Transfer Entropy Characterization of TBI Cases

Milena M. Arruda, Luciana R. Veloso and Francisco M. de Assis

***Abstract*— Traumatic brain injury (TBI) is an important public health problem worldwide. This paper introduces transfer entropy as a measure to identify any standard between arterial blood pressure and electrocardiogram signal for patients diagnosed with TBI. Therefore, we will review the basic definitions of information theory and transfer entropy, which interpretation is influenced not only by the Kullback-Leibler divergence, but also by conditioned mutual information. For transfer entropy measurement we used Kraskov-Stögbauer-Grassberger (KSG) technique. It is observed that directionality in transfer entropy can provide clinical decision support for TBI cases.**

***Keywords*— Arterial blood pressure, electrocardiogram, transfer entropy, traumatic brain injury.**

I. Introduction

Traumatic brain injury (TBI) is a non-degenerative, non-congenital assault to the brain from an external mechanical force, possibly leading to permanent or temporary damage of cognitive, physical and psychosocial functions, with an associated reduced or altered state of consciousness [2].

Information on TBI cases in Brazil is available on the database of the Information Technology Department of the Unified Health System (DATASUS), maintained by the Brazilian Ministry of Health and available on line at http://datasus.saude.gov.br/. According to registers, between January 2008 and December 2016, there were around 130,500 hospital admissions per year due to TBI, corresponding to incidence of 65.2 admissions per 100,000 inhabitants per year, considering Brazil's current estimated population (191 million). Besides, the average cost of hospital expenses per admission was nearly US$ 500 and the case fatality rate was 7.6%.

Clinical decision support on TBI cases is indispensable for changing these numbers. Actually, the pressure reactivity index has been addressed on diagnosis and prognosis and it's defined as the least square linear regression slope of intracranial pressure (ICP) versus arterial blood pressure (ABP) [6]. The relationship between ABP and heart rate was discussed by [7] for changes in posture. Based on their results it is possible to extend them to investigate the behavior of these signs for TBI cases.

A model-free approach will be used to detect causality between electrocardiogram (ECG) and ABP using the transfer entropy's concept. Transfer entropy is an asymmetric measure which can determine linear or non-linear coupling of two variables by quantifying the information transferred between them [3]. Thus, it is possible to identify patterns and to investigate the coupling of physiological variables in different scientific fields [8], [9].

This paper is structured as follows. Section II organizes notations, and section III reviews basic definitions of information theory such as: Shannon entropy, Kullback-Leibler divergence and mutual information in order to have a better understanding of the definition of transfer entropy. Section IV presents the methods for acquisition and processing of the database, including how transfer entropy may be estimated. Section V presents the results of transfer entropy estimation to physiological data. Finally, section VI concludes the paper.

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II. Notation and Terminology

To standardize our discussions, in this paper, we denote random variables with uppercase letters, stochastic processes with uppercase bold letters, their alphabets with calligraphic letters (e.g., $\mathcal{X}$ denotes the alphabet of random variable X) and their probability mass function with $p(\cdot)$. The nth output the process is indicated by subscripts, e. g., X_n. The finite length sequence with order (k) of a random variable is denoted by superscripts, e. g., $X_n^{(k)} = \{X_n, \cdots, X_{n-k+1}\}$. Throughout this paper, log refers to base 2, thus, information measured is always in bits.

III. Transfer Entropy

Transfer entropy's interpretation can be understood from the basic definitions of information theory, therefore, we will review some concepts starting with Shannon entropy [11]. For a random discrete variable X, the Shannon entropy is defined as

$$H(X) = -\sum_{x\in\mathcal{X}} p(x)\log p(x), \tag{1}$$

i. e., it is the average number of bits needed to optimally encode X with marginal probability mass function $p(x)$.

Related concepts involve the relative entropy or Kullback–Leibler divergence [12] and mutual information [13]. The Kullback-Leiber is a measure of the divergence between two distributions and to quantify the excess number of bits when distribution q(x) is used instead of p(x), defined as

$$D(p||q) = \sum_{x\in\mathcal{X}} p(x)\log\frac{p(x)}{q(x)}. \tag{2}$$

Mutual information is a trustful measure of dependency between random variables, which measures the uncertainty of a random variable that is reduced when we know the value of other random variable [14]. It can be interpreted as Kullback-Leibler divergence between the joint distribution and the product distribution besides, like in equation (4), or yet as

relationship of entropys, in equation (5) . Mutual information is defined by:

$$\begin{aligned} I(X;Y) &= \sum_{\mathcal{XY}} p(x,y)\log\frac{p(x,y)}{p(x)p(y)}, && (3)\\ &= D(p(x,y)||p(x)p(y)), && (4)\\ &= H(X) - H(X|Y), && (5) \end{aligned}$$

where $H(X)$ is the entropy of X and $H(X|Y)$ is the conditional entropy of Y relative to X.

These definitions can be extended to conditional probabilities of a random variable given another. For mutual information, the conditionality inserted in dependence between random variables reduces its uncertainty when the value of another random variable is given. Therefore, conditional mutual information definition [13] is

$$I(X;Y|Z) = H(X|Z) - H(X|Y,Z). \quad (6)$$

The definition of transfer entropy is broad and allows diverse interpretations. According to Schreiber [3] the most straightforward way to construct a mutual information rate considering the entropy rate for a single process and generalizing to two processes ($\mathbf{X}$ and $\mathbf{Y}$) is by measuring the deviation from independence.

Considering a single process that can be approximated by a stationary Markov with order (k), it is preferable to measure the deviation from conditional probability of a single process given their pass and conditional probability of two processes that are not independent. From the generalized Markov property

$$p\left(X_{n+1}|X_n^{(k)}\right) = p\left(X_{n+1}|X_n^{(k)}Y_n^{(l)}\right), \quad (7)$$

i. e., transfer entropy quantifies the information flow between two processes when they are not independent and can be approximated by a stationary Markov process. This concept is illustrated in Figure 1.

Transfer entropy is defined by Schreiber [3] as equation (8)

$$\begin{aligned} T_{\mathbf{Y}\to\mathbf{X}} &= \sum p(X_{n+1}, X_n^{(k)}, Y_n^{(l)}) \log \frac{p(X_{n+1}|X_n^{(k)}, Y_n^{(l)})}{p(X_{n+1}|X_n^{(k)})}, && (8)\\ &= H\left(X_{n+1}|X_n^{(k)}\right) - H\left(X_{n+1}|X_n^{(k)}, Y_n^{(l)}\right), && (9)\\ &= I\left(X_{n+1}; Y_n^{(l)}|X_n^{(k)}\right). && (10) \end{aligned}$$

Considering an incorrect assumption about the transition probabilities, this measure can be quantified by Kullback-Leibler divergence in equation (9). On the other hand, conditional mutual information is also able to quantify this dependence like in equation (10). In this case it is considered the uncertainty between two different process given the past of system under study.

Since transfer entropy is a measure of dependence of $\mathbf{X}$ on $\mathbf{Y}$ with directionality parameter, it is non-symmetric. Thus, when the state of Y has no influence on the transition probabilities on system $\mathbf{X}$, information flow from $\mathbf{Y}$ to $\mathbf{X}$ is zero.

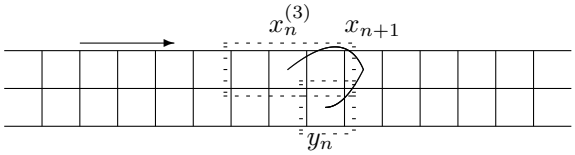

Fig. 1. Transfer entropy scheme when $k = 3$ and $l = 1$.

IV. Methods

A. Physiologic Datasets

Both ECG and ABP signals for healthy individuals and for patients with TBI were available in PhysioNet dataset [5] - free web access to the research resources for complex physiologic signals. PhysioBank databases are made available under the ODC Public Domain Dedication and License v1.0.

A collection of functions for reading, writing, and processing physiologic signals and time series in the formats used by PhysioBank databases, among others, is available for 64-bit MATLAB, WFDB Toolbox [5], [15].

Two datasets were studied: physiologic response to changes in posture (PRCP) and cerebral haemodynamic autoregulatory information system database (CHARIS DB). In total, twenty-one subjects compose the sample set of these bases (9 males, 8 females and 4 unidentified) with mean age of 38.9 ± 18.6. Among them, ten were healthy volunteers and eleven were diagnosed with traumatic brain injury.

The PRCP database contains ABP and ECG waveforms for participants that had no sign of cardiovascular disease. Each subject was instrumented with a standard clinical ECG monitor and a non-invasive blood pressure monitoring device (FINAPRES) [7]. After instrumentation, subjects rested on a tilt table with foot support and subsequently underwent a series of six changes in posture, but only the recording in the resting supine position were analyzed by us. The sampling rate was 250 Hz.

The CHARIS database contains multi-channel recordings of ECG, ABP, and ICP of patients diagnosed with TBI or its injury associated like as: cerebrovascular accident (CVA), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH) and subdural hematoma (SDH). Those signals were acquired from outputs of clinical monitors routinely employed, via isolated and filtered (25 Hz cutoff) outputs from a General Electric TRAM-rac 4A with a sampling rate of 50 Hz [6].

B. Estimation Technique

While concepts of information theory are relatively straightforward and mathematical formulations are objective, in practice, their estimation can be a complex process. Limitations as the finite number of samples and intrinsic properties of time-series data, restrict the use of some estimators that are subject to bias and variance.

For discrete variables, the approach for numerical estimation is simple and can be made by counting the configurations for each probability estimates. However, for continuous variables, the estimation should be more careful. One of the possibilities is to discretize or bin the data and use the discrete estimators, but it is likely that accuracy will be committed.

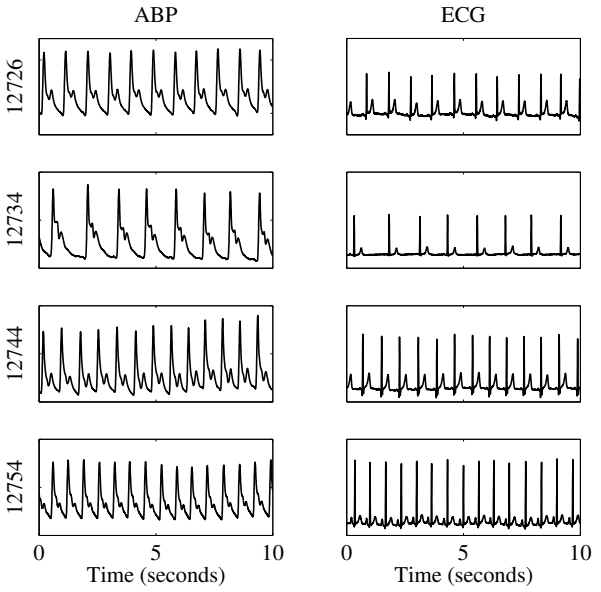

Fig. 2. Arterial blood pressure (ABP) - above - and Electrocardiogram (ECG) - below - signals for healthy volunteers.

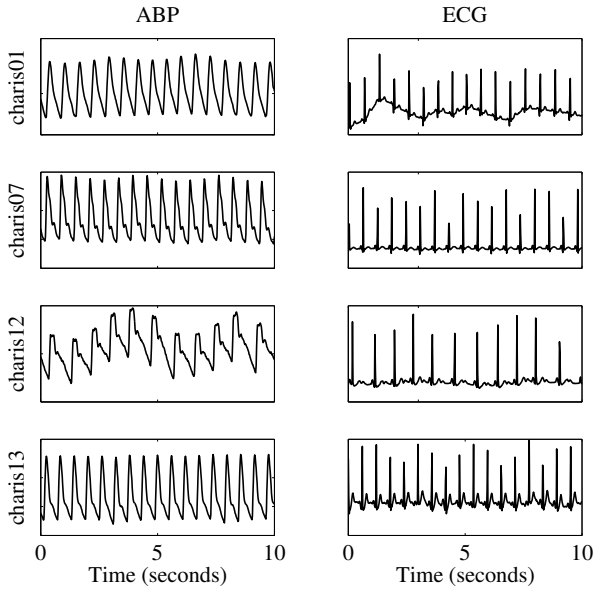

Fig. 3. Arterial blood pressure (ABP) - above - and Electrocardiogram (ECG) - below - signals for patients diagnosed with traumatic brain injury (TBI).

The estimators for continuous variables used were: Gaussian-distribution model, kernel estimation and Kraskov-Stögbauer-Grassberger (KSG) technique. This study used KSG technique because it was less sensitive to bias being more attractive in our application.

Toolboxes for transfer entropy estimation have been recently proposed, with special attention to the method of probability transition estimation. We used the KSG technique [4], implemented at v1.0 Java Information Dynamics Toolkit (JIDT) [10], an open-source code implementation for empirical estimation of information-theoretic measures from time-series data.

KSG technique includes the use of Kozachenko-Leonenko estimators of log-probabilities via nearest-neighbor counting; bias correction; and a fixed number K of nearest-neighbors in the full X-Y joint space, to reduce errors when handling a small number of observations [10]. In general, this technique smooths errors when estimating probability distribution function using a dynamically altered resolution to adjust the density of samples in the neighborhood of any given observation.

The estimator used implements a naive algorithm which refers to the first KSG algorithm. For estimation of $I(X;Y|Z)$, the algorithm measures similarity between samples using a resolutions r_z, r_{xz} and r_{yz} for each sample $\{x, y, z\}$ available as being maximum distance between sample and Kth nearest neighbor. Then, the number of neighbors within these widths are counted (n_z, n_{xz} and n_{yz}) and used to calculate:

$$I(X;Y|Z) = \psi(K) + \langle \psi(n_z + 1) - \psi(n_{xz} + 1) - \psi(n_{yz} + 1) \rangle , \quad (11)$$

where $\psi(\cdot)$ denotes the digamma function. For this study we used $K = 4$.

V. Results and Discussions

A bi-variate time series of ABP and ECG signals for four volunteer for each database is shown in Figure 2 and Figure 3. In that figures, the patients diagnosed with TBI have the following variations of injures in brain:

- charis01: SAH and SDH and TBI
- charis07: SAH
- charis12: SDH
- charis13: ICH and SDH

It is noticeable that the ABP signs have more differences between them, since cases of TBI occur when an external force injures the brain, mainly affecting the patient's arterial blood pressure.

The analysis of information flow directionality using transfer entropy for ABP and ECG signals, were performed for each subject. In order to verify the variation of the flow of information over time, we performed an average and standard deviation on 10 runs for different samples of 30 seconds each. These measurements are shown in Table I and Table II.

The results of the transfer entropy using this signal were possible because there is a causal relationship between it. This causality is also observed due to the non-zero values in the measurements. Therefore, a standard change regarding the intensity of the direction of the information flow that presents the highest bit rate for both cases (healthy and TBI cases) is identified.

Healthy subjects have a measurements of entropy transfer between process, in direction from ABP to ECG, lower than patients diagnosed with TBI. While in the opposite direction (ECG to ABP) the information measurements is lower for TBI cases (see Figure 4).

From these first results, we can introduce a new support for clinical decision on TBI cases. In Figure 4, areas of

TABLE I

COMPARISON OF TRANSFER ENTROPY DIRECTIONALITY IN BITS FOR ABP AND ECG SIGNALS FOR HEALTHY VOLUNTEERS.

Volunteer	ABP→ECG	ECG→ABP
12726	0.2063 ± 0.0303	0.3435 ± 0.0139
12734	0.1244 ± 0.0085	0.1340 ± 0.0165
12744	0.2849 ± 0.0086	0.3718 ± 0.0093
12754	0.1890 ± 0.0246	0.2765 ± 0.0311
12755	0.2686 ± 0.0284	0.4015 ± 0.0335
12814	0.1488 ± 0.0075	0.2414 ± 0.0158
12815	0.1645 ± 0.0069	0.3121 ± 0.0362
12819	0.3095 ± 0.0173	0.3707 ± 0.0286
12821	0.2748 ± 0.0052	0.4431 ± 0.0073
13960	0.1312 ± 0.0242	0.3051 ± 0.0404
Mean±std	0.2102 ± 0.0161	0.3200 ± 0.0233

TABLE II

COMPARISON OF TRANSFER ENTROPY DIRECTIONALITY IN BITS FOR ABP AND ECG SIGNALS FOR PATIENTS DIAGNOSED WITH TBI.

Volunteer	ABP→ECG	ECG→ABP
charis01	0.4945 ± 0.1319	0.2652 ± 0.1083
charis03	0.5935 ± 0.0585	0.3752 ± 0.0211
charis04	0.3548 ± 0.0990	0.0305 ± 0.0260
charis06	0.6110 ± 0.0514	0.4666 ± 0.0729
charis07	0.7500 ± 0.0514	0.5089 ± 0.0384
charis08	0.7672 ± 0.0666	0.2403 ± 0.0345
charis09	0.3529 ± 0.0731	0.1000 ± 0.0670
charis10	0.5762 ± 0.0698	0.3665 ± 0.0323
charis11	0.7900 ± 0.1111	0.4138 ± 0.0302
charis12	0.1611 ± 0.0837	0.1244 ± 0.0781
charis13	0.8637 ± 0.0601	0.5200 ± 0.0220
Mean±std	0.5741 ± 0.0779	0.3101 ± 0.0483

intersection are perceptible, due to the standard deviation of the samples analyzed for both cases of volunteers studied. However, regardless of these intersections, it is possible to identify from the higher level, in bits, for each directionality, if the subject should be diagnosed with TBI.

VI. CONCLUSIONS

Transfer entropy is an important method to detect the direct exchange of information between two physiological signals. However, the choice of the estimator that best fits the data to be processed is very important. It's essential for reducing both the bias and the computational cost involved. The best estimator is the one which can emphasize the properties of the signals and thus guarantee a good measure. In this case, the best estimator was the one based on KSG technique.

From the tests carried out with the open database, PhysioNet, it can be observed that the presented information measure can offer a valuable support for clinical decision in TBI cases. Patients diagnosed with TBI have transfer entropy greater in the direction of information flow ABP to ECG, whereas for healthy individuals the reverse happens.

Therefore, the importance of working with diagnostics is to explore methods that can simplify and automate medical procedures.

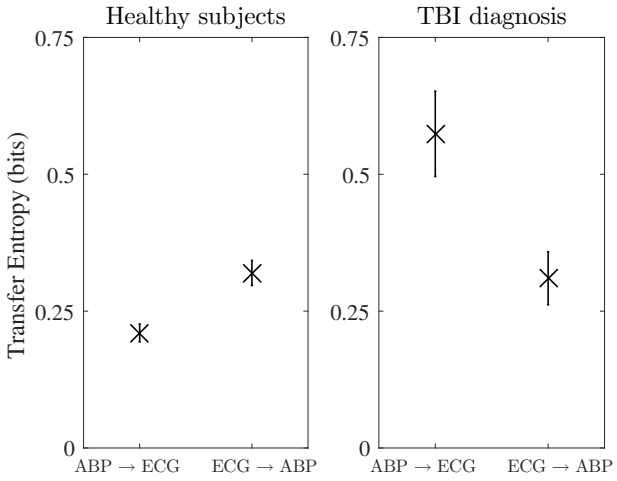

Fig. 4. Relationship between mean and standard deviation of transfer entropy measurements for healthy patients and TBI cases. On the left side we have the direction $ABP \rightarrow ECG$; On the right side $ECG \rightarrow ABP$.

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