ANALYSIS OF FETAL HEART RATE VARIABILITY SIGNAL TO SEPARATE DISTRESSED IUGR FETUSES FROM SGA FETUSES

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Abstract:
Intrauterine growth restriction (IUGR) is a common diagnosis in obstetrics and carries an increased risk of perinatal mortality and morbidity. Identification of IUGR is crucial because proper evaluation and management can result in a favourable outcome. However evidence-based guidelines for clinical surveillance are poor and lack of reliable indexes. This study introduces different procedures to extract parameters from the fetal heart rate signal. The parameters are the standard ones (time domain and frequency domain indexes) and the complexity measures (the Lempel Ziv complexity, the Approximate Entropy and the Sample Entropy). The analyses examine differences and analogies between the complexity parameters and their ability in separating the suffering IUGR fetuses from healthy ones . The results show that the LZ complexity is able to significantly discriminate severe IUGR (preterm delivered) from moderate IUGR (at term delivered) and healthy fetuses.

Introduction

The objective to thoroughly analyze the biological systems from the signals we can record often appears unfeasible. The knowledge we have about the system behavior is limited by their intrinsic complexity, which is basically produced by numerous interacting mechanisms contributing to the physiological system performance. There is no a unique and rigorous way of consistently defining complexity. The concept of complexity sometimes quantifies the difficulties we have in describing or understanding a signal. The cardiovascular system of fetus has different and more features than in the adult, as the heartbeat is driven not only by the nervous system (itself developing during the pregnancy) but also by external mechanical stimuli (umbilical cord pulses and uterine contractions).

The standard parameters of fetal heart rate (FHR) analysis have the purpose to identify critical variation from the physiological state, but they do not try to evaluate or to measure the complexity of heart system. Moreover these parameters did not yet demonstrate their efficacy in the identification of pathological or suffering fetuses: the false negatives are already a large number [1].

In this work we have introduced and evaluated different parameters, which allow capturing further information about the system. In particular, we have adopted as regularity index the Approximate Entropy (ApEn) and the Sample Entropy (SampEn) [2][3] and we propose herein as complexity measure the Lempel Ziv parameter (LZ) [4]. This class of indexes was selected as they represent an indirect measure of the system generating the signals.

In fact the purpose of ApEn and SampEn is to measure the signal "regularity" i.e. the presence of similar patterns in a time series. In the context of these parameters (ApEn, SampEn) the term complexity refers to the predictability of the system state location, by knowing the initial conditions. The less predictable the states are, the more complex the system is.

On the other hand, the Lempel Ziv complexity evaluates the gradual increase of new patterns along the given sequence. In this case the word complexity refers to the so-called algorithmic complexity, which is defined according to the Information Theory as the minimum quantity of information needed to define a binary string [5]. In case of random strings, the algorithmic complexity is the length of the string itself. In fact any compression effort will produce an information loss.

In this work we have firstly compared the behavior of the complexity parameters in order to illustrate analogies and differences. Successively we have investigated the ability of the standard indexes and the proposed parameters in a clinical application: the identification of severe Intrauterine Growth Restricted (IUGR) fetuses from Hear Rate Variability (HRV) signals.

Intrauterine growth restriction is a common diagnosis in obstetrics and carries an increased risk of perinatal mortality and morbidity. Identification of IUGR is essential because proper evaluation and management can result in a favourable outcome. Some pregnancies are at high risk for growth restriction, although a substantial percentage of cases occur in the general obstetric population. Dating accurately the fetal growth, early in pregnancy, is essential for a diagnosis of IUGR. The fetal biometry, which is based on non-invasive ultrasound techniques, is the gold standard for assessment of fetal size and of the amount of amniotic fluid.

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It is an useful tool to identify the Small for Gestational Age (SGA) fetuses. Preterm delivery is indicated if the fetus shows evidence of abnormal function on biophysical profile testing [6].

Two crucial problems are thus the separation of the pathological SGA, i.e. IUGR fetuses, from the healthy small fetuses and the lacking of evidence-based guidelines for clinical management. The goal of our work is to contribute in solving both problems.

Table I: Description of parameter used in this work

Long Term indexes **Parameters computed for each interval of signal, N=360 or 512 point long**		
FHR average value (bpm)	LTI (ms)	SampEn(1, 0.1)
LF-power (%)	LZ binary	ApEn(1, 0.1)
HF-power (%)	LZ ternary	SampEn(2, 0.15)
MF-power (%)	SampEn(1, 0.2)	ApEn(2, 0.15)
LF/(MF+HF)	ApEn(1, 0.2)	
Short Term indexes **Parameters computed for each interval of signal, N=120 point long**		
Delta (ms)	Interval Index	STV (ms)

Materials and Methods

We have analyzed heart rate (HR) signals belonging to fetuses, whose gestational age was comprised between the 27th and the 34th gestational week. A CTG monitor HP M1351A recorded the HRV signals. The recording time is about one hour.

The fetuses were then classified as normal, severe IUGR and not severe IUGR. The normal group includes 17 fetuses without pathologies, delivered by spontaneous labour and a good score at delivery. The severe IUGR group comprises 23 SGA fetuses with complications so that they were preterm delivered by a caesarean section. The not severe IUGR group includes 19 small fetuses with at term delivery even if classified as IUGR.

The HR signal is corrected before the analysis. As the CTG signal often appears corrupted by a large amount of noise, artifacts, or even signal loss, the HP-M1351A has a quality index, which quantifies three different levels of the FHR signal: optimal (green), acceptable quality (yellow), and insufficient quality and/or signal unavailable (red). The evaluation is based on the output of the autocorrelation procedure upon which the recording of FHR signal is based [7][8].

For all recordings a standard analysis procedure was carried out through the identification of the baseline and the detection of accelerations and decelerations.

As there aren't guidelines to extract the parameters and by now there aren't significant results about them, we computed the indexes in different manner. At first we used the traditional method, used also in preceding works [7] and adopted by the SEA2CTG software: each index is computed for contiguous intervals of signal, 360 point long for long term parameter and 120 point long for short term parameter, the considered parameter is the mean of the sequence of indexes. The signal subsets with insufficient quality were excluded from the analysis.

We have successively modified the method by adopting both signal intervals with 50% overlapping and intervals 512 point long.

We repeated the analysis by introducing a more restrictive criterion: the signal subsets containing zeros were excluded from the analysis (0 is the value that the HP monitor attributes when the signal is unavailable or the pre-processing procedure judges it unacceptable; it has no physiological meaning).

The parameters compared in this study are: (i) the time domain parameters, computed both over the original signal and by excluding the accelerations and decelerations, (ii) the frequency domain parameter, computed by adopting a power spectral estimation based on the nonparametric method, and (iii) the complexity parameters (table I). The time domain parameters are: mean value, DELTA, Short Time Variability (STV), Long Term Irregularity (LTI) and Interval Index (II) [7][9].

DELTA is the simplest measure of variability. Given a signal interval of one minute $T(i)$, expressed in millisecond, $\text{DELTA}=\max_i[T(i)]-\min_i[T(i)]$, where i is the number of samples in one minute. STV quantifies FHR variability over a very short time scale, usually on a beat to beat basis. $\text{STV}=\text{mean}[|T(i+1)-T(i)|]$.

LTI is defined as the interquartile range [1/4;3/4] of the modulus m distribution, where m is defined as $m(i)=\sqrt{T^2(i)+T^2(i+1)}$; i is the number of samples in three minutes.

The interval index was proposed as a long term variability statistic. It is defined as

$$\text{II}=\frac{\text{std}[|T(i+1)-T(i)|]}{STV}, \quad (1)$$

where i is the number of samples in one minute.

As frequency domain parameters we considered the power percentage of the following frequency band range: the Low Frequency component range (0.04-0.15Hz), MF power (0.15-0.5Hz, not present in adult human subjects), HF power (0.5-1.0Hz), the LF/(MF+HF) ratio.

The complexity parameters considered in this study are: the Approximate Entropy (ApEn) [2], the Sample entropy (SampEn) [3], the Lempel Ziv complexity with binary and ternary coding procedure [4][10][11].

The Approximate Entropy measures, with a tolerance r, the regularity of patterns comparing them to a given pattern of length m (m and r are fixed values: m is the detail level at which the signal is analyzed and r is a threshold, which filters out irregularities). The Sample entropy is a modification of ApEn. The differences with respect to ApEn are: (i) self-matches are not counted, (ii) only the first N-m vectors of length m are considered and (iii) the conditional probabilities are not estimated

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in a template manner: they do not adopt as probability measure the ratio of the logarithmic sums, but they compute directly the logarithm of conditional probability [12].

The values adopted in this work are m=1, 2 and r=0.1, 0.15, 0.2 both for ApEn and SampEn.

The measure of complexity introduced by Lempel and Ziv is associated to the number of distinct sub strings and to the rate of their recurrence; namely it reflects the gradual increase of new patterns along the given sequence. As suggested in [13], it is preferred to use the normalized complexity measure, i.e. the measure of complexity normalized by a factor depending on the sequence length. This permits to compare the complexity values of two strings different in length.

In order to estimate the complexity measure for the FHR time series, we transformed the signals into symbolic sequences. As the human cardiac control system is driven by nonlinear mechanisms and it is intrinsically a noisy system, we adopted the simple increase or decrease of the signal as coding criteria [14]. Let's consider a HR time series $\{x_n\}$, we can construct a new sequence via mapping the original one in the following manner: adopting a binary alphabet, we denote with 1 an increase of the signal ($x_{n+1}>x_n$) and with 0 a decrease ($x_{n+1}\leq x_n$); in the case of ternary alphabet we denote with 1 an increase of the signal ($x_{n+1}>x_n$) with 0 a decrease ($x_{n+1}<x_n$) and with 2 a stationary state ($x_{n+1}=x_n$).

Results

The preliminary analysis presents the performances of LZ complexity and regularity estimators. We evaluated their behavior for known signals: $1/f^{\alpha}$ noises, MIX(p) process, Logistic Map.

The MIX(p) process is defined as $(1-z)\cdot x+z\cdot y$, where z is a random variable, that assumes value 1 with probability p and 0 with probability $1-p$, x is a sequence generated by the equation $x_j=\sqrt{2}\sin(2\pi j/12)$ and y is a uniformly distributed variable on $[\sqrt{3},-\sqrt{3}]$. We have generated 5 sequence of N=30000 samples for each p (0÷0.9). Figure 1 illustrates results obtained with time series from a MIX(p) process. The lower is p, the more periodic and regular is the signal. As expected, time series corresponding to low p values show lower values of LZ complexity and entropy and the behavior of both LZ complexity and entropy indexes is comparable.

We have also generated 30000 point long time series from a Logistic Map process $x_i=x_{i-1}\cdot r\cdot(1-x_{i-1})$, by varying the r parameter (r=3÷4). In this case we have obtained the same performance as for the MIX(p) process, that is LZ and entropy indexes have increasing values for increasing r values.

Finally, the $1/f^{\alpha}$ signals were built by generating a $1/f^{\alpha}$ power spectral density, with random phases (uniformly distributed on $[-2\pi, 2\pi]$) and by applying the inverse Fast Fourier Transform (FFT). The α values range from 1 up to 2 and the time series generated are 30000 point long. In this case, LZ complexity index has a completely different trend from the entropy estimators. As the α parameter increases the signal appear more regular so the entropy estimators assign it a lower measure, whereas the LZ complexity maintains high values (Figure 2). This is in accordance to the unpredictability of 1/f process.

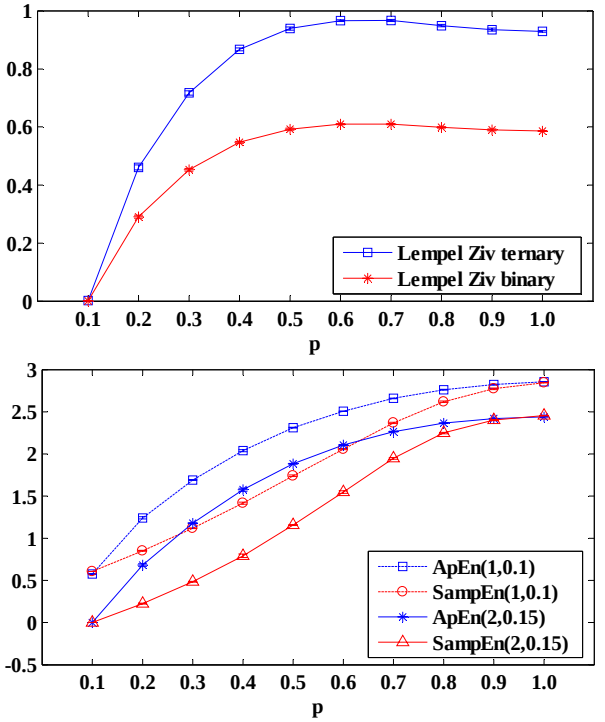

Figure 1. LZ complexity values (upper panel) and entropy values (lower panel) computed for a MIX(p) process. The values are plotted as a function of p.

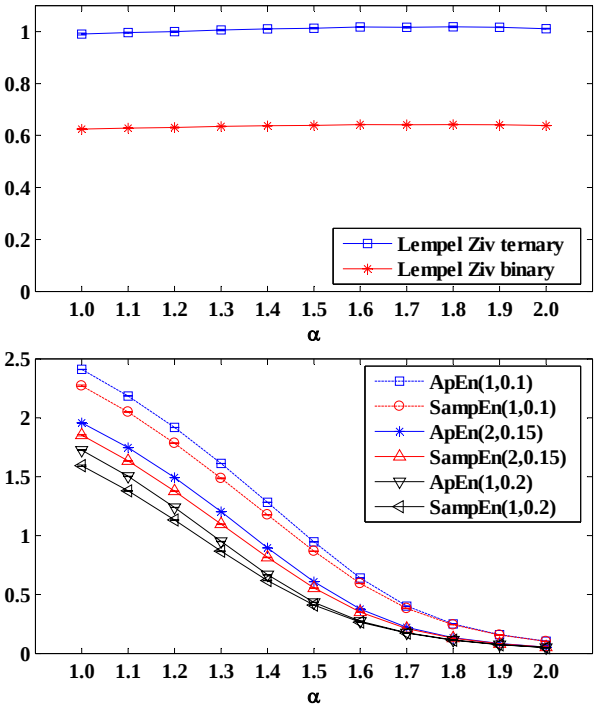

Figure 2. LZ complexity values (upper panels) and entropy values (lower panels) computed for $1/f^{\alpha}$ process. The values are plotted as a function of α.

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Table II: Parameters values obtained from the three groups (avg±std).
The results refer to the analysis over 360 points FHR overlapping subsets adopting the more restrictive criterion (absence of zeros). The symbol † means that the parameter discriminates the three groups of fetuses (P-value ANOVA<1% and P-value Scheffè test <5%). The symbol * means that the parameter discriminates the IUGR groups from healthy fetuses (P-value ANOVA<1% and P-value Scheffè test <5%).

	LZ (binary)	LZ (ternary)	ApEn(1,0.1)	SampEn(1,0.1)	ApEn(2,0.15)	SampEn(2,0.15)	ApEn(1,0.2)	SampEn(1,0.2)
Healthy	1,013±0,038	**0,887±0,029†**	1,220±0,159	1,169±0,219	0,764±0,099	0,790±0,169	0,790±0,159	0,671±0,160
severe IUGR	1,022±0,019	**0,951±0,028†**	1,308±0,200	1,304±0,273	0,786±0,094	0,906±0,233	0,862±0,191	0,750±0,193
not sev. IUGR	1,032±0,018	**0,914±0,035†**	1,302±0,146	1,276±0,184	0,811±0,082	0,880±0,155	0,845±0,149	0,728±0,140
	LF%	**MF%**	**HF%**	**LF/(MF+HF)%**	**LTI (msec)**	**DELTA(msec)**	**STV(msec)**	**II**
Healthy	85,401±2,567	11,530±1,783	3,069±1,130	6,730±1,280	22,954±6,061	**54,919±17,249***	**7,365±2,810***	0,856±0,043
severe IUGR	81,908±8,175	12,116±3,989	5,977±4,558	6,360±2,768	16,221±5,818	**32,636±15,985***	**4,043±2,077***	0,851±0,045
not sev. IUGR	84,415±3,773	11,310±2,577	4,275±2,156	6,670±1,871	19,817±6,112	**43,921±11,564***	**5,758±1,490***	0,852±0,043

The clinical study for the identification of distressed small fetuses has showed that only the LZ complexity index (ternary coding), the DELTA index and the STV are able to discriminate IUGR from healthy fetuses.

In particular, the DELTA and STV indexes perform well when they are computed in 360 point FHR intervals, both contiguous and with overlapping, and by adopting both the less restrictive (*sufficient quality*) and the more restrictive criteria (*absence of zeros*).

In addition only the LZ complexity index (ternary coding) significantly discriminates for all parameter extraction procedures.

However, the most important results were obtained when we analyzed overlapped intervals of 360 and 512 points and adopting the restrictive criterion: the Lempel Ziv complexity (ternary coding) discriminates significantly the three groups of fetuses (ANOVA test and Kruskall-Wallis test were performed between the three patient groups, then post-hoc comparisons are made by Scheffè test, P-value ANOVA<1% and P-value Scheffè test <5%. Some values are reported in table 2).

This results indicates that LZ index can efficiently separate the distressed IUGRs not only from healthy fetuses but also from the not severe SGA fetuses.

The final step of our analysis was to evaluate the correlation between the discriminating parameters. Only the LZ complexity is not correlated with the other two indexes, whereas DELTA and STV are correlated, as expected (Spearman coefficient ρ >0.8, *p*-value<1%). Some results are illustrated in figure 3.

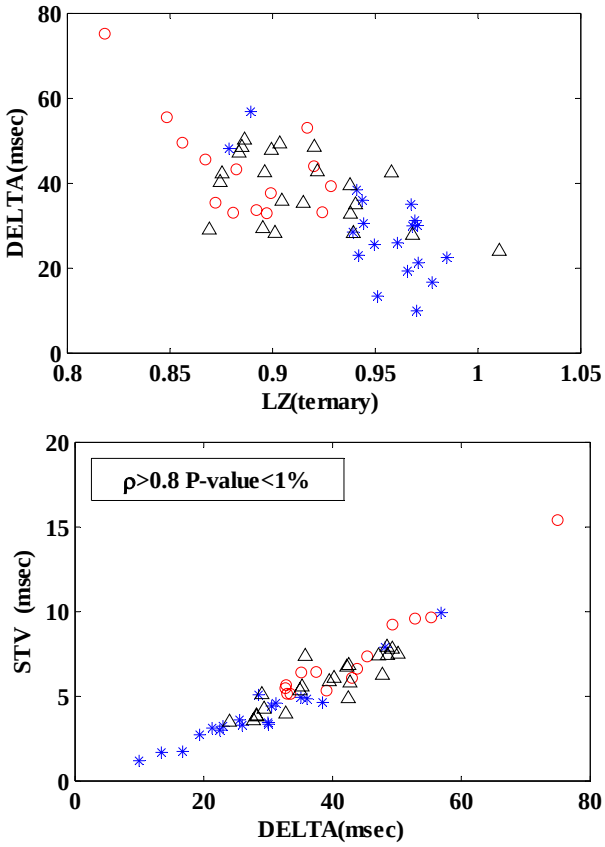

Figure 3. Scatter plot of LZ, DELTA and STV values computed for overlapped intervals of 360 points and by adopting the restrictive criterion (*absence of zeros*). The rounds refers to healthy fetuses, the asterisks to severe IUGR, the triangles to not severe IUGR.

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Discussion

The simulation results demonstrate that the complexity estimators proposed in this work provide different information about the time series. In fact in the case of $1/f^{\alpha}$ noise process, we have signals apparently more regular for increasing α, but which are generated by a stochastic process with long-term correlation.

This can be recovered in the index values. In fact the entropy values have a growing trend for increasing α: the signals are more regular and then the entropy estimators capture the repetitive patterns. The unpredictability nature of the signals is instead caught by the LZ parameter that evaluates the arising of new patterns along the time series. In this way the entropy and the LZ complexity indexes can be considered complementary parameters.

Furthermore the analysis about the fetal HRV shows that the Lempel Ziv complexity evaluation can be a possible solution to the clinical problem of the identification of distressed IUGR fetuses by separating them from the healthy SGA, whereas the introduction of the regularity estimators does not improve the FHR classification.

Moreover the analysis showed that the traditional parameters are insufficient to identify the sufferance in IUGR fetuses and thus they appear inadequate to be included in a evidence-based guidelines. As already obtained in previous analyses [15], these results seem to encourage the addition of complexity measure in the analysis of fetal heart rate signals.

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