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Automated EEG inter-burst interval detection in neonates with mild to moderate postasphyxial encephalopathy

Vladimir Matić, Perumpillichira J. Cherian, Katrien Jansen, Ninah Koolen, Gunnar Naulaers, Renate M. Swarte, Paul Govaert, Gerhard H. Visser, Sabine Van Huffel and Maarten De Vos

Abstract— **EEG inter-burst interval (IBI) and its evolution is a robust parameter for grading hypoxic encephalopathy and prognostication in newborns with perinatal asphyxia. We present a reliable algorithm for the automatic detection of IBIs. This automated approach is based on adaptive segmentation of EEG, classification of segments and use of temporal profiles to describe the global distribution of EEG activity. A pediatric neurologist has blindly scored data from 8 newborns with perinatal postasphyxial encephalopathy varying from mild to severe. 15 minutes of EEG have been scored per patient, thus totaling 2 hours of EEG that was used for validation. The algorithm shows good detection accuracy and provides insight into challenging cases that are difficult to detect.**

I. Introduction

Perinatal Hypoxic Ischemic Encephalopathy (HIE) in newborns is a major cause of morbidity and mortality world–wide [1]. Neurodevelopmental sequelae in survivors include cerebral palsy, epilepsy and sensory as well as cognitive problems [2, 3]. The degree of hypoxic brain injury and recovery is mainly determined by the severity and duration of insults [4]. However, secondary injury also develops over a time-period of several hours. This enables a potential "therapeutic time window" during which neuroprotective strategies are expected to work [5]. The most frequently applied and the most promising technique is therapeutic hypothermia. Both head cooling as well as whole body hypothermia safely improve the outcome at 12-24 months in infants with HIE [6]. Neonates with moderate to severe HIE within 6 hours of birth are suitable candidates for this treatment, making prompt and accurate classification a necessity. An electroencephalogram (EEG) is exquisitely sensitive to brain (dys)function, making it suitable as an objective method of quantifying the severity of HIE [7].

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V. Matic, M. De Vos, N. Koolen and S. Van Huffel are with the Department of Electrical Engineering (ESAT-SCD), Katholieke Universiteit Leuven, Belgium, and IBBT-K.U..Leuven Future Health Department, Leuven, Belgium. Vladimir.Matic@esat.kuleuven.be

M. De Vos is also with the Deparment of Psychology, University of Oldenburg, Oldenburg, Germany.

P. J. Cherian, G. H. Visser are with the section of Clinical Neurophysiology, Department of Neurology, Erasmus MC, Rotterdam, the Netherlands.

K. Jansen is with the Department of Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium.

G. Naulaers is with the Neonatal Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium.

R. M. Swarte, P. Govaert are with the Department of Neonatology, Sophia Children's Hospital, Erasmus MC, Rotterdam, the Netherlands.

EEG is a widely available and well-accepted non–invasive tool for monitoring the brain function in neonatal HIE. The earliest abnormality is the absence of a sleep-wake cycle. More severe dysfunction results in a discontinuous EEG background activity. Depending on the severity of injury, the discontinuous periods become prolonged (> 10 seconds) and suppressed (< 10 μV). In order to assess the severity of HIE using EEG, several visual scoring systems have been proposed in literature to grade the background. The most robust parameter used in all systems to grade EEG discontinuity is the inter-burst interval (IBI) [8].

Additionally, analysis of the evolution of the background EEG can provide an estimate of the lasting effect of the hypoxic insult and neurodevelopmental outcome of the newborn. For this purpose, recovery of the IBI is again the most frequently used parameter.

In [9], an efficient automated IBI detector has been developed using supervised machine learning techniques. It is based under the assumption that IBI can be seen as a global phenomenon where burst-suppression patterns are present globally and synchronously on all EEG channels. Hence, this approach processes features calculated as median values per each EEG channel. This is however the ideal definition of IBI and usually only valid in cases of moderate and severe hypoxic brain injuries. Here, we propose an algorithm that can also detect IBIs in mild HIE (e.g. shorter IBI < 10 seconds with higher amplitude activity present between bursts) where burst suppression alternations usually do not display a clear-cut transitions. In such EEGs, where milder discontinuities are present with unclear cut-off boundaries, the use of median values per channel to define IBIs could result in two extreme scenarios: either the whole discontinuous segment may be disregarded (without a single IBI being detected) or scored as a very long IBI.

The new algorithm starts with an adaptive segmentation of every EEG channel [10]. This approach has been successfully presented for the analysis of sleep in newborns [11]. Subsequently, segments are classified and IBIs are detected using a temporal profile membership signals. As IBI detection is notoriously difficult due to the lack of discontinuities with clear boundaries, we additionally propose a reliability measure for the detected IBIs.

A. Data

The EEGs of 8 neonates with mild to moderate HIE and no recorded seizures were selected from a data base of 119 newborns who underwent continuous EEG monitoring (cEEG) as part of a prospective study looking at the utility of cEEG in perinatal asphyxia, done at the NICU at Sophia Children Hospital, Erasmus MC, Rotterdam, the Netherlands. cEEG recordings were done during the first 6-72 hours post partum using 17 or 13 scalp electrodes applied according to the 10-20 International System. The sampling frequency was 256 Hz. An experienced clinical neurophysiologist (PJC) scored the background EEG according to the grading system presented in [12]. From each patient, 3 segments of 5 minutes each have been selected from the beginning, middle and ending phase of the recording. No segments were excluded based on the presence of EEG artifacts, channel asymmetries or changes in morphology and continuity caused by an evolution of the background activity.

An experienced pediatric neurologist (KJ) has visually marked the beginning and end points of each IBI. These detected IBIs were used for validation of the automated method.

B. Preprocessing of the EEG signal

Standard EEG filtering has been performed using highpass and lowpass FIR filters at 0.7 Hz and 20 Hz respectively. Note that the value of the highpass filter can influence the detection of suppression segments. Setting it on a higher value can filter out EEG activity consisting of slow waves and falsely enhance the EEG suppression.

Some EEG segments had pronounced muscle artifacts present continuously on several EEG channels. In such cases, *NeoGuard* (the software developed for the neonatal EEG analysis) automatically detected and removed them using Canonical Correlation Analysis as a method for Blind Source Separation [13]. This approach is similar to the one for the removing ECG and respiratory artifacts, previously described in [14].

II. METHODS

In literature, several definitions of inter-burst intervals have been presented [15]. We will consider an IBI as a suppression period longer than 3 seconds with voltage below 10 µV present in more than 50% of the EEG channels. Before and after the suppressed segment we assume bursts to be present.

The stages of the algorithm can be summarized into the following steps:

A. adaptive segmentation of the EEG channels into quasi stationary parts
B. clustering of segments into 3 classes depending on the voltage distribution (low, medium and high)
C. creating of a temporal profile for every voltage class and detecting inter-burst intervals.

A. Adaptive segmentation of the EEG

Each EEG channel is segmented using an adaptive segmentation algorithm [11]. It uses 2 fixed concatenated moving average windows and segments an EEG channel into quasi stationary epochs. This segmentation algorithm calculates a variable that is based on the amplitude difference and on the change in frequency between EEG values into two sliding windows [11]. Its local maxima are detected and they define the segment points. Additionally, we have introduced a constraint, in order not to create EEG segments shorter than 1 second. Too short segments can produce frequent changes in temporal profile class signals and can adversely affect the detection phase.

B. Classification of the EEG segments

Every EEG segment is further classified into one of the 3 categories according to the amplitude distributions as low, medium and high. At first, each EEG signal within segment is thresholded using the following function *amp*_10:

$$amp\_10(t) = \begin{cases} EEG(t) - 10, & EEG(t) > 10\mu\text{V} \\ 0, & -10\mu\text{V} \le EEG(t) \le 10\mu\text{V} \\ EEG(t) + 10, & EEG(t) < -10\mu\text{V} \end{cases}$$

For every *amp*_10 signal we calculate the energy of the segment and divide it by the duration of the segment expressed in seconds. Thus we obtain a variable *area_amp*_10 which attempts to mimic human interpretation of the EEG. At first, we verify whether the majority of EEG values are below ± 10 µV and yet we also tolerate some EEG activities that are present above these thresholds. Additionally, we repeat the process *amp*_10(t) once more onto an already thresholded EEG segment. Thus we create an *amp*_20 signal and a corresponding *area_amp*_20 variable. Classification of the segments is performed according to the following heuristic rule:

$$\begin{array}{l} \textit{if } area\_amp\_10 < 50 \textit{ then } CLASS = LOW \\ \quad \textit{else} \\ \quad\quad \textit{if } area\_amp\_20 < 100 \textit{ then } CLASS = MEDIUM \\ \quad\quad\quad \textit{else} \\ \quad\quad\quad\quad CLASS = HIGH \\ \quad\quad\quad \textit{end} \\ \quad \textit{end} \end{array}$$

These values have been chosen after optimizing the algorithm to distinguish suppressed segments, low amplitude bursts and bursts. Optimization has been performed together with visual analysis and assistance of a clinical neurophysiologist (PJC) on an independent training dataset. Calculating *area_amp*_10 and 20 provides us a robust method with high sensitivity to classify all suppressed segments into low voltage class. Even though suppressed segments can have sharp peaks of shorter duration above ±10 µV, calculating 'area' parameters will classify them correctly.

C. Detecting an inter-burst interval

For every class a temporal profile membership function is created. Values of these functions are obtained by counting the number of channels in which this class is present at every time instant. It enables us to follow the global distribution of the classified EEG segments. Each of these signals can range from 0 up to the total number of EEG channels used in montage mode.

We will focus on a temporal profile signal which represents the distribution of a low voltage segment class. Using the definition of the inter-burst intervals we will threshold this signal at a value of one more than half the number of channels according to the IBI definition. Depending on the number of electrodes and used montage mode, this value is 11 (or 7). The time that this signal is above the threshold defines the duration of a detected IBI.

The flow of the algorithm is illustrated in Fig. 1. The EEG signal is segmented and classification is depicted in colors blue, magenta and red respectively for low, medium and high voltage segments. In Fig. 2. the low voltage temporal profile is thresholded at value 11. Three IBIs are detected and marked with black rectangles in Fig. 1.

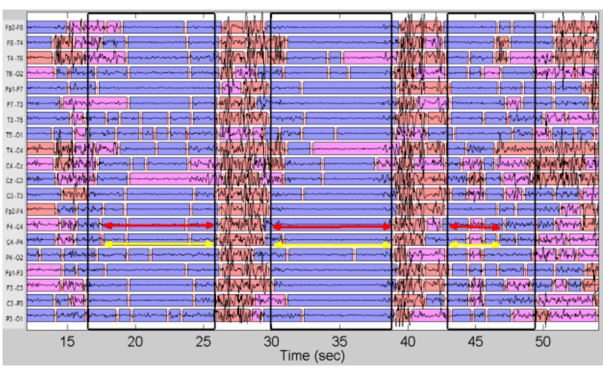

Figure 1. Classified EEG segments into low (blue), medium (magenta) and high (red) voltage classes. Black rectangles are detected IBIs; red arrows are IBIs marked by an EEG reader.

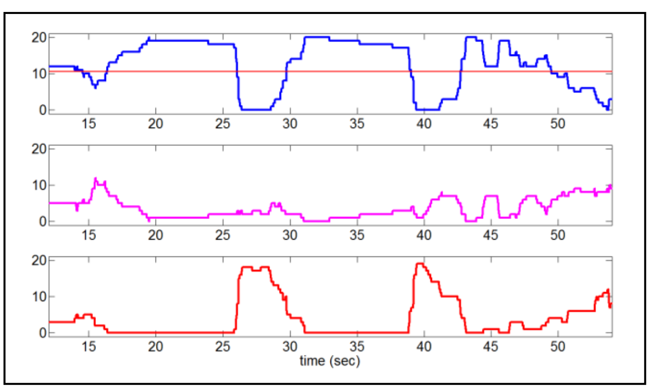

Figure 2. Temporal profile signals representing low (blue), medium (magenta) and high (red) amplitude voltage classes. Values of the y axis represent the number of the EEG channel

III. RESULTS

Validation of the algorithm is performed by the comparison of automatic and visually marked inter-burst intervals. The main goal of the automatic IBI detection is for further automatic scoring of the background EEG activity. Visual grading of the background EEG activity is obtained by classifying IBIs in the following four groups that correspond to the severity of hypoxia: I. normal (IBI < 5 s), II. mild (5s < IBI < 10s), III. moderate (10s < IBI <20s) and IV. severe (IBI > 20s). Hence, we have considered IBIs as *correctly detected* if an overlapping interval between two IBIs was higher than 80% of the total duration of the longer IBI (irrespective of whether it is the detected or the visually scored one). In Fig. 1. automatic detection of the IBI is marked with black rectangles; red lines signify rater's markings, whereas yellow lines represent an overlapping interval between corresponding IBIs. Results of the detection are presented in Table I. The appropriate columns correspond to the duration of 4 IBI groups. One particular type of error we will name as *misclassified* IBI. This means that suppressed parts of IBIs were detected, but suppression/burst transitioning time instances were not detected correctly. We consider IBIs as misclassified if there is a significant overlapping between 2 IBIs, but an automatically detected IBI does not fit into the same IBI group as the visually scored one. In Fig. 1, the third IBI will be classified as: *misclassified* – group I. In the case that there is no overlapping interval between IBIs we consider them as *completely missed* IBIs if the algorithm hasn't detected a visually marked IBI or as a *false positive* if the rater has not marked them.

TABLE I. RESULTS OF THE ALGORITHM VALIDATION

Detections	IBI group			
	I	***II***	***III***	***IV***
Visually marked	42	51	58	12
Correctly detected	22	39	38	9
Missclassified	20	9	18	3
Completely missed	0	3	2	0
False positive	15	2	4	0

Majority of IBIs were correctly detected. There were only a few *completely missed* and *false positives* IBIs. False positives are only high in group I since they were rather short (~ 3 seconds). By observing the number of misclassified segments, it is obvious that detecting transitions between bursts/suppressions is a challenging task. Many aspects influenced these misclassification errors. First of all, 2 out of 8 patients had a pronounced asymmetry at 50% of the channels which resulted in the algorithm not being able to detect IBIs correctly. This implies that for further improvements, verifying asymmetry index is a necessary step. Second, artifacts have contributed to the adverse performance of the algorithm. They have produced false detections of transition points (e.g. movement artifacts, EOG artifacts). A human EEG interpreter has the advantage of using the extra information from polygraphy channels to distinguish artifacts from EEG activity. Another type of error occurred due to low amplitude bursts (~10-15 μV) that were missed by the algorithm resulting in misclassification, producing longer IBIs. This occurred in the beginning of the recordings, few hours after the presumed hypoxic insult.

Lastly, the majority of visually marked IBIs that were misclassified did not fit nicely into our basic definition of IBI. As the algorithm was compared with an EEG reader who was not involved into the optimization of the algorithm, future research should focus on defining a more reliable "gold standard". Validation should initially be done using EEG data where inter-rater disagreement is low. Other researchers have faced similar problems of inter-rater disagreement in the detection of bursts in prematures [16].

IV. Discussion

A new IBI detector is presented and although the number of IBIs classified in a different way than a human reader is still high, the results are promising. Indeed, instead of trying to lower the number of misclassified IBIs, as there will be always substantial inter-rater disagreement, future research should focus on developing a framework to also automatically assign a reliability of the detected IBIs.

Keeping in mind that the final goal is to grade the severity of encephalopathy, we need to detect one of four groups where majority of the IBIs will be distributed. Hence, we can shift our goal from detecting every single IBI perfectly, to detecting some percent of them with a very high confidence level. That is, we can parameterize all automatically detected IBIs and select those that are correctly detected with the highest certainty. One way to do this is to mimic an approach of a human EEG reader who carefully examines an IBI. As the first step, we can additionally verify and describe how flat a suppressed part within a given IBI is. By monitoring temporal profile signal of low voltage class we can see how many EEG channels are attenuated. We can search for a pronounced EEG activity on the remaining channels using low and medium class temporal profiles. Fluctuations in these signals within IBI signify an activity in EEG - either from brain or artifacts. Pulse like shapes in the low class temporal profile signals are more likely to be accurately detected IBIs. In contrast, if low class temporal signal oscillates around values 12-13 (channels) it is likely that misclassification will happen. In Fig. 1., the second detected IBI is close to an ideal situation. It is suppressed in the majority of channels and has sharp suppression/burst transitioning edges in temporal profile low class signal. On the other hand, the third IBI has fluctuations in temporal profile signals without clear transitioning borders. Therefore, it would be better to discard this IBI from further analysis. Additionally, we can detect presence of bursts before and after suppressed segment using wavelets as they are very well suited for the detection of transient points. Preliminary results confirm that by transforming these specific steps into parameters we can assign appropriate confidence level to each detected IBI. In this way, we can select those that are certainly detected with a high degree of certainty and discard the others from further analysis.

The rationale behind this approach is in the fact that we can assume that brain activity after an insult like hypoxic injury is rather stable over periods of 1-2 hours as seen in the EEG signal. Recovery after hypoxic insult usually takes place over several hours. By shrinking all IBIs to a reduced set, we expect to retain enough correctly detected IBIs to estimate the appropriate distribution and statistics of IBIs per group and eventually represent the EEG evolution over time.

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