Mini-Symposia Title:

Complexity in cardiovascular and respiratory systems

Theme:

- 01. Biomedical Signal Processing
- 02. Biomedical Imaging and Image Processing
- 03. Micro/Nano-bioengineering; Cellular/Tissue Engineering &
- 04. Computational Systems & Synthetic Biology; Multiscale modeling
- (●) 05. Cardiovascular and Respiratory Systems Engineering
- 06. Neural and Rehabilitation Engineering
- 07. Biomedical Sensors and Wearable Systems
- 08. Biorobotics and Biomechanics
- 09. Therapeutic & Diagnostic Systems and Technologies
- 10. Biomedical & Health Informatics
- 11. Biomedical Engineering Education and Society
- 12. Translational Engineering for Healthcare Innovation and Commercialization

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Mini-Symposia Synopsis— Max 2000 Characters

The cardiovascular and respiratory systems interact between each other and with other physiological systems of the human body. Such interactions evolve in a complex and dynamical way producing fluctuations in the output of physiological processes. Researchers have investigated fluctuations in different biomedical signals, as the heart beat to beat interval and systolic blood pressure, analyzing characteristics as irregularity or entropy. However, later on, the term complexity appeared in the field to advance in the study of fluctuations attempting to highlight that physiological processes are carried out in different time scales. Nowadays, the concept of complexity reflects the ability of a biological system to adapt to the constantly changing environment. If a system gets sick, then this condition should be reflected in loss of complexity. Diverse complexity measures have been approached by techniques as multi-scale entropy, multiscale entropy based on symbolic dynamics, multifractal-multiscale detrended fluctuation analysis, among others, providing richer information possibly improving the understanding of different pathologic processes. In this sense, the goal of the minisymposium is to bring together recent proposed techniques to determine signal complexity as well as physiological interpretation to evidence alteration of the homeostasis in different pathological conditions.

Multifractal Multiscale DFA of Cardiovascular Signals: Removing the Estimation Bias from Short-term Coefficients

Paolo Castiglioni and Andrea Faini

***Abstract*— The Detrended Fluctuation Analysis (DFA) is now used to calculate the multifractal and multiscale self-similarity coefficients of the heart rate. However, the DFA coefficients may be overestimated at the shortest scales and this may alter the resulting multifractal-multiscale structure. The aim of this work is 1) to describe this error as a function of the multifractal order and scale and 2) to propose a way to mitigate this error.**

I. INTRODUCTION

The Detrended Fluctuation Analysis (DFA) describes the fractal nature of the cardiovascular series by splitting the integrated series into consecutive blocks of n beats, calculating the variance of the residuals after detrending in each block k, $\sigma^2_n(k)$, and evaluating the 2nd order moment of σ^2_n over all the k blocks, $F(n)$. The slope of log $F(n)$ vs. log n provides the self-similarity coefficient α. The DFA has been extended to evaluate the multifractal-multiscale dynamics calculating the q^{th} moment of σ^2_n, $F_q(n)$, and the $\alpha(q,n)$ coefficients as the local slopes of log $F_q(n)$ vs. log n [1]. However, the 2nd order DFA may overestimate α at the shortest scales [2]. If this error affects also $\alpha(q,n)$, it may alter the quantification of multifractality. Thus, we aim to evaluate whether $\alpha(q,n)$ is affected by an error that depends on n and q, and to propose a procedure to mitigate this error.

II. METHODS & RESULTS

To quantify the DFA estimation errors, we synthesized 10 series of 2^{14} samples from 3 monofractal-monoscale processes with known self-similarity coefficients: white (α=0.5), pink (α=1.0), and Brown (α=1.5) noise. We estimated $\alpha(q,n)$ between $-5 \le q \le 5$ and $8 \le n \le 512$. Figure 1 (upper panels) shows the average coefficients indicating that the DFA overestimates the true α. The error depends on the type of noise, being greater for white than Brown noise, and for each noise, it increases as n or q decreases.

The error is likely due to the occasional overfitting of the detrending polynomial that causes too low residual variances at the shortest scales that affect the $F_q(n)$ estimate mainly at $q<0$. Thus, we propose to remove these outliers not considering σ^2_n lower than a given threshold. The threshold is identified for each noise minimizing a recently proposed index of the degree of multifractality: the cumulative function of the negative-q squared increments [3]. The lower panels of Figure 1 show that the proposed correction eliminates most of the estimation bias affecting $\alpha(q,n)$ at negative q and small n.

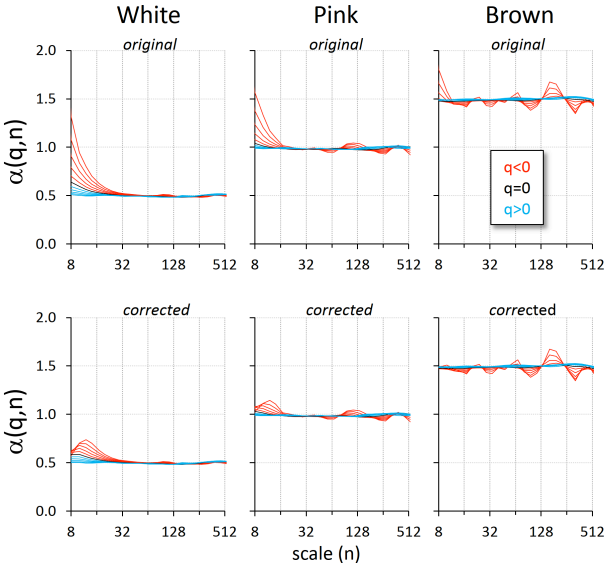

Figure 1. DFA coefficients of 3 monofractal monoscale processes. *Upper panels*: original estimates; *lower panels*: corrected estimates.

III. DISCUSSION & CONCLUSION

The DFA estimation bias may erroneously indicate the presence of multifractality at the shortest scales. The proposed correction method allows applying the multifractal multiscale DFA also at the shortest scales, potentially extending its use in studies of cardiovascular physiology.

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Proper Method Selection for the Meaningful Quantification of the Cardio-Respiratory Interactions

Anna M. Bianchi[1], Manuela Ferrario[1], Maria G. Signorini[1], Martin O. Mendez[1,2]

Abstract— **The well known approach for the quantification of the sympatho-vagal balance controlling heart rate, fails when the applications hypothesis are not fulfilled. Different models are introduced for a better characterization of the cardio-respiratory interactions in different conditions.**

I. INTRODUCTION

The effects of the rhythmical respiratory activity on the heart rate variability (HRV) signal, the well known Respiratory Sinus Arrhythmia (RSA), is commonly recognized as a marker of the vagal activity controlling the heart frequency. In the frequency domain it is usually identified in the high-frequency (HF) oscillations present in the power Spectral Density (PSD) of the HRV signal. It is synchronous with the respiratory rate and the associate power, in absolute value, as well as in normalized units is considered a quantitative marker of the parasympathetic activity acting on the heart [1]. Many different studies have also associated the low frequency (LF) rhythm, in the HRV PSD, to the orthosympathetic activity after observing a marked increase in its power following a sympathetic stimulations. Thus, the LF/HF ratio is commonly considered as an index of the sympatho-vagal balance. On the other hand, it is worth mentioning that this model fails when the application hypotheses are not fulfilled:

1. the respiration activity is not concentrated on the HF range, but spans covering also the LF range;
2. the respiration activity contains non-stationarities, thus the standard frequency domain techniques are not suited for the analysis;
3. the interactions between respiratory activity and HRV are not linear.

In the above cases other models are required, which take into account the complex characteristics of the cardio-respiratory system and the interacting relationships between the signals. In the present paper different models are presented and compared, while results are discussed.

II. METHODS

Bivariate frequency analysis. A bivariate autoregressive (AR) model was implemented for separating the HR beat-to-beat variability into activity synchronous with respiration, thus associated to the vagal activity, and activity non-synchronous with respiration [2]. The method was used to analyze a group of 69 (35 females) preschool healthy children (age: 64.3±4.5 months, mean±SD) exposed to the Strange Situation Procedure (SSP), intended to elicit stress through a standardized procedure.

Time frequency analysis. An AR bivariate model was made time-variant through recursive implementation with forgetting factor, in order to achieve a tracking of the changing interactions between the signals [3]. A group of 10 healthy subjects were analyzed during a tilt-test.

Transfer Entropy. The method was used to assess the directional coupling between respiration and HR incorporating both linear and non-linear interactions [4]. The analysis was performed on data acquired from 151 newborns.

Phase synchronization. Synchronization index quantifies the adjustment of the rhythms of self-sustained oscillators due to their interaction. A directionality index is also calculated [5]. The methodology was applied for the analysis of a group of newborn babies providing 279 segments in quiet sleep and 419 segments in active sleep [5].

III. RESULTS

Comparisons and statistical analysis demonstrate that the proposed methods are able to better quantify cardiorespiratory interactions, when the hypothesis required for the application of more traditional spectral analysis are not matched, in particular when respiration signal is not regular, when the signals are not stationary and when non-linear interactions are present.

IV. DISCUSSION & CONCLUSION

The examples here reported support the importance of the correct approach when analyzing physiological data. The recording conditions and the acquisition protocols, as well as the type of interaction relationships between signals, must always guide the selection of the most suited methodology.

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Characterization of Complex Cardiovascular Interactions in the ICU: a Sepsis Identification Study

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Abstract— **Early recognition and treatment of sepsis are proved to have a strong impact in reducing patient mortality. The two main sources of relevant information collected in the intensive care unit (ICU) are the electronic health records and vital sign waveforms continuously recorded at the bedside. Waveforms contain key instantaneous information aimed at inferring the physio-pathological condition of the patient and, if properly processed using mathematical models of the cardiovascular control system, they could eventually provide prompt and timely recommendations to the physicians. The goal of our research efforts is to demonstrate the critical role of measures describing cardiovascular interactions derived from monitored vital signs in ICU patients. Here, we focus on our latest results adding entropy measures from blood pressure time series to our modeling framework based on the statistical description of hearbeat dynamics generation, and we show their efficacy in improving the discriminant ability for sepsis identification within the first hour of admission in the ICU.**

I. INTRODUCTION

Sepsis, the dysregulated host response to infection, is considered one of the major conditions in intensive care units (ICU) [1]. Its final stage, septic shock, leads to a 38.9% mortality. Sepsis is known to strongly affect cardiovascular functioning, leading to strong impairment of both myocardial and autonomic functions. Vital signs like electrocardiogram (ECG) and arterial blood pressure (ABP), continuously monitored from patients admitted in the ICU, contain critical information about the state of the patient, with a high potential for extraction of features for developing predictive algorithms of having sepsis at the admission.

The general aim of our research is to validate a novel framework that fuses vital waveforms with data stored in the electronic health records of patients in the ICU. A few previous studies identified a reduction in heart rate variability (HRV) measures induced by sepsis in adults and particularly in non-linear measures like entropy, whereas only a few studies expanded non-linear analysis to the blood pressure time-series (BPTS), which investigated the association between blood pressure variability (BPV) and illness severity as well as the ability of complexity measures from BPTS in predicting sepsis, vasopressor independence at 24-hr and 28-day mortality. The presented exemplary study investigates if inclusion of a nonlinear characterization of the interactions between heart rate and blood pressure provides useful information for predicting sepsis.

II. METHODS AND RESULTS

The study includes data gathered from the PhysioNet MIMIC-III database [2]. Patients' data are time-aligned according to their ICU admission, and the first 1-hour electrocardiogram (ECG) and arterial blood pressure (ABP) recordings from ICU admission are extracted for sepsis prediction, resulting in 71 septic (third international consensus for Sepsis and Septic Shock) and 71 non-septic patients.

ECG and ABP waveforms are preprocessed and annotated to extract R peaks synchronized with systolic (S), diastolic (D) and onset fiducial points from ABP. In addition to standard HRV and ABP features, entropy features from RR and pressure (SAP, DAP) time-series as well as the cross-entropy between RR and SAP [3] are also derived. The entropy features are added to a previously developed machine learning (ML) model in order to assess whether, on the hidden test set (20%), they improve performances on sepsis identification.

When adjusting for common ICU confounders, main results indicate that entropy computed from RR (RR_SampEn) is not different between septic and non-septic subjects, whereas SAP and DAP entropy measures (SAP_SampEn, DAP_SampEn), as well as cross-entropy between RR-SAP time-series (XEn_RR-SAP), are significantly different between the two groups. Results obtained with a Logistic Regression model show an improvement in AUROC of 4% with respect to the best performance obtained without entropy features, resulting in an AUROC=0.95 on the test set.

III. DISCUSSION & CONCLUSION

Our latest results reveal the significant role of entropy features extracted from arterial blood pressure time-series in discriminating septic from non-septic subjects. More in general, the applications developed around our statistical learning framework demonstrate the feasibility of computational tools that could be implemented in monitoring devices able to continuously track patient's conditions and physio-pathological states, and to assist the practitioner's complicated decisions at the ICU bedside in a timely matter.

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Analysis of the respiratory signal during the A3-phases of the Cyclic Alternating Pattern of Sleep

Martin O. Mendez[1,2], Alfonso Alba[1], Ericka Reyes-Sanchez[1], Anna M. Bianchi[2]

***Abstract*— A-phases are cortical events of short duration occurring in the EEG during Non-REM sleep. A-phases are related to the sleep instability and to the homeostasis processes during sleep. A specific class of A-phases, A3-phases, is connected to the sleep stage transitions and to pathologic events during sleep, which directly affect the behavior of the cardiovascular and respiratory systems. The study aims to analyze the dynamics of the instantaneous phase of the airflow signal during the A3-phases in healthy subjects. The results showed a nonlinear behavior of the instantaneous phase 10s after A3-phase was initiated. This suggests a strong disruption of the respiratory pattern associated to the presence of the A3-phases.**

I. INTRODUCTION

Sleep is a process typical of the central nervous system which, otherwise, involves other different systems that compose the body, such the cardiovascular, respiratory and hormonal, which participate in an organized manner. The sleep time is segmented in two stages based mainly on the electrical activity of the brain. These stages are called REM and Non-REM and a REM/Non-REM cycle appears approximately four or five times during the sleep period. During Non-REM stage, it is possible to identify disruptions/modifications in the electrical activity of the brain for short periods of time. Some of these disruptions are named A-phases and present durations between 2s and 60s. Furthermore, A-phases are categorized as A1-phase, A2-phase or A3-phase based on the frequency content. From A-phases, it is possible to define the Cyclic Alternating Pattern (CAP) which is a useful clinical tool to quantify the sleep instability [1]. In literature, most of the studies of CAP are dedicated to analyze the behavior of the central system and just a few studies evaluate the effects of CAP over other systems. Thus, there exists a lack of information related to the CAP as a multi-system phenomenon. Specifically, the respiratory system is vital since it is responsible of the gases interchange needed for the body metabolism. During sleep, the respiratory system can be analyzed by the nasal airflow signal which appears as a mono-component fluctuation. This fluctuation could be modified by noxious events such apneas or cortical changes connected to the A-phases. The aim is to study the behavior of the respiratory system in relation to the A3-phases to understand better the effects of the CAP phenomenon in other systems.

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II. METHODS

Ten polysomnographic recordings of healthy participants with ages between 26 and 56 years were used. The acquisition and A-phase annotations were done in the Sleep Center of Parma, Italy. From the recordings, the airflow signal was analyzed. Here, the changes in the instantaneous phase of the airflow signal around the A3-phase onset were studied and compared with respect to an ideal linear model [1].

III. RESULTS

Fig. 1 shows an example of the instantaneous phase for the airflow signal before and during the A3-phase. We can observe a clear deviation with respect to a linear model during the A3-phase. In addition, the boxplots of the deviations for all the A3-phases are showed. We can observe an increase in the deviation (p-value < 0.05 using Wilcoxon test).

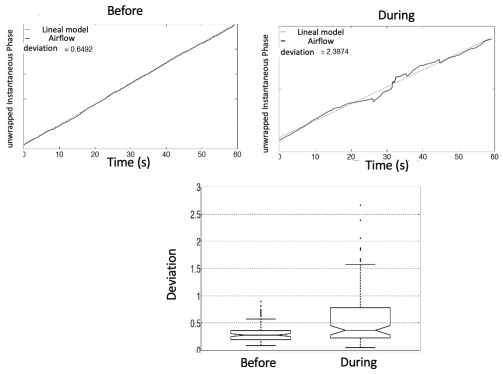

Figure 1. Deviation of the instantaneous phase of the airflow signal before and during the A3-phase.

IV. DISCUSSION & CONCLUSION

Variations in the fluctuations of the airflow signal occur at least 10 s after the initiation of the A3-phase, which are later with respect to the heart response. It could suggest a specific order in which the systems response to the A3-phase occurrence. This means, A3-phases need a minimum duration to generate quantifiable changes on the respiratory system.

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Disruption of the Cortical-Vagal Communication Network in Parkinson's Disease

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Abstract— **Parkinson's disease (PD) is a neuropathy characterized by motor disorders, but it has also been associated with the presence of autonomic alterations as a result of degradation of the dopaminergic system. Studying the relation between Band Power time series (BPts) and Heart Rate Variability (HRV), has been proposed as a tool to explore the bidirectional communication pathways between cortex and autonomic control. This work presents a primer analysis on study brain⇔heart interaction on a database of PD patients under two conditions: without and after levadopa (L-dopa) intake. Additionally, a healthy control population was also analyzed, and used as comparison level between both conditions. Results show PD affects pathways by reducing the number of connections, especially association of beta and power and the second faster component of HRV seems to be more sensitive to L-dopa administration.**

I. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative process that reduces the number of dopaminergic neurons [1]. Electroencephalographic (EEG) signal analysis has been explored to find useful biomarkers that can be used as diagnostic tool on early symptoms, evaluate disease progression or to increase knowledge about alterations related to PD evolution. Quantitative EEG analysis has shown that PD alters beta band. He et al. [2] observe an increase on the interhemispheric coherence on early onset patients.

Heart ⇔ brain interactions have been observed while in resting state in healthy subjects. In 2013, Liou et al. [3] showed correlations between HRV and EEG power over different bands and that this correlation changes depending on a breathing task.

Our results confirm that the network structure is altered on PD compared with a healthy control group, but also that L-dopa administration produces differential changes on networks associated with different spectral components of the HRV signal.

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II. METHODS

The HRV signal was interpolated at a sampling frequency of 10 sps using a cubic spline and decomposed into intrinsic mode functions (IMF) using the Empirical Mode Decomposition (EMD) method, obtaining up to four IMFs. The band power time series BPts were estimated for alpha (BPtsα, [8-12]Hz), beta (BPtsβ, [14-30]Hz), gamma (BPtsγ, [30-100]Hz) and theta (BPtsθ, [4-8]Hz) bands with a sliding window of two seconds and a sliding step of 0.1 seconds using the Welch periodogram estimator. A Granger causality test, on both directions, was run between the BPts of each EEG frequency band and channel (Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, and O2) and the HRV IMFs. A total of 306 possible connections were tested per each subject.

III. RESULTS

Comparison between the groups show that in general control group presents larger connection numbers than the other two groups in both directions, except for HRV⇔IMF2, indicating that presence of PD has effect on the cortical-ANS network. In general, medicated group achieves lower number of connections than non-medicated.

IV. DISCUSSION & CONCLUSION

Cortical-ANS network analysis suggests that PD could affect communication pathways between cortical centers and vagal effectors that control heart rate. For the four EEG bands analyzed, a reduction in the number of connections was observed for the medicated and non-medicated groups compared with control.

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Characterization of blood pressure signal in pregnant women with hypertensive disorders through symbolic dynamics

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***Abstract*— Identification of pregnancies at risk of developing preeclampsia before it manifests clinically is of great interest. Multiscale symbolic entropy of blood pressure signal was able to show a complexity decrease in preeclampsia patients in the first trimester of pregnancy.**

I. INTRODUCTION

During the pregnancy occurs maternal autonomic cardiovascular control changes with the aim to optimize maternal and fetal oxygen and nutrients support [1]. However, these cardiovascular control mechanisms can be disturbed generating hypertensive disorders, where the blood pressure and vascular resistance are increased, and blood volume is smaller [2]. One of these hypertensive disorders is preeclampsia (PE), which is a major cause of maternal and fetal mortality and morbidity. The early detection of PE is challenging since this disorder can be asymptomatic and the syndrome eventually resolves once the placenta is removed, which can complicate the delivery. Therefore, identification of pregnancies at risk of developing PE before it manifests clinically is of great interest, because maternal and fetal morbidity and mortality could be diminished, and the complications that PE can cause for both, mother and baby could be reduced.

Blood pressure variability analysis has been performed to find predictive factors that precede the origin of hypertensive disorders. Some approaches including symbolic dynamics, joint symbolic dynamics, and Lempel-Ziv complexity. However, the analyzed data generally are from the second and third trimester. Therefore, the data analysis from the first trimester could elucidate if it is possible to predict these hypertensive disorders in a very early phase.

II. METHODS

Data acquisition of 42 unigest pregnant women was performed at the Maternal-Fetal Medicine Research Unit (UNIMEF) of the National Institute of Perinatology Isidro Espinosa de los Reyes (INPer). The pregnant women were divided into three study groups with 14 participants each: normotensive women throughout pregnancy (N), normotensive women during pregnancy without comorbidities (S), and normotensive women who developed PE (PE). The clinical protocol was performed in the first trimester of pregnancy, defined as the period between weeks 11 and 14 of gestation and consisted of 5-minute supine recordings of non-invasive blood pressure (CNAP). The systolic and diastolic time series were extracted using the CNAP signal. Given a time series, x_n, consecutive coarse-grained time series corresponding to the scale factor τ is constructed. First, the initial time series is divided into non-overlapping windows of length τ; second, the data points inside each window are averaged. Then the new time series is transformed into an alphabet of four symbols based on the time series mean and a scale parameter [3]. Sequences composed of segments of three consecutive symbols (words) are formed. From the distribution of words, Shannon and Renyi entropies were obtained to measure the complexity of the distribution. Additionally, another alphabet was used, where the range of the time series is divided evenly in 6 levels (0-5). Then, words of length 3 are formed, which are grouped in 4 classes according to the variation of the word: 0V, 1V, 2LV and 2UV.

III. RESULTS

Fig. 1 shows significant differences (p<0.05, Kruskal-Wallis test) between normotensive group and PE group in the Shannon entropy value of the first 3 scales. Similar statistical differences were found considering Renyi entropy with q=0.25 and q=4 only for systolic time series.

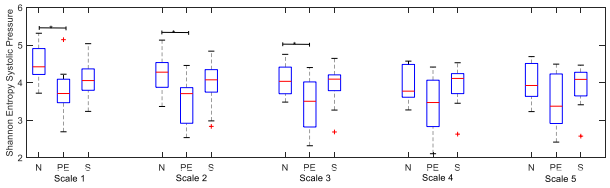

Figure 1. Multiscale symbolic entropy of systolic time series of pregnant women groups. * Significant differences with p<0.05.

IV. DISCUSSION & CONCLUSION

The multiscale symbolic entropy of systolic pressure showed a decreased complexity in the PE group in comparison with the normotensive group in a very early stage of pregnancy. This result is promising since could allow very early detection and a better prognosis of hypertensive disorders.

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