Application of the theory of probability and dynamic systems in the evaluation of cardiac dynamics: Study of diagnostic agreement

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Abstract. In the present work a new methodology was applied, to evaluate the cardiac status in 16 hours, in continuous electrocardiographic records and Holter, this by means of the theory of probability, and the occupation of spaces from attractors in the general space of Box-Counting, of recent development. 20 normal and 8 pathological records were analyzed, according to the conventional diagnosis. A simulation of the totality of the dynamics was made, taking into account the number of beats, and their maximum and minimum frequencies per hour, during 21 hours. With these data the attractors were built in a phase space. The calculation of the fractal dimension of the attractors was made from the evaluation of the spatial occupation of each one of them and through probability of occupation in the Box-Counting space, establishing its diagnosis with previous mathematical results. Finally, taking the conventional diagnosis as Gold-standard, this and the mathematical result were compared. In the states of normality, the probability of occupation values of the attractors was between 0.157 and 0.286, while for the pathological states, it was 0.019 and 0.141, thereby differentiating the normal and pathological states.

1. Introduction
In a given system, the states and their evolution can be studied through the theory of dynamic systems, through a graphic representation in an abstract space called phase space, in which graphic representations called attractors are constructed, since they show where the system tends to go [1]. The irregularity of attractors of chaotic type can be established through the concept of fractal dimension [2]. In the same way, the theory of probability had its origin in being able to quantify and number the eventual occurrence of a phenomenon, assigning to its possibility of occurrence, values between 0 and 1 [3,6]. The simultaneous use of both theories has allowed the development of novel diagnoses in the field of cardiology, achieving quantifications of cardiac status in fetuses [6, 7] and adults [8-10].

The majority of deaths worldwide are due to cardiovascular diseases; the trend is expected to continue in the future, and its incidence will increase [11]. Only in the American continent, according to WHO data published in 2017, 1.9% of deaths per year are due to cardiovascular diseases. 25% of the population suffers from this type of disease and, there are estimates that foresee that 23.6 million people may have died from this condition by the year 2030.

Continuous electrocardiographic (ECG) monitoring and the use of Holter have been designed to track cardiac conditions for prolonged periods. The monitoring is used mainly in the Intensive Care Unit, to
continuously assess the cardiac dynamics of patients in critical condition. The Holter is used on
ambulatory way in order to see irregularities in heart rhythm, ischemic heart disease or conduction
disorders, as well as treatment follow-up [11].

A recent study, developed by Rodríguez et al. (in evaluation for publication), showed that it is
possible to establish results that help to give reliable and reproducible diagnoses in the clinical
environment, through the use of probability theory and the theory of dynamic systems. Moreover, it is
possible to establish this method for continuous electrocardiographic and/or Holter registers of 16 hours.

In this sense, the purpose of this work is to confirm this methodology based on dynamic systems and
probability theory, as a tool for diagnostic help, through a blind study performed on cardiac dynamics
from Holter and continuous electrocardiographic records.

2. Methodology

2.1. Population
100 cardiac records were taken, which come from continuous ECG from Intensive Care Units and
ambulatory Holter records, in a lapse of 21 hours, all of people older than 21 years. There were 20
normal and 80 pathological, from the Insight group database.

2.2. Process
This is a study of diagnostic agreement, to evaluate a physical-mathematical diagnosis of cardiac
dynamics, with respect to the Gold Standard, by means of a blind study. The conventional diagnosis was
masked, and then the minimum and maximum heart rate, and the number of beats in each hour, of the
Holter and/or electrocardiographic recordings were taken. Next, a sequence of heart frequencies was
generated within the defined limits with the values obtained for each Holter, to construct an attractor, in
the space of the phases (see definitions).

Next, the occupation spaces of the attractor were calculated in the generalized space of Box Counting
with the Equation 1, based on which the fractal dimension of each of the attractors was calculated.
Subsequently, the probability of occupation spaces in the Kp grid was calculated (see Equation 2) and
based on this value, the mathematical physical diagnosis was determined, based on the previously
established parameters.

2.3. Definitions

2.3.1. Phase space. Geometric space made up of two or more dimensions, in which the dynamics of a
system is represented graphically; this by means of the spatial location of a dynamic variable in time, in
ordered pairs for the construction of attractors.

2.3.2. Fractal. It is an object devoid of regularity to which a dimension can be found, by different
methods, depending on the type of fractal object of study. The wild-type fractals are measured with the
Box-Counting method.

\[
D = -\frac{\log N(2^{-(j+1)}) - \log N2^{-j}}{\log 2^{j+1} - \log 2^{-j}} = \log_2 \left( \frac{N(2^{-(j+1)})}{N(2^{-j})} \right)
\]

where D is the fractal dimension, N corresponds to the number of frames occupied by the object, and
J is the degree of partition of the grid.

2.3.3. Occupation probability of the attractors OPA. Is the result of the division of number of frames
occupied by the cardiac attractor between the total number of frames of the generalized space of Box
Counting.
\[ P_{ DA} = \frac{\text{Number of occupied spaces by attractor}}{\text{Whole of spaces}} \]  

(2)

2.4. Statistical analysis

For the development of the blind study, the conventional diagnoses were unmasked, for patients diagnosed with acute and normal diseases, according to the conventional analysis, and this diagnosis was taken as Gold Standard. Measurements of specificity and sensitivity were made to compare this result with mathematical methodology.

These measurements were made through a binary classification, where the true positives corresponded to the number of continuous ECG and Holter records evaluated between limits of abnormality and that are within the mathematical values corresponding to the same diagnosis. False positives correspond to continuous ECG records and Holter that mathematically behave as studies within the abnormality and whose clinical evaluation is normal, false negatives are the number of continuous ECG records and Holter clinically evaluated as normal but whose values correspond to patients with disease, and finally the true negatives are defined as the continuous ECG and Holter records clinically evaluated as normal and whose mathematical values correspond to normality.

In order to evaluate the concordance between the mathematical physical values and the conventional clinical diagnosis, the Kappa coefficient was calculated, through the following Equation 3,

\[ K = \frac{C_0 - C_a}{T_0} \]

(3)

where, \( C_0 \) corresponds to the number of matches observed, that is, the number of patients with the same diagnosis, according to the proposed new methodology and the Gold Standard. \( T_0 \) is the totality of observations, namely, the totality of normal and pathological cases. \( C_a \) are the matches attributable to chance, which are calculated according to the Equation 4,

\[ C_a = \left[ f_1 \times C_1 / T_0 \right] + \left[ f_2 \times C_2 / T_0 \right] \]

(4)

where \( f_1 \) corresponds to the number of patients with mathematical values within normal limits, \( C_1 \) is the number of patients diagnosed clinically within normality, \( f_2 \) corresponds to the number of patients with mathematical values associated with disease, \( C_2 \) is the number of patients diagnosed clinically with disease and \( T_0 \) is the total number of normal cases and with disease.

3. Ethical aspects

The present study is declared as an investigation with minimal risk, according to Resolution 8430 of 1993 of the Colombian Ministry of Health, since physical and mathematical calculations are made on non-invasive exam and paraclinical reports that have been previously prescribed according to conventional medical protocols, protecting the anonymity and integrity of the participants. It also complies with the ethical principles set forth in the Declaration of Helsinki of the World Medical Association.

4. Results

The clinical diagnosis of the patients selected for the study can be seen in Table 1. It was found that the minimum and maximum values for the Kg values are 60 and 165 respectively, and for Kp are 204 and 371 in the normality states. Likewise, for disease states, these values were 10 and 64 for Kg and 25 and 183 for Kp. On the other hand, the fractal dimension found for the minimum and maximum values were 0.900 and 1.987 in states of normality, while for pathological states they were 1.059 and 1.954, making it clear that it is not possible through this value to determine a correct mathematical difference. Regarding the probabilities of occupation of the grids, these were, in their maximum and minimum
values, 0.157 and 0.286 respectively, in states of normality; for disease states were 0.019 and 0.141, clearly differentiating disease normality. Some of the results described above can be seen in Table 1.

| No. | Mathematical diagnosis | Kp | Kg | Df   | p     | Clinical evaluation   |
|-----|------------------------|----|----|------|-------|-----------------------|
| 1   | N                      | 308| 165| 0.900| 0.238 | Normal                |
| 2   | N                      | 371| 108| 1.780| 0.286 | Normal                |
| 3   | N                      | 215| 80 | 1.426| 0.166 | Normal                |
| 4   | N                      | 328| 128| 1.358| 0.253 | Normal                |
| 5   | N                      | 321| 81 | 1.987| 0.248 | Normal                |
| 6   | N                      | 204| 60 | 1.766| 0.157 | Normal                |
| 7   | N                      | 280| 108| 1.374| 0.216 | Normal                |
| 8   | D                      | 110| 30 | 1.870| 0.085 | Arrhythmia control    |
| 9   | D                      | 183| 64 | 1.516| 0.141 | Arrhythmia            |
| 10  | D                      | 125| 33 | 1.921| 0.096 | Ischemic dilated cardiomyopathy |
| 11  | D                      | 160| 59 | 1.439| 0.123 | Syncope analysis      |
| 12  | D                      | 82 | 31 | 1.403| 0.063 | Arrhythmia. moderate decrease in the variability of the HR. |
| 13  | D                      | 105| 37 | 1.505| 0.081 | Bradycardia           |
| 14  | D                      | 25 | 12 | 1.059| 0.019 | Acute infarction      |
| 15  | D                      | 58 | 22 | 1.399| 0.045 | Acute myocardial infarction, killip 1 |
| 16  | D                      | 62 | 16 | 1.954| 0.048 | Killip infarction1    |
| 17  | D                      | 34 | 10 | 1.766| 0.026 | Cardiogenic shock     |
| 18  | D                      | 65 | 29 | 1.164| 0.050 | Acute heart failure   |

Additionally, when unmasking the conventional diagnosis and comparing it with the mathematical physical diagnosis obtained, sensitivity values of 100% and specificity of 100% were found, and a Kappa coefficient of 1, which allows confirming the diagnostic capacity of the methodology.

5. Discussion
This is the first work in which the clinical applicability of this methodology developed for the evaluation of Holter can be confirmed, starting from dynamic systems, probability and fractal geometry, thus confirming its potential, as a tool for the realization of diagnoses. Additionally, it was verified that the methodology is applicable to any particular case, without taking into account type of pathology, ages or interventions in individuals older than 20 years; this shows that this method is useful when making distinctions between normality and disease and evidence of evolution from one state to another, which cannot always be detected under conventional parameters.

Thus, this methodology is a form of evaluation of electrocardiographic and Holter records, based on simple criteria and easy to apply. Its usefulness is shown in the evaluation of the effectiveness of pharmacological or surgical interventions, and likewise in the follow-up of patients of the ICU. With respect to the results of the statistical study, they show that according to their sensitivity of 100%, specificity of 100% and Kappa coefficient of 1, their efficacy and clinical applicability is optimal.

In the field of cardiology, the interest is currently the study of variability [12,13], although in this area it is not possible to establish, from an objective perspective, distinctions in each particular case. However, through this work, the possibility to improve these methods based on variability is shown, by means of use of quantifications that show a self-organization of the system, and thus differentiate health from disease, as well as being able to differentiate specific distinctions in singular cases, which are conventionally classified like as similar, serving as a tool to characterize transition states between normality and disease.
With physical and mathematical theories, different works have been developed in the diagnostic and predictive field, apart from the Holter evaluation methodology based on the special occupation of fractal attractors in the Box Counting space \[14\], which is one of the pillars of this work. This methodology has been confirmed, with values of sensitivity and specificity of 100\% \[15\]. In addition, an exponential law of diagnosis was developed, which has been confirmed in patients with arrhythmias, and in blind studies of diagnostic correspondence \[16\]. The spatial theory of cardiac attractors has allowed to observe measures that warn about the appearance of neonatal sepsis, 6 and 3 hours before its outcome \[17\]. Also, through the use of probability, differences have been established between normality and disease that detect sub diagnosed mild alterations; this methodology has been tested for its applicability in different studies, which include populations with arrhythmias and pacemakers \[18,19\]. The combination of theories of probability and dynamic systems, in addition to the s/k ratio of entropy, gave rise to a diagnosis that distinguishes cardiac dynamics in normal, chronic and acute states, as well as the stages of evolution between them \[20\]. Its use in follow-up of patients in the Coronary Care Unit has allowed evidence of exacerbation processes that are not detected using conventional methods \[21\]. Likewise, following this line of research, the present work is added to the previous ones, to corroborate that the use of physical and mathematical quantifications in the evaluation of objective form the evolution in the time of a patient, is of great utility to take measures of prevention at the clinical level, and likewise make an evaluation of the effectiveness of surgical and pharmacological interventions.

6. Conclusions
The present methodology demonstrates the possibility of evaluating cardiac dynamics based on the heart rate values recorded in continuous ECG and Holter equipment. For this it was necessary to generate cardiac attractors and to calculate the spaces occupied by the attractors as well as the probability of occupation of each of them. This new way of characterizing the behavior of cardiac dynamics allows to make more precise distinctions of the cardiac state of the patient. Additionally, it is a methodology that achieves, by increasing or decreasing the space occupied by the attractor, establishing more accurate diagnoses of cardiac dynamics in adults, becoming a diagnostic aid tool for clinical applicability, which allows to future developments of new systems for processing heart rate information in the context of the theory of dynamic systems.

Acknowledgments
This article is the result of the INV 1950 project funded by the Universidad Cooperativa de Colombia, Bogotá headquarters. We thank the Doctors, Fernando Colmenares, Research Director, Leonardo Galindo, National DINAI Director, Andrés Mena, DINAI Bogotá Director, Eva Prada, Bogotá headquarters Director, and Edgar López, Dean of the Faculty of Engineering, for her support our investigations.

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