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A nonlinear parameterization of multivariate electrohysterographical signals

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ABSTRACT

Electrohysterography is a technique which measures a bioelectrical activity of a uterus. This paper presents an application of a nonlinear parameterization of multivariate electrohysterographical signals for a uterine activity assessment to improve unsatisfactory a labor prediction accuracy by methods published in the literature. A multivariate sample entropy used for differentiated 4-channel electrohysterographical signals, general Spearman's correlation and a combined index being the sum of them, were tested. These nonlinear measures use joint information contained in a multivariate signal. The results confirm that the combined index provides the best assessment of uterine contractions: 87% sensitivity and 50% specificity of labor prediction in the studied data. These results should be verified in a prospective study.

1. Introduction

Monitoring of uterine contractions and fetal heart rate during the 3rd trimmest of pregnancy are crucial obstetrical procedures. From a clinical point of view, the identification of uterine contractions as well as changes in the cervix is very important because they indicate an approaching labor. The monitoring can also be useful to assess the risk of a preterm labor. Preterm labors usually imply neonatal complications that may lead to physical and mental disabilities such as infantile cerebral palsy [1]. Belated labor termination can cause fetal ischemia and related complications [2]. Thus, since preterm and belated labors generate high costs associated with neonatal intensive care and further medical and social rehabilitation, the monitoring of signals to determine uterine contractions during pregnancy could offer a better way to predict and handle the delivery.

Anatomical localization of the uterus strongly limits the capacity of methods measuring uterine contractions. Routinely, the contractions are monitored by tocography, *i.e.* a dynamometer measuring mechanical pressure in contracting uterine walls. However, this approach has disadvantages. First, tocography can only monitor uterine contractions locally, and does not allow tracking contractions through myometrium. Second, the correlation between mechanical pressure measured by this technique and intrauterine pressure with fetus moving through the cervix and vagina is low [3]. Third, tocography is ineffective for obese women because fatty tissue forcibly damps the mechanical pressure and thus the sensitivity of this method is significantly decreased [4]. To address these drawbacks, an alternative method called *electrohysterography* (EHG) has recently been proposed. It measures bioelectrical activities of the myometrium which precede its mechanical contractions. However, bioelectrical activities of the myometrium are not characterized by any constant pattern. Unlike ECG signals which predominantly contain periodical patterns, the EHG signals are rather similar to EMG or EEG signals which seem to be patterned poorly. For these reasons, it is difficult to find a parameterization of EHG signals that would highly correlate with the physiological state of the uterus. To address this issue linear parameterization methods, spectral analyses, and nonlinear methods have been proposed [5,6]. Methods relying on nonlinear analyses of uterine EHG signals seem to be most promising. Results obtained by Hassan et al. that support a hypothesis that EHG signals have nonlinear characteristics [7], and have been coherence studies on the multiscale model of a uterine electrical activity developed by Laforet et al. [8]. This model contains nonlinear differential equations which describe changes in biopotentials measured by electrodes in EHG devices.

Among different methods for nonlinear signal analyzes the *approximate entropy* (AppEn) as well as its unbiased version called *sample entropy* (SamEn) are frequently used for biological signal analysis. They are particularly useful in case a regularity of the analyzed signal needs to be associated with the clinical state of a patient [9]. The results obtained by Moslem et al. confirmed that

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AppEn and SamEn computed for EHG signals can predict contractile activities of the uterus. However, the predictions were determined basing on the values calculated for the singular and *a priori* selected EHG signals only [10]. Several other studies suggested that the use of a multichannel technique to monitor bioelectrical activity of the uterus could be more valuable. It would help reconstruct the spatial distribution of uterine biopotentials and visualize the propagation of bioelectrical waves during uterine contractions [11].

However, the literature on this subject is still scarce. In [7] a nonlinear correlation was proposed to analyze multivariate EHG signals from several channels by means of joint information contained in the EHG vector.

Here, a new approach is proposed to address the deficiency of analytical tools for studying uterine activities by means of multichannel monitoring techniques. The goal of this work was to investigate the prediction accuracy based on two parameterization methods: a *multivariate sample entropy* computed for a four elements vector of differentiated EHG signals, and a *generalized Spearman's correlation coefficient* between all components of EHG signals. A new index being a combination of the multivariate sample entropy and a general Spearman's correlation coefficient was also introduced and tested as a predictive variable of uterus contractions using real signals acquired from female subjects.

2. Materials and methods

2.1. Multichannel measuring system for EHG signals

A lack of EHG measuring standard causes that large variety of electrodes number and their localization on an abdominal skin which has been observed in the performed studies so far. The minimal number of the used measured channels was 2 and the maximal number was 16 channels arranged as a 4×4 matrix [12].

A four-channel system specifically designed for EHG signal acquisition [13] was used to collect data for this study. Localization of bipolar electrodes on an abdominal skin was concordant with the methodology presented by Euliano et al. in [3], *i.e.* the *up* channel was placed over the uterine fundus, the *right* and the *left* channels were localized over adequate sides of a uterus and the *down* channel was put over a uterine cervix. The reference electrode was affixed to subject's right hip. The pass band of the measuring system was 0.01–3 Hz, and the sampling frequency was 20 Hz. The system was equipped with self-tuning amplifier gains allowing for an optimal use of A/D conversion range [13].

2.2. Case and control subjects

Activities of uterine myometrium evidenced by Garfield and Maner in [14] suggest that even a few months before a labor an increasing number of gap junctions and ion channel changes in uterine muscle cells can be observed. Thus, there is a chance that very low but possibly detectable bioelectrical activity of myometrial fibers some EHG signals can be recorded on the skin surface long before an expected labor. The results from Garfield and Maner's study were taken into consideration to design the control group better. The case group contained 15 primigravidas being in 2nd period of a unifetal labor. The first control group contained 15 primigravidas being in their 3rd trimmester of the pregnancy yet not experiencing any uterine contractions, and the second control group contained 14 unpregnant women being in a folicular phase of a menstrual cycle. Both control groups were established to ensure the lowest or no contractile activities of their uteruses. No woman belonging to the control group had a pathology in her uterine cavity. To our best knowledge no studies utilizing two separate control cohorts for evaluation of bioelectrical activities in the uterus have so far been utilized to emphasize the nature of bioelectrical diversity in pregnant and unpregnant women. One 4-channel EHG signal lasting 15 min was recorded with each patient.

2.3. Nonlinearity assessment of EHG signals

The evidence exists in the literature that EHG signals could possess nonlinear characteristics. Results obtained by Hassan et al. [6] showed that nonlinear methods lead to a better labor prediction comparing to linear ones. Similar conclusion was drawn by Terrien et al. [15] who used surrogate data for a surrogate corrected nonlinear correlation coefficient H^2_{cx} as a test statistics. However, neither [6] nor [15] have explicitly shown a testing of a hypothesis on the nonlinearity of EHG dynamics. Moreover, the H^2_{cx} statistics can only measure nonlinearity of mutual association between signals rather than the dynamics of a univariate signal. Thus, we implemented the same methodology using an asymptotically unbiased estimate of the third-order moment of the univariate EHG signal following by Barnet and Wolfff [16]. It seems that this statistics suits better for the evaluation of the time-dependent dynamic of EHG signal rather than H^2_{cx} is, because the third-order moment of the univariate EHG signal contains interactions between time-shifted signal samples. The results of this experiment are shown below.

2.4. Multivariate sample entropy of differentiated EHG signals

Multivariate sample entropy is a generalization of sample entropy for multivariate time series introduced by Ahmed and Mandic in [17]. The main advantage of this generalization is the implementation of joint information embedded in a multivariate vector of an analyzed signal. To the best of our knowledge the majority of published works concerning nonlinear parametrization of EHG use raw (unprocessed) signals. However, our previous results [18] showed that the multivariate sample entropy computed for differentiated EHG signals had a higher labor prediction in comparison to findings obtained from raw EHG signals that were inferior. Thus, using this premise we have reasons to assume that the multivariate sample entropy becomes more sensitive to the dynamic of registered biopotentials in contrast to their instantaneous values that may be less sensitive [18].

Let us introduce a four element vector of the differentiated signals $\mathbf{X}(t) = \begin{bmatrix} x_1(t) & x_2(t) & x_3(t) & x_4(t) \end{bmatrix}$, where $x_1 = e\dot{h}g_{up}, x_2 = e\dot{h}g_{left}, x_3 = e\dot{h}g_{right}, x_4 = e\dot{h}g_{down}$ denote respective components of a differentiated EHG signal after a standardization. The multivariate time series $\mathbf{X}(t)$ has a length equaled to T.

According to classical nonlinear methods the composite delay vector must be created in the following form:

$$\mathbf{X}_m(t) = \begin{bmatrix} x_1(t) & x_1(t+\tau_1) & \cdots & x_1(t+(m_1-1)\tau_1) & \cdots \\ \cdots & x_2(t+\tau_2) & \cdots & x_2(t+(m_2-1)\tau_2) & \cdots \\ \cdots & x_3(t+\tau_3) & \cdots & x_3(t+(m_3-1)\tau_3) & \cdots \\ \cdots & x_4(t+\tau_4) & \cdots & x_4(t+(m_4-1)\tau_4) & \cdots \end{bmatrix} \quad (1)$$

$\mathbf{M} = \begin{bmatrix} m_1 & m_2 & m_3 & m_4 \end{bmatrix}$ is the respective embedding vector and $\tau = \begin{bmatrix} \tau_1 & \tau_2 & \tau_3 & \tau_4 \end{bmatrix}$ is the time delay vector. The lower index of $\mathbf{X}_m$ is $m = \sum_{i=1}^{4} m_i$.

Analogously to the sample entropy the multivariate sample entropy was estimated using the following procedure:

1. Create $T-n$ composite delay vectors $\mathbf{X}_m(i) \in \mathbb{R}^m$, where $i = 1, 2, \ldots T-n$ and $n = \max\{\mathbf{M}\}\max\{\boldsymbol{\tau}\}$
   Compute the distance between any two composite delay vectors