Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

New indexes from the Fetal Heart Rate analysis for the identification of severe intra uterine growth restricted fetuses

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Abstract—**This study proposes new indexes extracted from fetal heart rate signal in order to identify intrauterine growth restricted (IUGR) fetuses and separate them from healthy small for gestational age ones (SGA). Unfortunately evidence-based guidelines for clinical surveillance are poor and lack of reliable indexes. Therefore we proposed new parameters: the Lempel Ziv complexity (LZC) and the Multiscale entropy (MSE). The results show that the LZ complexity is able to significantly discriminate the severe IUGR (preterm delivered) from moderate IUGR (at term delivered) and healthy fetuses. Moreover the *k*-mean cluster analysis applied to these indexes was able to gather the severe IUGRs and to separate them from both not severe IUGRs and normal fetuses, which were included in the same cluster. The cluster analysis provides good values of sensitivity and accuracy.**

I. Introduction

A CRUCIAL problem in fetal monitoring is the correct interpretation of biophysical measurements. The innovative non-invasive ultrasound techniques have permitted to asses with high resolution the fetal biometry (i.e. abdominal and cranial circumferences, femur length, estimation of gestational age, fetal weight, etc). The comparison with population standards can thus identify the small for gestational age (SGA) fetuses, characterized by biometric dimension <10° percentile, unfortunately in this group the healthy fetuses of small size are taken in as well [1]. The important question is therefore how to decide if the small dimensions are physiological or due to a pathological condition. Moreover one of the most widespread pathology is the intrauterine growth restriction (IUGR): a metabolic dysfunction which does not allow the fetus to achieve its genetically predetermined size. The fetus is at risk of hypoxia and this condition is often associated with increased perinatal mortality and morbidity.

The surveillance and the correct identification of IUGR fetuses are very important in the early gestational period as it is fundamental to predict the possible complications and so to make the appropriate decisions, for example preterm delivery is indicated if the fetus shows evidence of abnormal function on biophysical profile testing [2]. Identification of IUGR is essential because proper evaluation and management can result in a favorable outcome. Dating accurately the fetal growth, early in pregnancy, is essential for a diagnosis of IUGR but the interpretation of clinical data in the very preterm period is often very difficult. Furthermore lack of evidence-based guidelines for clinical management does not help the process [2].

The goal of our work is to find one or more indexes which can identify the actual IUGRs and to separate them from the healthy SGAs through the analysis of fetal heart rate (FHR) signals, obtained from cardiotocographic recordings, during prenatal monitoring. The cardiotocography (CTG) is the most common ante partum monitoring technique and it is based on the detection of fetal heartbeats by Doppler Ultrasounds.

As the traditional parameters seem to be inadequate, we decided to apply new parameters: a complexity index, the Lempel Ziv complexity [3][4], and the Multiscale Entropy [5][6]. The Lempel Ziv Complexity (LZC) is associated to the number of distinct sub strings and to the rate of their recurrence; namely it quantifies the rate of new patterns arising with the evolving of the signal. On the other hand, the Multiscale Entropy (MSE) was proposed in order to capture HRV fluctuations at different degrees of resolution, i.e. in a multiscale manner.

II. Methodology

A. Data Collection

We analyzed FHR signals belonging to fetuses, whose gestational age ranged from the 27th to the 34th week at the recording time. Signals were recorded by a CTG monitor HP M1351A. The recording length is about one hour. The monitored fetuses were grouped as Normal, Severe IUGR and Not Severe IUGR. The control group included 17 fetuses without pathologies, delivered by spontaneous labor and a good Apgar score at delivery. The severe IUGR group contained 23 SGA fetuses, preterm (within 35th g.w.) delivered by a caesarean section because of the insurgence of a life-threatening condition. The not severe IUGR group included 19 small fetuses with at term delivery (after 38th g.w.) even if classified as IUGR.

As the CTG signal often appears corrupted by a large amount of noise, artifacts, or even signal loss, it was introduced a quality index. In the HP-M1351A, the quality index 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

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

B. Lempel Ziv complexity

The measure of complexity introduced by Lempel and Ziv assess 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 [3]. In case of random strings, the algorithmic complexity is the length of the string itself. In fact any compression effort will produces an information loss. The LZC quantifies the rate of new patterns arising with the evolving of the signal. The algorithm to assess LZC is described in [9]. As suggested in [10], it is preferred to use 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 LZC 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.

As suggested in [11], for a given HR time series $\{x_n\}$, the most straightforward procedure is to assign 1 to an increase of the signal ($x_{n+1}>x_n$) and 0 to a decrease ($x_{n+1}\leq x_n$). In case of a ternary coding, we could 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 ($x_{n+1}=x_n$, which holds as a result of the quantization procedure). Unfortunately this procedure could produce a dependence of the encoded string on the level of quantization by which the HR signal is obtained. In this work a new criterion to code the sequence is introduced. Given an HR signal $\{x_n\}$, the encoding rule adopted for the *binary* alphabet is the following: we assign 0 if $x_{n+1}\leq x_n+p\cdot x_n$, and 1 if $x_{n+1}>x_n+p\cdot x_n$. The rule for the *ternary* alphabet is: 2 if $x_n-p\cdot x_n\leq x_{n+1}\leq x_n+p\cdot x_n$, 0 if $x_{n+1}<x_n-p\cdot x_n$ and 1 if $x_{n+1}>x_n+p\cdot x_n$. The factor p is a fixed percentage: the current value is then classified as stationary if it lies in a p range around the previous sample. This procedure is proposed to limit the effect of additive noise and to exclude the dependence on signal quantization. For these analyses we considered the encoding parameter p=0.5%, 1%, 2% and 0% as well. In this last case, we consider as range around the current value the quantization level, which is actually ±0.5 bpm.

C. Multiscale Entropy

From the original time series, the first step to compute MSE is the construction of some coarse-grained time series. For each of these new time series, an entropy measure is calculated and the obtained value is plotted as a function of the coarse-graining scale factor [5]. Given a discrete time series $\{x_1,\ldots,x_n\}$ we construct the series $\{y^{(\tau)}\}$ as a function of the scale factor τ as reported in equation (1):

$$y_j^{(\tau)}=\frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau}x_i \text{ , for } \quad 1\leq j\leq\frac{N}{\tau} \qquad (1)$$

The length of the current series is the ratio between the length of the original series and τ. For τ=1, the series $\{y^{(1)}\}$ is simply the original one. The estimators we used for the MSE analysis are the Approximate Entropy (ApEn) [12] and the Sample Entropy (SampEn)[13].

D. Parameter extraction

The complexity index was computed for 50% overlapping 360 point long sequence. The HR signal was corrected before the analysis and the signal subsets with insufficient quality were excluded from the parameter estimation procedure, i.e. the signal chunks containing zeros were excluded from the analysis (0 is the value that the HP monitor attributes when the signal is unavailable or the preprocessing procedure judges it unacceptable; it has no physiological meaning). The evaluated index was the mean value of parameters computed on the intervals.

As regards the MSE analysis, we selected from the corrected sequences a 5000 point length subset by removing the first minute of recording. The parameters adopted for the computation of ApEn and SampEn are: m=1 and r=0.1, m=2 and r=0.15 and 0.2 and the scale factors analyzed range from 1 to 15.

According to these selection criteria for both LZC and MSE analysis, the number of subjects was reduced to 14 normal fetuses, 18 severe IUGRs and 19 not severe IUGRs.

III. Results

The *ternary* LZC can significant separate the three groups, in particular by adopting the encoding factor p=0%, 0.5% and 1% (ANOVA test and Kruskall-Wallis test were performed between the three patients groups, then post-hoc comparisons are made by Scheffè test, P-value ANOVA<1% and P-value Scheffè test <5%). Table 1 illustrates the LZC values obtained from the *ternary* coding procedures.

Figure 1 shows instead the percentage variation of the *ternary* and *binary* LZC values for the different encoding procedures, by taking as reference the values obtained for the coding parameter p=0%. The results proves that the parameters p selected in this work produce similar values (the percentage variation is quite zero for p=0.5% and 1%). Moreover the discriminating ability seems to be weakly dependent on the choice of the encoding parameter p.

Furthermore also the MSE analysis provided important results. In particular, the entropy values computed for scale factors τ>3 are able to separate significantly the severe IUGRs from both the not severe IUGRs and the normal fetuses (ANOVA test and Kruskall-Wallis test were performed, then post-hoc comparisons are made by Scheffè test, P-value ANOVA<1% and P-value Scheffè test <5%).
As it is shown in figure 2, the entropy values of severe IUGRs are lower than the other groups values, whereas the entropy values of not severe IUGRs and healthy subjects are very similar, moreover at the first scales factors the last two groups have an increasing trend greater than the severe IUGR one. These results were obtained for all the entropy estimators adopted in this study.

TABLE I
TERNARY LZC VALUES

Values obtained by adopting the encoding parameter p=0%, 0.5%, 1%, 2% The symbol † refers to the indexes which can significantly separate the three groups (P-value ANOVA<1% and P-value Scheffè test <5%).

	LZC(3,0)†	LZC(3,0.005)†	LZC(3,0.01)†	LZC(3,0.02)
Normal	0,886±0,032	0,886±0,032	0,887±0,031	0,889±0,027
sev. IUGR	0,952±0,028	0,952±0,028	0,952±0,027	0,954±0,023
not sev. IUGR	0,915±0,035	0,915±0,035	0,915±0,035	0,921±0,033

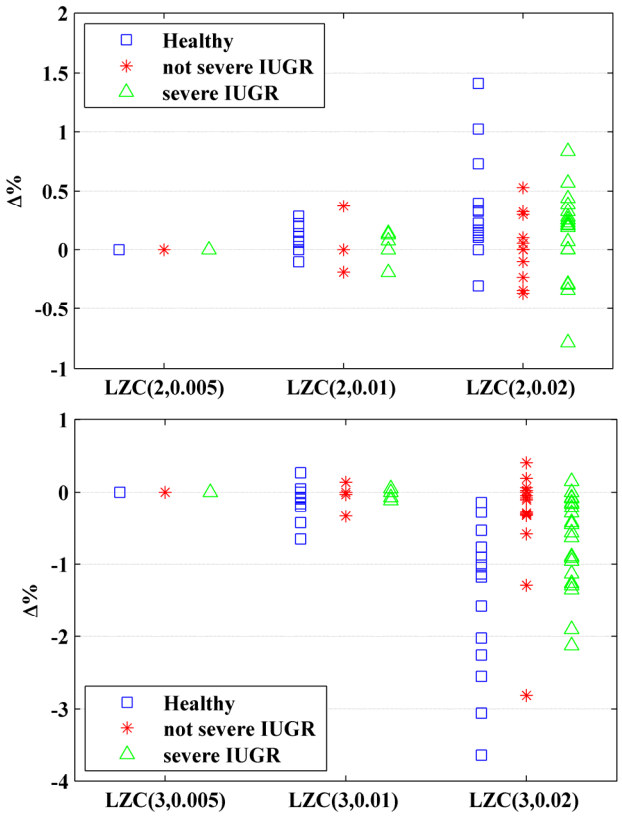

Figure 1: Percentage variation of LZC values obtained from the different encoding parameter p in respect on the coding parameter p=0%. Upper panel refers to *binary* coding, lower panel refers to *ternary* coding.

As previous works can demonstrate [5][6], not only the singular entropy values can be a pathology marker but also the values distribution along the different scale factors. In fact, how the entropy values distribute themselves along τ can provide important hints about the signal *structure* and the involved dynamic system. For this reasons, we decided to estimate a few interpolating lines on MSE and to consider their slopes as new indexes.

The most interesting results were obtained by taking into account both the *ternary* LZC and the slope α_1 assessed from the intercept of scale factors 1 and 2. The *k*-mean cluster analysis applied to these indexes produced the following results: it was able to gather the severe IUGRs and to separate them from both not severe IUGRs and normal fetuses, which were included in the same cluster. The best results were performed by the α_1 slope computed on the multiscale SampEn(2,0.15) and on the multiscale SampEn(2,0.2): the cluster analysis provided a sensitivity of 72.2% and an accuracy of 80.4% in the first case, whereas for the second pair of parameters Se=77.8% and Ac=82.4% (see figure 3). Notice that the same indexes separately analyzed produced a worse performance in term of accuracy: the cluster analysis provided for the *ternary* LZC Se=88.9% Ac=70.6%, for the α_1 slope computed on the multiscale SampEn(2,0.15) and SampEn(2,0.2) Se=61.1% Ac=74.4%. and Se=77.8% Ac=70.6% respectively.

IV. DISCUSSION AND CONCLUSION

The analyses show that the LZC and the MSE could be an efficient tool to identify the actual IUGRs and to separate them from the SGA.

In addition, our study has provided interesting hints about this pathological condition. As table 1 and figure 3 show, the IUGR condition is characterized by a higher complexity values, very close to 1, namely the theoretical value associated to a completely random string. This result suggests that the HR belonging to the severe IUGRs varies quite randomly and it is thus less predictable. Furthermore, the MSE analysis confirms that the entropy estimators computed on single-scale are not able to discriminate the

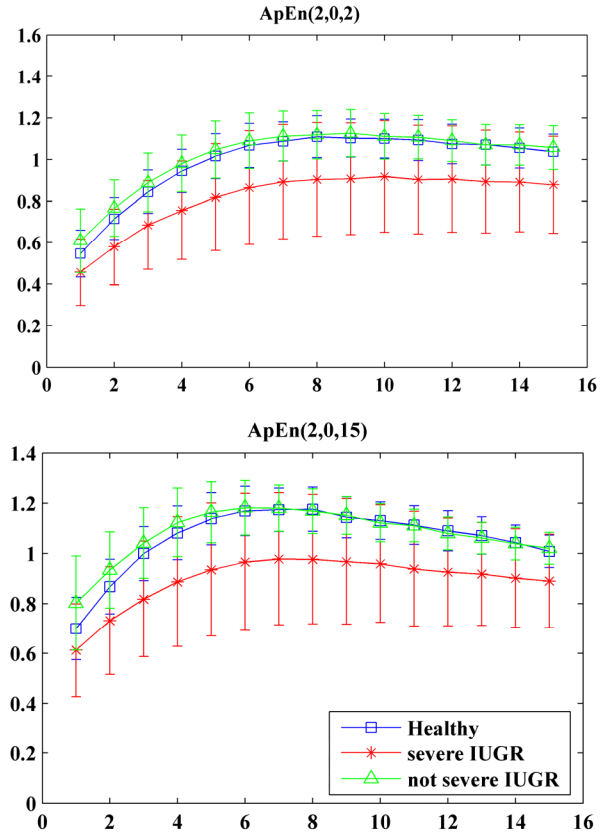

Figure 2: Entropy values of MSE analysis plotted versus the scale factor τ (from 1 up to 15). Upper panel refers to the values obtained by ApEn(2,0.2) and lower panel refers to the values obtained by ApEn(2,0.15).

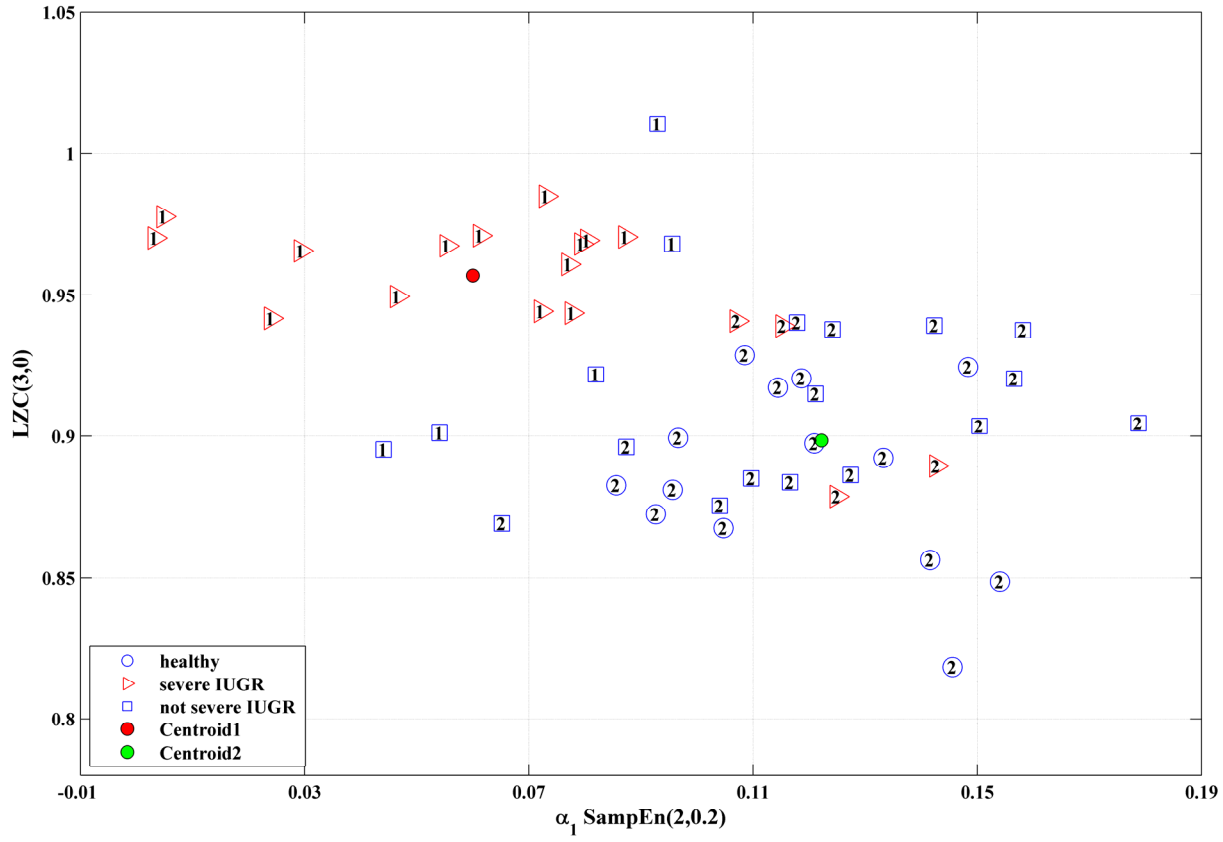

Figure 3: Results from the *k*-mean cluster analysis (the distance measure that *k*-mean minimizes with respect to is the squared Euclidean distance and each centroid is the mean of the points in that cluster). The numbers inside the markers refer to the clusters (1=pathological fetuses, 2=physiological condition). The α_1 slope refers to the multiscale SampEn(2,0.2).

the entropy indexes adopted in this study was able to differentiate the groups. Moreover, as it is previously outlined, the α_1 slope associated to the pathological fetuses is smaller than in healthy condition. We can then suppose that this figure could be a sign of the system alteration. In fact, as it was obtained in previous works [5] [6] different MSE trends can be associated to different dynamical systems and this could indicate a significant difference in the complexity of the dynamical systems generating the signals.

Furthermore these results demonstrate again how the LZC index provides a different information about the system generating the time series [4]. The LZC quantifies the rate of new patterns arising as the signal evolves along the time, whereas the entropy estimators quantify the recurrence of repetitive patterns, i.e. the signal regularity.

ACKNOWLEDGMENT

We gratefully thank Prof. D. Arduini for his support in the data collection process at the Ob-Gyn Clinic, Hospital "Fatebenefratelli", Rome.

REFERENCES

[1] P. Malcus, "Antenatal fetal surveillance", *Current opinion in Obstetrics and Gynaecology*, vol.16, pp123-128, 2004.

[2] A. Baschat, "Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters", *Ultrasound Obst Gyn*, vol. 21, pp.1-8, 2003.

[3] A. Lempel and J. Ziv, "On the complexity of finite sequences", *IEEE Trans. on Inf. Th,* vol. 22, no. 1, pp.75-81, 1976.

[4] M. Ferrario, M.G. Signorini, G. Magenes, "Comparison between fetal heart rate standard parameters and complexity indexes for the identification of severe intra uterine growth restriction", *Methods of Information in Medicine* (accepted, in press), 2006.

[5] M. Costa, A.L. Goldberger, C-K Peng, "Multiscale entropy analysis of biological signals", *Phys Rev E* vol. 71, pp. 021906, 2005.

[6] M. Ferrario, M.G. Signorini, G. Magenes, S. Cerutti, "Comparison of entropy-based regularity estimators: application to the fetal heart rate signal for the identification of fetal distress", *IEEE Trans Biomed Eng*., Vol. 53, no 1: pp. 119-25, 2006.

[7] M.G. Signorini, G. Magenes, S. Cerutti, D. Arduini, "Linear and Nonlinear Parameters for the Analysis of Fetal Heart Rate Signal from Cardiotocographic Recordings", *IEEE Trans Biom Eng*, vol.50(3), pp.365-375, Mar. 2003.

[8] G.W. Lawson, R. Belcher, G. S. Dawes, and C.W. Redman, "A comparison of ultrasound (with autocorrelation) and direct electrocardiogram fetal heart rate detector systems," *Amer. J. Obstet. Gynecol.*, vol. 147, no. 6, pp. 721–722, 1983.

[9] M. Ferrario, M.G. Signorini, S. Cerutti, "Complexity Analysis of 24 Hours Heart Rate Variability Time Series", *Proc. of the EMBC 04 Conference*, IEEE Press.

[10] F. Kaspar and H.G. Schuster, "Easily calculable measure for the complexity of spatiotemporal patterns", *Phys Rev A*, vol. 36, no. 2, pp. 842-848, 1987.

[11] A C-C Yang *et al*., "Linguistic Analysis of the human heartbeat using frequency and rank order statistics", *Phys Rev Letters*, vol.90, no.10, pp. 108103-1—108103-4, 2003.

[12] S.M. Pincus, "Approximate entropy as a measure of system complexity", in *Proc Natl Acad Sci USA*, vol.88, pp. 2297-2301, 1991.

[13] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy", *Am J Physiol Heart Circ Physiol*, vol. 278, pp. H2039-2049, Jun 2000.