The Cardiac Diagnostic Prediction Applied to a Designed Holter

Leonardo Juan Ramírez López, Javier Oswaldo Rodriguez Velasquez

***Abstract*—**We have designed a Holter that measures the heart´s activity for over 24 hours, implemented a prediction methodology, and generate alarms as well as indicators to patients and treating physicians. Various diagnostic advances have been developed in clinical cardiology thanks to Holter implementation; however, their interpretation has largely been conditioned to clinical analysis and measurements adjusted to diverse population characteristics, thus turning it into a subjective examination. This, however, requires vast population studies to be validated that, in turn, have not achieved the ultimate goal: mortality prediction. Given this context, our Insight Research Group developed a mathematical methodology that assesses cardiac dynamics through entropy and probability, creating a numerical and geometrical attractor which allows quantifying the normalcy of chronic and acute disease as well as the evolution between such states, and our Tigum Research Group developed a holter device with 12 channels and advanced computer software. This has been shown in different contexts with 100% sensitivity and specificity results.

***Keywords*—**Entropy, mathematical, prediction, cardiac, holter, attractor.

I. Introduction

CARDIOVASCULAR diseases –CVDs are caused by disorders of heart and blood vessels; those include coronary heart disease –heart attacks, cerebrovascular disease –stroke, raised blood pressure –hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease, heart failure, among other. Some causes of CVDs are stress, tobacco use, physical inactivity, an unhealthy diet, harmful use of alcohol, and more recently the change of natural environmental conditions. The CVDs are globally the first cause of death: annually die more people because of CVDs than because of any other cause [1]. Therefore, according to the World Health Organization –WHO, it is considered that by 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are expected to continue to be the leading causes of death in the world and with a tendency towards growth in poor countries [2].

The behavior of a system can be described through the temporary change of the dynamic variables of a system. Predicting and quantifying this behavior from the initial conditions of the system constitutes the central problem of the theory of dynamic systems [3], [4]. The dynamic variables of the system are represented graphically in the phase space, receiving the name of attractors [5]. If irregular attractor behavior is observed in the phase space, the attractor is chaotic; this type of attractor can be studied with fractal geometry. In addition, other experiments show a finite number of possible events, so with the theory of probability they study the possibility of occurrence of this event [6]. As for entropy, it has been redefined in different contexts, since its inception in the design of thermal machines [7], in the kinetic theory of gases, statistical mechanics [8] and in artificial intelligence [9], [10]. As a consequence of this situation, the area of cardiology has seen the need to implement new strategies that can contribute to the reduction of these causes of mortality, proposing research on walks to improve the protocols established for the correct monitoring of the patient, as well as improving the biomedical equipment with which the patient is monitored. Among this group of biomedical equipment most used in the area of cardiology is the Holter equipment, because it is a non-invasive examination that stores the electrical signals of the heart in a 24-hour period while the patient performs his daily activities. These teams identify significant changes in the heart rhythm with a transient characteristic, sudden presentation and asymptomatic conditions [11]. However, due to the amount of information derived from the reading of the stored electrical signals, the establishment of a unanimous diagnosis is not yet evident in the medical literature [12].

Based on the methodology developed by the INSIGHT group to assess cardiac dynamics through the proportions of entropy and in partnership with the TIGUM group of the New Granada Military University, a Holter electrocardiographic prototype was developed. The purpose of this paper is to present the results derived from the storage and processing of electrocardiographic signals from the methodology developed in the context of dynamic systems theory [13].

A. Holter

The analysis of the continuous electrocardiographic record and/or Holter [14]-[19], from the context of dynamic systems theory, has reevaluated the notions of heart rate variability – HRV as a diagnostic and predictive parameter of cardiac behavior. Thus, the new positions focused on the irregularity of cardiac dynamics [20], [21], developed within the framework of the theory of dynamic systems, have moved away from the conventional conceptions of regularity as an ideal in derivative medicine of the notion of homeostasis. In the research of Goldberger et al. [22] based on nonlinear dynamic systems, it has been found that cardiac dynamics with excessively random or regular behavior is associated with pathological cases, while the intermediate behavior between

Leonardo Juan Ramírez López is with the Universidad Militar Nueva Granada, Colombia (e-mail: leonardo.ramirez@unimilitar.edu.co).

Javier Oswaldo Rodriguez Velasquez is with the Universidad Militar Nueva Granada/ Research Center of Country Clinic, Colombia (e-mail: tigum@unimilitar.edu.co).

these two extremes is associated with health. In this context, more reliable predictors of death have been found through fractal dimensions in patients with acute myocardial infarction –AMI with ejection fraction less than 35% [23]. However, the clinical applicability of these last two investigations still does not reach completely satisfactory levels that require additional studies to confirm and, in many cases, adjust this applicability [24], [25].

The goal was to design a functional prototype Holter electrocardiogram to store, process and display signals and incorporate a mathematical methodology, based on the theory of dynamical systems, probability, and proportions of the entropy of the attractor.

II. Method

A. Terms

Delay map: Type of specific attractor that graphically represents the dynamics of a system, placing ordered pairs of values of a consecutive dynamic variable over time in a space of two or more dimensions.

Ordered heart rate pair: Any consecutive combination of two heart rates represented as (x, y) which will be contained in the delay map, being in the corresponding range of five according to their coordinates

Probability of consecutive ordered pairs in ranges of 5: The ratio between the number of ordered pairs that occupy said range and the total of ordered pairs of the entire plot.

$$P(X,Y) = \frac{\text{Number of ordered pairs found in the range X, Y}}{\text{Total pairs ordered on the plot}} \quad (1)$$

The following procedure was performed, explained in phases:

B. Phase 1: Record and Storage

The device captured and stored the electrocardiographic signal, by recording the value of the heart rate and the number of beats every hour, for a minimum of 18 continuous hours. These stored values are taken to the delay map to generate a numerical attractor [13], where the frequency of ordered pairs of the heart rate was plotted. Next, the firmware evaluated each of the regions, using the probability of occupancy with respect to the totality, quantifying the probability for each of the ranges of five in the phase space, where each pair of heart rates is considered as an event with (1). Next, he evaluated the entropy of each attractor with the following equation:

$$S = -k\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times LnP(X,Y) \quad (2)$$

The attractor regions previously established to be evaluated are region 1, which contains all the ranges of HR common to normal Holter electrocardiographic records. Region 2 corresponds to the totality of the ranges occupied by the normal Holter electrocardiographic records, excluding those of region 1. Region 3 corresponds to the total remaining region of the delay map, that is, the HR ranges that not they are occupied by normal Holter electrocardiographic records [13].

C. Phase 2: Mathematical Analysis

Subsequently, the team automatically cleared (2) leaving it in terms of the S/k ratio (see (3)), and then grouped the addends corresponding to probabilities associated with occupancy frequencies of units (U), tens (D), hundreds (C) and thousands (M), developing said sums with (3) to later evaluate the proportions existing between each sum with respect to the totality (S/k ratio) and the proportions between hundreds with respect to thousands and tens with respect to hundreds for each determined region (see (4)). After performing all these steps, the team finally applied the diagnostic parameters of the developed methodology [13], evaluating whether at least two of the proportions in any of the three regions are outside the normal limits, which is the differentiating parameter of normality abnormality.

$$\frac{S}{K} = \sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times LnP(X,Y) \quad (3)$$

where S is the entropy, K the Boltzmann constant (1.38 x 10^{-23} Joules/Kelvin), P (X, Y) is the probability for each range (X, Y). To explain (3) as follow:

$$\frac{S}{k} = \begin{cases} \sum_{U} P(U)\times LnP(U) & \text{Units (U)} \Rightarrow \text{(1 - 9)} \\ \sum_{D} P(D)\times LnP(D) & \text{Tens (D)} \Rightarrow \text{(10 - 99)} \\ \sum_{C} P(C)\times LnP(C) & \text{Hundreds (C)} \Rightarrow \text{(100 - 999)} \\ \sum_{M} P(M)\times LnP(M) & \text{Thousands (M)} \Rightarrow \text{(1000 - 9999)} \end{cases}$$

Equation (3) to be simplified is as follows:

$$\frac{S}{K} = T = U + D + C + M \quad (4)$$

where $T = \frac{S}{K}$. For (4), the proportions are between the parties: Units, Tens, Hundreds and, Thousands.

D. Phase 3: Processing

To quantify the level of severity of the pathological dynamics, taking as reference the previously defined extreme normal values [13], the upper limit of normality is subtracted from the proportions that are above these limits, while values below the minimum normal value were subtracted from the said limit value. Once the values of these differences are obtained, they are added according to the orders of magnitude of units, tens, hundreds and thousands, and finally, it is quantified how far or near they are from normality. Thus, higher values corresponded to more acute pathologies and lower values to less severe pathologies.

E. Phase 4: Validation

We proceeded to calculate sensitivity and specificity. We compared these results with the diagnoses issued on Holter records by expert specialists. Thus, mathematical evaluation was developed. For these calculations, cases that have been diagnosed as pathological by both methodologies are called true positives (VP), false positives (FP) to cases that were evaluated mathematically as patients and by the clinical expert as normal. False negatives (FN) are the cases that were mathematically diagnosed as normal but were classified by the expert as pathological, and finally, the true negatives (VN) were the cases diagnosed as within normal limits by both methodologies. The Kappa coefficient that assesses the concordance between the physical-mathematical diagnosis and the conventional diagnosis was also evaluated.

$$K = \frac{Co - Ca}{To - Ca} \tag{5}$$

where Co represents the number of observed matches that correspond to the number of patients with the same diagnosis from the mathematical methodology and from the standard Gold. To represents all cases, Ca corresponds to the number of randomly attributable matches that are calculated through:

$$Ca = [(f_1 x C_1)/To] + [(f_2 x C_2)/To] \tag{6}$$

where f1 equals the number of cases with mathematical values of normality; C1 represents the number of cases diagnosed as normal by the clinical expert; f2 represents the number of cases mathematically evaluated as a disease; *C2* represents the number of cases diagnosed from the conventional clinical; and, *To* represents the total number of cases.

III. Holter Design

The software developed allows analyzing the behavior of the heart through two different methodologies in the time domain: variability, and pNN50. The Holter was developed into two parts:

a. A firmware developed for a Raspberry PI card, which digitizes the cardiac signal obtained from 12 derivatives, detects the R peak and the time (ms) elapsed between R peaks for the analysis and calculation of the variables shown in Table I and storage of the data obtained.
b. User interfaces for computer developed in MATLAB®, which allows visualizing the data stored during the Holter register, the signal of the 12 derivatives and visualization of the entropy obtained during the registration.

Table I shows the VFC analysis parameters in the temporal dimension.

TABLE I
VFC Analysis Parameters in the Temporal Dimension [26]

Parameter	*Unit*	*Definition*
RR	ms	Intervals between beats (R peaks in the ECG)
AvRR	ms	Average duration of all intervals
RRSD	ms	The standard deviation of all intervals. It is known as total variability.
pNN50	%	Percentage of RR intervals, which differ more than 50 ms from each other.

These components are responsible for capturing the signals per patient, obtaining different variables and finally storing the information in an SD memory. The data stored later can be displayed on a computer.

A. Hardware

The following components were used for the development of the Holter device:

- Raspberry PI: Digital processing device
- EG12000: Cardiac signal acquisition card
- Clock module: In charge of keeping the date and time updated.
- Indicators
- Buttons
- Voltage regulator

The programming of the Raspberry pi controller card is done in Python 3.4 for the purpose of obtaining the information delivered by the EG12000 acquisition card. Thus, with the R peak, we are calculating the RR interval in milliseconds, as shown in Table I. Finally, the storage of the Holter record, signals, and alerts are on SD memory.

The signals are read by blocks (to see block identifier refer to manual EG12000), one of the blocks contains the derivatives of the members together with the first thoracic derivative V1, while another block contains the remaining thoracic derivatives. A third block contains the numerical value of the heart rate in beats per minute, which is obtained by averaging the last 12 heart rates (see manual EG12000).

The samples corresponding to each derivative are stored in an array, where they are stacked for later storage in the SD memory when a timer is executed every 10 seconds, adding at the end of the line of each file the new values per derivative captured. Derivatives information is stored in two text documents (.txt), one called hh.dd.mm.leads.Limb.txt and another hh.dd.mm.leads.Chest.txt. Together with this timer, alerts that have been generated in that ten-second interval are stored in a file called hh.dd.mm.Warning.txt, the alerts are generated by abrupt variations in heart rate or when bradycardia or tachycardia occurs. It is also possible to physically see them on the device when a light signal is turned on.

A second timer, executed every hour calculates the proportional entropy of the cardiac systems and stores the information delivered for the Holter record (Time, Number of beats, Minimum Frequency, and Maximum Frequency) in a file called hh.dd. mm.Entropy.txt, stacking the new time recorded at the end of the file. It also performs the calculation of the proportional entropy of the cardiac systems through the Entropy function, which takes as input parameters vectors, with the same dimensions, containing the number of beats, maximum frequency, and minimum frequency.

B. Software

The software or application for the visualization of the 12 derivatives and behavior of the proportional entropy for the Holter record during a certain time interval was carried out in MATLAB®.

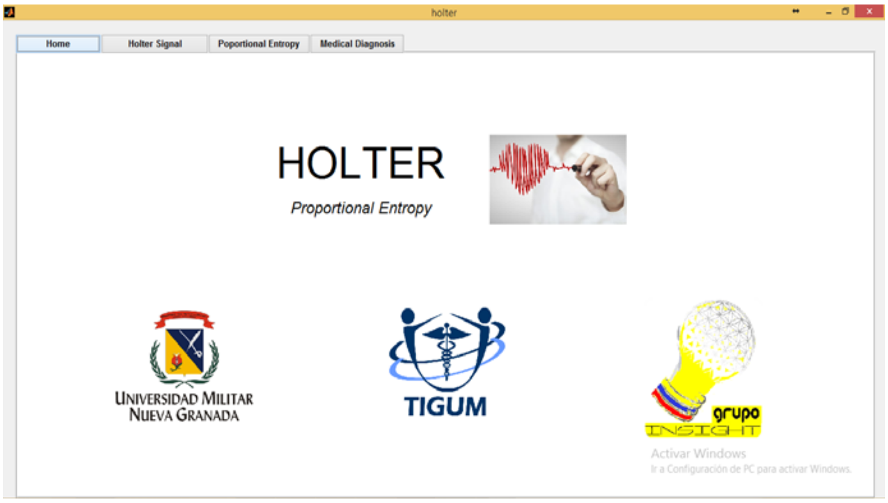

Fig. 1 Home interface

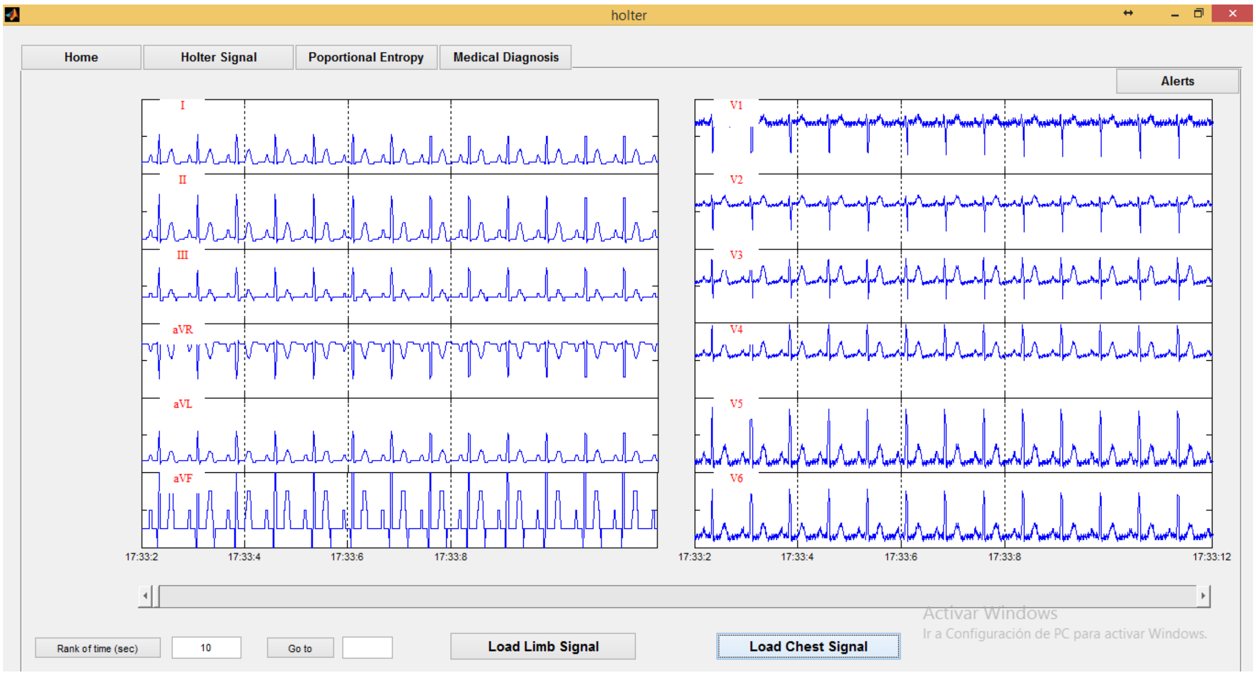

Fig. 2 EKG signals of holter

Fig. 1 shows the home interface. The application contains four windows: home, holter signal, proportional entropy, and medical diagnosis. Two of these windows are explained:

- Home: Main window shows welcome and informative images of the research groups and the university property.
- Holter Signal: Window for reviewing signals in the timeline allows to search for signals for hours, minutes and seconds, scroll through a navigation bar through time and define the time interval you want to see. The interval must be greater than 3 seconds.

Fig. 2 shows EKG signals. The Load Limb Signal button allows loading the register of the signals of the derivatives of the members that were taken through the Holter equipment. Only that button must be used to load the register of the derivatives of the members since they have a special format (hh; mm; ss; us;; I; II; III; aVR; aVF; aVL; C1;) and selecting another file could generate an error or an unexpected response.

The load Chest Signal button allows selecting the file corresponding to the precordial derivatives:

hh; mm; ss; us;
C2; C3; C4; C5; C6.

When selecting the appropriate file and pressing accept, the curves of the signals will be displayed in the corresponding window; the signals are identified with their name in the upper left of each grid in red.

At the bottom, there are five text boxes that indicate five instants of time that are divided proportionally in the range of the grid to indicate the time at which the signal was presented. Additionally, it has a navigation bar, which can be moved from left to right or vice versa to make the signal path through the entire register.

Pressing the Rank of time button defines the period of time that will be shown in the graphs, it can be defined by means of the adjacent text box expressing the time in seconds (s): the interval since 3 ate 10 s, by default.

The Go to button shows the signal from a specific time indicated by the user through the text box on the right, for this, it is necessary to write it in the following way hh: mm: ss (e.g. 16:20:05; place the start of the graph at 16 hours, 20 minutes and 5 seconds).

With the upper right button alerts, a list is displayed in which one can observe the alerts generated during registration. To load the alerts, it is necessary to select the Load Alerts button which in turn will open the file browser where the user can select the document corresponding to the alarms.

Once the document has been uploaded, the information will be displayed in the list, to see the signals at the time the alarm was presented, simply select the desired anomaly and the graphics will move until that time.

C. Proportional Entropy

The proportional entropy is show by men to the interface of new cardiac diagnostic prediction in Fig. 3. The window “proportional entropy” allows visualizing the matrix of attractors, highlighting region 3 in red, region 2 in green and region 1 in blue. The Holter register that has been loaded is shown in the upper right. The values obtained from the entropy for eighteen hours are shown in the middle right; the red squares mean that such values are outside the normal limits. The quantification of the evolution is presented in the lower right.

Once the record has been loaded, the data are shown in the upper-right table Holter Register where the time, the number of pulses, the minimum heart rate, the maximum heart rate (in beats per minute), its average, and its variance are presented in seconds for each hour of record. This allows the user to verify that it is the record he wants to analyze. In addition, the Calculate button is enabled.

At any time, the user can select from what time of the Holter record he wants to start the calculation of the proportional entropy, for this purpose it is necessary to select the cell that contains the time from which he wants the calculation to be made and then select the button Calculate by default the calculation is done with the registration from the first row.

The calculation of the Proportional Entropy of the Cardiac Systems is done with 18 hours of registration and the results are shown in the Numerical Chaotic Attractor and Entropy Proportions for Region matrices. If the record that is loaded has less than 18 hours, the calculation is made with the interval of hours that the user chooses (initial time selected until the last hour of the record), but the results obtained may not yet have interpretation (Entropy Algorithm Proportional Cardiac systems). If the record that is loaded has more than 18 hours, the calculation is made with the interval of hours that the user chooses (selected initial time until the following 18 hours. If selected less than 18 hours the calculation is made from the selected time until the last hour of the registration).

The Calculate button shows in the left matrix Numerical Chaotic Attractor. The attractor matrix obtained for the Proportional Entropy method of the cardiac systems; in the right middle table Entropy Proportions for Region shows the proportions by region of Units, Tens, Hundreds and Thousands.

In the lower table, “Quantification of evolution”, the quantification of the disease is presented in a record of 18 hours, therefore, if the record that has been loaded has more than 18 hours the software will present more than 2 rows in this table. Thus, for example, in the first row the results of the proportional entropy of the hour 1 to 18 are shown, in the second row of the hour 2 to 19, in the third row of the hour 3 to 20 and so successively. If, on the other hand, the Holter record has less than 18 hours, the result will be shown from the first hour to the last.

The entropy algorithm takes three parameters as a basis, the number of beats in one hour, the minimum and maximum heart rate in that hour. From these three data the whole algorithm is developed [14].

The diagnosis step allows predicting among seven different conditions of patient status. The Load Holter Register button allows to select the Holter log file that the doctor wants to analyze in txt format. Once the document has been loaded, the medical diagnosis is shown in the left table, if the record that has been loaded contains more than 18 hours, the diagnosis of 18-hour intervals will be presented. Thus, for example, in the first row, the results of the proportional entropy of the hour 1 to 18 are shown, in the second row of the hour 2 to 19, in the third row of the hour 3 to 20 and so successively.

IV. RESULTS

Using the values of the proportions of entropy, the prototype type electrocardiographic Holter performs mathematical distinctions between patients with normal and abnormal cardiac dynamics. The heart's electrical signals stored and interpreted from the electrocardiographic Holter prototype simplify all clinical parameters used to determine a specific cardiac pathology or clinical evolution of the patient undergoing therapeutic treatment.

The Holter electrocardiographic prototype greatly simplifies the time taken to formulate a diagnosis. It was also observed that the methodology, implemented through the development of this prototype, has the ability to quantitatively assess different degrees of abnormality, so that dynamics that are classified clinically as within normal limits were evaluated as evolving towards the disease by the mathematical methodology, showing the ability of the methodology to quantify changes in dynamics that are not noticeable from the conventional clinical classification.

The entropy values were between $6.51x10^{-23}$ and $7.03x10^{-23}$ for normal Holters, while those from the ICU were between $4.51x10^{-23}$ and $6.74x10^{-23}$; the entropy proportions allowed to differentiate normality of acute cases with sensitivity and specificity values of 100% with a Kappa coefficient of 1.

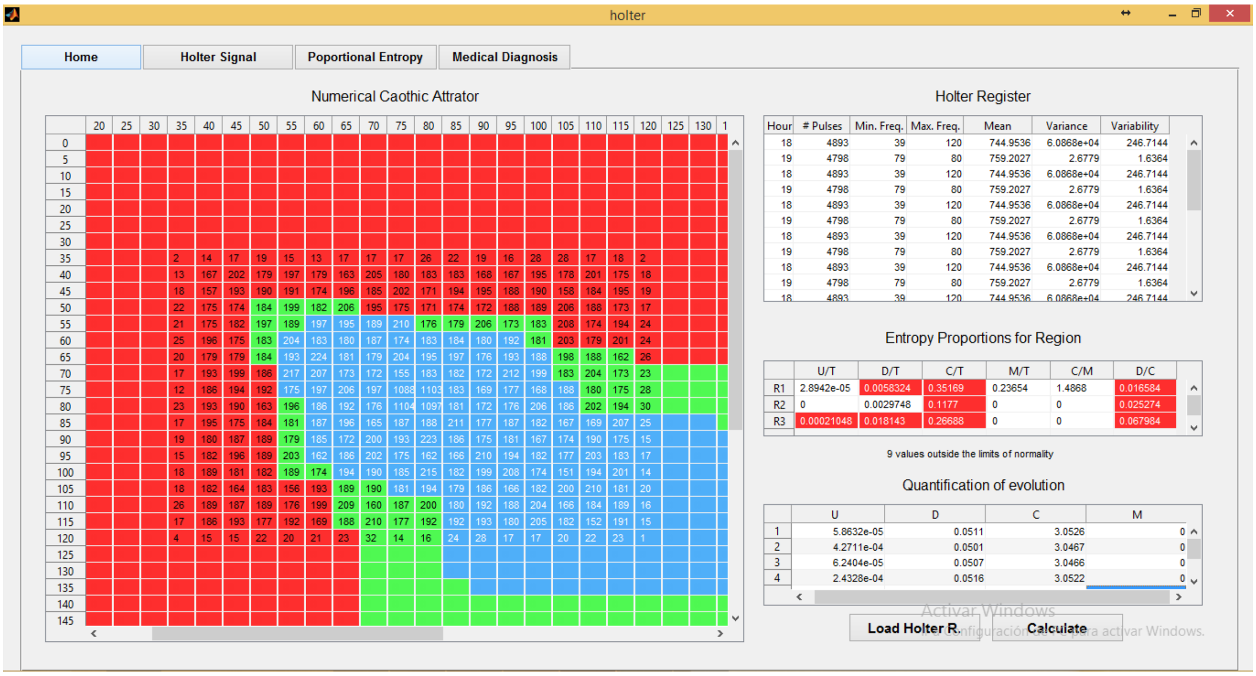

Fig. 3 The interface of new cardiac diagnostic prediction

V. Conclusions

The methodology allowed to evaluate mathematically normal cardiac dynamics and ICU patients, showing that the conventional diagnostic evaluation could be improved, which would be of great help in daily clinical practice.

The analyzes made from entropy and probability have allowed cardiology to differentiate the normality of the abnormality, giving way to the development of clinical application methodologies.

A methodology was developed within the context of a theoretical generalization, a process by which cardiac dynamics in the delay map were evaluated, calculating the fractal dimension from the box-counting method, finding an exponential law of clinical application, of which deduces all possible chaotic cardiac attractors, whose clinical applicability was confirmed in the context of a blind study in 115 EKG' holter, as well as in the evaluation of cardiac dynamics with diagnosis of arrhythmia [27].

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Leonardo Juan Ramírez López is a Colombian researcher, full Professor at Universidad Militar Nueva Granada. Ph.D. in Biomedical Engineering from Brazil, an MSc in Computer Science Engineering from Universidad Nacional of Colombia, and a degree in Electronic Instrumentation from Universidad Antonio Nariño in Colombia. Prof. Ramírez is currently conducting research on new methods to the education of health data, security, dynamical systems, probability, and entropy. He has published on topics related to communication systems, telemedicine architectures, telemedicine security, routing algorithms, and dynamical systems, probability and entropy applications.

Javier Oswaldo Rodríguez Velásquez is a Colombian researcher. A physician with a solid formation in theoretical physics and a deep academic knowledge related to medical sciences. I have developed predictions in different scenarios of medicine such as the epidemics of malaria, dengue or HIV and counts of CD4+ lymphocytes considering variables of blood counts such as total leukocytes and lymphocytes relying mainly on the concepts of probability and set theory. Dr. Rodriguez developed new methods of characterization and mathematical diagnosis in cardiac dynamics and morphology evaluated in different diagnostic test such as with Holter devices.