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Nonlinear Characterization and Complexity Analysis of Cardiotocographic Examinations using Entropy Measures

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Abstract

The nonlinear analysis of biological time series provides new possibilities to improve computer aided diagnostic systems, traditionally based on linear techniques. The Cardiotocography (CTG) examination records simultaneoulsly the fetal heart rate (FHR) and the maternal uterine contractions (UC). This paper shows, at first, that both signals present nonlinear components based on the surrogate data analysis technique and exploratory data analysis with the return (lag) plot. After that, a nonlinear complexity analysis is proposed considering two databases, intrapartum (CTG-I) and antepartum (CTG-A) with previously identified normal and suspicious/pathological groups. Approximate Entropy (ApEn) and Sample Entropy (SampEn), which are signal complexity measures, are calculated. The results show that low entropy values are found when the whole examination is considered, Apen=0,3244±0,1078 and SampEn=0,2351±0,0758 (average±standard deviation). Besides, no significant difference was found between the normal (Apen=0,3366±0,1250 and SampEn=0,2532±0,0818) and suspicious/pathological (Apen=0,3420±0,1220 and SampEn=0,2457±0,0850) groups for the CTG-A database. For a better analysis, this work proposes a windowed entropy calculation considering 5-minutes window. The windowed entropies presented higher average values (Apen=0,6505±0,2301 and SampEn=0,5290±0,1188) for the CTG-A and (Apen=0,5611±0,1970 and SampEn=0,4909±0,1782) for the CTG-I. The changes during specific long term events show that entropy can be considered as a first level indicator for strong FHR decelerations (Apen=0,1487±0,0341 and SampEn=0,1289±0,0301), FHR accelerations (Apen=0,1830±0,1078 and SampEn=0,1501±0,0703) and also for pathological behavior such as sinusoidal FHR (Apen=0,1808±0,0445 and SampEn=0,1621±0,0381).

Index Terms

Fetal Heart Rate (FHR), Uterine Contractions (UC), Cardiotocography (CTG), nonlinear analysis, entropy.

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I. Introduction

Biological time series interpretations require not only the definition of the appropriate method of analysis but also to characterize the signal according to its nature such as linear, nonlinear, random and chaotic. Many of these signals present nonlinearities and from a mathematical point of view a description using nonlinear models is more realistic than the linear systems usually applied [1].

According to [2], the processes inside biological systems can not be conventionally classified based on linear modeling. There are balanced dynamics in live beings with self-destroying and self-fixing mechanisms, usually submitted to constant changes in internal and external conditions, which results in a complex and multi-variable domain.

The heart signal has been extensively studied in several different aspects, such as detection, segmentation in several levels and feature extraction [3] [4] [5] with the aim to develop medical decision supporting systems. Nevertheless, the complexity of the parameters must be deeply analyzed to obtain underlying information from nonlinear characteristics that may not be considered in any visual analysis using time domain metrics.

The balance between the sympathetic and parasympathetic subsystems of the Autonomous Nervous System (ANS) is an example of dynamical balance resulting in oscillations of heart rate and intervals between beats. Actually, nonlinear modeling allows new interpretations of heart beat dynamics and its physiopathological representation [6].

In fetal monitoring area, the FHR and the UC signals can be simultaneously obtained from the CTG exam and are clinically relevant to detect problems and prevent fetal distress. For example, in FHR analysis the variability reflects the fetal development and is directly affected by pathological conditions. This signal may be characterized by its nonlinear irregularities and dynamics [7].

A nonlinear complexity analysis of biological systems is usually started by the meaning of complexity for that system and how it can be used to measure irregularities or the general behavior of that time series. A system can be classified as complex when many diferent and independent elements are continuously interacting in time, spontaneously reorganizing themselves resulting in more elaborated structures [8]. Those signals can be considered complex in space and time since they are composed by many interconnected feedback loops, many of them interdependent and sometimes redundant [9].

Many different nonlinear measures are proposed to quantify system complexity, such as Lempel-Ziv complexity [10], the Approximate Entropy (ApEn) [11], the Sample Entropy (SampEn) [12] and the Multiscale Entropy [13].

With all presented, the use of nonlinear metrics to support medical decision is a growing area of interest since it can establish new alarms and thresholds or even create new possibilities of interpretation for traditionally visual analysis in time based examinations.

Some of those metrics has been applied in biological signal and fetal heart rate analysis. Nevertheless, no consensus can be found yet when considering the evolution of nonlinear metrics according to the fetal age [14] and [15]. These conflicting results may be influenced because the entropy measure consider the whole examination and the long term changes in the signal may not be considered.

This paper presents a nonlinear characterization of FHR and UC signals and an innovative windowed complexity analysis of the FHR signals based on entropy measures. The entropy is calculated every 5 minutes interval to create a first level of triggers to support medical analysis, since the clinical use of CTG visual analysis is subjective and presents high levels of false positives and false negatives on fetal distress.

II. Materials and Methods

This section presents the main concepts about the nonlinear characterization and complexity analysis.

A. Development Environment and Databases

The system was developed using the Matlab scripting language and the implementations are based in two CTG databases provided by Trium Analysis Online, from Munich, Germany, partner of this project. The first database is identified as **CTG-I** and has 22 examinations during labour (intrapartum) all classified as normal examinations. The intrapartum examinations present a high level of dynamics inside the system, when uterine contractions are periodic and usually influences the FHR. The second database is **CTG-A** and presents 148 *antepartum* examinations (from 28 to 34 weeks of pregnancy), with 103 exams previously classified as normal and 45 as suspicious or pathological.

B. Nonlinearity Characterization

The first aspect of nonlinear analysis of biological time series is if they really have nonlinear components. The characterization of nonlinearity in both CTG signals presented in this paper consider the surrogate data analysis method and the exploratory data analysis based on the return map evaluation [16].

Consider $f(x)$ the original time series and $g(x)$ the surrogate data time series. The ApEn is considered as the nonlinear metric for the null hypothesis H_0 given by

$$ApEn[f(x)] = ApEn[g(x)], \tag{1}$$

where $ApEn[f(x)]$ is the Approximate Entropy of $f(x)$ and $ApEn[g(x)]$ is the Approximate Entropy of $g(x)$.

The whole set of samples are considered for this calculation. When H_0 is rejected then the existence of nonlinear components shall be considered. This is executed for both FHR and UC signals during antepartum and intrapartum times.

A graphic exploratory data analysis can be done with the time delay embedding plot, or return map, for the original and the surrogate data, i.e., the trace of $f(x)$ versus $f(x+\tau)$, where $\tau = 1$. Since both series have the same linear statistical properties, the differences in shape when comparing both plots can be classified as due to the influence of nonlinear components [17].

C. Approximate Entropy

The Approximate Entropy (*ApEn*) is a measure of the degree of data dispersion in a system. With a relatively small amount of data it is already possible to estimate the time series complexity, in the opposite of other measures which suffers of the curse of dimensionality.

The ApEn is robust against low frequency noise and the sparse occurrence of artifacts. The result of this logarithmic ratio entropy is a non negative number, where higher values indicate higher complexity. Moreover, it indicates patterns of time series changes usually not detected with classical tools based on statistical moments, like correlation and spectral analysis [18].

For a better comprehension about the signal complexity estimation using these entropies, it is necessary to understand the basic mathematical steps for the measure calculation.

Consider S_N as a time series with N samples $\{S_1,S_2,...,S_N\}$. Two input parameters m and r must be determined to calculate the Approximate Entropy $ApEn(S_N, m, r)$. The parameter m is the length of a subset of S_N, while r is the similarity criteria [11]. The subset of S_N with m samples starting on the i-th sample is named as $p_m(i)$.

Two subsets $p_m(i)$ and $p_m(j)$, starting on the i-th e j-th samples, respectively, are considered similares if the euclidean distance between them is less than r, i.e.

$$|S_{i+k} - S_{j+k}| < r, \text{ para } 0 \leq k < m. \tag{2}$$

Now consider P_m as the whole set of m-length patterns of S_N. The relationship can now be established

$$C_{i,m}(r) = \frac{n_{i,m}(r)}{N - m + 1}, \tag{3}$$

where $n_{i,m}(r)$ is the number of patterns in P_m that are similar to $p_m(i)$, according to the similarity criteria r. This calculation is done for each pattern of P_m. $C_m(r)$ is the average of all $C_{i,m}(r)$.

Finally, the Approximate Entropy $ApEn(S_N, m, r)$ of S_N, for m-length subsets and similarity criteria r can be defined as [11]

$$ApEn(S_N, m, r) = ln\frac{C_m(r)}{C_{m+1}(r)}, \tag{4}$$

D. Sample Entropy

The Sample Entropy $SampEn(S_N, m, r)$ for the S_N time series is calculated following the same procedure and parameters as in the ApEn.

The main difference between the two measures is the fact that subsets $p_m(i)$ self-matches are considered for the ApEn and must not be considered for the SampEn. This reduces the bias created by these self-matches, specially when there are just a few or no matches.

The statistical properties of the SampEn allow us to consider it as an useful for biological time series analysis [12].

1) Entropy Parameters: The parameter definition is not an easy task on complexity analysis because the number of samples N and the value of the parameters m and r could significantly influence on the results.

Previous works suggest optimized values for both parameters, e.g., for the ApEn are suggested $m = 2$ e $r = 0.2\sigma(S_N)$, where $\sigma(S_N)$ is the standard deviation of the time series [19]. Automatic r parameter adjustment was also proposed in [20], considering $r = 0.2\sigma(S_N)$ for low dynamics signals such as EKG time series, and an automatic calculation of r is proposed for high dynamics signals.

A mathematical approach for the SampEn parameters determination applied to heart rate signals can be found in [21]. A randomly determined training dataset extracted from a neonatus HR monitoring database is considered. The subset length $m = 2$ is estimated based on autoregressive (AR) models of various orders for this training dataset. The optimal parameter $r = 0.2\sigma(S_N)$ is found after calculating the SampEn for a wide range of different m and r for the training dataset and finding the maximum relative error based on a variance estimation.

E. Complexity Analysis

The FHR complexity analysis is based on the calculation of ApEn and SampEn considering the whole dataset and also different subsets of length Δt_e. The intervals were $\Delta t_e = \{1, 2, 5, 10\}$ minutes.

This analysis aims to suggests an optimal value for Δt_e which could represent the signal dynamics based on the entropy results and CTG biomedical premises.

The diagram presented in Figure 1 explains the approach presented in this paper to consider the use of windowed entropy analysis. The metrics calculated during FHR long term irregularities such as accelerations and decelerations are evaluated as possible detectors for CTG automatic analysis.

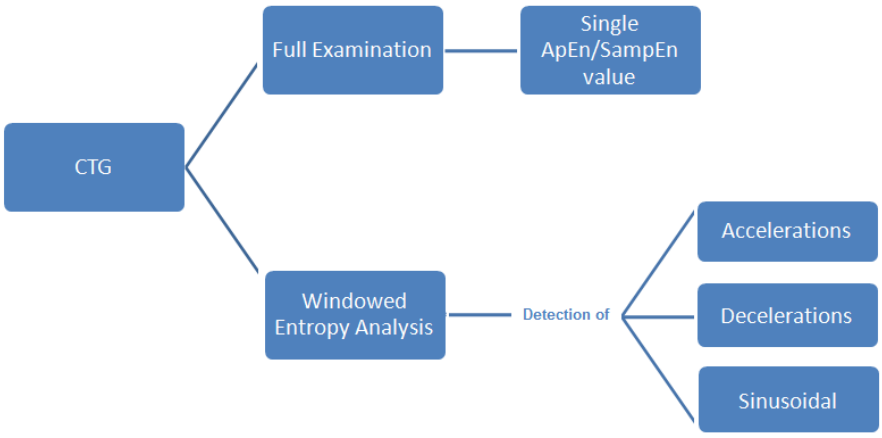

Figure 1. Block diagram with the windowed entropy analysis for the CTG examination.

Considering the other monitored signal, the uterine contractions are not considered to classify fetal status directly, but in conjunction with the FHR. For the presented database, it is available in two different conditions. The first one is for the antepartum database which is during the pregnancy, with low levels of changes in the uterine tonus. The second is during labour when the uterus muscles are active and dynamical, presenting contractions of different intensities, during periodic or aperiodic intervals.

The ApEn is used as the complexity measure to show that the nonlinear complexity increases significantly during labour. These nonlinearities may come from multiple interactions between different sources, like neural and hormonal subsystems.

III. Results and Validation

In this section, all the results for the proposed approaches are presented for FHR and UC signals.

A. Nonlinear Characterization

The surrogate data nonlinear characterization method is considered for the FHR for the whole dataset and also for the UC signal only for the CTG-I database, since in antepartum database there are only a few spaced uterine contractions. The ApEn is considered as the null-hypothesis nonlinear metric, with $m = 2$ and $r = 0.2\sigma(f(x))$.

Different ApEn values can be found for each execution because of the random components used in phase mixing of the surrogate data generation. Linear parameters considered are mean ($\mu[f(x)]$ and $\mu[g(x)]$) and variance ($\sigma^2[f(x)]$ and $\sigma^2[g(x)]$). The null hypothesis was rejected for all the examinations while the linear parameters remained constant for the original and surrogate data. An example set of 5 examinations is shown in Table I

For the uterine tonus contractions, measured in mmHg, similar results were found for the whole set of CTG-I database examinations, as can be seen in Table II.

Table I

FHR NONLINEARITY CHARACTERIZATION.

Examination	$\mu[f(x)] = \mu[g(x)]$	$\sigma^2[f(x)] = \sigma^2[g(x)]$	$ApEn[f(x)]$	$ApEn[g(x)]$
ctg20000101-0419153	131.09	271.73	0.22	0.38
ctg20000103-1637131	154.13	127.47	0.50	0.75
ctg20040113-0227251	156.56	152.40	0.52	0.78
ctg20040112-1053432	140.82	87.97	0.07	0.75
ctg20040111-0827261	139.96	281.49	0.24	0.36

Table II

UTERINE CONTRACTIONS NONLINEARITY CHARACTERIZATION.

Examination	$\mu[f(x)] = \mu[g(x)]$	$\sigma^2[f(x)] = \sigma^2[g(x)]$	$ApEn[f(x)]$	$ApEn[g(x)]$
ctg20040113-0227251	32.66	277.60	0.21	0.45
ctg20040112-1053432	19.83	105.05	0.16	0.53

The graphical return map analysis is used to complement the nonlinearity characterization analysis. In Figure 2 the original signal and the surrogate data return maps for an intrapartum CTG are presented. As shown in previous examples, the linear statistic measures are the same for both signals, hence the difference between them can be classified as a result of nonlinear components influences.

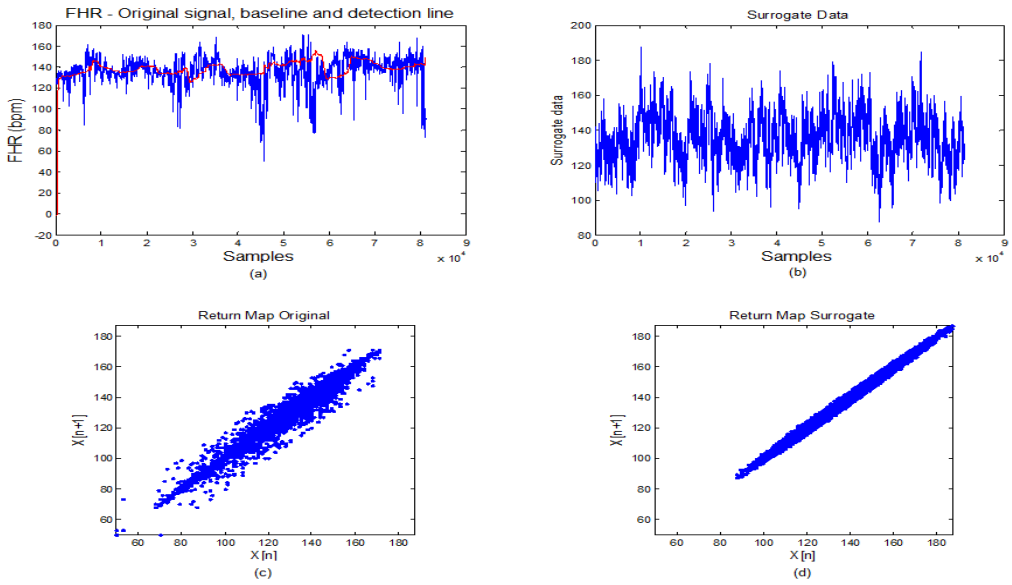

Figure 2. Nonlinear characterization: (a) FHR, (b) Surrogate data, (c) Return Map of original FHR data and (d) Return Map of surrogate data.

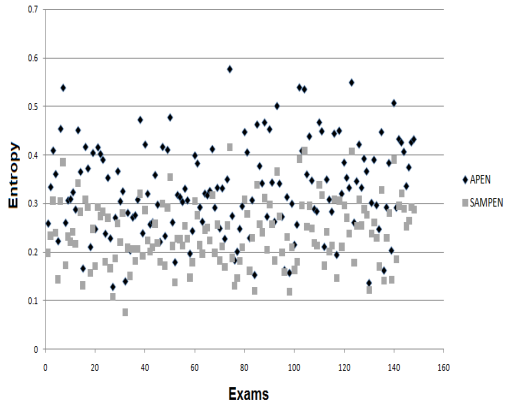

Figure 3. Run-sequence plot for the ApEn and Sampen values for the CTG-A database.

B. Windowed Entropy Analysis

Both ApEn and SampEn are calculated for the whole set of samples of each record, presenting a long term complexity metric about the signal. Furthermore, sample subsets are also considered, since one can determine the minimum amount of samples could also be used to analyze the complexity evolution in time.

The results show that low entropy values are found when the whole examination is considered, Apen=0,3244$\pm$0,1078 and SampEn=0,2351$\pm$0,0758 (average$\pm$standard deviation). Besides, no significant difference was found between the normal (Apen=0,3366$\pm$0,1250 and SampEn=0,2532$\pm$0,0818) and suspicious/pathological (Apen=0,3420$\pm$0,1220 and SampEn=0,2457$\pm$0,0850) groups for the CTG-A database based on statistical t-test evaluation.

A run-sequence plot for the CTG-A database is presented in Figure 3.

Four different plots for the *ctg20040214-0722052* examination are presented in Figure 4 with the ApEn and SampEn calculated for the proposed different windows of $\Delta t_e = (1, 2, 5, 10)$ minutes

Similar results were found for other examinations in both CTG-A and CTG-I databases. When considering small subsets, such as $\Delta t_e = 1$ and $\Delta t_e = 2$ minutes, the entropy need to be recalculated during long term changes in FHR as they usually take longer than 2 minutes.

Based on clinical analysis, experienced medical staff evaluation suggested windows of at least 5 minutes and no longer than 10 minutes for CTG analysis, since this exam is characterized for long term baseline determination and other significant changes.

For long subsets, $\Delta t_e = 2,400$ (10 minutes), small entropy values were usually found. This may hide the influence of long term variability in FHR. So, $\Delta t_e = 1,200$ (5 minutes) was chosen for the evaluated databases as the best window size that may represent the entropy oscillation according to time changes in FHR.

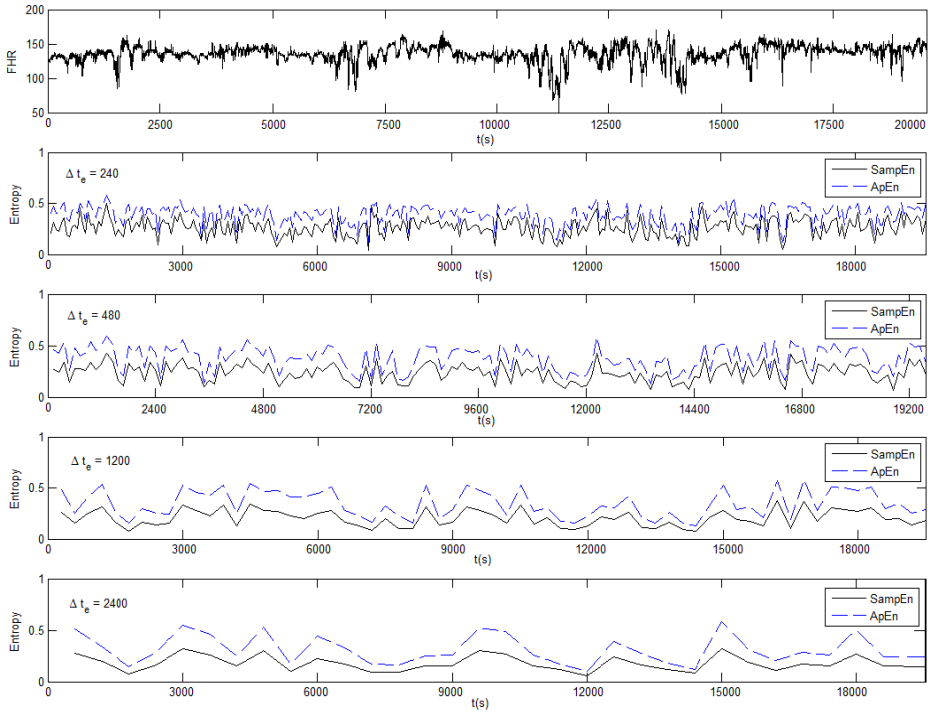

Figure 4. Windowed entropy calculation considering four different sample intervals for the *ctg20040214-0722052* examination.

After this analysis, the entropy parameters considered in the remaining calculations are $\Delta t_e = 5$ minutes, $m = 2$ and $r = 0.2\sigma(f(x))$.

The Figure 5 presents the traces for the FHR and entropies for the *ctg20000205-0209311* examination from the CTG-A database and for the *ctg20040128-0337182* examination from the CTG-I database.

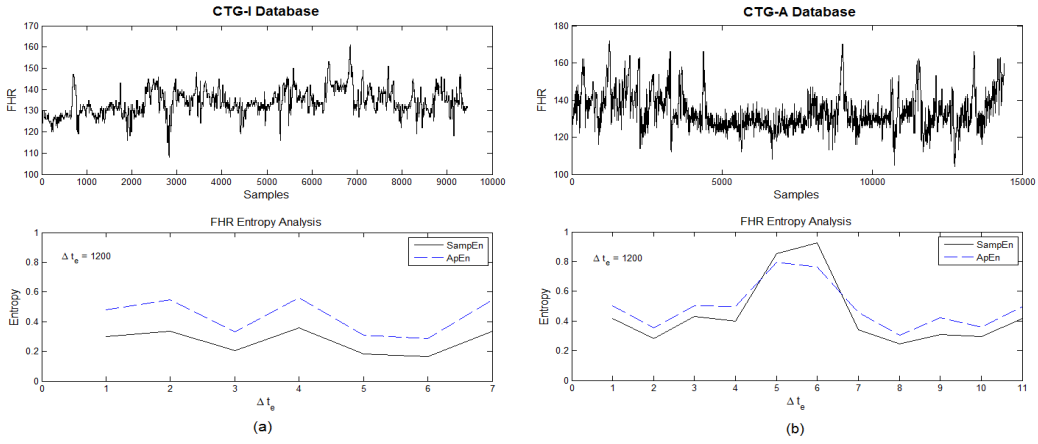

Figure 5. Illustration of entropy on both databases (a) CTG-I (b) CTG-A.

For the whole set of examinations in CTG-I and CTG-A databases, both entropies present similar graphics, since the theoretical assumptions for both measures are similar. The SampEn present smaller values because of the self-matches avoidance.

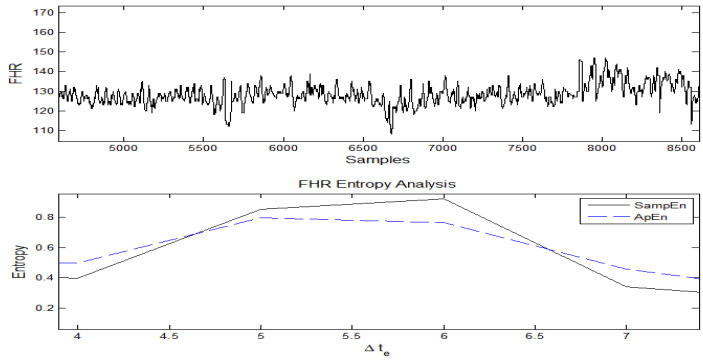

Figure 6. Windows of FHR high entropy values.

The windowed entropy analysis is them performed on CTG-A and CTG-I databases and the results are presented in Table III and Table IV. No significant difference could be found between normal and suspicious/pathological groups in CTG-A database, considering a t-test statistical analysis.

Table III

GENERAL ENTROPY RESULTS FOR THE ANTEPARTUM (CTG-A) DATABASE, WHERE A_{WA} IS THE AVERAGE AND SD_{WA} IS THE STANDARD DEVIATION OF THE WINDOWED APEN, WHILE A_{WS} IS THE AVERAGE AND SD_{WS} IS THE STANDARD DEVIATION OF THE WINDOWED SAMPEN.

CTG-A	A_{WA}	SD_{WA}	A_{WS}	SD_{WS}
All Examinations	0,6505	0.2301	0.5290	0.1188
Normal	0.6812	0.2221	0.5517	0.1403
Suspicious/Pathological	0.6413	0.2091	0.5301	0.1540

Table IV

GENERAL ENTROPY RESULTS FOR THE ANTEPARTUM (CTG-I) DATABASE, WHERE A_{WA} IS THE AVERAGE AND SD_{WA} IS THE STANDARD DEVIATION OF THE WINDOWED APEN, WHILE A_{WS} IS THE AVERAGE AND SD_{WS} IS THE STANDARD DEVIATION OF THE WINDOWED SAMPEN.

CTG-I	A_{WA}	SD_{WA}	A_{WS}	SD_{WS}
Normal	0.5611	0.1970	0,4909	0.1782

C. Entropy analysis for long term changes in CTG

For each long term change in the FHR signal, the complexity analysis is presented with illustrative examples.

At first, for the examination presented in Figure 5 (b), during $4 \leq \Delta t_e \leq 7$ windows, high entropy values can be found. Zooming at the original signal for this interval, many ascendent and descendent changes could be found, which allow us to consider that this is a high complexity period in FHR, as can be seen in Figure 6.

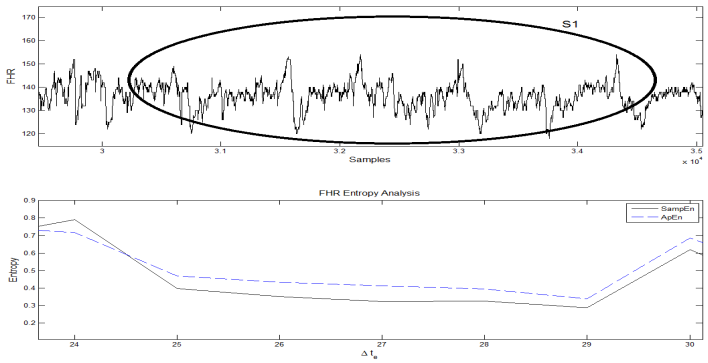

Figure 7. FHR low entropy values during *ctg20040215-0803261* examination.

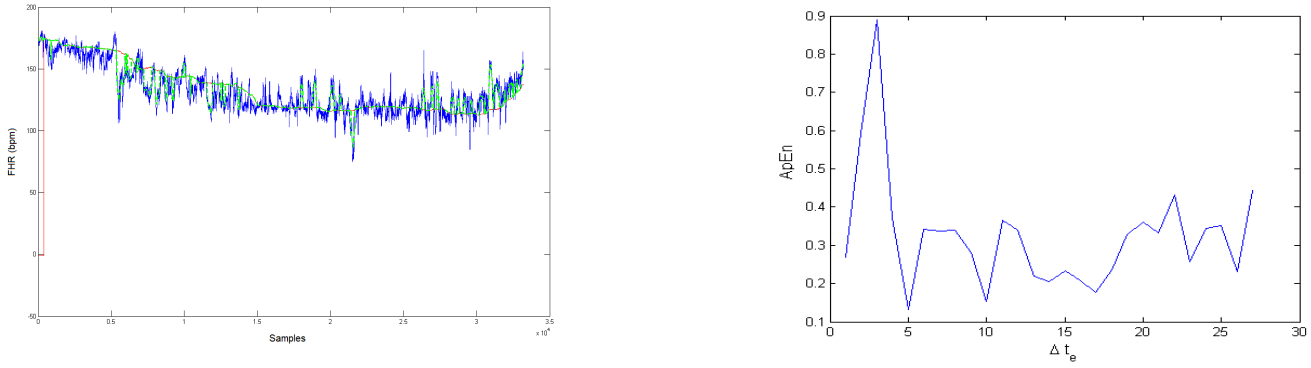

Figure 8. *ctg20011218-2348371* examination: (a) FHR baseline tending to normality and (b) FHR entropy behaviour.

For the *ctg20040215-0803261* exam, low entropy values are found during $25 \leq \Delta t_e \leq 29$ windows. A repetitive pattern can be detected in the original signal (region S1), tending to a sinusoidal behaviour, as can be seen in the subarea S1 from the Figure 7. This FHR behaviour could be classified as suspicious or pathological [22] and is very hard to be found in visual inspection.

Another examination previously classified as pathological, *ctg20011218-2348371*, is presented in Figure 8. At the beginning there is fetal tachycardia and a low short-term variability is expected. During the examination, there is a decrease in the FHR baseline, tending to normality. The entropy trace presents low value.

Many examinations presented FHR accelerations and decelerations and the FHR complexity was evaluated during those events as a possible indice of transitory changes in time.

The *ctg20040214-0722052* examination is shown in Figure 9. There are several strong FHR decelerations when the calculated entropies significantly fell down during the $36 \leq \Delta t_e \leq 40$ windows. This may indicate a loose of complexity in the system. Entropy values only increase when the FHR returns to its baseline.

For the FHR accelerations analysis, the *ctg20020124-1015523* examination is presented in Figure 10. This examination has

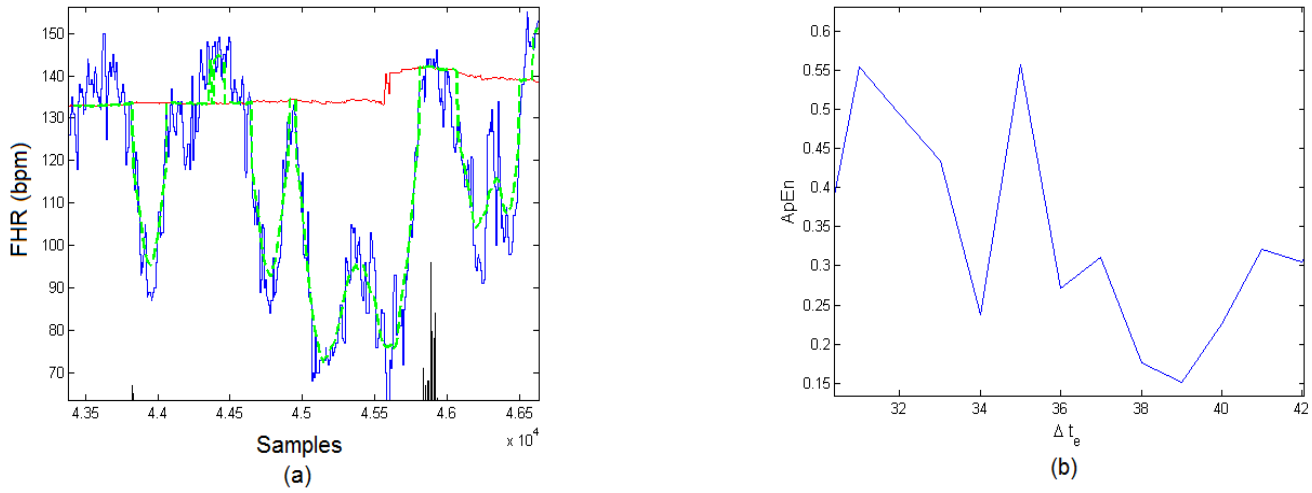

Figure 9. *ctg20040214-0722052* examination: (a) several FHR decelerations and (b) low entropy values.

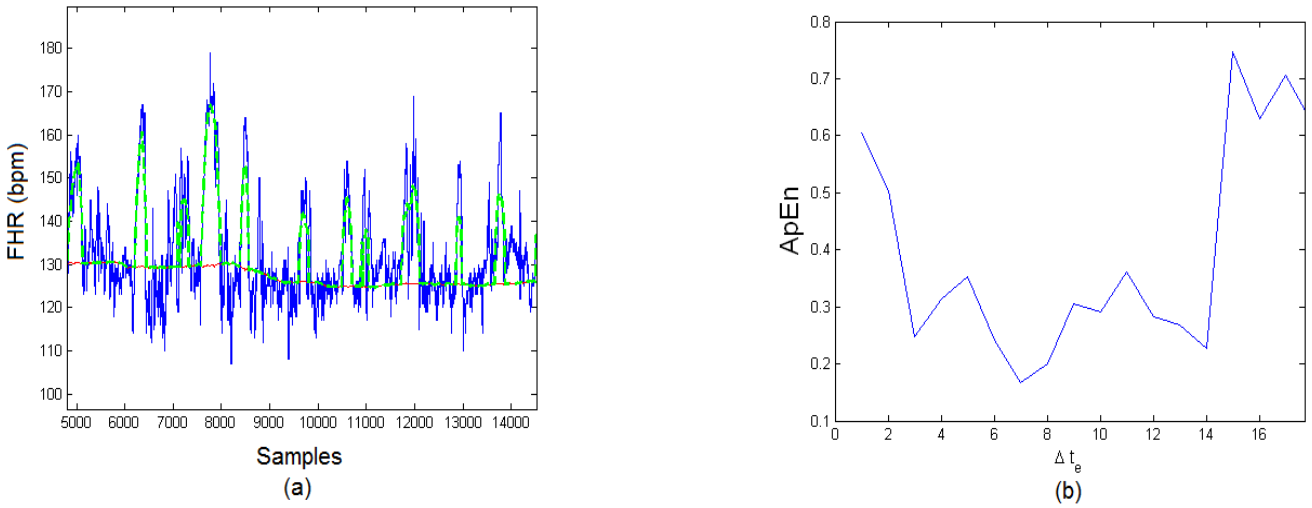

Figure 10. Part of the *ctg20020124-1015523* examination; (a) FHR accelerations and (b) low entropies as an measure of low complexity.

um large set of accelerations which results in a complexity diminution during the $5 \leq \Delta t_e \leq 12$ windows.

For the uterine contractions signal, the complexity analysis is performed only during intrapartum period of time. An illustrative example of the *ctg20040214-0722052* examination can be seen in Figure 11. The entropy results show, for the $20 \leq \Delta t_e \leq 45$ windows, that there are increases in the system complexity during strong uterine contractions.

After this qualitative presentation, the changes during specific long term events show that entropy can be considered as a first level indicator for significant FHR changes, as presented in Table

Finally, the last set of results are about the nonlinear complexity characterization for the uterine contraction signal $z(t)$, considering the significant changes from the antepartum to the intrapartum phase. In Table VI some exams from the antepartum

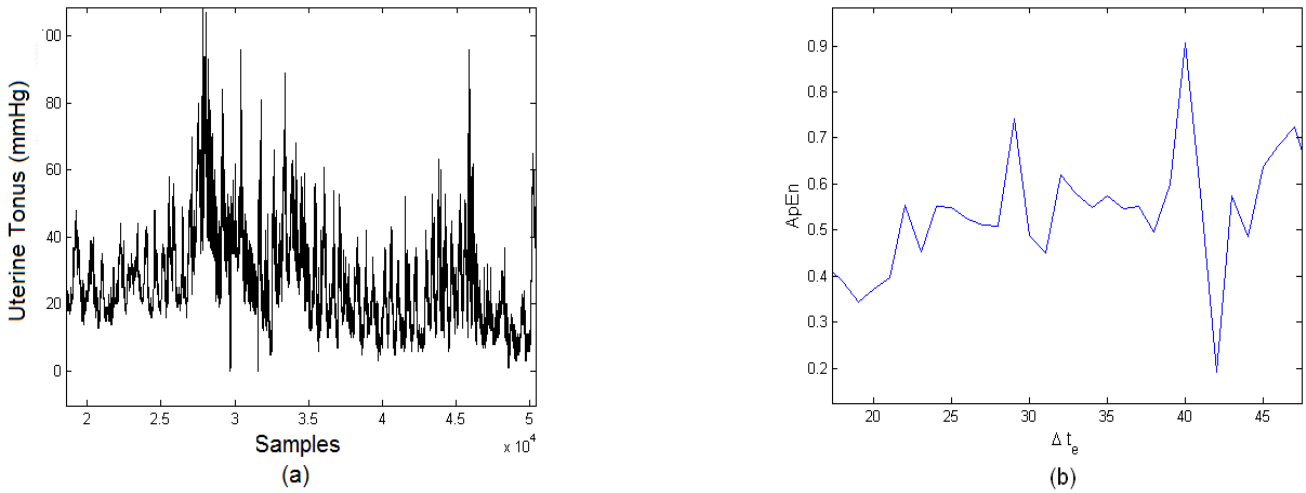

Figure 11. Part of the *ctg20040214-0722052* examination: (a) Uterine contractions occurence and (b) high entropy values during the contractions.

Table V

GENERAL ENTROPY RESULTS FOR THE ANTEPARTUM (CTG-I) DATABASE, WHERE A_{WA} IS THE AVERAGE AND SD_{WA} IS THE STANDARD DEVIATION OF THE WINDOWED APEN, WHILE A_{WS} IS THE AVERAGE AND SD_{WS} IS THE STANDARD DEVIATION OF THE WINDOWED SAMPEN.

Long term event	$ApEn$	$SampEn$
FHR decelerations	0,1487±0,0341	0,1289±0,0301
Strong FHR accelerations	Apen=0,1830±0,1078	0,1501±0,0703
Sinusoidal FHR	Apen=0,1808±0,0445	0,1621±0,0381

database are compared with intrapartum exams showing that the appearance of the uterine contractions increases the nonlinear irregularity inside the system, resulting in higher complexity.

Table VI

INCREASE OF UTERINE CONTRACTIONS SIGNAL COMPLEXITY DURING LABOUR.

Examination	Database	$ApEn[z(x)]$	$SampEn[z(x)]$
ctg20010223-1429403	CTG-A	0.002	0.001
ctg20020124-1015523	CTG-A	0.002	0.003
ctg20040122-2146381	CTG-I	0.102	0.041
ctg20040128-0337182	CTG-I	0.608	0.447
ctg20040113-0227251	CTG-I	0.964	0.642

IV. Discussion

Entropy calculation in biological time series analysis is being widely used, specially considering it as a measure of system complexity [6], [7], [13], [23], [24]. Besides, different applications of the SampEn in heart rate analysis can be found in [21] and [25].

The results presented for the nonlinear characterization for FHR and UC signals show that both are suited to present nonlinear components. The null hypothesis was reject for all the cases in the whole dataset and the comparison of the return map plot from the original time series and the surrogate data presented significant differences.

In this paper, ApEn and SampEn are evaluated as complexity analysis tool for CTG monitored signals. Their implementation differ in some important aspects, specially for time series with low number of matches and this must be considered when evaluating the ApEn calculation. It is important to notice that the underlying concept of nonlinear complexity is not only related to irregularity in time, i.e., low entropy values are not only found when the signal increases the regularity.

For the two databases evaluated in this work, in general both entropies presented similar results even when different number samples were considered.

Physiological interpretations can be done based on the results.

Low entropy values are found when all the samples are considered. This result may be influenced by the nature of the signal with long term oscillations around a baseline or even other long term and short term variability aspects.

A windowed entropy approach is them proposed with a 5 minutes windos as the best fitted to capture the signal dynamics, according to clinical evaluation.

According to the literature, higher entropy values are usually considered as a normality indice of the FHR long term variability which is an important neural development estimator. For the presented databases, higher entropy values could be found when using the windowed entropy approach.

When considering significant long term changes in FHR, the decrease in entropy values found in severe FHR accelerations and decelerations can provide a first level monitoring parameter for the detection of fetal distress.

Besides, low entropy values are also found for repetitive patterns around the FHR baseline which are not classified as accelerations or decelerations. These sinusoidal fluctuations are classified as suspicious or pathological and are usually hard to detect with the visual interpretation.

Finally, the last set of results are about the calculation of entropies for the uterine contraction signal $z(t)$, considering the significant change from the antepartum to the intrapartum phase. The increase of entropy values can be considered the increase of system complexity during labour.

V. Conclusion

This paper shows the nonlinear nonlinear characterization of FHR and maternal UC signals as a first relevant step to consider the application of nonlinear metrics for medical decision support. The windowed entropy calculation is them presented following clinical interpretation of the FHR.

The results present that is suitable to consider nonlinear analysis for FHR and UC signals using windowed entropy measures (ApEn and SampEn) as classification tools of normal variability and long and short term fetal heart rate changes in time.

Future works may consider other complexity measures based on different approaches, such as Multiscale Entropy and Lempel-Ziv complexity, to compare the results and propose sensitivity and specificity analysis.

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VII. Conflict of Interests

The authors declare no conflict of interest.

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