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# Multi-Scale Characteristics of Resampled Fetal Heart Rate Pattern provide novel Fetal Developmental Indices

Dirk Hoyer, Samuel Nowack, Uwe Schneider

*Abstract*—**The increasing functional integrity of the organism during fetal maturation is connected with increasing complex internal coordination mediated by the autonomic nervous system. We hypothesize that time scales of complex and dynamic inter-dependencies over more than one heart beat interval reflect the increasing complex adjustments within the fetal organism during its prenatal development. We investigated multi-scale complexity and time irreversibility from equidistantly resampled heart rate time series of 73 fetal magnetocardiographic recordings over the third trimester. We found scale dependent changes in complexity and time irreversibility. The functions obtained from equidistantly resampled heart rate time series showed qualitatively similar curves compared to those obtained from heart beat intervals series previously reported. Time scales of fetal heart rate characteristics may provide novel information for the identification of developmental disorders in prenatal diagnosis.**

## I. Introduction

THE increasing functional integrity of the organism during fetal maturation is connected with increasing complex internal coordination. Complexity and time irreversibility characteristics reflect different behavioral aspects of the growing and maturating 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. So far, multi-scale indices were estimated from heart beat interval series [1], but their analysis from equidistantly resampled time series like proposed for power spectral analysis [2] is pending.

It is objective of the present work to apply the mostly used mathematical approaches to multi-scale complexity and time irreversibility to equidistantly resampled heart rate time series and finally to show that the time scales dependencies provide important information about the fetal maturation.

Fetal heart rate variability (HRV) amplitudes were consistently reported as increasing with gestational age (GA) [3-6]. However, there is no consensus whether complexity is increasing or decreasing [3-5]. High complexity indicates a highly dimensional system itself or the effect of not-predictable influences. The time scales of autonomic information flow (AIF) functions indicate increasing short term complexity associated with decreasing long term complexity during fetal maturation [3]. Multi-scale entropy (MSE) of fetal heart rate traces showed complexity increasing with time scale in normal fetuses, that was reduced over a wide range of scales in growth restricted fetuses [7].

Time irreversibility is a fundamental attribute of non-equilibrium systems that was solely described in fetal heart rate patterns by Porta et al. [8]. The original approach is based on a multi-scale asymmetry (Asym) index that indicates time irreversibility decreasing with coarse graining time scale [9]. Further indices of time-irreversibility consider higher-dimensional embedding and advanced test statistics [8, 10, 11]. Time irreversibility is clearly developed in healthy adults, but altered due to higher aging or cardiovascular pathology [9].

In previous work fetal recordings of 30 min duration, that are comfortable for prenatal diagnosis of pregnant women, allowed a statistically sufficient multi-scale analysis of coarse graining scales up to 20 beat intervals (about 10 s) [12]. A corresponding analysis of equidistantly resample data is presented here.

## II. Methods

### A. 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 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 (range(mean), n=41) and an older subgroup 35-40(36.2) WGA (n=32). This selected data base was used in all investigations.

### B. Data Acquisition

All measurements were taken in a magnetically shielded room at the Biomagnetic Center using the vector-magnetograph ARGOS 200 (ATB Chieti, Italy) and a signal preprocessing toolbox (BMDSys, Jena). The pregnant women were positioned supine or with a slight twist to

D. Hoyer and S. Nowack are with the Biomagnetic Center, Hans Berger Department for Neurology, University Hospital, Friedrich Schiller University, Jena, Germany (corresponding author, e-mail: dirk.hoyer@biomag.uni-jena.de). U. Schneider is with the Department of Obstetrics, University Hospital, Friedrich Schiller University, Jena, Germany. DH, SN and US were supported by the German Research Foundation (HO 1634 12-2, Schn 775/2-3).

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 localisation, as close as possible to the maternal abdominal wall, without contact.

The MCG signal was recorded over a period of 30 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 analysed data sets, less than 2% of the incorrect detections appeared and were linearly interpolated in order to constitute artifact free data sets of 30 min duration.

For an adequate assessment of heart rate modulations the heart beat interval series were linearly resampled at 5 Hz constituting equidistant time series. The 200 ms resampling period is appropriate to the 350-550 ms beat interval range of the analysed data.

### C. Multi Scale Entropy

**Multiscale** entropy was introduced by [13] and briefly reviewed here. Given a one-dimensional discrete time series $\{x_1, x_2, ..., x_T\}$, 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 $y_j^{(s)}$ of the coarse-grained time series is calculated by $y_j^{(s)} = \frac{1}{s} \sum_{i=(j-1)s+1}^{js} x_i$, where s represents the scale factor, $1 \le j \le T/s$. 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=50 samples of the equidistant time series, leading to a maximum scale of 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) [14] and mutual information (MI) [15].

**SampEn** was calculated according to [14] 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 deviations (SD) of the resampled data of the entire data set that includes all recordings. A reference analysis using m=3 provided qualitatively consistent results in or data (not presented).

Costa at al. proposed to set r to 15% of the original time series data set SD and keep it constant for all resulting coarse-grained time series. In that way SampEn reflects a similar range of temporal structures independent of the individual time series SD [13]. In the present data this globally normalized range was r=3.67 ms.

In contrast, methods that use ordinal scales of amplitudes (see partitioning in the mutual information section) cover the whole individual amplitude range. In connection with the increasing amplitude of fluctuations during the maturation, individual r ranges (0.15 SD of individual data sets) may better reflect the individually predominant heart rate patterns. In order to compare those methods SampEn was additionally calculated using r values obtained from individual time series and/or coarse-gaining levels.

**Mutual information** (MI) was calculated according to [15] keeping in mind that the present study deals with the univariate time series, namely x(t)=z(t). Consider two stationary time series $\{x(t)\}_{t=1}^{T}$ and $\{z(t)\}_{t=1}^{T}$, that are characterized by the discrete joint probability distribution $\{s_{ij}\}_{i,j=1}^{K}$, where $s_{ij}$ represents the probability for the event $x(n) = x_i$ and $z(n) = z_j$. The corresponding marginal distributions are $p_i = \sum_j s_{ij}$ and $q_j = \sum_i s_{ij}$ of the x– and z–series, respectively. For the discrete probability distribution $\{p_i\}$, Shannons information measure is defined by $H_x = -\sum_i p_i \log_2 p_i$. Similar formulas provide $H_z$ and $H_{xz}$. Then, MI of the series is given by $MI_{xz} = H_x + H_z - H_{xz} = \sum_{ij} s_{ij} \log_2 \frac{s_{ij}}{p_i q_j}$. It measures the average information in x(t) on z(t) in units of "bit" as we take log with base 2.

We replace $z(t)$ by a m=2 dimensional delay embedding vector $(x(t-\tau), x(t))$. This leads to the mutual information function (MIF) $MIF_{xz}(\tau)$ like previously reported [16]. The amplitude range of the signal was partitioned with r=1/8 (3 bit) using as partitioning points $(i \times r)$ -quantiles.

### D. Time Irreversibility

Time irreversibility was assessed based on asymmetry of the empirical distributions (energy) of heart rate changes as a function of coarse grain level $\tau$ according to [9] and briefly reviews and adapted as follows. We map the original heart rate time series (inverse of beat interval sequence) $X = \{x_i\}$, $1 \le i \le N$, to a sequence of heart rate increases and decreases $Y = \{y_i\}$, $1 \le i \le N-1$, where $y_i = x_{i+1} - x_i$ and N is the number of data points. A multi-scale asymmetry index was estimated by

$$Asym(\tau) = \frac{\sum_{y_\tau > 0} \Pr(y_\tau) \ln(\Pr(y_\tau))}{\sum_{y_\tau} \Pr(y_\tau) \ln(\Pr(y_\tau))} - \frac{\sum_{y_\tau < 0} \Pr(y_\tau) \ln(\Pr(y_\tau))}{\sum_{y_\tau} \Pr(y_\tau) \ln(\Pr(y_\tau))},$$

where $\Pr(y_\tau)$ denotes the probability of the value $y_\tau$. If $Asym(\tau) \neq 0$, then for scale $\tau$ the time series is

irreversible. If $Asym(\tau)=0$, the time series may or may not be irreversible for scale $\tau$.

### E. Statistical analysis

The multi-scale functions were plotted as mean ± SEM. The comparison of the younger to older group was done by t-test separately for each time scale.

## III. Results

The data sets of 30 min recordings (about 4000 heart beat intervals) allowed a reliable estimation of all indices over the investigated scales.

### A. Multi Scale Complexity

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 original time series showed complexity increasing with GA over all scales (Fig.1).

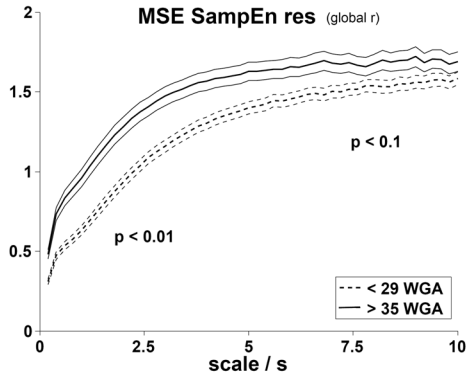


Fig. 1. Multi-scale Entropy (MSE) calculated by sample entropy (SampEn) over coarse graining scales from 1 to 10 s, mean±SEM. Group differences in predominant short term and long term scale assigned by p-values. r globally normalized (r=3.67 ms)

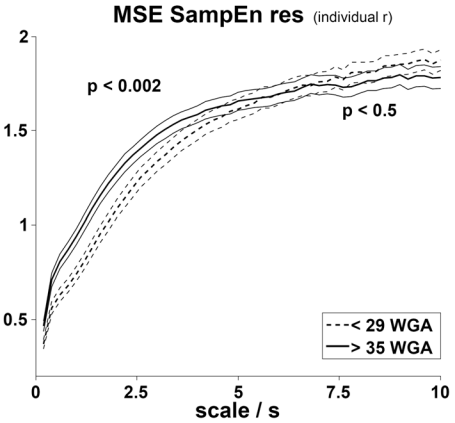


Fig. 2. MSE-SampEn like Fig. 1, r individually normalized (r=0.15 SD of individual data sets)

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. 2).

MSE calculated from MI (Fig. 3) showed qualitatively similar results like SampEn using individual r values. The gestational age dependent short scale complexity increase was stronger pronounced in SampEn, but the long scale complexity decrease was stronger pronounced in MI.

It should be noticed that a globally fixed r is recommended for SampEn estimation to compare similar functional structures independent of the signal amplitude. But ordinal scales, such as used in the present MI estimation, disregard the metric amplitude values and can consequently cover different signal structures both in individual and in not used global settings.

### B. Multi Scale Time Irreversibility

The positive Asym values indicate time irreversibility over all coarse grain levels with a peak around scales 2-7s and decreasing values in the larger time scales. This result may reflect clearly directed dynamics of cardiovascular control loops that are mediated by the autonomic nervous system and the overall systemic regulation. The decreasing

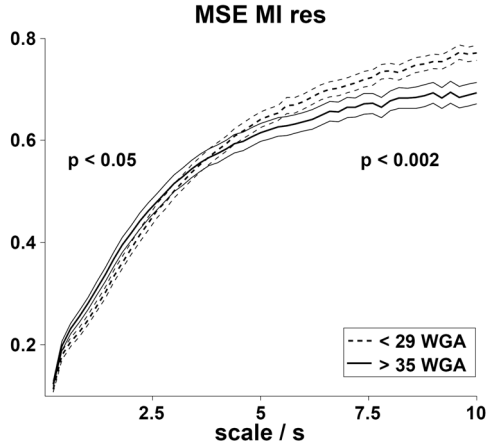


Fig. 3. MSE-MI like Fig. 2, individually normalized due to partitioning in the MI calculation algorithm

Asym with furthermore increasing scale is natural. The decreasing Asym with shorter time scale indicates a weaker consideration of cardiogenic and direct autonomic feedback.

In the older fetuses Asym is larger than in the younger fetuses in almost all time scales ($p<0.2$). After 10 s Asym seems to disappear in particular in the younger group. This result indicates a time scale depending level of irreversible dynamics which increases over the fetal developmental period investigated (Fig. 4).

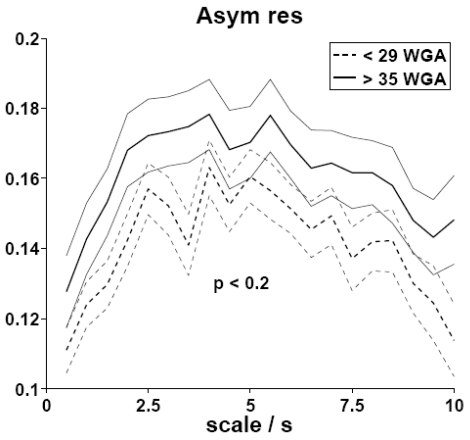


Fig. 4. Asymmetry (Asym) over coarse graining scales from 0.5 to 10 s, mean ±SEM. Average group difference over all scales assigned by p-value.

## IV. Discussion

Complex adjustments of cardiovascular control mediated by the autonomic nervous system arise during the third trimester of fetal development. They are reflected in fetal heart rate patterns which constitute essential information in prenatal functional diagnosis. From physiological and system theoretic point of view, time scales of complex processes play an important role in the complex regulation.

In the present paper different approaches to multi-scale specific heart rate characteristics are evaluated to assess complexity and time irreversibility as hallmarks of the developing fetal complex autonomic control. We investigated changes of these characteristics over the important developmental phase around 32 weeks gestational age between younger (< 29 WGA) and older (>35 WGA) fetuses from data sets of 30 min magnetocardiographic recordings. Results, previously obtained from heart beat interval series [12] were here confirmed from equidistantly resampled heart rate time series.

Complexity measures depend on the estimation parameters such as the range r. The resulting differences were demonstrated leading to opposite age dependencies with fetal maturation in the larger time scales. Those dependencies on signal amplitudes should carefully be taken into consideration concerning selection and comparison of methods. Increasing complexity as a sign of a growing and internally interconnecting system, but also decreasing complexity as a sign of functional integration and adjustments in the organism addresses a relevant aspects of fetal functional maturation [3,12].

Asym provided positive values over all time scales. In the older fetuses Asym is larger in almost all time scales indicating the development of time irreversible behavior. The strongest Asym values in coarse graining scales 2-7 indicate pronounced time irregularity in the complex cardiovascular-autonomic control system like previously shown in respective beat interval data [12].

In conclusion, for heart rate power spectral analysis equidistant resampling is recommended for an appropriate consideration of the cardiovascular-autonomic rhythms. The here investigated complexity and asymmetry functions from resampled data are qualitatively consistent with those of beat interval data from the identical data base [12]. The multi-scale characteristics provide information over complex inter-dependencies reflecting the developing functional integrity that cannot be found from a selected single scale. We were able to explore significant changes over the important fetal developmental period between 29 and 35 WGA.

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