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Clinical implementation of a neonatal seizure detection algorithm

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ABSTRACT

Technologies for automated detection of neonatal seizures are gradually moving towards cot-side implementation. The aim of this paper is to present different ways to visualize the output of a neonatal seizure detection system and analyse their influence on performance in a clinical environment. Three different ways to visualize the detector output are considered: a binary output, a probabilistic trace, and a spatio-temporal colormap of seizure observability. As an alternative to visual aids, audified neonatal EEG is also considered. Additionally, a survey on the usefulness and accuracy of the presented methods has been performed among clinical personnel. The main advantages and disadvantages of the presented methods are discussed. The connection between information visualization and different methods to compute conventional metrics is established. The results of the visualization methods along with the system validation results indicate that the developed neonatal seizure detector with its current level of performance would unambiguously be of benefit to clinicians as a decision support system. The results of the survey suggest that a suitable way to visualize the output of neonatal seizure detection systems in a clinical environment is a combination of a binary output and a probabilistic trace. The main healthcare benefits of the tool are outlined. The decision support system with the chosen visualization interface is currently undergoing pre-market European multi-centre clinical investigation to support its regulatory approval and clinical adoption.

1. Introduction

Neonatal seizures are the most common neurological emergency in the neonate and are a serious concern for clinicians and parents worldwide [1]. Only about one third of all neonatal seizures are clinically visible [2] and many remain undetected in the busy Neonatal Intensive Care Unit (NICU) environment. The only method available to detect all neonatal seizures accurately is continuous multi-channel EEG monitoring. Interpretation of neonatal EEG requires a neurophysiologist or paediatric neurologist with specific expertise in neonatal EEG. This expertise is not available on a 24 h basis, 7 days a week [3]. To fill the gap in the lack of availability of experts, clinical staff in the NICU are using a simpler form of EEG monitoring, called amplitude integrated EEG or aEEG [4]. Amplitude integrated EEG is a logarithmically-scaled, temporally-smoothed and compressed display of EEG which is usually computed from two EEG channels, one from each hemisphere. Despite the fact that many short and focal neonatal seizures are undetectable with aEEG and interobserver agreement is poor [5], aEEG currently serves as a trade-off between very inaccurate clinical detection of seizures and very accurate but scarcely available neurophysiologic expertise, and thus is widely adopted worldwide in the NICU [3].

As an alternative to aEEG usage, many groups in the world are working to develop algorithms for automated detection of neonatal seizures on continuous multi-channel EEG. An automated decision support system (DSS) that could detect and annotate seizures on the neonatal EEG would be extremely useful for clinicians in the NICU [44]. A number of methods have been previously proposed but to date their transition to clinical use has been limited due to: (i) the proof of concept nature of the work performed, which involved carefully selected short-duration EEG segments [6–9]; (ii) an unrealistic validation regime such as testing on training data or excluding the worst performing records [10–12]; and (iii) the provision of algorithm performance which is currently unacceptable in a clinical setting [13–17].

There are two key directions in automated neonatal seizure detection. The first follows analytical learning principles [18] and focuses on the creation of a set of heuristic rules and thresholds from clinical prior knowledge [6–8,10,12–15]. The resultant detectors analyse EEG using a small number of the descriptors from which a decision is made using empirically derived thresholds. Binary decisions are obtained with this approach. The second approach relies on inductive learning [18] and utilizes model-based parameterization [9,16] or statistical classifier based methods [11,19,20], which employ elements of machine learning to classify a set of features using a data-driven decision rule.

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This approach is capable of outputting continuous confidence of decisions such as probability of seizure.

Our group has recently developed [19,21], validated [20] and patented [22] an accurate and robust real-time neonatal seizure detection system combining both of these approaches. In order to have the system used at the cot-side, as well as to help achieve regulatory approval, we need to identify the most intuitive and synergetic way to convey the system output information to neonatal caregivers. In this context, when the developed technology approaches cot-side implementation, it becomes important to build a viable interface between the new engineering component and established medical environments [23–25]. The NICU environment (Fig. 1) already has plenty of technologies, including a number of physiological monitors; adding yet another 'technology' becomes a challenging task.

In this study, we propose and examine 3 different ways to visualize the output of an automated neonatal seizure detector: a binary output, a probabilistic output and a spatio-temporal colormap output. Additionally, the algorithm-driven audification of neonatal EEG is also explored as an alternative to a visual output. Five neonatologists with experience in interpreting the cotside EEG from the second largest maternity hospital in Europe (Cork University Maternity Hospital) were surveyed over approximately 1 h, answering over 100 questions, and the survey results are also reported in this work.

The paper is organized as follows: Section 2 briefly describes the neonatal seizure detection system developed by the group. Section 3 describes 3 different ways to visualize the system output information along with audification of neonatal EEG. A link between the ways that the metrics are computed and the system output is visualized are established in Section 4. Section 5 presents and discusses the survey results. Section 6 introduces the chosen interface for the developed DSS which is currently undergoing pre-market European multi-centre clinical investigation to support its regulatory approval and clinical adoption. Section 7 links the study to the theory of DSS. Economic benefits of the developed technology are outlined in Section 8. Our expectations from the results of the clinical trial are given in Section 9. Conclusions are drawn in Section 10.

2. Neonatal seizure detector

The developed automated neonatal seizure detection system is shown in Fig. 2. A video EEG machine was used to record multi-channel EEG using the 10–20 system of electrode placement modified for neonates. The following 8 EEG channels in bipolar pairs are used to feed the EEG data into the system: F4–C4, C4–O2, F3–C3, C3–O1, T4–C4, C4–Cz, Cz–C3 and C3–T3. It has been shown that frequencies of neonatal EEG seizures range between 0.5 and 13 Hz and the dominant frequencies of seizures vary between 0.5 and 6 Hz [26]. The EEG from the 8 channels is downsampled to 32 Hz with an anti-aliasing filter set at 12.8 Hz. The EEG is then split into 8 s epochs with 50% overlap between epochs. The most recent recommendations by the International Federation of Clinical Neurophysiology [27] suggest that 5 s is the minimum seizure duration if the background EEG is normal and 10 s if the background EEG is abnormal. A window length of 8 s was chosen given that hypoxic ischemic encephalopathy (HIE) is the commonest cause of seizure in the full term neonate and the background EEG is always abnormal in those with seizures. This window length would also prevent short duration seizure-like events (e.g. brief intermittent rhythmic discharges) being incorrectly detected as seizure events. A long feature vector which consists of fifty-five features is extracted from each epoch. The features are designed to convey both time and frequency domain characteristics as well as information theory based parameters.

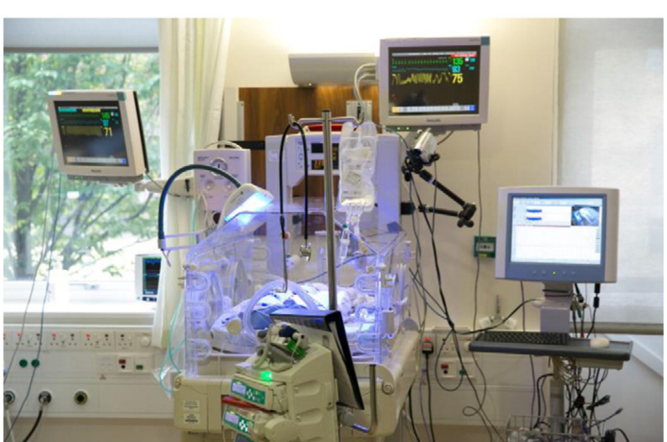

Fig. 1. Clinical environment in NICU with EEG monitoring system on the right.

A Support Vector Machine (SVM) classifier is trained on data which are normalized anisotropically by subtracting the mean and dividing by the standard deviation to assure commensurability of the various features. This normalizing template is then applied to the testing data. The obtained classifier is applied separately to each channel of the testing data as neonatal seizures can be localized to a single EEG channel. The output of the SVM is converted to probability-like values with a sigmoid function [28]. The probabilistic output is then time-wise smoothed with a moving average filter. Detailed information on the system can be found in [19].

Several important enhancements of the developed system have recently been investigated. A wider feature set which included spectral slope features from speech recognition has been examined in [29]. A Gaussian mixture model classifier has been developed in [30] and contrasted to SVM with the classifier combination performed in [31]. Adaptive spatial weighting of EEG channels based on the statistics of spatial neonatal seizure distributions has been introduced in [32]. Similarly, temporal weighting of the probabilistic output of the classifier based on the statistically most likely locations of neonatal seizures since the time of birth has been introduced in [21]. The short term seizure event context has been shown to increase the robustness of the detector to the seizure-like artefacts, in particular the respiration artefact [33].

The developed system has been validated in [20,21,33] using leave-one-patient-out (LOO) cross validation which is known to provide the least biased assessment of performance. This was achieved using a large clinical dataset, comprising long unedited multi-channel EEG recordings from 18 neonates with seizures and 20 neonates without seizures, totalling 1479 h of multi-channel EEG in duration and with 1389 seizures. Subsequently, the system was independently validated in [34] on a separate dataset of 41 neonates (full-term HIE, 7 with seizures, 377 seizures) and, more recently in [33], on a larger randomised dataset comprising 51 full-term neonates with HIE (24 with seizures, 1142 seizures, totalling 2540 h of multi-channel in duration). In both cases, retrospectively with LOO cross validation and using prospective datasets, similar levels of performance were achieved as measured by the mean area under the receiver operating characteristics curve (AUC) with 95.4% in [34], 96.1% in [33] and 96.7% in [21].

The system is currently undergoing a pre-market European multi-centre clinical investigation. The chosen way to visualize the system output in a clinical environment should maximise the synergy between the existing clinical practice and the support provided by the developed tool.

It is possible to see from Fig. 2 that the system can output multiple probabilistic traces, one per each channel. The maximum of the averaged probabilities across all channels can be computed to represent the final support of a seizure resulting in a single overall probabilistic trace. This probabilistic trace can be compared with a threshold to produce a trace of binary decisions: 1 for seizure and 0 for non-seizure. The 'collar' technique is applied last — every seizure decision is extended from either side to account for the delay introduced by the moving average smoothing and to compensate for possible difficulties in detecting