Fetal development assessed by heart rate patterns—Time scales of complex autonomic control

Dirk Hoyer a,*, Samuel Nowack a, Stephan Bauer a, Florian Tetschke a, Stefan Ludwig a, Liviu Morarua, Anja Rudoph a, b, Ulrike Wallwitz a, b, Franziska Jaenicke a, b, Jens Haueisen a, c, Ekkehard Schleußner b, Uwe Schneider b

a University Hospital, Biomagnetic Center, Hans Berger Clinic for Neurology, Friedrich Schiller University of Jena, Germany
b University Hospital, Department of Obstetrics, Friedrich Schiller University of Jena, Germany
c Institute of Biomedical Engineering and Informatics, Technical University of Ilmenau, Germany

ABSTRACT

The increasing functional integrity of the organism during fetal maturation is connected with increasing complex internal coordination. We hypothesize that time scales of complexity and dynamics of heart rate patterns reflect the increasing inter-dependencies within the fetal organism during its prenatal development. We investigated multi-scale complexity, time irreversibility and fractal scaling from 73 fetal magnetocardiographic 30 min recordings over the third trimester. We found different scale dependent complexity changes, increasing medium scale time irreversibility, and increasing long scale fractal correlations (all changes p < 0.05). The results confirm the importance of time scales to be considered in fetal heart rate based developmental indices.

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1. Introduction

The increasing functional integrity of the organism during fetal maturation is connected with increasing complex internal coordination. Complexity, time irreversibility, and fractal scaling characteristics reflect different aspects of the growing and maturing complex organism. Their joint analysis over the course of fetal maturation is pending. Various single results based on different populations, recording techniques, and mathematical approaches provided heterogeneous results, that can generally be interpreted as indices of increasing functional integrity.

The objective of the present work is to refer the mostly used mathematical approaches to multi-scale complexity, time irreversibility and fractal scaling, and finally, to show that the dependencies of those characteristics on time scales exceeding one heart beat interval provide important information about the fetal maturation.

Fetal heart rate variability (HRV) amplitudes were consistently considered in fetal heart rate based developmental indices. They are influenced by behavioral states in fetuses and neonates [7,8] and showed time scale dependent complexity that was furthermore influenced by behavioral states in fetuses and neonates [7,8] and by sympatho-vagal adjustment in fetal sheep [9,10]. In adults several cardiovascular disturbances caused an altered adjustment between short term and long term complexity [11–14].

Time irreversibility is a fundamental attribute of nonequilibrium systems that was solely described in fetal heart rate patterns by Porta et al. [15]. The original approach is based on a multi-scale asymmetry (Asym) index that indicates time irreversibility decreasing with coarse graining time scale [16]. Further indices of time-irreversibility consider higher-dimensional embedding and advanced test statistics [15,17,18]. Time irreversibility is clearly developed in healthy adults, but altered due to higher aging or cardiovascular pathology [16].

Fractal scaling exponents characterise self-similar organized processes over wide ranges of time scales. The most popular method of fractal heart rate analysis is detrended fluctuation analysis (DFA). Fractal scaling behavior typically appear in healthy subjects with normal sympatho-vagal balance in daily activity, however it is distorted due to selective predominance of sympathetic or vagal activity [19]. It is furthermore altered in various cardiovascular diseases [20,21] as well as in the elderly [22]. The only fetal DFA was done from maternal doppler recordings using...
an effective sampling rate of 2 ms of the heart beat intervals. The authors report a short-term and a long-term scaling range with a crossover point between around 30 s while both scaling exponents increased with fetal maturation [23]. A confirmation of these results using a higher sampling rate was not performed until now.

In the present work we test the hypotheses that:

- Short scale complexity increases while long scale complexity decreases.
- Time irreversibility increases over particular scales.
- Fractal correlations increase over long term scaling ranges.

during the third trimester of fetal development by analyzing all indices from the same database of 30 min fMCG recordings.

2. Methods

2.1. Subjects

The study database of the Biomagnetic Center/Department of Obstetrics consists of 114 normal fetuses, singletons, healthy according to standard obstetric observation methods, single recording in a non-stress situation that were recruited from the Department of Obstetrics University Hospital, Jena, in 2007–2010. In order to investigate the change over the developmental step around 30–34 weeks gestational age (WGA), we selected all recordings belonging to a younger subgroup 20–29(26.4) WGA around 30–34 weeks gestational age (WGA), and an older subgroup 35–40(36.2) WGA (n=32). This selected database was used in all investigations.

The exclusion criteria were:

(a) Maternal: administration of cardiovascular effective drugs, cardiovascular diseases, diabetes.
(b) Fetal: intrauterine growth restriction, non-reassuring non-stress test based on conventional CTG, known chromosomal abnormalities or congenital abnormalities based on ultrasound diagnosis, fetal arrhythmia, previous exposure to synthetic steroids in utero.

The study was approved by the Local Ethics Committee of the Friedrich Schiller University. All women signed a written, informed consent form.

2.2. Data acquisition

All measurements were taken in a magnetically shielded room at the Biomagnetic Center, Friedrich Schiller University Jena using the vector-magnetograph ARGOS 200 (195 channels, ATB Chieti, Italy).

The pregnant women were positioned supine or with a slight twist to either side to prevent compression of the inferior vena cava by the pregnant uterus. The dewar was positioned above the fetal heart determined by sonographic localization, as close as possible to the maternal abdominal wall, without contact.

The MCG signal was recorded over a period of thirty minutes with a sampling rate of 1024 Hz. The fetal heart beats were automatically detected in those magnetic channels with the highest signal to noise ratio and subsequently confirmed by an expert analyst. In all analyzed data sets, less than 2% of the incorrect detections appeared and were linearly interpolated in order to constitute artefact free data sets of 30 min duration.

Two examples of an early (< 29 WGA) and a later (> 35 WGA) fetal cardio-tachogram are shown in Fig. 1.

2.3. Signal analysis

2.3.1. Resampling

For an adequate assessment of heart rate modulations the heart beat interval series were linearly resampled at 5 Hz constituting equidistant time series. Both, the beat intervals series and the equidistant time series were analyzed, where appropriate.

2.3.2. Multi-scale entropy

Multiscale entropy was introduced by Costa et al. [13,24] and briefly reviewed here. Given a one-dimensional discrete time series \( x_1, x_2, ..., x_j \), first a ‘coarse-graining’ process is applied, constructing a consecutive coarse-grained time series \( y^{(s)} \) by averaging the data points in non-overlapping windows of length \( s \).

Each element \( y^{(s)}_i \) of the coarse-grained time series is calculated by

\[
y^{(s)}_i = \frac{1}{s} \sum_{j=1}^{s} x_{i+1}
\]

where \( s \) represents the scale factor, \( 1 \leq j \leq T/s \). For scale \( s = 1 \), the time series \( y^{(1)} \) is simply the original time series. In the present work coarse-grained time series were calculated up to \( s = 20 \) heart beat intervals and up to \( s = 50 \) samples of the equidistant time series, both leading to a maximum scale of about 10 s.

Entropy estimates of these coarse-grained time series plotted versus the scaling factor \( s \) constitutes the MSE characteristic curves. In the present work entropy was estimated by sample entropy (SampEn) [25] and mutual information (MI) [26].

2.3.2.1. Sample entropy.

SampEn was calculated according to [25] using the Matlab code provided by PhysioNet (http://www.physionet.org/physiotools/sampen/matlab/) with embedding dimension \( m=2 \) and tolerance \( r=0.15 \) standard deviation.

Costa at al. proposed to set \( r \) to 15% of the original time series dataset standard deviation and keep it constant for all resulting coarse-grained time series. In this way SampEn reflect changes of temporal structures independent of the individual time series standard deviation (SD) [24].

In contrast, methods that use ordinal scales of amplitudes (see partitioning in the mutual information Section 2.3.2.2) or amplitude pattern (see permutation entropy Section 2.3.3) cover the individual amplitude range and may lead to different complexity characteristics. In order to compare those methods, SampEn was additionally calculated using \( r \) values obtained from individual time series and coarse-graining levels.
2.3.2.2. Mutual information. Mutual information (MI) was calculated according to [26,28] keeping in mind that the present study deals with the univariate time series, namely \( x(t) = z(t) \). Consider two stationary time series \( \{x(t)\}_{t=1}^{N} \) and \( \{z(t)\}_{t=1}^{N} \), that are characterized by the discrete joint probability distribution \( \{ p_{ij} \}_{i,j} \). The corresponding marginal distributions are \( p_{i} = \sum_{j} p_{ij} \), and \( q_{j} = \sum_{i} p_{ij} \) of the \( x \) and \( z \)-series, respectively. For the discrete probability distribution \( \{ p_{ij} \} \), Shannon’s information measure is defined by \( \text{H}_{z} = -\sum_{p} p_{i} \log_{2} p_{i} \). Similar formulas provide \( \text{H}_{x} \), \( \text{H}_{x,z} \), \( \text{H}_{z,x} \), and \( \text{H}_{x}=\text{H}_{z}+\text{H}_{x,z} \). The mutual information function (MIF) \( \text{MIF}_{x,z}(\tau) \) is defined by \( \sum \log_{2} \frac{P_{i,j}(\tau)}{P_{i}P_{j}} \), where \( P_{i,j}(\tau) \) is the joint probability distribution \( \{ x(\tau), z(\tau) \} \). Thus MI is also a function of \( m \) and the embedding delay \( \tau \). The data sets of about 4000 heart beats (30 min recordings) were resampled data. MI was calculated using the overall fixed coarse grain level according to the MSE investigation and AsymMI were provided. In the present work both, AsymMI over coarse graining levels according to the MSE investigation and AsymMI were provided.

2.3.5. Detrended fluctuation analysis

DFA was calculated according to Peng et al. [20]. Concretely, the interbeat interval series (of total length \( N \)) is integrated, \( y(k) = (1/N) \sum_{k=1}^{N} y(k) \), where \( B(k) \) is the ith interbeat interval and \( B_{ave} \) the average interbeat interval. Next the integrated time series is divided into boxes of equal length \( n \). In each box of length \( n \), the integrated interbeat interval series is detrended by subtracting a least-squares line fit \( y_{n}(k) \) of the data. The root mean square fluctuation of this integrated and detrended time series is calculated by \( F(n) = \left( \frac{1}{N} \sum_{k=1}^{N} (y(k) - y_{n}(k))^{2} \right)^{1/2} \). This computation is repeated over all time scales (box sizes) to provide a relationship between \( F(n) \), the average fluctuation as a function of box size, and the box size \( n \).

2.4. Statistical analysis

The multi-scale functions were plotted as mean \( \pm \) SEM. The groups were compared by \( t \)-test separately for each time scales. Values of \( p < 0.05 \) were considered significant and given in more detail as \( p < 0.05, 0.02, 0.01, … \).

3. Results

The data sets of about 4000 heart beats (30 min recordings) allowed a reliable estimation of all indices over the investigated scales. Since RR interval series and resampled time series provided qualitatively similar results, only those of the RR interval series were documented by figures.

3.1. Multi-scale complexity

All complexity functions indicate that the use of a single time scale would ignore essential characteristics of the heart rate patterns. Complexity generally increased with increasing time scale which reflects the decreasing predictability over longer time. With regard to the fetal development we consistently found increasing complexity at short time scales but method dependent changes at large time scales.

MSE calculated from SampEn using a fixed \( r \) value obtained as mean percentage over all interbeat interval series showed complexity increasing with \( GA \) over all scales (Fig. 2a). The consideration of time scale dependent \( r \) values obtained as mean percentage over the respective coarse grained time series did not change that relationship (Fig. 2b). This result is consistent with the low SD decrease (about 10%) from coarse graining scale 1 up to scale 20.

MSE calculated from SampEn using individually set \( r \) value showed generally higher complexity values in the younger group but lower values in the older group compared to the values obtained using the overall fixed \( r \) value. Furthermore, SampEn of the younger group exceeded the values of the older group at large scales (Fig. 2c and d).

MSE calculated from MI and from SampEn using individual \( r \) values show qualitatively almost similar results (Fig. 3 versus Fig. 2d). The age dependent short term complexity increase was more pronounced in SampEn RR interval data \( p < 0.05 \), resampled data \( p < 0.001 \) than in MI based MSE (RR interval data \( p < 0.05 \), resampled data \( p < 0.05 \)). In contrast, the long term complexity decrease was more pronounced in MI (RR interval data \( p < 0.02 \).
The KLE functions showed the strongest predictability (inverse to complexity) at a scale of 4 heart beat intervals (resampled data \( t = 1.8 \text{s} \)) in the younger fetuses shifted to 3 heart beats (\( t = 1.4 \text{s} \)) in the older fetuses. The fetal age dependent decrease of KLE within scales of 4–12 beat intervals (\( t \approx 2–5 \text{s} \)) was better reflected in the resampled (\( p < 0.001 \)) than in the beat interval (\( p < 0.01 \)) data (Fig. 4). In an additional analysis the simple increase of the embedding time delay \( L \) was replaced by the corresponding coarse graining procedure. The resulting KLE–MSE curves were qualitatively similar, but the age group differences stronger pronounced (\( p < 0.005 \) in both beat interval and resampled data).

Fig. 2. (a–d) Multi-scale entropy (MSE) calculated by sample entropy (SampEn) over coarse graining scales from 1 to 20 heart beat intervals, obtained from beat interval series, mean \( \pm \text{SEM} \). Group differences in predominant short term and long term scale assigned by \( p \)-values. Dependencies on \( r \): (a) \( r \) (group data, scale1)=mean of 15\% SD of all original time series, (b) \( r \) (group data, scale)=mean of 15\% SD of all time series separately for each scale, (c) \( r \) (individual data, scale1)=15\% SD of each individual original time series, (d) \( r \) (individual data, scale)=15\% SD of each individual time series and scale.

Fig. 3. Multi-scale entropy (MSE) calculated by mutual information (MI) over coarse graining scales from 1 to 20 heart beat intervals, obtained from beat interval series, mean \( \pm \text{SEM} \). Group differences in predominant short term and long term scale assigned by \( p \)-values.

Fig. 4. Kullback–Leibler entropy (KLE) calculated by pattern entropy over embedding time delay from 1 to 40 heart beat intervals, obtained from beat interval series, mean \( \pm \text{SEM} \). Group differences in predominant short scale range assigned by \( p \)-value.
3.2. Multi-scale time irreversibility

The positive Asym values indicate time irreversibility over all 20 coarse grain levels with a peak over scales 3–7 and decreasing values in the larger time scales. In the older fetuses Asym is larger than in the younger fetuses in almost all time scales (p < 0.05). This result indicates a time-scale depending level of irreversible dynamics which increases over the fetal developmental period investigated (Fig. 4a). The integrative index increased with fetal age (< 29 WGA AsymInd = 2.12 ± 0.11, > 35 WGA AsymInd = 2.69 ± 0.2, p < 0.002). The resampled data provide a qualitatively almost similar behavior. However, the increase of AsymInd is less pronounced in the resampled data (p < 0.05) (Fig. 5).

3.3. Detrended fluctuation analysis

In the DFA functions a linear short term scaling range up to log(n) = 1.5 changes to a rather bended curve in the long term range where we fitted a line over log(n) = 1.8–2.6 (Fig. 6). In the latter range the fluctuation amplitudes were larger in the older compared to the younger fetuses (p < 0.01). The short scaling exponent of $x_1 < = 1.35 ± 0.02$ in the younger increased to $x_1 > = 1.41 ± 0.02$ (p < 0.01) in the older fetuses. The long scaling exponent of $x_2 < = 0.94 ± 0.03$ in the younger increased to $x_2 > = 1.05 ± 0.02$ (p < 0.05) in the older fetuses.

4. Discussion

The objective of the present work was to investigate whether multi-scale complexity, multi-scale time irreversibility as well as fractal scaling can be reliably estimated from 30 min heart rate recordings in order to comprehensively assess the changes over an essential fetal developmental step in the third trimester. This is the first time that all these aspects were investigated from an identical database with appropriate sampling rate and recording duration. Furthermore, methodological details such as those leading to different complexity estimates were analyzed.

The recommended sampling interval for fetal electrocardiogram (IECG) and magneto cardiology (fMCG) recordings should not exceed 1 ms [30]. Due to the lower technical sampling intervals (usually 4 or 8 ms depending on commercial device), the ultrasound based cardiotocography (CTG) technology, established for prenatal monitoring of dominant heart rate rhythms as well as accelerations and decelerations in connection with intrauterine contraction pressure, is not appropriate for a precise assessment of fast heart rate rhythms such as those of vagal modulations. On the other hand, IECG recordings are not always sufficient for the heart beat detection due to isolation effects of the vernix caseosa leading to a low signal to noise ratio. Therefore, fMCG recordings are still the method of choice for the prenatal HRV assessment. The qualitatively similar MSE result based on CTG [6] can be explained by the coarse graining low pass filter that disregards the fast vagal rhythms.

Recording times longer than 30 min are not tolerable for pregnant women in supine position required in our MCG equipment. The previously analyzed time scales of less than 60 s suggest sufficient statistical confidence if analyzed from recordings of 30 min length. Complexity increased at the scale of one heart beat interval (about 0.5 s) but decreased at very low frequency rhythms (AIF scaling range: 6.25–50 s) in the course of fetal maturation [1]. In adults, important multi-scale characteristics appeared in the scale range of 1–20 heart beat coarse graining levels (up to about 20 s) [13]. Time irreversibility of fetal heart rate pattern was described for the scale of one heart beat interval as well as for a scale according to the first zero of the autocorrelation function, however from data sets of 256 heart beats only [15]. In young healthy subjects time irreversibility was found at scales up to about 20 heart beat intervals (14–20 s). This range was reduced to scales of up to about 10 heart beat intervals in the elderly [16]. Fractal scaling of fetuses is characterized by a crossover point around 30 s [23]. The initially proposed scaling ranges ($x_1 = 4–16$, $x_2 = 16–64$ heart beats) in adults indicate important ranges that also not exceed 1 min [20]. Hence, important changes of complex dynamics in the course of maturation may also appear within scales less than 1 min.

The present results show that recordings of 30 min length are appropriate to analyze scales up to 20 heart beat intervals (about 10 s). Since the measurements were done between 8 a.m. and 6 p.m. a relevant influence of the daytime can be excluded [5].

RR interval data and the equidistantly resampled time series provided qualitatively similar results. In the most MSE cases the resampled data reflected the autonomic modulations better than the beat interval series. This result is consistent with the recommendations for heart rate power spectral analysis [31].
The complexity measures used here are based on metric [13,24] or ordinal [1,7,28] scales of RR interval amplitudes similar to the ones used in adult studies [14]. Consequently, different temporal structures might be considered. MSE-SampEn calculated using the standard fixed r value, increased with GA at all scales. In contrast, MSE-MI increased at small but decreased at large scales with GA. The MI quantile based quantization covers the whole amplitude range leading to similar results obtained in the MSE-SampEn characteristics for individually calculated r values. The generally higher SampEn in the younger group and the lower SampEn in the older group after individual r normalization can be explained by the amplitude range increasing with age [1]. However, the intersection indicates another, scale dependent change of functional structure. Heart rate acceleration patterns of 15–50 s duration are well defined integrative activations that are not yet developed at 29 WGA but almost fully developed after 35 WGA [1].

The permutation entropy is a robust and simple complexity measure for time series analysis in ordinal level. It measures the entropy of sequences of ordinal patterns derived from m-dimensional delay embedding vectors [29]. This statistical advantage of simple signal patterns in short data sets brings high significant group differences (p < 0.01) of the KLE functions. The integrative effect of an additional coarse graining procedure pronounced the group differences (p < 0.005).

Our initial investigation hypothesis based on individual amplitude range normalization of complexity estimates had to be revised and extended according to the global amplitude range normalization recommended in [24].

The increasing positive Asym values confirm increasing multi-scale time irregularity, a fundamental property of nonequilibrium systems, and hence an essential attribute of developing physiological systems. Our results are qualitatively consistent with an analysis of 5 min fetal recordings using Porta’s index [15]. The authors found a significant increase of their irregularity index between a 16–24 WGA group and a 25–32 WGA group, which is preserved on that level in a 33–40 WGA group. In the present work the increase of both, the time scale specific Asym values and the integrative AsymInd (younger fetuses: AsymInd=0.21 ± 0.11, older fetuses AsymInd=0.26 ± 0.2) may indicate a fetal developmental step towards the situation of fully matured healthy adults with AsymInd=0.868 ± 3.42 observed however from 24 h recordings [16].

DFA demonstrated fetal age dependent increase of fractal long range correlations. While our short term scaling exponents increased approaching fractal noise (γ = 1.5), the long term scale snowballing exponent increased approaching 1/2 fractal noise (γ = 1.0). Our results from DFA of 30 min recordings are consistent with those from up to 114 min recordings reported elsewhere [23]. The results may indicate a fetal developmental step towards the fully matured healthy adults with γ1=1.5 and γ2=1, obtained however from slightly different scaling ranges and from 24 h recordings [20].

The purpose of this study was a comprehensive assessment of fetal maturation during the third trimester. We found increasing complexity at short scales and both increasing and decreasing complexity at longer scales, depending on the amplitude ranges considered in the analysis. Time irreversibility increases over all scales. DFA indicates increasing long term fractal correlations. These comprehensive results are hallmarks for a growing complex system with increasing functional adjustments over increasing scales such as the human organism during the fetal period.

5. Summary

In the fetal developmental period around 29–35 WGA, essential changes in favor of functionally integrated behavior mediated by the autonomic nervous system and reflected in heart rate pattern take place. This involves essential inter-dependencies over time horizons of more than one heart beat interval. Multi-scale complexity, time irreversibility and fractal scaling address different aspects of complex system behavior. Entropy and asymmetry characteristics of coarse grain scales up to 20 heart beats and fractal scaling exponents up to 400 beats calculated from 30 min recordings may provide new insights into the identification of developmental disorders in prenatal diagnosis.

Conflict of interest statement
None declared.

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