

COMMUNITY STRUCTURE IN NETWORK REPRESENTATION OF INCREMENTS IN BEAT-TO-BEAT TIME INTERVALS OF THE HEART IN PATIENTS AFTER HEART TRANSPLANTATION*

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The network representations in the characterization of time series complexity is a relatively new but quickly developing branch of time series analysis. The changes in beat-to-beat time intervals, called *RR*-increments, can be mapped into the directed and weighted network. The vertices in this network represent *RR*-increments and edges correspond to pairs of subsequent increments. We show that community structure analysis, called *p*-core analysis, is an effective measure which allows the evaluation of the information on dynamical processes represented by networks constructed from *RR*-increments.

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1. Introduction

The decision to perform heart transplantation (HTX) is taken when the patient's life is at danger. However, in many cases already a short period after the surgery, it is amazing to see how the organism of the patient recovers [1].

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It is generally believed that the time intervals between subsequent heartbeats (so-called RR -intervals) carry information about the cardiac control system mainly driven by autonomic nervous system [2]. But heart transplantation interrupts the possibility of direct autonomic control over the heart beating. In consequence, heart rate variability in patients after HTX is different from that of healthy people. However, this provides us the unique opportunity to observe the heart at work when the natural control over healthy variability is removed.

Characterization of the complicated dynamics by examination of experimental time series is a fundamental problem of continuum interest in a wide variety of fields [3, 4]. The huge success of network approaches in explaining the phenomena in various fields has been observed in the last decade [5]. One of the particular reasons for the success of this approach is that it offers visualization of dependences which then can be easily read and quantified in a natural way.

Network techniques have also influenced analysis of time series. Closely linked to the pioneering ideas of Poincaré, recurrence networks provide tools for quantifying recurrence properties in the phase space [6]. It has been demonstrated that a variety of characteristics of recurrence networks yields new concepts for statistical evaluation of phase space structures captured in recurrence plots.

Recently, an effective framework for exploration of pseudoperiodic time series by complex networks has been published [7]. This technique enables one to study periodicity contained in a time series such as the human ECG recording with each cycle representing one heartbeat. With this method, the heart rhythms of healthy people were quite well separated from heart rhythms of people with arrhythmia [7]. On the other hand, the approach based on the so-called visibility graphs allows the investigation of fractal-like properties in any time series [8]. A tight relationship between time series and networks, and back is discussed by Campanharo *et al.* [9].

Understanding the relationship between the structure of a complex network and the dynamics (or function) it represents has shed some lights onto relevant issues in neuroscience [10, 11]. Therefore we believe that it should also help in understanding the control mechanisms of the cardiovascular system.

A variety of measures have been proposed to determine the relative importance of a single vertex within a graph [12, 13]. Examples of such measures are given by centrality degree (defined as the degree of a vertex), eigenvector centrality (defined as the dominant eigenvector of the adjacency matrix). Important nodes usually play a crucial role in the global organization of a network, which in turn has significant consequences for the

dynamical processes taking place on it. Another way to quantify the graph structure is based on the so-called communities, namely, on subgraphs with densely interconnected nodes [13–15].

The considerable success of the network approach motivated us to explore these ideas to identify patterns in *RR*-signals of people following HTX, and present them in a way which could be useful in clinical practice as an early warning of the rejection of the graft. The paper is a continuation of our earlier investigations (see [16, 17]). In distinction to our previous studies, here we search for the community structure of transition networks constructed from increments between subsequent *RR*-intervals. Hence, we study changes in the heart rhythm, and not the rhythm itself.

The transition network for *RR*-increments is a directed and weighted graph, where vertices represent *RR*-increments. Each vertex corresponds to a different value of *RR*-increment. A directed edge from a given vertex to another one accounts for an event in which, after an increment described by the former vertex, the next change in *RR* was equal to the label of the latter. This edge increases its weight each time this event is found.

In directed and weighted graphs, the community structure is encoded mainly in the edge weights [14]. Therefore, it is advisable to explore the network structure by the subsequent removal of vertices of a given weight p (= the sum of weights of in-coming and out-going edges) together with adjacent edges. Formally, the method applied by us to partition the networks into smaller subnetworks, is based on the so-called p -cores [18, 19].

In the following, this technique is introduced in Sec. 2 and then, in Sec. 3, we show results obtained from analysis of transition networks constructed from *RR*-increments representing healthy subjects and heart transplant patients. To get insights into the dynamics of underlying processes, the analysis is also run with specific synthetic signals. We show that the p -core is an effective node-importance measure that can evaluate the information on the dynamical processes represented by the networks considered.

2. Methods

2.1. Data acquisition

Two groups of signals are studied. The first group, called *healthy*, represents 41 recordings (21 women and 20 men, age 19–34) which were obtained from healthy, young people — students at the Medical University of Gdańsk. The second group, called HTX, is made up of 23 recordings taken from 12 patients following HTX. All the heart transplant patients were in a stable condition, with no signs or symptoms of rejection. The recordings were taken

from at least 12 months or more after HTX (the mean is 21 ± 4 months after HTX). Some signals were from the same patient but at different periods after the surgery.

All subjects underwent 24-hour Holter monitoring during normal sleep–wake rhythm. The Holter recordings were analyzed by Del Mar Reynolds Impresario software for premature, supraventricular and ventricular beats, missed beats and pauses. The QRS-complexes were detected and classified automatically by the software. Finally, we annotated them manually and then the series of time intervals between subsequent heart beats were obtained, together with the beat annotations. These signals are called *RR*-intervals.

In order to limit the natural variability caused by daily activity, we focused on recordings during nocturnal rest. From these parts, we constructed signals consisting of 15 000 *RR*-intervals between normal-to-normal beats by linking together sequences consisting of at least 500 consecutive normal-to-normal beats.

Our Holter equipment provided values with 128 Hz accuracy. Therefore, *RR*-intervals are given with 7.8125 ms resolution which can be well approximated by $\Delta_0 = 8$ ms. In consequence, the number of distinct values in *RR*-data is bounded. For this reason, we transferred signal real numbers into integer ones, which were then mapped onto the set of multiples of 8.

In order to get *RR*-increments, differences between subsequent values of *RR*-data were calculated. Each signal with *RR*-increments has become a sequence of integer values limited to $0, \pm 8, \pm 16, \pm 24, \dots$. These values will serve as labels for vertices in transition networks for *RR*-increments. Positive labels correspond to decelerations of the heart rhythm while negative ones correspond to accelerations.

It is said that by tests with surrogate data one can find the least interesting explanations for the studied phenomena that cannot be ruled out based on the data [20]. Therefore, in parallel, we performed analysis with two types of data that were artificially modified cardiac signals. We refer to *shuffled* signals if cardiac *RR*-intervals were randomly shuffled, and to *surrogate* signals if they were obtained by randomization of phases in the Fourier transform of cardiac *RR*-intervals. Both types of series were obtained with the help of TISEAN software [21]. For each cardiac signal, we constructed three signals of each type. The *shuffled* signals serve as detectors of independence among data, while the *surrogate* signals keep the linear correlation between cardiac data. In Fig. 1, we show an example of analyzed signal and its shuffled and surrogate versions.

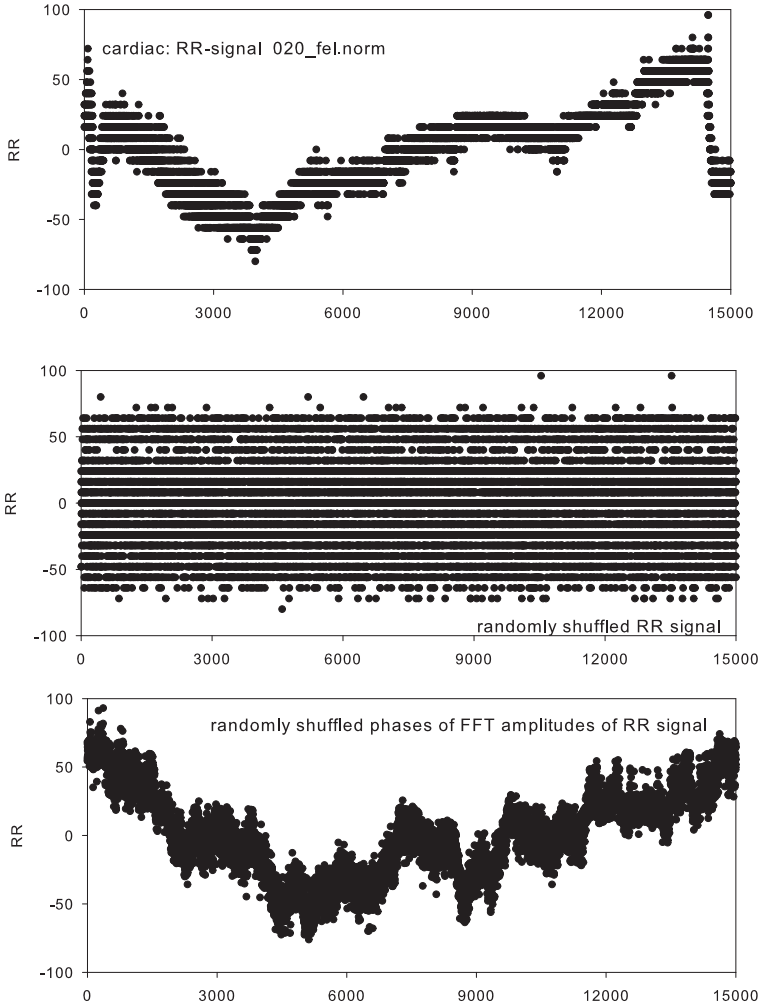


Fig. 1. Example of the cardiac signal of patient *fel* recorded 20 months after HTX (normalized — subtracted by the signal mean value), and its shuffled and surrogate partners.

2.2. Transition network for RR -increments

Let $\mathbf{b} = \{b_0, b_1, \dots, b_i, \dots, b_N\}$ be a sequence of RR -normalized. The subscript i refers to the time order. Let $\mathbf{c} = \{c_1, c_2, \dots, c_i, \dots, c_N\}$ be a sequence of RR -increments, *i.e.*, $c_i = b_i - b_{i-1}$.

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

in the network. These labels are separated by $\Delta_0 = 8$ msec and, therefore, there exists K such that

$$\begin{aligned} C^{\min} &= C^{(1)}, C^{(2)} = C^{(1)} + \Delta_0, \dots, \\ C^{\max} &= C^{(K)} = C^{(1)} + (K-1)\Delta_0. \end{aligned} \quad (1)$$

Thus, the set of vertices V in the transition network $N = (V, E)$ consists of K vertices labelled as (1). Since a vertex label describes a change in RR -interval length, negative labels correspond to events of accelerations while positive labels denote decelerations. The label 0 denotes no-change event.

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 a corresponding edge increases its weight with the number of occurrences. The loops, if they occur, denote the consecutive decelerations or accelerations of the same size. The loop accompanying vertex zero demonstrates the presence of two consecutive no-change events. In this way, the set of edges $E(V)$ of network N consists of directed and weighed edges.

The topology of a network $N = (V, E)$ is contained in the so-called adjacency matrix $\mathbf{A}$ — a $K \times K$ one whose elements $A_{(I)(J)}$ are equal to the weights of the edges going from vertex $C^{(I)}$ to vertex $C^{(J)}$, or are zero if there is no edge between these vertices.

The edge weight defines also the in- and out-degree, d_{in} and d_{out} respectively, of a vertex as follows

$$d_{\text{in}}(C^{(I)}) = \sum_{C^{(J)} \in V} A_{(J)(I)} \quad \text{and} \quad d_{\text{out}}(C^{(I)}) = \sum_{C^{(J)} \in V} A_{(I)(J)}. \quad (2)$$

2.3. Community detection

A network constructed from time series is specific in the sense that for each vertex the number of in-coming entries is equal to the number of out-going ones, except two vertices which correspond to the first and last values in a signal. This means that we have

$$\begin{aligned} d_{\text{in}}(C^{(I)}) &= d_{\text{out}}(C^{(I)}) & \text{for } \forall I \in \{2, \dots, K-1\}, \\ \left| d_{\text{in}}(C^{(I)}) - d_{\text{out}}(C^{(I)}) \right| &= 1 & \text{for } I \in \{1, K\}. \end{aligned} \quad (3)$$

By definition, the vertex degree is the same as the number of occurrences of a given value of RR -increment in a signal. Therefore, if we normalize vertex degrees by the length of a signal, we obtain the probabilities of events labelled by $C^{(1)}, \dots, C^{(K)}$.

The subgraph $H = (C, E(C))$ of the network $N = (V, E)$ induced by the set $C \subseteq V$ is called p -core at level $p > 0$ [18, 19], if

$$\forall_{C^{(I)} \in C}, \quad p \leq d_{\text{out}}(C^{(I)}) \quad (4)$$

and C is the maximal such set. In the case of a transition network where properties (3) hold, it is convenient to modify (4) in the following way

$$\forall_{C^{(I)} \in C}, \quad p \leq \text{Prob}(C^{(I)}) . \quad (5)$$

This relates the threshold value p , used in the construction of a subgraph, to the probability for a given event.

Since the structure of a network may be hierarchical, the investigation of the development of the community structure is performed by sweeping the weight threshold p within the range of interest [14]. Therefore, for each p , we estimate the ratio of transitions still present in a p -core subgraph H with respect to the whole network N . We will refer to this ratio as the *volume of a given p -core subgraph*, and the decay of this volume (with increasing parameter p) will be called *network disintegration*.

3. Results

3.1. Disintegration of transition networks of RR -increments

Disintegration of transition networks obtained from RR -increments of signals recorded from patients following HTX progresses differently from the disintegration of networks representing healthy, young people. In Fig. 2, we explain this property by presenting the decay of volume of p -core subgraphs with increasing threshold value p . The decay is observed in the mean networks obtained from RR -increments recorded for the two groups of signals *healthy* and HTX.

It is evident that the transition network for patients after HTX is significantly more resistant to the subsequent removal of vertices. For small values of p , when less important vertices are removed from the networks, the volume decays linearly. This decay is very fast for the *healthy* group, and rather slow in the case of network constructed from signals of patients following HTX. For example, the volume of 1%-core is 98% and 84% for the HTX and *healthy*, respectively. This may suggest that the significance of the less important vertices is different in both cases. Events with small

probability have little influence on the network structure in the case they represent *RR*-increments of a patient following HTX. But in networks for healthy, young people, the removal of any vertex significantly modifies the whole structure.

In order to determine the critical points in the process of disintegration in both networks, we follow properties of the variances of the means of p -core volumes. These variances are also shown in Fig. 2. It turns out that the critical change in networks of the *healthy* takes place at $p = 0.05$, while it appears at $p = 0.24$ for people who have had HTX. The network volume at the critical disintegration point is equal to 30% for the *healthy*, but reaches about 54% for the HTX.

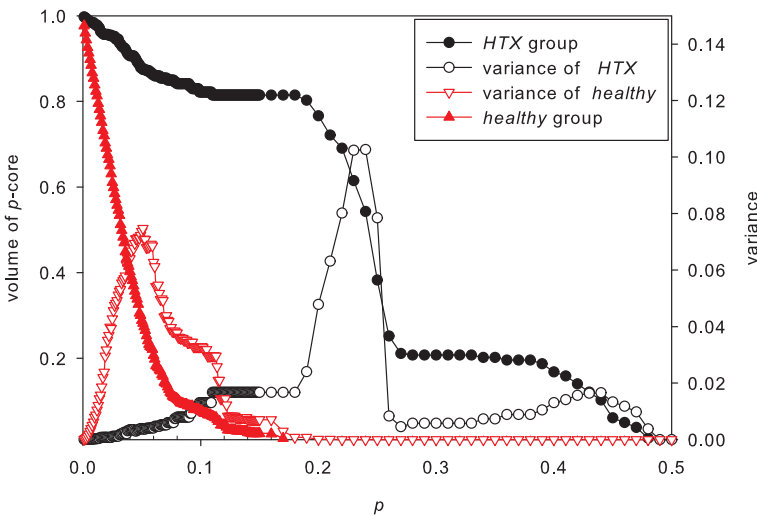


Fig. 2. Plots of decay of p -core volume in mean networks representing the *healthy* group and the HTX patients. Together variances of the corresponding average values are plotted.

These differences provide evidence for the fact that *RR*-signals of people following 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.

To see details of the differences between the two networks discussed, in Fig. 3 we show density plots of the mean of adjacency matrices for both types of networks. Scales in both plots are different to depict best the transitions of the greatest importance.

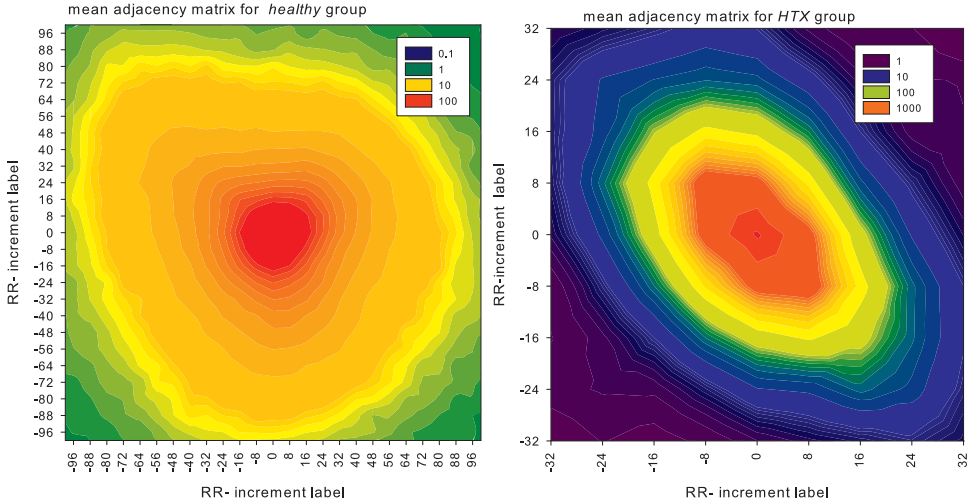


Fig. 3. Density plots for adjacency matrices of mean networks of RR -increments. Notice different scales between plots in both density and vertex labels.

There are a lot of transitions between RR -increments of similar importance in a healthy heart rhythm. They are spread almost uniformly around no change event, described here by a point (zero, zero). The highest transition value 160 (what in the case of 15 000 events means about 1%) is achieved for a no change event, and this count is only slightly greater than the transitions around, namely, transitions between RR -increments of +16, +8, 0, -8 and -16.

The network constructed from RR -increments of the HTX patients is concentrated on only a few transitions. Therefore, the importance of vertices for this network, measured within the core study by p value, is significantly larger. Since the mean network for the HTX group significantly does not change while $0.1 \leq p \leq 0.2$, we reconstruct this mean core in Fig. 4.

We add the mean counts of events at each transition. Other transitions have counts lower than 300, *i.e.*, their probability is less than 2%. It is easy to check that $d_{\text{out}}(+8) = d_{\text{out}}(-8) = 3200$, which is more than 20% of 15 000 transitions considered in total. However, a no change event (a loop over vertex zero) dominates. A sequence of accelerations or decelerations (loops at nodes other than zero) occurs 10 times less often than a no change event. One can conclude that changes in the heart rhythm: accelerations or decelerations, go very slowly, namely, with frequent stops at a no change event. The noticeable number of transitions between vertices +8 and -8 indicates the activity of control mechanisms, which are based on negative feedback reflexes.

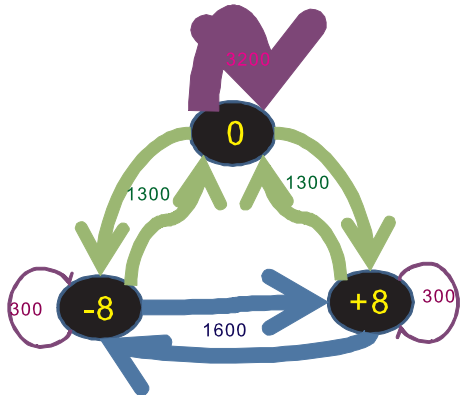


Fig. 4. Diagram of the mean network for 15% core (of the volume 80%) depicted from *RR*-increments of the HTX group. Numbers denote edge weights (out of 15 000). Additionally, edge weights are expressed by the edge widths.

The networks discussed so far were constructed with the natural resolution of recorded signals, namely 8 msec. It is tempting to check whether there exists such a resolution for vertex labels in which signals of young people lead to transition networks similar to those obtained for the HTX group. Rough investigations show that if *RR*-increments are represented as a multiplies of 64 msec then the similar picture is obtained. The results are presented in Fig. 5.

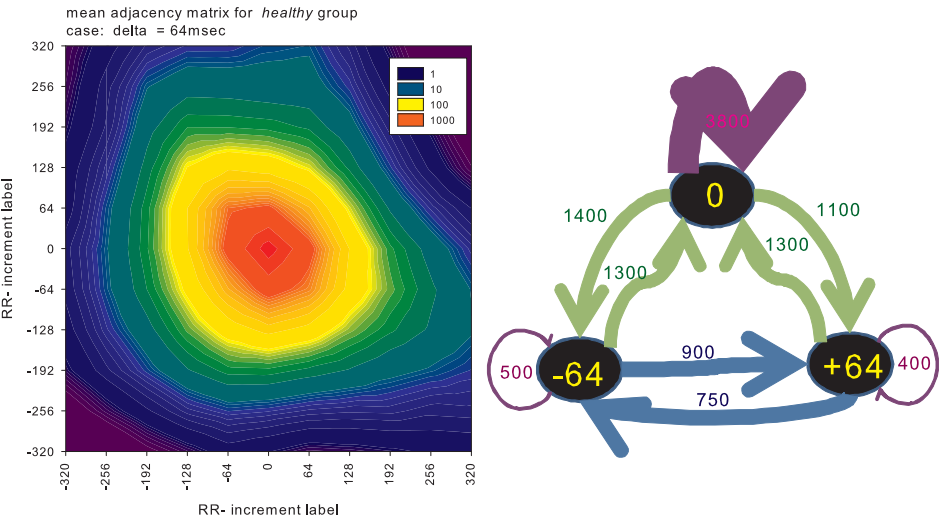


Fig. 5. Left: Density plot for adjacency matrix of the mean network for *RR*-increments for *healthy* group signals when they are mapped into a multiple of 64 msec. Right: Diagram for the corresponding mean network.

3.2. Disintegration of transition networks constructed from artificial signals: shuffled and surrogate cardiac data

In Fig. 6, we collect the results on the volume decay of p -core for the mean networks constructed from the two groups the *healthy* and HTX together with results provided by analysis of synthetic data: shuffled and surrogates, also averaged over the same groups as for the cardiac data. To emphasize properties of the *healthy* group, the p axis is changed to $\log p$.

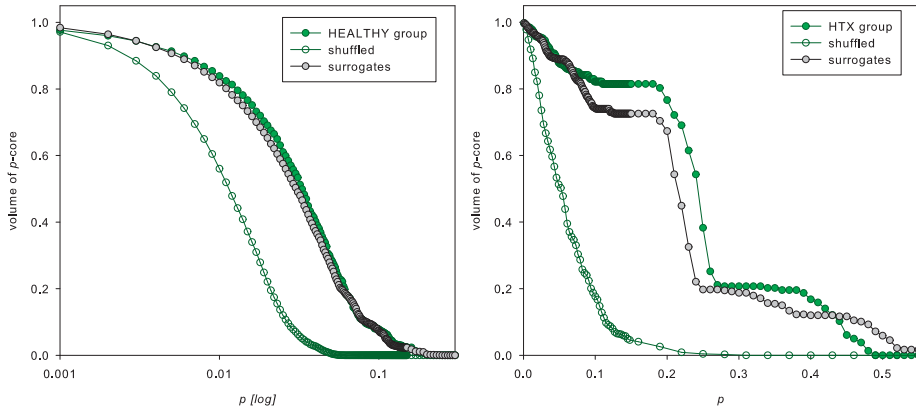


Fig. 6. Plots of decay of p -core volume for different groups of signals. The dependence for the *healthy* group is plotted in $\log p$ scale.

In the case of the *healthy* group, the decay is fast for cardiac and corresponding artificial signals. There is no evident difference between properties obtained from cardiac and surrogate groups of signals, though the decay of the network constructed from shuffled signals is different — it progresses faster. This can suggest the *RR*-increments are dependent, however this dependence can be described by a linear stochastic process.

One can notice that the network disintegration goes in two steps in the case of networks constructed for the HTX group. The same property is exhibited by the network constructed from surrogates. But there is some evident difference between these two groups of signals in the volume of the p -core network. In the case of 15%-core, the test of Kruskal–Wallis One Way Analysis of Variance on Ranks provides statistical significance of the difference in the median values. Precisely, the median in the group HTX: 0.85 is significantly different from the median of its surrogates: 0.73, with $P = 0.006$.

The shuffled signals provide the steady and fast decay of the p -core volume for signals from the HTX group. Since this behavior is completely different from properties of cardiac signals, it indicates the importance of dependences between *RR*-increments.

One can collect the above observations as indicating that the rhythm of the heart in patients following HTX is driven by nonlinear forces. Furthermore, supposing that stochastic linearity of the healthy dynamics is related to the direct influence of the autonomic nervous system, we can expect to observe the influence of this regulation by measuring the relation between a given cardiac signal and its corresponding surrogate one.

To test this hypothesis, we compared networks constructed from the same patient but at different time after the surgery. There are three patients in the HTX group considered, named *bur*, *sit* and *zal*, for each of whom we

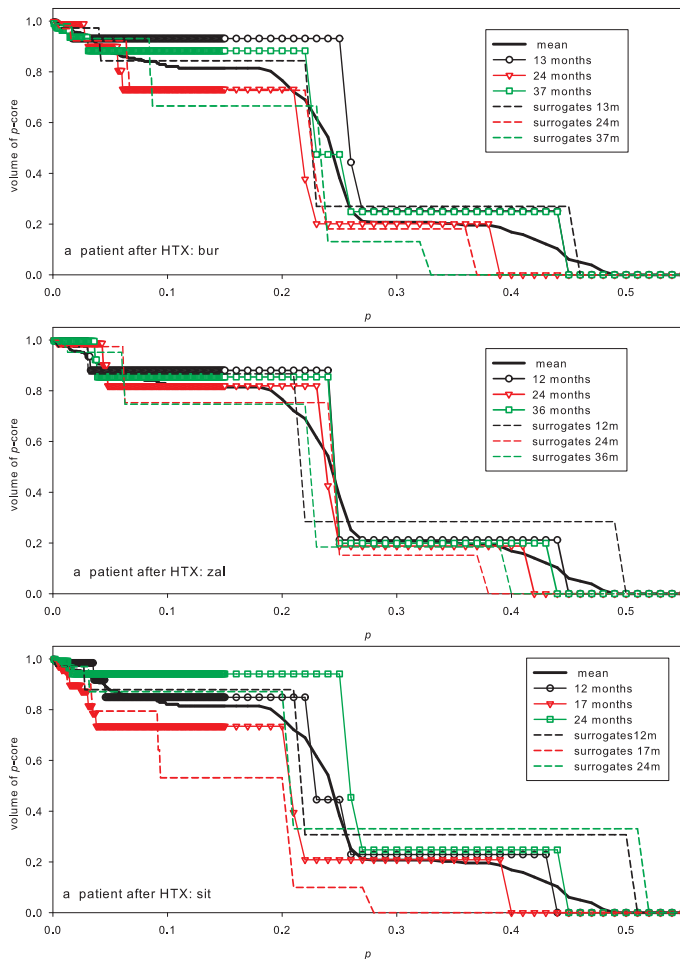


Fig. 7. Plots of decay of p -core volume for networks constructed from signals from individual patients which were recorded at different time after HTX. Dashed lines correspond to the surrogate signal.

have three signals. In Fig. 7, we show disintegration of the networks resulting from these signals together with plots of disintegration of the corresponding surrogate series.

It occurs that the decay of p -core volume weakly depends on the length of time passed since HTX in the case of the patients considered. The first step in the two-step decay is related to the three vertex core, shown in Fig. 4. The second step describes the role of the vertex with label 0. The disintegration of networks constructed from surrogates is similar but values of p -core volumes, especially for $p \in (0.1, 0.2)$, are usually lower. However, no direct dependence can be specified.

4. Conclusions and perspectives

Disintegration of the transition networks occurs by subsequent exclusions of events of equivalent role. In the case of heart rhythms of the young and healthy, the pool of equivalent transitions is large which results in a fast disintegration. But the networks of RR -increments constructed from signals of the patients following HTX have a strong structure in which no change transitions play a dominant role.

The networks of RR -increments can be directly related to one of the standard time-domain indices of the heart rate variability, *i.e.*, pNN50 which gives the ratio of pairs of successive normal RR -increments larger than 50 ms [2]. This index was reported to provide information about the control of sinus rhythm mostly related to influence of the parasympathetic part of autonomic regulation [22]. Moreover, pNN with lower thresholds (*e.g.*, pNN20 or less) was also able to differentiate healthy subjects from heart failure patients [23].

Parasympathetic reinnervation is the last step in the process of restoring autonomic influence on the heart rate after transplantation and is not the rule [1]. Therefore, we hypothesize that plain networks of our HTX patients, concentrated on transitions less than or equal to 8 ms, similarly to the small value of the pNN parameter, is a result of the lack of parasympathetic control of heart rate.

Our data set, especially of patients following HTX, is rather poor in a sense that it consists of signals from 12 patients only. But we believe that the differences obtained in the disintegration of the transition networks constructed from RR -increments would serve clinicians in the assessment of proper graft adaptation. Since the stability of the p -core seems to result from the non-linear dependences governing the heart dynamics, we hope to find indices qualifying dynamical features of the heart based on decay of networks constructed from surrogate signals. These are our tasks for the future.

Finally, there is a special objective for our studies. We want to propose an eye-catching representation of important aspects of the heart rate variability. Since the network of *RR*-increments can be plotted in easy-interpretable figures with a compact information about changes in the heart rate, therefore, it should meet the expectations of cardiologists.

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