



*Full Length Research Paper*

## Physical-mathematical diagnosis of cardiac dynamic on neonatal sepsis: predictions of clinical application

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### ABSTRACT

**Introduction:** new diagnosis and physical-mathematical predictions have been developed by dynamic systems theory in adults. Also there were developed mortality predictors for neonates with sepsis based on heart rate variability measures. **Objective:** to predict neonatal sepsis or sepsis-like dynamics appearance based on cardiac dynamics systems. **Materials and Methods:** since a mental experiment, developed on the context of dynamic system theory, and empirical data of clinical practice, from a previous work, there were studied neonate cardiac dynamic evolution from normality to sepsis or similar dynamics to sepsis and were built all the possible chaotic attractors of these dynamics on the Box-Counting universalized space. For that, there were taken minimal and maximum values of RR intervals of a neonate, assessed 6 days before sepsis, and 6 hours and 3 hours before sepsis. There were developed simulations of the dynamic, were built attractors for each state, and were assessed the differences on their spatial occupation. Finally, there was made a simulation of every possible attractors which progress from normality to sepsis or similar dynamics to sepsis in time, by an exponential law developed for cardiac dynamic in adults. **Results:** chaotic attractors differentiate normality from sepsis and similar dynamics to sepsis, as were as its evolution in time, finding that each assessed attractor can be differentiated by its spatial occupation, which presented values of 73, 130, y 34 squares on the Kp grille, for normality, 6-hours before, and 3-hours before sepsis respectively. There were established 2541 possible dynamics on the step from normality to sepsis, in the course of 6 hours. **Conclusions:** a new predictive physical mathematical diagnosis for preventive clinical application was developed, which reveal an non-causal self-organization of neonate cardiac dynamic, which allow diagnose and warn early the evolution of the system to sepsis or sepsis-like dynamics even 6 hours ahead of time.

**Keywords:** Diagnosis, Dynamical Systems, Attractor, neonate sepsis, mental experiment, RR intervals.

## INTRODUCTION

On the context of dynamic systems theory, state and evolution of a system can be evaluated geometrically starting from a phase space, constructing attractors that allow establish predictable or unpredictable character of the system and its evolution (Devaney, 1992). When obtained attractors go to a point or a cycle it correspond to a predictable dynamic, while chaotic attractors are related to a unpredictable dynamics. Usually there are distinguished two types of chaos is characterized by very irregular paths, resulting in a practical impossibility to predict the future evolution of the system, although it occurs deterministically (Girón, 2008). Stochastic chaos is characterized by its no-deterministic character (Calabrese, 1999), which is associated to unpredictable factors as randomized elements, involving the impossibility to establish probabilistic behaviors due to a null duration of statistical memory (Sánchez et al, 2008).

Unpredictable systems origins chaotic attractors, which can be measured by fractal dimensions, which allows quantify the complexity or irregularity of a system or an object (Mandelbrot, 1972). There are three types of fractals, each one with different methodologies to fractal dimension calculation: abstracts, statistical and wild fractals (Falconer, 2003). The last ones include chaotic attractors and its dimension is calculated by Box Counting method (Peitgen et al, 1992).

In cardiology, the application of dynamic systems theory has led a new conception of health and illness (Goldberger et al, 2002), showing that normality is an intermediate state between extreme irregularity and regularity, both seen as illness. On this context, Huikuri et al (2000) used fractal dimension measures as mortality predictors after a heart attack, in patients with 35% ejection fraction. Also a diagnostic methodology for clinical application was developed, based on dynamical systems, probability and entropy, which allow differentiate normality, chronic and acute illness, as well as quantify the evolution between these states (Rodríguez, 2010a). Its diagnostic capacity was confirmed statistically in a blind study with 450 normal cases and different pathologies obtaining 100% sensibility and specificity values, as were as 1 kappa coefficient (Rodríguez et al, 2013a). Subsequent studies demonstrated this methodology as a quantifier of the evolution of patients in Coronary Care Unit (CCU), allowing the prediction of worsening processes even in absence of evident clinical signs, as well as the impact of surgical or pharmacological interventions (Rodríguez et al, 2010a).

Rodríguez et al created an exponential law of cardiac dynamic systems (Rodríguez, 2011), that achieved differentiate normality from acute illness, and evolution between them, showing 100% specificity and sensibility

(Rodríguez et al, 2013b). This method establish a mathematical relation between the number of squares occupied by the atractor and fractal dimension, founding an exponential behavior, showing that variability measures of heart rate are not enough to establish predictive clinical affirmations (Rodríguez, 2011). To construct this law, a generalized Box Counting space previously developed was required (Rodríguez et al, 2010b), which allow describe at the same time all the attractors on the same space, as well as its comparison by superposition of two grilles on the context of Box-Counting method, where one side is the double of the other one (Rodríguez, 2011; Rodríguez et al, 2010c).

There was estimated that infections cause about 26% of neonate deaths during the first week after birth. Sepsis is developed approximately in 21% of premature neonate, with a mortality which reaches 18% (Cuestas et al, 2011). One problem of this pathological condition, is that its diagnosis can be hidden because sepsis is an asymptomatic phenomena, and its clinical exams has not enough sensitivity and specificity. On this context a lot of works have sought to characterize neonate cardiac dynamic as normal or associated to sepsis from heart rate variability measures (Griffin and Moorman, 2001; Griffin et al, 2005). Recent works have proven that abnormal changes in HR can be an early indicator of sepsis development even in subclinical stages (Griffin and Moorman, 2001; Fairchild and O'Shea, 2010; Griffin et al, 2007; Griffin et al, 2005). For example, Griffin et al, found that infants with sepsis proven by blood culture and those with a clinical diagnosis of sepsis but negative blood cultures presented an abnormal change of heart rate observable until 24 hours before clinical deterioration (Griffin and Moorman, 2001).

The objective of this work is to analyze the information given by Griffin et al, developing simulations of cardiac dynamic based on clinical measures (Griffin and Moorman, 2001), to establish predictive measures of sepsis or sepsis-like illness appearance in neonates from differences between normality, 3-hours and 6-hours before sepsis, by a mental experiment and following attractors construction on a delay map to the assessment of system evolution, to finally determine all the normal and evolution to sepsis dynamics or similar to sepsis dynamics based on exponential law of adults cardiac dynamic systems (Rodríguez, 2011).

## Definitions

**Neonatal delay map:** attractor built based on RR intervals observed in neonatology (Griffin and Moorman, 2001) and simulations of the total neonatal cardiac

dynamics developed from this information. The neonatal attractor is the graphical representation of the simulation in a delay map, where an RR interval is plotted on the x axis, respect to the next on the y axis, and the consecutive points obtained are united by a line. These attractors were evaluated by the Box-Counting method; two grids of 20 ms y 40 ms were used, and spatial occupation on each grids was established. After, the fractal dimension was found using the formula:

Equation 1: Box-Counting method

$$D = \frac{\text{Log}N(2^{-(K+1)}) - \text{Log}N(2^{-K})}{\text{Log}2^{k+1} - \text{Log}2^k} = \text{Log}_2 \frac{N(2^{-(k+1)})}{N(2^{-k})}$$

Where D: is the fractal dimension; N: the number of squares occupied by the object and K: the degree of partitioning grid.

## MATERIALS AND METHODS

The mental experiment creation starts from Box-Counting generalized space (Gendler, 2005), in which is possible to imagine the spatial position of points corresponding to a RR interval against the next one on the delay map. Given the results reported by Griffin et al (2001), which show that minimal and maximum values of these intervals vary according to the different moments assessed in time, and imagining how the points progressively fill the space between maximum and minimal intervals per each moment, it is possible to foresee the constructed attractors with different occupation spaces, allowing their mathematical differentiation, and the quantitative assessment of their evolution in time (Griffin and Moorman, 2001).

Later clinical information reported in Griffin et al. (2001) work was taken, assessing specifically neonate RR time sequence in three different moments: A normal moment, taken six days before a sepsis outcome; B moment, taken three hours before sepsis and C moment, taken six hours before sepsis. From these data there were developed one simulation of RR sequences for each moment, based on maximum and minimal values per each moment, by means of a randomized algorithm. Finally these values were taken to construct an attractor on the generalized phase space, where were drawn a RR interval against the next one.

Afterwards were measured the filled squares by the attractor and calculated its fractal dimension with the Box-Counting simplified method, in which is used only two grilles, where side square length of one grill is the double of the other one. Superposed grilles were of 20 milliseconds (ms) and 40 ms, so, the equation 1, used for calculation of fractal dimension, can be rewritten

to deduce the relations of occupation spaces respecting to fractal dimension, as described in equation 2:

Equation 2: Box-Counting simplified equation.

$$DF = \log_2 \frac{K_p}{K_g} \quad \left\{ \begin{array}{l} \Rightarrow K_p = K_g 2^{DF} \\ \Rightarrow K_g = \frac{K_p}{2^{DF}} \end{array} \right.$$

Where Kp: are the occupied spaces by the attractor on the small grille. Kg: the spaces occupied by the attractor on the big grille. DF: Fractal Dimension.

In this way, there were established the number of spaces occupied by each attractor on each state and their corresponding fractal dimension, comparing the obtained results to establish differences between them.

Next, following the methodology developed by Rodríguez (Rodríguez, 2011; Rodríguez et al, 2013b) in which is established an exponential law that allowed the total possible dynamic setting in adults following the equation 3, were determined all the possible dynamics in the evolution from normality to neonate sepsis following this equation:

**Equation 3:**

$$N_{AP} = (Mx - Mn + 1)^2 - \frac{1}{2}(Mx - Mn)(Mx - Mn + 1)$$

For that, first there were determined the dynamics from normality to 6-hours before sepsis state, and were determined the number of dynamics form 3-hours before sepsis to normality. For the first case, Mn corresponds to the number of big squares of normality and Mx is the number of big squares of the 6-hours before sepsis square; while for the second case Mn corresponds to the number of big squares of the 3-hours before sepsis attractor and Mx is the number of big squares obtained for normality.

Finally, there were developed two simulations of possible trajectories from normality to sepsis or sepsis-like illness dynamics, the first one, three hours before (1s, 2s), and the other six hours before (3s, 4s), to show how it is possible to make dynamic preventive measures of the evolution of neonate cardiac dynamic system.

## RESULTS

The normal attractor presented a fractal dimension equal to 1,5460, filled 25 squares on the Kg grille and 73 on the Kp grille. The corresponding attractor to 6 hours before sepsis dynamic, presented a fractal dimension of 1,6301, 42 filled squares on the Kg grille and 130 on the Kp grille. The 3 hours before sepsis dynamic attractor presented a fractal dimension of 1,2801, with spatial occupation

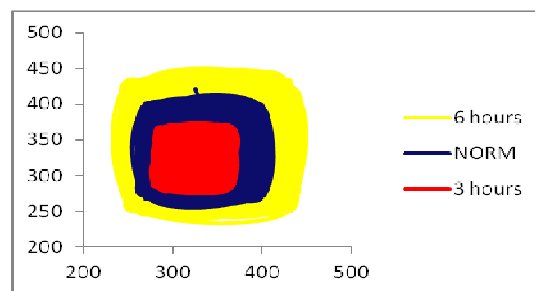
**Table 1.** Fractal dimension and occupation spaces of the three built attractors. Kp: occupied spaces by the attractor on the small grille. Kg: occupied spaces by the attractor on the big grille. DF: Fractal dimension.

	Kg	Kp	DF
<b>Normal</b>	25	73	1,5460
<b>6 hours before sepsis</b>	42	130	1,6301
<b>3 hours before sepsis</b>	14	34	1,2801

**Table 2.** Computational simulations of possible trajectories of the chaotic cardiac attractors from normality to 3 hours before sepsis or sepsis-like illness dynamics, and from normality to 6 hours before sepsis or sepsis-like illness dynamics. Kp: occupied spaces by the attractor on the small grille. Kg: the spaces occupied by the attractor on the big grille. DF: Fractal Dimension. **1s, 2s, 3s** and **4s**: specific simulations in time.

Simulation 1	Kg	Kp	DF	Simulation 2	Kg	Kp	DF
<b>Normal</b>	25	73	1,5460	<b>Normal</b>	25	73	1,5460
<b>1s</b>	19	55	1,5334	<b>3s</b>	25	93	1,8953
<b>2s</b>	16	46	1,5236	<b>4s</b>	30	107	1,8346
<b>3 hours before sepsis</b>	14	34	1,2801	<b>6 hours before sepsis</b>	42	130	1,6301

**Figure 1.** Neonate cardiac attractors: normal (blue), six hours (yellow) and three hours (red) before sepsis. The graphic variables correspond to the RR time consecutive intervals sequence simulation, one (x axis) respect to the next one (y axis).



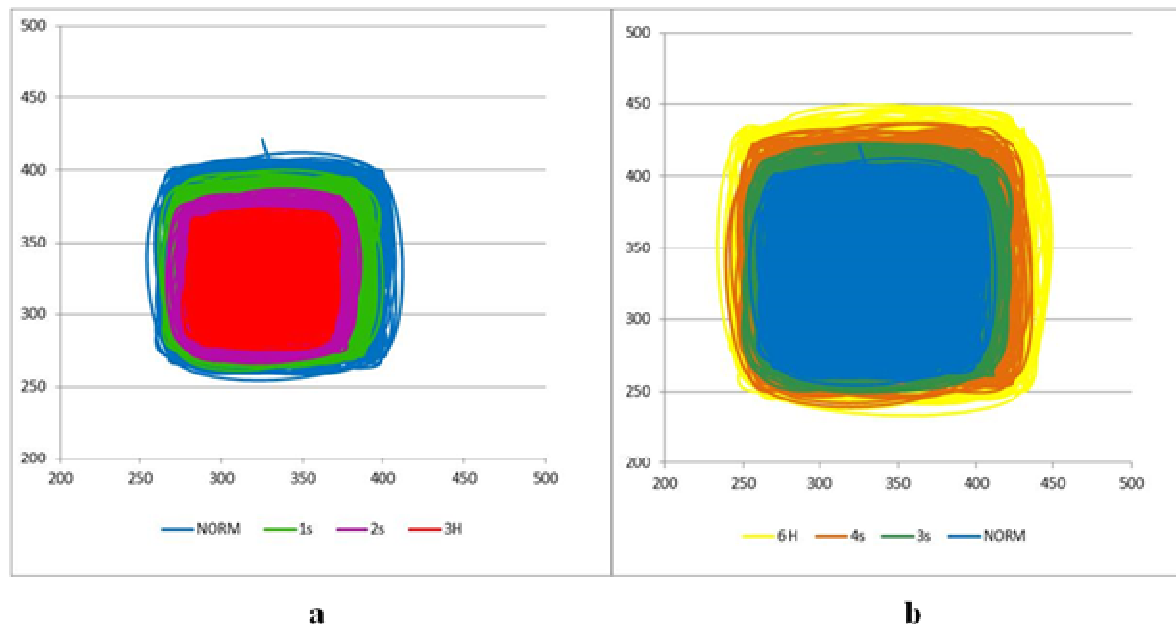
values on the Kg grille of 14 and 34 on the Kp grille (Table 1).

6 hours before sepsis attractor presented the biggest value of fractal dimension, while the corresponding attractor to 3 hours before sepsis dynamic presented the lowest value, and the normal attractor presented an intermediate value. Observing spatial occupation of the normal attractor regarding the 6 and 3 hours before sepsis attractors, it founded that 6 hours before it presented a bigger occupation than the normal attractor, while three hours before it occupies a smaller space than the normal attractor. This way, normality is in an intermediate state between two abnormality states, as

been observed with fractal dimension measures as spatial occupation measures; corresponding attractor to 6 hours before sepsis dynamic presented the biggest values for both measures, while the 3 hours before sepsis attractors presented the lowest values (Figure 1).

All the simulations of the trajectories had changes in the number of occupied squares up or downwards respecting to normality attractor and also were differentiated by means of the irregularity grade of the attractor (see table 2 and figure 2), being objective and reproducible measures of the evolution of the neonate cardiac dynamic system.

**Figure 2. a.** Chaotic attractors of the simulation 1, from 3 hours before sepsis or sepsis-like illness to normality dynamics. **b.** Chaotic attractors of the simulation 2, from normality to 6 hours before sepsis or sepsis-like illness dynamics. **1s, 2s, 3s** and **4s**: specific simulations in time.



These simulations (1s, 2s, 3s and 4s), together with the previous attractors, quantify mathematically with the occupied squares and the fractal dimensions, the evolution of the neonate cardiac dynamic system from three or six hours before sepsis or sepsis-like illness dynamics, to normality (see table 2 and figure 2).

Using equation 3, all the attractors between sepsis to normality states were calculated, so there were made two calculations, finding 1827 possible attractors from the normality attractor to the 6 hours before sepsis attractor, while it obtained 714 possible attractors from the 3 hours before sepsis attractor to the normality were obtained, resulting 2541 possible attractors on the evolution from normality to disease or disease to normality.

## DISCUSSION

This is the first work in which was developed a predictive diagnosis at clinical level of neonatal sepsis proven by blood culture and neonatal sepsis clinically defined (sepsis-like illness), based on an exponential law for neonatal cardiac dynamical systems, even before the presence of clinical symptoms. By this diagnosis, it is possible to predict at clinical level the evolution in time of cardiac dynamic towards this kind of dynamics in patients with risk factors for sepsis, constituting an early warning measure which detects disturbances even six hours before clinical manifestation of sepsis and sepsis-like

illness syndromes. Predictions were achieved by a previously developed methodology for diagnosing adult cardiac dynamic (Rodríguez, 2011; Rodríguez et al, 2010b), and a mental experiment based on empirical information of only one case of the patients group analyzed by Griffin and Moorman (2001) evaluated in three different times, a normality time and, the other two times, before onset of sepsis. It was established not only differences between the dynamics of each one of the evaluated states in time but the totality of possible cardiac dynamics of normal and septic or septic-like neonates, improving the measures developed by Griffin et al since that there were achieved specific predictions of individual application for each neonate regardless of statistical considerations in prior hours to the septic or septic-like outcome and quantifications of the evolution of the dynamic of clinical application (Griffin and Moorman, 2001).

If the chaotic attractor grows six hours before and then is going small to three hours before, as quantified the dynamic simulations, these dynamic measures of the system evolution are preventive and clinically applicable. For the clinical application of measures, it can be established that if the occupied spaces measures of a normal attractor are not increasing and the remaining paraclinical test as WBC, glucose, pH, platelet count, HCO<sub>3</sub>, pCO<sub>2</sub> and so on (Griffin et al, 2005) associated to the assessment of sepsis and sepsis-like behaviors are not altered too, it can be predicted that these

patients may not present complications associated to sepsis or sepsis - like illness, achieving a measure that could avoid the unnecessary use of antibiotic as a preventive measure at the Intensive Care Units, preventing the consequent antibiotic resistance.

The achieved simulation showed that is possible to find answers without the total recording of the sequence, like that previous works developed in cardiac dynamics (Rodríguez, 2010a; Rodríguez et al, 2013a; Rodríguez et al, 2010a; Rodríguez, 2011; Rodríguez et al, 2013b), allowing the assessment of essential characteristics of self-organization of the dynamic by means of fractal dimension measures and the occupied spaces in the box counting space along with determination of total dynamics of universe achieving diagnosis of clinical application. Moreover, due to systematic thought that underlies to this work, the maximum and minimal limits of RR intervals may vary modifying the totality of found attractors in generalization without altering the very essence of the methodology.

Based on the same deductive methodology followed for the development of the exponential law of adult cardiac dynamical systems, a law for neonatal cardiac dynamical systems was established which allows making early warning predictions in hours. Whereas the adult normal cardiac dynamic exhibits the highest values of occupied spaces, acute disease shows the lowest occupied spaces, and the evolution are between these states (Rodríguez, 2011; Rodríguez et al, 2013b), in the case of neonatal cardiac dynamic, it was observed that normality shows intermediate occupied spaces between evolution values towards sepsis, so that six hours before a greater number of occupied spaces are presented and three hours before a lower number of spaces with respect to normal attractor, doing possible to establish the totality of dynamics from normality to sepsis and to quantify their evolution in time. This behavior agrees with qualitative conception of health/disease derived from dynamical systems developed by Goldberger et al (2002), but in this work there is an objective and reproducible quantification of neonatal cardiac dynamics of clinical application.

The application of system dynamic theory to the cardiac dynamic allows remove problems of statistical analysis like RR means. In fact these measures were not very different between the three studied dynamics (Griffin and Moorman, 2001). The geometrical structure of atractor could show in the time how the points on the space concentration going to change in determinate places of the box-counting space, in this way the asymmetry of the histograms of RR intervals can to be observed from a geometric dynamic way, allowing to obtain better information because in the atractor is the whole dynamic in the time.

Since this research is based on a mental experiment, it follows an innovative way of research in the medical area, achieving results of clinical utility and making unnecessary the use of a large number of samples, decreasing the required human and economic resources. Mental experiments are one of the basis of so much physical and mathematical theories which have been developed along history (Gendler, 2005), and these have served as a base for new diagnostic methods in the adult cardiac dynamic

(Rodríguez, 2010a; Rodríguez, 2011) obtaining results independent of statistical studies.

Several works have been previously developed based on principles and laws of physics as well as in inductive forms of thought or mental experiments resulting in new causeless diagnosis and predictions of practical applicability, not only in cardiac dynamics but in other fields such as: histological and cellular morpho-physiology (Rodríguez et al, 2010c; Correa et al, 2012), immunology (Rodríguez et al, 2010d), prediction of malaria outbreaks (Rodríguez, 2010b) or infectology (Rodríguez, 2013c). These results show that this kind of research can provide solutions in all fields of medicine leading this discipline to the predictive level of physics.

## CONCLUSIONS

It was found a non-causal self-organization of neonatal cardiac dynamic system, expressed an exponential law, which allows to establish a predictive diagnosis of neonatal sepsis, applicable at clinical level to warn early the evolution of the cardiac system to sepsis or sepsis-like states even 6 hours ahead of time.

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### Dedication

To our children and all newborn around the world. A special dedication for all given blessings to Master Prajñananda and Master Bhadrayu. Infinite thanks for your love and blessings to our group.

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