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A Non-Invasive Approach for the Detection and Monitoring of Diabetes in Mexico

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Abstract

The approximation of a Real-Time System for Detecting and Monitoring Diabetes is a model and a simulation of a functional system to help detect and monitor Diabetes Mellitus (DM) using non-invasive input devices. First, the public health problem of this disease is discussed and then; the general and particular system architecture is presented along with the methodologies of system design in real time computer such as SA-RT, LACATRE as well as a detailed explanation of the diagrams and system modules, and an analysis of faults is performed using Markov chains, plus an approximation of a proposal of a mathematical model for the prototype of a device for non-invasive monitoring glucose. Furthermore, it is considered necessary, the collaborative work in synergy with multidisciplinary professionals that include: Computer Science, Electronics Sciences, Chemical Sciences and Health Sciences.

Keywords: non-invasive; real-time

1. Introduction

Presently, one of the most frequent and serious diseases in the world is Diabetes Mellitus, which shows alarming statistics figures in Mexico.

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The main factors to be considered to influence the development of this pathology are; the lack of information about the disease, the physical inactivity and a poor diet. This paper focuses on achieving an approximation to a model for a non-invasive measuring of glucose in real time, since these systems, besides interacting with the environment and various elements of the environment, work according to time, i.e. all activities are performed in a given time interval.

The estimated number of people with diabetes in Mexico fluctuates between 6.5 and 10 million i.e. 10.7% of Mexicans between 20 and 69 years of age suffer the ailment. DM is a group of metabolic disorders affecting various organs and tissues, it is progressive and characterized by increased levels of blood glucose; hyperglycemia, it is considered a disease of multifactorial evolution and metabolically dynamic, as it involves both carbohydrates and lipids, one of the main causes is the low production of the hormone insulin, secreted by the β cells of the islets of Langerhans of the endocrine pancreas, or by improper use by dependent tissues of this, which will affect the metabolism of carbohydrates, lipids and proteins. (Internet page of the Mexican Diabetes Federation)

1.1 Factors that Affecting Diabetes

Diabetic condition has been considered a multifactorial disease among which some are estimated to have a genetic origin; that is, there is a family history. Studies in monozygotic twins have shown that the concordance rate can reach 90% or more (So et al., 2000) significantly higher value than the observed 37 % concordance in dizygotic twins (Permutt et al ., 2005) . While they have discovered numerous genes with altered expression in diabetes cannot be assured, except in special cases, one of them is the only cause of this disease (So et al, 2000; Sreekumar, 2002; Carulli et al., 2005). The highest percentage of cases of DM2 without any pattern of Mendelian inheritance and only a small percentage of diabetes (<5%) known as MODY (Maturity Onset Diabetes of the Young) is inherited in an autosomal dominant manner (Malecki, 2005).

Moreover, studies using intervention lifestyle subjects with impaired glucose tolerance have shown that DM2 is preventable, or at least its appearance delayable (Erickson & Lindgärde , 1991; Pan et al., 1997; Tuomilehto et al., 2001;. Knowler et al., 2002; Kosaka et al., 2005; Ramachandran et al., 2006).

The duration of the interventions in these studies has been three to six years and have emphasized the control of body weight, physical activity and diet modification. The relative risk reduction achieved in the intervention group (versus control) varied between 30 and 67%, as demonstrated in a meta-analysis (Yamaoka & Tango, 2005). The Finnish Diabetes Prevention Study (Tuomilehto et al. , 2001) and the U.S. Diabetes Prevention Program (Knowler et al. , 2002) showed a 58% reduction in the relative risk of progression of IGT to DM2 , for a period intervention average of three years (Lindström et al. , 2006). These data together, it can say with certainty that interventions in lifestyle are closely related to the onset and time course of DM2. Surely, the association of these factors with other predisposing genetic factors interacts to determine a phenotype characterized by insulin-resistance and alterations in glucose metabolism. Current evidence allows to only observing an association between genetic factors environmental and DM2 and there is no single approach to explain the true origin of this disease.

Similarly, physical inactivity has been associated with major non communicable chronic diseases of modern life (Booth et al, 2002; Eaton & Eaton, 2003). Although there is ample evidence of the impact of an active life on the origin and control of chronic diseases such as hypertension, obesity, dyslipidemia and DM2 (Booth et al., 2000), so far there is no clear understanding of the mechanisms by which exercise maintains health and physical inactivity precipitates the onset of disease in patients with or without a genetic predisposition. As a starting point, it is necessary to show that physical inactivity is physiologically abnormal and therefore, its counterpart, the activity is a condition that serves to maintain a healthy state of life. According to Booth (2000), sedentary lifestyle prevalent today directly contradicts one of the natural forces that influence the evolution of our genes. In short, an environmental pressure (physical activity / inactivity) that selects certain genes during evolution (thrifty genotype) linked to epigenetic changes that occur during early life (thrifty phenotype) or late the individual condition the health of this in adulthood.

Physical exercise has been shown to positively impact the treatment of type DM2 (Kriska, 2003).

However, despite the beneficial effects in the majority of the population, there is great variation in the physiological responses between individuals from the same plan of exercise.

This suggests that such interindividual differences can be attributed, at least in part, to genetic factors. In this regard, it is important to show how different sequence variants in genes associated with DM2 may influence the response to exercise. Definitely, the study of the influence of genotype on the response to exercise in diabetic patients is a poorly studied area and is a challenge in the search for effective interventions in the prevention and treatment of this epidemic. Anyway, beyond the genetic makeup, it opens a new possibility to explain the relationship DM2 and physical activity, which could explain the increased prevalence of the disease, interindividual differences in the response to exercise and the fetal origins of type two diabetes induced by physical inactivity. This possibility is substantiated by an epigenetic origin.

2. Related Work of Non-Invasive Methods

There are several noninvasive methods for measuring glucose, each one of them varies in their features, and most are under development; however, it is important to review and analyze each one of them to verify their methods and the work it has been performed.

2.1 Urine Tests

It is performed by employing dry chemistry techniques (test strip). The technique involves an absorbent pad that has been impregnated with chemical, and specific enzymes (glucose oxidase - peroxidase) which react to the glucose present in the urine producing a change on the color of the pad, which by reflectometry is converted to a numerical value corresponding to the concentration of the metabolite in the primary specimen (Abdul- Ghani and DeFronzo, 2008).

Plasmatic glucose has a free passage of the kidney at glomerular level. However, 99.5 of it is reabsorbed in the proximal tubule, i.e. Only 0.5 of this would be in urine (normal range: <20 mg / dL or < 1.11 mmol / L). Theoretically, the increase in plasma glucose above the threshold of renal reabsorption (160 - 180 mg / dL) would trigger glucosuria events. However, recent studies have shown that patients with high blood-glucose inflammatory activity have increased their threshold, and this can be around 370 mg / dL.

2.2 Sweat Tests

Sweat is a body fluid that can be used as an emergent tool in correlation with plasma glucose. Said humor normally has glucose. However, this is found on a range smaller to 1% with respect to the circulating one, although this data presents a remote reality to what happens at a plasma level, there are indicators related to the segmented step of the metabolite to the external dermis. The techniques related to the plasma-sweat parallelism are based on ionophores' mobility, which by electrochemical bio sensors are detected by the passage of currents of low current (0.3 mA/cm2) distributed through anodes and cathodes. Biochemical movements of glucose through the skin, involving migration of sodium ions which in turn increase epithelial reactions involving glucose oxidation and formation of hydrogen peroxide, which is detected by amperometric bio sensors which accompanied by sodium reach the cathode, while at the anode the stoichiometric ratio of chlorine ion migration, which has a negative charge, is used (Kim et al., 2004).

2.3 Saliva Tests

The saliva tests have advantages over more conventional biological matrices such as blood and urine. Sampling is rapid, non- invasive, less objectionable to patients and it is easier on those with poor venous access. Moreover, it is not as stressful and it poses a slighter risk for the patient. Saliva can be collected at remote sites by non- specialized personnel, with certain collection devices, being stable at room temperature for long periods of time. The salivary glucose concentration is established in the range of 12 -28 mg / dL, and it has been established that in hyperglycemic events it rises linearly showing strong positive correlation with respect to the plasma (Guilbault and Palleschi, 1995).

While, on the other hand, some Authors differ from the correlation Saliva - Plasma in patients with advanced diabetic pathology or hypoglycemic consumption within their therapeutic, given that, in both cases, the secretion ability of the salivary glands is conditioned. The technology developed for the non-invasive methods for the determination of glucose bio sensors is supported by indirect reactions, which couple glucose itself, like the case of peroxides derived from intrinsic or lactate metabolism of cellular activity, and no chemical or enzymatic reactions targeting the same molecule (Guilbault and Palleschi, 1995).

Currently research groups are working in bio chips and sensors that determine glucose concentrations in saliva, leveraging from advances in nanotechnology as well as on surface plasmonics. The team at Brown University in America has advanced in the area through plasmonic interferometers, which can measure the concentration of glucose molecules present in a water sample. Their results indicate that this bio chip can detect glucose levels in saliva.

2.4 Nanotechnology Tests

Technological advances in the theoretical joint fluid, have led to the creation of various sensors. One of the most innovative technologies is associated with the infrared spectrum which can be used in several ways. The emission of light into vessels or capillaries from a medium to a high caliber is one of the most utilized technologies in the research. The principle of mobility of the particles is associated with the molecules in circulation. One of causes of delay in the transmission and reception of light, is the glucose, the higher concentration of it, the more delayed the light travels, so through various mathematical algorithms, a pattern of dispersion has been established, which when transduced with a sensor is converted into a number reflecting the probable concentration of the metabolite in plasma. On the other hand, there is the same principle applied in retinal nanotechnology sensors, which emit infrared light with a certain wavelength to impinge on the glucose molecules, taking advantage of the ability to polarize it, provided it is in its D-glucose form, which is the biologically active form and it is found in 99% of mammals.

The rotational capability of glucose by impinging light beam , polarizes it, the longer that polarization the greater number of glucose molecules passing through the point of incidence, and vice versa , from which it follows that the concentration thereof . Another technological adaptation is the application of infrared light on sensors coupled nanotubes containing the enzyme glucose oxidase, which is selective for interacting with glucose and produce hydrogen peroxide, the production of this is equimolar with glucose. In nanotubes have engaged surfaces ferricyanide , which is sensitive to peroxide , promoting change in the electron density of the nanotube and thus the optical properties , the nanotube when illuminated by an infrared laser can see difference in brightness with increasing or decreases the level of glucose (Ramos et al. , 2011).

3. Proposed System: Model of a Real-Time System for Detection and Monitoring of Diabetes Using Non-Invasive Methods

Real-Time System for Detecting and Monitoring Diabetes is an innovative model -based design methodology for Real Time Structured Analysis (SA-RT) (Yourdon, 2006), Langage d' Aide à la Conception Temps Réel (LACATRE) (Schwarz and Skubich, 1993) . The physical variables consist of the glucose variations that a patient suffering diabetes has. These variations allow real time monitoring of diabetes using a noninvasive device installed on each patient concerned, which will allow their Diabetes Monitoring in Real Time. Each patient has an independent monitoring device, which can be observed locally, but also the architecture design will allow displaying an interface via some software installed on the patient's personal computer or mobile device. The specialist can, through an extension of software designed for interacting with 'N' critical patients remotely monitor the status of critical care patients who are at higher risk. The design of the system (Figure 1) has a (GSM / 3G EV -DO) network that transmits wireless signals; these, in turn, are transmitted via the Internet to a Transmission System Data (STRD) which then sends them to the screen or device of the user, whether on the patient's computer or the medical specialist. The system, in time, saves your time data from a database and displays a warning signal when an abnormal glucose variation happens.

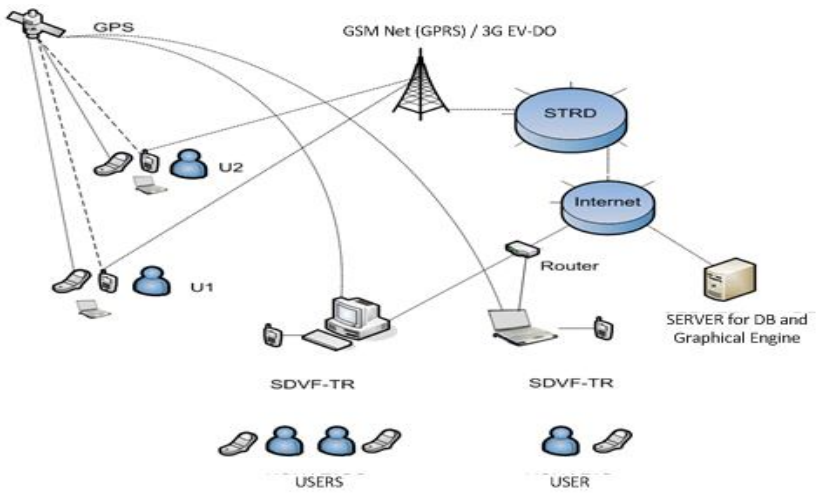

Figure 1: Architecture Proposal for the Overall System and its Multi-Sensor Reception

3.1. Mono-sensor Context Diagram

The Mono-Sensor Context Diagram System (noninvasive local device) for the Detection and Monitoring of Diabetes allows receiving the physical environmental variations, in this case, it is the glucose variations in the patient, perceived by noninvasive sensors, and it is responsible of sending variations on their behavior. The physical changes perceived by non- invasive sensors may include a trigger event or an accelerator event whose variations depend on the measurements or parameters obtained through measurements or specialized non- invasive sensors considering all processes and biological factors described in section 2. The noninvasive device transmits wireless signals, which in turn go through a data transmission system that sends the physical variations to the Monitoring System in Real Time, to process the bits received by the software in real time. Once the data is processed, they can be displayed on the user's device or computer's screen; they can be modeled in 2D or 3D and stored in a database. At the same time, there is an analysis subsystem to access the database to obtain, for instance, the history of monitoring (Figure 2).

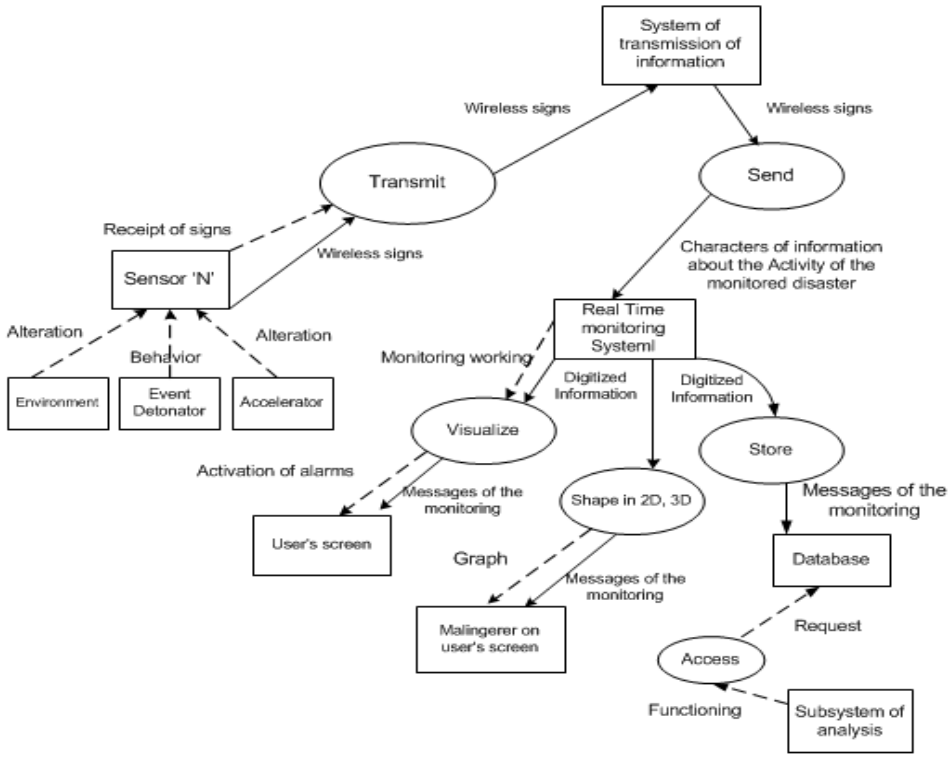

Figure 2: Diagram Context

3.2. Data Flow Diagram (DFD) Mono-Sensor

The Data Flow Diagram (DFD) System for the Detection and Monitoring of Diabetes, interacts with events in and out of the control bar (Figure 3). The generation of the initial event, the local environment, as well as the trigger event and accelerator, are the flow of data which the system will initially perceive and according to the behavior of the monitored event (diabetes), will enter or exit the bar control to perform certain actions. If an abnormal activity or danger occurs within the monitoring of an event, the following actions will return to the control bar, and they will generate other actions such as showing danger and will transmit danger messages to exhibit the event and notify specialists, who will determine whether to make any critical decision to avoid complications in patients.

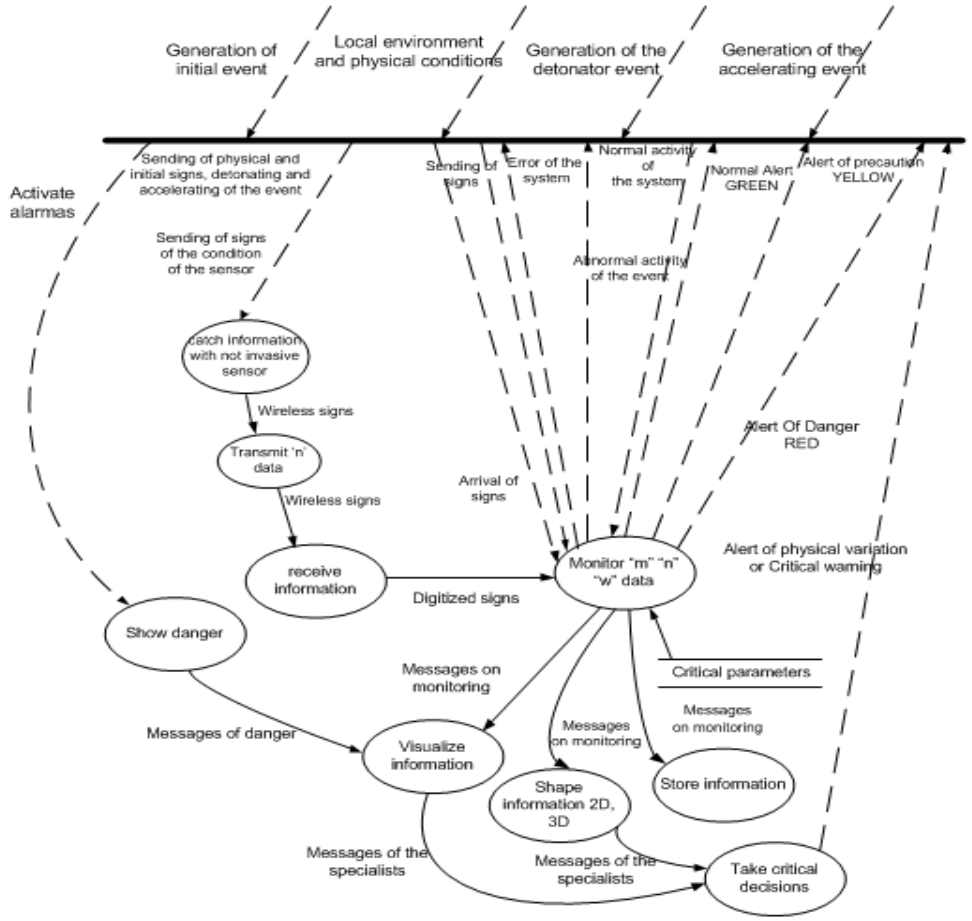

Figure 3: Data Flow Diagram DFD Mono-Sensor

3.3 States Transition Mono-sensor Diagram

The States Transition of the System Diagram allows the monitoring of the states of the system (Figure 4). Each patient has a sensor that can be monitored locally. The system has several states while operating, and it is logically related to the Data Flow Diagram. The sensor is initially, in a standby state, but when it receives a physical variation relating to a fluctuation in glucose, which is registered by a specialized sensor, it changes to a transmission state.

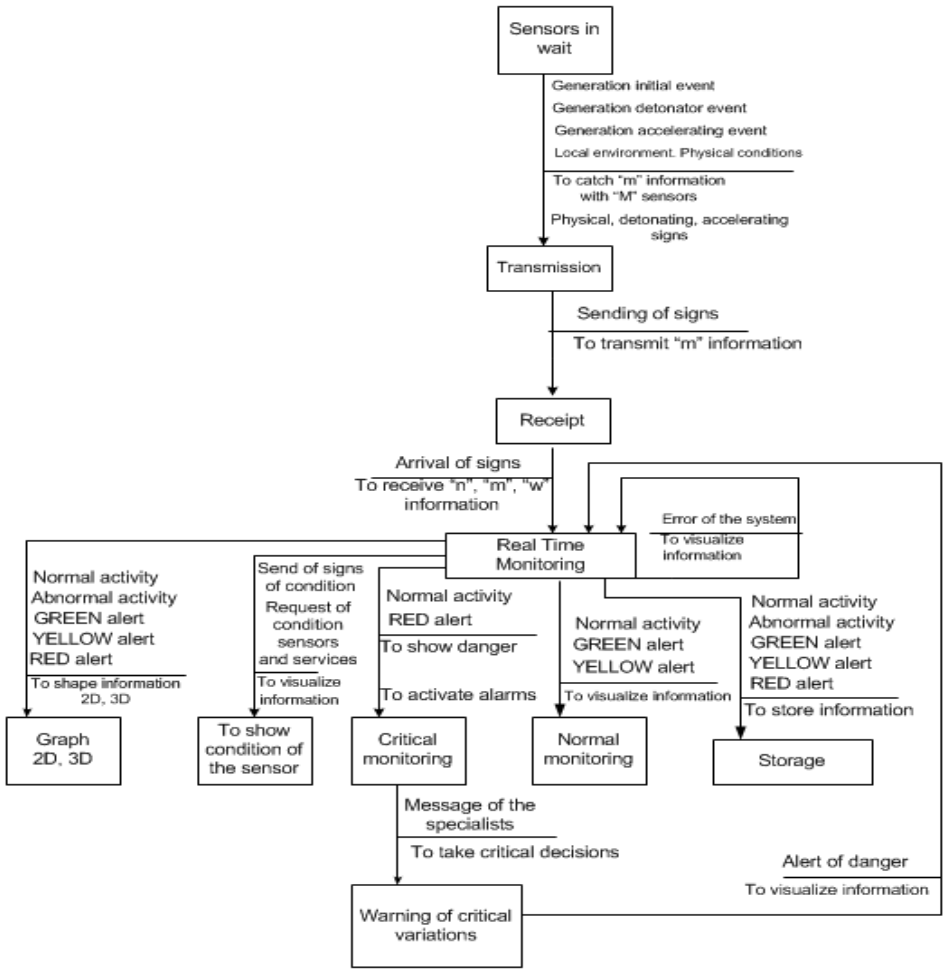

Figure 4: State Transition Diagram

Then you reach the reception status, where numerical information is received and the system accesses the monitoring state, whose alarms depend on the behavior of the monitoring event (diabetes).

The monitoring state receives the signals from specialized sensors, and their behavior will generate the next change of state. The system can detect diverse behaviors that are able to generate green, yellow, or red type alerts; if it detects any change within the critical parameters, the system will change to critical monitoring. In case of an emergency on one of the illest patients, the specialist is capable of knowing the status of the patient by communicating the system remotely, regardless the number of patients to be treated. When the red alert and an emergency happen, it is time to take preventive or emergency action. The system also possesses other states that may occur within the monitoring of patients, these being the states of storage, regular monitoring, data observation through the state of graphing in 2D or 3D, or by displaying the state of specialized sensors.

3.4. Mono-Sensor Architecture Context Diagram

The Mono-Sensor Architecture Context Diagram (Figure 5) integrates, in an abstract way, the functionality of all the elements of the system's architecture. The monitoring system in Real Time (Hardware and Software) has input signals; the users have access to a Human-Computer Interface (HMI) to interact with the system, the Real-Time System with a Data Transmission System, operators and output messages using a screen.

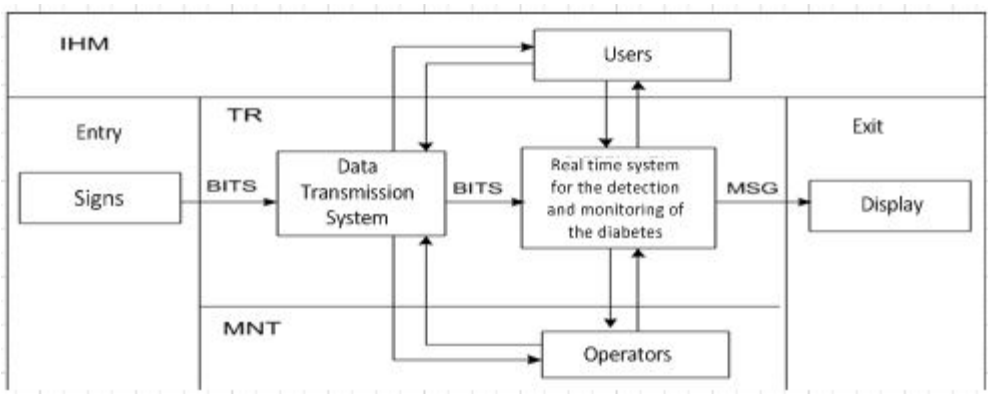

Figure 5: Mono-Sensor Architecture Context Diagram

3.5. Multi -Sensor Interconnection Diagram

The Multi -Sensor Interconnection Diagram allows understanding the abstraction of interconnection of the elements on the running system. All the inputs are sensors of different patients who have the device, in order to be monitored simultaneously by the specialist. The non-invasive sensors will have a wireless treatment system, which will communicate with the Data Transmission System, which in turn, via the Internet, will communicate to the specialist's computer, who owns the Real-Time Detection and Monitoring Diabetes Software. The Software will have its data and graphical outputs on a flat HMI screen in the computer of the specialist (Figure 6).

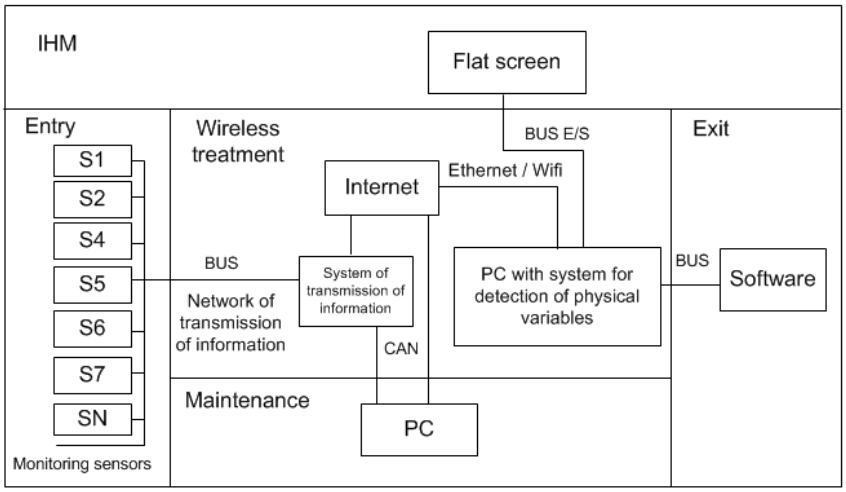

Figure 6: Interconnection Diagram Multi-Sensor

3.6 LACATRE Diagram Software for Monitoring Patients and for the Specialist of Multi-Sensor Type

The software design is represented by the Software diagram, with LACATRE design methodology that allows monitoring a great number of patients, and it is the logical abstraction for modeling the interaction between sensors and the overall system in Real Time (Figure 8). The MAIN module is divided into different modules tasks or threads:

P2: Sensor 1, with priority 1.
P3: Sensor 2 with priority 2.
P4: Sensor 'N' with priority 3.
P5: Monitoring, with priority 4.
P6: Alarm, with priority 6.
P7: 3D visual monitoring with Priority 5.
P8: Prediction, with priority 7.

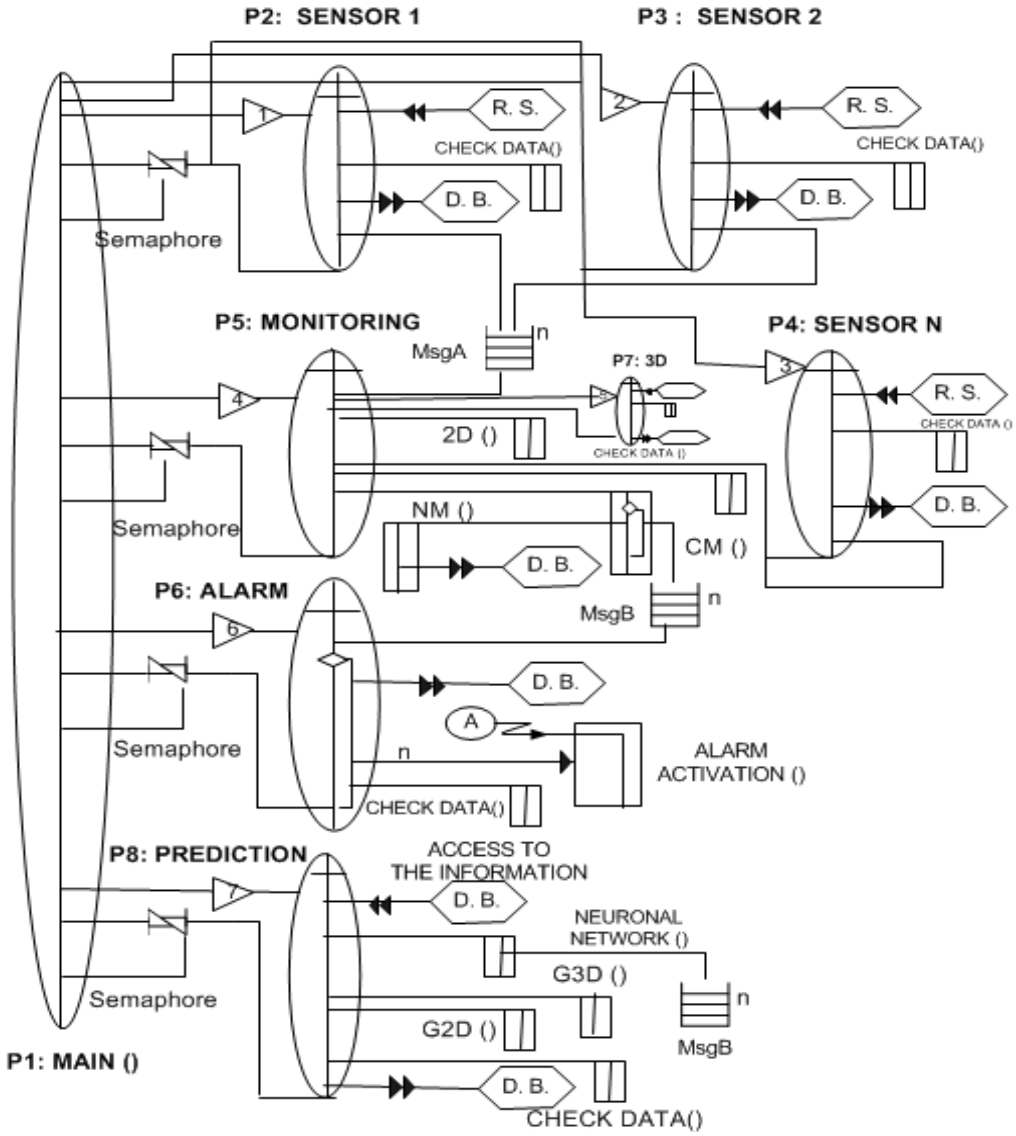

Figure 7: Diagram LACATRE Multi –Sensor

The threads are synchronized by semaphores to ensure that access data correctly. Each thread represents a sensor which obtains the glucose physical variations -these are sensors with a data resource (RS) - . The data can be obtained locally at all times by noninvasive sensors, and they can also be stored directly in the database (DB). All sensors communicate with the monitoring P5 thread, through messages, in a type FIFO structure, called MsgA. P5 takes data to monitor them, and the software allows analyzing and recording whether there are physical changes. The P5 module has the CHECK DATA() function, which shows data from the display output interface , should it experience significant physical variations, P5 has the function of Critical Monitoring CM(), that will send information to another type FIFO data structure called MsgB, which in turn will send an alarm message to the alarm thread module P6 . If variations are normal, they will be merely stored in the database (DB) through the Normal Monitoring NM() function. The P5 module also contains functions for plotting 2D behavior and an extra thread P7 to plot 3D behavior. If a variation of glucose present in critically ill patients, the P6 thread ALARM ACTIVATION() function will trigger an alarm, depending on the 'n' severity of the detected variation, when, after analyzing the correct biological parameters, a danger to the patient is shown, it will issue a warning to the specialists. P6 also contains the CHECK DATA() function. The System design of Real-Time Software also contains a thread P8 module for Predicting the behavior of physical variations in the patient. This module has access to the (RS) data and to the database for analysis with Artificial Neural Networks algorithms and evolutionary algorithms by Neural Networks() function, which will take care of making predictions about the behavior of the physical changes in glucose of each diabetic patient. In turn, this function can display the behavior function CHECK DATA() and store and graph the predictions made.

In addition, a failure analysis is carried out, using Markov chains as a first approach within this proposal, which will serve a priori for an improvement to the proposed system, the table below and the graph are placed (Figure 8) corresponding to the analysis that was performed.

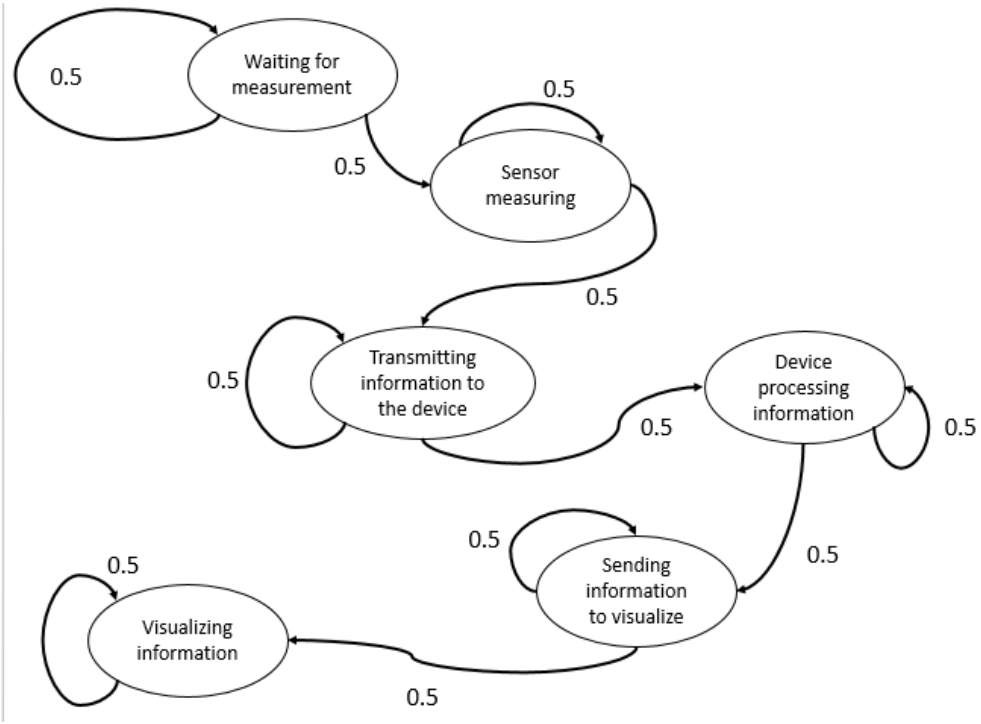

Figure 8: Graph of the Markov Chain

0.5	0.5	0	0	0	0
0	0.5	0.5	0	0	0
0	0	0.5	0.5	0	0
0	0	0	0.5	0.5	0
0	0	0	0	0.5	0
0	0	0	0	0	0.5

Table 1: Analysis of Markov

4. Hardware Prototype for the Non-Invasive Glucometer Approach

In recent years, wireless communication systems have evolved in many ways, for example, people can be connected through a network at anytime, anywhere.

As an example of some systems are wireless communication technologies such as long-range wireless networks, and satellite links. Wireless communication networks can provide important benefits to remote patient monitoring. The patient can be monitored from any place where some type of cellular or satellite coverage is available. Moreover, the data transmission is not only transferred to medical units, but it can go directly to the pertinent doctors, using common devices such as mobile phones.

This work is a model proposal that allows monitoring the glucose levels in persons by a non-invasive method, which is performed using sensors and electronic cards, making a correspondence of data with an invasive glucometer and the measurements, obtained by one GSR (Galvanic Skin Response) sensor. The signals obtained through this GSR, are variations in the electric potential present in the sweat of individuals, or in the skin itself, which is why, characterizations of the measurements obtained must be made. Besides, this device can easily be used as a mobile device.

The approach being investigated is the mathematical relationship which emerges from the data obtained from conductance and resistance; first, to perform this approximation it starts from the units in which the glucose levels measurements are performed, and given that there are two reference units, which are: mg/ml and mmol/L; once those units to be worked with are established, it is necessary to find a mathematical model that allows representing the correlation between glucose and resistance values obtained by the sensor GSR ; which sets out from the resistance values recorded by the GSR sensor, and by means of a mathematical model , it aims is to match the resistance values, with glucose values in the people. As a result, on the table 2 and Figure 8, some values are obtained from the approximation. This table can be considered as a piece of the behavior of the system results. The complete results that the non-invasive monitoring function to be work with will show similar but extensive values.

Resistance	Glucose
40000	2
48400	2.2
62500	2.5
78400	2.8
90000	3
96100	3.1
115600	3.4
122500	3.5
129600	3.6
152100	3.9
160000	4

Table 2: Approximate Values of the Proposed Model

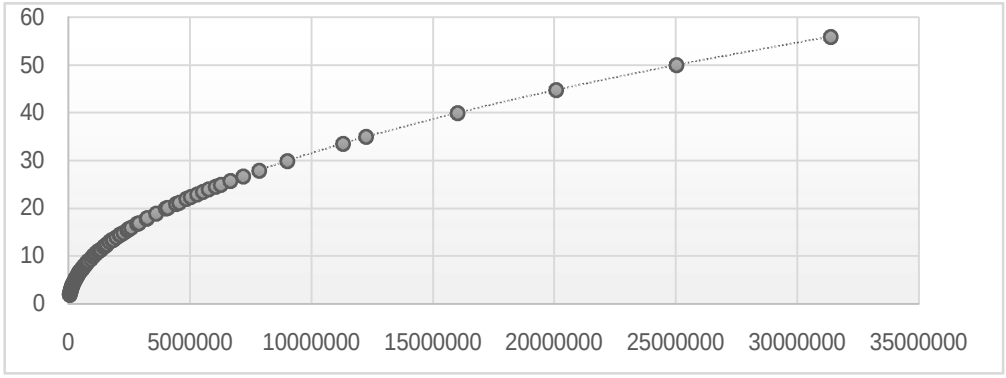

Figure 9: Graph of the Approximation of the Mathematical Model

Doing this correlation in people who are clearly classified considering their glucose levels, subsequently; these data will be integrated and thus related to the results obtained with the sensor; however, the way in which this procedure is performed, it is not inconsequential, as several factors must be considered when making measurements: from the skin nature of the person, or the place where the sensors are positioned, given that the capillarity of people may vary. It varies depending on the part of the body where the measuring of the GSR sensor is to be taken, other factors such as the medical history of people, their lifestyles, setting up a fasting pattern, so that their levels of both conductance, resistance and glucose are stable to avoid variations in the data obtained, must also be taken into consideration.

5. Conclusions and Future Work

As part of the prevention of economic and social disasters that currently generates diabetes, incorporating monitoring systems with non- invasive methods are indispensable for the near future, where the main objective is to save lives of patients as well as helping you a better quality of life that positively affects all aspects of society. The contribution of this work is the model for the generation of a prototype of a non-invasive glucometer using mobile technologies to monitor glucose levels and aid to people suffering from this disease.

In addition, collaborative and synergistic working with multidisciplinary professions that include Computer Science, Electronics Sciences, Chemical Sciences, Health Sciences, and Economics, to boost Mexico's economy, it is considered necessary to develop lifesaving devices at an affordable price, with the help both from state and federal governments. The Future work includes mainly physical and clinical testing from the model herein projected. So that the details are worked out to come up with a prototype that is effective in its operation, besides developing applications for mobile devices as well as the validation of a model of faults with Markov chains, Petri nets and fault trees.

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Legal Note

The Hardware prototype device, with the non-invasive glucometer model invention, the mathematical relationship and the utility models, is undergoing a patent process with the authors as inventors and the BUAP University as applicant before the Mexican IMPI office.

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