead City University, Ibadan and the Chemistry Advanced Research Centre, SHESTCO, Abuja, Nigeria for the support and facilities provided for the successful completion of this research project.

REFERENCES

[1] F. Faridbod, V. K. Gupta, and H. A. Zamani (2011) Electrochemical Sensors and Biosensors. International Journal of Electrochemistry, 2011, 1–2. doi:10.4061/2011/352546

[2] T. Sridara, J. Upan, G. Saianand, A. Tuantranont, C. Karuwan, and J. Jakmunee (2020). Non-Enzymatic Amperometric Glucose Sensor Based on Carbon Nanodots and Copper Oxide Nanocomposites Electrode. Sensors, 20(3), 808. doi:10.3390/s20030808

[3] C. Thunkhamrak, P. Chuntib, K. Ounnunkad, P. Banet, P.H. Aubert, G. Saianand, A.I. Gopalan, J. Jakmunee (2020) Highly sensitive voltammetric immunosensor for the detection of prostate specific antigen based on silver nanoprobe assisted graphene oxide modified screen printed carbon electrode. Talanta, 208, 120389.

[4] E. S. Paik, Y. R. Kim, H. G. Hong (2018) Amperometric Glucose Biosensor Utilizing Zinc Oxide-chitosan-glucose Oxidase Hybrid Composite Films on Electrodeposited Pt-Fe(III). Anal Sci. 2018;34(11):1271-1276. doi: 10.2116/analsci.18P054. PMID: 30416185.

[5] P. Pinyou, A. Ruff, S. Pöller, S. Barwe, M. Nebel, N. G. Alburquerque, E. Wischerhoff, A. Laschewsky, S. Schmaderer, J. Szeponik, N. Plumeré, W. Schuhmann (2015) Thermoresponsive amperometric glucose biosensor. Biointerphases. 2015 Mar 24;11(1):011001. doi: 10.1116/1.4938382. PMID: 26702635.

[6] R. B. Rakhi, P. Nayak, C. Xia, H. N. Alshareef (2016) Novel amperometric glucose biosensor based on MXene nanocomposite. Sci Rep. 2016 Nov 10;6:36422. doi: 10.1038/srep36422. Erratum in: Sci Rep. 2016 Dec 09;6:38465. PMID: 27830757; PMCID: PMC5103228.

[7] X. Liu, L. Shi, W. Niu, H. Li and G. Xu (2008) Amperometric glucose biosensor based on single-walled carbon nanohorns. Biosensors and Bioelectronics, 23(12), 1887–1890. doi:10.1016/j.bios.2008.02.016

[8] I. S. Kucherenko, D. Y. Didukh, O. O. Soldatkin, A. P. Soldatkin (2014) Amperometric biosensor system for simultaneous determination of adenosine-5'-triphosphate and glucose. Anal Chem. 2014 Jun 3;86(11):5455-62. doi: 10.1021/ac5006553. Epub 2014 May 21. PMID: 24810180.

[9] C. N. Kotanen, C. Tlili, A. Guiseppi-Elie (2013) Amperometric glucose biosensor based on electroconductive hydrogels. Talanta. 2013 Jan 15;103:228-35. doi: 10.1016/j.talanta.2012.10.037. Epub 2012 Nov 1. PMID: 23200382.

[10] L. F. Ang, L. Y. Por, M. F. Yam (2015) Development of an amperometric-based glucose biosensor to measure the glucose content of fruit. PLoS One. 2015 Mar 19;10(3):e0111859. doi: 10.1371/journal.pone.0111859. PMID: 25789757; PMCID: PMC4366129.

[11] D. Xiang, L. Yin, J. Ma, E. Guo, Q. Li, Z. Li, K. Liu (2015) Amperometric hydrogen peroxide and glucose biosensor based on NiFe2/ordered mesoporous carbon nanocomposites. Analyst. 2015 Jan 21;140(2):644-53. doi: 10.1039/c4an01549e. PMID: 25429370.

[12] M. C. Cebedio, L. A. Rabioglio, I. E. Gelosi, R. A. Ribas, A. J. Uriz, and J. C. Moreira (2020). Analysis and Design of a Microwave Coplanar Sensor for Non-Invasive Blood Glucose Measurements. IEEE Sensors Journal, 20(18), 10572–10581. doi:10.1109/jsen.2020.2993182

[13] N. Kim, K. Adhikari, R. Dhakal, Z. Chuluunbaatar, C. Wang, and E.-S. Kim (2015) Rapid, sensitive, and reusable detection of glucose by a robust radiofrequency integrated passive device biosensor chip," Rapid, sensitive, and reusable detection of glucose by a robust radiofrequency integrated passive device biosensor chip, vol. 5, 01 2015.

[14] E. Topsakal, T. Karacolak, and E. C. Moreland, (2011) Glucose-dependent dielectric properties of blood plasma," in 2011 XXXth URSI General Assembly and Scientific Symposium, Aug 2011, pp. 1–4.

[15] T. Yilmaz, R. Foster, and Y. Hao (2019) Radio-frequency and microwave techniques for non-invasive measurement of blood glucose levels, Diagnostics, vol. 9, no. 1, 2019.

[16] X. Strakosas, J. Selberg, P. Pansodtee, N. Yonas, P. Manapongpun, M. Teodorescu, and M. Rolandi, (2019) A non-enzymatic glucose biosensor enabled by bioelectronic pH control," *Science Reports*, vol. 9,7 pages, Jul. 2019.

[17] B. Prickril and A. Rasooly (Eds) (2017) Biosensors and Biodetection Methods and Protocols: Electrochemical, Bioelectronic, Piezoelectric, Cellular and Molecular Biosensors; Volume 2; Second Edition; Humana Press; Methods in Molecular Biology 11572; Springer Protocols; p. vii.

[18] E. H. Yoo, and Lee, S. Y. (2010). Glucose Biosensors: An Overview of Use in Clinical Practice. Sensors, 10(5), 4558–4576. doi:10.3390/s100504558

[19] F. Arslan and U. Beskan (2013) An amperometric biosensor for glucose detection from glucose oxidase immobilized in polyaniline–polyvinylsulfonate–potassium ferricyanide film. Artificial Cells, Nanomedicine, and Biotechnology, 42(4), 284–288. doi:10.3109/21691401.2013.812650

[20] C. Amarandei, E. Ungureanu, M. Leonida and C. Andronescu (2012) Glucose oxidase "wired" with potassium ferricyanide polypyrrole films; U.P.B. Sci. Bull., Series B, Vol. 74, Iss. 3, 2012

[21] O. Amor-Gutiérrez, E. Costa-Rama, and M. T. Fernández Abedul (2020) Determination of glucose with an enzymatic paper-based sensor. Laboratory Methods in Dynamic Electroanalysis, 257–265. doi:10.1016/b978-0-12-815932-3.00025-5

[22] J. Wang (2008) Electrochemical Glucose Biosensors. Chemical Reviews, 108(2), 814–825. doi:10.1021/cr068123a