Autonomic Stress in Plateau Waves of Intracranial Pressure: Spectral Mutual Information Rate Analysis

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***Abstract*—Plateau waves (PW) in intracranial pressure (ICP) often manifest in traumatic brain injury (TBI), presenting as abrupt increases in ICP exceeding 40 mmHg, accompanied by a decrease in cerebral perfusion pressure (CPP). The occurrence of PWs is a significant cerebrovascular phenomenon with potentially devastating effects for the patient, which is reflected in heart rate variability (HRV), typically assessed by RR intervals in electrocardiographic recordings. This study employs the spectral formulation of mutual information rate (MIR) to dynamically quantify the coupling between RR intervals and ICP across 27 episodes of PWs from 7 patients with TBI. Furthermore, this measure of information theory can be decomposed into entropy rate components related to complexity, each of which can be integrated into frequency bands with physiological significance. Our findings demonstrate the feasibility of using non-parametric spectral measures to analyze cardio-cerebral interactions. Specifically, during PW events, complexity decreases across all frequency bands examined, indicating increased regularity in RR intervals. Changes in dynamic coupling during PW may be linked to autonomic nervous system dysfunction, potentially stemming from the interaction between the parasympathetic system and ICP. These results suggest the potential inclusion of information-theoretic measures into intensive care units (ICU) monitors to improve the prediction and management of these stress episodes.**

***Keywords*—mutual information rate, plateau waves, spectral analysis, time series analysis, traumatic brain injury**

I. Introduction

Traumatic brain injury (TBI) is one of the common causes of acute brain injury (ABI) causing a significant global socioeconomic burden. In TBI, the occurrence of plateau waves (PWs) in intracranial pressure (ICP) monitoring poses a critical challenge. This prolonged increase in pressure, exceeding 40 mmHg for more than 5 minutes, can exacerbate secondary brain injury and complicate overall patient management [1]. Indeed, ICP peaks may vary in proportion based on cerebrospinal compliance, with a gradual alteration of the waveform as ICP rises, indicating an increased pathological stress. Furthermore, the autonomic nervous system (ANS) significantly influences the regulation of ICP and cerebral autoregulation, both of which are impacted by PWs. The autonomic stress that triggers PWs is reflected in Heart Rate Variability (HRV), as can be seen in Fig. 1 the stress episode decreases heart rate (HR). Past studies using conventional HRV methods [2] showed that median HRV spectral values, integrated in the low (LF, $0.04 - 0.15$ Hz) and high (HF, $0.15 - 0.4$ Hz) frequency bands, typically increase immediately before and during PWs, decrease after the event, and then rise during recovery.

Advancements in technology have equipped ICUs with devices enabling continuous brain monitoring, proving crucial for detecting secondary brain damage [3]. Multimodal Brain Monitoring (MBM) assesses cerebral function using multiple modalities in a single patient, offering an integrated interpretation of potential secondary insults. Simultaneous, time-synchronized data collection, and integrated display are essential for providing targeted, individualized care. In fact, the previous work of Almeida et al. [4] employed AutoRegressive Fractionally Integrated Moving Average Generalized Autoregressive Conditional Heteroskedasticity (ARFIMA-GARCH) modeling to effectively measure the extended correlations and fluctuating volatility of HRV. The application of this modeling approach, combined with MBM, was successful in assessing HRV dynamics in diverse acute cerebral conditions such as intracranial hypertension, decompressive craniectomy, and brain death. Their findings demonstrated the model capacity to capture alterations in HRV dynamics related to TBI and the impact of medical interventions. Some recent studies, using the integrative approach of Network Physiology [5], have employed multiscale partial information decomposition of Transfer Entropy (TE) within a Vector AutoRegressive Fractionally Integrated (VARFI) framework [6], [7], or frequency-based spectral decomposition with Vector AutoRegressive (VAR) modeling [8], demonstrating the efficacy of dynamic multiscale network analysis in characterizing HRV changes during PWs.

Information theory has proven to be a flexible and reliable

H.P and A.P.R were partially supported by CMUP, member of LASI, which is financed by national funds through FCT, under the project UIDB/00144/2020. H.P. thanks Fundação para a Ciência e Tecnologia (FCT), Portugal for the Ph.D. Grant 2022.11423.BD. L.S, Y.A. were supported by SiciliAn MicronanOTecH Research And Innovation CEnter "SAMOTHRACE" (MUR, PNRR-M4C2, ECS_00000022), spoke 3-Università degli Studi di Palermo S2-COMMs-Micro and Nanotechnologies for Smart & Sustainable Communities. R.P. was partially supported by European Social Fund (ESF) Complementary Operational Programme (POC) 2014/2020 of the Sicily Region.

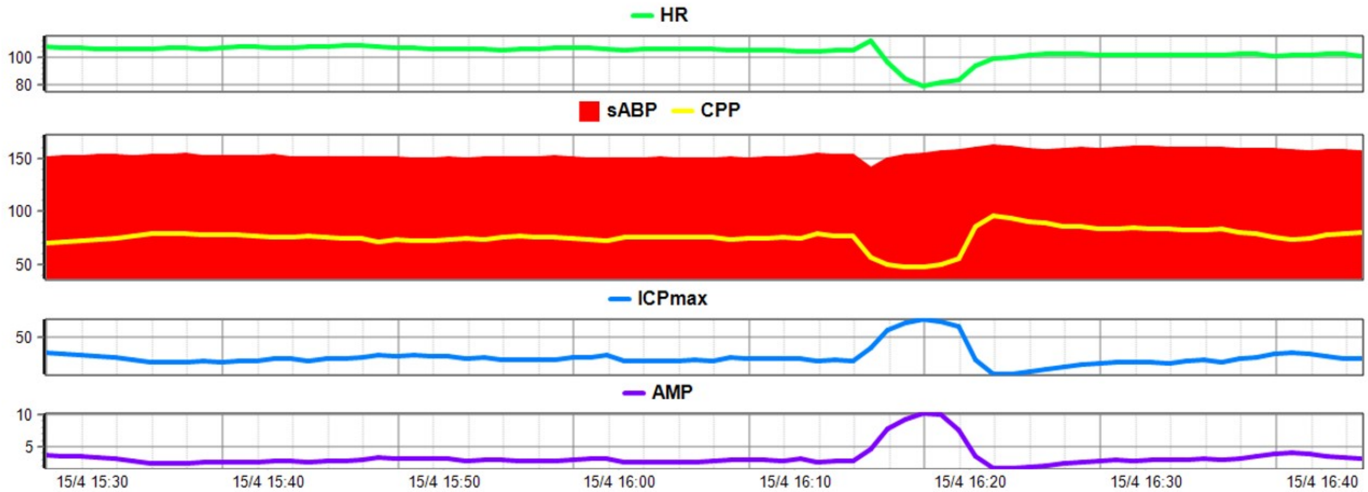

Fig. 1. PW episode and its preliminary analysis were conducted in ICM+ (Cambridge Enterprise, UK), with Heart Rate (HR, green) measured in beats per minute, Systolic Blood Pressure (sABP, red) along with Cerebral Perfusion Pressure (CPP, yellow) measured in mmHg, intracranial pressure (ICP, blue) recorded in mmHg, and Amplitude of ICP (AMP, purple) measured in mmHg.

framework for studying and describing the dynamics of complex systems. In this context, the Mutual Information Rate (MIR) quantifies the information shared by the two processes per unit of time and can be easily decomposed in the frequency domain thus allowing the study of physiological systems with a rich oscillatory content. With the aim of improving the understanding of the mechanisms underlying the interaction between RR and ICP, in this study MIR is used to assess brain/heart crosstalk in time and in specific frequency bands.

II. Spectral Mutual Information Rate

Let us consider two ergodic stationary stochastic processes X and Y with zero mean. Their current states are denoted by X_n and Y_n, and their past states by $X_n^q = [X_{n-1}, \ldots, X_{n-q}]$ and $Y_n^q = [Y_{n-1}, \ldots, Y_{n-q}]$, where q sets the history length (embedding dimension). The degree of association between the two processes is quantified by the MIR, an information-theoretic measure defined as [9]

$$I_{X;Y} = \lim_{q\to\infty} \frac{1}{q} I\left(X_n^q; Y_n^q\right). \tag{1}$$

where $I(\cdot;\cdot)$ denotes the Mutual Information (MI). Thus, the MIR is a symmetric measure quantifying the information shared between two random processes per unit of time. This measure of dynamic coupling can be decomposed in terms of other information-theoretic measures, offering valuable insights into the dynamics of each process and the coupling relationships within the analysed bivariate system. Specifically, the MIR can be decomposed as the sum of the entropy rates (ER) of the two involved processes X (H_X) and Y (H_Y), minus the joint ER of the two processes ($H_{X,Y}$) [9]

$$I_{X;Y} = H_X + H_Y - H_{X,Y}, \tag{2}$$

where the ERs can be written in terms of conditional entropies, $H_X = H(X_n \mid X_n^q)$, $H_Y = H(Y_n \mid Y_n^q)$, and $H_{X,Y} = H(X_n, Y_n \mid X_n^q, Y_n^q)$.

The MIR decomposition in (2) can be represented in the frequency domain, since spectral counterparts of the ERs can be defined starting from the power spectral density (PSD) of the bivariate process $[X, Y]$. The latter is a symmetric 2×2 matrix $P_{[XY]}(\omega)$ containing the spectra of the two scalar processes X and Y as diagonal elements ($P_X(\omega) = \mathfrak{F}\{R_X(k)\}$, $R_X(k) = \mathbb{E}[X_n X_{n-k}]$, and $P_Y(\omega) = \mathfrak{F}\{R_Y(k)\}$, $R_Y(k) = \mathbb{E}[Y_n Y_{n-k}]$), and their cross-spectra as off-diagonal elements ($P_{XY}(\omega) = \mathfrak{F}\{R_{XY}(k)\}$, $R_{XY}(k) = \mathbb{E}[X_n Y_{n-k}]$, where), where $\omega \in [-\pi, \pi]$ is the normalized frequency ($\omega = 2\pi \frac{f}{f_s}$ with $f \in \left[-\frac{f_s}{2}, \frac{f_s}{2}\right]$, f_s denoting the sampling frequency), and $\mathfrak{F}\{R.(k)\}$ is the Fourier transform of the autocorrelation or cross-correlation functions. Specifically, the spectral measure of ER of the process X (or, analogously, of Y) is defined as [10]

$$h_X(\omega) = \frac{1}{2}\log\left(2\pi e P_X(\omega)\right), \tag{3}$$

while a spectral measure of the MIR between the processes X and Y is given by [11]

$$i_{X;Y}(\omega) = \frac{1}{2}\log\frac{P_X(\omega)P_Y(\omega)}{\left|P_{[XY]}(\omega)\right|}, \tag{4}$$

where $|\cdot|$ stands for matrix determinant. Specifically, the spectral ER and MIR quantify the rate of generation of new information in a random process and the information shared by the two processes per unit of time at each frequency ω, respectively. Crucially, the spectral information measures defined in Eqs. (3) and (4) can be easily linked to the time-domain measures outlined in Eq. 2 through the spectral integration property [12]:

$$H_X = \frac{1}{2\pi}\int_{-\pi}^{\pi} h_X(\omega)\mathrm{d}\omega, \tag{5}$$

$$I_{X;Y} = \frac{1}{2\pi}\int_{-\pi}^{\pi} i_{X;Y}(\omega)\mathrm{d}\omega. \tag{6}$$

The spectral integration property has the dual role to link interaction measures in the time and frequency domains, but also to enable the quantification of these measures in specific spectral bands of physiological interest.

A. Non Parametric Estimator

Different methods exist to estimate the PSD of random processes, each with its own strengths and weaknesses. The selection of the method relies on signal traits, data availability, and analysis needs, often involving a trade-off among frequency resolution, variance reduction, and computational complexity [13], [14]. There are two different well-known typologies of methods: non-parametric algorithms and parametric approaches, as for example, the one based on VAR models [15]. In this work, the nonparametric weighted covariance (WC) method [16], which exploits the Fourier Transform of the sample auto-correlation and cross-correlation functions of the data, was employed. The WC estimator of the PSD computes the cross-PSD between X and Y as [14]

$$\hat{P}_{XY}(\omega) = \sum_{k=-\tau}^{\tau} w(k)\hat{R}_{XY}(k)e^{-\mathbf{j}\omega k}, \qquad (7)$$

where $\mathbf{j} = \sqrt{-1}$. Considering that L is the number of data samples, $\tau \leq L-1$ is the max lag for correlation, w is a lag window of width 2τ ($w(k) = 0$ for $|k| > \tau$), normalized ($0 \leq w(k) \leq 1$) and symmetric ($w(-k) = w(k)$), and $\hat{R}_{XY}(k)$ denotes the biased estimator of cross-correlation function [17]. In this study, the Parzen window was employed due to its significantly lower side-lobe level compared to the Hanning and Hamming windows. Additionally, it maintains non-negativity for all frequencies and yields non-negative spectral estimates [17]. For the Parzen window, the relationship between the bandwidth (B_w) of the spectral window and the lag τ at which correlation estimates are truncated is $B_w = 1.273 f_s/\tau$.

III. Application to Plateau Waves of Intracranial Pressure

A. Protocol, Signal Acquisition and Time Series Extraction

This study involves a dataset comprising 27 episodes of PWs from 7 patients (6 males, mean age 42) with severe TBI, monitored in the neurocritical care unit (NCCU) at Centro Hospitalar São João (CHSJ) [2]. Approval from the local research ethics committee and written consent from the patients were obtained. Using the ICM+® software, different signals were acquired, including electrocardiogram (ECG), arterial blood pressure (ABP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), and the expired CO_2 level, as detailed in [2].

The R-to-R intervals of the ECG (RR) and the amplitude of the ICP signal (AMP) time series were extracted and used in this work, the latter were calculated as the difference between systolic and diastolic ICP points within each cardiac cycle. For each patient, the two time series were segmented into six phases: two 15-minute baseline periods (B1 and B2) occurring prior to the onset of PW, until ICP increased by more than 20 mmHg; the PW phase, corresponding to ICP exceeding 40 mmHg; four 15-minute recovery baseline phases (B3-B6). A sliding window Hampel filter [18] was employed to detect and replace outliers. After visual inspection, the stationarity of the extracted segments was assessed using the augmented Dickey-Fuller (ADF) test [19].

B. Data Analysis and Statistical Analysis

To account for variations in heart rate within frequency bands with physiological meaning, the MIR between RR and AMP ($I_{RR;AMP}$), the ER of RR (H_{RR}), ER of AMP (H_{AMP}) and the joint ER ($H_{RR,AMP}$) were computed following the approach described in Sect. II. For each subject and segment, the truncation lag for the correlation estimates was obtained by fixing $B_w = 1.273 f_s/\tau = 0.015$ Hz [13] and setting $f_s = 1/\overline{RR}$, where $\overline{RR}$ is the mean RR. The spectral profiles of the ER and MIR measures were integrated in the low-frequency (LF, $0.04-0.15$ Hz) and high-frequency (HF, $0.15-0.4$ Hz) bands of the spectrum [20]. Time domain counterparts were obtained by integrating the spectral profiles along the whole frequency axis.

As regards data analysis, the differences between baseline and PW phases were evaluated through a Z-test with a significance level of $\alpha = 5\%$. This analysis considered the estimated marginal means (EMM) of the repeated measures model [21] and incorporated the Bonferroni correction for multiple comparisons, $n = \binom{7}{2} = 21$. The models EMM were computed using MATLAB R2023b software (MathWorks, Natick, MA, USA).

C. Results and Discussion

Results are shown in Fig. 2 in terms of violin plots with overlapping individual values of MIR and its decomposition terms. LF (panel a), HF (panel b) and the corresponding time-domain values (panel c).

In the LF band, H_{RR}, H_{AMP}, and $H_{RR,AMP}$, depicted respectively in Fig. 2(a1)-(a3), exhibit a significant decrease during the PW phase when compared with the baseline phases preceding the PW (B1 and B2), followed by a gradual increase (especially for $H_{RR,AMP}$). This is likely to indicate increased regularity in AMP and RR, and suggesting a slow recovery. Even after an hour, complete recovery may not be achieved, revealing the high level of stress in these episodes [22], [23]. On the other hand, $I_{RR;AMP}$ is significantly higher during the stress phase, particularly when compared with the baseline phases observed after the PW (B3, B4, B5, B6), this can be a result of the interaction between the slow waves of ICP and RR intervals [24].

In the HF frequency band, a similar trend is observed; specifically, a statistically significant decrease of H_{RR} moving from B1 to the PW phase is detected, as shown in Fig.2(b1). Additionally, both H_{AMP} and $H_{RR,AMP}$, displayed in Figs.2(b2)-(b3), exhibit significantly lower values in PW compared to all the baseline phases. Conversely, the rise in ICP during PW results in an increase of the dynamic coupling

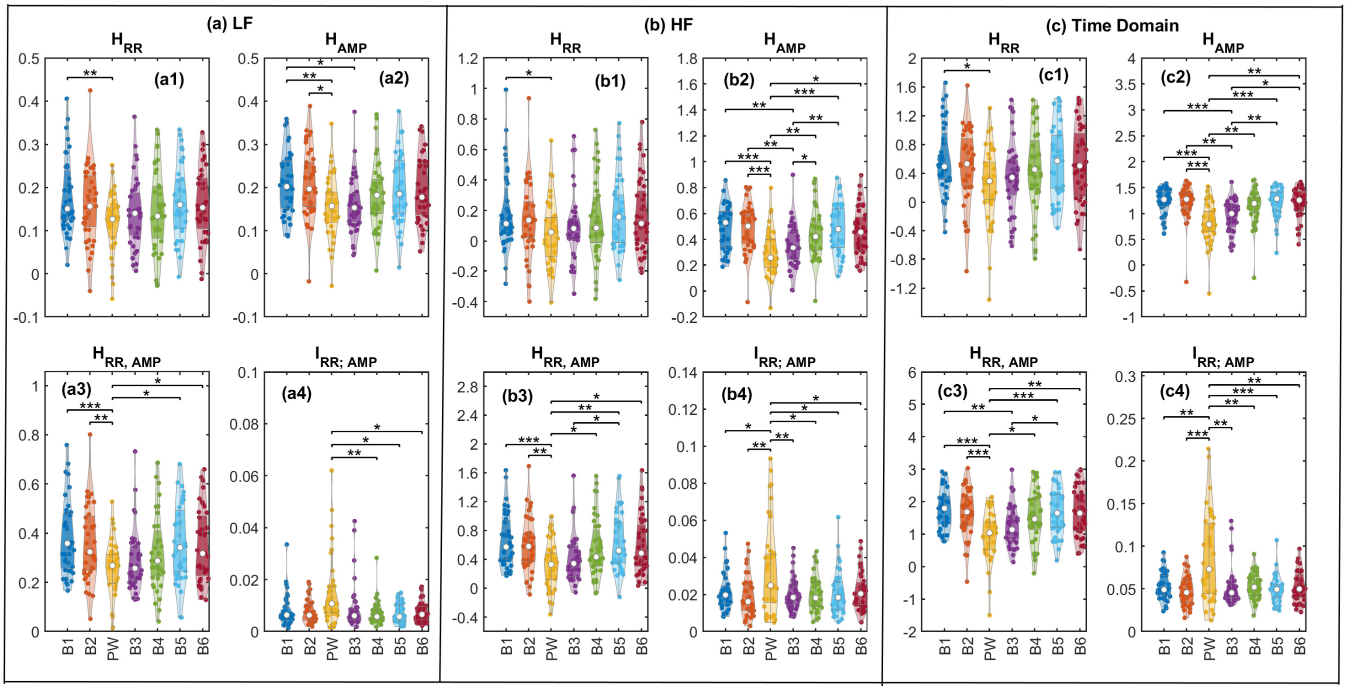

Fig. 2. Violin plots illustrating distributions of the spectral measures of MIR and its decomposition terms, alongside with individual values, across B1, B2, PW, B3, B4, B5, and B6 phases for the **(a)** LF and **(b)** HF frequency bands, and **(c)** the corresponding time domain measures obtained by integrating across all frequencies. The lines represent kernel density estimates of the data, and the shadow in the center of the violin represents the 25th and 75th percentiles, with the center point marking the median. Statistical analysis employed a post-hoc test with Bonferroni correction for estimated marginal means (EMM) within a repeated measures model: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

$I_{RR;AMP}$, as illustrated in Fig. 2(b4). However, contrarily to what happens in the LF band, $I_{RR;AMP}$ is significantly lower in phases B1 and B2 when compared to PW. These findings suggest a potential interaction between ICP and the parasympathetic system, which may be attempting to restore the declining cerebral blood flow observed during these intense stress events [23]. The analysis did not take into account the respiratory signal, despite evidence showing that higher respiratory frequency diminishes the amplitude of heart rate oscillations [25]. Conversely, increases in tidal or static lung volume tend to increase variability in the RR intervals [25]–[27]. Consequently, the impact of mechanical ventilation in the ICU could significantly affect HRV variation in the high-frequency band [28], so further studies must be conducted to assess this issue.

Finally, the time-domain measures reflect to some extent the behavior observed in the LF and HF bands, as shown in Fig. 2(c), since the time domain counterparts can be seen as average values of spectral measures integrated in these frequency bands. In summary, we observe a reduction in H_{RR}, H_{AMP}, and $H_{RR;AMP}$ (Figs. 2(c1)-(c3)), corroborating [22], where a parametric estimator accounting for long-range correlations was employed. The coupling, measured by $I_{RR;AMP}$, increases significantly during the stress phase compared with the baseline phases preceding and following the stress episode (Fig. 2(c4)). These findings further support the presence of a potential feedback loop from ICP to RR interval, particularly highlighting its amplification during episodes of PWs [29].

It is important to stress out that the time domain measures are not able to discriminate among different physiological effects associated with the activity of the ANS, hence the importance of integrating measurements into physiologically meaningful frequency bands [20]. For example, in Figure 2(c2), it is evident that the statistically significant differences in the time domain are primarily influenced by the values obtained in the HF band, as illustrated in Figure 2(b2). Regarding $I_{RR;AMP}$, Figure 2(c4), the significant decrease observed in baseline phases after the PW episode is mainly related to the LF band, as summarized in Figure 2(a4). This decrease possibly reflects sympathetic activation during the stress phase and subsequent recovery in the following baseline phases.

IV. Final Remarks

This study highlights the feasibility of examining cardio-cerebral interactions in pairs of physiological time series during PW episodes using the spectral formulation of MIR.

During plateau wave occurrences, complexity decreases, indicating increased regularity in RR intervals and AMP processes, often signaling a pathological state. The increase in dynamical coupling during this phase is possibly associated with the abrupt rise in ICP and its interaction with the parasympathetic system.

The obtained results suggest new possibilities for the quantitative analysis of plateau waves. Indeed, while some already used methods provide indicators or early warnings, an accurate prediction is still not feasible. Furthermore, integrating time varying methods [30] with information measures like MIR and its components could in perspective offer further valuable insights for predicting this stressful episode.

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