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A Generalized Linear Model for an ECG-based Neonatal Seizure Detector*

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Abstract— **Seizures represent one of the most challenging issues of the neonatal period's neurological emergency. Due to the heterogeneity of etiologies and clinical characteristics, seizures recognition is tricky and time-consuming. Currently, the gold standard for seizure diagnosis is Electroencephalography (EEG), whose correct interpretation requires a highly specialized team. Thus, to speed up and facilitate the detection of ictal events, several EEG-based Neonatal Seizure Detectors (NSDs) have been proposed in the literature. Research is currently exploiting more simple and less invasive approaches, such as Electrocardiography (ECG). This work aims at developing an ECG-based NSD using a Generalized Linear Model with features extracted from Heart Rate Variability (HRV) measures as input. The method is validated on a public dataset of 52 subjects (33 with seizures and 19 seizure-free). Achieved encouraging results show 69% Concatenated Area Under the ROC Curve (AUC_{cc}) for the automatic detection of windows with seizure events, confirming that HRV features can be useful to catch the cardio-regulatory system alterations due to neonatal seizure events, particularly those related to Hypoxic-Ischaemic Encephalopathies. Thus, results suggest the use of ECG-based NSDs in clinical practice, especially when a timely diagnosis is needed and EEG technologies are not readily available.**

Clinical Relevance— **An ECG-based Neonatal Seizure Detector could be a valid support to speed up the diagnosis of neonatal seizures, especially when EEG technologies for infants' neurological assessment are not readily available.**

I. Introduction

In recent years, the interest in neonatal seizures has progressively grown. As stated by a recent ILAE's (International League Against Epilepsy) position paper [1], neonatal seizures are among the most common clinical signs of possible neurological insult for the newborn during the first hours of life. Several hypotheses were proposed to establish the possible etiologies of neonatal seizures. However, there is still no unanimous consensus for their characterization and classification in the complex mosaic of epileptic or neurological disorders [1]. Moreover, their detection and diagnosis is still challenging, especially in the context of Neonatal Intensive Care Units (NICUs), and requires highly specialized expert staff available twenty-four hours a day. To date, the accepted gold standard for the diagnosis of neonatal seizures is Electroencephalography (EEG) [2]. The timely detection of seizures is crucial due to their significant impact on the infant's neurodevelopment [3]. Depending on the aetiology, they could be either a sign of undetected cerebral insults or systemic disorders [4].

Several EEG-based Neonatal Seizure Detectors (NSDs) were proposed in the literature [5, 6, 7]. Moreover, results suggest that Artificial Intelligence techniques could provide valid support to the clinical staff in the next future [8]. Recently, the possibility to develop NSDs without the use of EEG was evaluated [5]. In particular, ECG-based NSDs were proposed in the literature [9, 10]. The idea behind ECG-based NSDs is to use less invasive, more simple and readily available technologies than EEG-based NSDs. Indeed, neonatal seizures may induce direct and indirect alterations on the autonomic nervous systems, thus they could be better detected by ECG-based NSDs [1, 2, 11, 12]. Unfortunately, the performance of these detectors is still too low to represent a valid alternative to EEG [5]. However, progresses in nonlinear HRV analysis in newborns and recent findings on neonatal seizures [11, 12, 13, 14] open several ways to improve their performance. To this aim, in this work, we evaluated if nonlinear and linear HRV analysis might be a valid strategy to develop an ECG-based NSD when its features are considered as input for a Generalized Linear Model (GLM [15]). Achieved encouraging results are validated through a public dataset made of 52 newborns with and without seizures events collected at the Helsinki University Hospital [16].

This paper is organized as follows: in Section II, the HRV analysis tools and the procedure to obtain the GLM model are presented. In Section III, the GLM model, statistical results and NSD's validation performances are shown. Section IV focuses on discussing our findings with existing literature and possible future developments.

II. Material and Methods

Data from a public dataset collected at Helsinki University Hospital [16] were used to implement and validate the proposed methods. As described in [16], three experts evaluated the dataset to identify the newborns with seizures and those without any ictal events. From the entire dataset of 79 at-term newborns, we selected only the patients for which the experts gave unanimous consensus. Moreover, we discarded the recordings where ECG signals were not present or were highly corrupted by noise. After this selection process, our dataset was composed of 52 subjects: 33 with seizures and 19 seizure-free. HRV features were extracted using the Kubios software version 2.2 [17]. Statistical analysis and the GLM

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model validation were implemented under the MATLAB 2020b computing environment [18]. To increase the Signal to Noise Ratio (SNR), we applied to ECG recordings a band-pass FIR filter in the bandwidth 0,05Hz – 45Hz. For the HRV analysis, for each recording, we defined non-overlapping sliding time windows lasting 4 minutes [11]. Artifacts were removed using a first-order detrending step and a "medium correction" (for more details, see [17]).

According to [17, 19], the following statistical features have been computed: mean of RR intervals (mean_RR); standard deviation of RR intervals (std_RR); mean of HR (mean_HR); standard deviation of HRV (std_HRV); root mean square of subsequent RR interval differences (RMSSD); percentage of successive RR intervals that differ more than 50ms (pNN50); HRV triangular index (HRV_tri_ind); baseline width of the RR interval histogram (TINN). Moreover, in the frequency domain, we computed the Autoregressive (AR) model of order 16 [17] for the spectrum estimation, and we extracted the peak, absolute power (power) and relative power (power_prc) of Very Low (VLF), Low (LF) and High Frequencies (HF) indicated here as AR_LF_power, AR_HF_power, AR_LF_power_prc etc., respectively. Furthermore, we also analyzed the ECG-derived respiration (EDR). As in [11], we adapted the frequency bandwidth of LF and HF to the neonatal range, that is 0.04Hz-0.3Hz for LF and 0.3Hz-1.3Hz for HF.

Furthermore, the following nonlinear features have been included: the Poincarè plot standard deviation along the line of identity (SD2) [20]; Approximate and Sample Entropy (ApEn, SampEn); Multiscale Entropy (MSE); Detrending short- and long-term Fluctuation Analysis ($DFA_{\alpha1}$, $DFA_{\alpha2}$) and Correlation Dimension (CorDimD2). For the Entropy features, the embedding dimension was set to 2, and for SE and MSE, the tolerance was set to 0.2. Moreover, for a consistent estimation of the MSE features, the scales were computed up to level 6 (from MSE1 to MSE6) [21]. We remark that in this fashion, SampEn and MSE1 result to be the same. Finally, we also computed the following Recurrence Quantification Analysis (RQA) features: Maximum Line Length (Lmax); Mean Line Length (Lmean); Recurrence Rate (REC); Determinism (DET) and Shannon Entropy (ShanEn) [22].

We performed a Mann-Whitney Test (significance level α=0.05) between the medians of the windows of the seizure-free patients and those with one or more seizure events. This test aimed at assessing the statistical significance of HRV measures to discriminate windows with seizures events from seizure-free windows. The relevant features found after Mann-Whitney tests are shown in Table I.

TABLE I. SIGNIFICANT HRV FEATURES AFTER MANN-WHITNEY TEST (SIGNIFICANT DIFFERENCES IN MEDIANS WITH P-VALUE < 0.05).

Feature Name	p-value	Feature Name	p-value
std_RR	0.03	MSE3	0.001
std_HRV	0.03	MSE4	0.001
RMSSD	0.01	MSE5	0.006
HRV_tri_ind	0.004	MSE6	0.006
TINN	0.02	CorDimD2	0.02
AR_LF_power	0.01	RQA Lmean	0.009
AR_LF_power_prc	0.004	RQA REC	0.04
AR_HF_power	0.02	RQA ShanEn	0.02
MSE2	0.03		

To implement the GLM model for the NSD, we performed a stepwise regression procedure [18]. Starting from a model with only the intercept term and considering the subset of significant features found with the Mann-Whitney test, we used a forward and backward stepwise regression to determine the final model. The criterion used to add or remove terms was the Deviance Criterion [15, 18]. Moreover, we trained the GLM model using the Binomial Distribution for the response variable and a Logit link function [23]. The GLM model was built using all the considered time windows, including the interictal time windows that were not used for the statistical test. In total, we used 1067 windows from the 52 patients, 284 of which with seizure events. Before the stepwise procedure, we normalized the features by rescaling the data range in the interval [0,1], where 0 is the lowest value of the features across all windows and 1 is the highest value. Furthermore, we replaced missing values with the global medians of the features. The estimated coefficients and the statistical results concerning the GLM model are presented in Section III. To assess the model's performance in detecting windows with seizure events, from the model, we build the concatenated Area Under the ROC curve (AUC_{cc}) [7]. Furthermore, we also defined a Leave-One-Subject-Out Validation (LOSO), iteratively removing each patient and retraining the GLM model using the same formula shown in (1). We applied the LOSO procedure to avoid an overestimation of the neonatal seizure detection task [24]. To compare our results with the existing literature, we defined the following patient-independent performances: Accuracy (ACC), Sensitivity (SEN), Specificity (SPE) [9, 10]. Performances were obtained after the selection of the threshold parameter for the response variables. Results are presented in Section III.

III. RESULTS

The final model's formula obtained from the stepwise procedure is shown in equation 1 in compact symbolic form (i.e. showing only the interaction terms for RMSSD, MSE3 and MSE5):

$$\text{labels} \sim 1+\text{ARLF}_{\text{power}} + \text{RMSSD*MSE3} + \text{RMSSD*MSE5} \quad (1)$$

Table II shows the statistical results related to the GLM model. Both the nonlinear entropy features MSE3 and MSE5 and their interaction with RMSSD show a significant p-value (significance level α=0.05). Besides, we tested if the model significantly differs from a constant using a Deviance Test [18]. We obtained a χ^2 statistic vs constant model: 96.6 and p-value 1.3e-18. In Fig. 1, the partial dependence plots [25] of the predicted labels as a function of the predictor variables involved in the interaction terms (RMSSD, MSE3 and MSE5) are shown. Partial Dependence is defined as the relationships between predictor's variables and predicted labels.

TABLE II. ESTIMATED COEFFICIENTS OF THE PROPOSED GLM MODEL. THE MODEL WAS BUILT USING 1067 WINDOWS FROM 33 PATIENTS WITH SEIZURE EVENTS AND 19 SEIZURE-FREE SUBJECTS.

	Estimate	SE	tStat	p-value
Intercept	-0.33107	0.25393	-1.3038	0.19
RMSSD	-0.63561	1.6911	-0.37585	0.70
ARLF_power	-162.77	87.707	-1.8558	0.06
MSE3	-6.116	1.1778	-5.1928	2.07e-07
MSE5	6.7515	1.4574	4.6324	3.61e-06
RMSSD:MSE3	25.728	6.5232	3.9441	8.01e-05
RMSSD:MSE5	-42.402	9.9384	-4.2664	1.98e-05

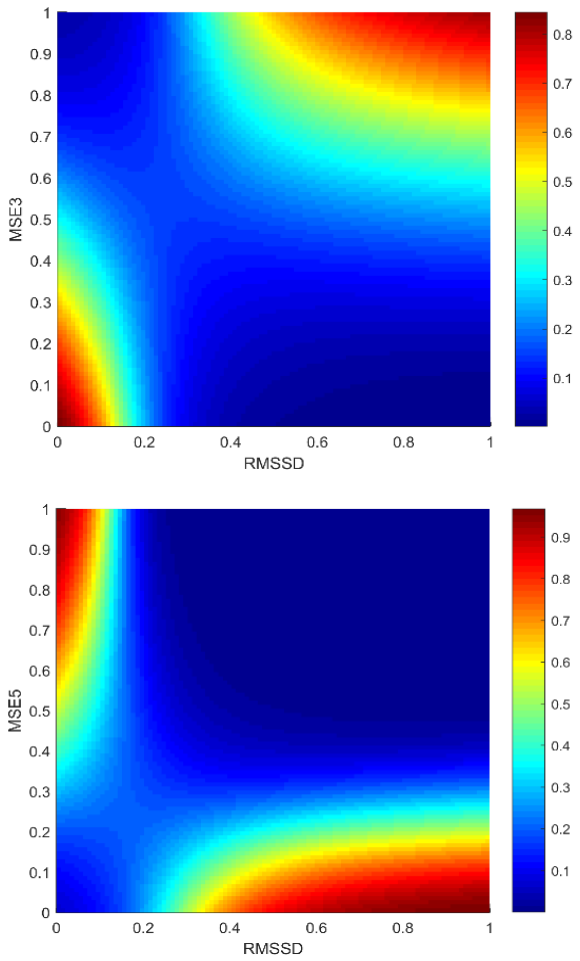

Figure 1 - Above: Partial Dependence Plot of normalized RMSSD and MSE3 as a function of the predicted labels (represented by the colormap). Below: Partial Dependence Plot of normalized RMSSD and MSE5 as a function of the predicted labels (represented by the colormap).

In Table III, the results of the GLM model as an ECG-based NSD are shown. For patient-independent metrics ACC, SEN and SPE, we reported the threshold (TH) used to obtain these performances and their mean values with standard deviations obtained after the LOSO validation on the 52 patients. The chosen TH value allowed a good compromise between SEN and SPE. The ROC curve related to the parameter AUC_{cc} is shown in Fig. 2. In the experimental phase, we also tested GLM models without the stepwise procedure or artifact correction before HRV features extraction. As they gave poor performances, the results are not reported here.

TABLE III. PERFORMANCES OF THE PROPOSED GLM MODEL.

Method	AUC_{cc} (%)	TH	ACC (%)	SEN (%)	SPE (%)
GLM (LOSO)	69.69	0.35	68±27	43±37	77±28

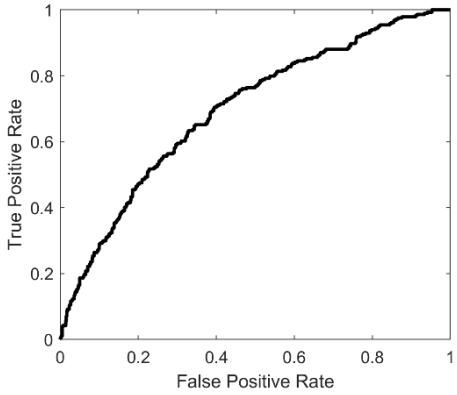

Figure 2 - ROC curve of the AUC_{cc} value reported in TABLE III.

IV. DISCUSSION AND CONCLUSION

This work aims at evaluating if HRV analysis and GLM models could help the development of an ECG-based NSD. The results reported in Table II show that the Multiscale Entropy contributes to characterize the seizure events with the model obtained. This possibility was not previously exploited [5, 9, 10]. The obtained performances confirm that EEG-based NSDs are still better than the ECG ones [5]. However, the AUC_{cc} obtained by the GLM model can be considered a relevant improvement for the development of ECG-based detectors [5, 10]. Furthermore, as in [11], we found significant differences both for HF features, as reported in Section II, where the Mann-Whitney tests gave p-values lower than 0.05. Significant differences were also found for the LF features. Considering the interactions shown in Fig. 1, it is interesting to highlight the information provided by RMSSD values: extreme values of this measure (very close to 0 and 1 in normalized values) reflect an abnormal parasympathetic activity inside the windows with seizure events. At the same time, at different scales, the MSE analysis (Fig. 1) catches useful information about abnormal heart rate dynamics related to seizure events (e.g., reduced variability or transient decelerations) [26]. Considering Table I, the multiscale approach (from MSE2 to MSE6) allows findings statistical differences between the ictal and the seizure-free periods that could not be detected with a single scale approach (by ApEn or MSE1/SampEn). Furthermore, low values for entropy indexes during ictal events are similar to the EEG case [27].

Our results confirm that neonatal seizures may alter the cardio-regulatory system, and an ECG-based NSD may detect these changes. It was already demonstrated [12] that HRV analysis can provide a reliable marker of brain damages in the case of Hypoxic-Ischaemic Encephalopathy (HIE), the most common etiology behind neonatal seizures [1]. However, this finding cannot be extended to all the newborns and seizures events considered. As shown in Table III, the high standard deviations obtained in LOSO validation mean that these alterations were not present for some patients, or the used HRV features cannot detect them. This is probably due to the possible different kinds of seizures' etiologies [1, 16].

Moreover, it is worthwhile noting that HRV analysis may be unspecific for the neonatal seizure detection problem. For example, motor activity during ictal events could lead to changes in heart rate and its variability, although very often neonatal seizures are evident only trough ECG [1]. Therefore, further analysis is needed to confirm the use of only HRV measures in NSDs. Moreover, our NSD is based on windows lasting 4 minutes that cannot detect seizures' exact temporal occurrence as their average duration is often lower than the window used [16] (about 80-100 seconds on average for this dataset). In other words, the proposed NSD can detect the windows containing one or more seizure events but cannot establish their exact onset and offset. This is a trade-off due to the limitations of the HRV feature extraction method with shorter windows [19]. However, other ECG-based NSDs could be developed in the next future based on short-time windows (i.e. less than 30-60 seconds). Our analysis concerned a total of 52 patients that, to the best of our knowledge, represent the largest validation dataset for an ECG-based NSD and the first one performed on this public dataset.

The proposed approach represents a valid support for the clinical decision process to detect newborns' ictal periods, capable of highlighting only the periods with seizures and thus reducing the number of recording hours to be inspected by the physician. In conclusion, considering the low invasiveness, low cost, and easier usability of ECG sensors with respect to EEG ones, our results suggest a possible integration of these systems in NICUs or any situation where EEG technologies are not easily and timely available.

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