Data-driven metric representing the maturation of preterm EEG

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***Abstract*— Essential information about early brain maturation can be retrieved from the preterm human electroencephalogram (EEG). This study proposes a new set of quantitative features that correlate with early maturation. We exploit the known early trend in EEG content from intermittent to continuous activity, which changes the line length content of the EEG. The developmental shift can be captured in the line length histogram, which we use to obtain 28 features; 20 histogram bins and 8 other statistical measurements. Using the mutual information, we select 6 features with high correlation to the infant's age. This subset appears promising to detect deviances from normal brain maturation. The presented data-driven index holds promise for developing into a computational EEG index of maturation that is highly needed for overall assessment in the Neonatal Intensive Care Units.**

I. Introduction

Premature babies are at high risk to develop mental or physical disabilities. Electroencephalogram (EEG) allows early diagnostics of neurological disorders, and a means for monitoring maturation of the preterm brain. However, the conventional clinical EEG inspection by visual reading is subjective, variable and time-consuming, which calls for development of automated and objective tools in EEG assessment. Due to the recent shift in attention in neonatal care from cardiorespiratory functions to neurological care, there has been a rapidly increasing need to incorporate EEG assessment into neonatal intensive care units, especially when supported by automated quantification methods that adapt to different maturational stages. Some EEG features are developed and used in the hospital environment [1].

Diagnosis of premature neurological adversities and hence, prognosis of neurological outcome is based on the information in the background EEG activity. The amount of EEG activity changes parallel to brain maturation which is reflected in both amplitude and frequency content [1-3]. Specific patterns related to the postmenstrual age (PMA) are observed: normal maturation is characterized by an initially very discontinuous pattern that evolves into a more continuous pattern towards term age. In the intermittent pattern, also known as discontinuous pattern, very low voltage EEG is interrupted by high frequency bursts of activity, and the maturation of the baby is reflected as an increase in amplitude content during low voltage intervals (*a.k.a.* interburstintervals). Adverse neurodevelopmental outcome is often related to very low early activity, seen as long low-voltage periods [4-6]. For that reason, recent studies have focused on detection of the high-activity bursts [7-10] to be used for subsequent quantitative indices. Notably, no gold standard describing this specific EEG event is available, so the detection algorithms are commonly compared to multiple clinical raters [11], but no larger scale validation or systematic comparisons have been published. To circumvent the challenges inherent to event detection, we propose a more data-driven feature that is able to index the maturation by exploiting on the raw statistical properties of the feature line length that we had previously used for the purpose of burst detection [9]. A schematic overview of the presented method can be found in Fig. 1.

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II. Methodology

A. Data Acquisition

EEG signals were recorded at eight standard electrode locations (Fp1, Fp2, C3, C4, T3, T4, O1, O2) and reference electrode placed at Cz, with OSG equipment (Rumst, Belgium). The sampling frequency was 250 Hz. The data set included 22 patients. They all had 2 to 6 subsequent recordings in order to see maturational brain processes, with on average two weeks in between the recordings, which gave in total 84 EEG recordings. They had a median postmenstrual age of 33.57 weeks (27-40 weeks). The protocol was approved by the ethics committee of the University Hospitals of Leuven, Belgium. First, a pre-processing step is performed; a 50 and 100 Notch filter and a 1-20 Hz band pass filter are applied before visual selection of two hours of EEG without major artefacts. Two hours long EEG epochs were used to include different sleep states that minimizes bias due to differences in histograms between them.

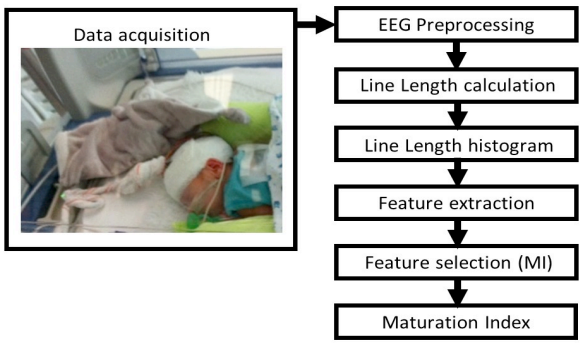

Figure 1: A schematic overview of the presented method.

B. *Line Length calculation*

Line length (LL) is a simplified form of the fractal dimension, reflecting the complexity of the signal. The more signal activity, the more of the time-amplitude plane is covered, and as a consequence the line length will increase. The LL is the running absolute sum between samples j in 1 second segments, with sampling frequency 250 Hz (1).

$$LL = \sum_{j=1}^{250-1} |x_{j+1} - x_j| \quad (1)$$

Every 2.5 minutes, LLs are normalized by the total sum of LLs in that window, to average out baseline effects [9]. For every single channel, we calculate the LL for the whole 2 hours of EEG recording.

LL will have large values for active periods as can be seen in continuous EEG patterns (Fig. 2A). In contrast, in the discontinuous pattern both small values (inactive periods) and large values (bursts) for LL are found (Fig. 2B). In a next step, we take the decimal logarithm of the LL curve to enlarge differences between small and large LL values.

C. *Histogram Distribution*

We decide to graphically summarize the distributions in histograms in order to capture the information about the log LL distributions at different ages. We calculate a histogram of log LLs with 20 predefined centers of the histogram bins [-3.1:0.1:-1.2]. In that way, we can compare the patients among each other to discover a shift in EEG content in function of the PMA. The number of data points in each bin has been used for describing this shift in the histogram distribution. In addition, we added several statistical measurements to characterize the LL histogram: mean, median, standard deviation, interquartile range, skewness, kurtosis and the 5th and 95th percentile values. We assume that rare outliers with long LL will not significantly influence the shape of the histogram.

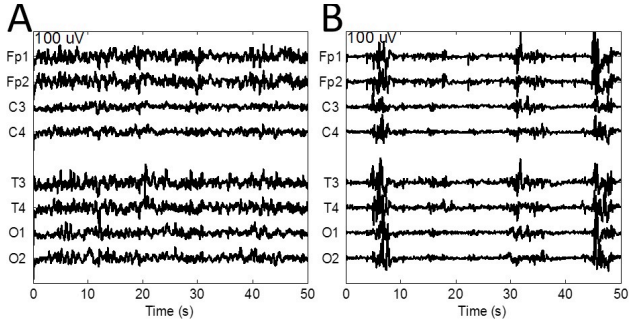

Figure 2: A. Example of continuous EEG pattern, B. Example of discontinuous EEG pattern.

D. *Feature Relevance*

After observing several developmental correlations between our features and the postmenstrual age, we were interested in exploring systematically whether each single feature could be used as a maturational feature. To measure the dependence between two variables (PMA and feature), we can use the correlation function or the mutual information (MI). However, we decide to continue using the MI (2), since it is well know that the MI captures the general dependence, while the correlation function estimates the linear dependence [12].

Amplitudes of the features and age values are quantized first in 8 quantization levels, after which the joint and individual probabilities of the amplitude levels are calculated. The MI is relative to the ratio of joint over individual probabilities, in which a_i is always the age and a_j the histogram-based signal feature.

$$MI(a_i, a_j) = \sum_{i,j} p(a_i, a_j) \log_2 \left(\frac{p(a_i, a_j)}{p(a_i)p(a_j)} \right) \quad (2)$$

III. Results and Discussion

Since no objective gold standard exists for correlating EEG to postmenstrual age, we decided to compare our data-driven features to postmenstrual age without further EEG correlations. The strength in our approach is that the method is fully ignorant to specific features or vigilance states. We do not preselect epochs or EEG events based on their intermittent features such as burst occurrence or length of interburstintervals.

A. *Line Length Histogram Evolution*

During early development, the EEG content transforms from a discontinuous pattern (where brain connections are still scarce and immature), towards a continuous active pattern (when brain connections are physically established). Line length catches their EEG reflections in a global way without being based on event detection. It is not necessary to pick up quick activity changes, though amplitude and frequency content is captured with the line length. As shown in Fig. 3A, we can see that in 5 weeks' time the histogram has shifted towards the right side, which includes the longer line lengths. This means concretely, more bursting activity is present. The overall trend of this shift is represented in Fig. 3B. For all 84 EEG selections (2 hours), the 28 defined features have been calculated in every channel. In certain histogram bins, we cannot find any maturation, whereas others correlate with the postmenstrual age, and hence parallel with brain development (Fig. 3C). On the other side, we can describe the shape change with global measurements (Fig. 3D). We see that the mean / median is increasing, which is analogously to our previous findings. The interquartile range is decreasing, which means that the EEG content is more concentrated in the same range of amplitudes and range of frequencies. The 95% percentile of

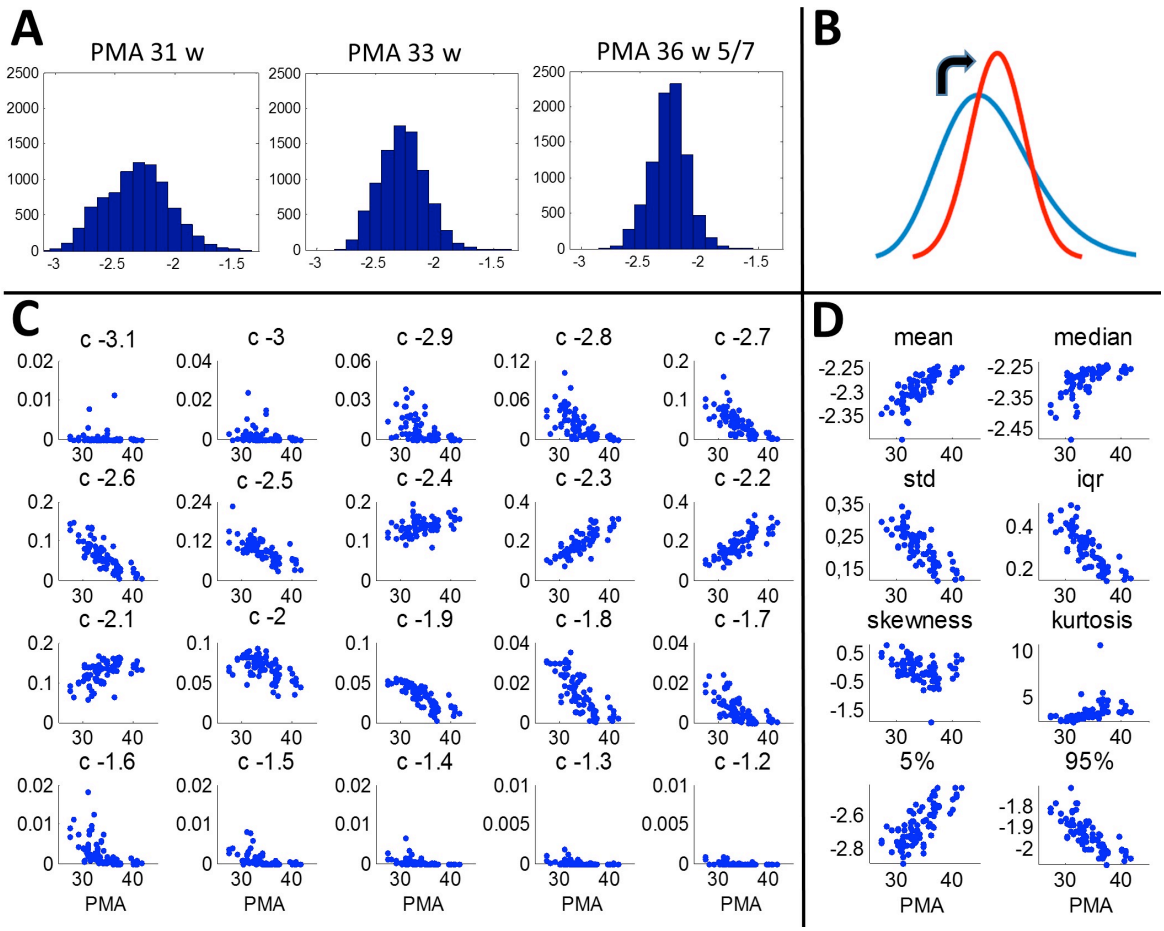

Figure 3: Concept of EEG content change by means of histogram change. A. Example histograms for one patient with 3 consecutive recordings, B. Schematic presentation of the trend change in the histogram shape, C. 20 defined bin heights (%) in function of the postmenstrual age (weeks) for channel C3, D. 8 defined statistical measurements in function of the postmenstrual age (weeks) for channel C3.

the histogram is also found to correlate with maturation, however the change (shift to the left) in the histogram may be counterintuitive at first sight. This is made more understandable by the idea that the bursting activity in the young preterm infants is of very high amplitude. The amplitudes of the bursts typically decrease parallel to the maturation. However, it implies they will have higher entropy and random organization.

B. Feature Relevance

The mutual information represents in a statistical way the relevance of the feature to predict the postmenstrual age. The information MI is zero if two variables are independent, and in case of strong dependence the MI is large. To build a maturational index, six relevant features have been selected based on the output of the feature relevance averaged over all EEG channels (Fig. 4). The selection includes three bins with centers -2.7, -2.2 and -1.8 (two bins decreasing and the middle one increasing), and 3 global measures (mean, interquartile range and 95% percentile).

C. Accuracy

For each of the six most descriptive features, the mean linear fit is determined through all the data points. Next, the residual error is calculated for each of the data points, which is the deviation from this curve in vertical direction; PMA will not change. After normalization - necessary to compare the errors the different features - the residual errors are averaged over the six features and subsequently over the consecutive EEG recordings of the same patient. In a last step, we took the mean over Fp1-Fp2, C3-C4, T3-T4 and O1-O2, to extract significant information about the different brain regions. The results for each individual patient can be found in Table 1. Outliers (>0.015) are underlined. EEG maturation was not appropriate for age by clinical labelling in patient 4, 8 and 22 and mildly abnormal in patient 7 and 21. We can distinct clearly patient 8 and 22 based on this method. Patient 4 had a very abnormal first recording, however, with a good maturational trend towards term age. This is confirmed in the individual analysis of the histograms. Patient 14 is an outlier. It could be explained by the fact that the 3rd EEG selection contains continuous active sleep parts and some longer periods of high voltage slow wave sleep (continuous EEG). Therefore, it looks 'more mature' than his actually 37 weeks PMA.

This new maturational index can be used in addition to other known maturational features, like the lengths of the interburstintervals, bursts, synchrony and frequency parameters [9, 13]. In addition, we were able to reduce the number of electrodes while maintaining the diagnostic power, using only central electrodes. The EEG grow chart composed with the help of computer-aided analysis will reduce the costs for the time-consuming clinical assessment.

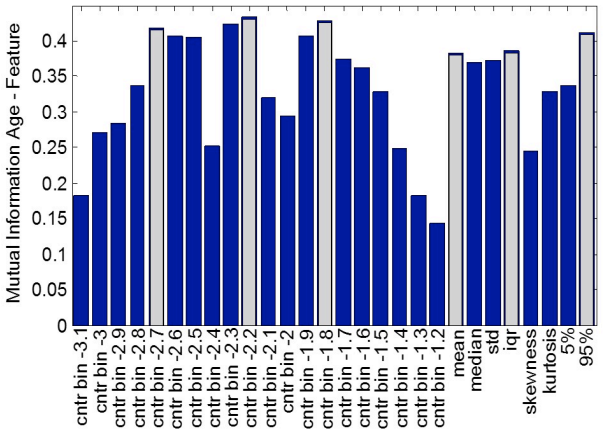

Figure 4: Feature relevance for maturation for the 28 predefined features. The grey features have been selected for further analysis.

TABLE 1: MEAN RESIDUAL ERROR USING THE 6 RELEVANT FEATURES, AVERAGED OVER THE CONSECUTIVE RECORDINGS FOR DIFFERENT REGIONS OF THE BRAIN

	Region of the brain			
	Frontal	*Central*	*Temporal*	*Occipital*
PT 1	0,011	0,010	0,011	0,013
PT 2	0,015	0,008	0,010	0,013
PT 3	0,008	0,012	0,010	0,010
PT 4	0,012	0,013	0,013	0,012
PT 5	0,008	0,010	0,012	0,012
PT 6	0,010	0,011	0,011	0,011
PT 7	0,017	0,016	0,017	0,015
PT 8	0,014	0,015	0,016	0,015
PT 9	0,009	0,006	0,008	0,007
PT 10	0,014	0,013	0,014	0,011
PT 11	0,009	0,006	0,005	0,009
PT 12	0,014	0,012	0,010	0,010
PT 13	0,015	0,013	0,014	0,013
PT 14	0,019	0,017	0,018	0,015
PT 15	0,007	0,007	0,007	0,009
PT 16	0,008	0,014	0,013	0,008
PT 17	0,009	0,009	0,009	0,006
PT 18	0,007	0,007	0,005	0,008
PT 19	0,015	0,012	0,011	0,011
PT 20	0,011	0,011	0,010	0,009
PT 21	0,011	0,016	0,014	0,018
PT 22	0,015	0,020	0,018	0,018

IV. CONCLUSION

The developed algorithm reveals an interesting maturational parameter, in addition to the traditional heuristic features, such as the bursts / interburstintervals and the synchrony. No preselection of data epochs is required if no major artefacts are present, which simplifies analysis procedure and removes one key subjective step in the preprocessing. Our method would also allow more global assessment by integrating over longer time periods, which would be challenging if not impossible to evaluate visually as is done in the conventional clinical EEG reading. In addition, our approach would allow objective and quantitative follow-up of the individual maturation over time, which opens a more sensitive means for discovering relative dysmaturity and/or neurological morbidities.

Our method was using linear regression to assess accuracy in developmental assessment, however future work with nonlinear regression with the postmenstrual age might provide better accuracy as suggested by the partly non-linear evolution of many of our features (see Fig2C). The residual error is calculated over the sequential recordings, some information about a single record can be lost. Therefore, a closer look to the individual histograms can add some information. We also want to acknowledge that LL maybe sensitive to the choice of filter settings, which could be optimized for the purpose as recently described [7]. Furthermore, we want to combine the retrieved maturational indexes in an EEG premature growth chart. Confidence bands, related to normality, with polynomial regression models will be defined. In this way, automated analysis would improve the neonatal assessment and be of high value in the clinic.

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