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Sequences and antisequences in hypertensive patients under therapyPlatform

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Abstract— **Baroreceptor reflex (baroreflex, BRR) is a domineering physiological regulator considering the systolic blood pressure (SBP) and heart rate (HR). It maintains the negative feedback equilibrium: if the blood pressure increase, heart rate decreases and vice versa. The aim of this study is to compare the number of baroreflex sequences in hypertensive patients before and after the drug administration, and to oppose the assumptions about their origin. Other methods that evaluate the mutual connection between the SBP and HR time series are investigated as well, such as cross-entropy, copula parameter, and probability integral transformed entropy. Surrogate data were used as a control.**

Keywords-baroreflex; hypertension; heart rate; systolic blood pressure; sequences; entropy; copula; probability integral transform;

I. INTRODUCTION

Baroreceptor reflex (baroreflex) is one of the most important mechanisms that maintains stable blood pressure and homeostasis of the organism. It starts in the specialized sensors - mechanoreceptors, called baroreceptors, located in the blood vessels. The sensors detect the blood vessels' stretching and contraction, thus detecting the blood pressure change. This information is transmitted via afferent neural fibers towards the central neural system (CNS). In a case of blood pressure increase, the CNS increases the activity of parasympaticus and decreases the activity of sympaticus, so the heart rate decreases and, as a consequence, the blood pressure decreases as well [1]. Failure in baroreflex may indicate a range of cardiovascular and other disorders, such as cognitive heart insufficiency, increased heart attack risk, hypertension, diabetes [2].

Multivariate analysis of cardiovascular time series has been the subject of numerous studies [3]. In addition to the method for the quantification of baroreflex sensitivity [4, 5], classical contributions rely on power spectrum density approach, as well as on multivariate autoregressive analysis [6]. More recent analyses implement tools designed specifically to assess the mutual orderliness of simultaneously recorded time series and the level of their (a)synchrony, such as cross-entropy [7, 8] and its variations such as [9], [10], [3], including the multi-scale cross-entropy [11, 12, 13, 14, 16].

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Copula density that visualize the beat-to-beat dependency structure of systolic blood pressure (SBP) and RR intervals (RRI) was proposed in [12]. Its relationship to the differentially coded cardiovascular time series and to the signals with portapres-induced errors are given in [16] and [9] respectively.

A survey of Verapamil in literature includes the effect considering cardiac arrhythmias [17], atrial fibrillation [18] and mortality after myocardial infarction [19], but without the assessment of SBP and RRI linear and non-linear relationship using cross-entropy and copula in connection to the baroreflex sensitivity.

In respect to the previous works, our analysis implement an original method that increases the reliability of cross-entropy [10], as well as the analysis of SBP-RRI dependency structures performed by copula density [12]. The aim of this study is to apply the modified cross-entropy and copula density methods in patients before and immediately after Verapamil administration and to test the possibilities of the methods to capture the changes in cardiovascular parameters methods in respect to the statistics of baroreflex sequences and antisequences.

II. MATERIALS AND METHODS

A. Signals

The research was conducted using the signals from 11 hypertensive patients, with the average age equaling to 53,09±10,67 [years]. The number of patients for our study was checked statistically using the software package 'Power Sample Size Calculation', available at [20], for power of 90%

and type I error probability of 0.05. In biomedical studies with ergodic set of subjects, the sufficient population size is smaller, reduced to 6 subjects, e.g. [21].

The monitoring was conducted using the TaskForce Monitor® before (CONTROL state) and after the verapamil administration (VERAPAMIL state). Signals for analysis were RR interval time series – RR is an interval between the adjacent R peaks of electrocardiogram (ECG), and systolic blood pressure (SBP) time series – SBP is a local maximum of blood pressure waveforms (BP). Both ECG and BP waveforms are digitalized with sampling rate of 1 kHz. After the pre-processing, two patients had to be removed, so total of 9 CONTROL and 9 VERAPAMIL signals remained for further analysis. Average signal duration was 18 minutes. Three patients returned for a control after one month of continuous therapy and they were included as an illustrative example (1 MONTH group). The experiment fulfils the ethical standards of Medical Faculty in Belgrade, and each patient gave a signed permission to allow the signals for the research purposes.

Task Force® Device monitors continuously cardiovascular parameters. It measures blood pressure waveforms using a finapress system [22] and it can estimate the baroreflex sensitivity and to apply spectral analysis [23].

Verapamil is frequently used for different arrythmia treatments, for angina pectoris, and for hypertension. Verapamil blocks voltage-dependent calcium channels, thus inducing the decrease the heart impulses conduction in atrioventricular and sinoatrial nodes (i.e. RR interval lengthening) and blood vessels dilatation (blood pressure decrease) [24].

For the signal control, we implemented isodistributional surrogate data (ID) time series. These time series have the same distribution as the original time series and they are obtained by randomizing the temporal order of the original signals. In this study they are used to investigate whether the sequences are random occurrences or an outcome of physiological processes [25]. For each signal we generated 50 surrogate signals and averaged the obtained results.

B. Sequence method

Sequence method and its numerous variants is the most frequently implemented method for non-invasive estimation of spontaneous baroreflex. Classical baroreflex investigation was invasive, and, since the blood pressure was artificially increased and decreased by administering the pharmacological drugs, the estimated baroreflex was not spontaneous but induced [4]. Besides, such methods could be used only in laboratory animals due to the side effects and their duration was limited [5]. Sequence method is one of the basic non-invasive methods [4], it has no side-effects, it yields the estimate of spontaneous BRR, and it can observe BRR over the long time period.

A sequence comprises adjacent increasing (or decreasing) samples of SBP signal – a SBP ramp, followed by adjacent increasing (or decreasing) samples of RRI signal – a RRI ramp, delayed 0, 1 or 2 heart beats in respect of the corresponding SBP ramp. Usually the number of SBP-RRI samples in a sequence should be above predefined threshold [26]. Sequences could comprise SBP and RRI signals both increasing (++) or both decreasing (--). The sequences when SBP ramp increases and RR ramp decreases (+-) or vice versa (-+) are considered as antisequences [25]. A slope of line fitted to a sequence in a SBP-RRI plane yields a particular spontaneous baroreflex sensitivity (*sBRR*) for this sequence, RRI = *sBRR* x SBP + *const*; averaging *sBRR* over all the sequences gives the spontaneous baroreflex sensitivity for the patient. For this reason, it is important to determine which sequences occurred due to the physiological reasons, and which ones are a consequence of random or other (mostly mechanical) reasons.

C. Copula method

While baroreflex clearly points out the linear negative feedback between the subsets of SBP and RRI signals (i.e. sequences), copula can capture and visualize linear and non-linear dependency structures [16]. The source of copula is the Sklar's theorem [27], stating that any joint distribution function $F_{SBP,RRI}$(SBP, RRI) with strictly increasing marginal distribution functions F_{SBP} and F_{RRI} may be written as:

$$F_{SBP,RRI}(\boldsymbol{SBP}, \boldsymbol{RRI})=C(F_{SBP}(\boldsymbol{SBP}),F_{RRI}(\boldsymbol{RRI}))=C(\boldsymbol{u},\boldsymbol{v})$$

$$C(\boldsymbol{u},\boldsymbol{v}) = C(F_{SBP}^{-1}(\boldsymbol{u}), F_{RRI}^{-1}(\boldsymbol{v})) \quad (1)$$

In other words, if the source random variables (i.e. signals SBP and RRI) are transformed via their respective empirical distribution functions (FSBP(SBP), FRRI(RRI)), the resulting transformed signals u and v would have uniform distributions. This simple transform is known as probability integral transform and the proof can be found in books on random variables and stochastic processes [28]. Their joint density function is known as copula density and it visualizes the dependency structure of signals SBP and RRI. Copula parameter Θ shows a level of their dependency. It is shown [12] that Frank copula family is the most adopted to cardiovascular signals, and for this reason it is used in this study.

D. Entropy methods

Approximate entropy (*ApEn*) and its improved version Sample entropy (*SampEn*) are unavoidable parameters in medical research, but mostly for the single time series. Their cross variants *XSampEn* and *XApEn* show the mutual unpredictability of the related time series – such as SBP and RRI – but they are less popular as their implementation requires a careful parameter selection.

ApEn is an empirical counterpart of Kolmogorov-Sinai entropy from which it cannot be theoretically derived, thus the name „approximate" [7]. To apply *XApEn*, both time series of length *N*, SBP and RRI, are partitioned into a series of *N*-*m*+1 overlapping vectors of length *m*. Then each one of the SBP vectors, in turn, serves as a 'template' that is compared to each one of the vectors in RRI time series in a procedure known as 'template matching'. If a difference between the template from SBP and the vector from RRI is below the predefined threshold *r*, the matching is counted as successful. The number of successful matching of a template no. *i*, divided by the number of vectors (*N*-*m*+1), yields a matching probability $p_m(i)$, with $-\log(p_m(i))$ corresponding to the level of information that the template *i* from SBP holds against all the vectors from RRI. Averaging information content over all the vectors gives the

information content of SBP in respect of RRI. The procedure is repeated for vectors of length m+1. The difference between these two averages (Eq. 2) gives the level of uncertainty that the bonding that exist between the two time series would remain intact if the matching vectors increase their length:

$$XApEn = \frac{1}{N-m+1-N_m}\sum_{i=1}^{N-m+1}\log(p_m(i)) - \frac{1}{N-m-N_{m+1}}\sum_{i=1}^{N-m}\log(p_{m+1}(i)) \quad (2)$$

Parameters N_m and N_{m+1} are the correction introduced in [10]: sometimes a template cannot find any matches, and the corresponding probability is zero, making the logarithm impossible. For this reason, the probability zero is omitted and the averaging performed without the omitted probability. Different ways of correction exist, systematized in [10], but the comparison to the theoretical (and therefore correct) values in artificial signals with known distributions has shown that this simple correction outperforms the more complex ones.

Sample entropy is introduced in [8] as a more robust *ApEn* counterpart. Instead of averaging logarithms (i.e. information), it averages probabilities and then takes the logarithm. Obviously, no correction is necessary.

$$XSampEn = \frac{1}{N-m}\log\left(\sum_{i=1}^{N-m}\log(p_m(i))\right) - \frac{1}{N-m}\log\left(\sum_{i=1}^{N-m}\log(p_{m+1}(i))\right) \quad (3)$$

Cross entropy for the source SBP and RRI signals show their mutual unpredictability regarding the amplitudes (that had to be normalized and centralized in order to be comparable [8]). To show the unpredictability of their dependency levels, we applied entropy analysis to probability integral transformed signals as well.

Baroreflex is the most significant regulator SBP-RRI linear relationship. Other, minor, linear and non-linear regulating factors exist as well, and even baroreflex itself is not linear within the border ranges of its values. For this reason, we opted for copula density: it visualize the dependency structures, while its parameter θ captures non-linear relationships as well, that Pearson's (linear) and Kendal's (rank) parameters omit. Besides, no tool exist mutual synchrony of parallel time series can be assessed observing the data through the sliding window, which is a characteristic of cross-approximate and sample entropy families. Baroreflex sequences are synchronously ordered parts of SBP and RRI signals, so it could be expected to be related to the copula and cross-entropy analysis.

III. SIGNAL PREPROCESSING

SBP and RRI signals, as it was mentioned in section II, were preprocessed in order to eliminate the artifacts. We used a filter from [29] designed for RR intervals, based on calculating the binomial filter series and adaptive statistical moments. We induced a correction that, if the original sample and filtered sample differ less than 15%, original sample value is retained. Since this filter was not designed for SBP time series, we corrected the artifacts manually. If a sample was an artifact (its change was greater than, or lesser than predefined threshold in respect to the previous sample), its correction was based on the following equation:

$$s(i) = \frac{s(i-1)+s(i+1)}{2} \quad (4)$$

If there were more than one artifacts in a row $(s(i), s(i+1), \ldots, s(i+m)$, their amplitude was changed according to the equation:

$$s(i+k) = \frac{s(i-1)+s(i+m+1+k)}{2} \quad (5)$$

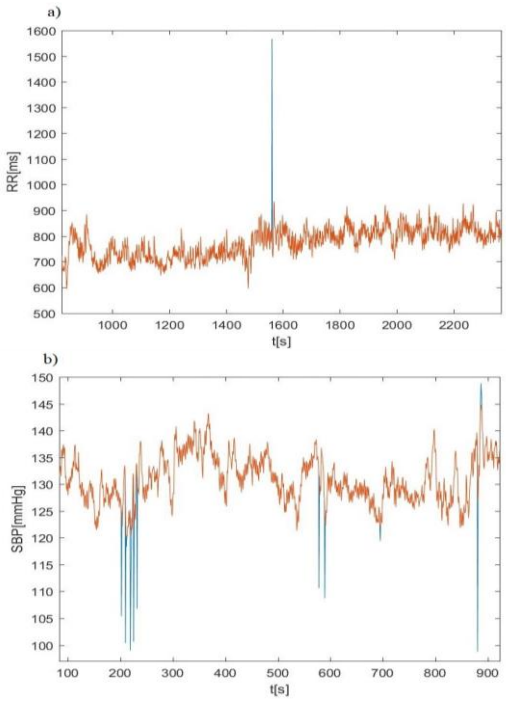

Figure 1. Artefact correction. a) RR interval time series; b) SBP time series. Blue line - before the correction, red line – after the correction.

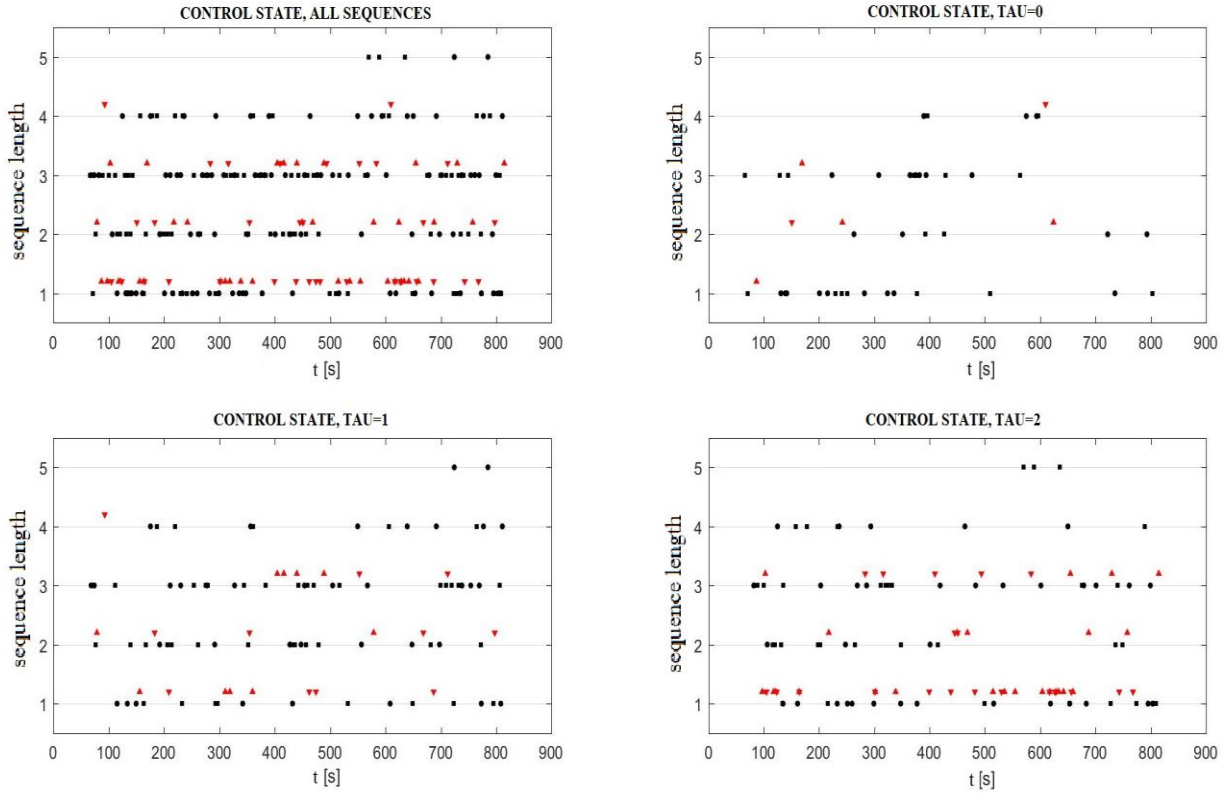

Figure 2. Sequences and antisequences; parameter tau is delay of RR ramp in respect to SBP ramp in the sequences; types of sequences and antisequences: ■ – SBP increase, RR increase (++), ● – SBP decrease and RR decrease (--), ▲ – SBP increase, but RR decrease (+-), ▼ – SBP decrease, but RR increase (-+)

Total of four signals recorded from two patients had to be discarded as their statistical analysis would be compromised due to the numerous artifacts. Examples of filtering outcomes are shown in Fig. 1.

IV. STATISTICAL ANALYSIS

For sequence analysis, the differences of adjacent SBP and RRI samples are determined, their sign, temporal position of ramp occurrence and ramp duration, as well as the delay of RR ramp in respect to SBP ramp. The sequences and antisequences were longer than 2 (shorter ones are more likely to be an outcome of a random occurrence). The sequences are divided into 12 groups, as shown in Fig. 2. For each one of 12 groups the number of sequences (antisequences), their mean, standard deviation and maximal length are determined. The values are divided by the time series lengths (to neutralize influence of time series length) and averaged over the patients. Furthermore, for each sequence *sBRR* was evaluated, as well as all the statistical parameters of *sBRR*. The same procedure is repeated in surrogate data signals.

The copula parameters were evaluated for delay time 0, 1 and 2. Entropy analysis was performed for source SBP and RRI data (normalized and centralized), as well as for PI-transformed data.

Results

The results show the effect of VERAPAMIL considering SBP and RR intervals, the outcome of sequence analysis, non-linear relationship via copula dependency structures and level of mutual unpredictability via entropy analysis.

Table I. shows SBP and RRI values of patients in CONTROL status (before the drug administration) and in VERAPAMIL status (immediately after the drug).

Three patients were also recorded after one month of continuous treatment by Verapamil. This is not sufficient for reliable analysis, but, for the sake of illustration, we have included the averages of these patients in line 3, 4 and 5 of Table I.

Table II shows an average number of sequences and antisequences per signal sample, scaled by 100 for simpler result interpretation. Table III shows maximal number of sequences and antisequences, while Table IV shows mean value and standard deviation of sequence/antisequence length. Histogram of *sBRR* coefficients is shown in Fig. 3.

Fig. 4 shows an illustrative example of copula density (density of the dependency structures), and the corresponding probability density function (amplitude concentration) for two patients that both have absolute copula parameter equal to 1.2, but with the opposite signs. Fig. 5 shows the scatterplot of the sequences that corresponds to the copula densities shown in Fig. 4. Table V shows the copula parameters for CONTROL and VERAPAMIL state, as well as the number of patients with positive, negative and small copula parameter.

Fig. 6 and 7 show the outcomes of the cross-entropy analysis.

TABLE I. **SBP** AND **RRI** OF PATIENTS BEFORE AND AFTER DRUG ADMINISTRATION; RESULTS ARE SHOWN AS MEAN±STANDARD DEVIATION

9 patients	**RR (ms)**	**SBP (mmHg)**
Control	822.87±98.53	132.81±15.62
Verapamil	810.14±88.60	135.88 ± 19.19
3 patients		
Control	808.50±138.64	143.30± 21.72
Verapamil	800.05 ±156.83	146.50±26.54
1 month Verapamil	940.77±113.27	122.29 ± 4.40

TABLE II. AVERAGE NUMBER OF SEQUENCES AND ANTISEQUENCES PER SIGNAL SAMPLE, SCALED BY 100

	tau = 0	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*
++	2.07	2.09	1.11	1.85	1.75	1.03	0.34	0.88	1.59
--	1.46	2.53	1.66	1.30	2.58	1.56	0.41	0.91	1.54
+-	0.43	1.81	3.11	0.51	1.18	1.95	0.35	0.90	1.28
-+	0.57	1.24	3.54	0.60	1.09	2.65	0.46	0.81	1.45

TABLE III. MAXIMAL SEQUENCE AND ANTISEQUENCE LENGTH

	Control			**Verapamil**			**Surrogate**		
	tau = 0	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*
++	11.3	11.7	5.3	17.4	17.9	10.9	2.4	7.7	13.8
--	7.8	15.2	8.4	12.4	28.6	15.9	2.6	7.6	12.7
+-	1.8	12.2	23.2	4.1	14	24.4	2.2	7	10.4
-+	2.4	7.8	28.4	4.7	12.9	36.1	2.8	6	12

TABLE IV. MEAN AND STANDARD DEFIATION OF SEQUENCE AND ANTISEQUENCE LENGTH

	tau = 0	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*	*tau = 0*	*tau = 1*	*tau = 2*
++	6.6 ± 5.1	6.6 ± 4.7	3.1 ± 1.9	10.5 ± 6.1	8.9 ± 8.1	4.8 ± 4.8	1.8 ± 0.9	5.1 ± 3.6	7.5 ± 8.9
--	4.2 ± 3.4	6.7 ± 6.7	4.3 ± 3.6	5.6 ± 5.4	10.6 ± 12.8	6.1 ± 6.6	1.8 ± 1.1	4.4 ± 4.4	7 ± 7.4
+-	1.1 ± 0.5	5.2 ± 5.9	8.7 ± 11.1	2.1 ± 1.4	4.9 ± 6.1	8 ± 11	1.6 ± 0.9	4.2 ± 3.5	5.8 3 ± 6

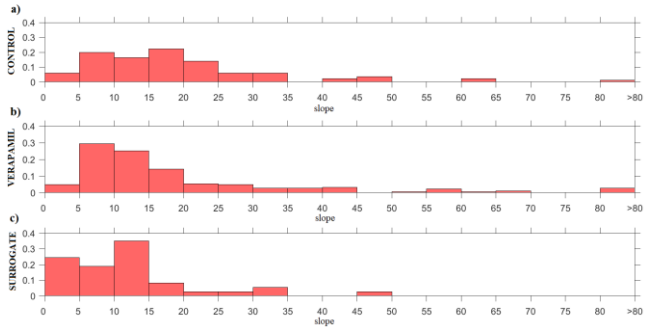

Figure 3. Histograms of the sBRR sensitivity (slope) a) CONTROL, b) VERAPAMIL, c) SURROGATE

TABLE V. COPULA PARAMETERS; RESULTS ARE SHOWN AS MEAN±STANDARD DEVIATION

	tau = 0	**tau = 1**	**tau = 2**
CONTROL	0.51 ±1.73	0.39 ± 1.13	0.09 ± 1.02
> 0.5	5	4	2
< -0.5	2	3	3
small	2	2	4
VERAPAMIL	0.12 ± 0.92	0.04 ± 0.88	0.06 ± 0.89
> 0.5	3	2	2
< -0.5	4	1	3
small	2	6	4

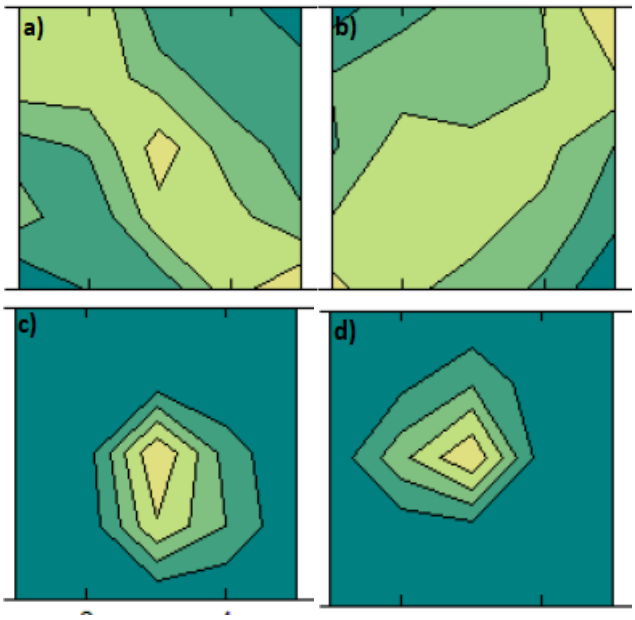

Figure 4. Upper panels: copuladensity for *tau* = 1, patients with a) Θ = -1.2 and b) Θ = +1.2; Lower panels, c) and d): the corresponding joint probability density functions.

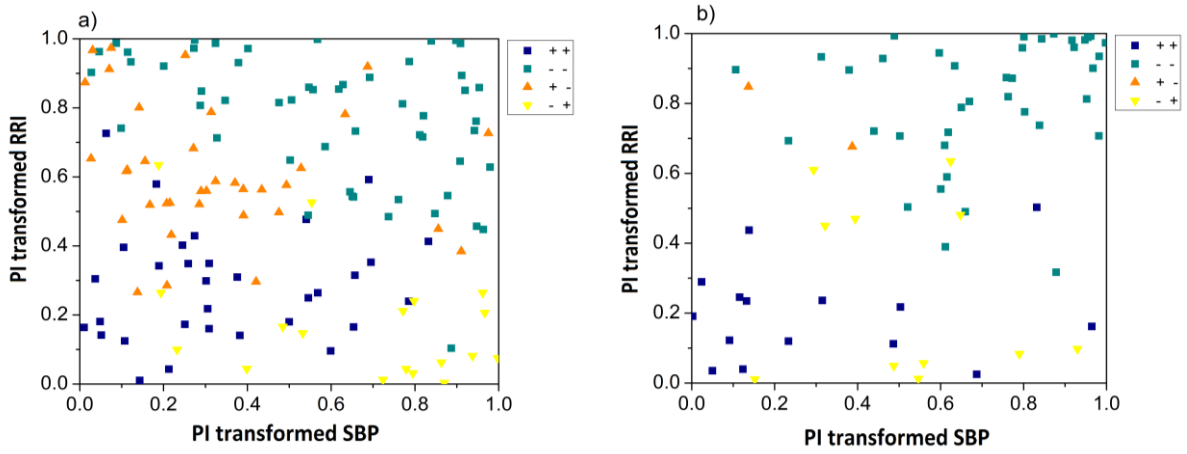

Figure 5. Scatterplots of sequences that correspond to copula densities shown in Fig. 4. Each point corresponds to the starting SBP-RRI pair (tau = 1)

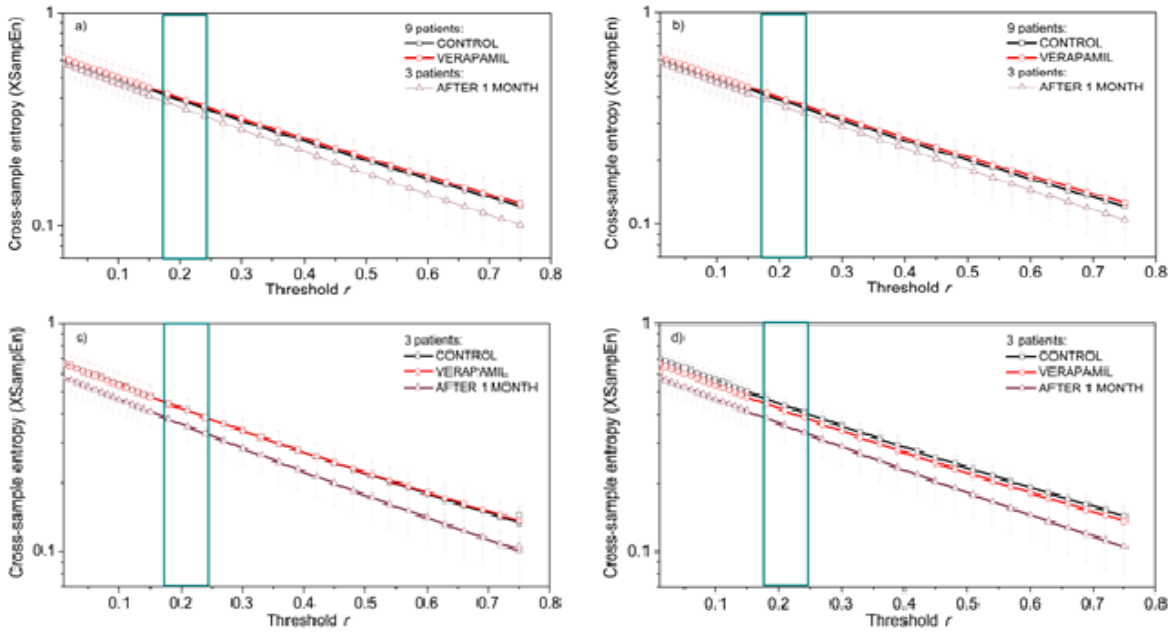

Figure 6. Entropy a) *XApEn* and b) *XSampEn* for all patients; c) *XApEn* and d) *XSampEn* for three patients that were examined after one month of continuous therapy. Green lines mark the boundaries of minimal threshold level that ensures reliably entropy estimate [15]

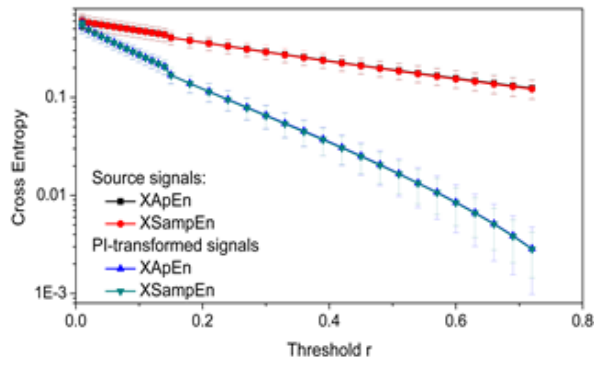

Figure 7. Entropy of the source signals and PI-transformed signals

V. Discussion and Conclusion

Observing the Table I, it can be deduced that there is no immediate response after the drug administration, neither in SBP, nor in RR interval. This is quite in accordance with the medical experience stating, after the first dose, the patient's status can be even worse before it becomes better after the long-term treatment. The three patients that were recorded after the full month's treatment prove it – their SBP is decreased and stable, and their heart rate (an inverse of RR interval) dropped. Table II shows that number of BRR sequences both in CONTROL and VERAPAMIL (++ and --) for delays *tau*=0 and *tau*=1 considerably larger than in surrogate data, showing

that the baroreflex function is considerably increased for these delays. For delay equal to 2 there is no significant difference between the number of sequences in surrogate and in source data, so this delay should not be considered. It is approved in Tables III. and IV. Average sequence length and maximal sequence lengths are decreased for delay *tau*=2. There is no significant difference in number of sequences before and after the drug administration, in accordance with the statement that after the first dose the effects are null. Considering the antisequences, their number increases in respect to sequences for delay *tau* =2. This increase is visible in CONTROL state, but not in VERAPAMIL state, opening new perspectives for further investigation.

Fig. 4 shows that, contrary to the probability density function which is nearly the same for the both patients in this illustrative example, the copula density exhibits the dependency structure. The sequences scatterplot shown in Fig. 5 establishes a connection between the copula density from Fig. 4 and positions of sequences in an abstract copula $[0\ 1]^2$ plane: the patient with the positive copula parameter has sequences mostly along the increasing diagonal, without many antisequences; the patient with negative parameter have increased number of antisequences and increased densities along the decreasing diagonal. Considering the copula parameter, Table V shows a great variability. Some patients have large absolute copula parameter (positive or negative), some have decreased copula parameter. However, for delays of 0 and 1 the parameter was larger than for delay of 2, in accordance with the previous findings.

Corrected *XApEn* is almost the same as *XSampEn* (Fig. 6) (it is not true for uncorrected version). Slight decrease in entropy occurs for patients that had been taking the therapy during the whole month. This decrease is not statistically significant and, besides, there were only three patients. The entropies before and after the first administration of drug are almost the same.

Fig. 7 shows entropy of source signals and entropy of PI-transformed signals. Entropy of the transformed signal (i.e. signal without the influence of the amplitude distribution) is lower, showing an increased level of orderliness. It can be concluded that amplitude fluctuations and not the connections between the SBP and RRI signals contribute to the mutual disorder of SBP and RRI signals.

Although it is generally accepted that the response of RRI in respect to SBP occurs for the delays of *tau* = 0, 1 and 2 in humans, the decrease of number of sequences and its length, and also decrease of copula parameter for *tau* = 2 shows that *tau* = 0 and *tau* = 1 are more relevant for the patients in this study.

The occurrence of sequences and antisequences is reflected in copula analysis. If sequences outnumber antisequnces, copula parameter is positive, and dependency is visualized along the auxiliary diagonal of copula density; if antisequeces domineer, copula parameter is negative, while the dependency is concentrated along the main diagonal of copula density.

In all the observed parameters (sequences, copula, cross-entropy), the drug administration induced statistically insignificant changes only, which confirms that a single dose, without the continuous therapy, has no effect at all.

However, the decrease of cross-entropy when calculated for probability integral transformed signals in respect to the cross-entropy calculated for the original SBP and RRI signals show that the major source of SBP and RRI asynchrony is due to their amplitude variations, and not due to their mutual relationship.

The results of this research open the opportunities for further work, in particular considering the relationship between the sequences, antisequences and copula dependency structures, considering the sequence 2D visualization and considering the statistics of sequences and antisequences in patients with therapy. Other methods for assessing baroreflex sensitivity implement the analysis in frequency domain, so cross-spectral method should be considered in future studies. Another, complementary, approach would be to implement non-linear analysis of 2-D scatterplots coupled with joint symbolic dynamic that might give a different interpretation of baroreflex.

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