Dispersion Entropy: A Measure of Electrohysterographic Complexity for Preterm Labor Discrimination

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Abstract: Although preterm labor is a major cause of neonatal death and often leaves health sequels in the survivors, there are no accurate and reliable clinical tools for preterm labor prediction. The Electrohysterogram (EHG) has arisen as a promising alternative that provides relevant information on uterine activity that could be useful in predicting preterm labor. In this work, we optimized and assessed the performance of the Dispersion Entropy (DispEn) metric and compared it to conventional Sample Entropy (SampEn) in EHG recordings to discriminate term from preterm deliveries. For this, we used the two public databases TPEHG and TPEHGT DS of EHG recordings collected from women during regular checkups. The 10^{th}, 50^{th} and 90^{th} percentiles of entropy metrics were computed on whole (WBW) and fast wave high (FWH) EHG bandwidths, sweeping the DispEn and SampEn internal parameters to optimize term/preterm discrimination. The results revealed that for both the FWH and WBW bandwidths the best separability was reached when computing the 10^{th} percentile, achieving a *p*-value (0.00007) for DispEn in FWH, $c = 7$ and $m = 2$, associated with lower complexity preterm deliveries, indicating that DispEn is a promising parameter for preterm labor prediction.

1 INTRODUCTION

A preterm birth (PB) is a high-risk situation and has a prevalence of up to 10% of all labor cases, affecting more than 15 million families worldwide (Fuchs et al., 2004). The consequences of PB affect maternal-fetal health and is the main cause of mortality in children under 5 years of age (Leung, 2004). It also has a high economic cost for national healthcare systems (Petrou et al., 2019). There are now several techniques available for preterm birth detection, mainly the measure of cervical length (O'Hara et al., 2013) and biochemical markers (Leung, 2004). However, while these techniques provide a highly negative predictive value, their positive predictive values are quite low and do not identify preterm deliveries (Berghella et al., 2008; Diaz-Martinez et al., 2020).

Intrauterine pressure catheter IUPC and tocodynamometry TOCO are the classical methods of measuring uterine dynamics. However, the former is an invasive method and involves risks, while the latter, although non-invasive, is neither very sensitive or precise (Euliano et al., 2016). The aim of the electrohysterographic technique is to deal with these limitations. The electrohysterogram (EHG) is the bioelectric signal recording of the muscular activity of the myometrium. The generation and propagation of action potentials through a suitable number of myometrial cells induce uterine muscle contractions and raise the internal uterine pressure. EHG can provide essential information on uterine activity (Devedeux et al., 1993). EHG energy is distributed between 0.1 and 4Hz and is composed of two waves. The slow wave (SW) has a period equal to the duration of contraction and as its bandwidth overlaps

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the baseline wander it is difficult to analyze and extract reliable information from it. The fast wave (FW) is superimposed on the slow wave signal and can be divided into two parts according to the frequency in which it is presented: *fast wave low* (FWL), whose frequency peak is between 0.13 and 0.26 Hz and is supposed to be associated with contraction propagation and *fast wave high* (FWH), whose frequency peak is between 0.26 and 0.88 Hz and is related to uterine cell excitability (Devedeux et al., 1993; Terrien et al., 2007)

Previous studies have shown that EHG signals include relevant information on the state of the uterine electrophysiology and are better able to detect real preterm cases (Devedeux et al., 1993). It has been shown that as labor approaches synchronization, amplitude and predictability increase, complexity is reduced and there is a shift of frequency content to high frequencies (Devedeux et al., 1993; Garfield & Maner, 2007). The literature proposes different non-linear parameters, such as entropy metrics, to characterize EHG. These latter reduce their values when regularity increases (Mischi et al., 2018).

Sample entropy (SampEn) (Richman and Moorman, 2000) is a widely used metric to discriminate preterm from term (Garcia-Casado et al., 2018). Studies in the literature suggest that SampEn performs best in discriminating term vs preterm deliveries in EHG recordings among the non-linear parameters tested (maximal Lyapunov exponent and correlation dimension) and even outperformed spectral parameters such as median frequency (Fele-Žorž et al., 2008; Rostaghi and Azami, 2016). In addition, SampEn have been used to analyze the feasibility of using EHG to discriminate women with threatened preterm labor who gave birth in less than 7 days from those who delivered in more than 7 days (Mas-Cabo, Prats-Boluda, Perales, et al., 2019).

Rostaghi & Azami (2016) proposed Dispersion entropy (DispEn) to deal with the limitations of SampEn, which is sensitive to changes in simultaneous frequency and amplitude. DispEn is a computationally efficient measure of the regularity of time series and outperforms entropy metrics for characterizing other biomedical signals (Rostaghi and Azami, 2016). The performance of DispEn has been explored in different biomedical signals, but in EHG not yet. Azami et al analyzed magnetoencephalogram MEG signals to discriminate Alzheimer's disease patients from an elderly control group. When SampEn, permutation entropy (PermEn) (Bandt & Pompe, 2002), fuzzy entropy (de Luca & Termini, 1993) and DispEn were computed for MEG signals, DispEn presented the highest separability between the groups than other entropy metrics(Azami, Rostaghi, et al., 2016). Kafantaris et al used DispEn to characterize electrocardiogram ECG signals with different types of heartbeat (normal-healthy hearbeats, atrial premature beats and premature ventricular contractions) and concluded that the algorithm is capable of producing significantly different DispEn distributions between the different groups of heartbeats (Kafantaris et al., 2019). Rostaghi & Azami studied electroencephalographic signals with DispEn to test their ability for discriminating focal and non-focal EEG signals and found that DispEn had better separability than SampEn and PermEn (Rostaghi and Azami, 2016). All these case studies suggest that DispEn is a good estimator of signal regularity and improves the separability of the groups under study.

In the present work, we attempted to optimize, assess and compare DispEn performance with SampEn to discriminate EHG recordings between term and preterm deliveries during routine checkups, when computed in the fast wave high and in the whole EHG bandwidth.

2 MATERIALS AND METHODS

2.1 EHG Data Bases

Two public EHG data bases available in Physionet were used for the case study, the "Term-Preterm EHG Database" (TPEHG) (Fele-Žorž et al., 2008) and the "The Term-Preterm EHG Dataset with tocogram" (TPEHGT DS) (Jager et al., 2018) Both have been widely used in comparative studies on term and preterm cases and were obtained by the Department of Obstetrics and Gynecology at the Ljubljana University Medical Center.

A total of 326 EHG signals with 275 term labor cases (labor > 37 weeks) and 51 preterm labor cases (labor < 37 weeks) were recorded during routine checkups of pregnant women between 22 and 37 weeks of gestation. No induced labor cases or caesarean deliveries were included.

Thirty-minute EHG signal were recorded in both databases with the same protocol, consisting of four disposable electrodes on the woman's abdomen at an interelectrode distance of 7cm (Fele-Žorž et al., 2008). Three bipolar channels, S1, S2 and S3, were obtained after removing the monopolar EHG recordings, as shown in Figure 1. Previous studies pointed out that EHG features from S3 outperform S1 and S2 channels in distinguishing term and preterm deliveries (Fele-Žorž et al., 2008; Mas-Cabo, Prats-

Boluda, Garcia-Casado, et al., 2019). Therefore, only channel S3 was analyzed in the present study. The bipolar signals were digitized at 20 samples per second, with a resolution of 16 bits and over a range of ±2.5 millivolts (Fele-Žorž et al., 2008).

2.2 EHG Signal Characterization

The EHG recordings were filtered in the range 0.1 to 4 Hz by a zero-phase shift 5th order Butterworth bandpass, since this bandwidth comprises the main content of EHG signals.

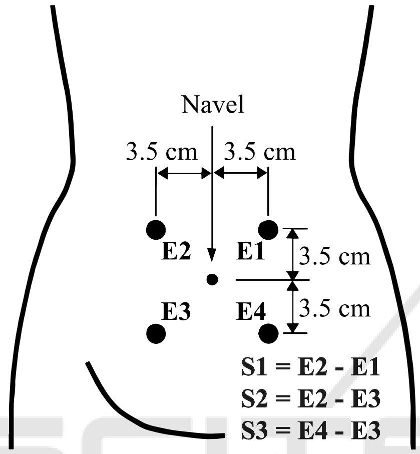

Figure 1: Recording protocol of EHG signals. Modified from (Jager et al., 2018).

Segments with motion artifacts were visually identified by experts and discarded from the study. The criteria adopted to discard EHG sections were: non-physiological events with a significant abrupt increase in amplitude compared to basal activity, and respiratory interference associated with the appearance of periodic components with frequencies in the band of 12 and 24cpm (0.2–0.4Hz). 220 term and 40 preterm EHG recordings were analyzed.

SampEn and DispEn parameters were computed in 120s EHG signal analysis windows with a 50% overlap (Mas-Cabo, Prats-Boluda, Perales, et al., 2019) to keep the EHG section at a reasonable computational cost with the minimal loss of information (Azami & Escudero, 2018). This analysis does not require contraction segmentation, which can be tedious and subjective, and is more suitable for future clinical use in real-time applications. SampEn and DispEn were computed for both whole EHG bandwidth (0.1-4Hz, WBW) and in the Fast Wave High bandwidth (0.34-4Hz, FWH).

2.2.1 Sample Entropy

SampEn is the negative natural logarithm of the probability that two similar sequences for *m* points in the time series remain similar at the next point, in which self-matches are not included in calculating the probability (Richman and Moorman, 2000), so that a lower SampEn value also indicates more self-similarity in the time series. SampEn is an improvement of approximate entropy (Pincus, 1991) and is a frequently used metric in EHG to distinguish between term and preterm cases for preterm birth detection (Fele-Žorž et al., 2008).

SampEn depends on two internal parameters: the length *m* of the templates to be compared constructed from the time series, and a filtering threshold *r*, the tolerance of mismatch between the corresponding elements of the templates. Typically, the value of *r* is considered as 0.15 to 0.25 times the value of standard deviation (SD) of the time series, avoiding most of the noise present in it. The value of *m* may be taken considering that the length of the time series is between 10^m and 10^{m+1}, although this latter is not so restrictive (Xiong et al., 2019).

For the present work *r* was considered as 0.2 times the value of SD and sweeping *m* from 2 to 5.

2.2.2 Dispersion Entropy

Rostaghi & Azami (2016) proposed a new irregularity indicator termed *dispersion entropy* (DispEn) based on symbolic dynamics or patterns, transforming data into a new signal with only a few different patterns and simplifying the study of dynamic time series to a distribution of symbol sequences. It was aimed at dealing with the shortcomings of other entropy parameters such as SampEn and PermEn. Thus, unlike other entropy metrics, DispEn is sensitive to changes in simultaneous frequency and amplitude values and discriminate diverse biomedical and mechanical states (Azami and Escudero, 2018).

DispEn depends on the mapping function and three internal parameters: the length *m* of templates; the number of classes *c* that determine the number of patterns or classes to be considered in the computation, and time delay *d*. It is recommended to assume $d = 1$ for the latter parameter and for *m* and *c* consider $c^m < N$, *N* being the length of the time series. If *c* is too low, always with $c > 1$, signal values are too far and it leads to being assigned to the same class, while if *c* is too high, small variations in the signal can cause a change of class, making it sensitive to noise (Rostaghi & Azami, 2016). Taking these considerations into account, in the present work *c* was swept between 3 and 9, *m* between 2 and 5 and d fixed to 1. The mapping functions considered were: linear mapping (*linear*), normal cumulative distribution function (*NCDF*), tangent sigmoid (*tansig*), logarithm sigmoid (*logsig*) and sorting method (*sort*).

2.2.3 Feature Extraction

A previous study revealed that the 10th and 90th percentiles outperform the 50th percentile of EHG parameters for differentiating between different obstetric scenarios, including preterm versus term delivery (Mas-Cabo et al., 2020). We thus aimed to consider the contractile activity present in the 120s window analysis without segmenting the EHG recordings. For complexity parameters such as SampEn, the 10th percentile has been found to perform best in discriminating term and preterm labor from EHG registers. We therefore worked out the 10th, 50th and 90th percentiles of SampEn and DispEn distributions.

2.2.4 Statistical Analysis

The Wilcoxon Rank-Sum Test was performed to compare SampEn and DispEn's ability to distinguish term and preterm deliveries from EHG recordings in routine checkups. This is a non-parametric statistical hypothesis test used to compare two related samples to assess whether their population mean ranks differ ($\alpha < 0.05$). It is also suitable for non-normal distributions such as SampEn and DispEn (see Figures 2-3).

3 RESULTS

Figures 2 and 3 show the box and whisker plots of the of 10th, 50th and 90th percentiles of EHG SampEn and DispEn metrics for term and preterm groups considering the combination of internal parameter sweeps mentioned in Materials and Methods. As in the case of DispEN the different mapping functions obtained similar results, only the values for *sort* mapping are represented.

In Figure 2, it can be seen that preterm group median values are lower than those of term for the 10th and 50th SampEn percentiles. This agrees with other studies in the literature that found the shorter the time to delivery the higher the predictability of the EHG signal, and the lower the entropy value. In addition, the median values seem to decrease as *m* passes from 2 to 3.

Table 1 contains the *p*-values of the Wilcoxon Rank-Sum Test of SampEn values for distinguishing term and preterm groups for each entropy parameter distribution considered. Only the 10th percentile of SampEn showed statistically significant differences (p-value < 0.05) between the term and preterm groups, and the results from the 10th to 90th percentile got worse as *m* increased. The *p*-values were lower in the FWH than WBW.

Table 1: *P*-values (Wilcoxon Rank-Sum Test) for SampEn computed with $r = 0.2 \cdot SD$ when comparing different term and preterm groups. Significant differences (p-value $<$ 0.05) are shaded and the minimum *p*-value for FWH and WBW bandwidths are in bold.

	m	2	3
10th	FWH	**0.00123**	0.00964
	WBW	**0.01071**	0.01432
50th	FWH	0.08753	0.28320
	WBW	0.20581	0.44725
90th	FWH	0.83969	0.68999
	WBW	0.82898	0.81121

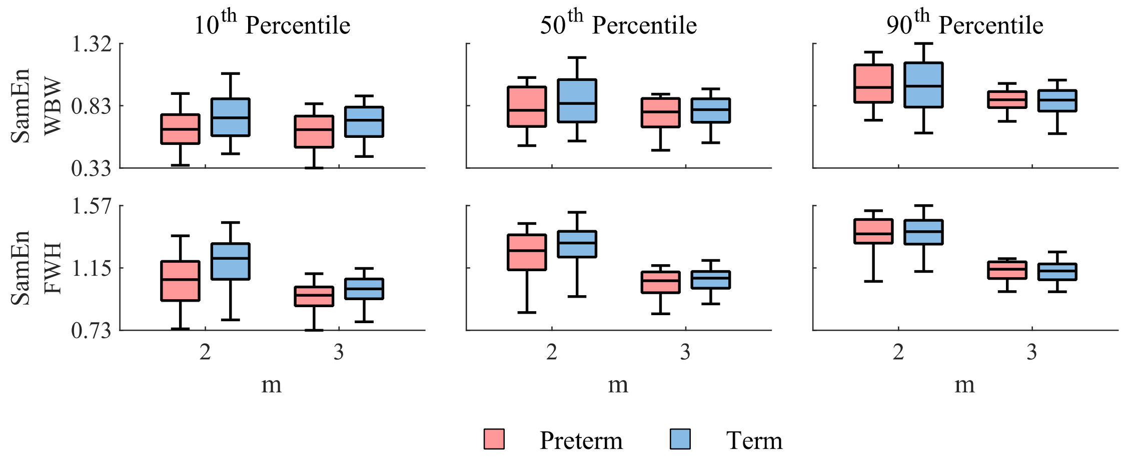

Figure 2: Boxplot SampEn distributions from EHG signals in different bandwidths and percentiles.

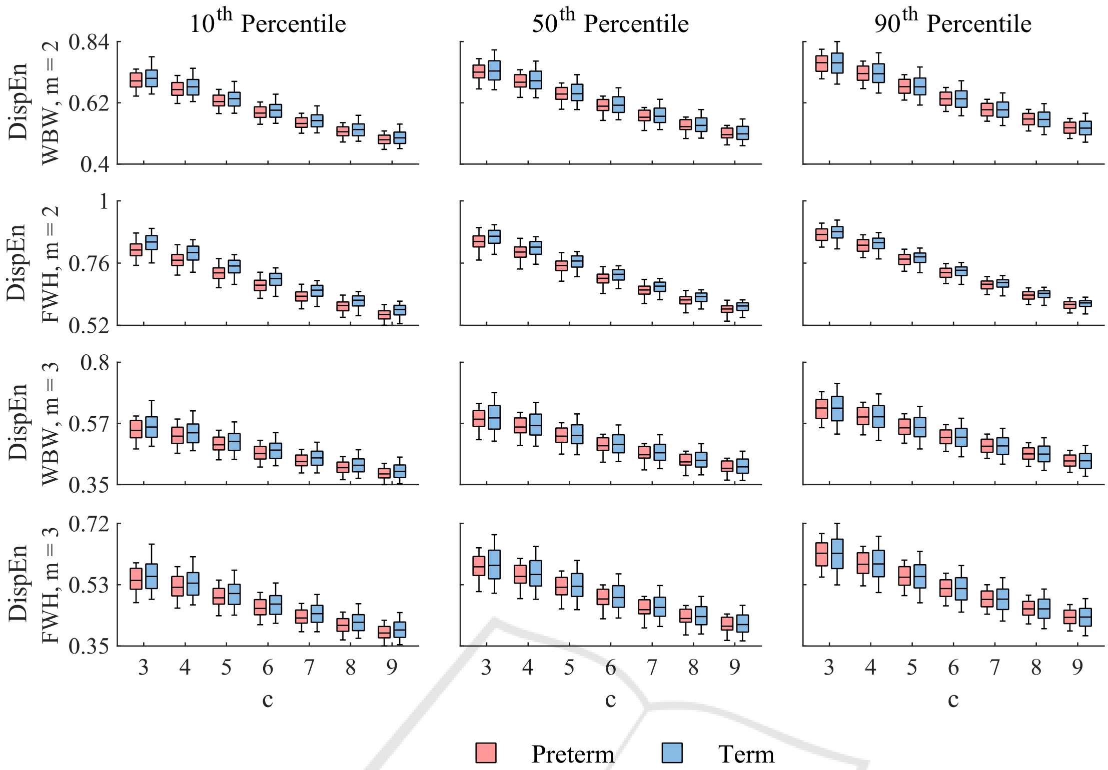

Figure 3: Box and whisker plot distributions of DispEn using sorting mapping function computed from EHG signals in different bandwidths and percentiles.

The distribution of the 10th and 50th DispEn percentiles had lower median values for the preterm than term group, as shown in Figure 3, confirming, as has been stated in the literature, that EHG signal predictability increases as time to delivery decreases, but this was not so clear for the 90th percentile. Also, the DispEn median values decreased as the m and c values increased. Although Figure 3 only shows the distribution obtained for *sort* mapping function, it is representative for the rest of the cases, because of their similar trend presented.

Tables 2 and 3 shows the p-values of the Wilcoxon Rank-Sum Test of DispEn values of the *sort* and *NCDF* mapping function. For the *sort* mapping (Table 2), statistically significant differences between term and preterm groups were only obtained for the 10th and 50th percentiles in FWH bandwidth for both $m = 2$ and 3. However, the lowest p-value was reached with $m = 2$ and $c = 7$ for the 10th percentile. There were thus no internal parameter combinations for WBW that achieved statistically significant differences (p-value < 0.05) between term and preterm groups with this mapping function. In the NCDF mapping function, p-values were lower than 0.05 in the 10th and 50th percentiles for FWH and in the 10th percentile for WBW. If Table 2 and Table 3 are compared it can be seen that although significant statistical results in WBW were reached using *NCDF*, the p-values were lower for FWH using *sort* mapping. The best discrimination between the groups was at $m = 2$ and $c = 7$, in which DispEn reached its optimum value in WBW and FWH, the latter having the lowest p-value.

Comparing the SampEn and DispEn outcomes, commonly is obtained that lower median values of the preterm than the term group were obtained and the median values of the 10th to 90th distributions decreased as m increased. Both entropy measures were best able to distinguish between term and preterm groups (lowest p-values in the test of Wilconxon) when $m = 2$ in the 10th percentile.

DispEn outperformed SampEn in discriminating in FWH (p-value, 0.00007), suggesting a better ability to separate term and preterm groups. However, in WBW SampEn reached a lower p-value, 0.01071 than DispEn.

4 DISCUSSION

SampEn is considered as one of the most used non-linear metrics to discriminate between term and preterm cases. One of the facts which do this possible is when SampEn is evaluated for women delivering prematurely, it is obtained a lower median value than those of term case (di Marco et al., 2014). This fact is consistent with the outcomes reaches in this study for SampEn, and in the same way, the mean values of DispEn acquired similar distributions. Consequently, DispEn might be considered as a replacement of SampEn in the measure of complexity in EHG signals for discriminate between term and preterm cases. Our findings reveal that DispEn better distinguishes term from preterm deliveries than SampEn when computed on EHG signal sections obtained in routine checkups, (p-value of 0.00007 vs 0.00123). The optimization of internal DispEn parameters was achieved for an embedding dimension of m = 2 and a number of classes c = 7, for the FWH and 10th percentile. This result agrees with our previous work that showed the 10th percentile of sample entropy and Lempel-Ziv non-linear parameters also outperformed the 50th for distinguishing term and preterm labor and other obstetric scenarios (Mas-Cabo et al., 2020). This suggests the possibility of characterizing contractile activity present in 120s EHG analysis windows without the need for segmentation.

However, other approaches should also be considered. The present study was performed using channel S3 only, which had outperformed channels S1 and S2 in term/preterm discrimination in previous studies (Ahmed and Mandic, 2011; Azami et al., 2019; Azami, Smith, et al., 2016). In future work it is aimed to extend this study by assessing the

Table 2: P-values (Wilcoxon Rank-Sum Test) for DispEn computed with *sort* mapping function when comparing different term and preterm groups. Significant differences (p-value < 0.05) are shaded and the minimum p-value is in bold.

m		c	3	4	5	6	7	8	9
2	10th	FWH	0.00015	0.00019	0.00012	0.00015	0.00018	0.00015	0.00016
		WBW	0.02078	0.02040	0.02732	0.03194	**0.01850**	0.02797	0.03176
	50th	FWH	0.00550	0.00611	0.00414	0.00393	0.00438	0.00594	0.00558
		WBW	0.27108	0.27912	0.30853	0.28115	0.28115	0.30314	0.31510
	90th	FWH	0.09229	0.13584	0.14194	0.12937	0.15148	0.15148	0.17418
		WBW	0.70182	0.66823	0.70691	0.77772	0.80236	0.76897	0.76548
3	10th	FWH	0.00020	0.00021	0.00017	0.00022	0.00022	0.00019	0.00020
		WBW	0.02913	0.02732	0.03362	0.03381	0.02247	0.03051	0.03381
	50th	FWH	0.00914	0.00932	0.00655	0.00582	0.00620	0.00866	0.00920
		WBW	0.23236	0.28525	0.29780	0.26515	0.27810	0.29044	0.30745
	90th	FWH	0.12538	0.17059	0.19301	0.20746	0.21751	0.22792	0.30962
		WBW	0.72398	0.71713	0.72912	0.78826	0.77947	0.76199	0.74637

Table 3: P-values (Wilcoxon Rank-Sum Test) for DispEn computed with mapping function *NCDF* when comparing different term and preterm groups. Significant differences (p-value < 0.05) are shaded and the minimum p-value is in bold.

m		c	3	4	5	6	7	8	9
2	10th	FWH	0.00015	0.00014	0.00009	0.00008	**0.00007**	0.00009	0.00008
		WBW	0.10883	0.08668	0.10053	0.09097	0.06042	0.07938	0.07516
	50th	FWH	0.00777	0.00692	0.00793	0.00849	0.00726	0.00772	0.00692
		WBW	0.41908	0.39326	0.46521	0.41777	0.39579	0.39579	0.39199
	90th	FWH	0.07667	0.10783	0.11241	0.09679	0.10486	0.11189	0.11241
		WBW	0.76199	0.80060	0.82720	0.85760	0.84684	0.84148	0.86299
3	10th	FWH	0.00019	0.00016	0.00011	0.00015	0.00012	0.00013	0.00011
		WBW	0.11138	0.09588	0.10148	0.08216	0.05856	0.07078	0.06168
	50th	FWH	0.01335	0.00938	0.01158	0.01121	0.00908	0.01121	0.01196
		WBW	0.41384	0.40734	0.46381	0.40476	0.39707	0.37330	0.36116
	90th	FWH	0.09497	0.15811	0.16846	0.18607	0.17274	0.20094	0.21077
		WBW	0.77597	0.77947	0.80944	0.85939	0.80060	0.84505	0.80944

performance of multivariate DispEn and other multivariate entropy algorithms (Mas-Cabo et al., 2020) in multichannel EHG databases so as to define an optimal set of features to develop a preterm labor predictor.

Other point to be considered is that SampEn has certain limitations, such as its higher computational cost than other entropies in similar assessment conditions and its undefined or unreliable results for short signals (Azami & Escudero, 2018). For a real-time or a fast post-processed application in preterm birth prediction with EHG signals may be useful provide of an algorithm capable to compute a measure of complexity of the signal as faster as it is possible. Thus, DispEn outperform SampEn and other relative entropy metric in which computational cost is referred (Azami and Escudero, 2018).

In addition, only a statistical approach of the separability of probability distributions of term and preterm registers is taken into account. However, for summiting a robust preterm labor discriminator, not only one metric is used. In this way, the complementation with other metrics related to EHG signals should be evaluated and so obtain if the append of DispEn outperforms the scores obtained with SampEn in similar conditions.

Although this work focused on term vs preterm discrimination with EHG entropy metrics, EHG can also be used in other obstetric scenarios (Mas-Cabo et al., 2020). DispEn may be suitable for the prediction of labor induction success (Benalcazar-Parra et al., 2019) or detecting imminent delivery in women with threatened preterm labor under tocolytic treatment (Mas-Cabo, Prats-Boluda, Perales, et al., 2019).

5 CONCLUSSIONS

This work assessed the performance of DispEn, a new complexity parameter in EHG characterization to distinguish term from preterm deliveries in EHG recordings picked up during regular checkups. Its performance was compared with the traditionally used SampEn. Both entropy metrics computed in window analyses of 120s show statistically significant differences (p-value < 0.05) in women who delivered at term from those who delivered preterm. DispEn outperformed SampEn discrimination in FWH, unlike WBW, for which SampEn reached a lower p-value. In both FWH and WBW the best discrimination was in the 10^{th} percentile, with the lowest p-value for DispEn in FWH and internal parameters $c = 7$ and $m = 2$, with lower entropy values for the preterm group.

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