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Complexity of the heart rhythm after heart transplantation by entropy of transition network for RR-increments of RR time intervals between heartbeats

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***Abstract*— Network models have been used to capture, represent and analyse characteristics of living organisms and general properties of complex systems. The use of network representations in the characterization of time series complexity is a relatively new but quickly developing branch of time series analysis. In particular, beat-to-beat heart rate variability can be mapped out in a network of RR-increments, which is a directed and weighted graph with vertices representing RR-increments and the edges of which correspond to subsequent increments. We evaluate entropy measures selected from these network representations in records of healthy subjects and heart transplant patients, and provide an interpretation of the results.**

I. INTRODUCTION

It is generally believed that RR-intervals — time intervals between heart contractions — carry information about the cardiac control system, mainly driven by the autonomic nervous system [1]. But heart transplantation (HTX) interrupts the possibility of direct autonomic control over the beating of the heart. As a consequence, heart rate variability in patients after HTX is different from that of healthy people. However, although the decision to transplant the heart is taken when the patient's life is in danger, in many cases already in a short time after the surgery, it is amazing to see how the organism of the patient recovers [2]. Therefore, when we investigate signals recorded from the same patient with the passing of time after HTX, we have a unique opportunity to observe the heart at work when the direct control over healthy variability is removed, and is then recovering, at least partially.

RR-signals, like any time series, can be easily mapped out in a directed graph where the vertices represent signal values and the edges are links between consecutive values in a signal [3], [4]. The considerable success of the network approach motivated us to explore these ideas to identify patterns in RR-signals of people after HTX, and present them in a way which could be useful in clinical practice to observe the emergence of autonomic regulation. This paper is a continuation of our earlier investigations (see [5], [6]). In distinction from our previous studies, here we search for the emergence of complexity in the transition networks constructed from increments between subsequent RR-intervals. Hence, we study changes in the heart rhythm, and not the rhythm itself.

A variety of measures have been proposed to determine the relative importance of a single vertex within a graph [7], [8]. Examples of such measures are given by centrality degree (defined as the degree of a vertex), or eigenvector centrality (defined as the dominant eigenvector of the adjacency matrix). The adjacency matrix keeps the whole of the information about the network. The transition matrix, obtained by the normalization of the adjacency matrix, introduces the probabilistic description. In the following, we investigate the entropy revealed in this description in order to assess the complexity of the signals studied.

II. DATA ACQUISITION

A. Groups of signals studied

In the following, two groups of signals are studied: *healthy* and *HTX*. The *healthy* group consists of 41 recordings (21 women and 20 men, age 19–34) which were obtained from healthy young people — students of Gdańsk Medical University. The *HTX* group is made of 25 recordings taken from 14 patients after HTX. For all the patients, it was at least 12 months since they had the HTX. The patients were all in a stable condition and with no signs or symptoms of rejection. Some recordings were taken from the same patient but at different periods after the surgery which allows the study of the progress in graft adaptation.

All the subjects underwent 24-hour Holter monitoring during a normal sleep-wake rhythm. The Holter recordings were analyzed by Delmar Reynolds Impresario software for premature, supraventricular and ventricular beats, missed beats and pauses. Finally, we annotated the signals manually, and time series with RR-intervals between subsequent heartbeats, together with beat annotations, were obtained.

The series for our studies were constructed from 15 000 normal-to-normal beats, and obtained by linking together sequences consisting of at least 500 consecutive beats. In order to limit the influence of daily activity, these sequences were selected from the nocturnal part of recordings.

B. Signal preprocessing

Our Holter equipment provided values with 128 Hz accuracy. Therefore, RR-intervals are given with 7.8125 ms resolution, which can be approximated by $\Delta_0 = 8$ ms. For

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this reason, we transferred signal numbers into multiples of 8. In order to get RR-increments, differences between subsequent values of RR-intervals were calculated. Thus, RR-increments are also multiples of 8 with values limited to $0, \pm 8, \pm 16 \pm 24 \ldots$. Here, negative values correspond to events of accelerations, positive values denote decelerations, and 0 describes no change events.

To decrease the number of different values in a sequence of RR-intervals, and as a consequence the number of distinct vertices in a network, we performed the standard binning procedure with bins based on multiples of the signal resolution, namely $\Delta = k\Delta_0$ for $k = 1, 2, \ldots$.

In parallel, we performed the same analysis with artificially modified cardiac signals. We refer to signals as *shuffled* if cardiac RR-intervals are randomly shuffled. By *surrogate* signals we mean signals obtained by randomization of phases of the Fourier transform of cardiac RR-intervals via iterative procedure focused on preserving the spectrum [9]. The *shuffled* signals indicate independence in the data, while the *surrogate* signals are said to preserve only linear correlations in cardiac data. With the help of TISEAN [10], we generated three shuffled and three surrogate signals for each set of individual cardiac data.

III. TRANSITION NETWORK FOR RR-INCREMENTS

Let $\mathbf{b} = \{b_0, b_1, \ldots, b_i, \ldots, b_N\}$ be a sequence of RR-intervals binned with some Δ. The subscript i refers to the time order. Let $\mathbf{c} = \{c_1, c_2, \ldots, c_i, \ldots, c_N\}$ be a sequence of corresponding RR-increments, i.e., $c_i = b_i - b_{i-1}$.

Since the number of different values is finite K, we can enumerate them from the smallest $C^{min} = \min_i\{c_1, c_2, \ldots c_N\}$ to the greatest $C^{max} = \max_i\{c_1, c_2, \ldots c_N\}$, and consider as labels for vertices in the network:

$$\begin{array}{l} C^{min} = C^{(1)}, \quad C^{(2)} = C^{(1)} + \Delta, \ldots, \\ C^{max} = C^{(K)} = C^{(1)} + (K-1)\Delta \end{array} . \tag{1}$$

Thus each vertex label denotes a change in RR-interval length.

A directed edge $(C^{(I)}, C^{(J)})$ between two vertices $C^{(I)}$ and $C^{(J)}$ is plotted if $C^{(I)}$ and $C^{(J)}$ represent a pair of consecutive events in a sequence $\mathbf{c}$, namely $(c_i = C^{(I)}, c_{i+1} = C^{(J)})$. If a given pair occurs many times in $\mathbf{c}$ then the weight of a corresponding edge increases to meet the counts of occurrences. The loops, if they appear, denote the consecutive decelerations or accelerations of the same size. The loop accompanying vertex 0 demonstrates the presence of two consecutive 'no change' events.

The entire topology of the network is entailed in the so-called adjacency matrix $\mathbf{A}$ —a $K \times K$ matrix of which the element $A_{(I)(J)}$ equals the weight of the out-going edge from vertex $C^{(I)}$ to vertex $C^{(J)}$, or is zero if there is no edge between these vertices. Since, the edges follow a time series order, each out-going edge is accompanied by an in-coming one. In consequence, the total of all weights of the out-going edges is equal to the sum of weights of the in-coming edges, and matches a given RR-increment occurrence of a signal. Therefore, if elements of each row $(I) : (1), \ldots, (K)$ of matrix $\mathbf{A}$ are divided by the total weight of vertex $C^{(I)}$, then the resulting matrix $\mathbf{T}$ describes the probability for transitions between two states given that the $C^{(I)}$ state occurs. $\mathbf{T}$ is right stochastic, i.e., the sum of each row is 1, and its maximal right eigenvalue is 1. The matrix $\mathbf{T}$, called the transition matrix, is said to describe a Markov walk on a network where a walker moves from the vertex $C^{(I)}$ to $C^{(J)}$ with probability $T_{(I)(J)}$.

The role of vertices in a network can be obtained from the stationary distribution arising from the transition matrix $\mathbf{T}$. The stationary state $\mu = \{\mu_{(I)} : (I) = C^{min}, \ldots, C^{max}\}$ is given as the eigenvector of $\mathbf{T}$ corresponding to eigenvalue 1. Consequently, we can calculate the entropy as follows:

$$S = -\sum_{(I)=1}^{K} \mu_{(I)} \sum_{(J)=1}^{K} T_{(I)(J)} \log T_{(I)(J)}. \tag{2}$$

IV. RESULTS

RR-signals of people after HTX are very plain. The absence of direct influence of the autonomic nervous system results in their very low variability. In consequence, the network representation of RR-increments consists of significantly fewer vertices. Let us explain this feature by presenting values of the mean adjacency matrices found for *healthy* and *HTX* signals. In Fig. 1 they are shown as density plots.

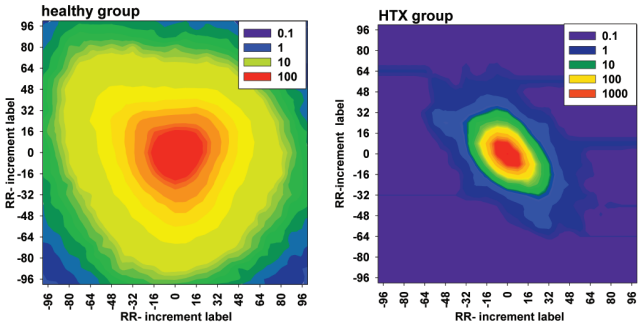

Fig. 1. Density plots for mean adjacency matrices obtained from RR-increments for the main cardiac groups: *healthy* and HTX at the signal resolution, i.e., $\Delta = 8$ ms. Notice the difference between scales in the plots.

From Fig. 1 we see that the network constructed from signals of *HTX* patients is sharply concentrated around the transition from a no change event to the smallest increments possible, namely to $0, \pm 8, \pm 16$. Signals from the *healthy* group lead to networks where there are many transitions playing an equivalent role. We illustrate this property in Fig 2. However, in order to make the network structure readable, the plotted networks are constructed from signals binned with $\Delta = 32$ and ignoring vertices of probability less than 1%. Since the binning is applied to RR-signals, any calculated change can be strengthened or weakened. Therefore, we cannot say exactly which elementary increments, even in the case of the loop over vertex 0, a given edge

represents. However, despite the no change event, most of them are related to subsequent RR-increments of $-16, -8$ or $8, 16$. There are counts given for some transitions along corresponding edges to illustrate their importance.

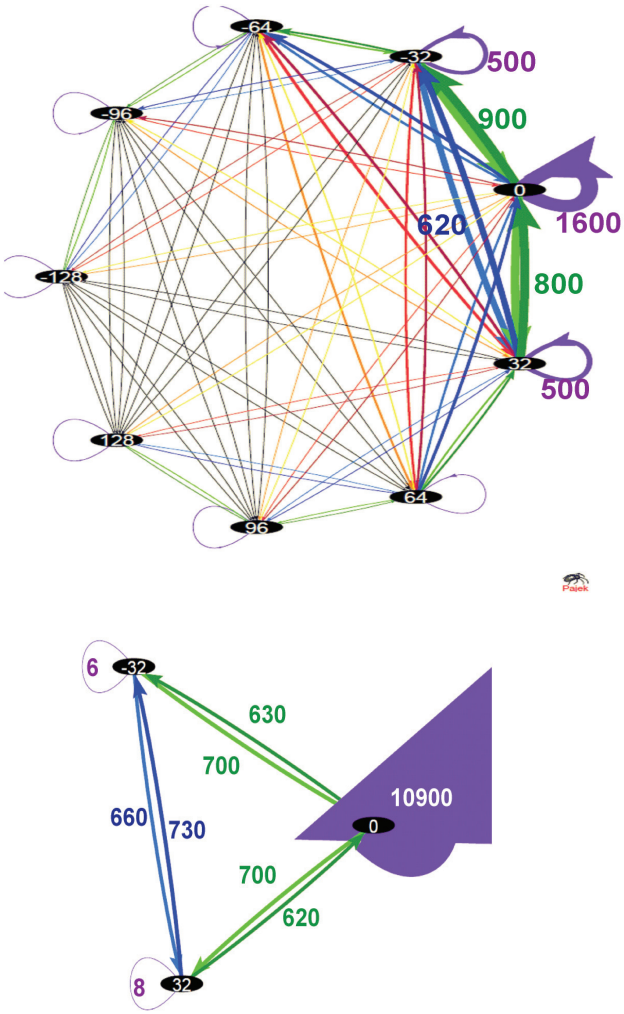

Fig. 2. The mean networks for the *healthy* (upper) and *HTX* (bottom) groups with counts for important transitions, and δ. The edge width mimics counts for given transitions. We use the following color scheme for edges: no change - violet; Δ- green; 2Δ - blue ; 3Δ - red; 4Δ - yellow; other cases - black. The diagrams were prepared with the help of Pajek[11].

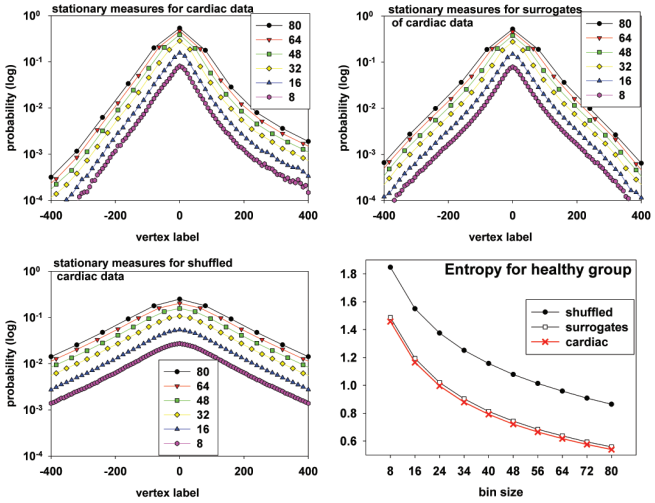

Fig. 3. The plots of eigenvectors for the eigenvalue 1 of the mean transition matrices obtained for signals of different types: cardiac, shuffled and surrogates, with different bin size Δ for the *healthy* group (log-plots), and resulting entropy.

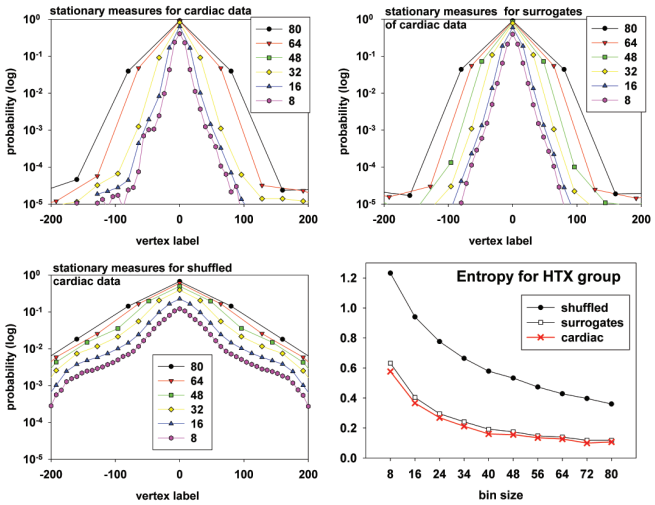

Fig. 4. The plots of eigenvectors for the eigenvalue 1 of the mean transition matrices obtained for signals of different types: cardiac, shuffled and surrogates, with different bin size Δ for the *HTX* group (log-plots), and resulting entropy.

Now let us present properties of stationary measures arising from the mean transition matrices. The mean matrices are found after averaging transition matrices obtained from the three types of signals considered: *cardiac*, *surrogates* and *shuffled* . In Fig. 3 properties obtained for the *healthy* group are presented, and in Fig. 4 features of the *HTX* group.

One should note that the binning procedure does not change the importance of vertices. For each group studied, the main measure is associated with no-change transitions. However, while in the case of the *healthy* group it takes values from 0.08, for $\Delta = 8$, to 0.47 for $\Delta = 80$, for signals from the *HTX* group we obtain 0.41 and 0.92, respectively. The surrogate data provide similar characteristics for the main transitions. One can find discrepancies when decelerations are large, namely for RR-increment > 150 ms. The shuffled signals provide completely different plots from the original signals.

The small difference between entropies found for cardiac and surrogate signals of the *healthy* group suggests that changes in RR-intervals follow linear stochastic dynamics, see Tab. I. However, in the case of *HTX* signals, we can expect that the rhythm of the heart in patients after HTX is driven by nonlinear interactions. Moreover, we can suppose that stochastic linearity of the healthy dynamics is related to the direct influence of the autonomic nervous system.

Finally, let us observe whether the entropy changes as time passes after the surgery. In Fig. 5 we show the entropy calculated for each individual *HTX* patient with indications of the time after HTX. It is shown that entropy increases in most cases, however the small group of signals considered

TABLE I

THE MEAN ENTROPY $\pm$ 0.95 CI OF THE MEAN AT MAXIMAL RESOLUTION Δ_0 FOR CONSIDERED GROUPS OF SIGNALS.

	cardiac	surrogates	shuffled
healthy	1.35 ± 0.06[1]	1.38 ± 0.04[1,2]	1.64 ± 0.02
HTX	0.54 ± 0.03	0.61 ± 0.02[2]	1.14 ± 0.04

[1]: all entries are significantly different (Mann-Whitney test, $P < 0.05$), except *healthy cardiac* versus *healthy surrogates* which are not significantly different.
[2]: entropy obtained for each surrogate signal is very similar to (at most a little greater than) the entropy found for each corresponding cardiac signal.

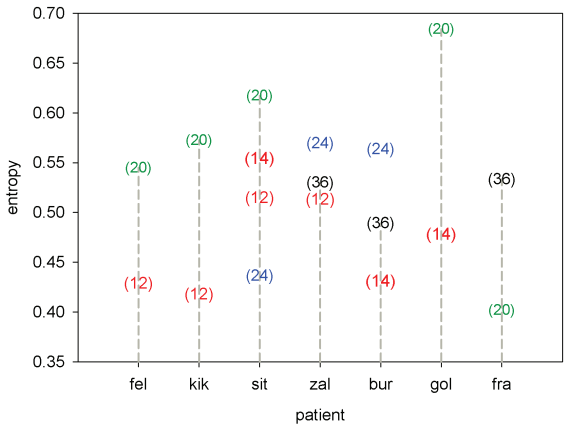

Fig. 5. Entropy obtained from individual signals of patients from the *HTX* group. Marks in the plot are numbers of months after HTX. The gray lines are used to lead the eye.

does not allow the derivation of a quantitative measure of the dynamics of this effect. This will, therefore, be the subject of future study.

V. CONCLUSIONS

The intrinsic cardiac nervous system remodels itself after cardiac transplantation, yet how the partially reconstituted, heterogeneous and inconsistent neuronal activity is reflected in heart rate variability is still an open question and the subject of intensive research [12], [13], [2].

Our results show a systematic increase with time after transplantation in network complexity reflected in entropy growth, for HTX patients. This may provide a unique new insight into quantifying the progress of the restoration of the dynamics of heart rate control in HTX patients.

Parasympathetic reinnervation is the last step in the process of restoring autonomic influence on the heart rate after transplantation and is not a rule [2]. Therefore, we can suspect that the fact that the networks for the HTX patients investigated concentrate on transitions less than or equal to 8 ms is due to the lack of the parasympathetic control of the heart rate.

Furthermore, both the networks of RR-increments and the corresponding entropy values, can be directly related to one of the standard time-domain indices of heart rate variability, i.e. pNN50, which quantifies the ratio of pairs of successive normal RR-increments larger than 50 ms. This index was reported to provide information about the control of the sinus rhythm mostly related to the influence of the parasympathetic part of autonomic regulation [14]. Indeed, the concentration on transitions less than or equal to 8 ms, observed in the HTX patients, corresponds with a small pNN parameter.

Analysis of networks constructed from shuffled signals provides yet another argument that there are correlations between the subsequent RR-intervals. Properties of networks obtained from surrogate signals indicate at a strong presence of linear stochastic dynamics which is impaired in the case of patients after HTX. The methodology presented may, therefore, be useful to gain further insight into the dynamical processes driving the changes in the heart rhythm.

Last but not least, our work may have a clinical application - the networks of RR-increments reflect the dynamics of heart rate and can be visualized in easy-interpretable graphical figures. They provide a uniform presentation of heart rate complexity which could potentially be appealing to cardiologists. The associated numerical values of graph entropy provide an accompanying quantitative measure of the graph complexity.

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