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RESEARCH ARTICLE

Electrochemical Biosensor-Based Point-of-Care Device for Metabolic Health Monitoring

JOSÉ FRANCISCO BELTRÁN-SÁNCHEZ¹, LAURA GARCÍA¹, GONZALO MARTÍNEZ-GARCÍA², JOAN GARCIA-HARO¹, (Member, IEEE), AND ANTONIO-JAVIER GARCIA-SANCHEZ¹

¹Universidad Politécnica de Cartagena member of European University of Technology EUT+, Department of Information and Communications Technologies, Edificio Antigones, Campus Muralla del Mar, 30202 Cartagena, Spain

²Department of Chemical and Environmental Technology, ESCET, Universidad Rey Juan Carlos, Móstoles, 28933 Madrid, Spain

Corresponding author: Laura García (laura.garcia@upct.es)

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ABSTRACT The non-invasive measurement of biomarkers in biological fluids represents a significant advancement in the diagnosis and monitoring of metabolic diseases. This progress is closely tied to the development of accessible biosensors that combine reliable analytical performance with wireless connectivity for real-time data applications. In this study, we present a portable, low-cost electrochemical sensing platform, built around an ESP32 microcontroller with the LMP91000 analog front-end and dual native Wi-Fi and BLE wireless connectivity, and validate it as a proof-of-concept toward future non-invasive salivary monitoring of cholesterol and β -hydroxybutyrate (BHB). The platform is intended as a research-grade tool that establishes the electronic feasibility of accessible alternatives to conventional blood-based methods. Although saliva poses analytical challenges such as low analyte concentrations, interindividual variability, and potential interferences, it remains a promising matrix for biomarker detection due to its ease of collection and suitability for continuous monitoring. The biosensing system is based on modified screen-printed electrodes (SPEs) with enzyme immobilization, and integrates a portable potentiostat with Wi-Fi and Bluetooth Low Energy (BLE) connectivity, enabling real-time data transmission and potential integration into wearable platforms; the device additionally implements on-board computation of the analyte concentration from the standard addition protocol and displays the result on its integrated screen, allowing fully standalone operation without a host computer or smartphone. As a proof-of-concept, the developed system was validated using spiked reconstituted human serum, demonstrating robust analytical performance. For cholesterol, it achieved a linear range of 0.94–3.49 mM with a limit of detection (LOD) of 0.64 mM and a sensitivity of 137.1 nA/mM ($R^2 > 0.99$). For β -hydroxybutyrate, the device showed a linear range of 0.04–0.13 mM with an LOD of 0.06 mM and a high sensitivity of 4294.5 nA/mM ($R^2 = 0.997$). These results highlight the potential of this technology for point-of-care applications as a proof-of-concept toward future continuous monitoring of metabolic health.

INDEX TERMS Amperometry, β -hydroxybutyrate, cholesterol, electrochemical determination, ketonic bodies, potentiostat, saliva sample, screen printed electrode.

I. INTRODUCTION

Monitoring metabolic health is essential for the early detection and management of various diseases. Biomarkers such as ketone bodies and cholesterol are key indicators of

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metabolic processes and can provide valuable information on an individual's health status. Ketone bodies are metabolic compounds generated during ketosis, a process activated when glycogen reserves in the liver are insufficient to meet the body's energy demands, inducing lipolysis and subsequent fatty acid oxidation [1]. The measurement of ketone bodies is useful for monitoring and managing metabolic conditions, particularly ketosis, both nutritional and pathological. In clinical contexts, evaluating ketone body concentrations is crucial for diagnosing diabetic ketoacidosis, a severe and potentially life-threatening complication of diabetes. Additionally, recent research suggests that controlled ketosis may play a therapeutic role in the treatment of neurodegenerative diseases [2] and other chronic conditions [3]. In sports science and carbohydrate-restrictive dietary regimes, quantifying ketone bodies facilitates the assessment of ketosis levels, allowing for the optimization of nutritional strategies aimed at improving lipid utilization efficiency.

Specifically, ketone body production is activated in situations such as: prolonged food deprivation, which leads to a significant decrease in glucose availability, forcing the body to metabolize adipose stores for energy, generating ketone bodies as metabolic byproducts [1], [4]; adherence to carbohydrate-restrictive dietary regimens, such as the ketogenic diet, which minimizes carbohydrate intake to promote nutritional ketosis [5]; strenuous physical activity, which can deplete muscle and liver glycogen stores, resulting in increased lipolysis and ketogenesis to meet energy demands [6]; unregulated type 1 diabetes mellitus, where insulin deficiency prevents efficient glucose utilization, forcing the body to rely on free fatty acid oxidation with subsequent ketone production [7]; and conditions of elevated metabolic stress due to illness or severe psychological stress [8].

Cholesterol is a vital lipid molecule involved in cell membrane integrity, steroid hormone synthesis, and bile acid production. However, elevated cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, are associated with an increased risk of cardiovascular diseases [9]. Monitoring cholesterol levels is essential for assessing cardiovascular risk, managing hypercholesterolemia, and preventing heart disease. Regular cholesterol screening aids in the early detection and management of dyslipidemia, improving patient outcomes. Similarly, cholesterol levels are influenced by dietary intake, genetic factors, lifestyle, and underlying health conditions. Diets high in saturated and trans fats, sedentary lifestyles, obesity, and genetic disorders like familial hypercholesterolemia can lead to elevated cholesterol levels [10]. This underscores the need for precise and reliable methods for monitoring ketone bodies and cholesterol in various clinical and research settings.

While significant progress has been made in sensor technology, the successful deployment of portable biosensors relies heavily on overcoming electronic design challenges [11]. Traditional electrochemical measurements require bulky benchtop potentiostats. Transitioning to

portable, handheld devices demands the development of highly integrated, compact circuits without compromising sensitivity. Recent innovations, such as the *KickStat* system [12], combine dedicated potentiostat chips (e.g., Texas Instruments LMP91000 [13]) with ultra-low-power microcontrollers (e.g., ARM Cortex-M0+ [14]) on miniaturized footprints. Such designs demonstrate resolution on the order of 1 mV and nanoampere current detection, comparable to laboratory equipment. Flexible SPE substrates further enable sensor integration into wearable formats, such as sweat sensors [15] and mouthguards [16].

For real-time monitoring and telemedicine, wireless data transmission is essential [17]. Modern microcontrollers with integrated Wi-Fi and Bluetooth capabilities enable seamless data communication without external modules. In particular, Bluetooth Low Energy (BLE) is preferred for its low power consumption while providing sufficient bandwidth to transmit biosensor data [18]. In many prototypes, the microcontroller digitizes the sensor signal and transmits it via BLE to a smartphone application for visualization and logging [19]. This connectivity not only enhances user experience but also facilitates cloud-based data management and remote clinical oversight [20].

Beyond electronic transduction, non-electrical biosensing modalities are also receiving increasing attention for non-invasive and wearable monitoring. Colorimetric and optical detection schemes, particularly when combined with microfluidic or microneedle platforms functionalized with metallic nanoparticles, have demonstrated the ability to quantify clinically relevant biomarkers without on-body electronics; a recent example is the wearable microneedle functionalized with gold nanoparticles for transdermal phospho-Tau 181 detection [21]. These platforms are complementary to electrochemical approaches: they avoid the need for batteries and instrumentation on the patient side, at the cost of more limited dynamic range and harder integration with continuous digital data pipelines. In the present work we adopt amperometric electrochemical detection because of its quantitative response over several orders of magnitude in current and its natural compatibility with the digital wireless infrastructure required for real-time data transmission to remote systems.

Portable biosensors typically operate on rechargeable batteries (e.g., 3.7 V Li-ion polymer). Therefore, maximizing battery life and ensuring safe operation are critical. Electronic design must focus on low-power microcontrollers, energy-efficient analog front-ends, and smart power management strategies (such as duty cycling). Techniques include using ultra-low-power operational amplifiers, integrating high-resolution ADCs, and employing efficient DC-DC converters [22], [23]. Although emerging concepts such as biofuel cell-powered sensors show promise [24], current systems rely on optimized battery management to achieve operational lifetimes of hours to days.

The design of these portable systems invariably involves trade-offs based on their target application. For instance,

platforms built on specialized potentiostat ICs offer excellent analytical performance but may present less flexibility for adapting to novel electrochemical techniques. Similarly, while Bluetooth Low Energy (BLE) is optimal for power efficiency in smartphone-centric models, use cases benefiting from direct-to-cloud data streaming are better served by protocols like Wi-Fi. This context motivates the exploration of an architecture that balances analytical performance, connectivity, and cost. To highlight the position of our work within the current landscape of portable electrochemical devices, Table 1 presents a comparison with other representative systems. While platforms like *CheapStat* [25] pioneered open-source potentiostats, they lack modern wireless connectivity. More recent devices like *KickStat* [12] achieve extreme miniaturization but often rely on limited user interfaces. Our system leverages the ESP32 SoC to offer a unique combination of dual-mode connectivity (Wi-Fi/BLE) and a standalone OLED interface, bridging the gap between basic data loggers and complex commercial analyzers.

It is also important to distinguish this programmable research platform from established commercial diagnostic solutions. While commercial devices for blood or breath monitoring are available, they typically operate as closed, proprietary systems with limited flexibility for research or integration into custom IoT ecosystems. Our work provides a programmable, customizable architecture intended as a research-grade proof-of-concept toward non-invasive salivary analysis. By leveraging the ESP32 SoC, the platform integrates direct-to-cloud connectivity and a standalone user interface, offering a configurable tool for the development of future point-of-care applications.

This paper presents the electronic design and implementation of a portable potentiostat for smart electrochemical biosensors with real-time data transmission capability. The main contributions of this paper are:

- Design and implementation of a complete Point-of-Care device for the amperometric quantification of metabolic biomarkers, integrating in a single ESP32-based architecture: a programmable LMP91000 analog front-end, native dual wireless connectivity (Wi-Fi + BLE), an on-device display and control interface enabling operation and result reading entirely in situ without a host computer or smartphone, and an open, programmable firmware. This combination of features is not found among the representative portable potentiostats surveyed in the literature.
- End-to-end validation of the full signal chain (biosensor $\rightarrow$ AFE $\rightarrow$ ADC $\rightarrow$ wireless) on β -hydroxybutyrate and cholesterol using enzymatic biosensors on modified screen-printed electrodes in spiked reconstituted human serum, with on-board implementation of the standard addition method including volume-dilution correction, as a proof-of-concept toward future non-invasive salivary monitoring.
- Open, low-cost architecture (BOM in the EUR 45–70 range) suitable for research instrumentation, with

extensibility to other amperometric biomarkers via firmware reconfiguration of the LMP91000 (programmable transimpedance gain and cell bias) and a characterized electronic chain whose noise floor is well below the analytical signals reported.

The rest of the paper is organized as follows. Section II presents the materials and methods used to develop the device for ketonic body and cholesterol monitoring. The results are discussed in Section III. Lastly, the conclusion and future work are presented in Section IV.

II. MATERIALS AND METHODS

The materials used to create our device for non-invasive ketone bodies and cholesterol detection and the employed methodology are presented in this section.

A. DEFINING MEASURABLE PARAMETERS, ANALYTICAL TECHNIQUES, AND FLUID ENVIRONMENTS

The ketone bodies include: acetoacetate, β -hydroxybutyrate (BHB), and acetone [30]. Acetoacetate is first formed from the breakdown of fatty acids in the liver and can subsequently be converted into BHB or degrade to produce acetone. BHB, although technically not a ketone body due to its chemical structure, is considered one due to its role in ketogenic metabolism and is the most quantified in clinical studies due to its stability in the blood. Acetone, less abundant and more volatile, is primarily excreted through respiration and urine.

BHB is the ketone body with the highest presence in both saliva and blood. Thus, it is the ketone body that has been studied the most and its enzymatic reactions are more widely used. The other two ketone bodies, acetone and acetoacetate, can be determined amperometrically by biosensors. However, scientific output related to the development of these sensors is considerably more limited due to the greater complexity and poor reproducibility associated with the required enzymes. Therefore, this paper focuses on detecting BHB. BHB can be found in blood, saliva, and urine. Using blood is safe and effective in hospital facilities, as trained medical staff perform the extractions and required analyses. However, it is an invasive method not viable for everyday users. BHB is not the predominant ketone body in urine. Furthermore, this medium would require strict sanitation of the device after use, which could lead to health problems if handled incorrectly. Consequently, this paper addresses the challenge of BHB detection within salivary concentration ranges. The concentration of BHB in blood ranges from 0.01 mM in healthy individuals at rest and not fasting, up to 15 mM in people with ketoacidosis who require urgent medical attention. In saliva, the concentration is between 6 and 7% of that present in blood, so these levels range from 6 nM to 1.05 mM [31]. Therefore, this application requires a very high sensitivity, and to our knowledge, no previous study has demonstrated such precision with a portable device. Therefore, the work presented here is focused on validating the technological feasibility of our platform to achieve the

TABLE 1. Comparison of the present platform with representative portable electrochemical instruments.

System	AFE / Controller	Wireless	Standalone display	Current resolution / noise	Open / proprietary	Reference
CheapStat	Discrete + AVR	USB only	LCD	nA precision [a]	Open	[25]
DStat	Discrete + USB MCU	USB only	None	picoampere range [b]	Open	[26]
Rodeostat	Discrete + SAMD51 (ItsyBitsy M4)	USB only	None	16-bit, 4 ranges ($\pm 1\text{--}1000\ \mu\text{A}$) [c]	Open	[27]
KickStat	LMP91000 + SAMD21 (Cortex-M0+)	USB only	None	4.5 nA instrumental LOD [d]	Open	[12]
FreiStat	AD5941 + SAMD21 + ATWINC1500	Wi-Fi (via add-on); BLE/LoRa	None	54 pA resolution [e]	Open	[28]
EmStat Pico / Sensit BT	ADuCM355 (integrated SoC)	BLE + USB	None	5.5 pA LSB on lowest range [f]	Proprietary	[29]
This work	LMP91000 + ESP-WROOM-32	Wi-Fi + BLE native	Yes (on-device)	$\sim 290\ \text{pA RMS}$ / $0.9\ \text{nA at } 3\sigma$ [g]	Open	this paper

Current-resolution metrics are reported as defined by each source: [a] reported by authors as “nanoampere precision”; [b] picoampere-range with ~ 23 -bit precision at low gain and slow sample rate; [c] 16-bit current ADC across four user-selectable ranges; [d] instrumental LOD from ferricyanide voltammetry; [e] reported resolution on a lactate biosensor measurement; [f] datasheet specification, 1 LSB of the lowest current range; [g] root-sum-of-squares input-referred current noise computed from datasheet parameters; an experimental noise floor of 1.09 nA RMS was measured (see the Electronic Validation Results subsection).

required sensitivity, even if it is in “Urgent/Non-urgent” ranges.

Analogous to β -hydroxybutyrate, cholesterol is also detected in multiple biological fluids; however, its measurement in saliva has gained interest due to its non-invasive nature. Salivary concentrations of total cholesterol are typically reported in the range of 0.5–4.6 mg/dL [32], [33], correlating well with serum levels of approximately 120–200 mg/dL. This correlation is particularly relevant for the early diagnosis of familial hypercholesterolemia, a genetic disorder that markedly elevates cardiovascular risk.

Similar to the approach adopted for β -hydroxybutyrate, our strategy for cholesterol detection involves an amperometric biosensor. In this case, a tri-enzymatic configuration is employed, utilizing cholesterol oxidase, cholesterol esterase, and peroxidase to catalyze the sequential reactions necessary to release cholesterol from its fatty acid complexes and oxidize it. The enzymatic reaction produces hydrogen peroxide as a measurable byproduct, which is detected using an electrode modified with nanomaterials and redox mediators. This configuration is designed to achieve a detection sensitivity sufficient to quantify cholesterol in the micromolar range (approximately $10\ \mu\text{M}$), thereby meeting the analytical challenges imposed by the low concentrations in saliva.

By integrating these considerations into our device design, we aim to establish a platform capable of addressing key sensitivity limitations and delivering reproducible measurements within the concentration ranges pertinent to future clinical applications.

The operating potentials selected for amperometric detection (0.00 V for BHB and +0.15 V for cholesterol, vs. pseudo-reference) were chosen based on prior cyclic

voltammetry characterization of the rGO/THI modified electrodes [34], which identifies the minimum overpotential required to drive the mediator redox process while avoiding direct oxidation of common interferents such as ascorbic or uric acids.

B. BIOSENSOR IMPLEMENTATION

Two distinct enzymatic biosensors were fabricated on the SPEs for the selective detection of BHB and cholesterol.

1) CHEMICALS AND MATERIALS

Screen-printed carbon electrodes (SPEs, Model DRP-C110 [35]) were obtained from Metrohm DropSens (Oviedo, Spain). Graphene Oxide (GO, Ref. NIT.GO.M.140.10) was purchased from Nanoinnova Technologies (Valladolid, Spain). For the synthesis of reduced graphene oxide (rGO), L-ascorbic acid (>99%) was obtained from Gerbu, and ammonia (32%) from Scharlau.

Thionine acetate salt (THI), β -Nicotinamide adenine dinucleotide hydrate (NAD^+), β -Hydroxybutyrate Dehydrogenase (from *Pseudomonas* sp.), Cholesterol Oxidase (ChOx, from *Streptomyces* sp.), Cholesterol Esterase, Horseradish Peroxidase, Chitosan, and other buffer reagents were purchased from Sigma-Aldrich or equivalent suppliers. All aqueous solutions were prepared using ultrapure water.

The reduced graphene oxide (rGO) was synthesized following an environmentally friendly procedure [36]. Briefly, a 1 mg/mL GO aqueous dispersion in deionized water was prepared by ultrasonic stirring for 4 h and then centrifuged at 10,000 g for 10 min. The precipitate was discarded and the supernatant liquid was treated with a 25% NH_3 solution to adjust the pH to 9–10. Further reduction of GO

was performed in the presence of 2 mM ascorbic acid by maintaining a temperature of 100 °C for 15 min.

2) β -HYDROXYBUTYRATE (BHB) SENSOR

The BHB biosensor follows the design previously developed by one of the present authors Martínez-García et al. [34]. The working electrode (WE) of the SPE was modified by drop-casting 5 μ L of a 1 mg/mL rGO suspension and drying under an infrared lamp. Subsequently, 15 μ L of 1 mM THI solution was incubated on the WE in a humid chamber at room temperature for 30 min, followed by rinsing with ultrapure water and drying under a nitrogen stream. Finally, 0.1 U (2 μ L of a 0.05 U/ μ L solution) of β -HBDH enzyme solution (containing NAD⁺ as cofactor) was deposited onto the modified WE and allowed to dry overnight at 4 °C via physical adsorption. The resulting biosensor operates amperometrically at an applied potential of 0.00 V (vs. pseudo-reference), detecting the NADH byproduct mediated by THI.

The measurement process is based on the determination of the NADH formed in the reaction as a by-product (β -HB + NAD⁺ $\rightarrow$ acetoacetate + NADH + H⁺), which is reduced at the expense of THI oxidation at a potential of 0.00 V by thionine mediation. The use of the THI mediator avoids the high overpotentials ($\sim$ +0.5 V) required for direct NADH oxidation and reduces interference from electroactive species such as ascorbate or urate; the rGO layer increases the electroactive surface area and facilitates electron transfer between the mediator and the carbon substrate. These optimal conditions allowed constructing the calibration curve shown in Figure 1.

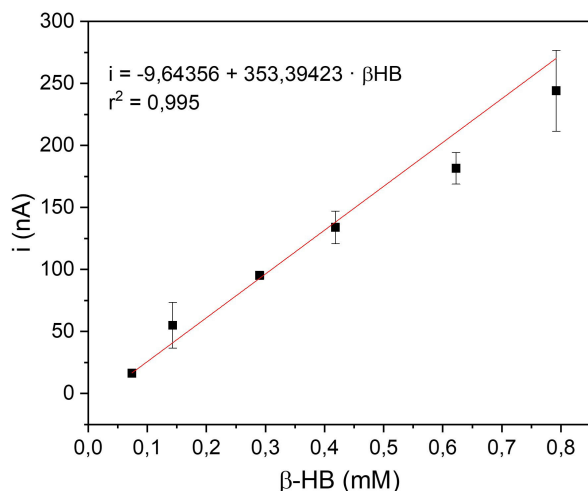


FIGURE 1. Calibration curve for enzymatic biosensor BHB.

Furthermore, the following analytical characteristics were determined under the same conditions.

The limit of detection (LOD) was calculated using the formula $LOD = 3s/b$, where s is the standard deviation obtained from ten replicates of the lowest calibration point

and b is the slope of the calibration curve. The resulting value was 0.06 mM.

The Relative Standard Deviation (RSD) was determined from six replicates of a 0.3 mM BHB concentration, yielding a value of 4.50% ($RSD = (s/\bar{x}) \cdot 100$).

3) CHOLESTEROL SENSOR

A similar initial modification with rGO and THI was performed as described for the BHB sensor. Following this, 5 μ L of a solution containing ChOx (1 mg/mL) and potentially Cholesterol Esterase/Peroxidase (if using the tri-enzymatic system mentioned in Section II-A) dissolved in 1% Chitosan solution (in acetic acid) was deposited onto the THI-modified WE. The Chitosan acts as an immobilization matrix after drying overnight at 4 °C. This sensor operates amperometrically at an applied potential of +0.15 V (vs. pseudo-reference), detecting hydrogen peroxide mediated by THI.

Mechanistically, the tri-enzymatic configuration enables the catalytic hydrolysis (mediated by cholesterol esterase) of esterified cholesterol to free cholesterol, which is subsequently oxidized by cholesterol oxidase (ChOx) in the presence of molecular oxygen, producing cholest-4-en-3-one and hydrogen peroxide ($\text{cholesterol} + \text{O}_2 \rightarrow \text{cholest-4-en-3-one} + \text{H}_2\text{O}_2$). Finally, peroxidase acts as an electrocatalyst for H₂O₂ reduction, enhancing signal transduction via THI mediation at +0.15 V vs. a pseudo-reference electrode, minimizing interference from other electroactive species. The chitosan matrix immobilizes the enzymes by physical adsorption and electrostatic interactions, preserving their activity while allowing analyte diffusion toward the electrode surface. This specific configuration was developed for the present work to extend the BHB platform to a second metabolite using the same hardware.

The design parameters of the biosensor were as follows: a commercial screen-printed electrode (SPE) with carbon working and counter electrodes and Ag/AgCl pseudo-reference. The working electrode was modified sequentially with 5 μ L of 1 mg/mL rGO (drying under IR lamp), 15 μ L of 1 mM THI (30 min incubation in a humid chamber, rinsed with ultrapure water, dried under N₂), and the enzyme layer (0.1 U β -HBDH for BHB; 5 μ L of 1 mg/mL ChOx in 1 % chitosan for cholesterol), dried overnight at 4 °C. Sensors were used within 10 days of preparation and stored at 4 °C in sealed containers.

C. ELECTRONIC SYSTEM DESIGN

Following the fabrication of the biosensor, a suitable device is required to acquire sensor data and present the information to the user. This subsection details the implementation of the portable potentiostat designed for the measurement of ketone bodies and cholesterol.

Several considerations were addressed to design a prototype suitable for rapid manufacturing and public accessibility. These included low industrialization costs, portability, regulatory compliance, component availability,

TABLE 2. Device Specifications.

Specifications	Observations
Size	125 mm × 40 mm × 8 mm
Connectivity	BLE (Bluetooth Low Energy) and Wi-Fi
Screen	0.96" OLED 128 × 64
Buttons	Navigation through the terminal options (UP, DOWN, ENTER, BACK) and on/off switch.
Indicators	LED (STATUS and POWER) and buzzer for acoustic warnings.
Power	Lithium polymer battery operation, with charging via micro USB connector.

and manufacturing techniques. With these aspects in mind, the final prototype specifications are detailed in Table 2.

The diagram of the main blocks and components of the system is presented in Figure 2. The Power Management block is responsible for managing the battery charge/discharge cycles, the power supply via the micro-USB port, protections, filters, voltage regulation for component operation, and the generation of reference voltages. The Analog Data Acquisition (DAQ) block provides the analog interface for substance measurement and determination. It consists of a potentiostat circuit for amperometric measurements, a variable voltage reference, and an analog-to-digital converter. The User Interface (UI) enables interaction between the device and the user, comprising a display, status LEDs, buttons, and a buzzer. A microcontroller performs system control and data processing functions. Finally, the connectivity block, integrated within the microcontroller, provides BLE and Wi-Fi communication.

1) POWER MANAGEMENT BLOCK

The power management block comprises several key elements. The micro USB connector draws a +5V voltage from an external standard USB power supply. This interface is ubiquitous in modern consumer electronics, and its usage utilizes low voltage levels that fall below the thresholds requiring strict Low Voltage Directive (LVD) certification compliance [37].

Since portability is a key specification, the device requires a battery for autonomous operation. While a wide range of battery technologies exists (both rechargeable and non-rechargeable), rechargeable LiPo (Lithium Polymer) 3.7 V, 190 mAh batteries were selected to minimize the environmental impact and recurring cost of disposable batteries. LiPo batteries are widely used in consumer electronics due to their high energy density-to-weight ratio and competitive pricing. A critical consideration for this technology is the requirement for protection electronics, as LiPo cells are susceptible to damage from under/over-voltage, over-current, or excessive discharge. Consequently, the selected commercial batteries include a built-in Protection Circuit Module (PCM).

The MCP73831 integrated circuit manages the charging of 1-cell Li-ion batteries from the +5 V supply provided

by the USB connector. The TLV75533, a +3.3 V, 500 mA Low-Dropout (LDO) regulator, supplies the operating voltage for the circuit components from the +3.7 V battery voltage. Furthermore, the REG71055 voltage booster and the LM4120-5 voltage regulator are responsible for generating a precise +5 V reference voltage from the battery supply. The REG71055 boosts the battery voltage to 5.5 V, providing the necessary headroom for the LM4120-5 to deliver a stable and regulated +5 V output.

2) ANALOG FRONT-END (AFE) AND DATA ACQUISITION

The analog DAQ block features the LMP91000, a programmable analog front-end (AFE) designed for amperometric measurements in electrochemical applications [13]. This component integrates the necessary analog circuitry to interface with an electrochemical cell and condition the signal. It incorporates a potentiostat circuit, a Transimpedance Amplifier (TIA), a temperature sensor for compensation, a reference voltage source, and an I2C interface for controller communication. It provides a complete signal conditioning solution, yielding an output voltage proportional to the sensor's working current, which can be digitized by an ADC. The programmability of the LMP91000 enables support for multiple electrochemical sensors. The TIA gain and the adjustable cell bias of the LMP91000 are programmable via the I2C interface. This interface also facilitates sensor diagnostics, as the integrated temperature sensor can be read to monitor conditions or apply signal corrections in the microcontroller. Finally, the LMP91000 is optimized for low-power applications, operating over a voltage range of 2.7 to 5.25 V with a total current consumption of less than 10 μ A.

The ADC161S626 is a 16-bit precision analog-to-digital converter that digitizes the analog voltage output from the LMP91000 potentiostat circuit. It delivers the converted 16-bit digital value to the microcontroller via an SPI bus.

Finally, to provide greater flexibility in the potentiostat voltage sweep and ADC voltage readout, an adjustable and precise voltage source is desirable. In this design, the MCP4725 12-bit digital-to-analog converter (DAC) was employed as a programmable voltage reference generator, allowing the microcontroller to adjust the output voltage via an I2C interface.

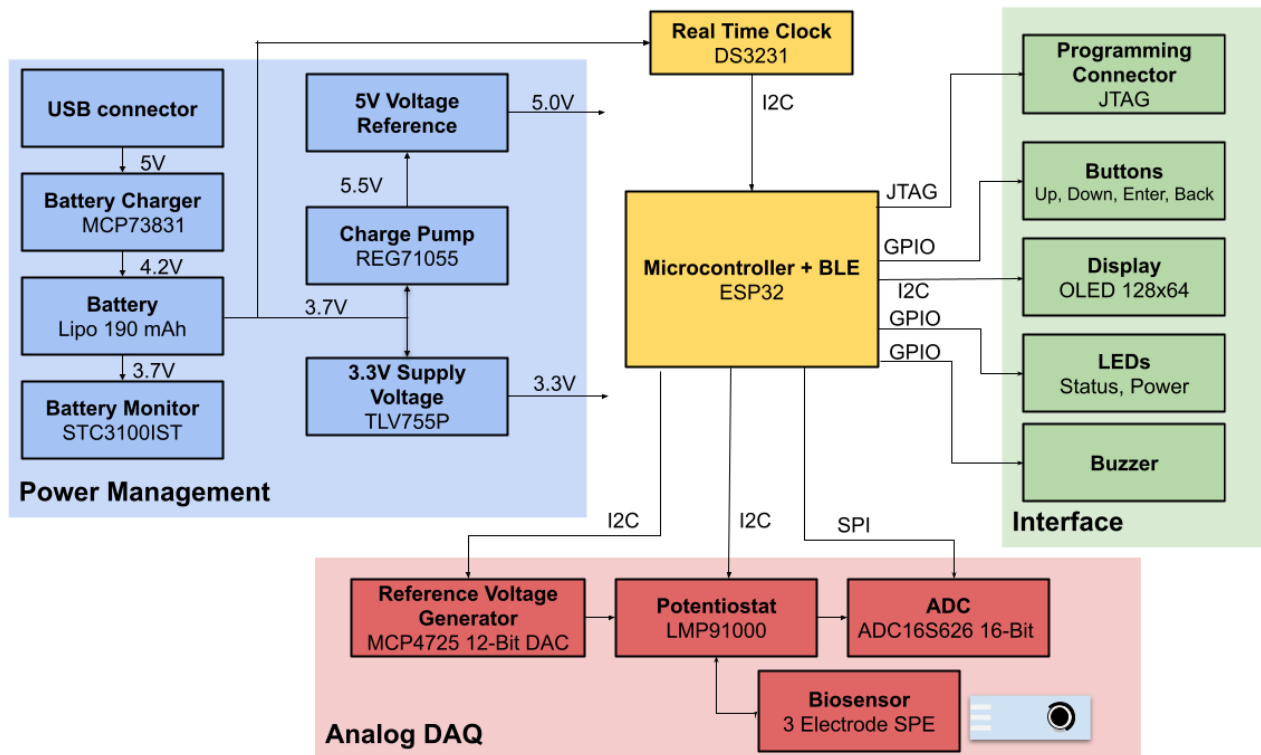


FIGURE 2. Block diagram and system components.

3) USER INTERFACE

The device includes a JTAG (Joint Test Action Group) connector for microcontroller programming and firmware debugging. User interaction is facilitated by four buttons: two for menu navigation, one for selection, and one for returning to the previous menu. An OLED 128×64 display was selected to present data and operational controls. This display type was chosen for its ability to show graphical information, compact size, and low power consumption. Alphanumeric displays were ruled out due to limited information density, while color LCDs were discarded due to higher power consumption and programming complexity. Consequently, a 0.96-inch monochromatic OLED screen was selected.

The device also incorporates two LEDs: a green LED to indicate operating status and a red LED for battery charging status. Additionally, a buzzer provides acoustic feedback during menu navigation, result presentation, or when user intervention is required.

4) CORE PROCESSING AND CONNECTIVITY

The current market offers a wide range of microcontrollers with integrated connectivity features such as Wi-Fi and Bluetooth Low Energy (BLE). Incorporating these features via System-on-Chip (SoC) solutions simplifies implementation and, as these modules are pre-certified, reduces the complexity of electromagnetic compatibility (EMC) certification. The microcontroller executes the firmware that controls

peripherals, sets operating modes, and processes/stores data. Key specifications for the microcontroller included BLE connectivity, I2C and SPI interfaces, and a 12-bit ADC. An integrated DAC was also considered a desirable feature to reduce external component count. All these features were required within a low-power envelope.

Table 3 presents the specifications of the microcontroller options evaluated. After careful consideration, Espressif's ESP32 (specifically the ESP-WROOM-32 module) was selected [38]. The rationale for this selection included: its dual Wi-Fi and Classic/BLE Bluetooth connectivity, offering future-proof interconnection possibilities; the integrated 12-bit ADC and dual 8-bit DACs, which eliminate the need for certain external components; a significantly lower unit cost compared to alternatives; robust manufacturer support and an active community; and long-term availability (production guaranteed until at least January 2028). While its power consumption is higher than some ultra-low-power alternatives, it remains within acceptable limits for a rechargeable handheld device designed for episodic rather than continuous operation.

The bill of materials (BOM) cost of the device, including the PCB fabrication and all electronic components, is approximately EUR 70 per unit in single-unit quantities and EUR 45 per unit at a batch of 1000 units. This figure covers only the electronic hardware; it does not include enclosure 3D-printing materials, assembly labor,

TABLE 3. Microcontroller comparative.

Manufacturer	Nordic Semiconductor	Cypress Semiconductor	Texas Instruments	Espressif
Chip Solution	nRF52832 [39]	PSoc 4 BLE [40]	TI CC2650 [41]	ESP32 [38]
Core	32-bit ARM Cortex-M4F 64 MHz	4-MHz Arm Cortex-M0	32-bit ARM Cortex-M3 48MHz	Tensilica LX6
Specifications	FPU (Float point unit) Bluetooth 5	LCD segment drive Programmable opamps	-	with Bluetooth classic and Wi-Fi HIGH power consumption ($\times 10$)
ADC	12-bit, 200 kSPS	12-bit SAR @ 1 MSPS	12-bit ADC, 200 kSPS	12-bit SAR ADCs
DAC	-	-	-	8-bit DAC x2
Module Solutions	Rigado Serie 300 (BMD-300, BMD-330, BMD-350) 7–10 € per unit Fanstel (BT832, BT832A, BT832AF, BC832) 3–9 € per unit	EZ-BLE cyble series 10–14 € per unit	CC2650MODA 9.50 € per unit	ESP-WROOM-32 3.80 € per unit

packaging, quality control, or regulatory certification, all of which would be required for a finished commercial product. Even so, this BOM cost positions the platform as a strong candidate for low-cost research instrumentation and, with appropriate productisation, for affordable point-of-care devices accessible to health care centers and end users.

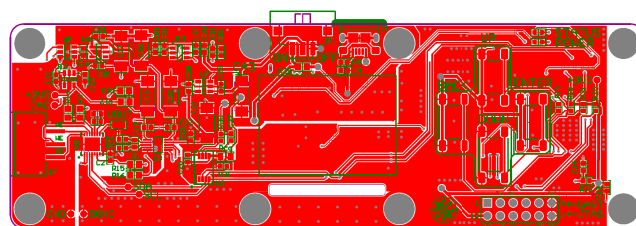
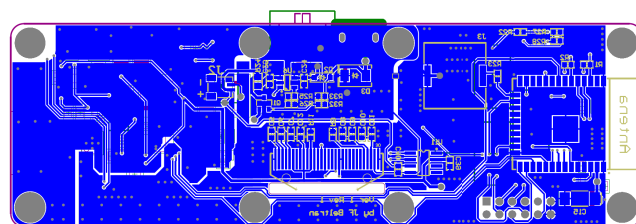
D. DESIGN FOR MANUFACTURABILITY OF PRINTED CIRCUIT BOARD

Once the main components of the design were selected, an engineering Design for Manufacturability (DFM) was carried out. This encompasses the layout and measurements of the main components on the printed circuit board, the circuit schematics, the printed circuit board design, and the 3D design of the prototype.

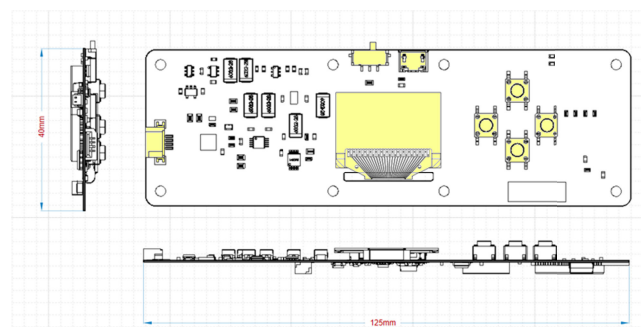
Figure 3 shows the layout proposed for the device. As can be seen, the connector for the printed electrodes is located on the left edge of the board (in the front view). The on/off switch and the micro USB port for charging the device are

placed at the top. The OLED display is located in the center. Finally, the button panel is on the right side of the board. The size of the developed board is 40 mm wide $\times$ 125 mm long.

To manufacture the circuit on a printed circuit board, it is necessary to make the design from the schematics of the board to be manufactured. Since it must be a product ready to be produced by the industry, the generated designs presented in Figures 4 and 5 were sent to a PCB manufacturer.

**FIGURE 4.** PCB view of top copper layer.**FIGURE 5.** PCB view of bottom copper layer.

The PCB follows a standard two-layer FR-4 stack-up with the usual copper, solder-mask, silkscreen, solder-paste, component-placement and drilling layers required for industrial fabrication. The design choices relevant to this

**FIGURE 3.** Component distribution and measurements of the PCB.

work are limited to the two-layer count itself (driven by the low-cost objective) and to the EMI-mitigation strategy described next.

Throughout the design process, special consideration was given to electromagnetic interference (EMI) mitigation to ensure signal integrity for the sensitive analog measurements. Key best practices were incorporated into the PCB layout. A primary strategy was the physical segregation of the analog front-end (AFE) circuitry from digital and radio-frequency (RF) components. To this end, the microcontroller and the BLE/Wi-Fi antenna were positioned on the opposite edge of the board from the AFE, maximizing the physical distance to minimize noise coupling. Furthermore, large, uninterrupted ground planes were implemented on both layers to provide effective shielding. A significant design trade-off was the selection of a 2-layer PCB over a 4-layer alternative to meet the low-cost objective. While a 4-layer stack-up offers superior EMI performance, the 2-layer design was deemed sufficient for this application due to the absence of high-speed digital interfaces and was compensated by the extensive ground planes. These choices represent a deliberate balance between manufacturing cost, EMI robustness, and analytical performance.

The resulting manufactured PCB is presented in Figures 6 and 7.

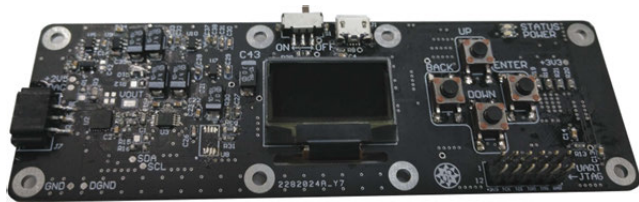


FIGURE 6. Frontal view of the manufactured PCB.

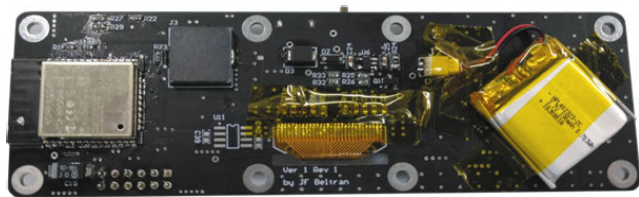


FIGURE 7. Bottom view of the manufactured PCB.

E. DEVICE ASSEMBLY AND ENCAPSULATION

The design and manufacture of an enclosure serves several functions. It protects the circuit contacts so that unwanted interconnections do not occur. It also provides mechanical protection from shock and environmental factors. It adds an aesthetic function to the prototype. It contains all components inside, where some such as display and battery are not glued to the PCB. Furthermore, using a metallic coating can provide isolation from ambient electrical noise. It is important to note that this coating must not be applied to the BLE transmission part of the device.

All components and sizes of the prototype have been taken into account for the design (see Figure 8). Specifically, those components with which the user has to interact, such as the display, switch, charging port, electrode connector, buttons, LEDs, and the programming port, must all be accessible. The design of the housing must provide robustness, as well as the ability for easy assembly and disassembly, so it consists of two parts: a housing that covers the device, and a back cover that is screwed to the housing. Cavities have been designed into the PCB at earlier stages in order to be able to insert these joining screws and stiffen the assembly.

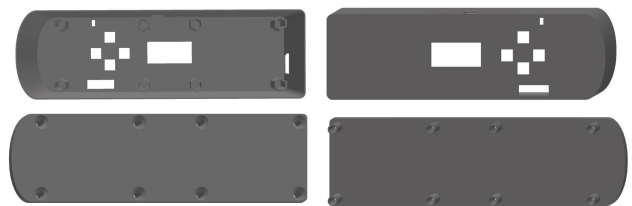


FIGURE 8. Different views of the housing model.

The material used to manufacture the housings of most electronic devices is based on plastic compounds. The industrial processes of housing manufacturing include techniques such as plastic injection molding, which are low cost when performed for many units, but whose price is very high for a small number of devices. Therefore, 3D printing is used to manufacture this housing, whose final quality and finish does not reach the standards of other techniques, but allows the low-cost production of a housing that helps validate the design and correctly meets the functional specifications.

F. FIRMWARE DEVELOPMENT

The ESP32 microcontroller from Espressif selected for the processing and control functions of the device is an integrated system-on-chip with Wi-Fi (2.4 GHz band), Bluetooth 4.2, a high-performance dual-core, ULP (Ultra Low Power Processor), and a large number of peripherals. Espressif provides various hardware and software resources to assist in the development of applications for the ESP32. The ESP32 allows writing applications that run natively on the device. It also allows compiling applications written in C programming language from a computer and deploying them on the device through a process known as flash.

In order to program the microcontroller, the application development framework provided by Espressif (ESP-IDF) was used [42]. It was designed to facilitate the development of applications for the Internet of Things (IoT) with Wi-Fi, Bluetooth, power management and other system functions. ESP-IDF (Espressif IoT Development Framework), is implemented on a version of FreeRTOS, an open source operating system developed for real-time applications [43]. It allows executing and organizing tasks under strict time conditions. The use of ESP32 functions and peripherals must be done

through an extensive library of APIs contained in the ESP-IDF, which are documented on the manufacturer's website.

The application for the ESP32 is written in C programming language. Regarding the graphical interface, the amperometry values are predetermined, and the interaction with the user is focused on functions such as start, stop, substance addition or synchronization. Some factors that were considered when implementing the code were power management, interaction with low-level hardware, and hardware error detection routines, among others.

The flowchart in Figure 9 outlines the sequence of operations performed by the firmware to control the user interface. The system allows the selection of the substance to be measured, and the execution of the debugging mode. The debugging mode allows the connection of the device to a computer with which the program execution log is displayed on the screen and the curves generated during the measurement can be viewed. This mode allows validating the proper functioning of the device in the developing stages. Once the configuration has been selected, the device executes the substance determination procedure. Depending on the selected substance, operating parameters are set (voltage, signal amplification, sampling rate, waiting times, sample size, etc.). The system then begins with the measurement, guiding the user through the OLED display and acoustic signals through the next steps to be performed.

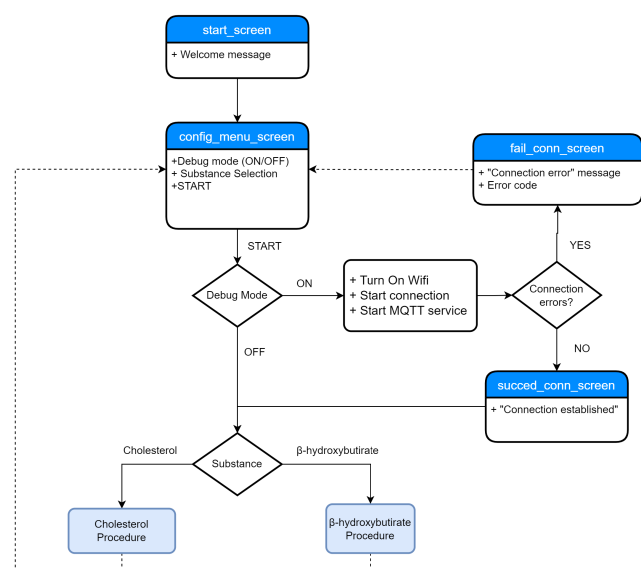


FIGURE 9. Firmware flowchart.

G. ELECTRONIC VALIDATION METHODOLOGY

The performance of the analog signal chain (LMP91000 transimpedance amplifier, ADC161S626 16-bit successive-approximation ADC, and LM4120-5 voltage reference) was characterized both theoretically and experimentally.

Regarding the theoretical noise budget, the intrinsic input-referred current noise was estimated by combining the dominant uncorrelated contributions, taken from the

corresponding component datasheets, in root-sum-of-squares. At the maximum TIA gain ($350\text{ k}\Omega$, $\sim 6.5\text{ kHz}$ bandwidth) the considered contributions are: the LMP91000 output noise voltage density ($250\text{ nV}/\sqrt{\text{Hz}}$ typ., integrated over the full TIA bandwidth) referred to the input through the TIA transimpedance; the ADC161S626 noise (1.3 LSB RMS at low sample rate, with $\text{LSB} = 76\text{ }\mu\text{V}$) referred to the input through the same TIA transimpedance; the LM4120-5 reference noise ($30\text{ }\mu\text{V}$ peak-to-peak in the $0.1\text{--}10\text{ Hz}$ band); and the Johnson noise of the $350\text{ k}\Omega$ feedback resistor at $25\text{ }^\circ\text{C}$. The resulting theoretical noise floor is reported in Section III-E.

The intrinsic noise floor of the assembled device was experimentally characterized using a $1\text{ M}\Omega$ metal-film resistor (1% tolerance) as a passive dummy cell, connected between the working-electrode terminal and the shorted counter/reference terminals of the SPE connector. This emulates an electrochemical cell of representative impedance while injecting no faradaic current. The device was powered from its USB input (no LiPo battery installed), placed on an open laboratory bench without additional electromagnetic shielding, and configured with the LMP91000 in amperometric mode at the chosen TIA gain and cell bias $= 0$. Amperometric data were captured at fixed sampling rates (10 SPS for long-duration drift characterization and 1 kSPS for short-duration spectral characterization) using the diagnostic firmware mode, with raw samples streamed via UART to the host. The DC offset was removed from the captured trace before computing the standard deviation, which is reported as the input-referred current noise σ at each TIA gain. The 3σ value is reported as the operational limit of detection of the electronics.

Instrumental linearity was assessed using the same $1\text{ M}\Omega$ dummy cell across the full programmable cell bias range of the LMP91000 (14 discrete settings from 0% to 24% of V_{DD} , corresponding to $0\text{--}792\text{ mV}$ applied to the dummy cell). At each bias setting, 100 amperometric samples were captured at 10 SPS after stabilization, and the mean current was computed. A least-squares linear regression was then performed on the (applied voltage, mean current) pairs, with the slope, intercept, and coefficient of determination R^2 reported. The expected theoretical slope is 1 nA/mV , derived from Ohm's law at the nominal $R_{\text{dummy}} = 1\text{ M}\Omega$.

Power consumption was characterized experimentally using a Nordic Power Profiler Kit II (PPK2) connected in series between the LiPo battery and the device input, sampling at 100 kS/s . The device was driven through a fixed sequence of operating modes (deep sleep, idle with the CPU active, active amperometric acquisition, Wi-Fi association, Wi-Fi connected idle, and Wi-Fi data transmission), each held for a defined duration, with explicit GPIO transition markers captured by the PPK2 digital channel to allow per-mode segmentation of the current trace. The mean current of each mode was integrated to derive the per-mode current draws and the autonomy estimates for representative measurement cycles, using the 3.7 V , 190 mAh LiPo battery capacity.

H. MEASUREMENT PROTOCOL

Direct quantification of biomarkers in complex biological fluids such as saliva or serum using external calibration curves (prepared in simple buffers) can lead to significant inaccuracies. This is primarily due to the presence of various interfering species and the inherent variability of the sample matrix composition (matrix effects), which can alter the electrochemical sensor's response compared to its behavior in a clean calibration standard. Furthermore, analyte concentrations in saliva are often low, demanding robust quantification techniques.

To address these challenges and ensure accurate determination of BHB and cholesterol concentrations in the presence of the sample matrix, the Standard Addition Method (SAM) was exclusively employed for all quantifications performed with the developed PoC device.

SAM is a widely accepted analytical tool that effectively compensates for matrix effects by performing the calibration curve generation *in situ*, within the actual sample [44]. The core principle involves measuring the analytical signal (in this case, amperometric current) from the neat sample and then subsequently measuring the signal after adding one or more known amounts (spikes) of the analyte standard directly to that same sample volume. By plotting the change in signal against the known concentrations of the added standard, a calibration curve specific to that sample matrix is obtained. The initial concentration of the analyte in the unknown sample is then determined by extrapolating the linear regression of this curve back to the concentration axis intercept (where the signal corresponds to the neat sample) or mathematically from the slope and intercept. This approach ensures that the calibration accurately reflects the sensor's performance under the specific conditions imposed by the individual sample matrix. The step-by-step implementation of this method within the device's operational workflow is detailed below.

- 1) **Baseline Stabilization:** The biosensor (BHB or Cholesterol) is inserted, and the device applies the corresponding operating potential (0.00 V for BHB, +0.15 V for Cholesterol). A 25 μL drop of the appropriate measurement buffer (Phosphate-Buffered Saline, PBS, for cholesterol; NAD^+ 0.1 mM in PB pH 7 for BHB) is deposited on the working electrode and the current is monitored until a stable baseline is achieved.
- 2) **Sample Addition:** The user is prompted via the OLED display to add the sample (e.g., reconstituted serum) as a 2.5 μL aliquot delivered with a fixed-volume micropipette. The device waits for a defined period (e.g., 150 s) for the signal to stabilize after sample introduction. The average current over the last portion of this period (e.g., 25 s) is recorded as the initial sample reading.
- 3) **Standard Additions:** The user is prompted sequentially to add known concentrations of the target analyte standard (three additions of 2.5 μL of the analyte

standard solution, namely 0.1 mM BHB or 5.2 mM cholesterol depending on the program selected, delivered with the same fixed-volume micropipette). After each addition, the device waits for signal stabilization (e.g., 150 s) and records the average current over the final part (e.g., 25 s). Acoustic and visual cues guide the user.

- 4) **Data Processing:** Standard addition methodology is applied to recover the analyte concentration of the sample in the presence of the complex matrix. For each segment k ($k = 0$ for the initial sample reading, $k = 1, 2, 3$ for the three standard additions), a cumulative effective added concentration in the drop is computed as $x_k = \sum_{j=1}^k C_{\text{stock}} V_{\text{spike}} / V_j$, where C_{stock} is the standard solution concentration (0.1 mM for BHB, 5.2 mM for cholesterol), $V_{\text{spike}} = 2.5 \mu\text{L}$ is the volume of each addition, and $V_j = 27.5 + 2.5j \mu\text{L}$ is the total drop volume after the j -th addition; $x_0 = 0$ by definition. The four $(x_k, \bar{I}_k)$ data points are fitted by a least-squares linear regression, and the analyte concentration in the drop is recovered from the standard addition formalism as $C_{\text{drop}} = |\text{intercept}|/\text{slope}$. The original sample concentration is then obtained by applying the dilution factor $C_{\text{sample}} = C_{\text{drop}} \cdot V_0 / V_{\text{sample}}$, with $V_0 = 27.5 \mu\text{L}$ the initial drop volume after sample loading and $V_{\text{sample}} = 2.5 \mu\text{L}$ the sample aliquot. In the autonomous proof-of-concept operating mode, the entire processing chain above is performed on the ESP32 microcontroller: as each chronoamperometric segment is completed, the firmware averages the last 25 s of the 150 s acquisition window (50 samples at 2 Hz) to obtain $\bar{I}_k$; once the four data points are available, the regression and the subsequent extrapolation and dilution correction are computed locally, and the resulting sample concentration is rendered on the OLED in millimolar. For the experimental validation reported in this work, the device was instead operated in a development mode that streams the raw amperometric signal via BLE to a host computer; this enables inspection of the complete chronoamperometric curve and manual selection of the stable current window, which was necessary for hardware validation but is not required for routine use.

The specific timing, number of data points averaged, and standard concentration ranges were optimized based on preliminary experiments. The operational workflow is visually represented in Figure 10, and the specific procedural steps for BHB detection are detailed in Figure 10a, while those for Cholesterol detection are shown in Figure 10b.

By design, all reagent volumes in this protocol are fixed at 2.5 μL (the sample aliquot and each of the three standard additions), so the manual operations reduce to depositing successive drops at the moments prompted by the device, rather than measuring volumes. This constrains the operator-dependent variability of the standard addition method to a minimum compatible with manual handling.

Full automation of sample delivery, for example through an integrated microfluidic cartridge, is identified as future work toward unsupervised end-user operation.

For validation purposes, a recovery study was performed. Reconstituted human serum was used as a base matrix. Aliquots of this serum were spiked with known concentrations of cholesterol and BHB standards at three different levels (low, medium, and high) covering the clinically relevant ranges. These samples were then analyzed using the standard addition protocol to determine the percentage of recovery, calculated as (concentration quantified / concentration added) $\times 100\%$.

III. RESULTS

This section presents the results obtained, including the final device prototype, cholesterol detection tests, and BHB detection tests.

A. STATISTICAL ANALYSIS

Analytical performance metrics in this work were determined as follows. The limit of detection (LOD) was calculated as $LOD = 3\sigma/b$ and the limit of quantification (LOQ) as $LOQ = 10\sigma/b$, where σ is the standard deviation of the current obtained from $n = 10$ independent replicates at the lowest calibration point and b is the slope of the calibration curve. The relative standard deviation (RSD) was determined over $n = 6$ independent replicates at a single representative concentration. Recovery values were calculated as the ratio between the concentration measured by the standard addition method and the concentration added to the matrix, expressed as a percentage. The coefficient of determination (R^2) was obtained from least-squares linear regression of the calibration data.

B. FABRICATED POC DEVICE

The integrated Point-of-Care (PoC) device, encompassing the custom PCB with the ESP32 microcontroller, LMP91000-based analog front-end, power management, and user interface within a 3D-printed enclosure, was successfully fabricated and assembled. Figure 11 presents the final handheld prototype with the OLED display fully operational.

C. CHOLESTEROL DETECTION PERFORMANCE

Amperometric measurements for cholesterol detection were performed using the PoC device at $+0.15$ V in reconstituted human serum spiked with cholesterol in different concentrations. Due to anticipated matrix effects in target samples, quantification relied on the standard addition method. Standard additions of cholesterol yielded a linear current response (Figure 12), demonstrating high linearity ($R^2 > 0.99$) over the tested concentration range of 0.94 to 3.49 mM (Table 5). The calculated limit of detection (LOD) for this sensor was 0.64 mM, and the limit of quantification (LOQ), calculated as $10\sigma/b$, was 2.13 mM. The sensitivity derived from the PoC device measurements was 137.1 nA/mM. This confirms the electronic system's

capability to reliably transduce the biosensor signal generated by the modified SPEs for cholesterol, consistent with initial sensor characterizations (Figure 13).

To further validate the accuracy of the method in a complex matrix, a recovery study was performed on reconstituted human serum samples spiked with known cholesterol concentrations at different levels. The device demonstrated recovery percentages ranging from 99.5% to 100.6% (Table 4), confirming the system's ability to accurately quantify cholesterol without significant interference from the sample matrix.

TABLE 4. Recovery study for Cholesterol determination in spiked reconstituted serum.

Cholesterol Added (mM)	Cholesterol Quantified (mM)	Recovery (%)
9.0	9.05	100.6
6.5	6.47	99.5
5.2	5.17	99.5
3.9	3.88	99.6

TABLE 5. Representative data from standard addition of cholesterol measured with the PoC device.

Added C, mM	Measured I, nA
0.94	93.20
1.82	212.40
2.67	332.30
3.49	441.90

D. β -HYDROXYBUTYRATE (BHB) DETECTION PERFORMANCE

Similarly, the PoC device was evaluated for BHB detection in a spiked biological matrix at an operating potential of 0.00 V, using modified SPEs for BHB. The standard addition technique was again employed to mitigate potential matrix effects inherent in biological fluids. Representative results are shown in Figure 14, where consecutive additions of BHB standards produced a distinct linear increase in the measured amperometric current. The corresponding data points are listed in Table 7.

Excellent linearity ($R^2 = 0.997$) was achieved with the PoC device over the tested concentration range (0.04 to 0.13 mM added concentration). The corresponding limit of detection (LOD) was determined to be 0.06 mM, and the limit of quantification (LOQ), calculated as $10\sigma/b$, was 0.20 mM. The sensitivity calculated from the slope of this standard addition curve, obtained using the PoC device, was 4294.5 nA/mM. The significant increase in sensitivity observed with the PoC device compared to the initial laboratory characterization (≈ 353.4 nA/mM) is attributed to the specific hardware configuration of the portable system. The LMP91000 AFE allows for programmable transimpedance gain (R_{TIA}), which was optimized in the PoC firmware to maximize signal resolution for the low analyte concentrations. This high-gain configuration, distinct from the settings of the benchtop

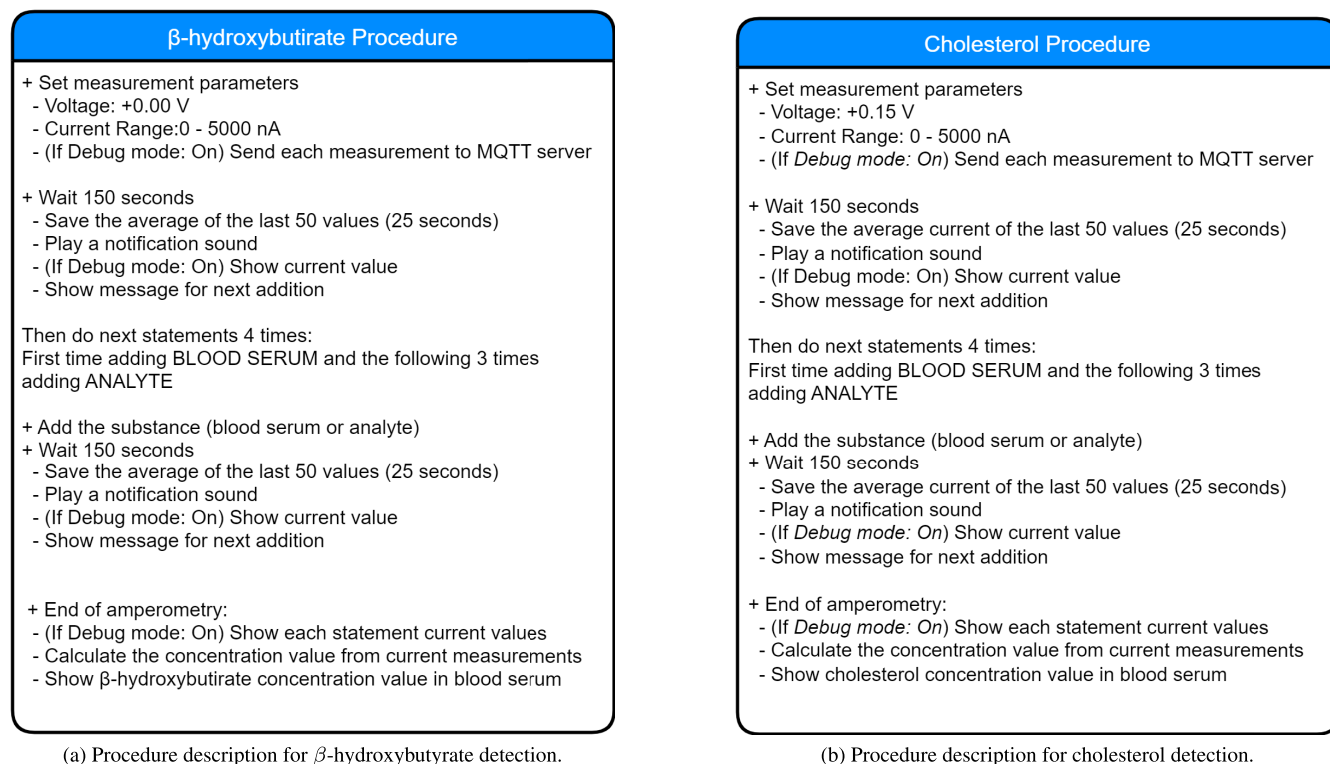


FIGURE 10. Procedure descriptions implemented in the device firmware for biomarker detection.



FIGURE 11. Photograph of the final assembled handheld PoC prototype.

potentiostat, amplifies the amperometric response. The PoC was configured at the LMP91000's maximum TIA setting (350 kΩ) to maximize signal resolution at the low analyte concentrations targeted in this work; this configuration alone accounts for a large multiplicative factor in the absolute current readout relative to the benchtop reference, while leaving the linear character of the response unchanged. Furthermore, batch-to-batch variations in the nanomodification of the screen-printed electrodes can influence the effective electroactive surface area, contributing to differences in absolute current magnitude. In addition, the standard addition method intrinsically reports a different slope from a direct calibration because both the matrix composition and the total drop volume change with each spike addition, so the slope-to-concentration relationship is not directly comparable across protocols. Crucially, the high linearity is maintained across both systems, and the recovery study reported in Table 6 confirms that the slope difference does not invalidate the device's quantitative behavior via the standard addition method.

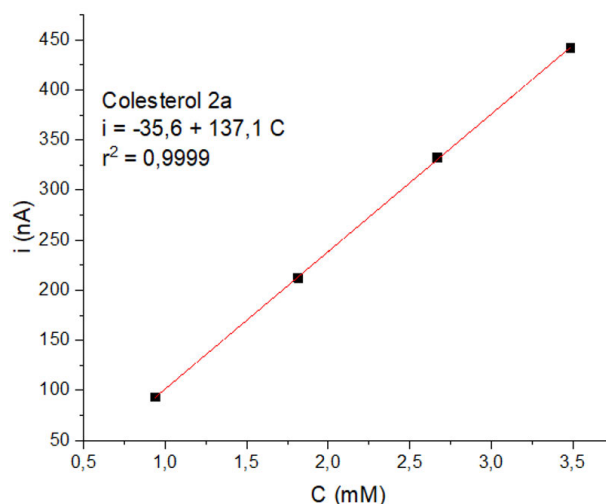


FIGURE 12. Representative standard addition plot for cholesterol detection obtained using the PoC device.

To assess the method's accuracy for BHB quantification, a recovery study was conducted using reconstituted human serum spiked at three distinct concentration levels (low, high, and extremely high). The results showed good recovery values, ranging from 91.6% to 116.8% (Table 6), which validates the biosensor's performance and its suitability for measurements in biological samples.

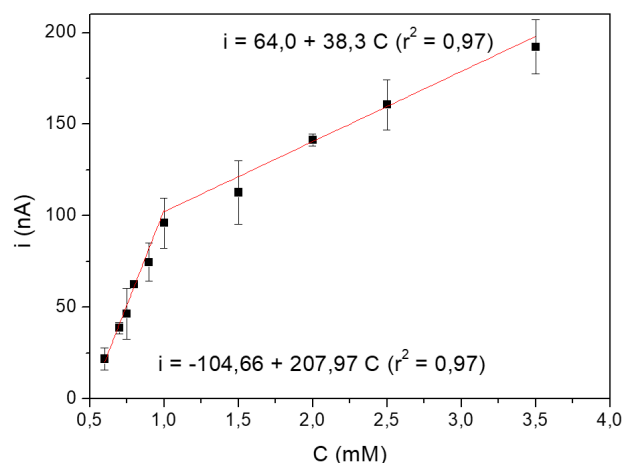


FIGURE 13. Initial calibration curve for the cholesterol biosensor (obtained prior to PoC device testing).

TABLE 6. Recovery study for β -hydroxybutyrate (BHB) determination in spiked reconstituted serum.

BHB Added (μ M)	BHB Quantified (μ M)	Recovery (%)
30.0	32.6	108.7
16.5	15.1	91.6
154.0	180.0	116.8

E. ELECTRONIC VALIDATION RESULTS

Regarding the noise floor, applying the methodology described in Section II-F, the dominant theoretical contributions to the input-referred current noise at maximum TIA gain (350 k Ω) are: the LMP91000 TIA ($\sim$ 57 pA RMS), the ADC161S626 ($\sim$ 283 pA RMS), the LM4120-5 reference ($\sim$ 14 pA RMS) and the Johnson noise of the feedback resistor ($\sim$ 17 pA RMS), yielding a root-sum-of-squares of approximately 290 pA RMS, equivalent to a theoretical electronic LOD of $\sim$ 0.9 nA at 3σ . Experimentally, with the device powered from its USB input and connected to the 1 M Ω dummy cell on an open laboratory bench, the standard deviation of 3000 amperometric samples captured at 10 SPS over 300 s at TIA = 350 k Ω and bias = 0 was σ = 1.09 nA RMS, consistent with σ = 1.20 nA RMS obtained from a 5000-sample, 1000 SPS burst over 5 s; the corresponding operational LOD at 3σ is approximately 3.3 nA. The measured value is a factor of $\sim$ 3.8 above the intrinsic theoretical floor, a difference attributable to non-modeled contributions including environmental electromagnetic interference (the device was operated on an open bench without a Faraday enclosure), thermal drift of the dummy cell and the AFE during the 5-minute capture, residual ripple on the USB supply rail, and noise pickup at the mechanical SPE connector. At lower TIA gains the measured noise scales as expected from the changing TIA gain (3.92 nA RMS at 35 k Ω and 44.4 nA RMS at 2.75 k Ω) and is dominated by ADC quantization ($\sim$ 1.6–1.8 LSB) rather than

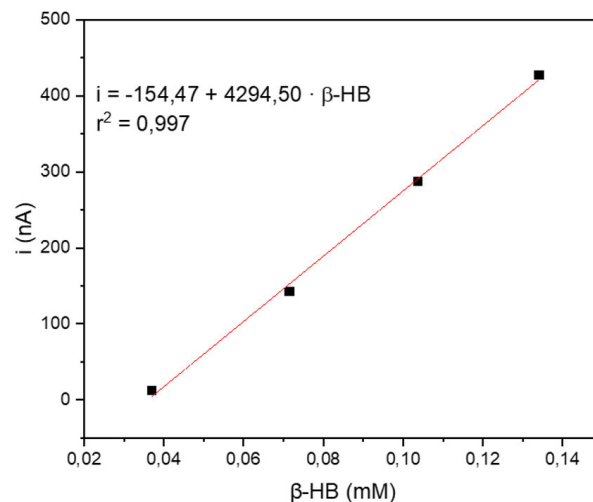


FIGURE 14. Linear adjustment for four consecutive additions of BHB solution on the enzymatic biosensor measured with the developed PoC potentiostat.

TABLE 7. Results obtained from four consecutive additions of BHB solution on the biosensor, measured with the PoC potentiostat.

C, mM	I, nA
0.04	12.30
0.07	142.50
0.10	287.50
0.13	427.50

by AFE noise, validating qualitatively the hierarchy of the theoretical budget. The operational noise floor of $\sim$ 3 nA at maximum gain is well below the smallest currents observed in the SAM protocol on spiked reconstituted serum (tens of nA), confirming experimentally that the electronic chain is not the limiting factor of the analytical performance reported in this work; the floor would become relevant only if the analytical sensitivity were extended toward lower-concentration regimes such as native salivary samples (sub-nA currents).

Regarding linearity, the 14-point bias sweep of the 1 M Ω dummy cell yielded a least-squares linear fit of R^2 = 0.999989 across the 13 non-saturated points (the single point at bias = 0 was at the TIA output rail due to the internal DC offset and was excluded from the regression), with slope = 0.7748 nA/mV and intercept = 0.692 nA. The deviation of the measured slope from the theoretical 1 nA/mV expected from Ohm's law at R_{dummy} = 1 M Ω is a multiplicative calibration factor (0.775) attributed to the manufacturing tolerance of the internal R_{TIA} of the LMP91000 (the datasheet does not specify a tighter bound on the discrete TIA gain steps) combined with the tolerance of the 1 M Ω metal-film resistor. This factor is constant across the entire operating range and does not affect the analytical results obtained with the standard addition method, which intrinsically cancels any multiplicative gain by performing

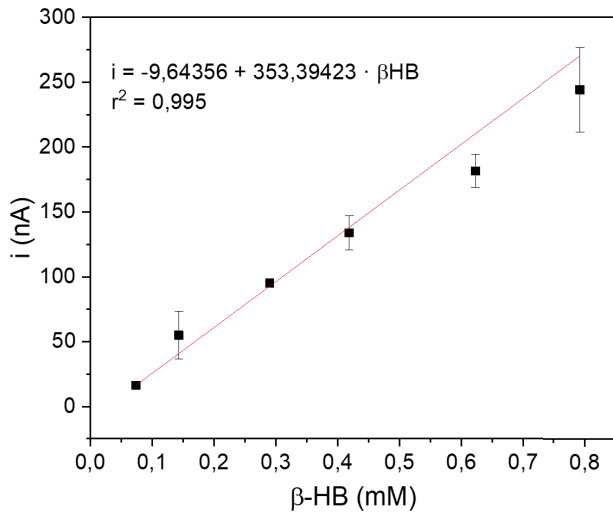


FIGURE 15. Initial calibration curve for the BHB biosensor (obtained prior to PoC device testing).

the calibration *in situ* for each measurement; nor does it invalidate the noise figure reported above, which would correspond to an even lower true current noise if the actual R_{TIA} were larger than nominal.

Regarding power consumption, the per-mode current draw measured with the PPK2 is summarized in Table 8. The complete system (ESP32, LMP91000, ADC161S626, MCP4725, OLED display and on-board regulators) draws approximately 5.8 mA in deep sleep, 6.8 mA in idle, and 7.2 mA during active amperometric acquisition; the analog front-end contributes only marginally, adding about 0.4 mA over idle. Wireless operation dominates the budget, with Wi-Fi connected idle at 10.8 mA and Wi-Fi data transmission at 22.4 mA (instantaneous transmission bursts reaching approximately 290 mA). A complete β -hydroxybutyrate measurement cycle (750 s, 1500 samples at 2 Hz) consumes 1.56 mAh in autonomous mode, with local display and no radio, and 4.89 mAh in connected mode, with real-time Wi-Fi data transmission. With the 190 mAh LiPo battery this corresponds to approximately 122 autonomous or 39 connected measurement cycles per charge; if the device is instead kept running continuously, the autonomy ranges from

TABLE 8. Measured power consumption of the complete device (PPK2, 190 mAh LiPo battery).

Operating mode	Typical current	Continuous-operation autonomy
Deep sleep	5.8 mA	~33 h
Idle (CPU active, no radio)	6.8 mA	~28 h
Active amperometric measurement	7.2 mA	~26 h
Wi-Fi connected, idle	10.8 mA	~17.6 h
Wi-Fi transmitting	22.4 mA	~8.5 h

about 33 h in permanent deep sleep down to about 8.5 h under continuous Wi-Fi transmission.

F. PERFORMANCE BENCHMARKING AND CONTEXTUAL VALIDATION

Table 1 positions the present platform within the landscape of portable electrochemical instruments reported in the literature and on the market. The selected systems span the three main families: open-source designs based on discrete analog front-ends (CheapStat, DStat, Rodeostat); open-source designs built around dedicated AFE integrated circuits (KickStat with the LMP91000, FreiStat with the AD5941); and commercial closed-source modules (PalmSens EmStat Pico / Sensit BT, built on the ADuCM355). Other portable potentiostats reported in the literature (e.g., SmartStat, ABE-Stat, PassStat) follow similar architectural patterns and are omitted here for conciseness. The reported current-resolution metrics are not strictly equivalent, since they are defined variably as least-significant-bit, instrumental detection limit, or root-sum-of-squares noise; the table is therefore intended as an overview of features and architecture rather than a direct ranking. With this caveat, the noise figure derived for the present platform (~ 290 pA RMS, 0.9 nA at 3σ) is consistent with the instrumental LOD reported by KickStat (4.5 nA), which uses the same LMP91000 AFE in a similar low-cost arrangement. Systems built on newer dedicated AFE chips (AD5941 in FreiStat, ADuCM355 in EmStat Pico/Sensit BT) reach finer resolution at the expense of either added wireless complexity (FreiStat requires a separate Wi-Fi module on top of the SAMD21) or a closed, proprietary ecosystem (Sensit BT). The distinguishing feature of the present platform is the integration of dual native wireless connectivity (Wi-Fi + BLE in the same SoC) with an on-device display and control interface that enables operation and result reading *in situ*, a combination not found in the systems surveyed, while preserving an open architecture and a BOM cost in the EUR 45–70 range.

The biosensor chemistries used to validate the platform (β -HBDH/THI/rGO for BHB and ChOx/chitosan/THI/rGO for cholesterol) are not the contribution of this paper but rather serve as a realistic analytical testbed for the complete signal chain. The β -hydroxybutyrate chemistry was previously developed and characterized on benchtop instrumentation by one of the present authors [34], reporting a limit of detection of $1.0 \mu\text{M}$ in spiked serum with multipoint direct calibration. The present platform, operated in a portable battery-powered configuration with a three-point standard addition protocol, reports a higher LOD (0.06 mM for BHB, 0.64 mM for cholesterol) that remains within the clinically relevant serum range (0.01–15 mM for BHB; 3.1–5.2 mM for the normal cholesterol serum range, with pathological values extending higher) and validates the end-to-end functionality of the electronics in a realistic biological matrix. Refining the sensitivity toward the salivary concentration regimes (6 nM–1.05 mM for BHB; 0.013–0.119 mM for cholesterol)

requires additional work on the biosensor side and is part of the future development of the platform.

IV. CONCLUSION

Guided by the potential of non-invasive metabolic monitoring with real-time wireless data transmission, this paper presented a comprehensive development of a functional, portable, and connected electrochemical biosensor system for metabolic biomarker analysis. The work successfully integrates custom-fabricated enzymatic biosensors on modified SPEs with a purpose-built, low-cost electronic platform based on the ESP32 microcontroller and the LMP91000 AFE. The system was specifically designed to address the challenges of proof-of-concept validation toward non-invasive monitoring of salivary BHB and cholesterol, employing amperometric detection at optimized potentials (+0.15 V / 0.00 V). Recognizing the complexities of saliva, the standard addition method was implemented within the device firmware, including the on-board linear regression and the on-OLED display of the resulting analyte concentration, which together enable fully autonomous operation in the intended proof-of-concept use mode. In this work, the method proved effective in achieving highly linear ($R^2 > 0.99$) calibration responses directly within a reconstituted human serum matrix, which served as a complex biological model to validate the system's performance and its ability to compensate for potential interferences in a proof-of-concept stage.

The quantitative performance of the integrated PoC device was validated through standard addition experiments, demonstrating its capability to transduce the low-level amperometric signals reliably. While comparisons with initial laboratory characterizations revealed differences in absolute sensitivity parameters, the portable device consistently reflected the expected linear relationship between analyte concentration and current response, which is fundamental for accurate quantification via standard addition.

Looking forward, the transition from laboratory validation to real-world application requires addressing several key areas. Rigorous clinical validation using authentic human saliva samples is paramount to establishing the device's accuracy and reliability in its intended matrix. Future work should focus on large-scale clinical trials and cross-validation against high-precision laboratory instrumentation to establish definitive salivary diagnostic thresholds. Improving the long-term stability of the biosensor component remains a critical challenge for practical usability. Further refinement of the system could include advanced power-saving modes for prolonged battery life, the integration of pre-calibrated cartridges and a microfluidic sample-delivery stage to remove the need for manual micropipetting and enable end-user operation, and expanding the platform for the detection of additional biomarkers. The regulatory pathway toward in vitro diagnostic certification is also identified as a necessary step for clinical deployment. The successful development of this adaptable platform lays the groundwork for future iterations aimed at creating truly wearable platforms for

continuous monitoring of salivary biosensor systems for holistic metabolic health assessment.

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JOSÉ FRANCISCO BELTRÁN-SÁNCHEZ received the B.Sc. degree in industrial electronics and automation engineering, the M.Sc. degree in industrial engineering, and the M.Sc. degree in electronic systems and instrumentation from the Technical University of Cartagena (UPCT), Cartagena, Spain, in 2010, 2016, and 2018, respectively, where he is currently pursuing the Ph.D. degree in information and communication technologies. Since 2018, he has been an Electronic Engineer in research projects with the Department of Information and Communication Technologies, Technical University of Cartagena. He has been involved in the design of hardware and firmware for amperometric devices for the electrochemical detection of analytes in biological samples, as well as in the development of WLAN-enabled electronic systems for distributed sensing applications. His research interests include electrochemical sensing systems, electronic instrumentation, embedded systems, and the Internet of Things (IoT) devices.



LAURA GARCÍA received the bachelor's degree in telecommunications technology engineering and the master's degree in digital post production from the Polytechnic University of Valencia, in 2015 and 2016, respectively, the master's degree in business administration from the Universidad Católica San Antonio de Murcia, in 2020, the Ph.D. degree in telecommunications from the Polytechnic University of Valencia, and the Ph.D. degree in computer science from the Université de Mulhouse Haute-Alsace, in September 2021. She is the author or co-author of 30 articles in international journals listed in the J.C.R., and 11 articles in other international journals. She is also the co-author of three book chapters. She has published 24 conference papers. She has been involved in several organization committees of international conferences, since 2016. Her research interests include precision agriculture and the IoT-based environmental monitoring systems, and the design of communication architectures and protocols for the aforementioned purposes.



GONZALO MARTÍNEZ-GARCÍA received the B.S., M.S., and Ph.D. degrees from the Complutense University of Madrid, Madrid, Spain, in 2012, 2013, and 2018, respectively. He completed a Predoctoral Research stay with the University of Coimbra, Portugal, and has been part of different research groups with the Complutense University of Madrid; the Technical University of Cartagena, Murcia, Spain; and Rey Juan Carlos University, Madrid, where he has been an

Associate Professor in the area of analytical chemistry, since 2020. His research has focused on the development of electrochemical (bio) sensors for the determination of clinically and pharmaceutically relevant compounds, contributing to the development of tools for the early diagnosis of metabolic, and cardiac diseases.



JOAN GARCIA-HARO (Member, IEEE) received the M.Sc. and Ph.D. degrees in telecommunications engineering from the Universitat Politècnica de Catalunya, Spain, in 1989 and 1995, respectively. He was a Visiting Scholar with Queen's University, Kingston, ON, Canada, from 1991 to 1992; and with Cornell University, Ithaca, NY, USA, from 2010 to 2011. He is currently a Full Professor with the Technical University of Cartagena (UPCT), Spain. He is the author or co-author of more than 100 journal articles, mainly in the fields of switching, wireless networking, and performance evaluation. He received the Honorable Mention for the IEEE Communications Society Best Tutorial Paper Award, in 1995. He served as the Editor-in-Chief for IEEE Global Communications Newsletter, including in *IEEE Communications Magazine*, from April 2002 to December 2004. He has been the Technical Editor of *IEEE Communications Magazine*, from March 2001 to December 2011.



ANTONIO-JAVIER GARCIA-SANCHEZ received the bachelor's degree in industrial electronic engineering, the master's degree in industrial engineering, and the Ph.D. degree from the Technical University of Cartagena (UPCT), Spain, in 1997, 2000, and 2005, respectively. He is a Full Professor in the area of telecommunication engineering with UPCT. Before starting his academic career, he was an Industrial Engineer with Centro para el Desarrollo Tecnológico Industrial (CDTI), evaluating research and development projects from Spanish companies, and later with Fertiberia S.A., where he was the Head of maintenance with Cartagena plant. He joined the Department of Information and Communication Technologies (DICT), UPCT, in 2002. He was the Head of the Department, from 2019 to 2023. He has also been distinguished several

times as a Distinguished Professor of the School of Telecommunications, UPCT. He has also carried out international research stays with the University of Bologna, Italy; Wageningen University, The Netherlands; and the University of Cali, Colombia. He has an extensive research record, being the author or co-author of more than 130 international scientific publications, including more than 80 papers indexed in *Journal Citation Reports* (JCR), many of them in Q1 and Q2 journals, as well as numerous IEEE and ACM conference papers. He has also participated in more than 35 international conference technical program committees and several organizing committees. He has been involved in a wide range of research and innovation projects, leading regional, national, and international initiatives, including European H2020 and Horizon Europe projects, as well as projects funded by research institutions and private industry. His work covers both fundamental research and technology transfer, and he is co-inventor of 16 patents or intellectual property records, including one registered in United States. In teaching, he has accumulated more than 3000 hours of academic instruction, participating in several teaching innovation projects and receiving multiple national recognitions for research, technology transfer, and teaching quality. Beyond academia, he is actively involved in technology transfer and entrepreneurship. He is the Co-Founder of QARTECH Innovations S.L., a technology spin-off focused on industry 4.0 solutions, where he served as a CTO. He is the Co-Founder and a CEO of QARTIA Smart Technologies S.L., a startup developing AI-based environmental monitoring and smart sensing solutions. Through these initiatives, he has led technology development projects for industrial clients and research institutions, contributing to the practical deployment of advanced the IoT and environmental monitoring technologies. His research interests include wireless sensor networks, the Internet of Things (IoT), non-cellular mesh network architectures, communication network performance evaluation, streaming services, smart data processing, and emerging nano-communication systems. He regularly serves as a reviewer for leading international journals, including IEEE INTERNET OF THINGS JOURNAL, IEEE JOURNAL ON SELECTED AREAS IN COMMUNICATIONS, IEEE TRANSACTIONS ON INDUSTRIAL ELECTRONICS, IEEE TRANSACTIONS ON NETWORK AND SERVICE MANAGEMENT, and *Computer Networks*.

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