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ORIGINAL ARTICLE

Development of technologies to support the diagnosis of infectious diseases and cancer to support the primary health care

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Abstract

Purpose Primary Health Care (PHC) is the coordinator of health care in Brazil and needs to be strengthened in the diagnostic field to increase health care quality. Aiming to improve the diagnostic tools currently available in PHC, this work describes the process of development and validation of two point-of-care biomedical devices for screening patients with syphilis or different kinds of cancer.

Methods The development of these devices followed nine stages of action based on the requirements established by the Ministry of Health. During development, both systems followed the stages of circuit planning, software simulation to verify the components used, cost assessment for the acquisition of features, simulation in contact matrix, development of the embedded system, and planning of the printed circuit board and storage box.

Results Both devices underwent preliminary functionality tests to assess their quality. The performance tests applied on the device to diagnose syphilis performed 8,733,194 requests, with a flow of 2426 requests/second, reaching the desired parameters of robustness, integrity, durability, and stability. In addition, functioning tests on the cancer-screening device indicated the ability to detect standard fluorescence in a minimal (150 uL) sample volume.

Conclusions Together, the methodology used for developing the devices resulted in promising equipment to improve the diagnosis and meet the requirements for executing technologies for testing and triaging patients in PHC.

Keywords Embedded system · Primary health care · Biosensors · Syphilis · Cancer

Background

Primary Health Care (PHC) is the coordinator of care and the main gateway to the national health system in Brazil, with more than 42 thousand Basic Health Units (UBS) existing in Brazil responsible for the daily contact with users of the system (Massuda et al. 2018, Macinko and Mendonça 2018, Pinto et al. 2014). Therefore, accurate diagnosis in PHC is considered a fundamental element in increasing the resolution of health problems at this level of care (Kameda and Pazello 2015, Santos et al. 2017).

However, the development of new technologies aimed at diagnosis is often directed to health care of medium and high complexity, which generates an increase in the costs of health care for the population, diagnosis in more advanced stages of diseases, and the difficulty in the population's timely access to health assistance, as in the case of care lines for cancer and some sexually transmitted infections (STIs) (Facchini et al. 2018, Macinko et al. 2017).

The improvement of diagnosis in PHC is a relevant factor for the qualification of care and health regulation processes. Thus, it represents the practical qualification of PHC in promoting equity in access to health services in the specialized network. Therefore, it is essential that new health technologies aimed at testing, screening, and diagnosis of cases, which do incorporate into PHC, have the following

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characteristics: low cost, portability, interoperability, connectivity, security of information, and sensitive personal data, as well as ease of operation during PHC routines.

The fight against STIs and the different types of cancer requires new strategies and diagnostic technologies developed specifically for this level of health care to expand adequate, timely, and quality access to treatment and consequently increase in success—therapeutics and the resoluteness of the health system (Valentim et al. 2018).

Concerning syphilis, a bacterial STI historically neglected by countries, the World Health Organization (WHO) estimated that in 2016 there were more than 1 million new cases of syphilis in pregnant women (Gottems and Pires 2009), while Brazil registered an increase of 4157% new cases of the disease between 2010 and 2018 (Chen 2017). The laboratory often diagnoses syphilis through treponemal or non-treponemal tests that aim to identify the presence of antibodies in peripheral blood samples (WHO 2018). However, the need for specialized equipment and professionals to perform the tests, the time to obtain the results, and the occurrence of false-negative and false-positive results, especially in screening tests, are elements that directly impact the patient's health and the efficiency of SUS (Dos Santos et al. 2020).

At the same time, the early diagnosis of different types of cancer in PHC remains a fundamental challenge for the definition of a unique therapeutic project and the success of the treatment, enabling better prognoses and significantly reducing the care costs related to the treatment (Ministry of Health 2010). According to the WHO, by 2030, there will be 24.6 million new cases and 13 million deaths related to different types of cancer, representing the second leading cause of death in most American countries. Furthermore, the annual cost associated with disease and lost productivity in 2010 was estimated at 1.16 trillion dollars (WHO 2017, Brasil 2020).

Among the new precision medicine strategies used to improve diagnosis, microRNAs (miRNAs) have excellent potential for application in PHC because it is a tool for diagnosing the disease in its early stages (Pinto et al. 2021; Galvão-Lima et al. 2021). In Brazil, among the primary forms of non-melanoma cancer diagnosed annually, the occurrence of breast, cervix, or prostate tumors stands out, which have high mortality associated with late diagnosis (Valentim et al. 2021, Andrade et al. 2020, Pinto et al. 2021).

Developing solutions for testing, screening, and diagnosis in PHC, considered point-of-care, represents modern strategies, particularly in Biomedical Engineering. Therefore, they are essential to increase the effectiveness of PHC and adequate access, when necessary, to other levels of health.

This article presents the development stages (prerequisites and specificities) that guided the creation of new technology architectures to diagnose syphilis, breast, cervical, and prostate cancer, contributing to the network of UBS services.

Materials and methods

Nine steps were performed (Fig. 1) in the biosensor development process. Initially, the circuit planning was carried out, the simulation in software to verify the components used, and the cost survey to be generated with the purchase of the features. Then, finally, contact matrix simulation, embedded system development, printed circuit board (PCB) and storage box planning, equipment assembly, and testing.

The development process for creating the two prototypes meets the requirements for implementing technologies in PHC (Fig. 2). Therefore, these prototypes were developed having as one of the principles the communication with the internet so that it was possible to integrate with cloud systems. Aiming at information security and, in particular, sensitive personal data, and an interoperability bus applied for the Open Fast Healthcare Interoperability Resources (FHIR)

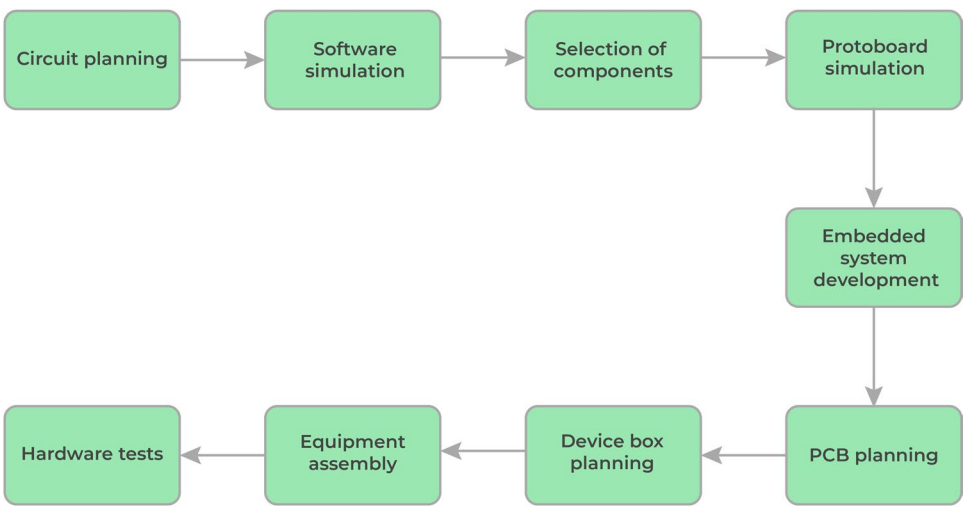

Fig. 1 Phases of the methodology implemented in this study

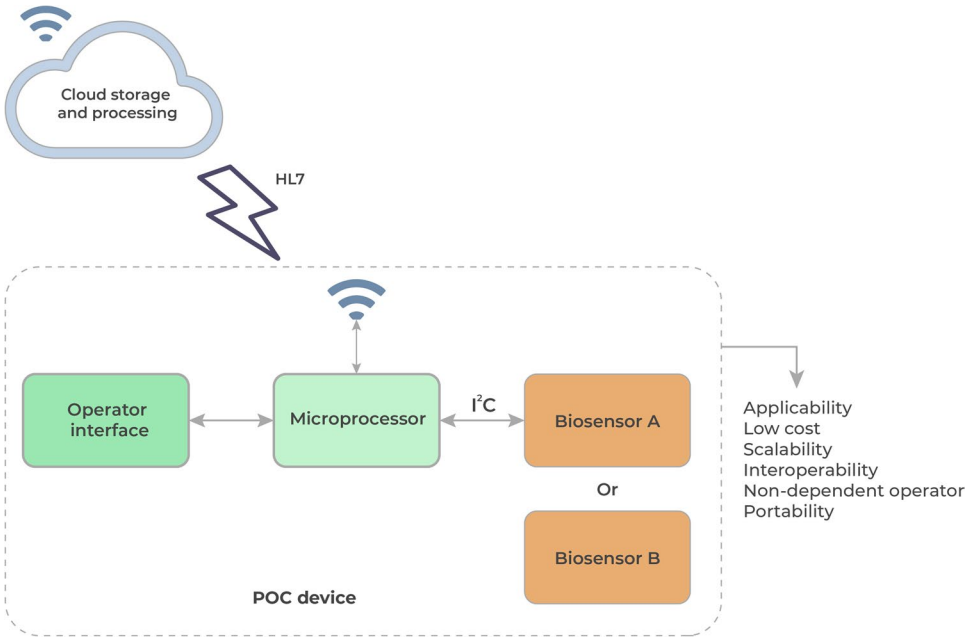

Fig. 2 Block diagram of the prototype and its connection

and Health Level 7 (HL7) protocols. Communication with the storage cloud occurred by sending packets in JSON format with the information collected from the patient, as well as the result obtained from the detection hardware.

Internally, the developed devices have a microprocessor, an interface with the operator, and a biosensor capable of communicating through the I^2C protocol. The core of the embedded system software architecture has three internal modules and two auxiliary modules (Fig. 3). The first internal module presents a graphical interface to enable the device to be operated by the user. In both cases, for the user to perform operations on the embedded system, it is

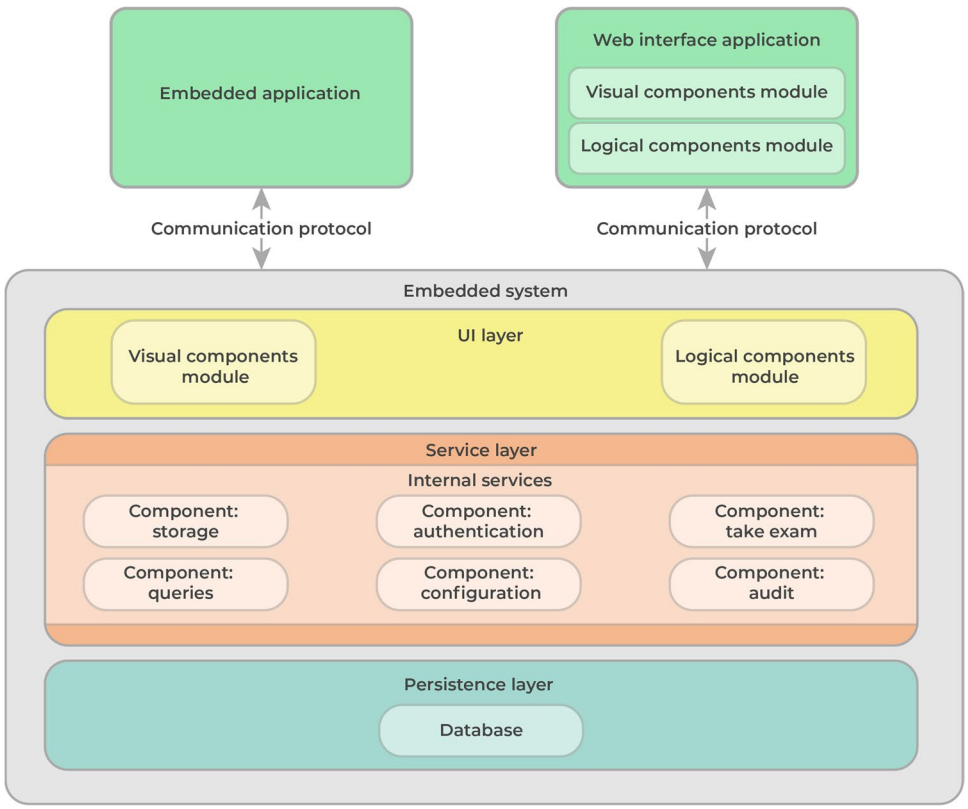

Fig. 3 Diagram of components of the analyzed systems

necessary to authenticate the same through biometrics and by a second authentication factor (communication with an external authentication server). In addition, usernames and passwords are stored internally with the PBKDF2 cryptographic function, as recommended by the United States National Institute of Standards and Technology (NIST). In addition to encryption, the embedded systems under analysis require a minimum of 8 characters and the presence of uppercase and lowercase letters, numbers, and symbols, which corroborates the increase in password entropy.

The second internal module consists of a set of services (audit, examination, user authentication) and communication and integration interfaces with other systems, based on the use of secure communication protocols and the sending of encrypted messages. The logic module is responsible for processing and storing data according to the business rules of each prototype, as well as defining the levels of access to the system according to the type of user logged in (superuser, operator, health unit manager, controller).

The third module represents the data persistence functionalities internally in the embedded system. This functionality exists to keep the data stored internally in case of communication failure with the central system receiving the data. In this way, users will be able to continue performing exams (up to the limit of the systems' internal storage capacity), even if there is no communication with the central system. When communication is re-established, all data related to the exam (patient, operator, date/time, exam results) will be forwarded to the central system responsible for data management, storage, and protection.

The auxiliary module for the web application interface makes it possible for prototypes to be deployed in a distributed system architecture with centralized reception of data. In this way, the prototypes are characterized by the ability to deploy at scale and the possibility of centralized management of information (collected by these devices). In a health management model with shared responsibilities between different levels of care and various spheres of government, this is a fundamental characteristic to support the implementation of public policies and the sustainability of these policies.

Development of a new device based on miRNA quantification to improve cancer screening in the PHC

The circuit was designed with a light exciter vertically aligned with the sample and the sensor so that when it perceives light, it generates a current to be amplified, converted, and read by the microcontroller and an electrical energy source responsible for powering the circuit. Thus, sensor and microcontroller polarization and an interface for triggering functions display information and results (Fig. 4A).

The samples were hybridized with fluorochromes that make them emit light proportionally to the amount of target present. These fluorochromes were excited with light of wavelength around 530 nm and emit light around 580 nm. The circuit was virtually simulated to validate the designed electronic properties and verify the defined requirements. Then, the choice of components with high sensitivity and detection specificity was based on the characteristics of the samples, and the sensor selected was an array of silicon photomultipliers (silicon photomultiplier–SIPM). The photon detection efficiency curve of the selected SIPM shows that at the wavelength in use, the efficiency is 22%.

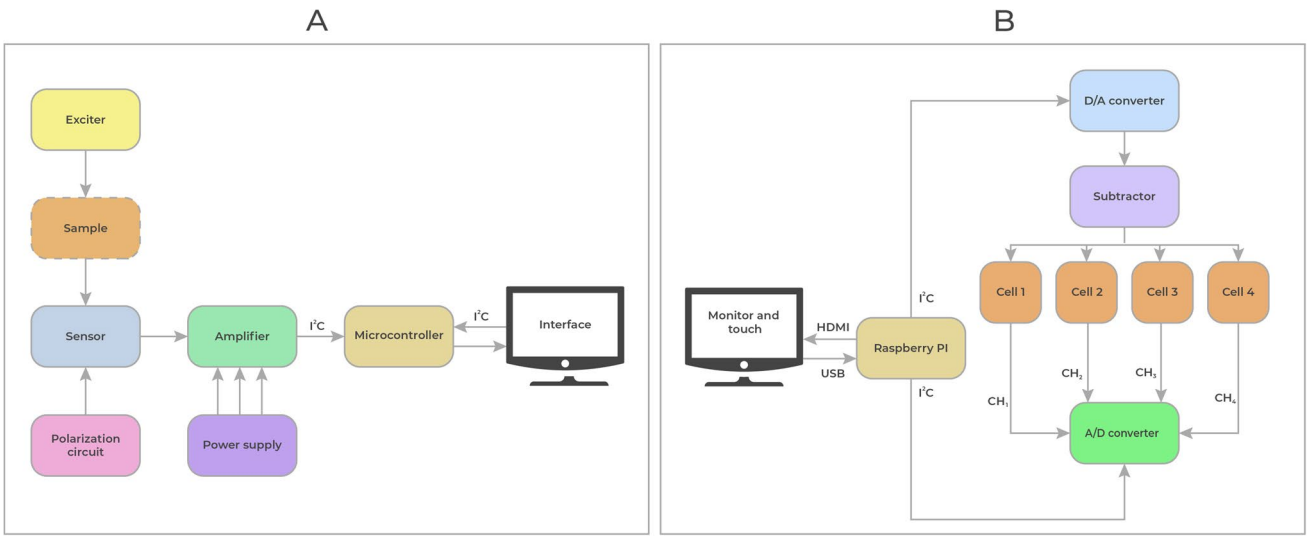

Fig. 4 **A** Block diagram of miRNA device. **B** Block diagram of syphilis device

An accurate simulation was performed from a contact matrix with the selected components. Exciter intensity control was performed by an analog potentiometer. An opaque box was used to minimize light interference external to the experiments. A LED and an optical sensor were placed internally, and the control circuit externally so that it could be connected to a benchtop digital oscilloscope. The oscilloscope used was the Tektronix TDS2024C.

Software written with the C programming language was developed to manage the graphic interface, the light exciter, and capture the optical sensor readings. The PCB was made from a copper-plated phenolite plate with a single face, an ultraviolet design transfer method, and etching with iron perchloride.

For validation, calibration and functioning tests of the device were carried out with a solution containing water and fluorochrome, which has the apex of the excitation curve when the wavelength is equal to 566 nm, to produce the luminous effect capable of being observed by the optical sensor (Fig. 5A). For excitation, a green LED was used as the fluorochrome exciter since it emits light in the spectrum from 530 to 560 nm, as well as a blue laser (450 nm). For each new experiment, a new assay plate was used. Well D3 received distilled water, and well E10 received the buffer solution. The experiments were performed using two different volumes of buffer solution and water: 100 µl and 150 µl, respectively.

Development of a new device based on bioimpedance to improve the laboratory diagnosis of syphilis

The circuit was planned with a Raspberry PI due to the ease of using a high-level language, using a touch-sensitive screen, and its low cost in order to obtain control of all peripherals and communicate with the servers that run storage and post-processing. A touchscreen monitor was used as the user interface for the device operator. A D/A converter (digital-analog) and a subtractor (operational amplifier in subtractor configuration) inject voltage levels into the electrochemical cells and, finally, the A/D converter (analog–digital) reads the voltages measured in the cells (Fig. 4B). To perform voltammetry with 9 ms steps on 4 electrochemical cells, the A/D must be able to perform at least 800 readings per second.

Then, the circuit was simulated in software (Proteus 8 from Labcenter Electronics) with modules for regulating the voltage of the general supply, controlling the electrochemical cells, and for the analog–digital conversion. After approval of the simulation stage, the selection of components that met the requirements of high sensitivity, low noise, and reading speed was performed. For this purpose, an operational amplifier with low input current, in the order of Femto amperes (10^{-15} A), with low noise, and a 16-bit analog-to-digital converter capable of performing up to 860 readings per second were selected.

A cyclic voltammetry was simulated, in which the voltage at the cell voltage is varied over time within a range specified by the user. In the project in question, the initial voltage was − 0.6 V and increased in steps of 5 mV every 9 ms, reaching a maximum of 0.5 V and returning, in the same way, to − 0.6 V.

In the next phase, the manufacture of the PCB and assembly of components began. A single-faced, copper-plated phonolite plate with an ultraviolet design transfer and iron perchloride etching method was used. The selected components were interconnected and assembled

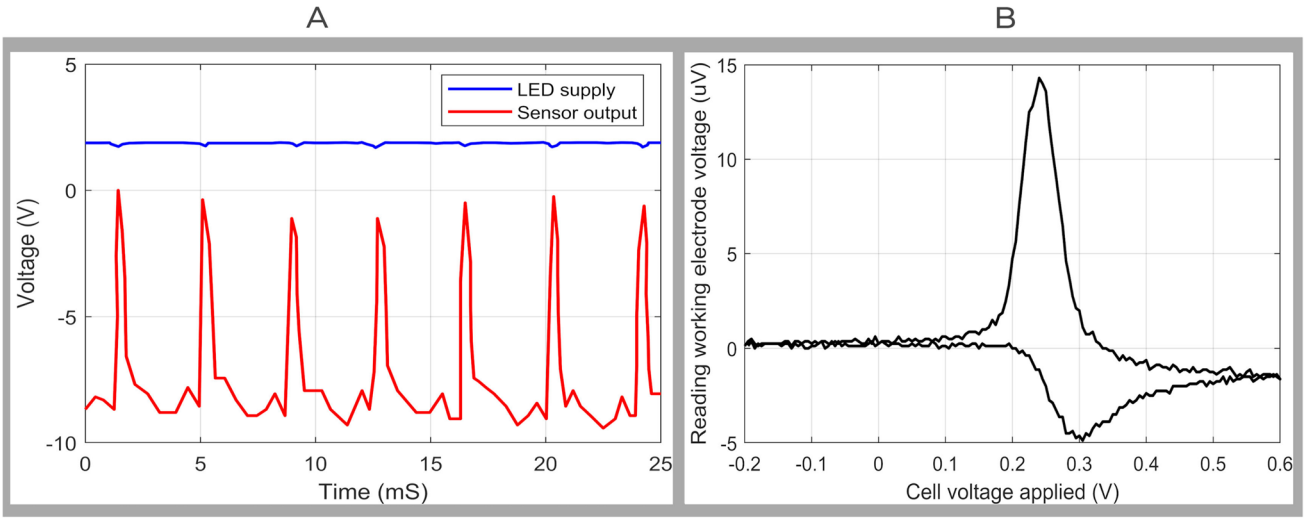

Fig. 5 **A** Graph of electrical current measurements generated by the fluorochrome used in the miRNA device test. **B** Graph of cyclic voltammetry in methylene blue solution used in syphilis device test

in a contact matrix for reading tests, whose results were saved in a text file for further analysis. As for the embedded system, an algorithm was developed in python to receive the input parameters: initial operating voltage, final operating voltage, reading step, and voltage per second.

The validation of the results obtained on the device took place with a comparative analysis using the PalmSens potentiostat and the equipment developed in this study. To perform the test, a methylene blue solution was used because it is an inert solvent and has a hydrogen potential (pH) between 7 and 7.4. In addition, all current reading data (Fig. 5B) were stored in a file for further analysis in software.

Finally, the system to aid the diagnosis of syphilis was submitted to a request verification test by the open-source application, Apache JMeter, to measure how much the storage web service would be able to support. The test proceeds with the client (JMeter) sending an HTTP request to the application, which processes the request data. First, through a series of middleware routines, which check the authentication header, validate if the user has the authorization to send the results of an exam, and confirm the request body. In business logic, the deserialization of data into Java objects takes place and triggers the interface to save the data in the system of records. In data logic, entities are coordinated for SQL queries to create records in the corresponding relationships.

Results

The proposed health technology development process enabled the construction of two hardware prototypes (Fig. 6). Finally, the devices were connected, enabling interaction between the user and the graphical interfaces, demonstrating full operation. The equipment development and construction process demonstrated in this work can be used to assemble other devices to analyze other infections and diseases. Even though they are biosensors of another species, the modules and the process are the same. If they are of the same species but for the detection of different targets, the necessary changes are in parameters and settings and the analysis and processing of the results.

Results of syphilis device

The outcome of the application for developing health technologies for the diagnosis of syphilis resulted in creating the prototype shown in Fig. 6B. The device is 30 cm wide, 24 cm high, 14 cm deep, and costs USD 299.00 (two hundred and ninety-nine dollars).

For the technological architecture of syphilis, 8,733,194 requests were made to the application server through JMeter during 1 h, presenting a throughput of 2426 requests per second (Table 1). JMeter sent 10.41 gigabytes and received 366.73 megabytes from the server. The average response time was 13 ms. The application did not show any errors during the execution of the experiments.

The results demonstrate the efficiency of the architecture, it meets the criteria of robustness, integrity, durability, and stability since no failures were recorded during the test execution. In addition, the flow of many requests in a short time favors the low cost and maintenance of the infrastructure.

Results of cancer-screening device

The device is 14 cm wide, 10 cm high, 10 cm deep, and costs USD 205.00 (two hundred and five dollars). Sensory evaluation tests with a water volume of 100 µL and green LED as an exciter resulted in a peak-to-peak voltage (Vpp) detection of 4.4 V. However, when using a sample of fluorochrome PE with the same exciter, the result of the detected voltage was 9.6 V (Table 2). In this way, using 150 µL, the water and fluorochrome PE samples

Fig. 6 **A** miRNA device. **B** Syphilis device

Table 1 Test results with JMeter on the system to aid in the diagnosis of syphilis

JMeter metric	Value
#Samples	8.733.194
Average	13 ms
Median	12 ms
Standard deviation	3.12 ms
Error %	0%
Throuqhput	2426.0/s
Received	101.87 KB/s
Sent	2892.71 KB/s

read 6.4 V and 8.4 V, respectively. Therefore, the equipment was able to distinguish the samples through the intensity of the light signal converted into a voltage level.

The same experiments were carried out with a blue laser as the sample exciter. The results obtained (Table 2) mean that the excitation happens outside the expected for the optical sensor, given that the wavelength emitted by the laser does not excite the samples, thus not producing a sufficient signal difference to differentiate them.

Discussion

Syphilis and cancer, despite being different diseases and requiring different technological approaches, both have points of unity when it comes to assessing the resilience of health systems and their social impact. Late or mistaken diagnosis directly impacts people's life quality, social stigma, reduced chances of successful treatments, increased treatment costs, and, consequently, inequity in the distribution of health resources. In Brazil, these issues also impact public financing of social security.

Regarding the relevance of performing point-care tests, the development of the miRNA quantification device prototype is considered to reduce the execution time of the diagnosis of complex diseases to optimize the process of early diseases, such as cancer. In this sense, considering that there are currently no devices in clinical use for detecting miRNAs and performing similar molecular assays (as RT-PCR, small RNA-sequencing, and other transcriptome analysis) may take hours to days until the final results, the preliminary results using this prototype indicated that the fluorescent signal present in the sample can be acquired in a few seconds by the sensor and a few minutes after the initial incubation it is possible to observe the saturation (stability) in the acquisition of the signal.

In addition, the cost of each device, the final price per exam, and the need for specialized professionals are also differentials between the prototype and traditional methods used to quantify miRNAs and other molecules (as DNA, RNA, and mRNA). However, the preliminary assays performed using the prototype need to be further explored to identify the sensitivity and specifics of the probes and the excitability and saturation of the sensors used. The development of new portable devices based on the matrix model allows a high degree of configuration and adaptation so that the system can be easily customized to diagnose other diseases using a low-cost screening platform that contributes to the dissemination of precision medicine in primary care.

Investment in primary health and technologies to support diagnosis and monitoring is one of the great challenges faced by SUS. Thus, solutions and applications that expand coverage streamline the process and favor the improvement of care are essential. It should be noted that the Digital Health Strategy (2020–2028), in its action plan, encourages innovation in its ecosystem in order to make the most of the interconnected environment in health, establishing itself as a large laboratory of open innovation, subject to the guidelines of the Ministry of Health. Therefore, the development of low-cost, high portability, and accessibility technologies should be the rule for application in PHC.

We must consider the recognition and importance of interoperability introduced by Ordinance MS nº 2073 of August 31, 2011. Medical treatments become faster, increasing the effectiveness of treatments. In the coming years, integrating patient data with a history of diagnoses, attendances, and medium and high-complexity procedures will allow the PHC to fulfill its role as an organizer of care. Scalability is a strategic point for implementing these models of embedded systems due to the heterogeneity of the computers used in PHC and in the perspective of future work.

The work presented plays a prominent role when evaluated under the dimension of analysis of the cost and the

Table 2 Experimental results for MiRNA's architecture

Sample	Green led (530 nm to560 nm)		Blue laser (450 nm)	
	Vpp* (with 100 µl)	Vpp* (with 150 µl)	Vpp* (with 100 µl)	Vpp* (with 150 µl)
Water	4.4 V	6.4 V	4.64 V	5.2 V
PE (fluorochrome)	9.6 V	8.4 V	4.48 V	4.72 V
Difference (PE –water)	5.2 V	2.0 V	−0.16 V	−0.48 V

*Vpp = Peak-to-peak voltage

potential benefit that will be made available in the PHC, as it brings applicability, the concern with the quality of the product, and the low production costs in the process of technological development, operation and qualification of testing, screening, and diagnosis of the conditions discussed here.

Conclusion

Biomedical systems to aid the diagnosis of syphilis and cancer provide diagnostic improvements by minimizing false positives and negatives; adequate technological support in UBS; improvement of prognoses with the expansion of testing; proper screening; and support for quality diagnosis for the definition of unique therapeutic projects and the regulation of medium and high complexity procedures. In addition, of course, it should be noted as a result, the reduction of direct and indirect costs generated by late treatment, in addition to the possibility of applying these systems to other infections and diseases, requiring only parameter and configuration changes, as well as analysis and processing of the results.

As a future evolution for devices, it is possible to expand the service architecture, implement artificial intelligence, and develop functionalities to automate the insertion of patient data in the software scope. Furthermore, in the hardware area, it is possible to optimize the dimensions of the devices using surface-mount device (SMD) components, use noise treatment filters and incorporate an industrial designer, providing greater robustness and safety. The work presented here brings an innovative and effective solution to improve the population's quality of life. The concern with meeting the demands of the health system through the development of innovative technologies, which combine scientific and technological knowledge, is a fundamental role of biomedical engineering.

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Author contribution LJGL, JPQS, ASC, and RAMV concept and design of the work; MACF, AILSM, DDAC, LJGL, and AHFM wrote the original draft; DMSB, JMOH, CADT, PG, CAPO, GAA, KDC, NNVM, CMGG, LPCFA, and RAMV contributed to the critical revision of the article. All named authors have given their approval for this version to be published.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any authors.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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