Modelling Interactions between Blood Pressure and Brain Activity in Preterm Neonates

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Abstract - Hypotension or low blood pressure (BP) is a common problem in preterm neonates and has been associated with adverse short and long-term outcomes. Deciding when and whether to treat hypotension relies on an understanding of the relations between blood pressure and brain function. This study aims to investigate the interaction between BP and multichannel EEG in preterm infants less than 32 weeks gestational age. The mutual information is chosen to model interaction. This measure is independent of absolute values of BP and electroencephalography (EEG) power and quantifies the level of coupling between the short-term dynamics in both signals. It is shown that while adverse health conditions as measured by higher clinical risk indices for babies (CRIB II) are accompanied by consistently lower blood pressure (r=0.43), no significant correlation was observed between CRIB scores and EEG spectral power. More importantly, the chosen measure of interaction between dynamics of EEG and BP was found to be more closely related to CRIB scores (r=0.49, p-value=0.012), with higher CRIB score associated with lower levels of interaction.

I. INTRODUCTION

Prematurity is the leading cause of death in children under the age of 5 [1] with more than 1 million children dying each year due to the complications of preterm birth. Hypotension or low blood pressure (BP) is a common problem in preterm babies, particularly in the first 72 hours after delivery. It may cause decreased cerebral perfusion resulting in impaired oxygen delivery to the brain [2]. The criteria which defines hypotension has not been clearly set yet [1] and the decision when and whether it should be treated remains disputed resulting in a considerable variability in practice [3]. The treatment method often involves administration of volume expanders and inotropes when the level of BP (in mm Hg) falls below the gestational age (GA) in weeks [4]; it should be noted that this is not supported by any robust scientific evidence [5]. At the same time, excessive intervention in order to treat hypotension in preterm infants has been associated with the adverse neurodevelopmental outcome including brain injury [6]. In fact, preterm infants with low BP often have no biochemical or clinical signs of shock, and thus, do not require any treatment. In this case a “permissive hypotension” approach may well be appropriate [7], where only preterms whose brain function is affected by low BP may need treatment.

EEG and Near Infrared Spectroscopy (NIRS) are among the most common technologies which are used to assess the brain health of a newborn. EEG provides information about cortical brain activity in the preterm neonate [3]. NIRS allows continuous monitoring of the regional cerebral oxygen saturation in the brain. Both methods are non-invasive and provide a real-time insight into brain function. Deciding when and whether to treat hypotension relies on our understanding of the relation between BP, oxygenation and brain activity. However, little is known about this relationship in preterm infants as these signals are rarely recorded simultaneously and extraction and investigation of the complex measures of signal interaction and signal dynamics have not been explored.

Several studies have tried to establish the relationship between EEG activity and BP. Shah et al. [8] identified that BP and EEG energy were associated with the flow in the superior vena cava carrying deoxygenated blood into the heart over the first 12h of life. However, West et al. [9] found no association between superior vena cava flow and EEG energy. Increased oxygen extraction was related to spontaneous activity transients observed in the EEG during the first 6h of life [10]. The levels of BP which results in abnormal cerebral activity, as quantified by EEG spectral features and peripheral blood flow measured with NIRS were studied in 35 very low birth weight infants [2]. It was reported that a low BP (below 23 mm Hg) caused an increase in EEG discontinuity and a decreased relative power of the delta band (0.5-3.5 Hz). Changes in preterm EEG spectral power with maturation were also observed in a study by Niemarkt et al [11]. Most of these studies were performed on short EEG recordings and operate with a single summary measure of the BP and EEG computed from a whole recording.

In contrast to the above mentioned works where linear methods were used to measure the relationship between BP and EEG, this study hypothesises that a measure of interaction between signal dynamics may be more sensitive to adverse health conditions. In particular, an insight into the temporal relationship between these physiological signals is provided by means of mutual information which

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is computed over EEG features and BP, and is contrasted with the clinical risk index for babies (CRIB II) [12], in order to assess the level of sensitivity of the measure.

II. MODELLING INTERACTIONS

The overall diagram of signal processing and interaction modelling is shown in Fig. 1.

A. Dataset

The analysis is performed on a database of 25 preterm infants, with mean GA of 27.7 weeks (range: 23 – 32 weeks) recorded at the Neonatal Intensive Care Unit of Cork University Maternity Hospital, Ireland. The data set included continuous multichannel EEG, simultaneous registration of BP, and availability of CRIB (CRIB II) scores. A Viasys NicOne video EEG machine (CareFusion Co., San Diego, USA) was used to record multi-channel EEG according to the international 10 to 20 system of electrode placement with the following 8 bipolar channels: F4–C4, C4–O2, F3–C3, C3–O1, T4–C4, C4–Cz, Cz–C3 and C3–T3. The duration of recordings used in this study totals 967 hours. EEG data were sampled at 256Hz or 1024Hz. Continuous invasive arterial BP monitoring was simultaneously performed via an umbilical arterial catheter, with BP data sampled at 1 Hz. Positioning of the tip of the umbilical catheter in the descending aorta was confirmed by chest radiograph. An example of 3 minutes of data is shown in Fig. 2. This study had full ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

B. Pre-processing, feature extraction & synchronization

The EEG signal is filtered to the range of 0.3-30Hz and down-sampled to 64 Hz. The signal in each channel is segmented into 1-minute epochs with a 1-second shift. The epoch of EEG was transformed into the frequency domain using the Discrete Fourier Transform (DFT). Sub-band powers in four frequency bands, 0.3–3, 3–8, 8–15 and 15–30 Hz, were used as EEG features. This division slightly differs from the standard delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz) and beta (13–30 Hz) frequency bands in order to better capture preterm brain dynamics [13]. For every feature, the median value across all eight channels is calculated in order to reduce the effect of focal artifacts.

The diastolic and systolic pressure were recorded every second and further used for mean arterial pressure (MAP) calculation as indicated in Fig. 1. In order to synchronize the features computed from the EEG and BP, a moving average filter was applied to MAP values using the same epoch length and shift which was used for the EEG (1 minute epoch with 1 second shift).

C. Interaction modelling

The resultant sequence of synchronized EEG and BP features is segmented into 30 minute epochs with a 30-seconds shift. This window length allows one to focus on short-term dynamics of both EEG and BP signals. A measure of interaction between MAP and EEG features is computed based on Mutual Information (MI). MI is an information theoretic measure of dependency between two random variables, which unlike correlation or coherence quantifies both linear and nonlinear dependence. An example is shown in Fig. 3 where both the correlation and mutual information are computed for one newborn. It can be seen that higher levels of both positive and negative correlation result in higher values of MI.

Similar to other information measures, the most common way for calculating MI from empirical data is to use histogram binning (labelling) in order to create an approximate probability density distribution. The choice of the number of bins into which the two sequences \((X, Y)\) are subdivided is important and may significantly affect the results. Fig. 4 illustrates an example of results of data labelling. It can be seen that the BP trace is quantized into 5 labels whereas the trace of EEG delta-band powers will be converted to 21 different labels.
In order to minimise the effect of the choice of the number of labels, the MI was calculated as an adjusted mutual information (AMI), which unlike conventional MI corrects the effect of agreement between two sequences which happens solely due to chance [14]. In particular, AMI accounts for the fact that MI tends to increase as the number of different labels increases, regardless of the actual amount of interaction between the two sequences. Once the sequence is binned, the AMI for two sequences (X and Y) is computed as:

$$AMI(X,Y) = \frac{MI(X,Y) - E[MI(X,Y)]}{\max(H(X),H(Y)) - E[MI(X,Y)]},$$

where $H(X), H(Y)$ are the Shannon entropy for sequences X and Y, and the mutual information $MI(X,Y)$ is defined as:

$$MI(X,Y) = \sum_{x \in X} \sum_{y \in Y} p(x,y) \log \left( \frac{p(x,y)}{p(x)p(y)} \right),$$

where $p(x), p(y)$ are the probabilities of occurrence of a particular label in the sequence X, Y; $p(x,y) = p(x)p(y|x)$, where $p(y|x)$ is the probability that a label occurs in sequence Y, given another label occurred in sequence X. The expected value of mutual information is defined as:

$$E[MI(X,Y)] = \sum_{x \in X} \sum_{y \in Y} \sum_{n_{xy} = (a_x + b_y - N)^+} \frac{n_{xy}}{N^{a_xb_y}} \frac{n_{xy}}{N^{a_xb_y}} \log \left( \frac{N^{a_xb_y}}{N^{a_xb_y}} \right) \log \left( \frac{N^{a_xb_y}}{N^{a_xb_y}} \right) \times \frac{N^{a_xb_y}}{N^{a_xb_y}}.$$  

where $\left(a_x + b_y - N\right)^+$ denotes $\max(1, a_x + b_y - N)$; $a_x$ and $b_y$ are partial sums of the contingency table; $a_x = \sum_{x \in X} n_{xy}$, $b_y = \sum_{y \in Y} n_{xy}$, with $n_{xy}$ as number of labels common in X and Y.

D. Simulations

As mentioned the AMI accounts for chance, e.g. increasing the number of labels (bins) will not increase the value of AMI. Thus, using AMI instead of MI is more computationally efficient i.e. there is no need to check the statistical significance of the obtained results. In order to illustrate this characteristic of AMI in practice surrogate tests were conducted. The surrogates are obtained by random permutation (shuffling) of the data which destroys the coupling between two sequences so that the resultant measure of AMI is indicative of interaction by chance only. First, toy data were artificially generated by adding random noise to a sum of sinusoids (Fig. 5). It can be seen from the histograms in Fig 6 (b), that the level of coupling measured by AMI for sequences with random interaction is centred on zero whereas the AMI values for correlated data is centred on 0.15. It can be seen that the AMI values even for strongly correlated data is rather conservative. Fig 6 (a) shows the same plot for real data from the database. For every 30-minute window, AMI is calculated for the original sequence of BP and EEG feature values and for permuted sequences. The distributions of the AMI values for real data and toy data are separated from corresponding surrogates, which implies the reliability of the calculated measure and the presence of non-random interactions in the real data.

In this study, the BP signal was binned into a number of labels equal to the range of integer BP values. This number of labels prevents the artificial creation of dynamics in the BP signal when the BP fluctuates insignificantly (within 1 mm/Hg). The sub-band EEG energy was binned into 35 bins. This number has been chosen as the one that maximizes the values of AMI.

E. Statistical analysis

The computed values AMI between BP and EEG features are summarized as a median across the whole recording for each newborn. To investigate the level of sensitivity of the developed measures to a physiological criterion, the AMI values are contrasted with the CRIB scores. This score is used for neonatal mortality risk prediction [12]. The CRIB scores are defined on a scale between 1 and 27, with higher
values indicating a higher risk of mortality. High values of CRIB score are strongly dependent on low GA, low birth weight and low temperature at admission. A regression line was fitted using the least squares method and the Pearson correlation and t-test are used to conduct hypothesis tests on the regression coefficients obtained.

III. RESULTS AND DISCUSSION

Fig. 7 shows the results of the regression analysis of BP, EEG delta-band energy and the measure of interaction (AMI) with respect to the CRIB scores. As expected, BP has a significant correlation with the CRIB score, Fig. 7(a), where higher risks of mortality are associated with lower MAP values \((r=-0.432, p\text{-value}=0.031)\). This correlation might result from the fact that the CRIB scores and MAP are both highly dependent on the GA. At the same time, the higher CRIB scores were not correlated with changes in any of EEG energy bands (\(r=0.3, p\text{-value}=0.2\); theta \(r=0.09, p\text{-value}=0.7\); alpha \(r=0.2, p\text{-value}=0.5\) and beta \(r=-0.2, p\text{-value}=0.3\)).

It can also be seen from Fig. 7 (b) that the CRIB score has marginally higher correlation with the developed measure of interaction between signal dynamics, AMI, than with MAP \((r=-0.493, p\text{-value}=0.012 vs r=-0.432, p\text{-value}=0.031)\). It is worth emphasising that this measure is independent of the absolute values of both BP and EEG energy and measures only the coupling between signal dynamics. Most information of preterm EEG is concentrated in the lower frequencies [15]. The levels of correlation between the CRIB score and the AMI for BP with other EEG sub-bands were lower (theta \(r=0.17, p\text{-value}=0.4\), alpha \(r=0.35, p\text{-value}=0.09\) and beta \(r=-0.4, p\text{-value}=0.05\)). Although the AMI values are independent of the absolute values of the BP and EEG features, there is a statistically significant correlation between AMI and MAP \((r=0.526, p\text{-value}=0.007)\). Thus, the measure of interaction which is developed to be independent on the absolute values of blood pressure, is correlated with BP, therefore can be related to hypotension problem, where dynamics of signals can be indicative of newborns well-being.

IV. CONCLUSIONS

This is the first study that investigates the relationship between short-term dynamics in BP and EEG energy in the preterm on a large dataset of continuous multi-channel unedited EEG recordings. The results reported in this study indicate that high risk health conditions of preterm infants represented by high CRIB scores are associated with the level of coupling between EEG activity and BP. The developed measure of interaction does not depend on BP, which makes it independent of a GA-based threshold. Future research will focus on understanding the nature of the coupling and interaction between EEG and NIRS.

REFERENCES