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Nonlinear methods for biopattern analysis: role and challenges

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Abstract—**An important trend in medical technology is towards support for personalised healthcare, fuelled by developments in genomic-based medicine. New computational intelligent techniques for biodata analysis will be needed to fully exploit the vast amounts of data that are being generated. Non-linear signal processing methods will form an important part of such computational intelligent techniques. This paper introduces some non-linear methods which are likely to play a role in the emerging area of biopattern and bioprofile analysis that will underpin personalized healthcare. We highlight their application to clinical problems involving EEG and fetal ECG and heart rate analysis, and issues that arise when they are applied to real world problems. The clinical problems include dementia assessment, drug administration and fetal monitoring. The potential role and challenges in the application of non-linear signal analysis of biopattern and bioprofile are highlighted within the context of a major EU project, BIOPATTERN.**

Keywords—**EEG, Anaesthesia, fetal ECG, dementia, biopattern, bioprofile, chaos, fractals, fractal dimension, bispectrum, ICA, fuzzy logic, neural networks.**

I. Introduction

Technology and the ability to produce vast amounts of biodata have outstripped our ability to sensibly deal with this data deluge and extract useful and meaningful information for decision making. Today, such data may come from novel biosensors, clinical practice and research (e.g. imaging, physiological measurements, laboratory tests, patient monitoring and clinical assessments), and bioinformatics. Genome-based research is providing new information about the root causes of diseases and how they might develop, but will generate more data and exacerbate the situation. New computational intelligence techniques for biodata analysis will be needed to fully exploit information from the vast amounts of data being generated in the post genome era. They will be needed in future innovative medical systems for a proper analysis and interpretation of data to support accurate prediction of the onset and progression of major diseases, their diagnosis, treatment and prognosis. They will make it possible, for example, to search for similarity in data, by data mining, to classify patterns by neural networks and to discover new knowledge.

A major EU-funded project, BIOPATTERN, which has recently started seeks to address some of the issues above to underpin eHealthcare. The Grand Vision of the project is to develop a pan-European, coherent and intelligent analysis of a citizen's bioprofile; to make the analysis of this bioprofile remotely accessible to patients and clinicians; and to exploit bioprofiles to combat major diseases such as cancer and brain diseases. A biopattern is the basic information (pattern) that provides clues about underlying clinical evidence for diagnosis and treatment of diseases. Typically, it is derived from specific data types, e.g. genomics information and vital biosignals such as the EEG and PET, in a single medical investigation using e.g. statistical signal processing, data mining and pattern recognition. A bioprofile is a personal 'fingerprint' that fuses together a person's current and past medical history, biopatterns and prognosis. It combines data, analysis and predications of possible susceptibility to diseases.

Nonlinear signal processing methods form an important part of the computational intelligence techniques that will be needed for biopattern and bioprofile analysis. In this paper, the aims are to introduce some of the nonlinear methods which are likely to play a role in biopattern/bioprofile analysis. Some of the methods are already being used to address clinical problems and we will highlight some of issues that arise when they are applied to real world problems. Their application to EEG and fetal ECG/heart rate analysis will be used to illustrate the issues. The potential role and challenges in nonlinear signal analysis and their relevance to biopattern analysis will be highlighted. The rest of the paper is organized as follows: In Section II, we introduce the nonlinear methods and point out the generic features and issues; in Sections III and IV, we illustrate their applications to clinical problems in EEG and fetal ECG analysis, respectively, and highlight the issues that arise as a result. In Section V we discuss their potential role in bioprofile analysis and conclude the paper.

II. NON-LINEAR SIGNAL PROCESSING METHODS

Many aspects of healthcare require the processing and analysis of biomedical signals such as the EEG, ECG and medical images. This may require tasks such as noise reduction, feature extraction/detection, pattern analysis/classification, visualisation and modelling. There are still enormous problems and challenges in medical signal processing, one of which is the difficulty of developing techniques that are truly robust. An understanding of the complexity of medical signals and the impact of signal processing techniques on the signals (and hence subsequent patient care) are essential for successful development of robust methods. Over the last decade, there have been significant advances in signal processing which have led to techniques that are beginning to cater for the enormous complexity of medical signals. Sophisticated non-linear signal processing techniques and tools now exist that

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can be used to handle problems associated with, for example, non-linearity, non-stationarity, non-Gaussianity, uncertainty and imprecision which are inherent in medical data. These include learning based methods (e.g. neural networks, independent component analysis and fuzzy logic), fractals and chaos-based methods and higher order statistics.

There are many types of non-linear signal processing methods [1,2]. In this paper, we will restrict the discussion to the three broad categories of non-linear signal processing methods described below which are widely used.

A. *Learning Based Methods*

In broad terms, learning based methods include independent component analysis (ICA)[3,4], artificial neural networks and fuzzy logic. ICA is an unsupervised technique to separate statistically independent non-Gaussian signals **s** from observed *linear* mixtures of these signals in **x**, such that **x=As**, where **A** is a constant and real *mxn* matrix. e.g. **x** might be multi-channel signals measured from the human scalp. The mixing matrix **A** is not known a-priory, but a pseudo-inverse **C** can be estimated using one of the ICA algorithms to find an estimate for **s**, such that **s=Cx**, where **C** is a real matrix of dimension *nxm*. Estimating **s** can be viewed as a means of blind source separation (BSS), signal enhancement, data reduction or feature extraction.

For ICA to be effective, it is a requirement that the independent signals **s** are non-Gaussian, the observed signals **x** are *linear* mixtures of the independent signals **s** and that **x** must contain at least as many (linearly independent) mixed observations as there are independent components (i.e. $m \geq n$). When ICA is applied to biomedical signals, practical problems can arise. E.g.: different ICA methods give different results; the sequence of the estimated components in **s** can vary; observed mixtures may well have non-linear interactions; if new unwanted signals are introduced, such as interference and noise, then ICA can fail if $m<n$; if there are variable delays in the biological conductive pathways, then this must be accounted for as ICA "out of the box" may fail.

Artificial neural networks, with their inherent non-linear characteristics provide a powerful framework for performing medical signal processing and analysis. In most cases, the motivation for using ANN is to exploit the ability to learn in both supervised and unsupervised modes. This is a reason ANNs are often used for feature/pattern detection/ classification. In practice, there are a number of technical aspects of neural computing which need to be addressed in order to arrive at an acceptable solution, including the issue of training, generalization, data pre-processing training and their use in clinical practice. In addition there are issues concerning safety, verification, validation, benchmarking against a 'gold' standard and acceptance of neural systems by healthcare providers and regulatory bodies.

Fuzzy logic is used to model and manipulate uncertainty and imprecision in medical data and systems [5-7].

B. *Chaos and Fractal Based Methods*

Chaos-based methods are now widely used in medical signal processing tasks. By treating the data as if they were produced from a chaotic system, appropriate nonlinear signal processing techniques may be used to analyse the data to obtain suitable measures of complexity to describe the underlying system.

In signal processing, fractal geometry provides a mathematical framework to describe and measure shapes. Before fractals were discovered the concept of dimension was equated to the number of independent coordinates necessary to specify a point within an object or set, this is the topological dimension, D_T. For example, the topological dimension of a point is zero, a line is one and a planar shape is two. A fractal is characterised by a number of dimensions, which is greater than the topological dimension and this dimension need not be integer.

The Fractal Dimension of biosignals gives a measure of signal complexity and it has been shown that this may be used as an index of abnormality. However, there is a problem with measuring the Fractal dimension of most biosignals because they exist in an affine space [8]. In an affine space the axes have incompatible units and there is no natural scaling between them (distance along the time axis cannot be compared with distance along the voltage axis). For example, the Divider Dimension of the EEG has been used to separate subjects with Alzheimer's disease from a group of normal subjects [9]. When this method was repeated on an Alzheimer's subject and a normal subject it was found that the arbitrary voltage/time scaling affected the results. Fortunately, there are more appropriate methods which have been investigated; the dimension of the zero set and the adapted box dimension [10].

C *Non-Linear Noise Reduction using Phase Space Reconstruction Methods*

This is a technique developed from chaos theory which can be used to iteratively separate independent signals from a single channel of composite data s_n. These signals might be genuine signals of interest or noise sources. This technique relies on the principle of phase space reconstruction through delay reconstruction, where points $\mathbf{s}_n = \left(s_{n-(m-1)v}, s_{n-(m-2)v} \ldots, s_{n-v}, s_n\right)$ are constructed from a *m*-tuple of consecutive samples, *v*-samples apart [11]. A sequence of points $\mathbf{s}_n$ that evolves over time is known as a trajectory, which is assumed to be bound to a finite region of space. After some period of time, these are observed to be attracted to some sub-set of phase space, known as an attractor. For non-linear systems, a limit cycle is a well known example of this. For chaotic systems, these form complex geometric shapes known as *strange-attractors*. Assuming that a given bio-signal is a mixture of a number of independent non-linear signal functions (or sources), it is assumed that each of these functions produce *distinct*

trajectories in phase space. This is the fundamental information used to separate the signals.

For non-linear noise reduction, a finite search is performed for all the neighbouring points within radius *r* of each point $\mathbf{s}_n$ to form neighbourhood sets $\mathrm{N}_r(\mathbf{s}_n)$. Each neighbourhood set is used to locally estimate the attractor **x**', typically by averaging or by forming a localized linear approximation about the point $s_{n-m/2}$. Each sample is then projected back on to the (estimated) attractor and reconstructed to form a de-noised/separated signal and a residual signal. For the simple averaging algorithm, **x**' is estimated by the following.

$$x'_{n-m/2} = \frac{1}{\left|\mathrm{N}_r(\mathbf{s}_n)\right|} \cdot \sum_{\mathbf{s}_n \in \mathrm{N}_r(\mathbf{s}_n)} s_{n-m/2} \cdot$$

With this technique we often assume the greatest difference between neighbours is due to noise rather than differences in true trajectory. The residual signal, which was considered to be noise, might now actually contain other signal components, so this process may be repeated using different parameters. A difficulty is obtaining the optimum parameters *m*, *v* and *r*.

D. Higher Order Statistical/Polyspectral Analysis

In power spectral estimation, the signal under consideration is processed in such a way that the phase relations between components are lost. The information contained in the power spectrum is essentially that which is present in the auto-correlation sequence and is sufficient to describe a Gaussian signal completely. However, there are practical situations, including EEG analysis, where it is useful to extract information regarding deviation from Gaussianity and the presence of phase relations. In these situations polyspectra (also known as higher order spectra), defined in terms of higher order statistics ("cumulants") of a signal, are useful. Particular cases of higher order spectra are the third order spectrum also called the Bispectrum which is by definition the Fourier transform of the third order statistics, and the Trispectrum (fourth-order spectrum).

Higher order statistics provide a way of describing biosignals such as the EEG without the need for prior assumptions as to the nature of the signal. The motivations behind the use of higher order statistics in signal processing include [12] their ability extract information due to deviations from Gaussianity and detect and characterise non-linear properties in signals as well as identify non-linear systems.

III. NONLINEAR METHODS IN EEG ANALYSIS

The EEG is widely used in the diagnosis and evaluation of treatment of brain diseases (if available) such as epilepsy and dementia, and more recently in monitoring patients during surgery. The amplitudes, frequencies and the spatio-temporal distribution of EEG features are affected by factors such as artefacts, medication, age, brain disease and sleep. In diseases brains, there are often marked changes in the features of the EEG.

A variety of nonlinear signal processing techniques are widely used in EEG analysis, including ICA, fractals and bispectral analysis. Makeig et al. [13] showed a first application of ICA to decomposition of rest state EEG and averaged event-related potential (ERP) data sets. The assumption made is that the EEG, as measured from the scalp, is a linear mixture of a finite number of independent signal sources from within the brain, and although this has been criticized, ICA has been effectively used to remove artefacts.

A Detection of dementia by analysis of the fractal dimension of the EEG

Fractal-based methods have been used, with some success, in the analysis of EEGs of subjects with Alzheimer's diseases and other forms of dementia. By treating the shape of EEG trace as a fractal, Fractal Dimension (FD) was used in group comparison studies to differentiate subjects with Alzheimer's disease from a group of normal subjects [9].

Unfortunately, in this and subsequent studies inappropriate methods were used to measure FD [9, 10] (e.g. the divider dimension). In more recent studies [10], this has been remedied by measuring FD of the EEG for normal and demented subjects using more appropriate methods (e.g. adapted box dimension and the dimension of the zero set). The motivation in the recent studies was to investigate the potential of FD analysis of the EEG as a basis for the detection of dementia in the large ageing population. Such a method could provide a basis for the development of a low-cost tool for early detection of the on-set of dementia, objective monitoring of its progression and the effectiveness of treatment, if available, on an individual basis. Unlike previous methods which concentrated on group comparisons and analysis of isolated (snap shot) EEGs, automated, FD based, subject specific EEG analysis is used. By subject specific we mean comparing an EEG to those taken previously from the same subject; looking for trends in FD indexes that arise over time rather than comparing an EEG to what is normal within the population. Figure 2 illustrates hypothetical changes in the FD index over time before and after the on-set of dementia. The results of a recent study of changes in the FD are summarized in Figure 2. In the study, it was found that the FD of the auto-correlation of EEG data is generally lower for subjects with dementia than for normal subjects. The studies showed that an appropriate FD measure can achieve 67% sensitivity to probable Alzheimer's disease (as confirmed by a clinical neurophysiologist from the EEG) with a specificity of 99.9%. Further work is required to validate the results in both normal and patient subjects.

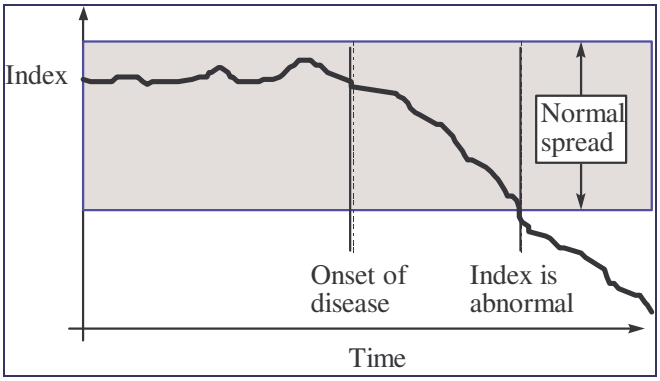

Figure 1. Conceptual index progression with time.

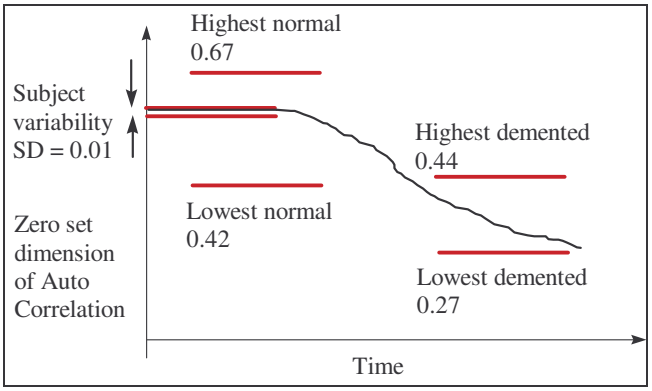

Figure 2. Subject Specific Variability

In a new fundamental study, the fractal nature of EEG was questioned. It was shown that the fractal nature of the EEG (should it exist at all) does not contribute to the success of the FD measure. The success is due to the detail of the EEG power spectral density and a natural robustness of the method.

Chaos-based dimensional complexity methods have also been exploited in EEG analysis. As the brain is constructed of synapses and neurones which have non-linear behaviour, it has been suggested that the brain could, in a mathematical sense, be chaotic. Early work in this field found that a healthy brain exhibits high complexity when it is active. If the brain exhibits low complexity when awake, this is a sign of brain dysfunction. A loss of complexity has been associated with ageing and a loss of the ability to adapt to physiological stress. However, it has been reported that normal EEG may be high dimensional and does not represent low-dimensional chaos. It was also suggested that non-linear behaviour could be confused with low-dimensional chaos.

B. Bispectrum Analysis in Anaesthesia

Bispectrum Analysis of the EEG has been successfully exploited for monitoring depth of anaesthesia (Aspect Medical Systems, Inc). During anaesthesia, the features of the EEG are altered significantly by the effects of anaesthetic agents and sedatives. The changes are progressive with increasing sedation and bispectrum analysis offers a reliable way to detect, quantify and track the changes in the EEG, and hence the brain, during anaesthesia [14, 15]. The bispectral index (Aspect Meical Systems) measures the effects of anaesthetic agents an sedatives on the brain to give an indication of the levels of hypnosis [14].

In Plymouth, we have been investigating the potential of this technology for automated drug administration that may enable both sedation and anaesthesia to be controlled with greater precision and in a less operator dependent manner [15]. The goal is to reduce the need for guess work in estimating what target concentration is appropriate for the needs of an individual patient. Potentially, this would offer smoother, safer sedation/light anaesthesia with enhanced quality care. We have developed a closed-loop system in which raw EEG is collected from the patient, processed to produce the derivative Bispectral Index which is then fed to an anaesthesia control system with additional rules which calculates an appropriate target drug concentration for the patient and adjusts the rate of infusion pump. The Bispectral Index (BIS) is a composite, numerical index ranging from 0 to 100 showing hypnotic states/sedation levels and has been prospectively validated with a large clinical database.

In one of the studies, the performance of the system was evaluated on patients undergoing surgery to provide experience in its use in clinical practice. The clinical study was approved by the Ethical Committee and all subjects/patients gave formal consent in writing. A lumber epidural catheter was placed under local anaesthesia either before (n=4) or after (n=2) starting sedation, and a regional block established. The BIS target was initially set at 65 and then adjusted at clinical discretion. Closed loop sedation was maintained throughout surgery. We studied six male patients (ASA status I-II, age 25-39 years, weight 70-100 kg). Sedation at the initial BIS target was established in minutes (mean SD). The changes of patient position and other stimuli during the placement of the lumbar epidural catheter in the first four patients were associated with rapid changes of BIS and variable levels of consciousness. As shown in Figure 3, two extra boluses were given to this patient after the initial bolus by the CLAN system to achieve the sedation target. Stable sedation was established after the over-sedation (indicated by the arrow marked with '1'). Between the 45th and 65th minute BIS remained below the target for 20 minutes without drug infusion at all due to the apparently developed natural sleep, consequently the patient 'awoke'. This resulted in the sharp rise in BIS (indicated by the arrow marked with '2') a few seconds later. However, the BIS target was achieved again quickly and maintained until the termination of the sedation.

Although the closed system was initially able to induce and maintain sedation, the response of the controller to persistent small errors caused progressive withdrawal of the sedative agent which gave clinically unsatisfactory sedation in two patients. We hypothesise that this was due to the

establishment of natural sleep in those subjects and that the actual propofol concentration might not be enough to sustain the sedation level once the natural sleep state was broken by stimulation. Thus, a minimal effect site propofol concentration constraint was added into the system for the next clinical study. We have subsequently evaluated the modified system in nine patients undergoing back surgery and found that more stable sedation level was achieved in this study than in the previous one. The studies illustrate the need to understand the nature and complexities of the medical signals if we are to make the best use of nonlinear methods.

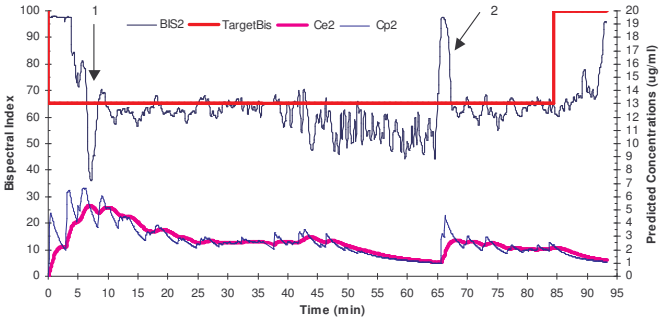

Figure 3 -4 BIS (upper thin line) and its target (upper thick line) and predicted plasma (lower thin line) and effect site (lower thick line) propofol concentration in a patient (arrow 1- over-shoot in anaesthesia induction; arrow 2 – patient unexpectedly awakened from natural sleep)

III. NONLINEAR METHODS IN FETAL ECG AND HEART RATE ANALYSIS

Electronic fetal heart monitoring (EFM) has been used for over 30 years with the specific purpose of reducing injury to the unborn baby during labour. A key objective is to detect when a baby is not coping with the stress of labour and is at risk of sustaining brain damage. It is routine clinical practise to monitor the fetal heart-rate (fHR) pattern, and more recently the morphology of the fetal electrocardiogram (fECG) signal when available [16]. Key problems include poor or variable signal quality, missing data, maternal ECG (mECG) interference, muscle noise, low-frequency noise and the non-stationary nature of the fHR. A major challenge is to gain a greater understanding of the underlying dynamics of the fetal cardiovascular system (fCVS) and autonomic nervous system (fANS) through analysis of patterns in fHR and fECG. Furthermore, making use of this data for bioprofiling is important to enable long term follow up on the effects of labour on health in later life.

Non-linear signal processing has been applied to this application to tackle many of the difficult problems that remain partially unresolved. These include separation of the fetal and maternal components of ECG measured from the maternal abdomen, noise reduction [3], detection of individual heart beats and characterisation of fetal heart rate dynamics.

A. *Learning-Based Methods*

Independent Component Analysis. The problem of separating the fetal and maternal ECG (mECG) signals measured using skin electrodes attached to the maternal abdomen can be performed using ICA [17, 18]. ICA will blindly separate the fECG, mECG and much of the noise without the use of additional reference leads. The signal-to-noise ratio is critical and ICA is most successful when (i) the fetal signal is visible above the noise floor and (ii) there are at many more measurements than the 2 (mECG + singleton), 3 (twins) or 4 (triplets) desired independent signals due to the variable number of noise sources. A continuous signal is important for subsequent analysis but this requires (i) very good electrode connections and (ii) for the patient to lie still and relax. It was reported that in the case of triplets, up to 15 channels are needed for this technique to be effective [17].

Abdominal monitoring is attractive as it is non-invasive and can potentially produce accurate fHR for antenatal monitoring, but it might be difficult to implement in routine clinical practise. It is unclear if this technique can be used during labour itself given the levels of uterine muscle noise and the mothers need for mobility.

Fuzzy Inference. The most common clinical variable used for EFM is still the cardiotocogram (CTG), which is the combined and continuous presentation of the fHR and uterine contractions. Interpretation of the CTG is a difficult task requiring expertise which is not always available day and night. Difficulties in interpretation of the CTG have led to unnecessary clinical intervention as well as failure to intervene when necessary. These problems led to a number of computerized systems to provide decision support for CTG interpretation [18,19], but very little of this is available in routine clinical practise.

For CTG analysis, expert systems (ES) are suggested to be an appropriate method to model clinical knowledge as part of a decision support system. Such rule-based systems are preferred because there is a traceable link between the behaviour of the system and knowledge contained within. Unlike the ANN, knowledge modelled with rules can be readily inspected, validated and maintained which is more acceptable to the regulatory bodies that control medical devices. Unfortunately expert systems suffer from over sensitivity to uncertainty in the data and knowledge due to the use of sharp decision boundaries (discontinuities) in the rules. Discontinuities in the knowledge space of a model produce symptoms such as outputs jittering between states due to minor changes at an input. Fuzzy logic removes any discontinuities or overly sharp derivatives in the knowledge space by using continuous and smooth functions (and subsequent derivatives). The model is therefore much less sensitive to noise or even uncertainty in the knowledge itself. Two fuzzy systems were developed by Garibaldi [7] and Skinner [20] to provide more objectives measures of birth outcome. The first analyses blood gasses in the umbilical cord and the second retrospectively analyses the

CTG. With further development, the combined systems will ultimately be integrated to produce a single objective outcome measure for labour. A notable problem for fuzzy inference systems is how to interpret the analogue outputs. A crisp decision must ultimately be made, either by machine or man. Another problem is measuring the performance of such systems. Our work on evaluating performance of intelligent systems, described by Tilbury [21], is still ongoing.

B Nonlinear noise reduction for fECG.

Another approach to blind separation of fECG and mECG that uses only one channel of data from the maternal abdomen (3-leads) is nonlinear noise reduction as described earlier in sec. II-D, [11] and [22]. A fetal signal is first obtained by careful choice of electrode position and adjusting the mother's posture. We found the fECG and mECG signals to be separable because they each follow distinct trajectories in phase space.

An example of some data we collected is shown in Figure 5, where the larger maternal component is clearly visible. In this application we assume (i) the mECG has larger peak amplitude than the fECG, (ii) the amplitudes of the mECG and fECG signals are constant, (iii) neighbouring trajectory points correspond to equal relative points in the cardiac cycle from different beats and (iv) low frequency (LF) noise has been removed. The latter point in important as LF noise is not part of the underlying dynamics. This technique first considers the fECG to be part of the noise, and extracts a clean maternal vector from the composite abdominal signal. The process is repeated (with different parameters) on the residual vector containing only fECG and noise to enhance the fetal signal (Figure 6). In practise, data is processed in blocks of typically 30 beats. A difficulty is choosing the optimum parameters m, v and r. In this application $m \approx 15$ (for $Fs=500Hz$) and $v=1$. The choice of r depended on the peak-amplitude of the mECG and fECG. We plan to investigate these techniques further using multi-lead configurations and compare the results with ICA.

C Chaos Based Techniques for Fetal Heart Rate Analysis

Chaotic and highly non-linear autonomous systems can also demonstrate irregular behaviour. It is important to remember that non-linear systems with random external inputs also produce such behaviour [11]. Chaos based techniques assume an autonomous system is being analysed although the techniques are still useful when external random inputs are present, and this is the case for fetal heart rate (FHR) analysis during labour. It is believed that the fetal heart rate acts as a mirror on the fetal Autonomic Nervous Systems (fANS) and Cardiovascular System (fCVS).

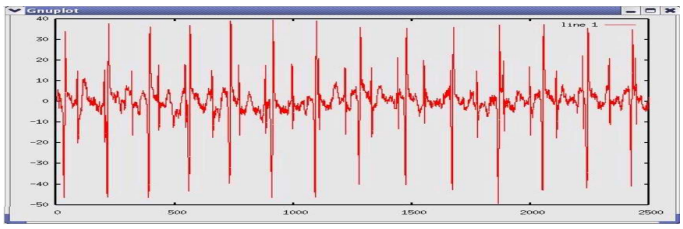

Figure 5. Composite abdominal ECG (fECG + mECG + noise)

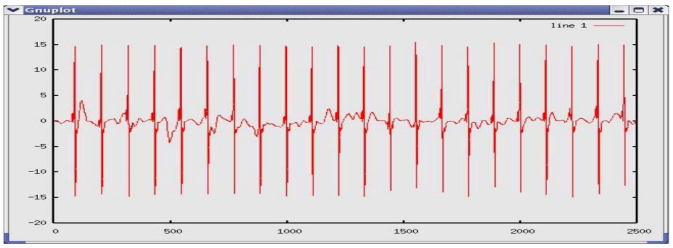

Figure 6. Noise-free fECG

This can be viewed as a non-linear closed loop control system, with external random inputs (e.g. uterine contractions), often demonstrating highly non-stationary statistical behaviour. A healthy fetus is often characterised by a "reactive" fHR trace, typically quantified as having higher complexity or entropy. A very unhealthy fetus is characterised by a fHR trace which is less complex and of lower entropy. In the limit, the fHR becomes smooth and even flat in the event of death. Metrics such as fractal dimension, correlation dimension and Lyapunov exponents are of potential interest, but are more readily applied to antenatal monitoring where there are less external influences. The most challenging but clinically important situation is fHR analysis during labour. During labour, the fHR cannot be assumed to be regulated by a strictly autonomous system given that the external events in labour, such as uterine contractions (see Figure 7), umbilical cord occlusions and also where the administration of drugs are known to affect fHR. A potentially contentious issue is that of baseline heart rate, where the local mean of the fHR varies slowly over time. Techniques such as approximate entropy (AppEn), correlation dimension and estimates of Lyapunov exponents all require the location of neighbouring points in phase space, yet observed self-similar patterns in fHR with different baseline fHR will not be matched as neighbours. De-trending of the fHR of baseline fHR will increase the number of neighbours, but is controversial because baseline fHR is considered to be part of the underlying dynamics of the fHR.

It remains a challenge to gain a further insight into the dynamics of the fANS and fCVS during labour and to relate them to fHR patterns during labour. This is an application of particular interest and presents major challenges. Today we have access to over 20,000 fetal heart recordings, and with the support of industry and the EU funded BIOPATTERN project [23], we plan to investigate this area further.

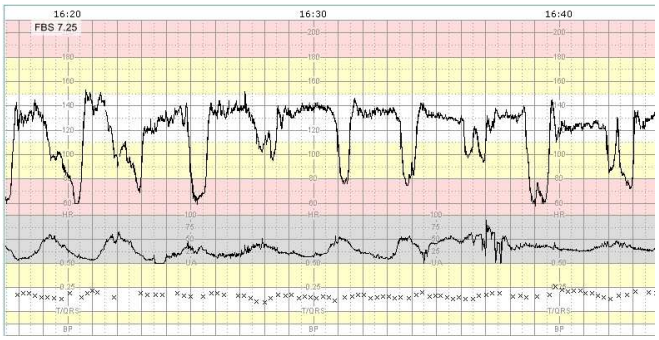

Figure 7. A cardiotocogram showing HR decelerations (top) due to uterine contractions (middle); fECG morphology quantified on the lower trace (courtesy of Neoveanta Medical AB)

V CONCLUSIONS AND THE FUTURE

In the post genome era, with the vast amounts of biodata being generated, new computational intelligent techniques will be needed in future innovative medical systems for a proper analysis and interpretation of data to help combat major diseases (e.g. to support accurate prediction of the onset and progression of major diseases, their diagnosis, treatment and prognosis). Nonlinear methods will play an important role in this.

The potential role of nonlinear methods should be seen against grand visions such as that of BIOPATTERN where they will be needed for the analysis and use of biopatterns and bioprofiles. Aspects of *bioprofiles* could exist in databases, distributed across multi-centres, and accessible on-line in a secure way. On-line resources would be used for, e.g., data analysis and evaluation, remote diagnosis, decision support, epidemiological studies, trials and research purposes. For example, for diagnosis, an authorized user (anywhere) would supply the necessary bioprofile, an appropriate set of algorithms are then used to analyse the bioprofile, on suitable machines which may be distributed across the world, possibly utilizing large distributed database(s) of examples, and the outcome of the analysis is then returned to the user. We envisage that it may be necessary to extend existing nonlinear methods to deal with the emerging need for bioprofile and biopattern analysis and to handle large and complex data sets.

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